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Original Contribution

Pregnancy Outcomes, Infant Mortality, and Arsenic in Drinking Water in West Bengal, India

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Between 2001 and 2003, the authors studied pregnancy outcomes and infant mortality among 202 married women in West Bengal, India. Reproductive histories were ascertained using structured interviews. Arsenic exposure during each pregnancy, including all water sources used, was assessed; this involved measurements from 409 wells. Odds ratios for spontaneous abortion, stillbirth, neonatal mortality, and infant mortality were estimated with logistic regression based on the method of generalized estimating equations. Exposure to high concentrations of arsenic ($\geq$200 μg/liter) during pregnancy was associated with a sixfold increased risk of stillbirth after adjustment for potential confounders (odds ratio (OR) = 6.07, 95% confidence interval (CI): 1.54, 24.0; $p = 0.01$). Arsenic-related skin lesions were found in 12 women who had a substantially increased risk of stillbirth (OR = 13.1, 95% CI: 3.17, 54.0; $p = 0.002$). The odds ratio for neonatal death was 2.81 (95% CI: 0.73, 10.8). No association was found between arsenic exposure and spontaneous abortion (OR = 1.01, 95% CI: 0.38, 2.70) or overall infant mortality (OR = 1.33, 95% CI: 0.43, 4.04). This study adds to the limited evidence that exposure to high concentrations of arsenic during pregnancy increases the risk of stillbirth. However, there was no indication of the increased rates of spontaneous abortion and overall infant mortality that have been reported in some studies.

arsenic; India; infant mortality; pregnancy outcomes; stillbirth; water pollutants

Abbreviations: CI, confidence interval; GEE, generalized estimating equations; OR, odds ratio.

Worldwide, millions of people are currently drinking groundwater that contains inorganic arsenic in concentrations above 10 μg/liter, the US Environmental Protection Agency maximum contaminant level and the standard recommended by the World Health Organization (1–4). South Asia is particularly affected by naturally occurring arsenic in well water, and exposures to concentrations above 100 μg/liter are widespread in arsenic-affected areas. West Bengal, India, and neighboring Bangladesh constitute the most extensively contaminated region in the world (5–8).

Health effects associated with long-term consumption of arsenic-contaminated water include cancers of the bladder, kidney, lung, and skin (9–12), as well as chronic nonmalignant conditions, the most frequently observed being characteristic skin lesions (13, 14). Although recently more attention has been focused on the reproductive health effects of arsenic, the findings are still inconclusive (15–20). A few investigations have related arsenic concentrations above 50 μg/liter in drinking water to increased risks of spontaneous abortion, stillbirth, preterm delivery, and infant mortality

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(15–19). In Taiwan and Chile, average birth weight was lower in regions with increased arsenic in drinking water (18, 21). Recently, one study from Bangladesh suggested that increases in spontaneous abortion, stillbirth, and neonatal death rates were associated with levels of arsenic in drinking water greater than 50 μg/liter (22).

We conducted a study of the relation of arsenic exposure during pregnancy to pregnancy outcome and infant mortality among 202 married women in West Bengal, India. To our knowledge, this was the first pregnancy-outcome study of drinking-water arsenic considering spontaneous abortion, stillbirth, and infant mortality that employed detailed interviews concerning all drinking-water sources used during each pregnancy and had water measurements from the majority of them.

MATERIALS AND METHODS

Study design and selection of participants

This study was carried out between 2001 and 2003. Women were selected on the basis of a 1995–1996 cross-sectional survey of 7,683 people conducted in 21 villages in West Bengal, India (South 24-Parganas district) (23). The study was cross-sectional in design, but past exposure data were incorporated into the selection of subjects in order to ensure contrasts in arsenic exposure during women's pregnancies.

