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Maternal perchlorate exposure in pregnancy and altered birth outcomes☆

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ABSTRACT

Background:: At high medicinal doses perchlorate is known to decrease the production of thyroid hormone, a critical factor for fetal development. In a large and uniquely exposed cohort of pregnant women, we recently identified associations between environmental perchlorate exposures and decreased maternal thyroid hormone during pregnancy. Here, we investigate whether perchlorate might be associated with birthweight or preterm birth in the offspring of these women.

Methods:: Maternal urinary perchlorate, serum thyroid hormone concentrations, birthweight, gestational age, and urinary nitrate, thiocyanate, and iodide were collected in 1957 mother-infant pairs from San Diego County during 2000–2003, a period when the county's water supply was contaminated with perchlorate. Associations between perchlorate exposure and birth outcomes were examined using linear and logistic regression analyses adjusted for maternal age, weight, race/ethnicity, and other factors.

Results:: Perchlorate was not associated with birth outcomes in the overall population. However, in analyses confined to male infants, $\log_{10}$ maternal perchlorate concentrations were associated with increasing birthweight ($\beta = 143.1$ gm, $p = 0.01$), especially among preterm births ($\beta = 829.1$ g, $p < 0.001$). Perchlorate was associated with male preterm births ≥ 2500 g (odds ratio = 3.03, 95% confidence interval = 1.09–8.40, p-trend = 0.03). Similar associations were not seen in females.

Conclusions:: This is the first study to identify associations between perchlorate and increasing birthweight. Further research is needed to explore the differences we identified related to infant sex, preterm birth, and other factors. Given that perchlorate exposure is ubiquitous, and that long-term impacts can follow altered birth outcomes, future research on perchlorate could have widespread public health importance.

1. Introduction

Perchlorate (ClO_4^-) is a highly stable oxidizing chemical component of missile fuel, road flares, and other products. Perchlorate exposure in the US is ubiquitous, typically occurring through contaminated food or water. In a recent nationwide US survey, perchlorate was detected in the urine of every person tested (Blount et al., 2006).

At medicinal levels (e.g. 800 mg), perchlorate competitively inhibits uptake of iodide by the sodium iodide symporter (NIS) in the thyroid gland (Tonacchera et al., 2004). Iodide is the predominant form of iodine found in diet. Iodide anion accounts of > 90% of total iodine in urine and is the biologically available form that is transported into the thyroid to produce thyroid hormones. Since iodide is a key component of thyroid hormone, inhibiting its uptake into the thyroid can decrease

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thyroid hormone production. In the developing fetus and child, thyroid hormone is vital for proper development, and decreases in this hormone have been linked to significant decreases in IQ and other adverse neurologic outcomes (Haddow et al., 1999; Pop et al., 2003, 1999; Henrichs et al., 2013). Pregnancy is a time of thyroid stress and increased iodine demands, and this could lead to pregnancy being a period of particular susceptibility to perchlorate (Miller et al., 2009).

Thyroxine (T4) is the major circulating form of thyroid hormone, and free thyroxine (fT4) is its non-protein bound form. Thyroid stimulating hormone (TSH) is produced by the pituitary in response to low thyroid hormone concentrations in plasma, and stimulates the thyroid to produce more T4. Elevated TSH acts as a sensitive marker for thyroid stress since TSH is commonly effective at maintaining adequate serum concentrations of T4. In the largest study to date of perchlorate in pregnant women, we identified statistically significant associations between increasing urinary perchlorate concentrations and decreasing serum T4 and fT4 and increasing TSH concentrations (Steinmaus et al., 2015). This study involved samples and data collected from pregnant women who gave birth in San Diego County between November 2000 and March 2003. This was a time when a large groundwater plume of perchlorate from a former perchlorate manufacturing plant contaminated the Las Vegas Wash, a tributary of the Colorado River (US EPA, 2005). This contamination led to widespread perchlorate exposure, since the Colorado River supplies drinking water for 15–20 million people in Nevada, Arizona, and California, including much of San Diego County. The contamination resulted in perchlorate concentrations approaching the current California regulatory standard of 6 μg/L in the county's major drinking water supply. Other water sources in the county had much lower perchlorate concentrations. This exposure situation, combined with likely variations in intake of perchlorate from food, provided a wide range of perchlorate exposure among county residents.

