

## CLINICAL REPORT

Guidance for the Clinician in Rendering Pediatric Care

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## Infant Methemoglobinemia: The Role of Dietary Nitrate in Food and Water

**ABSTRACT.** Infants for whom formula may be prepared with well water remain a high-risk group for nitrate poisoning. This clinical report reinforces the need for testing of well water for nitrate content. There seems to be little or no risk of nitrate poisoning from commercially prepared infant foods in the United States. However, reports of nitrate poisoning from home-prepared vegetable foods for infants continue to occur. Breastfeeding infants are not at risk of methemoglobinemia even when mothers ingest water with very high concentrations of nitrate nitrogen (100 ppm). *Pediatrics* 2005;116:784-786; *methemoglobinemia*.

### INTRODUCTION

Nitrate poisoning resulting in methemoglobinemia continues to be a problem in infants in the United States. Most reported cases have been ascribed to the use of contaminated well water for preparation of infant formula.<sup>1-3</sup> Fifteen million families in the United States obtain their drinking water from unregulated wells.<sup>4</sup> In a survey of 5500 private water supplies from 9 Midwestern states, 13% of the wells were found to have nitrate concentrations >10 mg/L or 10 ppm nitrate nitrogen,<sup>5</sup> the federal maximum contaminant level.<sup>6</sup> It is estimated that 2 million families drink water from private wells that fail to meet the federal drinking-water standard for nitrate, and 40 000 infants younger than 6 months live in homes that have nitrate-contaminated water supplies.<sup>4</sup> In urban areas, municipal wastewater-treatment discharges (a source of nutrients) on surrounding farmland aggravate the problem.<sup>7</sup>

There have been occasional cases of nitrate poisoning in infants from ingestion of plant nitrates,<sup>8-13</sup> only one of which was reported from the United States.<sup>9</sup> Nitrates are natural constituents of plant material, and the effect of commercial nitrate-containing fertilizers on the nitrate content of vegetables is inconsistent.<sup>14</sup> Because the intake of naturally occurring nitrates from foods such as green beans, carrots,

squash, spinach, and beets can be as high as or higher than that from well water, these foods should be avoided before 3 months of age, although there is no nutritional indication to add complementary foods to the diet of the healthy term infant before 4 to 6 months of age.<sup>14,15</sup> Some commercially prepared infant food vegetables are voluntarily monitored for nitrate content by private industry, including spinach, squash, and carrots. A target concentration of nitrate nitrogen for food of <100 ppm is desirable for infants. Because this concentration is frequently exceeded in spinach, this product is often labeled not to be used in infants younger than 3 months.

For breastfed infants, there is no evidence of an increased risk of methemoglobinemia from maternal ingestion of water with nitrate nitrogen concentrations as high as 100 ppm, because these mothers do not produce milk with high nitrate concentrations.<sup>16</sup> Furthermore, the predominant organism in the gastrointestinal tract (*Lactobacillus* species) of the breastfed infant does not reduce nitrate to nitrite (see following section).<sup>14</sup>

### PATHOPHYSIOLOGY

The potential hazard of nitrate in either food or water is from its conversion to methemoglobin-producing nitrites before and/or after ingestion. The nitrite ion oxidizes ferrous iron in hemoglobin to the ferric state. The resulting compound, methemoglobin, is incapable of binding molecular oxygen and produces a leftward shift in the oxygen-dissociation curve, which results in hypoxemia. Absorbed nitrate that has not been converted to nitrite can be readily excreted in the urine without adverse effects.<sup>14</sup>

There are many factors that influence the incidence of methemoglobinemia in infancy.<sup>14,17</sup> The gastric pH of infants is higher than that in older children and adults, with resultant proliferation of intestinal flora that can reduce the ingested nitrate to nitrite. Fetal hemoglobin, the predominant form in infants up to 3 months of age, is oxidized more readily to methemoglobin by nitrite than is adult hemoglobin. Red blood cells contain methemoglobin reductases that convert methemoglobin back to hemoglobin. Ninety-nine percent of this reduction activity is accounted for by cytochrome-b<sub>5</sub> methemoglobin reductase; the activity of this enzyme is reduced by half in

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doi:10.1542/peds.2005-1497

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infants compared with adults.<sup>18</sup> Although these factors explain the higher incidence of methemoglobinemia in infants, there are not enough data to identify a specific level of nitrate intake that is safe for all infants.