The details of participant selection are somewhat complex, because the study was conducted in parallel with a study of chronic respiratory disease. In the respiratory disease study, groups of ''high-exposure'' and ''low-exposure'' participants were identified from the cross-sectional survey conducted in 1995–1996. In the respiratory disease study, all participants from the 1995–1996 survey who had drinking-water arsenic concentrations greater than 400 μg/liter and also showed signs of arsenic-caused skin lesions were selected for the ''high-exposure'' group. Participants placed in the ''low-exposure'' group in the respiratory disease study had drinking water containing less than 50 μg/liter of arsenic and were not found to have arsenic-caused skin lesions. For each ''high-exposure'' participant, a ''low-exposure'' participant was randomly selected, matched by age (within 5 years) and gender.

For the pregnancy outcome study, we selected participants from the chronic respiratory disease study to obtain high- and low-exposure groups in the following manner. If a participant in the respiratory disease study was a married woman in the age range 20–40 years, she was invited to participate in the pregnancy study. If not, married women in the same household or close female neighbors who had drunk the same water in 1995–1996 and were currently aged 20–40 years were invited to participate. In general, the pregnancy study participants were daughters-in-law, wives, or (occasionally) close neighbors of the respiratory disease study participants who were using the same tube wells for drinking water.

We identified and approached 205 eligible women matching the selection criteria. Informed consent was obtained from all subjects. The study was approved by the institutional review boards of the Institute of Postgraduate Medical Research and Education (Kolkata, India) and the University of California, Berkeley (Berkeley, California).

Interviews

In-depth face-to-face structured interviews were conducted in the participants' homes by a female physician who was blind to the water concentrations of arsenic in tube wells used by participants during their pregnancies. We assessed reproductive histories in detail, including each pregnancy and its outcome, identifying spontaneous abortions, therapeutic abortions, stillbirths, livebirths, and neonatal and infant deaths. The interview also included probing with different wording and the use of contextual questions to trigger participants' memories; for example, participants were asked about ''miscarriages'' and missed menstrual periods and the duration of time intervals without menstrual periods. The correct timing of events was assessed using milestones such as the assassination of former Prime Minister Indira Gandhi. Information from birth certificates, if available, was recorded. Residential and job history, lifetime smoking history, and demographic variables, including education and type of housing material (mud, mixed, or concrete), were assessed. Dietary intake was also assessed but is not discussed in this paper.

Physical examination for skin lesions

Following the assessment of reproductive history, a careful examination of the skin was conducted by a trained field physician in a well-lit area outdoors under natural light. Visible or palpable dermal lesions were documented, with the field physician noting the location and appearance and whether the patterns were characteristic of arsenic-induced skin toxicity. Lesions were classified by the field physician into one of four categories: definitely, probably, possibly, or not related to arsenic.

Exposure assessment

The field team collected water samples from all functioning tube wells that had been used by participants for at least 6 months since their first pregnancy. Some wells had been closed because of damaged filters or other mechanical problems or because they were known to have arsenic contamination. When available, such measurements were incorporated into data analysis. For many of these closed tube wells, we located past arsenic concentration measurements obtained before the wells were closed ($n = 48$). We collected samples from 361 functioning tube wells in the 21 villages in the study region. Private tube wells were sometimes used by just one household, whereas government tube wells were used by multiple families. Water samples were stored in a cooler containing an ice block and transported to the laboratory in Kolkata on the same day. The water samples were then kept frozen at –20°C until they were analyzed. Total water arsenic level was measured by flow injection analysis using atomic fluorescence detection with in-line photooxidation and continuous hydride generation (24). The lower limit of quantification was less than

1 μg/liter. We provided the results of drinking-water arsenic measurements to the women and their families.

