A Prospective Study of Spontaneous Abortion: Relation to Amount and Source of Drinking Water Consumed in Early Pregnancy

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In 1992, we published four retrospective studies, conducted primarily within a single California county, which found higher spontaneous abortion rates among women who drank more tapwater than bottled water in early pregnancy. The current prospective study extends that investigation to other water systems. Pregnant women from three regions in California were interviewed during their first trimester. Multivariate analyses modeled the amount and type of water consumed at 8 weeks' gestation in each region in relation to spontaneous abortion rate. In Region I, which was within the previous study area, the adjusted odds ratio (OR) comparing high (≥6 glasses per day) consumption of cold tapwater with none was 2.17 [95% confidence interval (CI) = 1.22-3.87]. Furthermore, when women with high cold tapwater and no bottled water consumption were compared with those with high bottled water and no cold tapwater consumption, the adjusted odds ratio was 4.58 (95% CI = 1.97-10.64). Conversely, women with high bottled water consumption and no tapwater had a reduced rate of spontaneous abortion compared with those drinking tapwater and no bottled water (adjusted OR = 0.22; 95% CI = 0.09-0.51). Neither tap nor bottled water consumption altered the risk of spontaneous abortion in Regions II and III. Although controlling for age, prior spontaneous abortion, race, gestational age at interview, and weight somewhat strengthened the association in Region I, the distribution of these confounders did not vary appreciably across regions. This study confirms the association between cold tapwater and spontaneous abortion first seen in this county in 1980. If causal, the agent(s) is not ubiquitous but is likely to have been present in Region I for some time.

Key words: spontaneous abortion, drinking water, tapwater, bottled water.

In 1992, a single issue of this journal reported a series of retrospective studies in which the risk of spontaneous abortion was examined in relation to the source and amount of drinking water consumed during early pregnancy.[1-5] These studies included subjects, residing primarily in a single California county, who became pregnant between 1980 and 1987. Study designs differed (two cross-sectional,[1,2] one case-cohort,[3] and two case-control[4,5]), but all had retrospective assessment of water exposure. The strongest associations were seen in the two cross-sectional studies, in which considerable publicity made subjects aware of the study hypothesis. Data from four studies were consistent with a 10-50% greater risk of spontaneous abortion in women who drank tap (or mostly tap) water compared with those who drank no tapwater.[6] One smaller study in the same county did not find this association, although its power was limited.[5] Two accompanying commentaries[7,8] and a discussion on sources of bias and confounding[9] proposed recall bias as a likely explanation.

The current study was conducted to extend this investigation to a later time period and to different water systems, as well as to eliminate recall bias by using a prospective design. We selected three regions in California, representing a range of water systems, for study. Here, we present region-specific results on spontaneous abortion risk by amount and source of drinking water. No

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analysis of water constituents or water companies is given here; an analysis of chlorination by-products and spontaneous abortion risk in this dataset is published separately.[10]

Subjects and Methods

Study Regions and Populations

The study population was recruited between January 1990 and September 1991. Collaboration with the Division of Research of the Kaiser Permanente Medical Care Program, a large managed health care organization in California, enabled us to identify and interview women early in pregnancy and ensured nearly complete ascertainment of pregnancy outcomes. The areas served by three Kaiser facilities that provide prenatal care constitute the study regions; approximately equal numbers of women were recruited from each. Regions I and II are in northern California, and Region III is in southern California. Region I is located within the county we studied previously,[1-5] in which homes receive a mixture of groundwater and surface water, except for a few small areas served exclusively groundwater. Region II is served primarily by surface water, whereas large areas of Region III receive only groundwater.

When a woman called to schedule her first prenatal visit, the appointment clerk determined whether she was eligible ($\geq$18 years old, $\leq$13 weeks' gestation, and Spanish or English speaking) and willing to participate. Of 7,881 women evaluated, 6,179 (78.4%) were eligible and willing to be interviewed. Interviews were completed by 5,342 of these women (86.5%). Among the 837 women without completed interviews, 268 were no longer pregnant when reached for an interview, including 186 who had miscarried in the short time (8 days on average) since initial contact. To maintain the prospective nature of the study, these women were not interviewed. The median gestational age at interview was 8 weeks.

