Published in final edited form as:

Int J Hyg Environ Health. 2014 September ; 217(7): 709–719. doi:10.1016/j.ijheh.2014.03.004.

Maternal arsenic exposure and birth outcomes: A comprehensive review of the epidemiologic literature focused on drinking water

Michael S. Bloom^{1,2,*}, Simona Surdu¹, Iulia A. Neamtiu³, and Eugen S. Gurzau^{3,4}

¹ Department of Environmental Health Sciences, University at Albany, State University of New York, Rensselaer, NY USA

² Department of Epidemiology and Biostatistics. University at Albany, State University of New York, Rensselaer, NY USA

³ Environmental Health Center, Cluj-Napoca, Romania

⁴ University of Medicine and Pharmacy "Iuliu Hatieganu," Cluj-Napoca, Romania

Abstract

Inorganic arsenic (iAs) is a human toxicant to which populations may be exposed through consumption of geogenically contaminated groundwater. A growing body of experimental literature corroborates the reproductive toxicity of iAs; however, the results of human studies are inconsistent. Therefore, we conducted a comprehensive review of epidemiologic studies focused on drinking water iAs exposure and birth outcomes to assess the evidence for causality and to make recommendations for future study. We reviewed 18 English language papers assessing birth weight, gestational age, and birth size. Thirteen of the studies were conducted among populations with frequent exposure to high-level groundwater iAs contamination ($>10 \mu\text{g/L}$) and five studies were conducted in areas without recognized contamination. Most studies comprised small samples and used cross-sectional designs, often with ecologic exposure assessment strategies, although several large prospective investigations and studies with individual-level measurements were also reported. We conclude that: 1) the epidemiologic evidence for an increased risk of low birth weight ($<2,500$ grams) is insufficient, although there exists limited evidence for birth weight decreases; 2) the evidence for increased preterm delivery is insufficient; and, 3) there exists minimal evidence for decreased birth size. In further investigation of birth weight and size, we recommend incorporation of individual susceptibility measures using appropriate biomarkers, with collection timed to windows of vulnerability and speciated arsenic analysis, as well as consideration of populations exposed primarily to drinking water iAs contamination $<10 \mu\text{g/L}$.

© 2014 Published by Elsevier GmbH.

* Author to whom correspondence should be addressed: Michael S. Bloom, PhD, Department of Environmental Health Sciences, University at Albany, School of Public Health Rm. #157, Rensselaer, NY 12144; mbloom@albany.edu; P: (518) 473-1821; F: (518) 474-9899.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Given the large potential public health impact, additional, high quality epidemiologic studies are necessary to more definitively assess the risk.

Keywords

Arsenic (As); birth weight; birth size; epidemiology; gestation; drinking water

1. Introduction

The extensive distribution of inorganic arsenic (iAs) in the earth's crust leads to local and regional contamination of ground drinking water supplies and widespread human exposure (Amini et al., 2008; Smedley and Kinniburgh, 2002). Inorganic arsenic is well-absorbed by the mammalian gastrointestinal tract and numerous adverse health effects have been described in association with long-term exposure to concentrations $>10 \mu\text{g/L}$ (Naujokas et al., 2013). In so-called 'arsenic endemic' regions, drinking water is often contaminated by $>10 \mu\text{g/L}$ iAs and frequently higher than $50 \mu\text{g/L}$ iAs, including areas of Bangladesh, West Bengal India, Taiwan, Northern Chile, and Central and Eastern Europe. (Smedley and Kinniburgh, 2002). However, exposure to drinking water sources contaminated primarily by $<10 \mu\text{g/L}$ iAs is more widespread (Amini et al., 2008), and may also pose health risks. The World Health Organization and other regulatory bodies have set a maximum contaminant limit (MCL) of $10 \mu\text{g/L}$ iAs in drinking water for the protection of human health predicated on reducing cancer risk (WHO, 2004), yet this limit does not account for non-cancer endpoints, such as reproductive effects.

Concern is growing with respect to an increased risk for adverse birth outcomes associated with chronic drinking water iAs exposure, including lower birth weight, earlier delivery and smaller neonatal size in exposed mothers and their fetuses (Vahter, 2009). Previously, we reviewed the epidemiologic evidence for causal associations between drinking water iAs and pregnancy loss, and suggested that long-term exposure to iAs $>10 \mu\text{g/L}$ increases the risk, but with a need for additional investigation into effect at $<10 \mu\text{g/L}$ iAs (Bloom et al., 2010). Inorganic arsenic crosses the human placenta, and accumulates in the developing organs and systems of a fetus, posing an increased risk potential (Concha et al., 1998). A recent study reports detectable levels in newborn meconium (Vall et al., 2012). Experimental and observational evidence suggests that iAs accumulates in and disrupts placental function (Ahmed et al., 2011) and alters cord blood methylation (Pilsner et al., 2012).

Abnormal placentation is a strong risk factor for preterm delivery and restricted fetal growth (Murphy et al., 2006). Altered vasculogenesis leading to dysplastic placental development (He et al., 2007), modification of epigenetic markers (Tsang et al., 2012), and *in vitro* changes in placental levels of reactive oxygen species (Massrieh et al., 2006) have been reported following iAs treatment. Increased inflammatory processes were also reported for newborns exposed *in utero* via maternal consumption of iAs contaminated drinking water (Ahmed et al., 2011; Fry et al., 2007); inflammation is also a predictor of growth restriction and preterm delivery (Challis et al., 2009). Recently, a study of ultrasound measurements suggested restricted *in utero* growth with increased iAs exposure among male

fetuses (Kippler et al., 2012). Studies have also demonstrated genotoxic (Chou et al., 2012) and anti-estrogenic (Davey et al., 2007) properties for iAs, as well as modified expression of genes associated with immune function (Andrew et al., 2008; Wu et al., 2003) and developmental processes (Andrew et al., 2008).

Adverse birth outcomes (WHO, 1977), including low birth weight (LBW; neonatal weight <2,500 g at term) and preterm delivery (PD; live birth before 37 weeks completed gestation) are associated with a lifelong increased mortality risk (Crump et al., 2011). LBW and PD are also associated with an increased risk for various morbidities including neurodevelopmental disorders (Mwaniki et al., 2012), cardiovascular diseases and endocrine disorders (Barker, 2004). In 2010, approximately 11.1% of deliveries were preterm worldwide (Blencowe et al., 2012) and approximately 15% of newborns weighed <2,500 g (UNICEF, 2012). Coupled to the widespread distribution of iAs contaminated drinking water, the high prevalence of LBW and PD makes even a modest increase in risk a significant global public health concern.

The animal evidence to date is controversial with respect to adverse birth outcomes and iAs exposure, primarily reporting associations at maternally toxic doses (Wang et al., 2006). Experimental studies, using high-dose intraperitoneal (Zirakjavanmard et al., 2011) or oral iAs treatment during gestation (Tsang et al., 2012), described decreased fetal or neonatal body weight or size. Low-dose iAs administration via drinking water to dams did not influence birth outcomes in one recent study, yet was associated with reduced postnatal growth (Kozul-Horvath et al., 2012). Substantial inter-species differences in the rates of iAs methylation and excretion (Vahter, 1999) make extrapolation of animal results to humans tenuous, and underscore the need for epidemiologic investigation. In fact, humans are likely to be more sensitive to arsenic toxicity than experimental animals (Mead, 2005). Therefore, our aim was to comprehensively assess the epidemiologic literature published to date and to characterize the strength of the evidence for causal associations between drinking water iAs exposure and birth outcomes. We also provide recommendations for future investigations to address existing data gaps.

2. Methods

We searched the scholarly literature using SCOPUS, a comprehensive abstract and citation database of research literature, which indexes 20,000 peer-reviewed journals worldwide including Medline (<http://www.info.sciverse.com/scopus/>). Our initial search was limited to original human research articles published in the English language through August 27th, 2013. To identify candidate papers we used the keyword combinations: 1. “arsenic” AND “birth outcomes” (19 papers identified); 2. “arsenic” AND “birth weight” (38 papers identified); 3. “arsenic” AND “birth size” (12 papers identified); 4. “arsenic” AND “reproductive outcomes” (22 papers identified); and 5. “arsenic” AND “newborn outcomes” (24 papers identified). We manually searched reference lists in selected papers and also employed reference lists from review papers to identify one additional publication. Paper titles and abstracts were reviewed and retained if arsenic exposure via drinking water and birth weight, gestational age and/or birth size was a study hypothesis. On January 1st, 2014

we updated the search to include two papers in addition to 16 papers retained from the initial search.

For each study, we abstracted and summarized the location and population sampled, epidemiologic design, sample size, exposure and outcome assessment strategies, covariates considered and the magnitude and precision of effect estimates. These characteristics were used in a qualitative evaluation of each study and to assess the impact of the reported results. Larger, prospective studies and those using individual exposure assessment strategies were afforded greater consideration than smaller, cross-sectional studies and those using ecologic exposure assessment strategies. Furthermore, the timing and nature of individual exposure assessment strategies were considered. We expressed study results as prevalence proportion ratios (PPR), odds ratios (OR), or average change per unit increase of exposure (β) and corresponding 95% confidence intervals (95% CIs) or P-values, as reported by the authors. If possible, we used SAS v.9.3 (SAS Institute, Inc. Cary, North Carolina USA) to calculate the PPR and 95% CIs for studies that did not report measures of effect. The overall strength and consistency of associations and evidence for a temporal relation in which exposure clearly preceded outcome were used to assess the evidence for causality and to make recommendations for future studies (Hill, 1965).