Statistical analyses

Women's histories of arsenic exposure since their first pregnancy were constructed on the basis of information about tube well usage at each residence and work site, if applicable, and the results of the arsenic measurements. A few participants reported that they had, at times, used surface pond water for drinking. Because concentrations of arsenic in pond test samples were very low or nondetectable (ranging from less than 0.2 μg/liter to 4.2 μg/liter), we used zero as the concentration for all pond water sources. Annual average water arsenic concentrations were first calculated for participants for each calendar year on the basis of measured concentrations in each tube well used in that year and the fraction of their drinking water participants had obtained from the respective source in that year (e.g., 75 percent from one tube well and 25 percent from another tube well). Arsenic exposure during each pregnancy was then calculated using the annual averages, weighting them for the time fraction of each pregnancy period that fell into a particular calendar year. For livebirths, average arsenic levels were calculated likewise for the first 12 months of life or until the month of death if the child died within this time period. Pregnancies and first-year-of-life periods with no exposure information were excluded from further analyses. The arsenic value was unknown for fractions of 11 prenatal time periods and two first-year-of-life time periods, so for those time periods, the known average arsenic value of the remaining time period was applied.

Reproductive and other characteristics of the study population were first assessed in univariate analyses. The associations between prenatal arsenic exposure (in categories: 0–49 μg/liter, 50–199 μg/liter, and $\geq$200 μg/liter) and adverse pregnancy outcomes (spontaneous abortion and stillbirth), neonatal death (death occurring in the first month after birth), and infant death (death occurring in the first 12 months of life) were assessed in stratified analyses using chi-squared tests. The stratification of arsenic at 50 μg/liter was chosen because this was the drinking water standard in India, and the stratification at 200 μg/liter was chosen to achieve sufficient numbers in the first stratum above the drinking water standard. We additionally assessed infant mortality in relation to drinking-water arsenic concentration during the first 12 months of life (or until the month of the child's death). We also compared the frequencies of adverse outcomes according to whether or not the mother had arsenic-caused skin lesions. The denominator used for calculating the rate of spontaneous abortion was all pregnancies; that used for calculation of stillbirths was all livebirths plus stillbirths; and that used for calculation of neonatal death and infant death was all livebirths.

For further evaluation of the association between adverse pregnancy outcomes, infant mortality, and prenatal and first-year-of-life (for infant mortality) arsenic exposure, we used logistic regression models based on the method of generalized estimating equations (GEE) to calculate crude and adjusted odds ratios with 95 percent confidence intervals, accounting for multiple pregnancies in the same subject (25). Pregnancies and first-year-of-life periods for which there was no exposure information were excluded from the regression analysis. Indicator variables were used for the different arsenic exposure categories. After univariate analyses, all potentially confounding factors for which we had data were included in the full multivariate models. Potentially confounding factors were known risk factors for the outcomes or factors, such as socioeconomic status, that might reasonably be assumed to be related to the outcomes. The full models included mother's age at the child's birth, body mass index (weight (kg)/height $(m)^2$), maternal education, education of the head of the household (no formal education, primary school, secondary school or higher), and type of housing material (mud, brick, mixed materials) as a measure of socioeconomic status. We also evaluated smoking status and occupational history. Smoking was not included in the model, because only one woman reported ever smoking; occupational history was not included either, because only one woman reported ever having had a job other than homemaker.

There were only 12 women with skin lesions, so crude GEE-based odds ratios were estimated for their adverse outcomes, and Fisher's exact test was used to assess significance. All p values shown are two-sided. All data analyses were carried out using the SAS statistical program (version 8.0e; SAS Institute, Inc., Cary, North Carolina).

RESULTS

Of the 205 women who were identified and approached, 203 (99 percent) agreed to participate in the pregnancy study. One woman was excluded from the analyses of reproductive outcomes because she reported having had no pregnancies. General and reproductive characteristics of the study population are summarized in table 1. Approximately 32 percent of the women reported having one or two pregnancies; more than half of the women reported having three or four pregnancies; and 16 percent reported having five or more pregnancies. Complete information about arsenic concentrations in the drinking water used during pregnancy was obtained for 633 of the 660 pregnancies (95.9 percent). For an additional 11 of the 660 pregnancies, arsenic values were available for part of the pregnancy period. Similarly, complete information on arsenic exposure was obtained for the first year of life for 522 of 540 livebirths (96.7 percent), with partial information being available for two additional livebirths. The average prenatal concentration of arsenic in drinking water was 101.7 μg/liter, with 18.2 percent of pregnant women being exposed to levels greater than or equal to 200 μg/liter (table 2).

