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Health Effects Among Newborns after Prenatal Exposure to ClO_2-Disinfected Drinking Water

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Because chlorination of potable surface waters may be associated with increased risk of carcinogenicity, substitute methods for the routine disinfection of public water supplies are being explored. As part of this search, it is especially important that the potential health effects of each alternative method should be considered. Chemical treatment of drinking water by chlorine dioxide (ClO_2) is a likely alternative mode of disinfection. Two common by-products of the ClO_2 disinfection of surface water are chlorate and chlorite. These oxidants may have negative health effects on certain high risk groups. Newborns, in particular, would seem to be at increased risk to red cell damage from oxidant stress.

The historical record study being reported here compares the morbidity and mortality experience of newborns in two similar communities, one of which used chlorination and the other which used high levels of chlorine dioxide for potable water disinfection. A statistically significant positive association was found between exposure of the mother to ClO_2-treated water during pregnancy and prematurity of the newborn as assessed by the attending physician and by a greater weight loss after birth. The rates of jaundice, birth defects and fetal and neonatal mortality did not differ significantly between communities. Because of the limitations of the study design, the findings reported here should be considered suggestive rather than definitive.

Chlorine is the traditional method for disinfecting potable water supplies. However, recent studies have demonstrated that the interaction of chlorine with naturally occurring humic acids in drinking water results in the formation of trihalomethanes (*1,2*), some of which are known or suspected carcinogens (*3,4*). The most common of these trihalomethanes, chloroform, has been shown in laboratory studies to produce hepatomas in selected mouse and rat strains in the exposure range of 90-447 mg/kg of body weight (*5*). Further, a number of ecological epidemiological studies have suggested a positive association between the practice of water chlorination and cancer mortality (*6,7*), although not all similar studies have supported this association (*8*). Preliminary results of the more recent case-control studies are reported in a review by Crump et al. (*9*).

Presently, alternative disinfection methods are being actively explored as possible substitutes for chlorination of potable water supplies. Chlorine dioxide (ClO_2) disinfection is among the alternatives being considered for adoption. The oxidants chlorate and chlorite are the primary by-products resulting from ClO_2 disinfection of surface water (*4,10*). The levels of these compounds can exist in significant amounts in ClO_2-dosed water supplies although they vary with different water characteristics and treatment conditions. Chlorites may appear in concentrations of up to 50 percent of the ClO_2 demand (*10*).

There is evidence indicating that chlorates and chlorites may themselves pose a hazard to health. The oral administration of chlorates to mice in large amounts has been shown to produce methemoglobinemia with blood destruction (*11*). Richardson suggested that similar changes might develop in chronic poisoning with manifestations of anemia,

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uremia, and evidence of nephritis. Chlorite and hypochlorite are thought to oxidize hemoglobin even more rapidly than chlorate (*12*).

Heffernan et al. (*13*) exposed cats and rats to sodium chlorite in drinking water and demonstrated dose-related decreases in erythrocyte glutathione levels at chlorite concentrations as low as 50 ppm. Additionally, an increased turnover of red blood cells of cats exposed to ClO_2 suggested that a compensated hemolytic anemia had occurred. Heffernan concluded that particular attention must be paid to the exposures of individuals sensitive to hemolytic anemia.

There is evidence that the fetus *in utero* (*14*) and the newborn appear to be at increased risk to red cell damage from oxidant stress. Fetal hemoglobin is more readily oxidizible than is adult hemoglobin (*15*), and infants have a lower enzymatic capacity to reduce methemoglobin once formed (*16*). Newborns also have a flavine and vitamin E deficiency (*16*), and these substances are thought to be important antioxidant compounds. Finally, since infants consume about three times more liquid per pound of body weight than do adults (*17*), this group would be maximally exposed to the products of ClO_2 water disinfection.

The study being reported here was designed to investigate likely health effects among newborns with prenatal exposure to ClO_2-disinfected water. It was hypothesized that certain health effects might result from oxidant stress to the fetus or newborn because of the exposure of the mother to chlorate and chlorite. The hypothesis tested was that newborns with prenatal exposure to ClO_2-treated drinking water consumed by their mothers would show increased rates of jaundice, prematurity, reduced birth weight, failure to thrive and possibly higher fetal and neonatal mortality.

Methods

Since there were no water supplies in the United States known to be employing ClO_2 at high levels for disinfectant purposes, the current study was carried out using records from the 1940s. The morbidity and mortality experience of infants born in a Massachusetts community using relatively high levels of ClO_2 for water disinfection was compared to that of infants in a suitable comparison community practicing conventional chlorination of drinking water supplies.

