Drinking Water and Pregnancy Outcome in Central North Carolina: Source, Amount, and Trihalomethane Levels

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In spite of the recognition of potentially toxic chemicals in chlorinated drinking water, few studies have evaluated reproductive health consequences of such exposure. Using data from a case–control study of miscarriage, preterm delivery, and low birth weight in central North Carolina, we evaluated risk associated with water source, amount, and trihalomethane (THM) concentration. Water source was not related to any of those pregnancy outcomes, but an increasing amount of ingested water was associated with decreased risks of all three outcomes (odds ratios around 1.5 for 0 glasses per day relative to 1–3 glasses per day, falling to 0.8 for 4+ glasses per day). THM concentration and dose (concentration × amount) were not related to pregnancy outcome, with the possible exception of an increased risk of miscarriage in the highest sextile of THM concentration (adjusted odds ratio = 2.8, 95% confidence interval = 1.1–2.7), which was not part of an overall dose–response gradient. These data do not indicate a strong association between chlorination by-products and adverse pregnancy outcome, but given the limited quality of our exposure assessment and the increased miscarriage risk in the highest exposure group, more refined evaluation is warranted.
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It has been known for nearly 20 years that chlorination of surface waters produces small amounts of chloroform and other potentially toxic by-products (*1*). Ingestion of these agents by large numbers of people over extended periods of time has generated considerable concern with potential adverse health effects. Most of that concern has focused on carcinogenicity, with studies providing mixed support for an association between chlorination by-product concentrations and the risk of bladder and colon cancer (*2*).

Reproductive outcomes, known to be sensitive to environmental toxicants, have received much less attention. In addition to the obvious public health impact of congenital malformations and fetal and infant death, studies of reproductive consequences have the logistical advantage of a shorter interval between exposure and disease manifestation. This briefer period of interest facilitates more accurate recall of consumption over the relevant time period and improved estimation of contaminant concentration. The seasonal variation in chlorination by-product levels (higher in the summer) can be incorporated into reproductive health studies as a component of the exposure variability that is analyzed.

Laboratory research relevant to chlorination by-products and reproduction is limited (*3,4*) with most evaluations focused on single chemicals rather than the complex mixture encountered by humans in treated water. At exposure levels orders of magnitude higher than those encountered naturally, developmental toxicity in the form of reduced fetal weight, heart malformations, and reproductive toxicity related to adverse effects on sperm has been demonstrated for chloroform, bromoform, haloacetic acids, and related compounds (*3*). However, it is not clear whether they produce toxic effects at the low exposure levels of concern.

Prior research on the outcomes of interest, fetal loss, preterm delivery, and low birth weight, is limited in both quantity and quality (*4*). In the most thorough effort to evaluate preterm delivery, low birth weight, and small for gestational age (SGA), Kramer et al. (*5*) conducted a study in Iowa. Exposure was classified based on the community of residence in conjunction with a survey of chlorination by-products. Chloroform concentrations above 10 ppb in drinking water were associated with a small increase in risk of low birth weight [adjusted odds ratio (OR) = 1.3] and a somewhat greater risk of SGA (adjusted OR = 1.8). As noted by the investigators, there was no opportunity to consider fluctuations in the contaminant levels over time or individual variability in water consumption.

The only other study that considered trihalomethane (THM) levels in the community supply was conducted in northern New Jersey (*6*) using birth and fetal death certificates to identify birth weight, low birth weight (<2500 g), very low birth weight (<1500 g), term low birth weight, preterm delivery, SGA births, and fetal deaths. Mean birthweight was reduced slightly in relation to use of surface water supplies and in relation to use of water with THM concentrations above the federal standard of 100 ppb (*7*) as reflected in the nearest quarterly sample. The risk of adverse outcomes was generally elevated slightly in relation to both surface (versus ground) water use and elevated THM levels, with adjusted OR, in the range of 1.1–1.4. Except for a closer temporal relation between the pregnancy and the measurement, the same limitations noted for the Iowa study are applicable to the New Jersey study.

