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Placental arsenic concentrations in relation to both maternal and infant biomarkers of exposure in a US cohort

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Abstract

Arsenic crosses the placenta and may have adverse consequences *in utero* and later in life. At present, little is known about arsenic concentrations in placenta and their relation to maternal and infant exposures particularly at common levels of exposure.

We measured placenta arsenic in a US cohort potentially exposed via drinking water from private wells, and evaluated the relationships between placenta and maternal and infant biomarker arsenic concentrations.

We measured total arsenic concentrations in placental samples from women enrolled in the New Hampshire Birth Cohort Study (N=766). We compared these data to maternal urinary arsenic (total arsenic and individual species) collected at approximately 24–28 week gestation, along with maternal post-partum toenails and infant toenails using non-parametric multivariate analysis of $\log_{10}$-transformed data. We also examined the association between placental arsenic and household drinking water arsenic.

Placenta arsenic concentrations were related to arsenic concentrations in maternal urine (β 0.55, *P* value <0.0001), maternal (β 0.30, *P* value 0.0196) and infant toenails (β 0.40, *P* value 0.0293) and household drinking water (β 0.09, *P* value <0.0001). Thus, our data suggest that placenta arsenic concentrations reflect both maternal and infant exposures.

Keywords

Arsenic; placenta; biomarker; low-level

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INTRODUCTION

Arsenic readily crosses the placenta, and may adversely affect fetal development.[1] Early life exposure to arsenic has also been linked to adverse health effects later in life. These include an increased risk of lower respiratory tract infection in children[2, 3] and higher risk of cancer in both animal models and from emerging epidemiological studies of highly exposed populations.[2, 4–7] The biological and health effects of low dose arsenic exposure are poorly understood and in some studies contrast with effects seen at higher doses, suggesting a complex dose-response relationship.[8] Moreover, populations may experience differences in their underlying risk of disease and lifestyle factors such as dietary habits, which may play a role in susceptibility to arsenic-induced health effects, by influencing arsenic metabolism.[9–11]

The placenta has critical functions in nutrient and waste transport between mother and fetus and in hormonally regulating the progression of pregnancy, and may be vulnerable to the impacts of arsenic.[12] Despite the non-invasive nature of placental tissue collection, and early observations that placental metal levels correlated with those measured in maternal and fetal blood,[13, 14] the potential of the placenta as a pregnancy biomarker[15] has not been fully realized. Recently placenta has been used to identify early effects of exposure to numerous environmental contaminant metals and metalloids, including lead, mercury and cadmium[5], but studies on arsenic are lacking. Even in highly exposed populations, arsenic concentrations are in the ng/g range,[16] which present technical challenges for accurate measurement. As a result there are very few epidemiological studies of arsenic in placenta. Therefore, we used sensitive ICP-MS methods to determine whether placenta arsenic concentrations were related to drinking water arsenic and other biomarkers of arsenic exposure in a US birth cohort with a range of concentrations from private well water.

MATERIAL AND METHODS

The study protocols for the New Hampshire Birth Cohort Study (NHBCS) were approved by the Committee for the Protection of Human Subjects at Dartmouth College. All study participants provided written informed consent.

The New Hampshire Birth Cohort Study

To be eligible for the New Hampshire Birth Cohort Study, women were: a) currently pregnant, b) 18 to 45 years old, c) receiving routine prenatal care at one of the study clinics, d) living at residence served by a private water system (e.g., serving <15 households or 25 individuals), e) residing in the same place since their last menstrual period, using the same water supply, and f) not planning to move prior to delivery.

Data and Sample Collection

At the enrolment visit (approximately 24–28 weeks gestation), study participants were asked to complete a prenatal questionnaire about their pregnancy. Participants were also provided with a kit for collecting a sample of their home tap water using a commercially washed, high-density polyethylene bottle that met the Environmental Protection Agency's water collection standards. Water samples were stored at −20°C or lower until analysis. Tap water

samples were analyzed for total arsenic concentration by inductively coupled plasma mass spectrometry (ICP-MS) using an Agilent 7700x (Santa Clara, CA). The detection limit for arsenic in water ranged from 0.009 – 0.074 μg/L and 96% of water samples exceeded the detection limit.

