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Association between prenatal arsenic exposure, birth outcomes, and pregnancy complications: An observational study within the National Children's Study Cohort

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Abstract

Background: Chronic arsenic exposure has been associated with pregnancy complications and reduced fetal growth in populations where total arsenic exposure exceeds 50 μg/L. However, the potential effect on pregnancy outcomes remains unclear at lower levels of arsenic exposure, such as those most commonly observed in the United States.

Objectives: We evaluated the associations between arsenic exposure during pregnancy with fetal growth and risk of pregnancy complications using data from mother-infant pairs participating in the National Children's Study.

Methods: Prenatal arsenic exposure was measured using maternal urine collected during the third trimester. Information about pregnancy complications was abstracted from medical records. Fetal growth, including gestational age, birth weight, birth length, head circumference, and ponderal index, was ascertained through physical measurement at birth and extracted from medical records.

Results: Medians [interquartile range (IQR)] of maternal urinary total arsenic and dimethylarsinic acid (DMA) were 7.77 μg/L (7.98) and 3.44 μg/L (3.13), respectively. Each increase in IQR of prenatal total arsenic level was associated with greater birth length (+0.28 cm; 95% CI: 0.14, 0.42), greater head circumference (+0.12 cm; 95% CI: 0.04, 0.21), and lower ponderal index (−0.37 kg/m^3; 95% CI: −0.58, −0.17). Similar results were obtained for levels of prenatal DMA. Tests for multiplicative interaction indicate that prenatal urinary DMA was negatively associated with gestational age among female infants (−0.44 week decrease in gestational age estimated for each IQR increase in DMA; 95% CI: −0.84, −0.05), while no

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association was observed among male infants ($p_{interaction}$ = 0.02). No significant associations were detected between arsenic and birth weight or pregnancy complications.

Conclusions: Higher prenatal arsenic exposure was associated with longer birth length, greater head circumference, and lower ponderal index. Associations between arsenic and gestational age may be modified by infant sex.

Keywords

Arsenic; prenatal exposure; birth outcomes; pregnancy complications

1. Introduction

Naturally occurring arsenic in the earth's crust leads to widespread human exposure. Arsenic-contaminated drinking water is the major pathway of exposure (Chung et al. 2014), but arsenic exposure through occupation, diet, and air pollution can also lead to clinically significant exposure in populations with no known water exposure (Bulka et al. 2017; Meharg et al. 2009). Chronic exposure to arsenic is linked with numerous detrimental health outcomes, including cancers (skin, lung, liver, bladder, kidney, and prostate), skin lesions, cardiovascular disease, respiratory disease, and diabetes mellitus (Abdul et al. 2015; Maull et al. 2012; Moon et al. 2012; MM Rahman et al. 2009; Sanchez et al. 2016).

Pregnant women and their offspring may be particularly susceptible to the toxic effects of arsenic exposure due to changes in hormone levels of pregnant women and hemodynamics associated with pregnancy, and the immature immune system, rapid differentiation, and tissue/organ growth of developing fetuses (Cunningham et al. 2010). While it is known that arsenic exposure to a pregnant woman transfers to the developing fetus (Concha et al. 1998; Hall et al. 2007), there is growing consensus among the existing evidence to indicate that arsenic exposure affects fetal growth. Four recent systematic reviews evaluated existing epidemiologic evidence for the effects of arsenic exposure on birth weight (Bloom et al. 2014; Milton et al. 2017; Quansah et al. 2015; Rahman et al. 2017): two conclude that there is limited evidence of a negative relationship between arsenic exposure and birth weight (Bloom et al. 2014; Rahman et al. 2017); one meta-analysis reports a significant reduction in birth weight in relation to arsenic exposure based on four studies (Quansah et al. 2015); the fourth concludes that evidence of such an association is convincing, specifically for higher levels of arsenic exposure (>50 ppb) (Milton et al. 2017). While other fetal growth-related measures (i.e., birth length, head circumference, and ponderal index) have been studied (Bermudez et al. 2015; Bloom et al. 2016; Chou et al. 2014; Gilbert-Diamond et al. 2016; Henn et al. 2016; Laine et al. 2015; Liao et al. 2018), evidence for an effect of arsenic exposure on birth length, head circumference, and ponderal index is inconclusive. Similarly, arsenic exposure may exert a role in the development of pregnancy complications (e.g., gestational diabetes and preeclampsia) (Farzan et al. 2016; Marie et al. 2018; Peng et al. 2015), which, in turn, may increase later-life risks of adverse health outcomes such as type 2 diabetes and cardiometabolic disease (Baz et al. 2016; Bellamy et al. 2009; Chen et al. 2014; Murphy and Smith 2016). However, epidemiologic research evaluating these associations is limited.

Most previous epidemiologic studies on arsenic exposure and maternal and child health were performed in populations with higher levels of arsenic exposure, such as those found in Bangladesh and Mexico (Laine et al. 2015; A Rahman et al. 2009). Few studies have evaluated these relationships in regions (e.g., United States and Canada) with lower levels of water arsenic (Ettinger et al. 2009; Gilbert-Diamond et al. 2016). Although the public health implications are large, it remains unclear whether results based on populations receiving high-level arsenic exposures are relevant to populations receiving low- or moderate-level arsenic exposures.

Here, we sought to understand the impacts of arsenic exposure during pregnancy on fetal growth and risk of pregnancy complications in a population of pregnant women with levels of exposure that are typical in the United States using data from a cohort of mother-infant pairs who participated in the National Children's Study (NCS).