Ascertainment and Definition of Pregnancy Outcomes

Pregnancy outcomes were first ascertained from computerized hospital records (73%) and medical records (18%). Follow-up telephone interviews, mailed questionnaires, or matches to California vital records provided the remaining outcomes. Less than 1% (N = 35) of outcomes could not be determined. The majority of spontaneous abortions (about 84%) were validated by medical record review. We used the first day of the last menstrual period, as given in the interview, to calculate gestational age. We verified extreme gestational ages at outcome (<4 or >45 weeks) against medical records, when possible, and corrected them if warranted. We defined pregnancies ending before 21 completed weeks of gestation as spontaneous abortions (N = 499), and fetal losses between 21 and 27 weeks as stillbirths (N = 32). We excluded elective terminations (N = 128), ectopic (N = 13), and molar pregnancies (N = 4) from analysis. We considered multiple births (N = 55) a single pregnancy outcome. The spontaneous abortion rate is the ratio of spontaneous abortions to the sum of livebirths, stillbirths, and spontaneous abortions.

Interview and Assessment of Water Exposure

The interview, conducted using a computer-assisted telephone interview, queried women regarding demographics; medical and reproductive history, including date of last menstrual period; use of alcohol, tobacco, and caffeine-containing beverages; occupation-, industry-, and job-related exposures such as physical exertion; psychosocial stress; and life events. Questions concerning water (and other) consumption were asked with respect to both the week beginning with the last menstrual period and the week before interview. If, for any consumption variables, the amount consumed before and during

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pregnancy differed, women were asked when the change occurred. Consumption was ascertained for four types of water: cold tapwater (or drinks made from cold tapwater) at home, heated tapwater (or drinks made from heated tapwater) at home, bottled (noncarbonated) water, and carbonated water. Since women often reported soda as carbonated water, and water source for most soda is unknown, carbonated water was not included in these analyses. Women reporting consumption of any tapwater in either week were asked how they usually drank their tapwater (straight from the tap, let it stand, or refrigerated it first), as well as their use of a water filter/purifier (and type). All women were asked to identify the water company and brand of bottled water when relevant. In addition, number of showers weekly, and their average length, was asked of all subjects. We calculated weekly duration of showering as frequency times average length of showering.

Statistical Analyses

We estimated water consumption (glasses per day) at 8 weeks, the average gestational age at interview. If the interview occurred before that time, we assumed that consumption at 8 weeks was equal to consumption in the week before interview. If the interview occurred at 8 weeks or later, and there was no change in water consumption before 8 weeks, we set consumption equal to that in the last menstrual period week. Otherwise, consumption equaled the amount consumed after the change. We explored the sensitivity of the analysis to this choice of exposure time by also modeling the association between spontaneous abortion and water consumed before pregnancy, and in the last menstrual period week.

We stratified water consumption into none, moderate, and high. Consumption of 6-8 glasses a day of water is often recommended to pregnant women. Nevertheless, the proportion of women drinking ≥8 or more glasses of cold tapwater per day was small (5.5%). Therefore, we selected ≥6 glasses per day as the cutoff defining "high consumption." The selection of ≥6 glasses per day classifies 10.2%, 15.4%, and 14.4% of women as "high" consumers of cold tap, total (hot and cold) tap, and bottled water, respectively, across all regions. We also report results of multivariate models that use alternative cutpoints to define "high" consumption.

Because the three study regions differed in demographic composition, water consumption patterns, and water source, we conducted separate analyses in each study region. Covariates considered for inclusion in multivariate models were those previously associated with spontaneous abortion. We initially considered: age, parity, prior fetal loss, body weight, smoking alcohol, caffeine, education, race, marital status, and all water variables. With a few exceptions, we retained variables that altered the adjusted odds ratio by 10% or more for the Region I analysis of high cold tapwater consumption. We used the same variables to model all exposures (cold tap, total tap, whether mixed with bottled or not) and regions, so that odds ratios could be compared.