Maternal Urine

At enrollment participants were asked to provide a urine sample. Samples were analyzed at the University of Arizona using high performance liquid chromatography (HPLC) interfaced with ICP-MS to detect arsenate, arsenite, monomethylarsonic acid (MMA) dimethylarsinic acid (DMA) and arsenobetaine. Detection limits for all species in urine ranged from 0.10–0.15 μg/L. The total arsenic concentration used in statistical analysis is the sum of arsenate, arsenite, MMA and DMA, and excludes arsenobetaine, an unmetabolized form of arsenic that is considered non-toxic. Urinary creatinine was determined using Cayman's Creatinine Assay Kit (Cayman Chemical Company, Ann Arbor, MI).

Placenta

Placental biopsies were uniformly collected from the fetal side, at the base of the cord insertion avoiding vasculature, and measure approximately 1 cm deep and approximately 1–2 cm in diameter. The maternal decidua was removed to avoid inclusion of calcium (Ca) deposits and connective tissue. Biopsies were placed in metal-free tubes and stored at −80°C until analysis.

Prior to analysis samples were transferred to a −20°C freezer, then to 4°C for a maximum of 2 days, and lastly to room temperature. 1 ml of HNO_3/HCl at 9:1 ratio (Optima™) was added to samples with of up to 500 mg mass, and 2 ml of was added to samples greater than 500 mg. Samples were digested via microwave (CEM, Microwave Assisted Reaction System), ramping the temperature to 95°C in 15 minutes, and holding at this temperature for 45 minutes. 0.25–0.35 ml H_2O_2 was added to each tube and the microwave digestion sequence was repeated. Quality control procedures for this study included the use of a laboratory-made reference placental digest and internal standards. For the placental reference digest, de-identified placental tissue was subsampled to aliquots at the midpoint of the sample weight range, subject to the open-vessel digestion, and then pooled. The pooled sample was mixed, analyzed and an aliquot was included with each batch of placental samples analyzed. Arsenic was analyzed by ICP-MS using He as a collision gas on the Agilent 7700x. NIST 1566b Oyster Tissue was digested and analyzed as a reference material; recovery was 93% ± 7% (n=33). Analysis of batches of placental tissues routinely used internal standards, initial calibration verification, initial calibration blanks continuing, calibration verification and analytical duplicates and spikes. The detection limit for arsenic in placenta was 0.0148 ng/g.

Maternal and Infant Nails

At two weeks post partum, participants received an information packet requesting maternal and infant toenail clippings within eight weeks of birth, a timing which was consistent with other studies.[17,18] Maternal toenails underwent an additional washing procedure that included manual removal of visible dirt and five washes in an ultrasonic bath using Triton

X-100 (LabChem Inc., PA) and acetone followed by deionized water, and allowed to dry. All toenail samples were subject to low-pressure microwave digestion using the method outlined above for placenta digestions and were analyzed via ICP-MS. The detection limit differs on a sample-by-sample basis because of the difference in sample weights used for digestion and analysis. The detection limit of arsenic in maternal toenails ranged from 0.001 – 0.41 μg/g and for infant toenails ranged from 0.005 – 2.5 μg/g. The detection limit differs on a sample-by-sample basis because of the difference in sample weights used for digestion and analysis. The high maximum value was due to the very low mass of some of the infant toenails.