Other reports of less direct relevance found that stillbirth risk was associated with chlorinated versus chloraminated water supplies in Massachusetts (*8*) and that the use of bottled water rather than tap water may be associated with a reduced risk of spontaneous abortion in Northern California (*9*). However, the investigators suggested that a reporting bias may account for the latter association (*10*).

Given current knowledge, additional work is clearly needed to evaluate whether the previous suggestions of small adverse effects on pregnancy are likely to be causal. Data collected from interviews of women who experienced miscarriage, preterm delivery, and low birth weight births as well as term, normal birth weight controls allow for an examination of individual water consumption in relation to water source and measured community THM levels.

Methods

A population-based case–control study of miscarriage, preterm delivery, and low birth weight was conducted in Alamance, Durham, and Orange Counties in central North Carolina. The region was originally chosen for the concentration of textile industry employment in Alamance County and expanded to include the larger, more sociodemographically diverse populations of Durham and Orange counties.

All medically treated miscarriage cases among women in Alamance County during the period September 1988 through August 1991 were identified through medical care providers, including hospitals and private clinics, as described in detail elsewhere (*11*). Preterm deliveries (<37 weeks completed gestation) and low birth weight infants (<2,500 g) were identified at six area hospitals covering virtually all births to area residents during the period September 1988 to August 1989 in Orange and

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Durham Counties, and September 1988 to April 1991 in Alamance County. There was substantial overlap between the preterm and low birth weight groups, with 34% of eligible live birth cases preterm and not low birth weight, 17% low birth weight and not preterm, and 50% both preterm and low birth weight.

Controls were selected in a one-to-one ratio to live birth cases from the deliveries immediately following a preterm or low birth weight case of the same race and hospital as the case, but restricted to term, normal weight births. The controls selected for preterm and low birth weight cases in Alamance County also served as controls for the miscarriage cases. We considered the controls as a hospital- and race-stratified sample from the population. Therefore, we did not analyze the data as a pair-matched sample but controlled as needed for race and hospital in the analysis.

Ten to fifteen percent of cases and controls were lost due to subject refusal (higher for miscarriage cases than the other groups), and an additional 11 to 16% were lost due to being untraceable (Table 1). An abbreviated form of the questionnaire which did not include the questions pertaining to drinking water was used for subjects who would have otherwise refused (short questionnaire). Final response proportions ranged from 62 to 71%, lowest for miscarriage cases and highest for preterm delivery cases.

Telephone interviews were used to ascertain information on a wide range of potential risk factors for adverse pregnancy outcome, including sociodemographic attributes (age, race, education, marital status, income), pregnancy history, tobacco and alcohol use, prenatal care, physical exertion, psychological stress, and employment. Each woman was asked, What was your primary source of drinking water at home? Was it supplied by the community water company, from a private well, or bottled water? This was followed by the question, About how many glasses of water did you drink per day around the time of your pregnancy?

After analyzing water source and amount, we restricted the sample to women who were served by public supplies and who reported drinking one or more glasses of water daily (omitting approximately 30% of eligible subjects; see Table 1). A woman's address was used to assign her to one of the five public water supplies serving residences in this region. Although we did not have information on changes in water consumption during pregnancy, we were able to consider the changes in THM concentrations over time. The dates of pregnancy were used to assign the reported quarterly average THM value from the appropriate supplier as her THM score. For miscarriage cases and their controls, the fourth week of pregnancy was the time period used for making that assignment, and for preterm delivery cases, low birth weight cases, and their controls, the 28th week of pregnancy was used to assign the nearest THM value. These periods reflect the most likely intervals in which any adverse effects would occur.