3. Results and Discussion

We evaluated 16 peer-reviewed studies that addressed drinking water iAs and birth weight (Table 1), nine studies that captured gestational age (Table 2) and five studies that addressed birth size (Table 3). Many studies captured multiple endpoints and most were conducted among populations residing in the so-called ‘arsenic-endemic’ regions of India, Bangladesh, China, and Taiwan, where drinking water iAs contamination is high, widespread and well-known.

3.1 Epidemiologic Studies in south Asia

3.1.1 India—Approximately 6,000,000 persons residing in the West Bengal region of the Ganga Plain in eastern India may be at risk for exposure to iAs in ground water at levels of <10 $\mu\text{g/L}$ to 3,200 $\mu\text{g/L}$ (Nordstrom, 2002). Large scale contamination also occurs in other Ganga Plain India locales, including Bihar (Chakraborti et al., 2003). Yet, only three published cross-sectional studies assessed the impact on birth outcomes in India. This work was completed in the context of large drinking water surveys conducted in the West Bengal and Bihar regions, where women employed sources contaminated by <3 $\mu\text{g/L}$ iAs to as much as 1,474 $\mu\text{g/L}$ iAs.

In a small study of 16 Bihari women reporting 64 pregnancies, increased rates of LBW (PPR = 8.33, 95% CI = 1.03, 67.14; Table 1) and PD (PPR = 3.33, 95% CI = 0.92, 12.11; Table 2) were associated with the use of wells contaminated by 463-1,025 $\mu\text{g/L}$ iAs (Chakraborti et al., 2003). In contrast, no associations (PPR = 0.79 and 1.05, respectively) were reported in a small follow-up study of 18 Bengali women with at least one prior pregnancy (Chakraborti et al., 2004). Whereas reference women in the Bihari study were exposed to 7-459 $\mu\text{g/L}$ iAs (Chakraborti et al., 2003), those in the Bengali study were exposed to concentrations sufficient to manifest skin lesions in all participants (200-400

µg/L iAs), possibly accounting for the null results (Chakraborti et al., 2004). However, a third study of 65 pregnancies in 17 Bengali women exposed to iAs contaminated drinking water (n=11 with 284-400 µg/L and n=6 with 401-1,474 µg/L), reported increased LBW (PPR = 2.57, 95% CI = 0.59, 11.20; PPR = 2.45, 95% CI = 0.61, 9.88, respectively; Table 1) and PD (PPR = 3.43, 95% CI = 0.83, 14.13; PPR = 2.45, 95% CI = 0.61, 9.88, respectively; Table 2) relative to 18 pregnancies in seven reference women (<3 µg/L) (Mukherjee et al., 2005). Furthermore, women exposed to contaminated wells for more than 10 years (n=7) in that study had higher LBW (PPR = 1.83, 95% CI = 0.81, 4.13) but lower PD (PPR = 1.83, 95% CI = 0.39, 1.73) than women (n=10) with less than 10 years of exposure (Mukherjee et al., 2005).

The three Indian studies were cross-sectional in nature, comprised by only few participants and produced imprecise effect estimates. Study participation rates were not reported, although Chakraborti and colleagues noted that fear of stigmatization was likely to have limited enrollment (Chakraborti et al., 2003). In addition, pregnancies and pregnancy outcomes were assessed retrospectively by interview, without clinical confirmation. Thus it is difficult to ascertain underlying associations between iAs exposure distributions and study outcomes. In West Bengal, many drinking water wells have been tested for iAs and colored to indicate the relative level of iAs contamination level (i.e., green well, <50 µg/L; red well, >50 µg/L), although the accuracy of these assessments has been questioned (Rahman et al., 2002). Given recognition of the ground water iAs contamination issues in the study areas, positive associations might reflect increased reporting rates among women using tainted wells. In addition, exposure was assigned using an ecologic strategy according to measured concentrations in wells, and without taking duration of exposure into consideration for two of three studies. However, such misclassification would likely be non-differential by outcome and bias results towards the null hypothesis. Importantly, there was no assessment made for confounding by covariates of importance including age (Newburn-Cook and Onyskiw, 2005; Vahter et al., 2007) and nutritional status (Chakraborti et al., 2004; Deb et al., 2013). For example, the positive association between duration of contaminated well use and LBW might simply reflect more advanced maternal age. In addition, other agents that also contaminate groundwater sources in India (Bacquart et al., 2012), such as manganese, may also impact fetal growth and development (Zota et al., 2009), and thus might have confounded the reported associations. Given these limitations we propose that the results of these studies though provocative, add little weight to the evidence for causal associations between drinking water iAs exposure and birth outcomes.

3.1.2 Bangladesh—In Bangladesh, there are approximately 30,000,000 individuals at risk for exposure to iAs via contaminated drinking water (iAs <1 to 2,500 µg/L) (Nordstrom, 2002). We identified three cross-sectional and two prospective cohort studies of birth outcomes conducted to date in Bangladesh.

A cross-sectional study of 113 pregnancies reported increased LBW for 18 women exposed to 501-1,200 µg/L iAs and four women exposed to 201-500 µg/L iAs (PPR = 3.36, 95% CI = 0.70, 15.05; PPR = 2.35, 95% CI = 0.24, 23.47, respectively; Table 1), compared to 18 unexposed referents (Ahamed et al., 2006). Women in the high exposure group also reported an more PD (PPR = 4.20, 95% CI = 0.51, 34.67; Table 2). Point estimates were fairly strong,

although imprecise. The exposed women resided in rural villages whereas referents resided in urban and suburban locales; however, differences likely to be inherent to these groups, including socioeconomic and nutritional factors were not addressed thus raising the possibility for confounding. As noted above for the arsenic-endemic areas of West Bengal, drinking water iAs contamination is widely recognized and many wells have been painted to alert consumers (Rahman et al., 2002). Women with recognized exposures might have been more likely to report adverse outcomes than those with lower exposure raising the possibility for a bias away from the null hypothesis. The use of self-reported birth outcomes without benefit of clinical confirmation may have increased this possibility. An additional concern pertains to the participation rates, which were not reported and so factors that might distinguish participants from non-participants are not clear. Similar to the aforementioned studies in India, concurrent contamination of wells by other potentially important trace elements, such as manganese, might have confounded results reported from Bangladesh (Rahman et al., 2013).

A larger cross-sectional study (Ahmad et al., 2001), reported increased PD for 359 pregnancies in 96 women (Table 2) consuming water contaminated by $>50 \mu\text{g/L}$ iAs for at least five years, compared to 309 pregnancies in 96 referents exposed to $<20 \mu\text{g/L}$ iAs (PPR = 2.54, $P = 0.018$). The sample size was determined *a priori* to ensure adequate statistical power. The investigators systematically recruited participants, matching referents to exposed women by age at interview and marriage, education and socioeconomic status. Rates of PD were also increased among women exposed to $>10 \mu\text{g/L}$ iAs for at least 15 years vs. less than 15 years (PPR = 2.56, $P = 0.021$). Exposure was assigned by the iAs concentration previously reported for source wells, although consumption volume and duration was not accommodated (with the exception of the dichotomized time analysis). Whereas iAs concentrations in Bangladeshi wells are likely constant over short time intervals, additional evidence suggests mild to marked variability in association with climatic events in particular for more shallow aquifers (Bhattacharya et al., 2011; Cheng et al., 2005); thus exposure measurement misclassification error was possible. Birth outcomes were collected by standardized personal interview, without clinical confirmation, again raising the possibility for self-reporting biases.

An even larger cross-sectional study was conducted among 2,006 women residing in rural areas of Bangladesh who delivered singleton live births during 2002 (Kwok et al., 2006). All women participated in a prenatal health program at Community Nutrition Centers developed under the Bangladesh Integrated Nutrition Programme and administered by a non-governmental organization. Home visits were conducted in 2003 and 0-668 $\mu\text{g/L}$ iAs was measured in local drinking wells. No association was suggested between drinking water iAs exposure and LBW (OR = 1.00, 95% CI = 0.997, 1.001, $P = 0.768$), adjusted for maternal age and baseline body mass index (BMI), household assets, smoking in the household, parity, weight-gained during pregnancy, maternal height, newborn sex and time period of well use (Table 1). The authors opted to use outcome data collected by maternal interview as these were considered of higher quality than data recorded by the community nutrition centers. Over 90% of the 2,200 women comprising the study population agreed to participate providing adequate power to detect a 50% increase in odds. While robust, the

exclusion of PD from the analysis of birth weight may have introduced collider stratification under a causal graphing framework (Hernan et al., 2004), or have ‘over-adjusted’ for a causal intermediate and thereby biased study results toward the null hypothesis. Still, this is a high quality epidemiologic study with a large number of participants, individual drinking water exposure measures, capture of incident pregnancy events and comprehensive evaluation of confounding.