Our prior studies and initial analyses indicated that both tap and bottled water altered risk in Region I: tapwater increased risk, and bottled water decreased it. Moreover, tap and bottled water consumption are inversely correlated. Therefore, our regression analyses of tapwater consumption controlled for bottled water in the following two ways. First, we asked, among women with high water consumption (≥6 glasses of either tap or bottled water per day), how do spontaneous abortion rates for tapwater and bottled water drinkers compare? In this comparison, exposures are "mixed," since some tapwater drinkers also consumed bottled water, and conversely. Second, we asked, how do spontaneous abortion rates among women consuming ≥6 glasses of tapwater and no bottled water compare with those for women drinking ≥6 glasses of bottled water and no tapwater? The latter is an undiluted, or "pure," comparison of tap and bottled water at the same level of consumption. Moderate consumers

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were all women who did not fall into these two extreme groups.

Results

Demographics

The spontaneous abortion rate (9.7%) varied somewhat by region, being lowest in Region I (9.2%) and highest in Region II (10.1%). Table 1 contains a summary of univariate associations between spontaneous abortion and demographic and other risk factors. Region I included the highest proportion of Asians, Region II the highest proportion of whites, and Region III the highest proportions of nonwhites, predominantly Hispanics. Women in Region III were also somewhat younger, less educated, and more likely to be unmarried. Pregnancy history, nausea, cigarette smoking, and gestational age at interview differed littleacross regions. Risk of spontaneous abortion was approximately doubled in women who were≥35 years of age or among those with a history of two or more prior losses, consistent with the literature.[11] Region III differed from Regions I and II in the absence of an association between spontaneous abortion and early gestational age at interview, ethnicity, and marital status.

TABLE 1

Spontaneous Abortion (SAB) Rates by Demographic and Life-Style Factors

	Region I				Region II				Region III			
			Mean Water*				Mean Water*				Mean Water*	
Variable	N	% SAB	Tap	Bottled	N	% SAB	Tap	Bottled	N	% SAB	Tap	Bottled
Maternal age (years)												
<35	1,455	8.5	1.7	2.7	1,542	9.0	2.2	2.3	1,586	8.7	2.4	2.3
≥35	191	14.1	1.8	2.6	215	17.7	2.5	1.5	155	21.3	2.6	2.2
Gestational age at interview (weeks)												
≤8	1,009	11.3	1.6	2.7	1,177	11.6	2.2	2.1	1,101	10.3	2.5	2.3
>8	637	5.8	1.8	2.7	577	6.9	2.1	2.4	633	9.0	2.4	2.2
Pregnancy history												
Nulliparous	457	9.2	1.6	2.8	461	8.7	2.1	2.4	402	7.2	2.4	2.5
Multiparous												
<2 prior SABs	1,098	8.7	1.7	2.7	1,217	10.0	2.2	2.1	1,254	9.9	2.4	2.2
≥2 prior SABs	89	14.6	1.8	2.4	75	20.0	2.4	2.4	83	21.7	2.9	2.3
Race												
Hispanic	292	8.2	1.7	2.6	159	6.3	2.0	2.7	494	8.9	2.3	2.2
White	1,001	8.5	1.8	2.8	1,392	9.7	2.3	2.2	997	10.0	2.6	2.2
Asian	238	10.5	1.6	2.5	127	15.0	2.0	2.2	51	9.8	2.2	2.3
Black/other	115	14.8	1.4	3.0	79	16.5	1.7	2.2	199	11.0	2.1	2.7
Marital status												
Separated/divorced	32	15.6	1.5	1.9	23	21.7	2.3	1.5	53	11.3	2.6	2.5
Married/other	1,614	9.0	1.7	2.7	1,734	9.9	2.2	2.2	1,688	9.8	2.4	2.2
Nausea during pregnancy												