In the GEE-based logistic regression models, increased concentrations of arsenic in drinking water during pregnancy were related to an almost fivefold increase in risk of stillbirth at the highest exposure level of $\geq$200 μg/liter in comparison with levels below 50 μg/liter. Further adjustment for socioeconomic variables, mother's age at child's birth, and body mass index led to an adjusted odds ratio for stillbirth of 6.07 (95 percent confidence interval (CI): 1.54,

TABLE 1. Demographic and reproductive baseline characteristics of participants in a study of drinking-water arsenic and pregnancy outcomes ($n = 202$), West Bengal, India, 2001–2003

Characteristic	No.	%	Rate per 1,000
Age (years) at time of interview			
Median	31		
Range	20–40		
Age (years) at marriage			
≤16	106	52.5	
>16	96	47.5	
Maternal education			
No formal education	73	36.1	
Primary school	46	22.8	
Secondary school or higher	83	41.1	
Education of the household head			
No formal education	35	17.3	
Primary school	68	33.7	
Secondary school or higher	99	49.0	
Type of housing			
Mud	70	34.7	
Mixed materials	76	37.6	
Brick	56	27.7	
Ever smoking	1	0.5	
No. of pregnancies per woman			
1–2	64	31.7	
3–4	105	52.0	
≥5	33	16.3	
Body mass index*			
<18.4	50	25	
≥18.4, <20.6	51	25	
≥20.6, <23.1	49	24	
≥23.1	52	26	
Pregnancy outcome			
Spontaneous abortion	30		45.5†
Therapeutic abortion	74		112.1†
Stillbirth	18		32.3‡
Neonatal death	12		22.2§
Infant death	21		38.9§

* Weight (kg)/height (m)^2.
† Denominator: all pregnancies ($n = 660$).
‡ Denominator: all livebirths plus stillbirths ($n = 558$).
§ Denominator: all livebirths ($n = 540$).

24.0; $p = 0.01$). No increase in risk of stillbirth was seen at levels between 50 μg/liter and 199 μg/liter (adjusted odds ratio (OR) = 0.80, 95 percent CI: 0.10, 6.66). The risk of neonatal death was increased more than twofold at exposure levels of ≥200 μg/liter compared with levels below 50 μg/liter after adjustment for potential confounders, but the confidence interval was wide and included unity (OR = 2.81, 95 percent CI: 0.73, 10.8). An association between arsenic and spontaneous abortion was not found (adjusted OR = 1.01, 95 percent CI: 0.38, 2.70). No increase in overall infant mortality was seen with prenatal arsenic exposure (table 3) or exposure during the first year of life (data not shown). Disentangling prenatal arsenic exposure and arsenic exposure during the first 12 months of life was difficult, since water sources generally did not change directly after birth.

Separately, we analyzed the associations between mothers' arsenic-related skin lesions and adverse outcomes (table 4). Using the GEE-based regression model, the risk of stillbirth was substantially elevated among all pregnancies in mothers who had arsenic-related skin lesions (OR = 14.4, 95 percent CI: 3.59, 58.1; $p < 0.001$). Removing multiple stillbirths in the same woman by considering the number of women who had ever had a stillbirth similarly demonstrated increased risks (OR = 13.1, 95 percent CI: 3.17, 54.0; $p = 0.002$). Further adjustment could not be carried out because of the small numbers of women with skin lesions. No effect on spontaneous abortion was seen, and no neonatal deaths occurred among women with skin lesions. Furthermore, the presence of skin lesions was not associated with overall infant mortality when we compared numbers of deaths among all livebirths in mothers with (2/43) and without (19/497) skin lesions (OR = 1.23, 95 percent CI: 0.20, 7.62). Both recorded deaths of infants of mothers with skin lesions occurred during the postneonatal period. Considering only this period, an increase in risk was seen (2/43 vs. 7/497; OR = 3.42, 95 percent CI: 0.5, 23.0), but the confidence interval was very wide.