A small prospective study was conducted among 52 Bangladeshi women attending a prenatal care clinic with singleton pregnancies of less than 28 weeks completed gestation (Huyck et al., 2007). At the 1st prenatal health care visit investigators collected maternal hair and toenail specimens for total arsenic analysis and also a residential drinking water sample. Median drinking water iAs exposure was low (1.29 µg/L), but 25% of mothers were exposed to 9.03-734 µg/L. A one µg/g increase in the level of total maternal hair arsenic was associated with a -193.5 g decrease in birth weight (95% CI = -369.9, -13.95), adjusted for gestational age at the 1st prenatal visit, activity level and maternal weight gain during pregnancy, and gestational age at delivery (Table 1). Yet, maternal hair arsenic was not correlated to drinking water iAs concentration ($r = 0.23$, $P = 0.10$) and no associations were indicated for drinking water iAs. Modestly elevated adjusted odds ratios were also reported for total arsenic in maternal hair (OR = 2.50, 95% CI = 0.74, 8.33) and toenails (OR = 1.20, 95% CI = 0.70, 2.08) at the 1st prenatal visit and birth weight <2,750 g, although not of statistical significance. Hair and toenails reflect long term exposure but their validity and reliability have been questioned as biomarkers of exposure given concerns with respect to contamination from exogenous sources, such as iAs in bathing water, and contributions from innocuous organic species in dietary sources, such as seafood (Marchiset-Ferlay et al., 2012). These limitations appeared less relevant to toenails across a spectrum of exposure levels (Karagas et al., 2000; Mandal et al., 2004; Slotnick et al., 2007). No significant birth weight associations were detected using a second set of postnatal specimens. Although prospective and with collection of both biologic and environmental media, the small sample size and inconsistent results across exposure metrics undermines the impact of the positive result.

A much larger prospective study was conducted on 1,578 Bangladeshi women with singleton pregnancies and participating in an ongoing maternal and infant nutrition intervention study (Rahman et al., 2009). Urine specimens were collected from mothers at eight and 30 weeks gestation. Birth outcomes were assessed using records stored by local health centers and augmented by home visits. The median (range) for urine iAs and its metabolites was 95 µg/L (6-978). Statistical models including a product term for urine iAs dichotomized at 100 µg/L, and adjusted for maternal BMI and socioeconomic status, indicated several associations among women exposed to iAs <100 µg/L urine, but not for women exposed to iAs ≥ 100 µg/L urine. A one µg/L increase in averaged urine iAs values was associated with a -1.68 g (95% CI = -2.90, -0.44, $P = 0.007$; Table 1) birth weight decrease, a -0.05 mm head circumference decrease (95% CI = -0.11, 0.001, $P = 0.041$; Table 3), a -0.14 mm chest circumference decrease (95% CI = -0.20, -0.08, $P = 0.001$; Table 3) and a -0.06 mm birth length decrease (95% CI = -0.12, 0.00, $P = 0.078$; Table 3), although the latter not statistically significant. This prospective study involved a large number of participants with biologic measures averaging exposure across early and late gestation (to accommodate changes in water source or dietary exposures) in addition to

adjusting for a comprehensive panel of confounding variables. Effects were observed only for women with lower iAs exposures raising the possibility of a competing pregnancy loss risk at higher exposures or an enhancing of birth weight at iAs >100 µg/L by chance only.

3.2 Epidemiologic Studies in East Asia

3.2.1 China and Taiwan—Up to 600,000 individuals residing in Inner Mongolia, China and 200,000 residing in Taiwan are at risk for exposure to <1 to 2,400 µg/L iAs and 10 to 1,820 µg/L iAs, respectively, in contaminated drinking water sources (Nordstrom, 2002). Yet, we identified only one cross-sectional study of birth outcomes in an arsenic endemic region of Inner Mongolia and one prospective cohort study of birth outcomes conducted in an arsenic endemic region of Taiwan. Two additional cross-sectional studies were conducted in China, and one in Taiwan, in areas without recognized groundwater iAs contamination.

A large cross-sectional investigation conducted in Inner Mongolia assessed singleton deliveries in 9,890 women using maternal and newborn health records stored by local clinics (Myers et al., 2010). This area is known for groundwater iAs contamination, and the investigators sampled water from wells suspected of contamination. Term infants born to mothers consuming water contaminated by >100 µg/L iAs were 50 g heavier (95% CI = 20, 80) on average, than those born to mothers consuming water with <20 µg/L, adjusted for prenatal care (Table 1). No association was detected for PD (OR = 1.02, 95% CI = 0.72, 1.44; Table 2). Exposure was assigned as the average sub-village well iAs concentration, which is likely to have misclassified exposure for some women. An exposure validation substudy conducted among n=111 corroborates the likelihood. In fact, the investigators were unable to link more than half of the women to exposure data as they were presumed to employ uncontaminated wells. Women without exposure data were more likely to be primigravid and to have received adequate prenatal care and so a bias may have been introduced. Again, limiting the birth weight analysis to full term deliveries may have introduced a collider-stratification or over-adjustment bias as described earlier.

A very large prospective study conducted in northeastern Taiwan captured more than 18,000 primiparous, singleton deliveries (Yang et al., 2003). Using registry data, investigators compared birth weights and gestational age at delivery between 3,872 women residing in areas with 0-3,590 µg/L groundwater iAs contamination and 14,387 women residing in an area free from groundwater iAs contamination, matched by degree of urbanization. Term infants delivered to women residing in the exposed area weighed -29.05 g (95% CI = -44.55, -13.55, P = 0.002; Table 1) less on average, adjusted for maternal age, newborn sex, marital status and education. In addition, exposed women had higher odds for PD (OR = 1.10; 95% CI = 0.91, 1.33; Table 2), although the effect was modest and not of statistical significance. Though the sample size was large, the ecologic exposure assessment (i.e., 'exposed' vs. 'unexposed') is expected to have introduced exposure measurement misclassification error into the study results. Despite what was likely to be a consequent bias towards the null hypothesis, the authors identified a small but statistically significant decrease in birth weight, suggesting that the 'true' underlying effect may in fact be larger than that reported. Still, regional comparisons might reflect sociodemographic differences between groups, and although the authors matched by a village urbanization index and

adjusted their analysis for years of formal education, residual confounding remains a possibility.

Two additional cross-sectional studies were conducted in areas of China without recognized groundwater iAs contamination. In one, investigators recruited and interviewed 142 women with singleton pregnancies receiving prenatal care at one of two Shanghai City hospitals (Xu et al., 2011). Total arsenic was measured in maternal blood (mean = 4.13 µg/L, range = 0.63-30.45) and umbilical cord blood (mean = 3.82 µg/L, range = 0.31-33.54) at the time of delivery. Among 71 male newborns, a ten-fold increase in the maternal arsenic level was associated with a -354.41 g decrease in birth weight (95% CI = -677.53, -31.28; Table 1), adjusted for maternal height and gestational age, and also with a -1.51 days decrease in gestational age (95% CI = -2.50, -0.51; Table 2). Yet, no associations were detected for 71 female newborns. In another study, 125 women were recruited from a primary delivery center in Dalian City (Guan et al., 2012). Total arsenic was measured in maternal blood collected upon admission for delivery (median = 5.30 µg/L, range = 0- ~25) and umbilical cord blood collected prior to passage of the placenta (median = 3.71 µg/L, range = 0- ~25). Women with delivery at <32 weeks gestation or <1,500 g birth weight, birth defects, and multiple gestations or severe illnesses were excluded (n=6). A one µg/L increase in maternal blood arsenic was associated with a -20 g decrease in birth weight (95% CI -39.60, -0.40, P = 0.015; Table 1), adjusted for maternal BMI and gestational age at delivery, a -1.0 mm (95% CI -1.59, -0.41; P = 0.001; Table 3) decrease in newborn chest circumference adjusted for maternal BMI and gestational age at delivery, and with a -1.0 mm (95% CI -1.78, -0.22; P = 0.017) decrease in birth length, adjusted for maternal BMI, gestational age at delivery and newborn sex. In addition, a one µg/L increase in umbilical cord arsenic was associated with a -0.6 mm (95% CI -1.19, -0.01; P = 0.021) decrease in neonatal head circumference, adjusted for maternal BMI and gestational age at delivery.

Though the authors of these cross-sectional studies employed hospital delivery records and biomarkers of exposure, the use of total blood arsenic raises concern (Guan et al., 2012; Xu et al., 2011). Total blood arsenic incorporates both iAs as well as the comparatively non-toxic organic arsenic species (Akter et al., 2006) to which humans are exposed when consuming seafood (Le et al., 1994; Navas-Acien et al., 2011). This approach is likely to misclassify exposure, in particular for frequent seafood consumers (Marchiset-Ferlay et al., 2012), and might introduce positive confounding by reproductive toxicants also found in seafood (Bushkin-Bedient and Carpenter, 2010), such as persistent organohalogen pollutants or mercury (Wigle et al., 2008), driving associations away from the null hypothesis. In contrast, confounding by beneficial agents in seafood such as n-3 fatty acids (Brantsæter et al., 2012) are anticipated to negatively confound associations towards the null hypothesis. Furthermore, arsenic is cleared from the blood in a few hours and therefore is not recommended as a biomarker for exposure, particularly at low levels of exposure (ATSDR, 2007).