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Yes	1,342	7.0	1.7	2.7	1,381	8.2	2.2	2.2	1,405	7.6	2.5	2.2
No/do not know	304	18.8	1.6	2.6	376	16.8	2.3	2.2	336	19.0	2.4	2.4
Employment during pregnancy												
Employed	1,321	9.3	1.6	2.8	1,427	10.6	2.1	2.3	1,316	10.3	2.3	2.4
Not employed	325	8.6	2.0	2.4	330	7.9	2.6	1.8	425	8.2	2.9	1.7
Education												
High school or less	636	7.4	1.6	2.7	618	8.6	1.9	2.4	873	10.3	2.4	2.2
Other	1,010	10.3	1.7	2.7	1,139	10.9	2.4	2.1	868	9.3	2.5	2.3
Cigarette consumption (interview week)												
None	1,454	9.3	1.6	2.7	1,586	9.9	2.2	2.2	1,567	9.1	2.4	2.3
Any	191	8.4	2.3	2.6	171	11.7	2.0	2.2	174	16.1	2.6	1.9
Weight												
Lowest quartile	508	8.3	1.5	2.4	518	10.2	2.2	2.0	469	10.2	2.3	2.0
Intra quartile	691	10.0	1.6	2.8	790	10.0	2.2	2.2	688	7.4	2.3	2.3
Highest quartile	425	8.9	2.0	3.0	437	9.8	2.3	2.6	571	12.4	2.8	2.4
Total	1,646	9.2	1.7	2.7	1,757	10.1	2.2	2.2	1,740	9.8	2.4	2.3

* Glasses per day of cold tapwater at home or bottled consumed at 8 weeks' gestation.

Table 1 also presents mean glasses of tap and bottled water consumed per day for each stratum of these covariates. Overall, women consumed an average of 2.2 glasses of cold tapwater and 2.4 glasses of bottled water per day. Women in Region I consumed less tap and more bottled water than those in Regions II and III, perhaps because of community concern about tapwater in that area. Mean amounts of tap plus bottled water were similar in Regions I and II (about 4.4 glasses per day), but higher in Region III (4.7 glasses per day), which has a warmer climate. Women in the highest quartile of body weight consumed more water than others, particularly in Region I. Neither tap nor bottled water consumption varied markedly across strata of demographic variables.

Univariate Analysis of Water Consumption Variables

Unadjusted spontaneous abortion rates within each region are shown in Table 2 for each combination of water type. If we rank combinations of tap and bottled water from "least risky" (high bottled and no cold tapwater) to "most risky" (high cold tap and no bottled water), a strong gradient of increasing risk of spontaneous abortion is seen in Region I (6.5% to 17.9%). The slight trends in Regions II (12.8% to 9.9%) and III (11.0% to 8.0%) are opposite to that seen in Region I.

TABLE 2

Water Consumption Variables: Distribution and Spontaneous Abortion Rates in Three Regions

	Region I			Region II			Region III		
Variable*	**N**	**%†**	**% SAB**	**N**	**%†**	**% SAB**	**N**	**%†**	**% SAB**
Consumption of bottled water (glasses/day)									
0	548	33.3	11.5	781	44.4	10.9	775	44.5	9.8
0.5-5.5	826	50.2	8.0	746	42.5	9.0	726	41.7	10.1

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≥6	271	16.5	8.1	230	13.1	10.9	239	13.7	9.2
≥6 and no cold tapwater	184	11.2	6.5	149	8.5	12.8	137	7.9	11.0
Consumption of total tapwater (glasses/day)									
0	565	34.3	8.7	457	26.0	9.4	441	25.3	10.4
0.5-5.5	879	53.4	8.5	1,008	57.4	10.3	1,000	57.4	10.0
≥6	200	12.2	13.0	291	16.6	10.3	300	17.2	8.3
≥6 and no bottled water	148	9.0	14.9	241	13.7	9.5	234	13.4	8.1
Consumption of cold tapwater (glasses/day)									
0	771	46.8	8.4	619	35.2	9.7	535	30.7	11.4
0.5-5.5	753	45.7	8.9	955	54.4	10.4	981	56.4	9.5
≥6	120	7.3	15.0	182	10.4	9.9	225	12.9	7.6
≥6 and no bottled water	95	5.8	17.9	162	9.2	9.9	187	10.7	8.0
Showering (minutes/week)									
None	28	1.7	21.4	16	1.0	31.2	39	2.2	10.3
>0 and <70	551	33.5	8.0	578	32.9	9.3	376	21.6	9.0
70	388	23.6	10.3	463	26.4	9.7	374	21.5	10.4
71-105	375	22.8	9.6	421	24.0	9.3	488	28.0	10.0
>105	302	18.4	8.0	277	15.8	12.3	460	26.4	9.6
Filter use‡									
None	836	77.5	8.4	1,115	85.8	10.3	1,034	79.5	10.4
Any	236	21.9	12.7	183	14.1	10.4	264	20.3	6.4
Method of drinking tapwater‡									
Straight from tap	515	47.7	8.9	715	55.0	11.3	652	50.2	8.9
Refrigerate and/or let stand	385	35.7	10.9	436	33.6	8.0	561	43.2	9.8

* Tapwater consumed at home at 8 weeks' gestation; bottled water consumed anywhere at 8 weeks' gestation. Total tap = cold + hot tapwater, including drinks made from tapwater.