2. Methods

2.1. Study population

Participants included for analysis are women and children enrolled in the Initial Vanguard Study of the NCS. Information regarding recruitment of women is detailed elsewhere (Stanford et al. 2015). The Initial Vanguard Study was conducted in seven primary sampling units (i.e., Queens County, New York; Montgomery County, Pennsylvania; Waukesha County, Wisconsin; Brookings County, South Dakota, and Yellow Medicine, Pipestone, and Lincoln counties, Minnesota; Orange County, California; Salt Lake County, Utah; Duplin County, North Carolina) using a geographically based probability sample design from January 2009–September 2010. According to estimates from the United States Geological Survey, the groundwater in each of these counties is estimated to contain less than the US Environmental Protection Agency (EPA) limit of 10 μg/L of arsenic (Ayotte et al. 2017; EPA 2001).

In order to be included in the study, the following eligibility criteria needed to be met: household screening performed during or before the woman's pregnancy, current pregnancy or high probability of pregnancy, and ability to grant informed consent; 618 mother-infant pairs met these criteria and were enrolled in the study. Enrolled women completed up to two pregnancy visits that consisted of extensive interview, self-administered questionnaires, a physical examination, and biospecimen (blood and urine) and environmental sample collections.

Since the purpose of the Initial Vanguard Study was to test study procedures and feasibilities, many changes were made over the course of the 2-year study period. Specifically, changes to the data collection protocols led to only a subset of mother-infant pairs with all study variables collected. Of the 618 mother-infant pairs, 212 pairs without missing data were included to evaluate the association between birth outcome and DMA, and 114 pairs without missing data were included in relation to total arsenic. For adverse health outcomes during pregnancy, 208 and 112 women without missing data were included to investigate the association with DMA and total arsenic, respectively. The flowchart in Figure 1 depicts the acquisition of final sample sizes for each analysis.

2.2. Assessment of prenatal arsenic exposure

A spot urine sample was collected during the third trimester from a subset of participants. Urine was collected into a pre-screened metal-free container and was frozen locally until shipment on dry ice to the NCS Repository (Fisher Bioservices, Rockville, MD). Urine was aliquoted into pre-screened metal-free cryovials and stored at −80 °C until shipment on dry ice to the US Centers for Disease Control's National Center for Environmental Health. Since the initial purpose of laboratory testing of the Initial Vanguard Study was operational quality control assessment, urine samples were selected for measuring total arsenic and arsenic species based on availability across study sites (without any additional criteria). Further, experiments for total arsenic and arsenic species were administered at different time points, resulting in different sample sizes available for the analyses in the current study. Urinary total arsenic concentration was measured by inductively-coupled-plasma dynamic-reaction-cell mass spectrometry (ICP-DRC-MS), with a limit of detection (LOD) of 1.25 μg/L. Concentrations of urinary arsenic species were measured using high-performance liquid chromatography (HPLC) coupled to ICP-DRC-MS. The LODs were as follows: arsenic acid (1 μg/L), arsenobetaine (0.4 μg/L), arsenocholine (0.6 μg/L), arsenous acid (1.2 μg/L), DMA (1.7 μg/L), MMA (0.9 μg/L), and trimethylarsine oxide (1 μg/L). For analytical results below the LOD, an imputed value equivalent to the LOD divided by the square-root of two was assigned. Here, total arsenic (0% < 1.25 μg/L) and DMA (23.1% < 1.7 μg/L) were analyzed as main exposure variables since a significant percentage of samples (> 60%) had concentrations of other metabolites (i.e., arsenic acid, arsenobetaine, arsenocholine, arsenous acid, MMA, and trimethylarsine oxide) below the LOD.

2.3. Assessment of outcomes

The NCS protocol included physical examination of children at birth. Birth length (cm) and head circumference (cm) were measured twice, and the average of the two readings was used. For offspring without measures of length (n=17) and head circumference (n=15), values were abstracted from medical records using Community Health Information Architecture (CHITA) instruments. Birth weight was not measured during the physical exam and was therefore extracted from medical records. Ponderal index, an indicator of infant adiposity, is a measure of *in utero* growth retardation (Vintzileos et al. 1986; Yagel et al. 1987). Thus, we derived ponderal index by dividing birth weight in kilograms by cubed birth length in meters (kg/m^3). Gestational age was also collected from medical records, and preterm birth was defined less than 37 completed weeks of gestational.

Information regarding complications during pregnancy was abstracted from medical records at the final birth visit. Three dichotomous (yes, no) outcome variables were included in our analyses: any complication, gestational diabetes, and preeclampsia. Any complication was defined as conditions including gestational diabetes, preeclampsia, placenta previa, preterm birth, and significant vaginal bleeding (excluding previa).

2.4. Assessment of covariates

Maternal characteristics, including age, race/ethnicity, education level, family income, and number of previous live births, were obtained from the first pregnancy interview. Self-reported weight and height before pregnancy were also recorded, and pre-pregnancy body

mass index (BMI) was calculated as weight (kg)/[height (m)]^2. Infant sex was ascertained from medical records. Concentrations of creatinine were measured in spot urine samples collected during the third trimester from all women using the Roche Hitachi Modular P Chemistry Analyzer and Creatinine Plus Assay reagents by NCEH's laboratory.

