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Consumption of arsenic-contaminated drinking water and anemia among pregnant and non-pregnant women in northwestern Romania

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Abstract

Anemia is a global health problem. To evaluate the impact of low-moderate water arsenic exposure (mostly <10 μg/L) on anemia, we conducted a cross-sectional study of 217 Romanian women. The adjusted prevalences for 'any' anemia (prevalence proportion ratio (PPR)=1.71, 95% CI 0.75-3.88) and pregnancy anemia (PPR=2.87, 95% CI 0.62-13.26) were higher among drinking water arsenic exposed women than among unexposed women. These preliminary data underscore the need for a more definitive study in this area.

Keywords

Arsenic; drinking water; anemia; women; pregnancy

1. Introduction

Anemia is a global problem with negative impacts on human health, including increased risks of maternal and child mortality and adverse effects on cognitive and physical development (Allen, 2000). Despite the high prevalence, particularly in regions that also

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experience groundwater arsenic contamination (WHO, 2008), few epidemiologic studies have investigated the impact of arsenic exposure on anemia. There is even less evidence on the risk of anemia in pregnant women consuming arsenic-contaminated drinking water, particularly in association with low-moderate levels (<50 μg/L) which are found in large regions around the world (Amini et al., 2008). To date, three epidemiologic studies investigated the risk of anemia related to high-level exposure to arsenic via drinking water in arsenic-endemic regions of Bangladesh and West Bengal, India (Heck et al., 2008; Majumdar et al., 2009; Merrill et al., 2012). Only one epidemiologic study, conducted in Chile, focused on anemia in pregnancy and a potential link to moderate level arsenic exposure (Hopenhayn et al., 2006). To address the existing data gap concerning low-moderate drinking water arsenic exposure and anemia, we conducted an exploratory, cross-sectional investigation among women enrolled in a study recently completed in northwestern Romania. This area is recognized for geogenic contamination of underground drinking water, with low to moderate concentrations (Neamtiu et al., 2015).

2. Material and methods

Participants included pregnant women 18-44 years of age and residing in Timis County, Romania recruited between December 2011 and January 2013. Participants (n=297) were initially recruited to a case-control study of drinking water arsenic exposure and pregnancy loss. A detailed description of the recruitment strategy is provided elsewhere (Bloom et al., 2014). Briefly, we enrolled 150 women receiving treatment for incident spontaneous pregnancy loss of 5-20 weeks completed gestation as case participants, and 150 women receiving routine prenatal care for ongoing pregnancies matched to case participants by gestational age (within 1 week) as controls (n=3 participated first as a control and then as a case). The participants completed a physician-administered study questionnaire, including detailed questions concerning demographics, lifestyle factors, and medical, reproductive, residential, and occupational histories. All women provided written informed consent and the study protocol was approved by the Institutional Review Boards of the Emergency County Hospital in Timisoara, Romania and the University at Albany, U.S.

The current study outcome was defined as self-report of having ever received a clinician diagnosis of anemia. We used questionnaire data to further qualify cases as ‘pregnancy anemia’ and ‘non-pregnancy anemia.’ ‘Pregnancy anemia’ was defined as a reported diagnosis during the study pregnancy or within one year of a reported previous pregnancy; all other diagnoses were defined as ‘non-pregnancy anemia.’ To preclude exposure measurement misclassification associated with residential mobility we restricted cases to women who received the anemia diagnosis while residing in their current residence, from which we collected drinking water samples (i.e., n=67 excluded).

We reconstructed drinking water exposure histories based on questionnaire data weighted by arsenic measured in drinking water. The details of water collection and arsenic determination are provided elsewhere (Bloom et al., 2014). In brief, we collected water samples from reported residential sources into arsenic free containers and used a method based on hydride generation-atomic absorption spectrometry for arsenic determination. The limit of detection (LOD) was 0.5 μg/L; to preclude bias we did not impute values below the

LOD (Schisterman et al., 2006). Average arsenic concentration was calculated as the mean of arsenic determinations made in up to two residential drinking water sources. To focus on exposures 'common' in our study population, we excluded n=13 extreme outliers from further analysis; observations more than three interquartile ranges above the 75th%tile of the sample distribution (Kitchens, 1998).