Although several studies, including ours, have linked perchlorate to impacts on thyroid function, few studies have examined perchlorate in relation to overt adverse health effects. Based on the associations we identified in our previous study, and the well-known role thyroid hormone plays in fetal development, we investigated whether maternal perchlorate may have impacted birthweight or gestational age in our San Diego cohort. We also evaluated whether any associations we identified might be greater in certain potentially susceptible subpopulations. In previous research, perchlorate-thyroid hormone associations were greatest in subjects with elevated intakes of thiocyanate and nitrate, or with very high or low urinary levels of iodide (Blount et al., 2006; Steinmaus et al., 2015, 2007). Thiocyanate (from foods or tobacco smoke) and nitrate (from foods or contaminated water) also competitively inhibit thyroid iodide uptake, and may have additive impacts with perchlorate (Tonacchera et al., 2004). Previous research has also shown that birth outcomes or the adverse effects of environmental chemicals may be related to gender, ethnicity or race, or migration status (Heck et al., 2016; United Nations Development Programme, 2011), and we assessed potential susceptibility related to these factors as well.

2. Methods

2.1. Study design and data collection

Subjects were a convenience sample of pregnant women and their newborns from San Diego County, delivered from November 2000 to March 2003, and already recruited as part of Project Baby's Breath (PBB), a study of tobacco and other environmental exposures during pregnancy. PBB involved 14 hospitals and 41 community clinics and obstetrical care providers widely spread throughout the county, and the collection and frozen storage of urine, blood, and cord blood samples originally obtained for non-study purposes. Urine samples assayed for the present analysis were left over from spot urine samples collected from PBB subjects for pregnancy tests at a median of seven weeks gestation. After pregnancy testing, clinic staff transferred the remaining urine into 5 mL Corning cryovials that were refrigerated and transferred within one day to a central laboratory for storage at –20 °C. Perchlorate is stable for many months in water at room temperature (Stetson et al., 2006), and for years in frozen urine (Blount et al., 2007). Serum samples assayed for the present analysis were left over from samples collected by obstetrical care providers at approximately 15–20 weeks gestation from PBB subjects who participated in the California Prenatal Screening (PNS) Program (California Department of Public Health, 2010). After collection in 4 mL serum separator tubes, specimens were spun down and tested for chromosomal abnormalities and neural tube defects, with a median time between collection and PNS testing of three days. After PNS testing and 1–2 days of refrigeration, remaining serum from PBB study participants was transferred to 4 mL Corning cryovials and stored at –20 °C. Samples not assayed within seven days of collection were excluded from the PNS and not available for PBB. Mannisto *et al.* reported that fT4 or TSH were relatively stable for 6 days at 4 °C and up to 23 years at −25 °C (Mannisto et al., 2007). Information on mother's age, highest education, prenatal weight, payment method (e.g., private insurance vs. MediCal), and race/ethnicity was collected from birth records. Information on prenatal weight was derived from the PNS program. Gestational age was calculated using the date of conception estimated from ultrasound and information on last menstrual period collected during prenatal screening, a method that produces more accurate gestational age estimates than relying on last menstrual period dates from birth records (Dietz et al., 2007; Pearl et al., 2007). For subjects not participating in prenatal screening (approximately 10%), gestational age was based on the date of last menstrual period recorded on birth records. Urine and serum samples, PNS program data, and birth records were linked using probabilistic matching software. PNS to birth match rates using this method are generally 93% (Kharrazi et al., 2012). Informed consent was obtained for collection of leftover urine and blood specimens for the PBB study and for future testing of stored specimens for environmental contaminants. PNS program participants signed a consent/refusal form and received a privacy notification regarding research use of their specimen. The PBB study and the study presented here were approved by the State of California Committee for the Protection of Human Subjects.

2.2. Laboratory measurements

Urinary perchlorate is the most common biomarker for evaluating perchlorate exposure, since most ingested perchlorate is excreted unchanged in the urine (Blount and Valentin-Blasini, 2007). Urine samples were shipped overnight to the Centers for Disease Control and Prevention (CDC) on dry ice and analyzed by the CDC's Perchlorate Biomonitoring Laboratory for perchlorate (detection limit, 0.05 μg/L), thiocyanate (20 μg/L), nitrate (700 μg/L), and iodide (0.5 μg/L) using ion chromatography tandem mass spectrometry (Valentin-Blasini et al., 2007). Urinary cotinine levels were measured in 856 subjects by the CDC as part of a previous study. Results met the division's quality control criteria for accuracy and precision similar to those outlined in Caudill *et al.* Caudill et al. (2008). After overnight shipping on dry ice, serum samples were measured for total T_4, free thyroxine (fT_4), thyroid stimulating hormone (TSH)), and thyroperoxidase (TPO) and thyroglobulin (Tg) antibody concentrations at the University of Washington, Seattle, using a Beckman automated immunoassay chemiluminescence platform and microparticle enzyme immunoassay (Beckman Coulter). Quality control measures included 2-level quantitative controls for each assay on every reagent run, monitoring run integrity using Levey-Jennings charts, and participation in proficiency surveys by the College of American Pathologists. Manufacturers' values for TPO and Tg antibody positivity are > 9 and > 4 IU/mL, respectively.

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