A large prospective cohort study was conducted on 309 women with uncomplicated singleton pregnancies and attending an obstetrics clinic in an area of central Taiwan without groundwater iAs contamination (Chou et al., 2012). Women were interviewed to capture reproductive and medical histories, and urine specimens were also collected during the 3rd

trimester for analysis of iAs and its metabolites (Mean = 0.8 µg/g creatinine, 5th %tile, 95th%tile = 0.2-3.9). No association was detected for maternal iAs exposure and LBW (OR = 1.02; 95% CI = 0.78, 1.34; P = 0.314; Table 1). Odds were increased for head circumference <340 mm (OR = 6.16, 95% CI 0.17, 10.84, P = 0.318; Table 3) and chest circumference <320 mm (OR = 11.69, 95% CI 0.51, 12.51, P = 0.123; Table 3), although confidence intervals were wide. In contrast, the odds were reduced for birth length <450 mm (OR = 0.13, 95% CI = 0.01, 8.13, P = 0.318; Table 3), again with a wide confidence interval. The authors adjusted for maternal age, cigarette smoking, alcohol consumption and newborn sex. Although the sample size was substantial, 28% of the participants were lost to follow-up, which may or may not have biased study results contingent on the iAs-birth outcomes association in that group; data were not available to compare characteristics for the two. Furthermore, spot urine samples collected in the 3rd trimester of pregnancy may not represent the biologically effective dose at ‘critical windows’ of vulnerability (Buck Louis et al., 2006), as iAs has a half-life of approximately 10 hours (ATSDR, 2007) and metabolic efficiency appears to improve during pregnancy (Concha et al., 1998; Gardner et al., 2011). Such ‘mistimed’ specimen collection is expected to bias study results towards the null hypothesis.

3.2.2 Japan—An additional prospective cohort study was conducted in Tokyo, Japan, a non-arsenic endemic area (Shirai et al., 2010). The authors recruited 78 pregnant women receiving prenatal care in gestational weeks 9-40, from a single hospital, and determined total arsenic in spot urine specimens. The geometric mean was 76.9 µg/g creatinine (range = 9.81-1,603). The authors did not specify the effects of arsenic exposure, but reported that there were no associations with birth weight (Table 1), head circumference or birth length (Table 3), adjusted for maternal age and BMI, cigarette smoking and gestational age at delivery. Though prospective in nature and with person-level exposure assessment as well as adjustment for confounding variables, this small study was likely underpowered to detect associations given the low levels of exposure. Furthermore, the use of a total arsenic biomarker in a population of frequent seafood consumers coupled to the timing of urine collection for some participants predisposed the results to the aforementioned biases and confounding by additional related reproductive toxicants.

3.3 Epidemiologic Studies in South America and Europe

3.3.1 Chile—Prior to the implementation of drinking water iAs mitigation technologies in the 1970s, approximately 400,000 individuals were exposed to 10-1,000 µg/L iAs in Chile (Nordstrom, 2002), although the population currently at risk is difficult to ascertain (Bundschuh et al., 2012). We identified one prospective cohort study conducted in an arsenic endemic region of northern Chile.

Employing the public health care system in Chile, 844 pregnant women were recruited to a prospective study during prenatal care visits at 16 to 35 weeks gestation (Hopenhayn et al., 2003). Women had resided for a minimum of 12 months in the city of Antofagasta, which was supplied by water sources contaminated by 32.9-52.7 µg/L iAs, or in the city of Valparaiso, which was supplied by comparatively uncontaminated water sources (0.5-1.1 µg/L iAs). The average urine total iAs concentration was approximately 10-fold higher

among women residing in Antofagasta (54.3 µg/L) than in Valparaíso (5.3 µg/L). A non-significant -26 g (95% CI = -85, 31) decrease in newborn birth weight was reported per one µg/L increase in maternal urine iAs (Table 1). Compared by city of residence, average birth weights were -57 g (95% CI = -123, 9) lower for Antofagasta neonates compared to Valparaíso neonates, and -107 g (95% CI = -265, 50) lower when restricted to infants with <38 weeks completed gestation at delivery, although not of statistical significance. The authors adjusted for maternal age, BMI, height and parity, cigarette smoking, gestational age at delivery, cigarette smoking, household income, prenatal care and newborn sex. The ecologic exposure assignment strategy suggested a decreased birth weight in association with higher maternal drinking water iAs, but the results were not statistically significant and the individual exposure assessment approach indicated no association; however, the direction of the effect estimates was consistent. Collection of biospecimens later in pregnancy was likely to have introduced exposure measurement misclassification into the study results, with an ensuing bias towards the null hypothesis, and thus might account for the non-significant birth weight decrease. However, the sample size was large, outcomes were abstracted from clinical records, and confounding variables were considered.

3.3.2 Romania and Spain—Approximately 400,000 people are exposed to as much as 167 µg/L iAs in Hungary and western Romania, and more than 50,000 Spaniards are likely exposed to up to 100 µg/L iAs (Nordstrom, 2002). We identified one cross-sectional study conducted in an arsenic endemic region of western Romania. While we found one study conducted on the Spanish Tenerife Island, this area is not known for groundwater iAs contamination.

A recent cross-sectional study described 38 women residing in Arad County, Romania with uncomplicated, full-term singleton deliveries in the 10 previous years, and having resided in the same locale for at least 18 years (Germann et al., 2013). Women were recruited from four villages with known drinking groundwater iAs contamination (>10 µg/L) and four villages accessing uncontaminated water sources (<1 µg/L). Data were captured by personal interview and drinking water, urine and toenail specimens were collected. Although no association was reported for drinking water iAs and birth weight (Table 1), women with a LBW delivery were significantly ($P = 0.019$) more likely to have had the sum of urine iAs and its metabolites >9 µg/L (67%) compared to women with a normal birth weight delivery (10%). Ratios of iAs metabolites in urine, methylarsonate (MMA) and dimethylarsinate (DMA) were used to identify women with higher and lower rates of iAs metabolism (Vahter and Concha, 2001). Yet, these were not associated with birth weight nor was toenail iAs. The results suggested that mothers with a history of LBW were less likely to partition iAs internally than mothers without LBW and that factors in addition to metabolism may designate women to higher risk for adverse birth outcomes in association with iAs exposure (Germann et al., 2013). However, the small sample size was unlikely to be sufficiently powered to detect subtle differences in drinking water iAs, in particular at the low levels measured in this study. The comparisons were not adjusted for confounding variables, although bivariate analysis suggested that the groups were mostly similar in terms of sociodemographic factors and health-related behaviors. Still, the cross-sectional nature of this study precludes temporality, coupled to the short half-life of iAs which as noted earlier

introduces potential exposure measurement misclassification error, especially for older deliveries.

Another recent cross-sectional study conducted in Tenerife, Spain described 96 women and their newborns, with maternal completion of a structured questionnaire and collection of meconium from newborn diapers with total arsenic analysis (Vall et al., 2012). Arsenic was detected in 37 meconium specimens (0.10-31.40 ng/g), presumably representing cumulative exposure starting in the 12th week of gestation. Babies (n=76) with detectable arsenic were 223.8 g heavier on average than those without (P=0.043; Table 1), although gestational ages (n=72) were similar (P=0.813; Table 2). Yet, meconium arsenic concentration was unrelated to reported maternal drinking water source (P=0.582). As noted above, for populations with low drinking water iAs exposure and high rates of seafood consumption total arsenic most likely reflects dietary exposure to the innocuous organic arsenic species. Furthermore, the latter likely results in confounding by additional, unmeasured agents found in seafood that may have positively or negatively confounded the associations.

4. Synthesis

Whereas the evidence from animal and *in vitro* studies provides sufficient biologic plausibility for iAs as a reproductive toxicant, the evidence from the epidemiologic literature is inconsistent. We noted wide variation in the quality and rigor of the studies reviewed, particularly in terms of sample size, study design, exposure assessment strategies and adjustment for confounding. Furthermore, differences exist in populations studied in terms of residence in iAs or non-iAs endemic regions, and thus the extent of exposure through consumption of contaminated drinking water.

Exposure to iAs decreased birth weight in some studies (Chakraborti et al., 2003; Guan et al., 2012; Huyck et al., 2007; Xu et al., 2011), including in two large, high quality prospective investigations (Rahman et al., 2009; Yang et al., 2003). A decrease was suggested, although not detected in another large and high-quality prospective study (Hopenhayn et al., 2003). In contrast, no effect or an increase in birth weight was reported in several other studies (Ahamed et al., 2006; Chakraborti et al., 2004; Chou et al., 2012; Gelmann et al., 2013; Mukherjee et al., 2005; Shirai et al., 2010; Vall et al., 2012) including two large cross-sectional studies of high quality (Kwok et al., 2006; Myers et al., 2010). Based on our review of the literature, we conclude that insufficient epidemiologic evidence exists to corroborate an increase in LBW as a clinical outcome. However, there exists limited evidence for a continuous decrease in birth weight across the distribution, but also some evidence for an increase with iAs.

Very few studies detected associations between gestational age and drinking water iAs, with only two reports of significant decreases reported from cross-sectional investigations (Ahmad et al., 2001; Xu et al., 2011). In contrast, two very large studies conducted in arsenic endemic areas, one cross-sectional (Myers et al., 2010) and one prospective (Yang et al., 2003), reported no association for drinking water iAs and gestational age, in populations with exposure to drinking water sources contaminated by well over 50 µg/L iAs. Based on our review of the epidemiologic evidence published to date, we conclude that insufficient

evidence exists for a causal association between drinking water iAs exposure and gestational age. However, as the number of studies capturing gestational age was limited, a potential association cannot be ruled out.