2.5. Statistical analysis

All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC). Demographic variables, maternal characteristics, and infant physical measures were summarized overall (212 mother-infant pairs without missing data on DMA, birth outcomes, or covariates of interest) and by quartiles of prenatal DMA concentrations. Differences between quartiles of exposure were assessed using chi-square test for categorical variables, analysis of variance (ANOVA) test for normally distributed continuous variables (maternal age, pre-pregnancy BMI, gestational age, birth weight, birth length, head circumference, and ponderal index), and Kruskal-Wallis test for non-normally distributed continuous variables (urinary total arsenic and creatinine).

The association between arsenic exposure and pregnancy complications was assessed using multivariable logistic regression, with odds ratios and 95% confidence intervals (CIs) reported. Analyses were adjusted for urinary creatinine (μg/L), maternal age (years), race/ethnicity (Caucasian, African American, other races), maternal education (<high school, high school graduate, >high school), family income (≤$29999, $30000–$74999, ≥$75000), and continuous pre-pregnancy BMI (kg/m^2). For preterm birth, the analysis additionally controlled for infant sex and parity number (0, 1, ≥2). Given the limited sample size, only DMA was evaluated in the analyses of pregnancy complications. DMA was modeled as an un-transformed continuous variable. DMA was also modeled as quartiles of exposure only for the association in relation to the pregnancy complication summary variable.

For birth outcomes, we applied a multivariable linear regression model adjusted for urinary creatinine, maternal age, race/ethnicity, maternal education, family income, pre-pregnancy BMI, infant sex, parity number, and gestational age (months) to obtain expected changes and 95% CIs. Both total arsenic and DMA were modeled as quartile categories as well as un-transformed continuous variables.

To test for linear trends by quartile of exposure, *p*-values were obtained by treating quartiles of exposure as ordinal variables and repeating the above analyses. Previous studies suggested potential sex-specific effects of arsenic exposure on birth outcomes (Cooperstock and Campbell 1996; Gilbert-Diamond et al. 2016; Zeitlin et al. 2002); thus, multivariable regression models with cross-product terms between prenatal arsenic exposure and infant sex were conducted to assess modification by infant sex. For all analyses conducted, a *p*-value less than 0.05 was considered statistically significant.

Four sensitivity analyses were conducted. The first was performed in relation to birth outcomes (i.e., birthweight, birth length, head circumference, and ponderal index) restricted to 204 mother-infant pairs (107 pairs for total arsenic) with gestation age ≥ 37 weeks (Wilcox et al. 2011). The second sensitivity analysis was conducted using gestational age and sex-standardized z-scores of birth outcomes (i.e., birth weight, birth length, and head

circumference) calculated based on Fenton's growth chart (Fenton and Kim 2013). The third sensitivity analysis was implemented to evaluate potential residual confounding effects from gestational diabetes and preeclampsia (as well as delivery mode (vaginal, cesarean) for head circumference) on the associations between arsenic exposure and birth outcomes. For the last sensitivity analysis, we used a residual-based method (Jones et al. 2016) to remove the impact of seafood-derived organic arsenic on urinary total arsenic and DMA by accounting for arsenobetaine. We obtained model residuals by regressing log-transformed total arsenic and DMA on log-transformed arsenobetaine. Estimated non-seafood concentrations of total arsenic and DMA were then calculated by adding the means of total arsenic and DMA among participants with low arsenobetaine (< 1 μg/L) back to the residuals. The fully adjusted regression models were rerun with estimated total arsenic and DMA exposures for both birth outcomes and pregnancy complications.

3. Results

Table 1 shows the distribution of selected characteristics for 212 mother-infant pairs. Results by exposure quartile are not shown for variables with <10 participants in each quartile following the disclosure policies of the NCS. Most women included in our analyses were Caucasian (n = 169, 79.7%). Mean maternal age was 28.6 years, and mean pre-pregnancy BMI was 25.8 kg/m^2. Median prenatal urinary concentrations of total arsenic and DMA were 7.77 and 3.44 μg/L, respectively. Pregnancy complications were reported in 80 (38.5%) of the 208 women in the study, including 18 (8.7%) with gestational diabetes and 10 (4.8%) with preeclampsia. Mean ponderal index significantly differed across quartiles of maternal urinary DMA, with the lowest mean ponderal index observed among infants with the highest prenatal DMA levels. Supplemental Table 1 shows the distribution of selected maternal characteristics among 283 mother-infant pairs with neonatal medical records available, 212 pairs for DMA analysis, and 114 pairs for total arsenic analysis. The distributions between these three study samples are not appreciably different from each other. Table 2 summarizes results from the multivariable analysis. Prenatal urinary total arsenic exposure was positively associated with infant birth length and head circumference and negatively associated with ponderal index. A one-interquartile range (IQR) increase in total arsenic was associated with a 0.28-cm (95% CI: 0.14, 0.42) increase in birth length, a 0.12-cm (95% CI: 0.04, 0.21) increase in head circumference, and a 0.37-kg/m^3 (95% CI: −0.58, −0.17) decrease in ponderal index. When modeling arsenic exposure as quartiles, infants in the highest quartile of total arsenic had birth length and head circumference 2.21 cm (95% CI: 0.87, 3.55) and 0.97 cm (95% CI: 0.16, 1.77) greater than those in the lowest quartile, respectively. Infants in the top quartile of total arsenic exposure had a ponderal index that was 2.41 kg/m^3 (95% CI: −4.37, −0.44) less than those in the lowest quartile. Linear dose-response relationships between total arsenic exposure, birth length, head circumference, and ponderal index were supported by statistically significant trend tests ($p_{trend} < 0.05$).