With this information, we were able to analyze several indices of water exposure: 1) source: community supply, private well (referent), bottled water; 2) amount (glasses per day): 0, 1–3 (referent), 4+; 3) source × amount: private well, 1–3 glasses per day (referent); private well, 4+ glasses per day; community supply, 1–3 glasses per day; community supply, 4+ glasses per day; bottled (regardless of amount); 4) THM concentration: analyzed as a continuous measure and divided into tertiles based on distribution of controls, categorized separately for analyses of miscarriage and the live birth outcomes (as indicated in Tables 2–4); 5) THM dose (glasses per day × concentration): analyzed as continuous measure and divided into tertiles based on distribution of controls, categorized separately for analyses of miscarriage and the live birth outcomes as indicated in Tables 2–4.

The ORs were calculated comparing exposures of cases to that of controls, e.g., community versus private source or higher versus lower THM concentrations. The ORs provide an estimate of the relative risk, i.e., the magnitude of increased risk associated with the exposed versus the referent category. The confidence intervals (CIs) provide an indication of the statistical precision of those estimates.

Based on preliminary analyses to identify factors associated with adverse pregnancy outcomes, potential confounders included maternal age, race, hospital (for preterm delivery and low birth weight only) education, marital status, poverty level, smoking, alcohol consumption, employment, and nausea (for miscarriage only). Crude and adjusted ORs were compared, with adjustment for each of the above covariates one at a time. When the adjusted OR differed from the crude by 10% or more, the variable was considered as a confounder and incorporated into the adjusted ORs presented. When multiple confounders were identified, a logistic regression model was developed to simultaneously adjust for those confounders. Therefore, the adjusted ORs presented in the tables can be interpreted as free from confounding by all of the above variables, but only the subset that influenced the results (if any) were considered directly. Given the small numbers of subjects in some cells and the lack of a biological basis for postulating effect modification, we did

Table 1. Number of eligible and interviewed participants: Alamance, Durham, and Orange counties, North Carolina, 1988–1991

	Miscarriage analysis				Preterm and LBW analysis					
	Cases		Controls		Preterm cases		LBW cases		Controls	
	No.	%	No.	%	No.	%	No.	%	No.	%
Eligible	418	100.0	341	100.0	586	100.0	464	100.0	782	100.0
Physician refusal	9	2.2	1	0.3	3	0.5	4	0.9	5	0.6
Patient refusal	63	15.1	39	11.4	52	8.9	53	11.4	85	10.9
Untraceable	48	11.5	34	10.0	70	11.9	74	15.9	84	10.7
Other	18	4.3	4	1.2	6	1.0	7	1.5	4	0.5
Short questionnaire	12	2.9	22	6.5	39	6.7	25	5.4	51	6.5
Missing water data										
Source only	1	0.2	0	0.0	1	0.2	1	0.2	0	0.0
Amount only	0	0.0	0	0.0	1	0.2	1	0.2	3	0.4
Source and amount	6	1.4	4	1.2	2	0.3	3	0.6	7	0.9
Complete water data	261	62.4	237	69.5	412	70.3	296	63.8	543	69.4
Restriction for THM analysis										
No water consumed	40	9.6	22	6.5	44	7.5	35	7.5	40	5.1
Bottled or well water	77	18.4	70	20.5	104	17.7	67	14.4	141	18.0
Missing date/THM data	18	4.3	23	6.7	20	3.4	16	3.4	29	3.7
Complete THM data	126	30.1	122	35.8	244	41.6	178	38.4	333	42.6

Abbreviations: LBW, low birth weight; THM, trihalomethane.

not examine interactions between water exposures and other variables.

Results

Relative to women served by community supplies, women served by private wells were more likely to be white and somewhat more likely to be married, but were otherwise similar with respect to education, tobacco and alcohol use, and reproductive history. Bottled-water users were less likely to use tobacco and were more highly educated. The amount of water consumed was somewhat lower for women who were parous, white, and less educated. THM concentrations were somewhat higher for women who reported using tobacco or marijuana during pregnancy. In general, these potential confounders (which were controlled, as needed, in the analysis) were not strongly associated with water characteristics.