† Percentages are of women within region (excluding "do not know" or missing).

‡ Filter use and method are among women drinking any tapwater.

Spontaneous abortion rates were not appreciably elevated among the large group of women classified as low to moderate consumers of cold tapwater (0.5-5.5 glasses per day) in any region. Low to moderate consumption of bottled water was associated with a decreased rate of spontaneous abortion in Region I (8.0%), but not elsewhere.

Use of a water filter was reported less often in Region II than in Regions I and III. Based on crude rates, filter use was positively associated with spontaneous abortion among cold tapwater drinkers in Region I, and negatively in Region III. Filteruse was not included in multivariate models since it did not confound the association with amount of water consumed. In Region I, however, the spontaneous abortion rate was higher among cold tapwater drinkers who used a filter, particularly inwomen consuming ≥6 glasses of cold tapwater (27.3%).

We asked women who consumed cold tapwater about their usual consumption patterns, reasoning that a volatile agent in the water would be reduced by letting the water stand before drinking it. Overall, nearly half of the women (42.3%) reported that they either refrigerated the water or let it stand before drinking it, and this practice was not associated with the spontaneous abortion rate.

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A positive association between spontaneous abortion and increased duration of bathing and showering would suggest a volatile agent. We only asked women about their frequency and duration of showering, not bathing, so we had no way to compare these two exposures. Women who reported not showering (N = 62), who were likely to have been bathers, had increasedspontaneous abortion rates in Regions I and II. Since this variable was also related to tapwater consumption (over 50% of nonshowerers in Region I drank no tapwater), it was retained in the multivariate model. Among women who showered, little association was seen between time spent showering and risk of spontaneous abortion.

Multivariate Analyses

Because of the heterogeneity of associations across regions, we conducted separate multivariate analyses within each region.As the univariate analyses in Table 2 imply, there was no evidence that tapwater increased the risk of spontaneous abortion, or that bottled water decreased risk, in Regions II and III. In fact, when the two areas were combined, tapwater drinkers were at slightly lower risk relative to bottled water drinkers. In these regions combined, the adjusted odds ratio for high consumption of cold tapwater and no bottled water was 0.66 [95% confidence interval (CI) = 0.39-1.11], whereas for high total consumption, it was 0.63 (95% CI = 0.37-1.05). Therefore, further analyses were limited to Region I.

Table 3 contains unadjusted and adjusted odds ratios for high and moderate levels of consumption for each water type. Multivariate adjustment increased the odds ratio for tapwater, particularly for high consumption of "pure" cold tapwater (unadjusted odds ratio = 3.12; adjusted odds ratio = 4.58). Principal confounders were gestational age at interview, ethnicity,body weight, and not showering. Smoking, alcohol, caffeine, employment, marital status, season (at interview), and educationdid not confound this analysis and were not included further. Maternal age and prior spontaneous abortion, while not strong confounders, were included in multivariate models because they are well accepted risk factors for spontaneous abortion. Interestingly, adding pre-pregnant weight to the model, a correlate of "dose" for a waterborne agent, strengthened the association; without this variable in the model, the odds ratio for ≥6 glasses per day (cold tapwater drinkers who do not drink bottled water compared with high bottled water drinkers who do not drink cold tapwater) was 4.13, compared with 4.58 after adding pre-pregnancy weight to the model.