DISCUSSION

We investigated the association of pregnancy outcomes and infant mortality with arsenic exposure during pregnancy and during the 12 months after birth in a highly arsenic-affected area in West Bengal, India. We found a sixfold increase in risk of stillbirth at high arsenic levels of ≥200 μg/liter, after adjusting for socioeconomic variables and other potential confounders. Women with arsenic-related skin lesions had a 13 times' higher risk of ever having a stillbirth than women without skin lesions, although the number of women was small ($n = 12$). Weaker effects were seen for neonatal death, while no association with arsenic concentrations was found for spontaneous abortion or overall infant mortality prenatally or during the 12 months after birth.

Only a few investigators have considered pregnancy outcomes and infant death in relation to arsenic levels in drinking water (15–17, 19, 22), and so far none of these studies have individually assessed arsenic concentrations in all water sources used during each pregnancy in relation to spontaneous abortion, stillbirth, and infant mortality. Recently, a study conducted in Bangladesh showed an increased risk of stillbirth for women with current arsenic levels greater than 100 μg/liter, although the risk estimates (OR = 2.9, 95 percent CI: 1.5, 5.9) were smaller than those in our study. The authors further reported effects for spontaneous abortion, which we did not see in our study in West Bengal (OR = 2.5, 95 percent CI: 1.5, 4.4) (22). No information

TABLE 2. Exposure to arsenic in drinking water during pregnancy and the child's first year of life and prevalence of women's arsenic-related skin lesions, West Bengal, India, 2001–2003

Exposure measure	Mean or no.	%	Range
Mean arsenic concentration* (μg/liter)			
Prenatal†	101.7 (9.2)‡		<1–2,536
First year of life§	94.2 (9.4)		<1–2,480
Prenatal arsenic concentration (μg/liter)			
0–49	470	73.0	
50–99	28	4.3	
100–199	29	4.5	
200–299	26	4.0	
300–399	21	3.3	
400–499	41	6.4	
≥500	29	4.5	
Women's arsenic-related skin lesions ($n = 202$)			
"Probable" or "definite"	8	4.0	
"Possible"	4	2.0	

* Information on drinking-water arsenic levels was available for 644 of 660 pregnancies and for 524 of 540 children in the first year of life. Pregnancies and first-year-of-life time periods with no available information on arsenic exposure were excluded.

† On the basis of all water sources used for at least 6 months, a yearly weighted average arsenic exposure value was calculated for each woman during each pregnancy time period.

‡ Numbers in parentheses, standard error.

§ To calculate exposure in the first year of life for all livebirths, we used women's exposure during that time period, assuming that their children would be using the same water source.

on arsenic exposure during pregnancy was available, and high exposure levels of ≥200 μg/liter were not considered separately in that study. One earlier cross-sectional study from Bangladesh compared rates of spontaneous abortion, stillbirth, and preterm delivery between 96 women in one village who were exposed to more than 100 μg/liter of arsenic with rates among 96 women in another village who were exposed to less than 20 μg/liter, and found that rates were 2–3 times higher among exposed women (15). Both Bangladeshi studies reported a relation to overall duration of women's exposure without taking into account exposure during the actual time period of their pregnancies (15, 22). Neonatal death risks were investigated only in the recent study by Milton et al. (22), who found risks similar to those observed in our study. In an ecologic study carried out in Chile, stillbirths (rate ratio = 1.7, 95 percent CI: 1.5, 1.9) and neonatal and postneonatal infant mortality were found to be increased in the high-arsenic-exposure city of Antofagasta as compared with the low-exposure city of Valparaiso (16).