Risk of miscarriage was slightly increased among women who reported using bottled water compared to those who used private wells (Table 2), but this observation was based on few exposed cases. Also, bottled water users were not at increased risk relative to women served by community supplies (Table 2). Regardless of water source, women who reported not drinking any water were at highest risk and those drinking the largest amounts at slightly decreased risk. This pattern was also apparent in the analysis of source by amount and possibly reflected in the reduced risk in the highest tertile of THM dose (THM concentration × amount). THM concentration was not associated with miscarriage risk in the categorical analysis, yet the continuous measure predicted a rather substantial association, with an odds ratio of 1.7 per 50 ppb increment. This was attributable to a much higher risk associated in the highest sextile of exposure (adjusted OR = 2.8, 95% CI = 1.2–6.1) with an anomalously low risk in the second to highest sextile (adjusted OR = 0.2, 95% CI = 0.0–0.5) (not shown).

Preterm delivery showed virtually no association with water source, THM concentration, or THM dose; all adjusted ORs were between 0.8 and 1.2 (Table 3). The number of glasses of water consumed per day showed the same pattern as for miscarriage, with decreasing risk with increasing amount. The estimates were much more precise than for miscarriage, due to a case group nearly twice as large and a control group nearly three times as large.

Analysis of low birth weight (Table 4) indicated no association with water source and a decreased risk with increasing number of glasses per day. Categorical analysis of THM concentration indicated the lowest risk in the referent group but no trend of increasing risk across the middle and highest categories. Analysis using the continuous dose did not indicate a positive association.

Discussion

Overall, drinking water source was not related to the risk of adverse pregnancy outcome, with the possible exception of an increased risk of miscarriage among bottled water versus private well users. We considered only medically treated miscarriages and found some evidence of differential under-ascertainment related to social class (*11*). The association between miscarriage

Table 2. Miscarriage in relation to drinking water characteristics: Alamance County, North Carolina, 1988–1991

	Cases	Controls	Crude OR	Adjusted OR[a]	95% CI
Water source					
Private well[b]	78	68	1.0	1.0	—
Community	171	159	0.9	1.0	0.7–1.6
Bottled	12	10	1.0	1.6	0.6–4.3
Water amount (glasses per day)					
0	40	22	1.6	1.6	0.9–2.8
1–3[b]	137	120	1.0	1.0	—
4+	84	95	0.8	0.8	0.5–1.1
Water source × amount					
Private well/1–3[b]	36	29	1.0	1.0	—
Private well/4+	29	31	0.8	1.2	0.6–2.4
Community/1–3	95	85	0.9	0.8	0.4–1.4
Community/4+	49	60	0.7	0.6	0.3–1.2
Bottled/1+	12	10	1.0	1.0	0.3–3.1
THM concentration (ppb)					
40.8–59.9[b]	37	35	1.0	1.0	—
60.0–81.0	43	44	0.9	1.0	0.5–2.0
81.1–168.8	46	43	1.0	1.2	0.6–2.4
Per ppb change	126	122	1.5	1.7	1.1–2.7
THM dose (ppb × glasses/day)					
40.8–139.9[b]	50	47	1.0	1.0	—
140.0–275.0	45	40	1.1	1.0	0.6–1.9
275.1–1171.0	31	35	0.8	0.6	0.3–1.2
Per 250 unit change	126	122	1.0	1.0	0.7–1.2

Abbreviations: OR, odds ratio; THM, trihalomethane.
[a]Adjusted as needed for potential confounders listed in text; if no confounders identified, the crude OR is presented.
[b]Referent category.