TABLE 3

Spontaneous Abortion Rates and Odds Ratios by Water Type and Amount in Region I

Water Type* and Comparison (Glasses/Day)	UOR† (95% CI)	AOR‡ (95% CI)
Bottled water		
0.5-5.5 *vs* 0	0.66 (0.46-0.95)	0.68 (0.47-0.99)
≥6 *vs* 0	0.68 (0.41-1.13)	0.60 (0.35-1.03)
≥6 and no cold tap *vs* 0 and ≥6 cold tap	0.32 (0.15-0.70)	0.22 (0.09-0.51)
Total tapwater§		
0.5-5.5 *vs* 0	0.98 (0.68-1.43)	1.03 (0.70-1.52)
≥6 *vs* 0	1.57 (0.95-2.61)	1.66 (0.99-2.78)
≥6 and no bottled *vs* 0 and ≥6 bottled	2.50 (1.11-5.64)	3.51 (1.43-8.63)
Cold tapwater		
0.5-5.5 *vs* 0	1.06 (0.74-1.52)	1.10 (0.76-1.59)

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≥6 *vs* 0	1.92 (1.09-3.36)	2.17 (1.22-3.87)
≥6 and no bottled *vs* 0 and ≥6 bottled	3.12 (1.42-6.86)	4.58 (1.97-10.64)

* Tapwater consumed at home at 8 weeks' gestation; bottled water consumed anywhere at 8 weeks' gestation. Total tapwater = cold + heated tapwater, including drinks made from tapwater.

† Unadjusted odds ratio.

‡ Odds ratio adjusted for age, prior spontaneous abortion, race, gestational age at interview, showering, weight.

§ Total tapwater = cold + heated tapwater.

Spontaneous abortion risk was approximately doubled among women drinking≥6 glasses of cold tapwater compared with women drinking no tapwater (adjusted OR = 2.17). In this "mixed" comparison, bottled water consumption is not restricted. In the "pure" comparison (comparing high cold tapwater drinkers who do not drink bottled water to high bottled water drinkers who do not drink cold tapwater), the adjusted odds ratio was increased to 4.58 (95% CI = 1.97-10.64). When we limited the multivariate analysis for "pure" cold tapwater to women who did not use a water filter, the adjusted odds ratio was somewhat reduced (adjusted OR = 3.29; 95% CI = 0.80-13.48).

Among the 95 women in Region I who drank≥6 glasses of cold tapwater per day and no bottled water, only 12 (12.6%) let the water stand before drinking it. Among these women, the association was particularly strong (adjusted OR = 10.39; 95% CI = 2.58-41.81), although the estimate was very unstable owing to small numbers. Among the 31 women who refrigeratedtheir water before drinking it, the odds ratio was similar to that for women who drank it straight from the tap (adjusted OR = 3.85; 95% CI = 1.20-12.41).

Total tapwater includes cold and heated tapwater (and drinks made from these). It was not possible to look at the risk of consumption of≥6 glasses of heated tapwater and no cold tapwater because of small numbers (N = 5). Nevertheless, theassociation with high cold tapwater consumption was attenuated by adding heated tapwater; for total tapwater, the adjusted odds ratio for high consumption, regardless of bottled water, was 1.66 (95% CI = 0.99-2.78). For high total tap excluding bottled water, it was 3.51 (95% CI = 1.43-8.63).

Even moderate amounts of bottled water consumption appeared to decrease the risk of spontaneous abortion in Region I (adjusted OR = 0.68; 95% CI = 0.47-0.99). Conversely, moderate consumption of cold tap or total tapwater did not alter spontaneous abortion risk (adjusted OR = 1.10 for cold tapwater and 1.03 for total tapwater, respectively). This "moderate group" was large, however, and the amount consumed varied widely (0.5-5.5 glasses per day). Therefore, we explored thesensitivity of our analysis to the choice of the cutpoint defining "high" consumption. In Table 4, we present the adjusted odds ratios for a range of cutpoints, from ≥2 glasses per day to ≥8 glasses per day. An approximately linear relation is seen as thecutpoint is increased, with some suggestion of a "plateau" at 6-7 glasses per day. Risk was increased (adjusted OR = 1.71;95% CI = 1.13-2.60), even among women drinking≥2 glasses of cold tapwater per day (and no bottled water), compared with women drinking≥2 glasses of bottled water per day (and no cold tapwater). Conversely, there was little variation in risk by amount of bottled water consumed.