Few investigations incorporated measures of birth size as study endpoints. A large, well-conducted prospective cohort study reported significantly decreased head and chest circumference, with a 'borderline' significant decrease in birth length among infants delivered to mothers residing in an iAs endemic region of Bangladesh (Rahman et al., 2009), and significant decreases for head circumference, chest circumference and birth length were reported from a small cross-sectional study conducted in a non-iAs-endemic region of China (Guan et al., 2012). Three additional studies did not report significant cross-sectional associations among populations residing in non-iAs-endemic regions. However the effect estimates for one study were quite strong, although imprecise (Chou et al., 2012), no effect estimates were reported for another (Shirai et al., 2010) and exposure assessment issues limit the interpretability of the results from the third (Vall et al., 2012). Therefore we suggest there that minimal evidence exists for a causal association between maternal drinking water iAs exposure and reduced birth size.

5. Recommendations

Several salient methodologic issues limit the studies we reviewed herein, and might account, at least in part for the inconsistency of the reported results, or likewise have biased results towards the null hypothesis and obscured associations. However, investigations of populations exposed to high levels of drinking water iAs were often conducted in underdeveloped regions, introducing practical and financial limitations into study designs. Still, it seems constructive to discuss issues for consideration in future study design, to more conclusively assess risks. In addition to the methodologic limitations raised earlier, variable susceptibility to iAs toxicity, dietary sources of iAs exposure and paternal effects may also be important. Consideration of these issues will require attention to further clarify the impact of drinking water iAs exposure in future investigation of birth weight and birth size.

Vulnerability to the toxic effects of iAs varies substantially between pregnant women, independent of gestational length (Li et al., 2008), and overlooking this issue may overshadow or otherwise bias associations between maternal iAs exposure and birth outcomes. Several factors including polymorphisms in the *AS3MT* and *MTHFR* genes (Lindberg et al., 2007) and nutritional status for folate, glutathione and methionine (Vahter, 2002) impact the metabolism of iAs. Adjustment for maternal BMI or height can serve as a proxy for general nutritional status (Guan et al., 2012; Hopenhayn et al., 2003; Kwok et al., 2006; Rahman et al., 2009; Shirai et al., 2010; Xu et al., 2011); however, an explicit evaluation of the mediating effects of these factors is necessary. The Romanian study (Gelman et al., 2013) assessed inter-individual differences in metabolism using ratios of iAs, DMA and MMA as a proxy for metabolic efficacy (Vahter and Concha, 2001), but further suggested that variability in excretion and sequestration are also important. Although a study conducted in a non-iAs contaminated region of Taiwan evaluated iAs metabolites in urine, associations were not assessed using these ratios (Chou et al., 2012). In many cases, the expense of these types of speciated analysis may preclude incorporation into smaller

studies. However, to clarify issues related to iAs and birth weight and iAs and birth size a comprehensive approach accommodating inter-individual differences may be necessary.

Dietary iAs exposures are also of increasing concern worldwide, with substantial contributions resulting from the preparation and consumption of rice in arsenic-endemic (Rahman and Hasegawa, 2011) and in non-endemic regions (Gilbert-Diamond et al., 2011), which are not effectively captured by studies assigning exposure by drinking water source. In areas with high rates of consumption of iAs contaminated foods, and low drinking water iAs contamination, it is important to augment environmental sampling with dietary data, or to employ appropriately timed collection of exposure biomarkers with a speciated analysis to isolate the internal dose of iAs and its metabolites. While ideal, the latter may not be feasible in isolated and underdeveloped areas.

Curiously, no studies to date have investigated a possible paternal effect. Though maternal exposures are likely to be of greater importance, evidence from studies conducted in populations with and without assisted reproduction suggests the relevance of paternal factors for placental function, and possibly for preterm delivery (Sartorius and Nieschlag, 2010). While associations have been reported for environmental iAs exposure and semen quality in animals (Li et al., 2012) and men (Xu et al., 2012), data to specifically address DNA adducts and fragmentation in association with iAs exposure among men has not yet been published to the best of our knowledge. Given the couple-based nature of human reproduction investigation into potential effects for male exposure is warranted.

6. Conclusions

Despite methodological limitations and questionable generalizability, study results published to date suggest that lower birth weight and smaller birth size may be associated with maternal exposure to iAs in drinking water. Although evidence for associations with clinical outcomes is insufficient, we call for a guarded approach to protecting the most vulnerable members of exposed populations, fetuses falling within the lower tail of the birth weight and size distributions for whom small shifts might lead to clinical outcomes (Schmidt, 2013). Little data are available to assess reproductive risks at exposures below the currently WHO MCL of 10 µg/L iAs, a value intended to reduce cancer risks. Yet, the evidence from populations with predominantly medium and high-level exposure is insufficient to speculate as to the impact of low-level (<10 µg/L iAs) effects. Furthermore, there exists a dearth of experimental data to more precisely support plausible biologic mechanisms for effects at low doses. Given the wide global distribution of low-level drinking water iAs contamination we must be circumspect in considering potential public health impacts and target studies to further investigate the risk.

Large prospective studies, with pre-conception or early 1st trimester enrollment of both the mother and the father, longitudinal collection of biospecimens and drinking water samples for speciated arsenic analysis at critical windows for reproduction (i.e., conception, embryo implantation and placentation, embryonic development and fetal development), and capture of birth outcomes from standardized health provider delivery records, will be required to more conclusively assess the reproductive impact of human exposure to iAs contaminated

drinking water sources. Furthermore, comprehensive assessment and capture of covariates that might confound associations, and stratification by factors that might mediate associations, will also be necessary. Given the widespread global distribution of drinking water sources contaminated with iAs and the high background rate for adverse birth outcomes which convey lifetime health sequelae, further investigation is needed to assess the relevance of iAs as a causal factor and to help guide prevention efforts.

References

- Ahamed S, Sengupta MK, Mukherjee SC, Pati S, Mukherjee A, Rahman MM, Hossain MA, Das B, Nayak B, Pal A, Zafar A, Kabir S, Banu SA, Morshed S, Islam T, Quamruzzaman Q, Chakraborti D. An eight-year study report on arsenic contamination in groundwater and health effects in Eruani Village, Bangladesh and an approach for its mitigation. *J. Health Popul. Nutr.* 2006; 24:129–141. [PubMed: 17195555]
- Ahmad SA, Salim Ullah Sayed MH, Barua S, Haque Khan M, Faruquee MH, Jalil A, Abdul Hadi S, Kabir Talukder H. Arsenic in drinking water and pregnancy outcomes. *Environ. Health Perspect.* 2001; 109:629–631. [PubMed: 11445518]
- Ahmed S, Mahabbat-e Khoda S, Rekha RS, Gardner RM, Ameer SS, Moore S, Ekström EC, Vahter M, Raqib R. Arsenic-associated oxidative stress, inflammation, and immune disruption in human placenta and cord blood. *Environ. Health Perspect.* 2011; 119:258–264. [PubMed: 20940111]
- Akter KF, Owens G, Davey DE, Naidu R. Arsenic speciation and toxicity in biological systems. *Rev. Environ. Contam. Toxicol.* 2006; 184:97–149. [PubMed: 15790174]
- Amini M, Abbaspour KC, Berg M, Winkel L, Hug SJ, Hoehn E, Yang H, Johnson CA. Statistical modeling of global geogenic arsenic contamination in groundwater. *Environ. Sci. Technol.* 2008; 42:3669–3675. [PubMed: 18546706]
- Andrew AS, Jewell DA, Mason RA, Whitfield ML, Moore JH, Karagas MR. Drinking-water arsenic exposure modulates gene expression in human lymphocytes from a U.S. population. *Environ. Health Perspect.* 2008; 116:524–531. [PubMed: 18414638]
- ATSDR. Toxicological profile for arsenic. U.S. Agency for Toxic Substances and Disease Registry. U.S. Agency for Toxic Substances and Disease Registry; Atlanta, GA.: 2007.
- Bacquart T, Bradshaw K, Frisbie S, Mitchell E, Springston G, Defelice J, Dustin H, Sarkar B. A survey of arsenic, manganese, boron, thorium, and other toxic metals in the groundwater of a West Bengal, India neighbourhood. *Metallomics.* 2012; 4:653–659. [PubMed: 22491819]
- Barker DJP. The developmental origins of adult disease. *J. Am. Coll. Nutr.* 2004; 23:588S–595S. [PubMed: 15640511]
- Bhattacharya P, Hossain M, Rahman SN, Robinson C, Nath B, Rahman M, Islam MM, Von Brömssen M, Ahmed KM, Jacks G, Chowdhury D, Jakariya M, Persson LÅ, Vahter M. Temporal and seasonal variability of arsenic in drinking water wells in Matlab, southeastern Bangladesh: A preliminary evaluation on the basis of a 4 year study. *J. Environ. Sci. Heal. A.* 2011; 46:1177–1184.
- Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, Adler A, Vera Garcia C, Rohde S, Say L, Lawn JE. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications. *The Lancet.* 2012; 379:2162–2172.
- Bloom MS, Fitzgerald EF, Kim K, Neamtiu I, Gurzau ES. Spontaneous pregnancy loss in humans and exposure to arsenic in drinking water. *Int. J. Hyg. Environ. Health.* 2010; 213:401–413. [PubMed: 20889375]
- Brantsæter AL, Birgisdottir BE, Meltzer HM, Kvale HE, Alexander J, Magnus P, Haugen M. Maternal seafood consumption and infant birth weight, length and head circumference in the Norwegian Mother and Child Cohort Study. *Br. J. Nutr.* 2012; 107:436–444. [PubMed: 21767447]
- Buck Louis GM, Lynch CD, Cooney MA. Environmental influences on female fecundity and fertility. *Semin. Reprod. Med.* 2006; 24:147–155. [PubMed: 16804813]