Infants born in a one-year period following a complete year of the highest ClO_2 usage were chosen for the study to maximize the probability of observing adverse health effects should they exist. In the first step, data from birth records were linked to hospital medical records of the child and mother for both communities. Secondly, a trend analysis of fetal, neonatal, and infant mortality in the two communities was carried out to assess any mortality differences between the communities before, during and immediately following the five-year period of ClO_2 usage.

Chicopee, Massachusetts, was one of approximately 150 United States public water supplies which used chlorine dioxide for water treatment between 1944 and 1958. However, these communities generally used ClO_2 at low concentrations for taste and odor control. Chicopee initiated treatment with ClO_2 in 1945 at relatively high levels for water disinfection as well as to overcome a taste and odor problem resulting from organic and other contamination in runoff from Westover Air Force Base. Traditional chlorination had proven unsatisfactory in treating this problem.

While the ClO_2 concentration formed was not directly measured, the concentration of sodium chlorite added post treatment, and the residual of chorine species, can be used as an indicator of ClO_2. As indicated in Figure 1, the highest levels of sodium chlorite were added in 1945 with a monthly high of 0.56 ppm, a monthly average of 0.32 ppm and residuals of chlorine species exceeding 0.30 ppm. Levels of sodium chlorite added declined after 1945 to levels of 0.16 ppm prior to September 1950 when the changeover was made to Quabbin, MDC water.

Holyoke, a geographically contiguous community, was selected as a comparison community. The two communities largely shared the same maternity facilities, and, as Table 1 shows, they were relatively similar in socioeconomic characteristics affecting neonatal morbidity and fetal and neonatal mortality.

Results

Neonatal Morbidity

Over 94% of the 1068 births registered to Chicopee mothers and 98% of the 1244 Holyoke births were identified as occurring in the four major hospital maternity centers. The location of births and reasons for exclusion from the study are detailed in Table 2. It should be noted that the majority of Chicopee mothers delivered at Providence Hospital or the Springfield Hospitals. For Holyoke mothers the majority of deliveries were in Providence and Holyoke hospitals. Home births, missing or destroyed records and exclusion for other reasons reduced the final study group to 903 (84.6%) of the Chicopee infants and 1112 (89.4%) of the Holyoke births. The exclusion rate was similar for the three hospital groups. It should be noted that the difference between