TABLE 4

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Odds Ratios for High Cold Tapwater Consumption (No Bottled Water Intake) Compared with High Bottled Water Consumption (No Cold Tapwater Intake) in Region I: Varying Definition of "High Consumption"

	High Cold Tap and No Bottled*		High Bottled and No Cold Tap*			
"High" Consumption (Glasses/Day)	N	% SAB	N	% SAB	AOR	95% CI†
≥2	406	12.8	613	8.3	1.71	1.13-2.60
≥3	307	12.4	499	6.8	2.10	1.28-3.47
≥4	220	13.6	372	7.0	2.42	1.36-4.29
≥5	140	15.7	245	7.4	3.10	1.55-6.21
≥6	95	17.9	184	6.5	4.58	1.97-10.64
≥7	62	19.4	125	7.2	4.63	1.69-12.71
≥8	52	19.2	108	7.4	4.36	1.46-13.01

* Tapwater consumed at home at 8 weeks' gestation; bottled water consumed anywhere at 8 weeks' gestation.

† Adjusted for age, prior spontaneous abortion, race, gestational age at interview, showering, weight.

We did not include nausea in the multivariate analysis, although it is inversely related to risk of spontaneous abortion in all regions, because its absence is likely to be a measure of a failed pregnancy, and thus on the causal pathway to the endpoint under study.[12] Nausea did not modify the association with tapwater. The spontaneous abortion rate among women with high cold tapwater consumption (and no bottled water) was 2.7 times that of high bottled water consumers (drinking no cold tapwater) both in women with (14.1% *vs* 5.2%) and without (35.3% *vs* 13.3%) nausea.

When we selected 8 weeks as the exposure window for study, we did so because it was the mean gestational age at interview. For exposure during the week beginning with the last menstrual period and during the interview week, the adjusted odds ratios (for ≥6 glasses of cold tapwater and no bottled water *vs* ≥6 glasses of bottled water and no cold tapwater) were 3.65 and 4.09, respectively, compared with 4.58 at 8 weeks' gestation. This finding suggests that 8 weeks may be the critical window for this exposure.

Discussion

Before our report in 1989,[13] spontaneous abortion had not been studied in relation to water consumption. Since then, little work has been done to investigate water consumption as a risk factor for spontaneous abortion, aside from our subsequent studies.[1-5] Savitz *et al*[14] found a slight decrease in spontaneous abortion rates among women drinking ≥4 glasses compared with 1-3 glasses of water per day, regardless of source of water. Most work on reproductive effects of drinking water has focused on chlorination by-products,[14-16] except for one study looking at late pregnancy outcomes in relation to a variety of water constituents.[17]

In our prior studies, which found an association with tapwater, the relative risk estimates (unadjusted) for any cold tapwater, compared with none, ranged from 1.1 to 3.9 (with one higher point estimate undefined because all spontaneous abortions were among tapwater drinkers). The association with

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bottled water was weaker, although a negative dose response was seen in one case-control study.[4] In the present study, the crude rate ratio for any cold tapwater compared with none in Region I was 1.15, consistent with the range of results from these prior studies. In the two earlier cross-sectional studies, in which water consumption was quantified, spontaneous abortion rates for women consuming higher levels of tapwater were similar to thoseseen in the present study. For consumption of ≥4 glasses of tapwater, spontaneous abortion rates were 14.2% in the study by Deane *et al*[1] and 12.7% in that of Wrensch *et al*,[2] compared with 12.4% in the present study. Thus, results in Region I reported here are consistent with our previous findings. These results are also consistent with the results of two rodent studies[18,19] that found modestly increased rates of fetal resorption in rats which were given tapwater from homes of study subjects inRegion I.

The findings we published in 1992 were based on retrospective studies that included over 5,000 women. Here, we present a large prospective study which finds an association between tapwater and spontaneous abortion risk within the same study area. We[9] and others[7,8] had previously suggested that recall bias was a plausible explanation for our 1992 findings, particularly because two of these retrospective studies were conducted in an atmosphere of great community concern about the possible adverse reproductive effects of drinking water. Since recall bias is not an issue in this prospective study, however, differential recall seems less likely an explanation for the results of our former studies as well. In 1992, we discussed the possibility thatour results were due to confounding.[9] The results of the current study suggest that confounding is unlikely to explain either ourprior findings or our current results. First, after more careful measurement of confounders, multivariate adjustment served only to increase the effect estimates at high exposure levels. Moreover, for an unmeasured confounder (such as a health-protective behavior which reduced spontaneous abortion risk and which was more prevalent among bottled water drinkers) to explainour results, this factor must have been present only among bottled water drinkers in Region I. We explored this scenario using discriminant analysis to search for factors among our measured confounders which differentiate bottled water drinkers in Region I from those in Regions II and III. As can be seen in Table 1, stratum-specific amounts of tap and bottled water did not vary appreciably across regions. Nevertheless, we cannot rule out a strong unmeasured confounder present only in Region I, perhaps related to community concern in that area.