Statistical Analysis

We used Spearman's correlation coefficients to evaluate relationships between placenta arsenic and maternal and infant biomarkers, and between placenta arsenic and household water arsenic concentrations. We further used linear regression, and to improve model fit and normalize residuals all arsenic biomarker variables (arsenic concentration in maternal urine, maternal toenails, infant toenails and placenta arsenic concentrations) were $\log_{10}$-transformed. All parameters estimates were exponentiated (10^{β} for covariates and 2^{β} for dependent variables) representing the percent change in the covariates, and a doubling in the dependent variables respectively. We examined a variety of potential confounders such as maternal age upon enrollment, pre-pregnancy maternal body mass index (BMI), maternal smoking status, infant sex, birth weight and season of toenail collection. We assessed covariates individually in univariate associations with placental arsenic concentration as well on other exposure measures of interest. We used a one-way analysis of variance test to detect whether the season of tap water collection had any influence on the arsenic concentration ($\log_{10}$-transformed). All statistical analyses were conducted in JMP version 11 (The SAS Institute, Cary, NC). Participants for whom data were missing, for example in the analysis of infant toenail arsenic (N=153), were excluded from our regression models and Spearman's correlations.

RESULTS

Descriptive characteristics of the cohort

At the time of this study the total number of NHBCS participants was 1033. The number of participants providing infant toenail clippings was 153. The characteristics of this group of participants did not differ from those presented in Table 1. The study population was predominantly white, with an average age of 31.3 and a mean body mass index (BMI) of 25.3 kg/m^2 (10^{th} – 90^{th} percentile range of 20.0–32.1), primarily full term pregnancies (>37 weeks) with an equal male/female distribution and an average birthweight of 3455g (±SD 519) (Table 1). Median arsenic concentrations were 78 (SD = 81) ng/g (N=579) for maternal toenail arsenic, 68 (SD = 253) ng/g for infant toenail arsenic concentrations (N=153), 3.62 (SD = 14.7) μg/L for maternal urinary total arsenic (the sum of inorganic and organic species, excluding arsenobetaine) (N=623), and 0.38 (SD = 11.9) μg/L for household drinking water arsenic concentrations (N=716). We used a oneway analysis of variance test to detect any influence of the season of tap water collection on the arsenic concentration. Data for arsenic concentration of household tap water were not normally distributed and

were log_{10}-transformed. This analysis showed that season of collection does not significantly influence household tap water arsenic concentration (F ratio 0.7526, *P* value 0.5211). Season of collection was unrelated to household drinking water arsenic concentration (ANOVA F ratio 0.7526, *P* value 0.5211). Arsenic in maternal urine was predominantly present in the organic form DMA (dimethylarsinic acid) (mean 80.8% SD=11.9%), with an average of 9.1% MMA (monomethylarsonic acid) (SD = 6.4%). Inorganic arsenic constituted the remaining 10.1% of urinary arsenic, with on average 5.9% arsenite (SD=4.7%) and 4.1% arsenate (SD=7.5%). In the current subgroup of the NHBCS, 9% of participants' household drinking water exceeded the EPA's MCL for arsenic of 10 μg/L.

Placenta arsenic concentrations did not differ significantly across the selected maternal and infant characteristics, which included maternal age, pre-pregnancy BMI, smoking status, parity, infant sex, or low birth weight (<2500g). Placenta arsenic concentrations ranged from below detection limits (0.01 ng/g) to 18.35 ng/g (Table 1), with a median of 0.76 ng/g and an interquartile range of 0.83 ng/g.

Correlations between arsenic in placenta, maternal and infant biomarkers and tap water

Positive correlations were observed with placental arsenic and maternal postpartum toenail, maternal gestational urine and infant urine (Figure 1). In our regression models, a doubling of arsenic concentration in maternal urine, maternal toenail and infant toenails, was associated with 31.0%, 13.2% and 18.9% increases in placental arsenic concentrations of respectively (Table 2). The regression model between placenta arsenic and maternal urinary arsenic concentrations was adjusted for urinary creatinine concentration, but urinary arsenic levels are expressed as μg/L throughout to remain comparable with prior work [19, 20]. Placental arsenic concentrations also were positively associated with measured household water arsenic concentrations (Table 2). For this model, none of the covariates appreciably altered the parameter estimate, and therefore were not adjusted for in the analysis. This model predicted that for a 1 μg/L increase in household water arsenic concentration increased placental arsenic by 2.1%.