Similar findings were observed for prenatal DMA exposure. An IQR increase in DMA was associated with a 0.40-cm (95% CI: 0.13, 0.66) increase in birth length, a 0.18-cm (95% CI: 0.02, 0.33) increase in head circumference, and a 0.63-kg/m^3 (95% CI: −1.02, −0.25) decrease in ponderal index. When treating arsenic exposure as quartiles, infants in the top quartile of DMA exposure had birth length that was 1.25 cm (95% CI: 0.07, 2.42) longer

than those in the lowest quartile, and infants in the highest quartile of DMA had a ponderal index 1.99 kg/m^3 (95% CI: − 3.68, −0.29) less than those in the lowest quartile. Significant p for trend was observed for DMA when treating quartiles of exposure as an ordinal variable, suggesting an increasing linear relationship between prenatal DMA exposure and birth length as well as a decreasing linear trend in relation to ponderal index. A non-significant suggestive linear trend was observed for head circumference.

No significant association in relation to prenatal urinary arsenic exposure was observed for gestational age and birth weight (Table 2). These null results were consistently observed for both total arsenic and DMA in relation to gestational age and birth weight. No significant association was observed between prenatal urinary DMA exposure and any complication during pregnancy, gestational diabetes, preeclampsia, or preterm birth (Supplemental Table 2).

Table 3 presents results from analyses examining potential effect modification by infant sex. Prenatal total arsenic exposure was negatively associated with ponderal index among both male and female infants, but the association was stronger in females ($p_{\text{interaction}} = 0.08$). Prenatal urinary DMA exposure was negatively associated with gestational age among female infants ($p_{\text{interaction}} = 0.02$). Among female infants, for every IQR increase in DMA concentration, gestational age decreased by 0.44 week (95% CI: −0.84, −0.05); no statistically significant association was observed among male infants.

Findings from the sensitivity analysis restricted to 204 mother-infant pairs with gestational age ≥ 37 weeks were not appreciably different from the overall analyses presented (data not shown). As shown in Supplemental Tables 3, analyses using z-scores of birth outcomes generated similar results as compared to the analyses using original values. Results from the sensitivity analysis further adjusting arsenic exposure and birth outcome models for gestational diabetes and preeclampsia (as well as delivery mode for head circumference) were also consistent (data not shown), suggesting no important confounding by these variables. A sensitivity analysis using estimated total arsenic and DMA exposures was also conducted to account for organic arsenic (i.e, arsenobetaine) from seafood intake based on the method of Jones et al. Supplemental Tables 4–6 show results for the associations of estimated arsenic exposures with birth outcomes and pregnancy complications. Findings from these analyses were not appreciably different from the original analyses (Table 2 & Table 3); however, an inverse association between estimated total arsenic exposure and ponderal index was observed to be stronger in male infants in these analyses.

4. Discussion

We assessed the impact of prenatal arsenic exposure measured from maternal urine at the third trimester on the risk of complications during pregnancy as well as birth outcomes using a sample of mother-infant pairs from the US-based NCS. Prenatal exposure to total arsenic as well as DMA was positively associated with birth length and head circumference and negatively associated with ponderal index. Our results from analyses evaluating effect modification by infant sex further found a negative association between concentration of DMA and gestational age only among female infants. Maternal urinary arsenic at the third

trimester was not significantly associated with birth weight or complications during pregnancy. Given the rigorous study design, good exposure metric (i.e., urinary arsenic biomarker), and critical exposure time window selected, this study adds valuable information to current evidence on the impact of low-level prenatal arsenic exposure on birth outcomes.

A positive relationship between arsenic exposure and birth length was previously observed in a large prospective cohort study conducted in New Hampshire of 706 mother-infant pairs with similar levels of arsenic exposure (Gilbert-Diamond et al. 2016). That study reported a 0.22-cm and 0.21-cm increase in birth length in relation to each unit increase in log-transformed prenatal DMA and total arsenic concentrations, respectively, measured from maternal urine at the second trimester. Further, the study demonstrated that a positive association between arsenic exposure and birth length was primarily driven by male infants. Six other prospective studies evaluated this relationship; no significant association was found in five of the studies conducted in Bangladesh, Romania, Mexico, and Taiwan (Bloom et al. 2016; Chou et al. 2014; Laine et al. 2015; Liao et al. 2018; A Rahman et al. 2009), while a study in a Chinese population reported a negative association between urinary arsenic exposure and birth length (Liu et al. 2018). The potential for arsenic to enhance birth length (and subsequently ponderal index) may be attributable to effects on bone development. An in vitro study suggested that arsenic trioxide, an oxide of arsenic, exerts different effects on osteoblast growth based on the given dosage (Xu et al. 2014)—while high dose of arsenic trioxide (5, 10, and 20 μM) induced apoptosis of osteoblasts, results demonstrated a significantly enhanced viability of cultured osteoblasts as well as increased collagen synthesis following exposure to a low dose (0.25, 0.5, and 1 μM) of arsenic trioxide. Therefore, the unexpected findings connecting higher (but still moderate) arsenic exposure to longer birth length may be related to this or a similar phenomenon.