Table 3. Preterm delivery in relation to drinking water characteristics: Alamance, Durham, and Orange counties, North Carolina, 1988–1991

	Cases	Controls	Crude OR	Adjusted OR[a]	95% CI
Water source					
Private well[b]	95	114	1.0	1.0	—
Community	294	388	0.9	0.9	0.7–1.2
Bottled	24	43	0.7	0.8	0.4–1.4
Water amount (glasses per day)					
0	44	40	1.4	1.4	0.9–2.2
1–3[b]	212	261	1.0	1.0	—
4+	157	244	0.8	0.8	0.6–1.0
Water source × amount					
Private well/1–3[b]	46	50	1.0	1.0	—
Private well/4+	34	48	0.8	0.7	0.4–1.3
Community/1–3	153	189	0.9	0.9	0.6–1.4
Community/4+	111	173	0.7	0.8	0.5–1.3
Bottled/1+	24	43	0.6	0.6	0.3–1.3
THM concentration (ppb)					
40.8–63.3[b]	80	110	1.0	1.0	—
63.4–82.7	102	118	1.2	1.2	0.8–1.8
82.8–168.8	62	105	0.8	0.9	0.6–1.5
Per 50 ppb change	244	333	0.8	0.8	0.6–1.2
THM dose (ppb × glasses/day)					
44.0–169.9[b]	78	108	1.0	1.0	—
170.0–330.8	97	115	1.2	1.2	0.8–1.7
330.9–1171.0	69	110	0.9	0.9	0.6–1.3
Per 250 unit change	244	333	0.9	0.9	0.8–1.1

Abbreviations: OR, odds ratio; THM, trihalomethane.
[a]Adjusted as needed for potential confounders listed in text; if no confounders identified, the crude OR is presented.
[b]Referent category.

and bottled water use may reflect a systematic tendency for bottled water users to more comprehensively seek medical care for miscarriages or for women with heightened health concerns to drink bottled water. Socioeconomic status may influence both miscarriage identification and bottled water use, but the associations we reported were adjusted for mother's education and family income.

A consistent pattern of decreasing risk with increasing consumption of water suggests either a genuine beneficial effect of such consumption or a reporting artifact. There are potential benefits of increased fluid consumption during pregnancy since the plasma volume must expand markedly in that period (*12*), but it is not clear that restricted fluid intake would influence the outcomes we addressed. With the available data, we could not examine total fluid consumption or consider beverages prepared from tap water. Analysis of water source by amount added little additional insight to this pattern.

Analysis of THM concentrations yielded some indication of an association with miscarriage, with a notably increased risk in the most highly exposed subset driving a linear dose–response pattern. Analysis by tertiles yielded little evidence of increased risk, whereas isolation of the most highly exposed sextile generated a pronounced association, with an aberrantly low risk in the next to highest sextile. Although limited by imprecision, these data encourage further examination of women who drink water with THM levels in the range of 100 ppb and above, which is the federal standard. Preterm delivery was unrelated to THM concentration but low birth weight risk was reduced among women in the lowest tertile of exposure with no increase in risk above that exposure level. Total dose of THM (incorporating THM concentration and amount consumed) yielded little association with any of the outcomes.

The miscarriage results have few prior studies to which they can be compared, but appear not to support the previous observation of decreased risk among bottled water users (*9*). The absence of association with water source is consistent with the report of Aschengrau et al. (*8*), that risk was similar in Massachusetts communities served by chlorinated versus chloraminated supplies. To our knowledge, no previous study has explicitly evaluated THM concentration in relation to miscarriage.

Preterm delivery and low birth weight results may be compared to those from Iowa (*5*) and New Jersey (*6*). The absence of association with preterm delivery in our study is consistent with the lack of association found in Iowa (*5*), but is not notably discrepant with the small associations (ORs <1.5) found in New Jersey (*6*). The small increase in risk of low birth weight for the upper two tertiles in the present study is likewise compatible with small increases reported in each of the other two studies (*5,6*). We were not able to examine risk of SGA births for comparison to the strongest findings of Kramer et al. (*5*) due to our method of selecting cases. Term births who weighed >2500 g, a large proportion of all SGA deliveries, were not selected as cases in our study.