In rural West Bengal, no medical records on adverse pregnancy outcomes and infant deaths are available. Therefore, self-reported reproductive histories are the only source of information. The reliability of retrospectively assessed reproductive histories depends on the completeness of mothers' reports and the accuracy of their recall and reporting of dates. Women in rural West Bengal do not necessarily have accurate information on the timing of past events in relation to calendar years, but other important events are recalled accurately. Our questionnaire-based interview involved the use of salient events as milestones, such as the death of Indira Gandhi, which is a significant date for all Indians and can be used as a memory anchor as well as for determining the timing of events.

In contrast to wells in Bangladesh, wells in West Bengal have not been color-marked (red) for high arsenic exposure. The women had little information about their drinking-water arsenic exposure currently or earlier in life; therefore, self-reports are highly unlikely to have been differentially related to exposure in our study. We assessed detailed exposure histories of women considering all water sources used for at least 6 months since their first pregnancy, allowing the determination of exposure levels during the months of each pregnancy. If differential recall bias had been operating, overreporting of all considered adverse pregnancy outcomes would have occurred. Spontaneous abortions are much more susceptible to recall bias than discrete events known to the whole family and neighbors, such as a stillbirth. However, we did not find an association between spontaneous abortion and arsenic, which further supports the notion that differential recall was not operating and cannot account for the large effect estimate we found for stillbirth.

In an earlier study from Argentina, Concha et al. (26) reported that breastfeeding protected infants from high levels of arsenic in drinking water. We found no difference in risk of infant mortality between first-year-of-life arsenic exposure and prenatal arsenic exposure. Unfortunately, we did not have adequate data on breastfeeding with which to assess breastfeeding in this analysis.

TABLE 3. Odds ratios for adverse pregnancy outcomes and neonatal and infant mortality in relation to arsenic exposure during pregnancy, West Bengal, India, 2001–2003

Outcome and arsenic level (μg/liter)	No.		Unadjusted OR*,†	95% CI*	Adjusted‡ OR†	95% CI
	Yes	No				
Spontaneous abortion ($n = 644$§)						
0–49	21	449	1		1	
50–199	2	55	0.78	0.21, 2.83	0.91	0.25, 3.34
≥200	5	112	0.95	0.36, 2.50	1.01	0.38, 2.70
Stillbirth ($n = 545$¶)						
0–49	8	384	1		1	
50–199	1	51	0.94	0.11, 8.07	0.80	0.10, 6.66
≥200	9	92	4.70	1.21, 18.2	6.07	1.54, 24.0
Neonatal death# ($n = 527$**)						
0–49	5	379	1		1	
50–199	1	50	1.52	0.17, 13.5	1.21	0.09, 15.4
≥200	4	88	3.45	0.78, 15.1	2.81	0.73, 10.8
Infant mortality†† ($n = 527$**)						
0–49	13	371	1		1	
50–199	2	49	1.16	0.25, 5.54	0.82	0.13, 5.25
≥200	4	88	1.30	0.36, 4.61	1.33	0.43, 4.04

* OR, odds ratio; CI, confidence interval.

† Logistic regression analysis based on the method of generalized estimating equations.

‡ Adjusted for the following variables: mother's age at birth (in 5-year categories), mother's body mass index (in quartiles), maternal education (no formal education, primary school, secondary school or higher), education of the household head (no formal education or primary school vs. secondary school or higher) (except for neonatal death), and type of housing material (mud, mixed, brick).

§ All pregnancies.

¶ All births (livebirths plus stillbirths).

Neonatal death was defined as death occurring in the first month after birth.

** All livebirths.

†† Infant mortality was defined as death occurring in the first 12 months of life.