A major strength of this study lies is its prospective design, since recall bias was the most likely noncausal explanation for the prior findings. In addition, subjects were identified early in pregnancy, so that reliable information on periconceptional aswell as first trimester consumption could be ascertained. Furthermore, our study population was large enough to stratify the analysisby region, although not large enough to provide reliable information on specific water company or brand of bottled water. Small numbers also prevented us from looking at filter type. Thus, we could not explore the finding of a particularly high risk ofspontaneous abortion among cold tapwater drinkers in Region I who used a water filter. Although this may be a chancefinding, it suggests that more detailed study of filter type and frequency of servicing of the filter may be warranted.[20]

Another strength of this study is the virtually complete ascertainment (99%) of pregnancy outcomes among interviewed subjects. Among these women, the spontaneous abortion rate (9.7%) was similar to estimates from our previous cohort studies (9.4%, 9.8%, and 11.3% in studies by Hertz-Picciotto *et al*,[3] Wrensch *et al*,[2] and Deane *et al*,[1] respectively). Nevertheless, we had little information on the 186 women who miscarried between recruitment and contact for interview. Hadall of these outcomes been verified, the spontaneous abortion rate would have been 12.9%. Unfortunately, we have no information on water consumption for these noninterviewed cases, so we could not assess the

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possible bias due to their exclusion.

Despite the detail with which we questioned women about their water consumption, exposure misclassification may have beenappreciable. Tapwater consumption was undoubtedly underestimated, since we only asked subjects about their hometapwater consumption. Moreover, among pregnant women, only 54% of total water intake (which includes water contained infoods and added during food processing) is in the form of tapwater, and only 58% of tapwater is consumed in the form of drinking water.[21] Unmeasured water consumption is unlikely to be differential, however, and thus any exposure misclassification that it produced should have resulted in an underestimate of the relative risk.[22]

Moreover, the relevant exposure is probably not tapwater, *per se*, but rather some specific constituent more prevalent in Region I. Aside from data on trihalomethanes, discussed elsewhere;[10] little is known about the constituents of the water consumed by our subjects, except that waters met regulatory standards. Although we collected samples of water delivered tothe home for about 2% of study subjects, samples were not collected concurrent with pregnancy, and the sample size was too small to make valid inferences regarding the total population.

We stratified tapwater drinkers by water company and bottled water drinkers by brand of bottled water. The number of women per company or brand was small for most. No single water company or brand of bottled water was identified that could account for the associations reported here.

Our prior studies suggested that the relation between spontaneous abortion and tapwater was independent of chlorination by-products, since the strongest associations were seen in the two studies conducted in areas served only by unchlorinatedgroundwater.[1,2] Additionally, in the two rodent studies we conducted,[18,19] a trend toward increased rates of fetal resorption was seen in rats drinking unchlorinated groundwater, compared with bottled water. In our current study, as discussed in the study by Waller *et al*,[10] spontaneous abortion risk was increased by exposure to specific chlorination by-products in all regions. Nevertheless, we believe that the associations with cold tapwater and bottled water presented here, which are specific to Region I, cannot be explained by exposure to chlorination by-products, because the association is seen in the absence ofhigh levels of these chemicals. Moreover, the practice of letting water stand before drinking it, which allows chlorination by-products to volatilize, should decrease the risk of chlorination by-products. In this study, to the contrary, the association in Region I appeared stronger in heavily exposed women who followed that practice, although numbers were small.

The strong associations between spontaneous abortion risk and both cold tapwater and bottled water consumption that we present here are stronger than those reported by us in 1992. Moreover, we have now shown that recall bias and confoundingare not likely explanations for these findings. If causal, the agent(s) is not ubiquitous but is likely to have been present in RegionI for some time.

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