The limitations in our study should be noted. A sizable fraction of nonrespondents (due to refusal, being untraceable, or having key water information unavailable) raises the question of whether the participants differed from nonparticipants in a manner that would distort exposure–disease associations. The interview itself may generate erroneous reports, particularly of the amount of water consumed. We did not ask about preparation of cold beverages from tap water, such as frozen orange juice. Furthermore, we did not ask where the water was consumed (home, work, or elsewhere), or whether home filters were used. Thus, inferences about chlorination by-product exposure based on available data are subject to error.

The link to water suppliers is likely to be accurate, but the assignment of a particular THM score based on the nearest measurement day is certain to contain error relative to the true THM values over the etiologic period of interest. The THM sample is taken from an approximately appropriate point in time at locations other than the occupant's home. Furthermore, the pattern of home water use and ventilation could produce rather different exposures even for a given tap water THM concentration. Changes in water consumption during the course of pregnancy were not ascertained, requiring respondents to provide an average value for the entire pregnancy that may differ from the consumption in the etiologically relevant time period. Most of these sources of error are likely to be similar for cases and controls, yielding relative risk estimates that are biased toward the null value (*13*). Given the seasonal patterns in THM levels, matching controls on time of birth could have further biased the results towards the null value (*13*), but analyses adjusted for season (summer versus other) did not differ substantially from those reported.

On the other hand, along with Bove et al. (*6*), our study was among the first to try to link THM measurements in both time and space to study subjects. Availability of data on water ingestion and a wide array of potential confounders distinguishes this study from previous record-based investigations (*5,6*). Accuracy of identifying pregnancy outcomes is also certain to be improved using hospital data as opposed to birth certificate information. Finally, because of the extensive array of information we obtained through the interview, we were able to examine

Table 4. Low birth weight in relation to drinking water characteristics: Alamance, Durham, and Orange counties, North Carolina, 1988–1991

	Cases	Controls	Crude OR	Adjusted OR[a]	95% CI
Water source					
Private well[b]	63	114	1.0	1.0	—
Community	225	388	1.0	1.0	0.7–1.4
Bottled	13	43	0.5	0.8	0.4–1.6
Water amount (glasses per day)					
0	35	40	1.5	1.5	0.9–2.5
1–3[b]	150	261	1.0	1.0	—
4+	116	244	0.8	0.6	0.6–1.1
Water source × amount					
Private well/1–3[b]	32	50	1.0	1.0	—
Private well/4+	22	48	0.7	0.8	0.4–1.6
Community/1–3	12	189	0.9	0.8	0.4–1.3
Community/4+	86	173	0.8	0.8	0.5–1.4
Bottled/1+	13	43	0.5	0.6	0.3–1.6
THM concentration (ppb)					
40.8–63.3[b]	48	110	1.0	1.0	—
63.4–82.7	74	118	1.5	1.5	1.0–2.3
82.8–168.8	57	105	1.3	1.3	0.8–2.1
Per 50 ppb change	178	333	1.1	0.9	0.6–1.4
THM doses (ppb × glasses/day)					
44.0–169.9[b]	60	108	1.0	1.0	—
170.0–330.8	63	115	1.0	1.0	0.6–1.5
330.9–1171.0	55	110	0.9	0.8	0.5–1.3
Per 250 unit change	178	333	1.0	1.0	0.8–1.2

Abbreviations: OR, odds ratio; THM, trihalomethane.
[a]Adjusted as needed for potential confounders listed in text; if no confounders identified, the crude OR is presented.
[b]Referent category.

and control for confounding much more effectively than studies based on birth certificates.

The challenge in interpreting our results and the literature as a whole is that we would like to distinguish between the absence of association and the presence of a modest association. To do so with confidence requires large studies with refined exposure assessment. Subject to some uncertainty, literature suggests that there is not a strong association between THM exposure and adverse pregnancy outcome but provides some tentative suggestions that risk of miscarriage (based on the present study) and low birth weight or small-for-gestational-age births (based on previous studies) may be affected. More sophisticated approaches to exposure assessment through water quality models in the context of rigorous epidemiologic study designs can be expected to help reduce the uncertainty.

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