Discussion

Within the NHBCS, total urinary arsenic and toenail arsenic concentrations have been shown previously to correlate with the arsenic concentration of household drinking water [21, 22], and with the consumption of certain dietary items known to contain elevated concentrations of arsenic [17, 19, 20]. The arsenic biomarkers reported in this study, in addition to placenta, mirror previous findings. When participants are grouped in to those with household drinking water either below or above the MCA for arsenic (10 μg/L), there is a significant difference between the arsenic concentrations measured in maternal urine, maternal toenails and placenta (Supplemental Table 1). These differences are less pronounced for infant toenail arsenic concentration, but this may be a result of the smaller number of infant toenails that were available for our analysis.

We detected correlations between the concentration of arsenic in placental tissue and that of both maternal and infant biomarkers. Further, the arsenic burden of the placenta was related to the concentration of arsenic in household drinking water.

To date, only a small number of studies have measured concentrations of arsenic in placenta (summarized in Table 3).[16, 23–29] Placental arsenic concentrations reported worldwide between 1976–2000[30] were on average 6 ng/g (range: 3–12 ng/g) (wet weight). More recently Jin et al[24] measured placental arsenic concentrations as part of a study of neural tube defects in a rural area of the Shanxi Province in northern China. Among controls, placenta arsenic concentrations were 11.8 (± SD 7.9) ng/g on average (N=80). In a smaller study of arsenic concentrations in placental tissue from participants living close to a copper smelter in Bulgaria,[28] mean arsenic concentrations of 23 (± SD 21) ng/g were detected in placentas of participants living near the smelter (n=30), whereas an average of 7 (± SD 4) ng/g arsenic was measured in placental samples from those outside of the smelter area (N=15). Previous studies have been hindered by instrumental detection limits[23, 29], whereas we had the advantage of using ICP-MS for ultra-trace arsenic detection. In light of our low detection limits and our findings of a range of placenta arsenic concentrations that extend below levels previously reported upwards to levels reported in industrially exposed communities, our study presents new information.

Of the prior investigations of placental arsenic, none to our knowledge have directly compared placenta arsenic levels to those measured in other biomarkers. Tabacova et al[28] estimated that 34% of the variation in placental arsenic could be explained by the participants' place of residence relative to a copper smelter area in Bulgaria. Those living closest to the smelter had a fourfold higher placental arsenic concentration than those living in a non-smelter area. Concha et al[16] reported placental arsenic levels from a group exposed to drinking water containing ≈200 μg/L arsenic (34 ng/g dry weight) compared to the non-exposed group (7 ng/g dry weight) previously reported in Tabacova et al.[28] However, they were unable to compute correlations between placental arsenic and other biomarkers. In addition to correlations with infant and maternal biomarkers, we found drinking water to be a source of arsenic exposure in our study population that is reflected placental arsenic concentrations.

The limitations of our study included the relatively small number of infant toenail samples, which reduced the precision of our analysis. While we only had toenail arsenic concentration for 153 infants, the association with placenta data was statistically significant. Additionally, comparison of the selected characteristics of our study cohort (Table 1) with those for whom infant toenail arsenic data was available showed no significant differences. The collection of infant toenails 8 weeks after birth may also raise concerns that post-natal arsenic exposure is reflected in addition to *in utero* exposure. However, given the slow rate of infant nail growth (estimated to be between 1–3 mm per month[31]) it is unlikely that post-natal nail growth would have reached the distal nail edge at the time of sampling.[31] Nail growth arises from the proximal end of the nail, under the epidermis; whereas it is the free margin at the distal end of the nail that is sampled.

The collection of a single water sample for arsenic determination from study participants may also be viewed as a limitation in the light of recent studies on temporal variability in well water arsenic concentrations[32], but our early study of reproducibility of sequential water samples suggests this is not an issue[33].