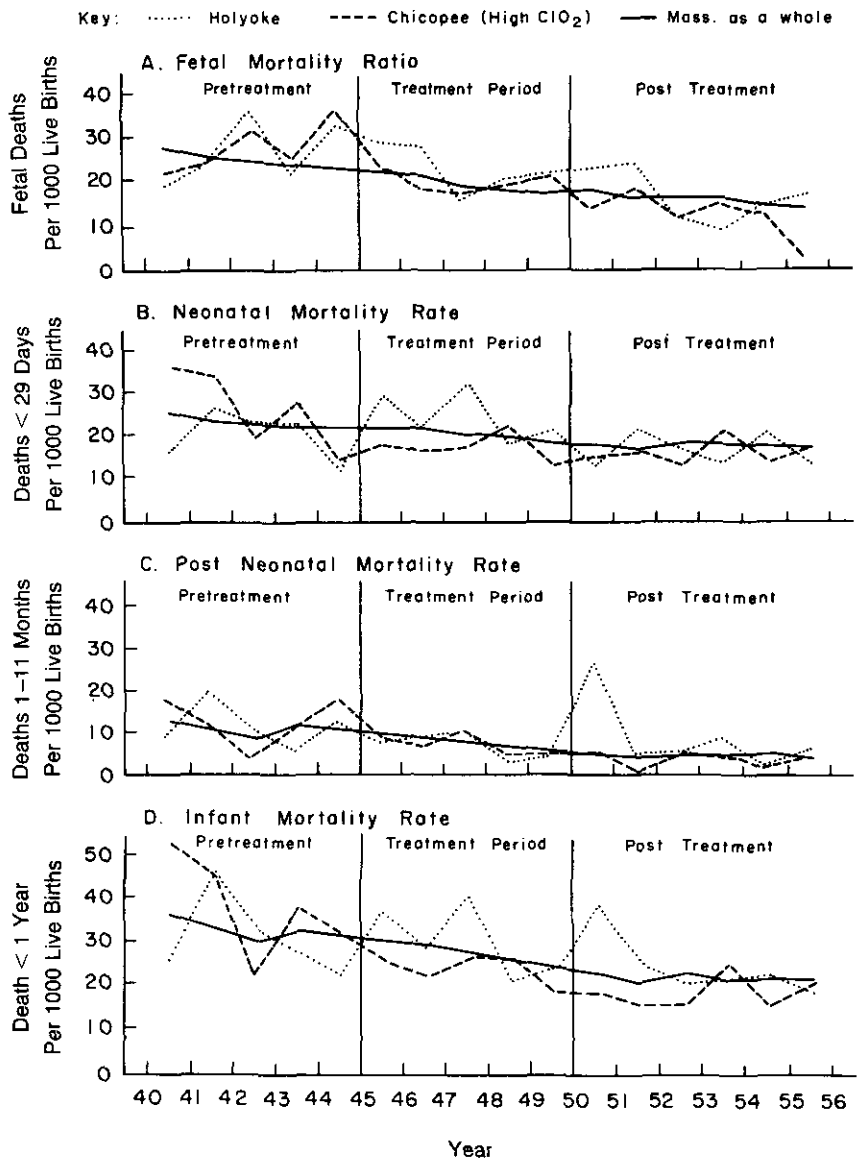

FIGURE 1. Fetal, neonatal, postnatal and infant mortality ratio in Chicopee and Holyoke, 1940–1955. Source: Annual Vital Data Reports, Massachusetts Department of Health.

the communities in the proportion of births at each hospital required that all data analyses be controlled for hospital of occurrence of the birth.

The initial examination of the data, including the Kolmogorov-Smirnov one-sample test for normality, indicated that the continuous study variables were from nonnormal population distributions. Therefore, all statistical analyses were carried out by nonparametric methods.

The Wilcoxon stratified (partial rank sum) test was used to assess statistically significant differences in continuous outcome and control variables between communities while stratifying by hospital.

Table 1. Comparison of demographic characteristics in Chicopee and Holyoke, Massachusetts, in 1950.[a]

	Chicopee	Holyoke
Total population (all ages)	49,211	54,661
Females (ages 15-44)	11,339	11,939
Nonwhite, %	0.8	0.6
Foreign-born, %	15.1	17.0
% of males 14+ engaged in manufacturing	61.9	53.0
Median income, $	3,103	2,817
Median education for persons aged 14+, years	9.1	9.9
General fertility rate	9.3	9.2

[a]Source: U.S. Bureau of the Census (*18*).

Table 2. Location of births to Chicopee and Holyoke mothers by place of occurrence in 1946 and reasons for exclusion.

	Chicopee Mothers	Hoyoke Mothers
Location of birth		
At home	29 (2.7)	15 (1.2)
Holyoke Hospital, Holyoke	81 (7.6)	481 (38.7)
Providence Hospital, Holyoke	444 (41.6)	701 (56.4)
Wesson or Mercy, Springfield	439 (41.1)	23 (1.8)
Infirmary, Springfield	31 (2.9)	1 (0.1)
Records not located[a]	44 (4.1)	23 (1.8)
Total registered births[b]	1068 (100.0)	1244 (100.0)
Source of exclusions		
Home births, no records	29 (2.7)	15 (1.2)
Records not located[a]	44 (4.1)	23 (1.8)
Records discarded[c]	31 (2.9)	1 (0.1)
Excluded for other reasons[d]	61 (5.7)	93 (7.5)
Final study sample	903 (84.6)	1112 (89.4)

[a]Hospital of birth had no medical record in their files that could be found.
[b]All registered births to Chicopee and Holyoke mothers in 1946 were accounted for.
[c]Springfield Infirmary closed down in 1947, and all medical records were subsequently discarded.
[d]Other exclusions included twins, stillborns, infants with erythroblastosis fetalis, nonwhite infants and births to Westover Air Force Base mothers who lived on the base and received a separate water supply.

Table 3. Distribution of key outcome and control variable values by hospital and community.