Our results linking higher arsenic exposure with greater head circumference at birth are in contrast to existing evidence suggesting a negative association (Gilbert-Diamond et al. 2016; Henn et al. 2016; Liao et al. 2018; A Rahman et al. 2009). Specifically, three prospective cohort studies conducted in Bangladesh and the US observed significant associations of maternal urinary total arsenic and blood arsenic levels with smaller head circumference (Gilbert-Diamond et al. 2016; Henn et al. 2016; A Rahman et al. 2009). However, multiple other studies have reported null associations (Bermudez et al. 2015; Bloom et al. 2016; Chou et al. 2014; Laine et al. 2015). Given the inconsistencies with previous research and no apparent biological mechanism, the observed positive association between arsenic exposure and head circumference in the current analysis might be spurious. Taken together, these conflicting findings suggest that further research is needed with a larger sample size and comprehensive measurement of potential confounders.

Our observed association with ponderal index represents only the third study to examine this measure of possible intrauterine growth restriction. The previous research has been mixed, with one study also reporting that lower ponderal index is associated with maternal urinary arsenic levels (Gilbert-Diamond et al. 2016) and the other finding null results overall, but a significant positive association among female infants (Bloom et al. 2016). Future research

investigating the effect of arsenic on ponderal index and the potential interaction effect with sex is still needed.

Gestational age has been assessed as an outcome in multiple previous studies of arsenic exposure. Generally, these past studies reported a significant relationship between decreased gestational age and arsenic exposure measured in drinking water, maternal urine, and maternal blood (Henn et al. 2016; Laine et al. 2015; Xu et al. 2011). Specifically, a study conducted in China observed a negative association in male but not female infants (Xu et al. 2011). In contrast, we observed a negative association between arsenic exposure and gestational age only in female infants. Differences in the exposure concentrations, dietary or behavioral practices, or ancestry of the study samples may account for the differences observed between these studies. Although the evidence connecting arsenic exposure to decreased gestational age is compelling, further confirmation by additional studies is needed to evaluate whether effect modification of this association by infant sex is more widely seen.

While gestational age and birth weight are biologically related, we observed no significant association between prenatal arsenic exposure and birth weight in the current study. A systematic review published in 2017 indicated that there is a convincing evidence on the association between higher levels of arsenic exposure (>50 ppb) and decreased birth weight. Further, in a recent meta-analysis using data from 12 studies, prenatal arsenic exposure was significantly associated with decreased birth weight, and this observed negative association persisted after restricting to 4 studies in populations with lower levels of arsenic exposure (three U.S. and one Chile) (Zhong et al. 2019). However, in an U.S. prospective cohort study that is not included in the aforementioned meta-analysis, no significant association was observed in relation to birth weight (Gilbert-Diamond et al. 2016). Although it is possible that we had insufficient statistical power with the given sample to observe an association between low-level arsenic exposure and birth weight, further research in population with lower levels of arsenic exposure is still needed to evaluate this association.

Previous literature on the association between arsenic exposure and pregnancy complications is relatively limited and reports mixed findings, possibly due to the heterogeneity of study designs and exposure metrics used across studies. While several studies have reported significant associations between arsenic exposure and preterm birth (Ahmad et al. 2001; Almberg et al. 2017; Huang et al. 2018; Rahman et al. 2018), others have observed no association (Kim et al. 2018; Myers et al. 2010). No significant association with gestational diabetes has been observed for drinking water arsenic and prenatal urinary arsenic concentrations (Bloom et al. 2016; Gilbert-Diamond et al. 2016). Yet, studies that relied on maternal blood (Ettinger et al. 2009; Shapiro et al. 2015), maternal serum (Xia et al. 2018), maternal toenail (Farzan et al. 2016), and drinking water (Farzan et al. 2016; Marie et al. 2018) samples have shown significant associations of arsenic exposure with increased risk of gestational diabetes or impaired glucose tolerance; no association was found in relation to maternal urinary arsenic (Farzan et al. 2016). Two case-control studies evaluated the relationship between arsenic exposure and risk of preeclampsia, reporting no significant association (Elongi Moyene et al. 2016; Sandoval-Carrillo et al. 2016). Our findings, which used internal biomarkers of exposure, are consistent with these previous findings, suggesting no association between urinary arsenic and pregnancy complications of gestational diabetes

and preeclampsia. Still, the mixed evidence underscores a need for further prospective studies assessing a larger number of events.

In this study, two exposure variables (i.e., total arsenic and DMA) were used to represent levels of arsenic exposure. Total arsenic is a mixture of organic and inorganic arsenic, while DMA is one of the organic metabolites after the methylation of inorganic arsenic. Although absolute value of DMA was used for the current analyses, DMA concentration may still imply two circumstances: (1) higher arsenic metabolism efficiency; or (2) higher inorganic arsenic exposure. This may explain the different findings in relation to total arsenic and DMA in our sex-stratified analyses. In a study reporting results for the associations of both total arsenic and DMA with birth outcomes, findings were similar between total arsenic and DMA (Gilbert-Diamond et al. 2016). They also supported our findings of positive associations between DMA and birth length as well as negative associations in relation to ponderal index. Further, no significant association was found in relation to arsenic methylation efficiency indices (i.e., MMA/inorganic arsenic and DMA/MMA) with birth outcomes in the aforementioned study.