We characterized the overall distributions for participants' demographics, lifestyle factors, and arsenic exposure, and compared them by anemia status. We used Poisson regression models with robust variance estimation to assess prevalence proportion ratios (PPRs) and 95% confidence intervals (CI) for associations between arsenic exposure and anemia, adjusted for cigarette smoking and education as confounders based on the literature. We also considered the influence of self-reported continuous maternal pre-pregnancy body mass index (BMI) and self-report of having ever received a physician diagnosis of kidney disease, by entering them as covariates in the models. We first defined qualitative exposure as 'unexposed' (0 μg/L) and use of residential water sources with 'any' arsenic contamination (>0 μg/L). We next categorized average arsenic exposure in a semi-quantitative scale as 'unexposed' (0 μg/L), 'low exposure' (>0-5 μg/L), and 'moderate exposure' (>5 μg/L), using a cut-off value equal to half the 10 μg/L World Health Organization drinking water standard (WHO, 2011). We also tested the P for trend by entering semi-quantitative arsenic exposure as an ordinal variable into Poisson regression models.

To assess the impact of participants recall and exposure misclassification associated with time since diagnosis, we conducted a sensitivity analysis by restricting the study sample to participants diagnosed with anemia during the study pregnancy. To help guide a future investigation, we determined the sample size required for detecting adjusted associations at P<0.05 with 80% statistical power. All statistical analyses were conducted using SAS v.9.3 (SAS Institute, Cary, NC) and we used PASS 12.0 (NCSS LLC, Kaysville, UT) to determine sample size. Statistical significance was defined as P<0.05 for a two-tailed test.

3. Results

The current analysis included n=217 with an anemia diagnosis while living in the study residence or without history of anemia, and with average drinking water arsenic concentration less than 15 μg/L. A total of 25 women reported a history of clinician-diagnosed anemia while residing in the study household, 192 did not (Table 1). Overall, more women with a history co anemia lacked a high school degree, never smoked cigarettes, and had a history of kidney disease than women without anemia, although the differences were not statistically significant. Women with and without anemia had similar BMI and similar duration residing at the study address. Compared to women without anemia, women with anemia had higher drinking water arsenic concentrations (median=1.46 vs. 0.10 μg/L; P=0.080). The concentration was particularly high in 10 women with pregnancy anemia (median=3.34 μg/L).

Table 2 presents unadjusted and multivariable-adjusted regression results. The effect estimate for 'any' anemia suggested a near doubling in prevalence associated with qualitative arsenic exposure (i.e., >0 μg/L vs. 0 μg/L), adjusted for education and cigarette

smoking (PPR=1.71, 95% CI 0.75-3.88). The suggested effect was even stronger for pregnancy anemia, in which arsenic-exposed women had an almost three-fold higher confounder-adjusted prevalence than unexposed women, although the confidence interval was wide (PPR=2.87, 95% CI 0.62-13.26).

In contrast, the effect estimate for non-pregnancy anemia was closer to the null hypothesis. Considering arsenic exposure as a semi-quantitative variable, confounder-adjusted prevalences were 1.81 (95% CI 0.77-4.26) and 3.44 (95% CI 0.74-16.08) fold higher for any anemia and pregnancy anemia, respectively, among women exposed to >0-5 μg/L arsenic relative to 0 μg/L. The confounder-adjusted effect estimates were lower for women exposed to >5 μg/L arsenic relative to 0 μg/L, although these were based on very few exposed cases. The unadjusted effects were similar and somewhat stronger than the confounder-adjusted estimates.

The effect estimates were comparable although less precise when we included BMI as a covariate in regression models (data not shown) and when we included self-reported history of kidney disease as a covariate in regression models (Table 2). Also, results were similar when we restricted the analysis to n=6 cases of pregnancy anemia diagnosed within one year of study enrollment (data not shown). Our analysis further indicated the requirement for n=587 and n=246 women to detect PPR=1.71 for any anemia and PPR=2.87 for pregnancy anemia, at $P<0.05$ with 80% statistical power.