- Bundschuh J, Litter MI, Parvez F, Román-Ross G, Nicolli HB, Jean J-S, Liu C-W, López D, Armienta MA, Guilherme LRG, Cuevas AG, Cornejo L, Cumbal L, Toujaguez R. One century of arsenic exposure in Latin America: A review of history and occurrence from 14 countries. *Sci. Total Environ.* 2012; 429:2–35. [PubMed: 21959248]
- Bushkin-Bedient S, Carpenter DO. Benefits versus risks associated with consumption of fish and other seafood. *Rev. Environ. Health.* 2010; 25:161–191. [PubMed: 21038755]
- Chakraborti D, Mukherjee SC, Pati S, Sengupta MK, Rahman MM, Chowdhury UK, Lodh D, Chanda CR, Chakraborti AK, Basu GK. Arsenic groundwater contamination in Middle Ganga Plain, Bihar, India: A future danger? *Environ. Health Perspect.* 2003; 111:1194–1201. [PubMed: 12842773]
- Chakraborti D, Sengupta MK, Rahman MM, Ahamed S, Chowdhury UK, Hossain MA, Mukherjee SC, Pati S, Saha KC, Dutta RN, Quamruzzaman Q. Groundwater arsenic contamination and its health effects in the Ganga-Meghna-Brahmaputra plain. *J. Environ. Monit.* 2004; 6:74N–83N.
- Challis JR, Lockwood CJ, Myatt L, Norman JE, Strauss Iii JF, Petraglia F. Inflammation and pregnancy. *Reprod. Sci.* 2009; 16:206–215. [PubMed: 19208789]
- Cheng Z, Van Geen A, Seddique AA, Ahmed KM. Limited temporal variability of arsenic concentrations in 20 wells monitored for 3 years in Araihaaz, Bangladesh. *Environ. Sci. Technol.* 2005; 39:4759–4766. [PubMed: 16053073]
- Chou, WC.; Chuang, CY.; Huang, PC.; Wang, CJ.; Chen, HY.; Chuang, YD.; Wang, SL.; Yu, ZH. Arsenic exposure in pregnancy increases the risk of adverse birth outcomes of newborn in Taiwan.. *Proceedings of 4th International Congress: Arsenic in the Environment*; Cairns, Australia. 2012. p. 157-158.
- Concha G, Vogler G, Lezcano D, Nermell B, Vahter M. Exposure to inorganic arsenic metabolites during early human development. *Toxicol. Sci.* 1998; 44:185–190. [PubMed: 9742656]
- Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational age at birth and mortality in young adulthood. *J. Am. Med. Assoc.* 2011; 306:1233–1240.
- Davey JC, Bodwell JE, Gosse JA, Hamilton JW. Arsenic as an endocrine disruptor: Effects of arsenic on estrogen receptor-mediated gene expression in vivo and in cell culture. *Toxicol. Sci.* 2007; 98:75–86. [PubMed: 17283378]
- Deb D, Biswas A, Ghose A, Das A, Majumdar KK, Guha Mazumder DN. Nutritional deficiency and arsenical manifestations: A perspective study in an arsenic-endemic region of West Bengal, India. *Pub. Health Nutr.* 2013; 16:1644–1655. [PubMed: 23182268]
- Fry RC, Navasumrit P, Valiathan C, Svensson JP, Hogan BJ, Luo M, Bhattacharya S, Kandjanapa K, Soontararuks S, Nookabkaew S, Mahidol C, Ruchirawat M, Samson LD. Activation of inflammation/NF-kappaB signaling in infants born to arsenic-exposed mothers. *PLoS Genet.* 2007; 3:2180–2189.
- Gardner RM, Nermell B, Kippler M, Grandér M, Li L, Ekström E-C, Rahman A, Lönnerdal B, Hoque AMW, Vahter M. Arsenic methylation efficiency increases during the first trimester of pregnancy independent of folate status. *Reprod. Toxicol.* 2011; 31:210–218. [PubMed: 21078382]
- Gelmann ER, Gurzau E, Gurzau A, Goessler W, Kunrath J, Yeckel CW, McCarty KM. A pilot study: The importance of inter-individual differences in inorganic arsenic metabolism for birth weight outcome. *Environ. Toxicol. Pharmacol.* 2013; 36:1266–1275. [PubMed: 24211595]
- Gilbert-Diamond D, Cottingham KL, Gruber JF, Punshon T, Sayarath V, Gandolfi AJ, Baker ER, Jackson BP, Folt CL, Karagas MR. Rice consumption contributes to arsenic exposure in US women. *Proc. Natl. Acad. Sci. U. S. A.* 2011; 108:20656–20660. [PubMed: 22143778]
- Guan H, Piao F, Zhang X, Li X, Li Q, Xu L, Kitamura F, Yokoyama K. Prenatal exposure to arsenic and its effects on fetal development in the general population of Dalian. *Biol. Trace Elem. Res.* 2012; 149:10–15. [PubMed: 22451376]
- He W, Greenwell RJ, Brooks DM, Calderón-Garcidueñas L, Beall HD, Coffin JD. Arsenic exposure in pregnant mice disrupts placental vasculogenesis and causes spontaneous abortion. *Toxicol. Sci.* 2007; 99:244–253. [PubMed: 17569693]
- Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology.* 2004; 15:615–625. [PubMed: 15308962]

- Hill AB. The environment and disease: Association or causation? *Proc. R. Soc. Med.* 1965; 58:295–300. [PubMed: 14283879]
- Hopenhayn C, Ferreccio C, Browning SR, Huang B, Peralta C, Gibb H, Hertz-Picciotto I. Arsenic exposure from drinking water and birth weight. *Epidemiology.* 2003; 14:593–602. [PubMed: 14501275]
- Huyck KL, Kile ML, Mahiuddin G, Quamruzzaman Q, Rahman M, Breton CV, Dobson CB, Frelich J, Hoffman E, Yousuf J, Afroz S, Islam S, Christiani DC. Maternal arsenic exposure associated with low birth weight in Bangladesh. *J. Occup. Environ. Med.* 2007; 49:1097–1104. [PubMed: 18000415]
- Karagas MR, Tosteson TD, Blum J, Klaue B, Weiss JE, Stannard V, Spate V, Morris JS. Measurement of low levels of arsenic exposure: A comparison of water and toenail concentrations. *Am. J. Epidemiol.* 2000; 152:84–90. [PubMed: 10901333]
- Kippler M, Wagatsuma Y, Rahman A, Nermell B, Persson L-Å, Raqib R, Vahter M. Environmental exposure to arsenic and cadmium during pregnancy and fetal size: A longitudinal study in rural Bangladesh. *Reprod. Toxicol.* 2012; 34:504–511. [PubMed: 22985739]
- Kozul-Horvath CD, Zandbergen F, Jackson BP, Enelow RI, Hamilton JW. Effects of low-dose drinking water arsenic on mouse fetal and postnatal growth and development. *PLoS ONE.* 2012; 7:1–9.
- Kwok RK, Kaufmann RB, Jakariya M. Arsenic in drinking-water and reproductive health outcomes: A study of participants in the Bangladesh integrated nutrition programme. *J. Health Popul. Nutr.* 2006; 24:190–205. [PubMed: 17195560]
- Le X, Cullen W, Reimer K. Human urinary arsenic excretion after one-time ingestion of seaweed, crab, and shrimp. *Clin. Chem.* 1994; 40:617–624. [PubMed: 8149620]
- Li L, Ekstrom EC, Goessler W, Lonnerdal B, Nermell B, Yunus M, Rahman A, El Arifeen S, Persson LÅ, Vahter M. Nutritional status has marginal influence on the metabolism of inorganic arsenic in pregnant Bangladeshi women. *Environ. Health Perspect.* 2008; 116:315–321. [PubMed: 18335097]
- Li Y, Wang M, Piao F, Wang X. Subchronic exposure to arsenic inhibits spermatogenesis and downregulates the expression of Ddx3y in testis and epididymis of mice. *Toxicol. Sci.* 2012; 128:482–489. [PubMed: 22581830]
- Lindberg AL, Kumar R, Goessler W, Thirumaran R, Gurzau E, Koppova K, Rudnai P, Leonardi G, Fletcher T, Vahter M. Metabolism of low-dose inorganic arsenic in a Central European population: Influence of sex and genetic polymorphisms. *Environ. Health Perspect.* 2007; 115:1081–1086. [PubMed: 17637926]
- Mandal BK, Ogra Y, Anzai K, Suzuki KT. Speciation of arsenic in biological samples. *Toxicol. Appl. Pharmacol.* 2004; 198:307–318. [PubMed: 15276410]
- Marchiset-Ferlay N, Savanovitch C, Sauviant-Rochat MP. What is the best biomarker to assess arsenic exposure via drinking water? *Environ. Int.* 2012; 39:150–171. [PubMed: 22208756]
- Massrieh W, Derjuga A, Blank V. Induction of endogenous Nrf2/small Maf heterodimers by arsenic-mediated stress in placental choriocarcinoma cells. *Antioxid. Redox Signal.* 2006; 8:53–59. [PubMed: 16487037]
- Mead MN. Arsenic: In search of an antidote to a global poison. *Environ. Health Perspect.* 2005; 113:A378–A386. [PubMed: 15929879]
- Mukherjee SC, Saha KC, Pati S, Dutta RN, Rahman MM, Sengupta MK, Ahamed S, Lodh D, Das B, Hossain M, Nayak B, Mukherjee A, Chakraborti D, Dulta SK, Palit SK, Kaies I, Barua AK, Asad KA. Murshidabad -One of the nine groundwater arsenic-affected districts of West Bengal, India. Part II: Dermatological, neurological, and obstetric findings. *Clin. Toxicol.* 2005; 43:835–848.
- Murphy VE, Smith R, Giles WB, Clifton VL. Endocrine regulation of human fetal growth: The role of the mother, placenta, and fetus. *Endocr. Rev.* 2006; 27:141–169. [PubMed: 16434511]
- Mwaniki MK, Atieno M, Lawn JE, Newton CRJC. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: A systematic review. *The Lancet.* 2012; 379:445–452.
- Myers SL, Lobdell DT, Liu Z, Xia Y, Ren H, Li Y, Kwok RK, Mumford JL, Mendola P. Maternal drinking water arsenic exposure and perinatal outcomes in Inner Mongolia, China. *J. Epidemiol. Community Health.* 2010; 64:325–329. [PubMed: 19692727]