The conclusions of this study could be strengthened by future research. First, the exposure assessment, while an accurate biomarker of arsenic exposure, captures exposure during the third trimester only. The third-trimester urine sample may reflect exposure after the time that is most critical for developing pregnancy complications, and potential misclassification of prenatal arsenic exposure may exist due to the relatively short half-life of arsenic in urine. Furthermore, the laboratory method used for measuring arsenobetaine in this study had a higher LOD (0.4 μg/L) as compared to some previous studies (Gilbert-Diamond et al. 2016; Laine et al. 2015), and 67% of samples (n=143) had arsenobetaine concentrations below the LOD. Therefore, the estimated non-seafood arsenic exposures used in the sensitivity analyses may not be accurate. We further compared the percentage below the LOD and level of arsenobetaine between women in the 2003–2010 National Health and Nutrition Examination Survey (NHANES) cycles and the NCS (Supplemental Table 7). Within the NHANES sample, pregnant women had lower mean arsenobetaine concentrations compared to non-pregnant women of child-bearing age (20–44 years of age). Among pregnant women, the concentration of arsenobetaine was comparable between NHANES and NCS. We consider arsenic exposures measured in NCS are unlikely to be substantially influenced by seafood intake since women tend to lower their seafood consumption during pregnancy based on the seafood consumption advice issued by the Food and Drug Administration (Oken et al. 2003). Second, the statistical power to conduct sex-stratified analyses for the total arsenic exposure metric (male infants (n = 57); female infants (n = 57)) may be insufficient to identify effect modification by infant sex, potentially explaining the inconsistent findings for ponderal index in the main and sensitivity analyses. Also, the statistical power of this study was limited to evaluate individual pregnancy complications, given the small number of women diagnosed with gestational diabetes (n = 18) and preeclampsia (n = 10). Given the different biological mechanisms that underpin these health outcomes, studies that focus on individual birth complications could provide additional insight. Third, our results may be affected by multiple statistical testing, which may explain the positive association observed between arsenic exposure and head circumference. Forth, humans are often exposed to mixtures of metals rather than arsenic alone. Evaluating only

arsenic exposure without accounting for potential interactions or confounding by other metals may under- or overestimate the effect of arsenic exposure. However, for the purposes of this analysis, only arsenic was available for analysis. This study was also limited by potential residual confounding based on maternal characteristics, such as genetic factors, dietary behaviors, supplement intake during pregnancy (e.g., folate intake), or other socioeconomic status-related variables. Finally, the racial makeup of this sample was not representative of the general US population since ~80% of the women in the study sample were white. Thus, findings from the present study may not be generalizable to all pregnant women in the US.

In summary, findings from the current analyses are congruent with other prospective cohort studies, and this study adds to current evidence on the impact of low-level prenatal arsenic exposure on birth outcomes at exposure levels that are typical in the US. Our study suggests two major findings. First, prenatal exposure to arsenic, even at low levels, may impact fetal growth. Specifically, elevated prenatal arsenic exposure may increase birth length but decrease ponderal index, suggesting that there is not an exposure threshold for the effect of arsenic on these outcomes given the low-level exposures in the study sample. Second, we observed that associations of arsenic exposure with gestational age may be modified by infant sex. Future longitudinal cohort studies are warranted to investigate the impacts of prenatal or early-life arsenic exposure on children's growth and other health effects later in life. Further, additional analyses using data from the NCS are needed to evaluate the potential effects of metal mixtures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Effect on pregnancy outcomes remains unclear at lower levels of arsenic exposure, commonly observed in the United States
- Increased prenatal arsenic exposure was associated with longer birth length, greater head circumference, and lower ponderal index
- Associations between arsenic and gestational age may be modified by infant sex