4. Discussion

We found that women with exposure to low-moderate levels of arsenic via residential drinking water were approximately 2-3 times more likely to report a previous diagnosis of anemia than unexposed women. Effects were stronger for pregnancy anemia, particularly for women exposed to >0-5 μg/L drinking water arsenic, but confidence intervals were wide due to a limited number of cases. Our study appears to be the first report to suggest a higher prevalence of pregnancy anemia among women with low-moderate level drinking water arsenic exposure.

Only a handful of epidemiologic studies previously investigated the link between arsenic exposure and anemia in women and reported results similar to ours. The investigators of a cohort study in Chile (Hopenhayn et al., 2006) found that women exposed to 33-53 μg/L arsenic in drinking water had higher anemia rates, compared to an unexposed group. A cross-sectional study in Bangladesh (Heck et al., 2008), where a large population consumes highly contaminated drinking water, reported lower hemoglobin levels in association with high arsenic exposure, although another cross-sectional study (Merrill et al., 2012) found no association between anemia and arsenic exposure. A large cross-sectional study conducted in an arsenic-endemic region of West Bengal, India, reported an elevated odds ratio of anemia (3.85, 95% CI 2.6-5.5) in women exposed to >800 μg/L arsenic in drinking water relative to women exposed to <50 μg/L (Majumdar et al., 2009).

The biologic mechanisms involved in drinking water arsenic-induced anemia are largely unknown, but several experimental animal studies and studies of human hematological indicators provide clues. It was observed that arsenic induces oxidative damage to human

erythrocytes producing anemia-related changes including alterations in shape, deformability, agreeability, and osmotic fragility (Bollini et al., 2010). Studies in human populations highly exposed to arsenic in drinking water also reported structural and functional hemoglobin and erythrocyte alterations due to oxidative stress, and as a result, diminished oxygen binding affinity (Mondal et al., 2012) and premature cell death (Biswas et al., 2008), alterations likely to lead to clinical anemia.

Our study is inherently limited by its secondary, exploratory nature, cross-sectional design, and small sample size. We used retrospective self-report of anemia diagnosis coupled to current residential drinking water arsenic levels; we are therefore unable to establish a temporal sequence in which exposure preceded outcome. Consequently, our results can be interpreted only as hypothesis generating. Our use of self-reported anemia diagnoses and exclusion of women not diagnosed while residing at the study address are also likely to have misclassified some women, and would have benefitted from clinical confirmation, which was unfortunately unavailable. However, we have no reason to anticipate that anemia misclassification would have varied by drinking water arsenic exposure and thus any bias is likely to have been towards the null hypothesis. Further, we found similar results in sensitivity analyses restricted to cases diagnosed for the study pregnancy. The limited number of study participants decreased the statistical power and led to imprecise effect estimates. However, our post-hoc power analysis suggested that a modest increase in sample size to n=246 will provide statistical power sufficient to detect an association between pregnancy anemia and drinking water arsenic exposure.

We used an indirect exposure measure, employing study questionnaire data weighted by environmental sampling, which is vulnerable to measurement misclassification error. Still, our questionnaire was previously validated and administered face-to-face by a physician. Furthermore, our study hypothesis was unknown to participants. Groundwater arsenic levels tend to be stable over limited time intervals, and we included only women who received an anemia diagnosis while residing at the study address, for who we could therefore collect water samples representing a relevant exposure interval. Non-cases and cases had a similar median duration of time residing at the study address (8 years and 9 years, respectively) and so we expect that any exposure misclassification would have been similar between the two groups and bias towards the null hypothesis. We also did not account for potential arsenic exposures in the workplace or from contaminated foods, introducing an additional limitation into our exposure assessment strategy. However, no women reported employment with potential occupational exposure, and rice consumption, an important source of arsenic exposure in some populations, is not common in this region of Romania (Neamtiu et al, 2015). We used education level and BMI as proxies for socioeconomic and nutrition status in general, but were unable to evaluate the presence of specific concurrent micronutrient deficiencies, and therefore a potential confounding effect from these factors cannot be excluded. We did not adjust for pregnancy loss, as there was no overall association with arsenic exposure in our earlier work (Bloom et al., 2014).