- Naujokas MF, Anderson B, Ahsan H, Aposhian VH, Graziano JH, Thompson C, Suk WA. The broad scope of health effects from chronic arsenic exposure: Update on a worldwide public health problem. *Environ. Health Perspect.* 2013; 121:295–302. [PubMed: 23458756]
- Navas-Acien A, Francesconi KA, Silbergeld EK, Guallar E. Seafood intake and urine concentrations of total arsenic, dimethylarsinate and arsenobetaine in the US population. *Environ. Res.* 2011; 111:110–118. [PubMed: 21093857]
- Newburn-Cook CV, Onyskiw JE. Is older maternal age a risk factor for preterm birth and fetal growth restriction? A systematic review. *Health Care Women Int.* 2005; 26:852–875. [PubMed: 16214797]
- Nordstrom DK. Worldwide occurrences of arsenic in ground water. *Science.* 2002; 296
- Pilsner JR, Hall MN, Liu X, Ilievski V, Slavkovich V, Levy D, Factor-Litvak P, Yunus M, Rahman M, Graziano JH, Gamble MV. Influence of prenatal arsenic exposure and newborn sex on global methylation of cord blood DNA. *PLoS ONE.* 2012; 7
- Rahman A, Vahter M, Smith AH, Nermell B, Yunus M, El Arifeen S, Persson L-A, Ekstrom E-C. Arsenic exposure during pregnancy and size at birth: A prospective cohort study in Bangladesh. *Am. J. Epidemiol.* 2009; 169:304–312. [PubMed: 19037006]
- Rahman MA, Hasegawa H. High levels of inorganic arsenic in rice in areas where arsenic-contaminated water is used for irrigation and cooking. *Sci. Total Environ.* 2011; 409:4645–4655. [PubMed: 21899878]
- Rahman MM, Mukherjee D, Sengupta MK, Chowdhury UK, Lodh D, Chanda CR, Roy S, Selim M, Quamruzzaman Q, Milton AH, Shahidullah SM, Tofizur RM, Chakraborti D. Effectiveness and reliability of arsenic field testing kits: Are the million dollar screening projects effective or not? *Environ. Sci. Technol.* 2002; 36:5385–5394. [PubMed: 12521165]
- Rahman SM, Åkesson A, Kippler M, Grandér M, De Hamadani J, Streatfield PK, Persson LÅ, Arifeen SE, Vahter M. Elevated manganese concentrations in drinking water may be beneficial for fetal survival. *PLoS ONE.* 2013; 8
- Sartorius GA, Nieschlag E. Paternal age and reproduction. *Hum. Reprod. Update.* 2010; 16:65–79. [PubMed: 19696093]
- Schmidt CW. Beyond uncertainty factors: Protecting the tails of the bell curve. *Environ. Health Perspect.* 2013; 121:A26–A29. [PubMed: 23286931]
- Shirai S, Suzuki Y, Yoshinaga J, Mizumoto Y. Maternal exposure to low-level heavy metals during pregnancy and birth size. *J. Environ. Sci. Heal. A.* 2010; 45:1468–1474.
- Slotnick MJ, Meliker JR, Avruskin GA, Ghosh D, Nriagu JO. Toenails as a biomarker of inorganic arsenic intake from drinking water and foods. *J. Toxicol. Environ. Health A.* 2007; 70:148–158. [PubMed: 17365576]
- Smedley PL, Kinniburgh DG. A review of the source, behaviour and distribution of arsenic in natural waters. *Appl. Geochem.* 2002; 17:517–568.
- Tsang V, Fry RC, Niculescu MD, Rager JE, Saunders J, Paul DS, Zeisel SH, Waalkes MP, Stýblo M, Drobná Z. The epigenetic effects of a high prenatal folate intake in male mouse fetuses exposed in utero to arsenic. *Toxicol. Appl. Pharmacol.* 2012; 264:439–450. [PubMed: 22959928]
- UNICEF. The State of the World's Children 2012: Children in and Urban World. United Nations Children's Fund; United Nations, New York: 2012.
- Vahter M. Effects of arsenic on maternal and fetal health. *Annu. Rev. Nutr.* 2009; 29:381–399. [PubMed: 19575603]
- Vahter M. Mechanisms of arsenic biotransformation. *Toxicology.* 2002; 181–182 211–217. [PubMed: 11893417]
- Vahter M. Methylation of inorganic arsenic in different mammalian species and population groups. *Sci. Prog.* 1999; 82:69–88. [PubMed: 10445007]
- Vahter M, Åkesson A, Liden C, Ceccatelli S, Berglund M. Gender differences in the disposition and toxicity of metals. *Environ. Res.* 2007; 104:85–95. [PubMed: 16996054]
- Vahter M, Concha G. Role of metabolism in arsenic toxicity. *Pharmacol. Toxicol.* 2001; 89:1–5. [PubMed: 11484904]

- Vall O, Gómez-Culebras M, Garcia-Algar O, Joya X, Velez D, Rodríguez-Carrasco E, Puig C. Assessment of prenatal exposure to arsenic in Tenerife Island. *PLoS ONE*. 2012; 7:e50463. [PubMed: 23209747]
- Wang A, Holladay SD, Wolf DC, Ahmed SA, Robertson JL. Reproductive and developmental toxicity of arsenic in rodents: A review. *Int. J. Toxicol*. 2006; 25:319–331. [PubMed: 16940004]
- WHO. Some drinking-water disinfectants and contaminants, including arsenic. World Health Organization (WHO); Geneva, Switzerland: 2004.
- WHO. World Health Organization: Recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. *Acta Obstet. Gynecol. Scand*. 1977; 56:247–253. [PubMed: 560099]
- Wigle DT, Arbuckle TE, Turner MC, Berube A, Yang Q, Liu S, Krewski D. Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. *J. Environ. Sci. Heal. B Crit. Rev*. 2008; 11:373–517.
- Wu MM, Chiou HY, Ho IC, Chen CJ, Lee TC. Gene expression of inflammatory molecules in circulating lymphocytes from arsenic-exposed human subjects. *Environ. Health Perspect*. 2003; 111:1429–1438. [PubMed: 12928151]
- Xu L, Yokoyama K, Tian Y, Piao FY, Kitamura F, Kida H, Wang P. Decrease in birth weight and gestational age by arsenic among the newborn in Shanghai, China. *Nihon Koshu Eisei Zasshi*. 2011; 58:89–95. [PubMed: 21473424]
- Xu W, Bao H, Liu F, Liu L, Zhu Y-G, She J, Dong S, Cai M, Li L, Li C, Shen H. Environmental exposure to arsenic may reduce human semen quality: Associations derived from a Chinese cross-sectional study. *Environ. Health*. 2012; 11:46. [PubMed: 22776062]
- Yang CY, Chang CC, Tsai SS, Chuang HY, Ho CK, Wu TN. Arsenic in drinking water and adverse pregnancy outcome in an arseniasis-endemic area in northeastern Taiwan. *Environ. Res*. 2003; 91:29–34. [PubMed: 12550085]
- Zirakjavanmard M, Kaul JM, Paul S. Embryotoxicity of sodium arsenate in mouse. *J. Med. Toxicol. Legal Med*. 2011; 13:1–7.
- Zota AR, Ettinger AS, Bouchard M, Amarasiwardena CJ, Schwartz J, Hu H, Wright RO. Maternal blood manganese levels and infant birth weight. *Epidemiology*. 2009; 20:367–373. [PubMed: 19289966]

Table 1

Epidemiologic studies evaluating drinking water arsenic exposure and birth weight.