		Hospital			
	City	Providence	Holyoke	Wesson/Mercy	All
Number of births	Chicopee	421	79	403	903
	Holyoke	629	462	21	1112
Outcome variables					
Premature by physician assessment, %	Chicopee	10.7	6.3	1.7	7.8
	Holyoke	6.7	4.6	0.0	5.8
Birth condition listed as fair or poor, %	Chicopee	5.7	6.3	2.7	4.4
	Holyoke	5.4	3.0	0.0	4.3
Premature by birth weight, %	Chicopee	7.4	3.8	5.0	6.0
	Holyoke	6.4	6.7	0.0	6.4
Premature by gestational age (< 37 weeks), %	Chicopee	40.1	–	17.6	–
	Holyoke	41.2	–	19.1	–
Mean birth weight, g	Chicopee	3265.2	3293.7	3300.4	3283.0
	Holyoke	3318.1	3258.7	3461.8	3296.0
Mean maximum weight loss, g	Chicopee	–158.0	–157.8	–208.8	–180.6
	Holyoke	–145.1	–171.2	–208.1	–157.1
Mean weight loss at six days, g	Chicopee	–109.0	–63.4	–135.8	–117.2
	Holyoke	–93.0	–89.2	–154.0	–92.6
Control variables					
Infants formula fed, %	Chicopee	44.6	33.8	35.4	39.5
	Holyoke	52.6	43.0	23.8	48.0
Mean age of mother	Chicopee	27.1	27.1	27.2	27.1
	Holyoke	27.9	27.5	27.7	27.7
Mean vitamin K dose	Chicopee	2.73	3.21	0.85	1.92
	Holyoke	2.74	3.31	1.33	2.95

The dichotomous variables were analyzed using an extension of the Mantel-Haentzel procedure for summing 2 × 2 tables.

Using the above approach, there were several statistically significant differences between newborns of the two communities. As indicated in Table 3, a greater proportion of Chicopee infants were premature by physician assessment ($p < 0.05$). Although the proportion of infants defined as premature by physician assessment differed considerably by hospital, Chicopee infants were more often rated premature in all three hospitals. In concert with the assessment, a greater proportion of infants from Chicopee were rated as being in fair or poor condition at birth in all three hospitals, although the difference overall is not statistically significant.

Several other commonly used measures of prematurity did not lend consistent support to the physician assessment of prematurity. Although a statistically significantly greater proportion of Chicopee infants were premature by birth weight (<2500 g) in Providence hospital, that effect was not consistent for the other hospitals, and the overall difference, irrespective of hospital, was in the opposite direction and not statistically significantly different. Prematurity as judged by gestational age (< 37 weeks) showed a lower proportion of Chicopee infants with a shorter estimated gestational age. However, data on gestational age were not available from Holyoke hospital birth records. Finally, mean birth weight, although statistically significantly lower for Chicopee infants overall ($p < 0.05$), was not consistently lower for all three hospitals.

There were no statistically significant differences between communities for the following birth outcome variables: jaundice, birth defects, discharge condition rated fair to poor, death in the first year, maximum weight loss, weight loss at six days or birth length.

Among the potential control variables, there were no statistically significant differences between the communities for the following: proportion of male births, maternal risk factors present, previous pregnancy loss, maternal gravidity, proportion lower social class, or proportion primiparous. Differences that did exist between communities were a lower percent of Chicopee infants formula fed ($p < 0.05$), a lower mean ($p < 0.05$) age of Chicopee mothers, and a lower vitamin K dose for Chicopee infants ($p < 0.05$). In the case of the formula feeding, Providence hospital showed the greatest difference. Age of Chicopee mothers was consistently younger in all hospitals, although Providence hospital had the greatest difference. The vitamin K disparity was found primarily in the Wesson-Mercy hospitals. Social class differences between communities were found when social class was categorized into five groups ($p < 0.01$), but social class was unrelated to any of the significant outcome variables of prematurity or weight change after birth.

Age of mother was both different between communities and positively related to birth weight while mode of feeding was different between communities and related to weight loss among the infants after birth. Because of the possibility of negative confounding, further analyses were carried out to examine the effects of controlling birth weight differences by age, and of controlling the weight change variables by mode of feeding. A Wilcoxon stratified (partial rank sum) test was used to assess the birth weight differences between the communities when stratifying by age of mother and by hospital. Controlling for age considerably reduced the earlier differences in mean birth weight between infants of the two communities and the differences were no longer statistically significant.

The same approach was used to assess the differences in weight change between the communities' infants when controlling for mode of feeding by the mother and for hospital site. For weight at six days compared to birth weight there was a statistically significant overall difference in mean weight loss ranks between the infants of the two communities. The difference was consistent in both hospitals for breast-fed and mixed-fed babies but there was a small difference of opposite direction between the formula-fed groups in either hospital. A similar analysis of maximum weight loss in the first six days showed an overall statistically significant difference ($p < 0.01$) although there was an inconsistent direction of the association in the Holyoke-Wesson/Mercy hospital group compared to the consistently greater maximum weight loss for Chicopee infants for all feeding groups in Providence Hospital.

Infant Mortality

The mortality analysis over time showed no clear or consistent patterns of fetal, neonatal, post neonatal, or infant mortality in the ClO_2 usage community versus the comparison community. These results are detailed in Figure 2.