5. Conclusion

To our knowledge, this study is the first to report a higher prevalence of anemia in pregnancy among women with exposure to arsenic in residential drinking water <5 μg/L, a value that is 1/2 of the current WHO drinking water guideline. Several factors limit our study results, stemming primarily from the secondary and exploratory natures. However, to better understand the impact of these results, particularly in pregnant women, a longitudinal study is needed with sufficient sample size to characterize potentially modest effects and including a comprehensive exposure assessment integrating personal biomarkers.

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References

Allen LH. Anemia and iron deficiency: effects on pregnancy outcome. Am J Clin Nutr. 2000; 71:1280S–1284S. [PubMed: 10799402]

Amini M, Abbaspour KC, Berg M, Winkel L, Hug SJ, Hoehn E, Yang H, Johnson CA. Statistical modeling of gobal geogenic arsenic contamination in groundwater. Environ Sci Technol. 2008; 42:3669–3675. [PubMed: 18546706]

Biswas D, Banerjee M, Sen G, Das JK, Banerjee A, Sau TJ, Pandit S, Giri AK, Biswas T. Mechanism of erythrocyte death in human population exposed to arsenic through drinking water. Toxicol Appl Pharmacol. 2008; 230:57–66. [PubMed: 18377941]

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

Bollini A, Huarte M, Hernandez G, Bazzoni G, Piehl L, Mengarelli G, Rubin de Celis E, Rasia M. Arsenic intoxication, a hemorheologic view. Clin Hemorheol Microcirc. 2010; 44:3–17. [PubMed: 20134088]

Heck JE, Chen Y, Grann VR, Slavkovich V, Parvez F, Ahsan H. Arsenic exposure and anemia in Bangladesh: A population-based study. J Occup Environ Med. 2008; 50:80–87. [PubMed: 18188085]

Hopenhayn C, Bush HM, Bingcang A, Hertz-Picciotto I. Association between arsenic exposure from drinking water and anemia during pregnancy. J Occup Environ Med. 2006; 48:635–643. [PubMed: 16766928]

Kitchens, LJ. Exploring statistics: a modern introduction to data analysis and inference. Duxbury Press; Pacific Grove, CA: 1998.

Majumdar KK, Mazumder DNG, Ghose N, Ghose A, Lahiri S. Systemic manifestations in chronic arsenic toxicity in absence of skin lesions in West Bengal. Indian J Med Res. 2009; 129:75–82. [PubMed: 19287062]

Merrill RD, Shamim AA, Ali H, Labrique AB, Schulze K, Christian P, West KP Jr. High prevalence of anemia with lack of iron deficiency among women in rural Bangladesh: a role for thalassemia and iron in groundwater. Asia Pac J Clin Nutr. 2012; 21:416–424. [PubMed: 22705433]

Mondal B, Chatterjee D, Bhattacharyya M. Structure-function alteration of hemoglobin in arsenicosis patients: a probable pathway to exert toxicity. J Appl Toxicol. 2012; 32:581–589. [PubMed: 21394736]

Neamtiu I, Bloom MS, Gati G, Goessler W, Surdu S, Pop C, Braeuer S, Fitzgerald EF, Baciu C, Al-Abed S, Lupsa IR, Anastasiu D, Gurzau E. Pregnant women in Timis County, Romania are exposed primarily to low-level (<10(μg/l) arsenic through residential drinking water consumption. Int J Hyg Environ Health. 2015 In press.

Schisterman EF, Vexler A, Whitcomb BW, Liu A. The limitations due to exposure detection limits for regression models. Am J Epidemiol. 2006; 163:374–383. [PubMed: 16394206]

WHO. Worldwide prevalence of anaemia 1993-1995: WHO global database on anaemia. World Health Organization (WHO); Geneva, Switzerland: 2008.

WHO. Arsenic in drinking-water Background document for development of WHO guidelines for drinking-water quality. World Health Organization (WHO); Geneva, Switzerland: 2011.