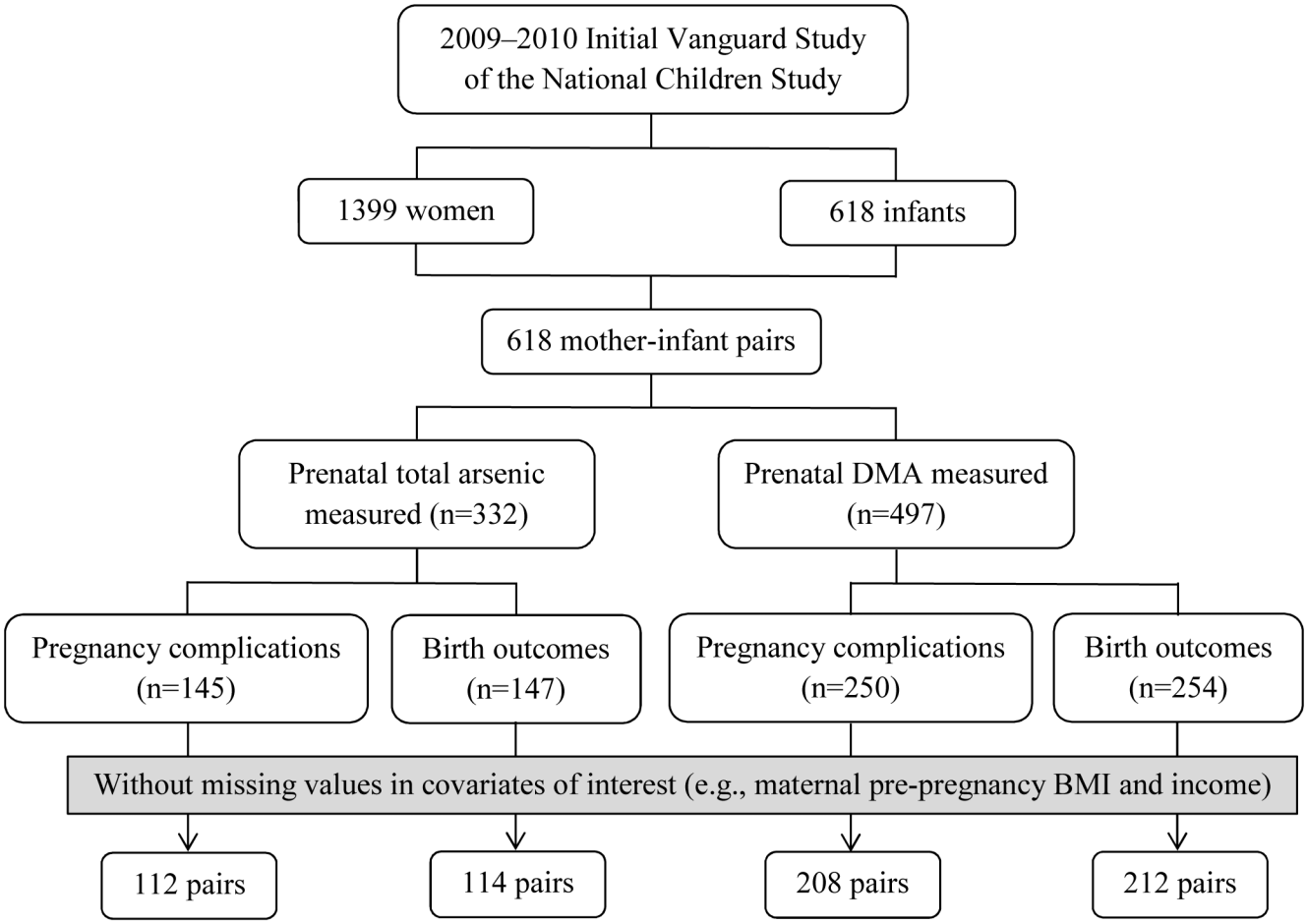

Figure 1.
Inclusion of National Children's Study participants to achieve final sample sizes.

Table 1.

Selected characteristics of 212 mothers and their infants in the National Children's Study.

Characteristic	All (N=212)	Urinary dimethylarsinic acid (μg/L) Q1 (≤1.93) (n=51)	Q2 (1.94–3.50) (n=55)	Q3 (3.51–5.72) (n=62)	Q4 (>5.72) (n=44)	*p*-value
Race/ethnicity						0.26
Caucasian	169 (79.7)	43 (25.4)	46 (27.2)	48 (28.4)	32 (18.9)	
African American	11 (5.2)	--	--	--	--	
Other	32 (15.1)	--	--	--	--	
Maternal age (year) (mean ± SD)	28.58 (5.78)	28.25 (6.69)	28.45 (4.83)	28.35 (5.85)	29.43 (5.72)	0.75
Education level [n(%)]						0.80
<High school	21 (9.9)	--	--	--	--	
High school graduate	99 (46.7)	27 (27.3)	23 (23.2)	29 (29.3)	20 (20.2)	
>High school	92 (43.4)	19 (20.7)	28 (30.4)	25 (27.2)	20 (21.7)	
Family income [n(%)]						0.13
≤$29,999	55 (25.9)	13 (23.6)	14 (25.5)	16 (29.1)	12 (21.8)	
$30,000–$74,999	86 (40.6)	23 (26.7)	14 (16.3)	30 (34.9)	19 (22.1)	
≥$75,000	71 (33.5)	--	--	--	--	
Number of previous live births [n(%)]						0.25
0	69 (32.6)	21 (30.4)	14 (20.3)	16 (23.2)	18 (26.1)	
1	79 (37.3)	17 (21.5)	25 (31.7)	26 (32.9)	11 (13.9)	
≥2	64 (30.2)	13(20.3)	16 (25.0)	20 (31.3)	15 (23.4)	
Pre-pregnancy BMI (kg/m^2) (mean ± SD)	25.80(6.49)	26.58 (6.16)	25.84 (6.81)	25.69 (6.24)	24.99 (6.93)	0.70
Urinary arsenic (fig/L) [median (IQR)]						
Total arsenic (n=114)	7.77 (7.98)	2.63 (1.13)	4.87 (4.35)	9.12(3.16)	16.10(17.96)	<0.0001
Dimethylarsinic acid (DMA)	3.44(3.13)	1.20 (0.00)	2.72 (0.85)	4.38 (0.82)	7.49 (2.63)	--
Urinary creatinine (fig/L) [median (IQR)]	94.77 (72.15)	47.82 (36.56)	92.22 (60.82)	121.83 (76.67)	129.93 (70.27)	<0.0001
Pregnancy complication [n(%)] (n=208)						
Any complication	80 (38.46)	23 (46.00)	20 (37.04)	22 (35.48)	15 (35.71)	0.66
Gestational diabetes	18(8.65)	--	--	--	--	0.94
Preeclampsia	10(4.81)	-	-	-	-	0.77
Preterm birth	--	--	--	--	--	0.24