### CLINICAL MANIFESTATION

Methemoglobinemia generally manifests with few clinical signs other than cyanosis. Methemoglobin represents only 1% of the total hemoglobin of the healthy adult, although it can be slightly higher in preterm and term newborn infants.<sup>19</sup> Obvious cyanosis can occur with methemoglobin concentrations as low as 3% in infants with low hemoglobin concentrations. Symptoms are usually minimal until methemoglobin concentrations exceed 20%.<sup>20</sup> The mucous membranes of infants with methemoglobinemia tend to have brown (rather than blue) discoloration. This discoloration increases with the concentration of methemoglobin, as do the manifestations of irritability, tachypnea, and altered mental status.<sup>20</sup> In the absence of respiratory symptoms, history of cardiovascular disease, abnormal pulse, or abnormal pulse oximetry, a diagnosis of methemoglobinemia should be considered in a child who becomes acutely cyanotic and fails to respond to oxygen administration. When significant concentrations of methemoglobin (>30%) are present, a pulse oximeter is very misleading and will detect only mild to moderate oxygen desaturations in the 82% to 86% range.<sup>20</sup>

### TREATMENT AND PREVENTION

Health care professionals who suspect that an infant has methemoglobinemia are advised to consult with the local poison control center or a toxicologist to help guide management. An asymptomatic infant with cyanosis who has a methemoglobin concentration of <20% usually requires no treatment other than identifying and eliminating the source of exposure (assuming a normal hematocrit). Anemic children will display toxicity at lower methemoglobin concentrations. More detailed information on diagnosis and treatment has been reviewed elsewhere.<sup>20</sup>

Clinical diagnosis and treatment for methemoglobinemia is not sufficient. Preventive strategies are needed to identify and eliminate the sources of exposure.<sup>21</sup> Assessment of potential nitrate exposure includes questions about the family residence, parental occupations, drinking water, foods ingested, topical medications, and folk remedies. Prenatal and newborn care for patients with private wells should include recommendation for testing well water for nitrate contamination. Water with high nitrate concentrations should not be ingested by the infant or used for preparation of infant formulas or infant foods. Use of alternative sources of water should be advised, including deeper wells, public water supplies, or bottled water free of nitrate. Boiling water with nitrate nitrogen concentrations of <10 ppm for 1 minute generally is sufficient to kill microorganisms without over concentrating nitrate.<sup>21</sup>

Effective in-home systems for nitrate removal include ion-exchange resins and reverse osmosis; however, these systems can be expensive. Ordinary water

softeners used in the home do not remove nitrates.<sup>22</sup> Water testing for nitrate can be obtained from any reference or public health laboratory using laboratory methods approved by the US Environmental Protection Agency. Most state health departments have listings of these certified laboratories.

There is limited information on the nitrate content of commercial infant foods, although the highest concentrations (>100 ppm of nitrate nitrogen) are found in beets, carrots, spinach, squash, and green beans.<sup>14,15</sup> Preventive strategy would be not to introduce home preparations of these vegetables to infants before 3 months of age, although there is no nutritional indication to add complementary foods to the diet of the healthy term infant before 4 to 6 months of age.<sup>23</sup> Infants fed commercially prepared infant foods after 3 months of age generally are not at risk of nitrate poisoning, although the containers should be refrigerated after first use and discarded within 24 hours of opening.

### SUMMARY

1. The greatest risk of nitrate poisoning (methemoglobinemia) occurs in infants fed well water contaminated with nitrates. All prenatal and well-infant visits should include questions about the home water supply. If the source is a private well, the water should be tested for nitrate. The nitrate nitrogen concentration of the water should be <10 ppm.
2. Infants fed commercially prepared infant foods generally are not at risk of nitrate poisoning. However, home-prepared infant foods from vegetables (eg, spinach, beets, green beans, squash, carrots) should be avoided until infants are 3 months or older, although there is no nutritional indication to add complementary foods to the diet of the healthy term infant before 4 to 6 months of age.
3. Breastfed infants are not at risk of nitrate poisoning from mothers who ingest water with high nitrate content (up to 100 ppm nitrate nitrogen), because nitrate concentration does not increase significantly in the milk.

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*Pediatrics* 2005;116:784

DOI: 10.1542/peds.2005-1497

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