Highlights

- We investigated 25 women with anemia and 192 without anemia residing in Romania.
- Pregnancy/non-pregnancy anemia was ascertained by face-to-face interview.
- Exposure was estimated using drinking water arsenic levels and consumption data.
- Higher prevalence of anemia suggested for pregnant women with arsenic exposure.

Table 1

Characteristics of study participants, by anemia status.

Characteristics Education, n (%)	Anemia (n=25)	No Anemia (n=192)	P-value
Less than high school	7 (28.0)	41 (21.4)	0.752
High school	8 (32.0)	66 (34.4)	
University	10 (40.0)	85 (44.3)	
Cigarette smoking, n (%)			
Never	19 (76.0)	129 (67.2)	0.374
Ever	6 (24.0)	63 (32.8)	
Kidney disease, n (%)			
No	20 (83.3)	177 (92.2)	0.149
Yes	4 (16.7)	15 (7.8)	
Maternal body max index, median (25^{th}, 75^{th} %tile)			
kg/m^2	22.1 (20.4, 23.0)	22.0 (20.1, 24.6)	0.808
Duration of residence at study address, median (25^{th}, 75^{th} %tile)			
Years	9 (3, 18)	8 (3, 21)	0.383
Age at diagnosis, median (25^{th}, 75^{th} %tile)			
Years	23 (20, 26)	-	-
Time since diagnosis, median (25^{th}, 75^{th} %tile)			
Years	6 (0, 12)	-	-
Average arsenic concentration, median (25^{th}, 75^{th} %tile)			
µg/L	1.46 (0, 3.61)	0.10 (0, 2.39)	0.080

NOTE: Mann-Whitney U and χ^2 tests used to compare continuous and categorical variables, respectively.

Table 2

Unadjusted and multivariable adjusted associations between residential drinking water arsenic exposure and anemia.

Average arsenic concentration (μg/L)	Anemia	Unadjusted estimates		Multivariable model 1 [a, b]		Multivariable model 2 [c]	
	(Yes/No)	PPR	95% CI	PPR	95% CI	PPR	95% CI
Any anemia							
0 μg/L	8/92	1.00	Referent	1.00	Referent	1.00	Referent
>0 μg/L	17/100	1.82	0.82-4.03	1.71	0.75-3.88	1.62	0.70-3.76
>0-5 μg/L	13/72	1.91	0.83-4.39	1.81	0.77-4.26	1.71	0.71-4.15
>5 μg/L	4/28	1.56	0.50-4.85	1.41	0.44-4.47	1.39	0.46-4.22
P for trend	-	0.214	-	0.328	-	0.368	-
Pregnancy anemia							
0 μg/L	2/92	1.00	Referent	1.00	Referent	1.00	Referent
>0 μg/L	8/100	3.48	0.76-15.99	2.87	0.62-13.26	2.44	0.50-11.87
>0-5 μg/L	7/72	4.16	0.89-19.48	3.44	0.74-16.08	2.86	0.57-14.42
>5 μg/L	1/28	1.62	0.15-17.23	1.25	0.12-12.94	1.26	0.13-12.04
P for trend	-	0.174	-	0.402	-	0.478	-
Non-pregnancy anemia							
0 μg/L	6/92	1.00	Referent	1.00	Referent	1.00	Referent
>0 μg/L	9/100	1.35	0.50-3.65	1.31	0.47-3.65	1.34	0.48-3.75
>0-5 μg/L	6/72	1.26	0.42-3.74	1.26	0.41-3.84	1.29	0.42-3.97
>5 μg/L	3/28	1.58	0.42-5.95	1.44	0.38-5.50	1.45	0.38-5.43
P for trend	-	0.489	-	0.568	-	0.550	-

[a] Adjusted for education (less than high school, high school, university degree) and cigarette smoking (never, ever).

[b] Additional adjustment for continuous maternal pre-pregnancy body mass index did not meaningfully impact the effect estimates.

[c] Adjusted for education (less than high school, high school, university degree), cigarette smoking (never, ever), and self-reported history of physician diagnosed kidney disease (no, yes).

CI, confidence interval; PPR, prevalence proportion ratio.