Discussion

Few towns, if any, in the United States employed ClO_2 as a disinfectant at the time this study was carried out. Those towns that currently use ClO_2 use it at a low level for taste and color control.

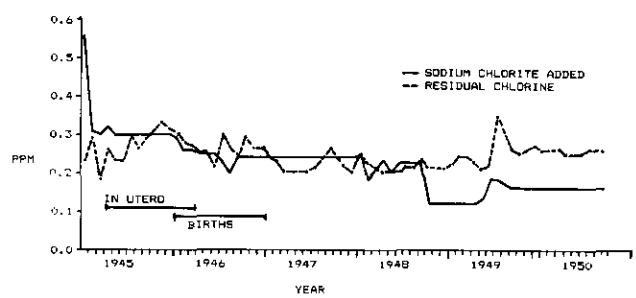

FIGURE 2. Average monthly values of $NaClO_2$ added (ppm) and residual chlorine (ppm) in Chicopee, Mass., water supply, 1945–1950. Source: chemist's reports, Chicopee Water Department.

Therefore, the methodological options for studying the health effects of ClO_2-treated drinking water on human population were limited to a historical study design of an ecological nature.

The retrospective study design imposed several limitations. Information on important control variables such as smoking, drinking, and nutritional habits of the mother during pregnancy was not available, although these habits may not have differed between communities. Additionally, the length of residence of the mother in the community could not be determined for the vast majority of test mothers. This may have resulted in inclusion of infants in the test group who were not in fact exposed to ClO_2-disinfected water during the entire length of gestation. Such a factor would have worked against finding the hypothesized relationships regarding fetal development.

An important limitation of the study resulted from the subjectivity of some of the outcome measures. The presence of jaundice, the general physical condition at birth and at discharge, and the physicians' assessment of prematurity were not clearly defined nor necessarily uniformly recorded by the physicians in 1946.

Unfortunately, the criteria for the physicians' assessment of prematurity were not specified in the records of the study hospitals, although the physicians were probably noting reflexes, muscle tone, skin appearance and other external features in making their judgments. Clearly, the physicians' assessments of prematurity were consistently higher for Chicopee infants in all three hospitals. As well, the percent of infants classified premature by the physicians did differ dramatically by hospital. The difference between communities for all hospitals combined is affected by both the big differences between hospitals as well as the differential weighting of the Holyoke and the Wesson/Mercy hospitals caused by Holyoke hospital being used predominately by Holyoke mothers and Wesson/Mercy almost exclusively by Chicopee mothers. These differences in premature assessment practices between communities could be due to differences in physicians' criteria, hospital policies, or the nature of the mothers who selectively attended that hospital. Unfortunately, the large number of attending physicians and the small number of patients seen by each physician made control for attending physician, within or between hospitals, impossible. The selective attendance problems cannot be fully assessed, although it was not related to age of mother or socioeconomic status.

Although fraught with difficulties, the study was deemed important because of the potential health implications of the proposed adoption of ClO_2 disinfection. It was felt that given the sample size and the relatively high concentration of chlorine dioxide employed in water treatment during the years studied, significant adverse health effects of prenatal exposure to treated water would be observed if they indeed existed.

Conclusions

The study found a higher percent of Chicopee newborns judged premature by physician assessment. This finding was consistent in direction for all hospitals and was unaffected by other differences between the communities. Although birth weight appeared initially lower in Chicopee infants, after controlling for the age of the mother, this difference between the communities essentially disappeared. Several other measures of prematurity likewise did not support the difference in physician assessments.

There was an indication that Chicopee infants suffered a greater maximum weight loss after birth and a smaller weight gain at six days. After controlling for mode of feeding practiced by the mother, this difference between communities remained but was not consistent in direction for all hospital/mode of feeding groups.

The limited negative health effects identified in this study were not severe or life threatening in and of themselves. However, in considering the larger significance of these findings, ClO_2 exposure should be considered as it acts in concert with other factors to produce oxygen stress. The implications of added oxidant stress from ClO_2-treated water on infants exposed to high levels of nitrites or other hemoglobin oxidizing agents, or in infants with metabolic (G6PD-deficiency) or dietary deficiencies (vitamin E) which contribute to oxidant stress could be profound. Before ClO_2 is recommended for wide use in the United States as a water disinfectant, procedures should be established to insure minimal chlorite/chlorate formation during the water treatment process. Additional studies should be undertaken to more accurately assess the potential health effects of chlorite exposure on susceptible populations before widespread use of ClO_2 is encouraged or mandated.

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