Characteristic	Urinary dimethylarsinic acid (μg/L)					*p*-value
	All (N=212)	Q1 (≤1.93) (n=51)	Q2 (1.94–3.50) (n=55)	Q3 (3.51–5.72) (n=62)	Q4 (>5.72) (n=44)	
Infant sex [n(%)]						0.07
Male	114 (53.8)	30 (26.3)	35 (30.7)	25 (21.9)	24 (21.1)	
Female	98 (46.2)	21 (21.4)	20 (20.4)	37 (37.8)	20 (20.4)	
Infant birth outcomes						
Gestational age (weeks) (mean ± SD)	38.75 (1.41)	38.55 (1.78)	38.89 (1.36)	38.90 (1.13)	38.59 (1.35)	0.41
Birth weight (kg) (mean ± SD)	3.38 (0.49)	3.33 (0.46)	3.47 (0.50)	3.43 (0.51)	3.28 (0.49)	0.22
Birth length (cm) (mean ± SD)	50.06 (2.91)	49.99 (3.23)	50.17 (2.74)	49.80 (2.66)	50.38 (3.14)	0.78
Head circumference (cm) (mean ± SD)	34.78 (1.65)	34.51 (1.68)	35.05 (1.71)	34.75 (1.61)	34.80 (1.59)	0.43
Ponderal index (kg/m^3) (mean ± SD)	27.05 (3.74)	26.76 (3.59)	27.50 (3.56)	27.76 (3.39)	25.85 (4.36)	0.05

*Chi-square test for categorical variables, ANOVA test for normally distributed continuous variables, and Kruskal-Wallis test for non-normal distributed continuous variables

Table 2.

Adjusted expected change (95% confidence interval) for birth outcomes in relation to maternal 3rd-trimester urinary arsenic.

Arsenic exposure (fig/L)	n	Gestational age (weeks)[a]	Birthweight (g)[b]	Birth length (cm)[b]	Head circumference (cm)[b]	Ponderal index (kg/m^3)[b]
Total arsenic (n=114)						
Per IQR (8.27) increase		0.06 (−0.03, 0.16)	1.95 (−21.75, 25.65)	0.28 (0.14, 0.42)	0.12 (0.04, 0.21)	−0.37 (−0.58, −0.17)
Q1 (≤4.00)	32	Ref	Ref	Ref	Ref	Ref
Q2 (4.01–7.55)	24	0.03 (−0.86, 0.92)	94.58 (−125.17, 314.33)	1.30 (−0.03, 2.63)	0.37 (−0.43, 1.17)	−1.19 (−3.14, 0.76)
Q3 (7.56–12.26)	33	0.08 (−0.76, 0.92)	85.79 (−121.21, 292.79)	1.66 (0.40, 2.91)	0.67 (−0.08, 1.43)	−1.94 (−3.78, −0.10)
Q4 (>12.26)	25	0.24 (−0.66, 1.14)	87.71 (−133.66, 309.08)	2.21 (0.87, 3.55)	0.97 (0.16, 1.77)	−2.41 (−4.37, −0.44)
p for trend		0.61	0.45	0.001	0.02	0.01
DMA (n=212)						
Per IQR (3.79) increase		−0.01 (−0.16, 0.14)	−10.67 (−64.31, 24.97)	0.40 (0.13, 0.66)	0.18 (0.02, 0.33)	−0.63 (−1.02, −0.25)
Q1 (≤1.93)	51	Ref	Ref	Ref	Ref	Ref
Q2 (1.94–3.50)	55	0.28 (−0.28, 0.83)	77.28 (−88.73, 243.29)	0.26 (−0.74, 1.26)	0.51 (−0.08, 1.10)	0.10 (−1.34, 1.55)
Q3 (3.51–5.72)	62	0.21 (−0.40, 0.81)	73.72 (−107.36, 254.80)	0.58 (−0.52, 1.67)	0.56 (−0.08, 1.20)	0.48 (−2.06, 1.10)
Q4 (>5.72)	44	−0.08 (−0.74, 0.57)	−13.51 (−208.29, 181.27)	1.25 (0.07, 2.42)	0.65 (−0.04, 1.34)	−1.99 (−3.68, −0.29)
p for trend		0.69	0.81	0.03	0.09	0.01

[a]Models adjusted for urinary creatinine, maternal age, race/ethnicity, maternal education, income, pre-pregnancy BMI, infant sex, and number of live births.

[b]Model additionally adjusted for gestational age.

Table 3.

Adjusted expected change (95% confidence interval) for birth outcomes in relation to maternal 3rd-trimester urinary arsenic, stratified by infant sex.

Per IQR (ng/L) increase	Gestational age (weeks)[a]	Birth weight (g)[b]	Birth length (cm)[b]	Head circumference (cm)[b]	Ponderal index (kg/m^3)[b]
Total arsenic (n=114)					
Male infants (n=57)	0.07 (−0.03, 0.16)	3.36 (−20.69, 27.41)	0.27 (0.13, 0.41)	0.11 (0.03, 0.20)	−0.34 (−0.55, −0.14)
Female infants (n=57)	−0.05 (−0.46, 0.37)	−30.61 (−132.90, 71.67)	0.59 (−0.02, 1.19)	0.29 (−0.07, 0.66)	−1.14 (−2.01, −0.26)
p for interaction	*0.59*	*0.52*	*0.31*	*0.35*	*0.08*
DMA (n=212)					
Male infants (n=114)	0.05 (−0.10, 0.21)	−20.27 (−67.40, 26.88)	0.39 (0.11, 0.67)	0.19 (0.03, 0.36)	−0.60 (−1.01, −0.19)
Female infants (n=98)	−0.44 (−0.84, −0.05)	−15.28 (−136.54, 105.98)	0.48 (−0.25, 1.20)	0.07 (−0.36, 0.49)	−0.89 (−1.94, 0.16)
p for interaction	*0.02*	*0.94*	*0.82*	*0.59*	*0.61*

[a]Models adjusted for urinary creatinine, maternal age, race/ethnicity, maternal education, income, pre-pregnancy BMI, infant sex, and number of live births.

[b]Model additionally adjusted for gestational age.