TABLE 4. Unadjusted* odds ratios for spontaneous abortion and stillbirth in relation to the mother's skin lesion status†, West Bengal, India, 2001–2003

	Spontaneous abortion‡				Stillbirth§			
	No	Yes	OR¶	95% CI¶	No	Yes	OR	95% CI
Pregnancies#			1.19	0.33, 4.30			14.4	3.59, 58.1
No skin lesions (no.)	576	27			497	8		
Skin lesions (no.)	54	3			43	10		
Fisher's exact test *p* value			0.74				<0.001	
Mothers**			1.38	0.29, 6.70			13.1	3.17, 54.0
No skin lesions (no.)	166	24			183	7		
Skin lesions (no.)	10	2			8	4		
Fisher's exact test *p* value			0.66				0.002	

* Because of low numbers of subjects in the different strata, adjusted odds ratios were not calculated.

† Definition of maternal skin lesions: a diagnosis of "definite," "probable," or "possible" arsenic-induced skin lesions made by a trained field physician.

‡ The total number of pregnancies ($n = 660$) was used as the denominator for spontaneous abortions.

§ The number of livebirths plus the number of stillbirths ($n = 558$) was used as the denominator for stillbirths.

¶ OR, odds ratio; CI, confidence interval.

Logistic regression analysis based on the method of generalized estimating equations.

** One event (spontaneous abortion or stillbirth, respectively) was considered per woman.

In most countries, non-livebirths are underascertained in surveys and medical assessments (27). The incidence rates for neonatal mortality (22.2 per 1,000 livebirths) and infant mortality (38.9 per 1,000 livebirths) overall were lower in our study than rates reported for rural West Bengal in the Indian National Family Health Survey for the time period 1994–1998 (27). The ratio of neonatal mortality to overall infant mortality in our study was 0.57, which was slightly lower than the rate of 0.69 reported in the Indian National Family Health Survey. Rates of reported spontaneous abortion and stillbirth were somewhat higher in our study (45.5 per 1,000 livebirths and 32.3 per 1,000 livebirths, respectively) than in the Indian National Family Health Survey (40 per 1,000 livebirths and 18 per 1,000 livebirths, respectively) (27), potentially reflecting the effect of arsenic in our study area, but lower than the rates reported from an arsenic-affected area in Bangladesh (22).

Because of the small number of women with skin lesions ($n = 12$), we could not reasonably adjust the estimates for any other variable; related findings are limited and must be interpreted cautiously, as indicated by the wide 95 percent confidence intervals. Although women with skin lesions were older at the time of the interview (median age, 37 years) than women without skin lesions (median age, 31 years), this difference is unlikely to have biased the estimates towards higher risks of stillbirth, since all stillbirths in our study were reported at maternal ages below 30 years; no difference in age was found between exposed and unexposed women or according to skin lesion status. For the purpose of this analysis, we defined arsenic-related skin lesions on the basis of the field physician's diagnosis as ''definitely,'' ''probably,'' or ''possibly'' due to arsenic exposure. Findings did not change if we excluded from the analyses those subjects with ''possibly'' arsenic-related skin lesions.

The reproductive toxicity of inorganic arsenic has been well documented in many animal studies, usually after very few high doses (28–32). Arsenic metabolites have been found in umbilical cord blood and the placenta (33). The biologic effect mechanism by which arsenic may affect the developing fetus is still unclear, and whether differences in arsenic methylation during pregnancy may be related to particular susceptibility of the fetus to arsenic is unknown.

In conclusion, we observed pronounced effects of drinking-water arsenic on stillbirth rates at relatively high concentrations, with an approximately sixfold risk increase; and although numbers were small, women with arsenic-related skin lesions appeared to be especially at risk. There was little evidence for other adverse pregnancy outcomes or increased infant mortality. The findings concerning stillbirth need to be confirmed, ideally in a prospective pregnancy study, but the existing evidence warrants preventive actions designed to reduce the exposure of childbearing-age women in regions with high levels of arsenic in water.

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