In conclusion, we found positive associations between placental arsenic concentration and both maternal and infant biomarker concentrations as well as household drinking water arsenic concentration. These data suggest inter-marker reliability between our placental arsenic measurements and arsenic measurements from urine and toenails. Although the magnitude of the correlations were relatively low (<0.2), placenta still may have value as a biomarker of maternal and infant exposures, and be particularly important when considering molecular effects on the placenta as it provides an opportunity to link a biomarker of exposure and biomarker of effect (e.g., changes in gene expression or DNA methylation alterations) in the same functional tissue sample.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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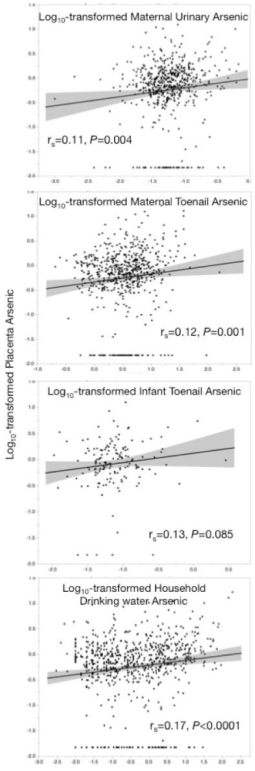

Figure 1.

Pairwise correlations between $\log_{10}$-transformed placenta arsenic concentration and $\log_{10}$-transformed maternal and infant biomarkers, and arsenic concentration of household drink water. On each panel, the line of fit is shown with 95% confidence intervals, and results of Spearman's correlation (r_s) and *P* value are shown.

Table 1

Selected characteristics of the New Hampshire Birth Cohort Study participants according to arsenic concentrations in placenta.

Characteristics	N (%)	Placenta As (ng/g) Mean (± SD)
Maternal:		
Age at enrollment (years):		
< 30 years	308 (40)	1.08 (1.52)
≥30 years	456 (60)	1.15 (1.64)
BMI (kg/m^2)		
Normal (BMI <25)	397 (58)	1.16 (1.63)
Overweight (≥25 to < 30)	170 (25)	1.06 (1.25)
Obese (≥30)	114 (17)	0.92 (0.93)
Smoking status		
Smoker	44 (6)	0.96 (0.85)
Non-smoker	649 (94)	1.10 (1.42)
Parity		
First live birth	307 (41)	1.16 (1.42)
1 or more live birth	447 (59)	1.12 (1.72)
Infant:		
Sex		
Female	378 (50)	1.13 (1.55)
Male	385 (50)	1.15 (1.64)
Birth weight (g)		
Low (<2,500)	28 (4)	1.04 (1.22)
Normal (≥2,500)	725 (96)	1.14 (1.62)

Table 2

Change in placenta arsenic concentration in relation to maternal and infant arsenic variables.

Arsenic Variable	% Increase in placental Arsenic (95% CI)	*N*	*P*
Biomarkers			
Maternal urinary[a, b] (μg/L)	31.0 (15.4, 48.7)	431	<0.0001
Maternal toenail[§] (μg/g)	13.2 (2.0, 25.7)	579	0.0196
Infant toenail[c] (μg/g)	18.9 (1.8, 38.8)	151	0.0293
Exposure[d]			
Household drinking water[§] (μg/L)	2.1 (1.3, 3.9)	716	<0.0001

[a] Excluding arsenobetaine

[b] Adjusted for creatinine concentration (mg/dL)

[c] Adjusted for parity

[d] Based on a doubling of exposure

[§] No factors appreciably altered the estimates (see text).

Table 3

Summary of studies reporting arsenic measurements in human placenta.

First author	Year	Country	N	Other Biomarkers	Placenta As (ng/g)	Exposure/(water μg/L)
Tabacova	1994	Bulgaria	49	*M*, *C* blood	7, 23[D]	smelter
Concha	1998	Argentina	11	*M*, *C* blood, *M* urine, breastmilk	34[W]	200
Llanos	2009	Chile	40	none	170, 280[D]	-
Kippler	2010	Bangladesh	44	none	152[D]	1–1,470
Zadorozhnaja	2010	Ukraine	200	none	378[*D]	
Amaya	2013	Spain	137	none	not determined	
Leino	2013	Finland	130	none	5.68[W]	
Jin	2013	China	130	none	6.4–17[W]	

W wet weight measurement

D dry weight measurement

* maximum

M maternal

C infant cordblood

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