Authors	Locale	Design	Sample size	Endpoint	Exposed group ($\mu\text{g/L}$) ^a	Reference group ($\mu\text{g/L}$) ^a	Effect estimate	95% CI	Adjusted?
Chakraborti et al., 2003	India	Cross-sectional	64 ^b	<2,500 g	463-1,025	7-459	PPR=8.33 ^c	1.03, 67.14 ^c	No
Chakraborti et al., 2004	India	Cross-sectional	18	<2,500 g	401-1,474	200-400	PPR=0.79 ^c	NE ^d	No
Mukherjee et al., 2005	India	Cross-sectional	83 ^e	<2,500 g	401-1,474	<3	PPR=2.45 ^c	0.61, 9.88 ^c	No
Ahamed et al., 2006	Bangladesh	Cross-sectional	113 ^f	<2,500 g	501-1,200 201-500	0	PPR=3.36 ^c PPR=2.35 ^c	0.70, 15.05 ^c 0.24, 23.47 ^c	No
Kwok et al., 2006	Bangladesh	Cross-sectional	2,006	<2,500 g	1 unit	0-668	OR=0.999	0.997, 1.001	Yes
Huyek et al., 2007	Bangladesh	Prospective	52	BW (g) <2,750 ^g	1 unit	0.14-3.28 ^g 0.14-3.28 ^g 0.19-6.15 ^h	$\beta=-193.5$ OR=2.50 OR=1.20	-369.9, -13.95 0.74, 8.33 0.70, 2.08	Yes
Rahman et al., 2009	Bangladesh	Prospective	1,578	BW (g)	1 unit	6-100 ⁱ	$\beta=-1.68$	-2.90, -0.46	Yes
Myers et al., 2010	China	Cross-sectional	9,890	BW (g)	>100 51-100 21-50	0-20	$\beta=50$ $\beta=20$ $\beta=-10$	20, 80 -10, 60 -30, 10	Yes
Yang et al., 2003	Taiwan	Prospective	18,259	BW (g)	>0-3,590	0	$\beta=-29.05$	-44.55, -13.55	Yes
Xu et al., 2011	China	Cross-sectional	142	BW (g)	1 log unit	0.63-30.45 ^j	$\beta=-354.41$ ^k	-677.53, -31.28 ^k	Yes
Guan et al., 2012	China	Cross-sectional	125	BW (g)	1 unit	0-~25 ^j	$\beta=-20$ ^l	-39.60, -0.40 ^l	Yes
Chou et al., 2012	Taiwan	Prospective	309	<2,500 g	1 unit	0.2-3.9 ^m	OR=1.02	0.78, 1.34	Yes
Shirai et al., 2010	Japan	Prospective	78	BW (g)	1 unit	9.81-1,603 ^m	NE	NE	Yes
Hopenhayn et al., 2003	Chile	Prospective	844	BW (g)	1 unit	Antofagasta = 54.3 ± 33.8 ^{n o} Valparaiso = 5.3 ± 3.3 ^{n o}	$\beta=-26$	-85, 31	Yes
Gelmann et al., 2013	Romania	Cross-sectional	38	<2,500 g	54.4 ± 27.0 ⁿ >9 ^o	1.1 ± 0.1 ⁿ <9 ^o	NE 57% ^p	NE $P=0.019$	No
Vall et al., 2012	Spain	Cross-sectional	76	BW (g)	0.1-31.4 ^q	<0.10 ^q	$\beta=223.8$	$P=0.043$	No

NOTE: Effect estimates with P<0.05 in italics; β , slope of linear regression line; δ , mean difference; NE, no effect.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

a Arsenic concentrations in water unless otherwise noted

b 64 pregnancies in 16 women

c prevalence proportion ratio (PPR) and 95% confidence interval (CI) calculated based on data presented in the paper

d number of events and pregnancies used to calculate prevalence proportions not reported and so we were unable to generate the confidence interval, but authors reported 'no change'

e 83 pregnancies in 24 women

f 113 pregnancies in 40 women

g maternal hair at 1st prenatal visit (µg/g)

h maternal toenails at 1st prenatal visit (µg/g)

i specific gravity adjusted maternal urine

j maternal blood

k among 71 male newborns

l among newborns 32 weeks gestational age or 1,500 grams

m µg/g maternal urine creatinine

n mean ± standard deviation

o µg/L maternal urine

p % difference between groups

q µg/g newborn meconium.

Table 2

Epidemiologic studies evaluating drinking water arsenic exposure and gestational age/preterm delivery.

Authors	Locale	Design	Sample size	Endpoint	Exposed group ($\mu\text{g/L}$) ^a	Reference group ($\mu\text{g/L}$) ^a	Effect estimate	95% CI	Adjusted?
Chakraborti et al., 2003	India	Cross-sectional	64 ^b	<37 weeks gestation	463-1,025	7-459	PPR=3.33 ^c	0.92, 12.11 ^c	No
Chakraborti et al., 2004	India	Cross-sectional	18	<37 weeks gestation	401-1,474	200-400	PPR=1.05 ^c	NE ^d	No
Mukherjee et al., 2005	India	Cross-sectional	83 ^e	<37 weeks gestation	401-1,474	<3	PPR=2.45 ^c	0.61; 9.88 ^c	No
Ahamed et al., 2006	Bangladesh	Cross-sectional	103 ^f	<37 weeks gestation	501-1,200	0	PPR=4.20 ^c	0.51, 34.67 ^c	No
Ahmad et al., 2001	Bangladesh	Cross-Sectional	668 ^g	<37 weeks gestation	>50	<20	PPR=2.54	P=0.018	Yes
Myers et al., 2010	China	Cross-sectional	9,890	<37 weeks gestation	>50	<50	OR=1.02	0.72, 1.44	Yes
Yang et al., 2003	Taiwan	Prospective	18,259	<37 weeks gestation	>0-3,590	0	OR=1.10	0.91, 1.33	Yes
Xu et al., 2011	China	Cross-sectional	142	Gestational age (weeks)	1 log unit	0.63-30.45 ^h	$\beta = -1.51^i$	-2.50, -0.51 ^j	Yes
Vall et al., 2012	Spain	Cross-sectional	72	Gestational age (weeks)	0.1-31.4 ^j	<0.10 ^j	$\beta = 0.1$	P=0.813	No

NOTE: Effect estimates with P<0.05 in italics; β , slope of linear regression line; NE, no effect.

^a Arsenic concentrations in water unless otherwise noted

^b 64 pregnancies in 16 women

^c prevalence proportion ratio (PPR) and 95% confidence interval (CI) calculated based on data presented in the paper

^d number of events and pregnancies used to calculate prevalence proportions not reported and so we were unable to generate the confidence interval

^e 83 pregnancies in 24 women

^f 103 pregnancies in 36 women

^g 668 pregnancies in 192 women

^h maternal blood

ⁱ among 71 male newborns

^j ng/g newborn meconium.

Table 3

Epidemiologic studies of drinking water arsenic exposure and birth size.

Authors	Locale	Design	Sample size	Endpoint (mm)	Exposed group ^a	Reference group ^a	Effect estimate	95% CI	Adjusted?
Rahman et al., 2009	Bangladesh	Prospective	1,578	Head circ. ^b Chest circ. ^b Length ^b	1 unit	6-100 (6-978 for length) ^c	$\beta = -0.05$ $\beta = -0.14$ $\beta = -0.06$	$-0.11, 0.001$ $-0.20, -0.08$ $-0.12, 0.00$	Yes
Guan et al., 2012	China	Cross-sectional	125	Head circ. Chest circ. Length	1 unit	0-~25 ^d 0-~25 ^e 0-~25 ^e	$\beta = -0.6^f$ $\beta = -1.0^f$ $\beta = -1.0^f$	$-1.19, -0.01^f$ $-1.59, -0.41^f$ $-1.78, -0.22^f$	Yes
Chou et al., 2012	Taiwan	Prospective	309	Head circ. <340 Chest circ. <320 Length <450	1 unit	0.2-3.9	OR=6.16 OR=11.69 OR=0.13	0.17, 10.84 0.51, 12.51 0.01, 8.13	Yes
Shirai et al., 2010	Japan	Prospective	78	Head circ. Length	1 unit	9.81-1,603	NE NE	NE NE	Yes
Vall et al., 2012	Spain	Cross-sectional	69 76	Head circ. Length	0.1-31.4 ^g	<0.10 ^g	$\beta = 4$ $\beta = 5$	P=0.196 P=0.282	No

NOTE: Effect estimates with P<0.05 in italics; β , slope of linear regression line; circ., circumference; NE, no effect.

^a Arsenic concentrations in $\mu\text{g/g}$ creatinine maternal urine unless otherwise noted

^b among women with <100 $\mu\text{g/L}$ urine inorganic arsenic

^c specific gravity adjusted maternal urine ($\mu\text{g/L}$)

^d umbilical cord blood ($\mu\text{g/L}$)

^e maternal blood ($\mu\text{g/L}$)

^f among newborns 32 weeks gestational age or 1,500 grams

^g ng/g meconium.