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Association of prenatal perchlorate, thiocyanate, and nitrate exposure with neonatal size and gestational age

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ABSTRACT

Background: Perchlorate and similar anions compete with iodine for uptake into the thyroid by the sodium iodide symporter (NIS). This may restrict fetal growth via impaired thyroid hormone production.
Methods: We collected urine samples from 107 pregnant women and used linear regression to estimate differences in newborn size and gestational age associated with increases in perchlorate, thiocyanate, nitrate, and perchlorate equivalence concentrations (PEC; measure of total NIS inhibitor exposure).
Results: NIS inhibitor concentrations were not associated with newborn weight, length, or gestational age. Each 2.62 ng/μg creatinine increase in perchlorate was associated with smaller head circumference (0.32 cm; 95% CI: −0.66, 0.01), but each 3.38 ng/μg increase in PEC was associated with larger head circumference (0.48 cm; −0.01, 0.97).
Conclusions: These anions may have effects on fetal development (e.g. neurocognitive) that are not reflected in gross measures. Future research should focus on other abnormalities in neonates exposed to NIS inhibitors.

1. Introduction

Perchlorate (ClO_4^-) is an inorganic ion that is commercially produced for use as an oxidant in explosives, pyrotechnics, and rocket fuel [1,2]. Perchlorate can also form naturally through atmospheric reactions, and human exposure can occur via groundwater contamination and dietary intake of contaminated food crops [2]. In 2011 the United States Environmental Protection Agency (EPA) determined that perchlorate met the criteria for regulation as a drinking water contaminant, primarily based on the scientific evidence of perchlorate's effects on thyroid function [3–4]. Perchlorate competes with iodide for transport into the thyroid via the sodium/iodide symporter (NIS), thus inhibiting iodide uptake into the thyroid and possibly reducing thyroid hormone production [5–6].

Thiocyanate (SCN^-) and nitrate (NO_3^-) anions are also competitive inhibitors of thyroidal iodide uptake via the NIS [5], though their potencies for inhibiting iodide transport are only 1/15 and 1/240 that of perchlorate, respectively [4]. Thiocyanate is a byproduct of the breakdown of hydrogen cyanide in cigarette smoke, and it is also produced during the digestion and metabolism of some plant foods [7]. Nitrates also occur naturally in many plants [8]. and are common components of agricultural fertilizers and sewage which can contaminate drinking water sources [9].

Pregnant women and their fetuses comprise a particularly vulnerable population for whom the inhibition of iodide uptake can have substantial consequences. Fetal growth, particularly fetal brain development, is largely dependent on the bioavailability of iodide for thyroid hormone production in both the mother and fetus [10]. The NIS is also expressed in the placenta, thus providing a route for iodide transport from maternal to fetal circulation. NIS expression in placenta, however, can also facilitate transport of perchlorate, thiocyanate, and nitrate into the fetal compartment [11]. leading to fetal exposure, which may threaten thyroid function and fetal growth. Impairments in maternal thyroid hormone production during pregnancy may also contribute to shortened gestation and an increased risk of preterm birth [12–14]. Though

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several studies have examined the relationship between prenatal exposure to NIS inhibitors and neonatal thyroid hormones, these studies have relied mainly on ecologically based exposure measures such as contaminant concentrations in local drinking water [15–21]. Few studies have examined the association between fetal growth and prenatal exposure to NIS inhibitors.

Previously, we reported strong positive correlations between maternal urinary concentrations of NIS inhibitors and concentrations in cord blood and amniotic fluid [22]. suggesting that maternal urinary measures of these NIS inhibitors may be effective surrogates for fetal exposures. Though our prior study did not show an association between fetal growth and NIS inhibitor concentrations in cord blood, the study population consisted of healthy, iodine-replete pregnant women undergoing elective cesarean sections.

To date, no study has examined the relationship between maternal urinary levels of NIS-inhibitors and fetal growth, nor has any study examined this relationship among pregnant women at high-risk for alterations in fetal growth. Therefore, we conducted a prospective study of the association between NIS inhibitor concentrations in maternal urine samples throughout pregnancy and anthropometric measures at birth among a sample of women at risk for adverse pregnancy outcomes. We hypothesized that maternal urinary levels of perchlorate, thiocyanate, and nitrate during pregnancy would be negatively associated with neonatal weight, length, head circumference, and gestational age.

2. Methods

2.1. Study population

The study population and protocol for this study have been described previously [23]. Briefly, we recruited 107 pregnant women (9–39 weeks gestation at enrollment) between December 2008 and July 2010 from the High-Risk Obstetric Clinic at Robert Wood Johnson University Hospital. Having a previous preterm delivery was the most common indication for a high-risk pregnancy among the sample (33%), followed by hypertension (19%) and diabetes (16%; Table 1). Subjects were at least 18 years old and expecting singleton infants. All subjects provided informed consent prior to participation in the study, which was approved by the Institutional Review Board at the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School. The Centers for Disease Control and Prevention (CDC) involvement was limited to analyzing coded specimens and interpreting results.

Table 1
Characteristics of study subjects.

	N (%)
Infant gender	
Male	59 (55)
Female	48 (45)
Preterm birth(≤36 weeks; study pregnancy)	26 (25)
Maternal age	
20–24	20 (19)
25–29	28 (26)
30–34	17 (16)
35–39	29 (27)
≥40	13 (12)
Maternal race/ethnicity	
White	33 (31)
Black	27 (25)
Hispanic	35 (33)
Other	11 (10)
Missing	1 (1)
Maternal education	
<High school graduate	20 (19)
High school graduate	26 (24)
Some college	27 (25)
College degree	33 (31)
Missing	1 (1)
Maternal employment status	
Employed	50 (47)
Unemployed	51 (48)
Missing	6 (6)
Smoked during pregnancy	
Never	86 (82)
Rarely	3 (3)
Sometimes	5 (5)
Often	11 (10)
Number of previous pregnancies	
0	17 (16)
1	29 (27)
2	21 (20)
3	21 (20)
≥4	19 (18)
Indication for high-risk pregnancy	
Congenital anomaly	4 (4)
Previous preterm delivery	35 (33)
Diabetes	17 (16)
Hypertension	21 (19)
Urinary infection	8 (7)
Febrile illness	14 (13)
Missing	8 (7)

2.2. Study protocol

All mothers initially provided a detailed medical history and information on household product use, occupation, hobbies, diet, and demographic variables. At each subsequent clinic visit, mothers provided a clean-catch urine sample. The total number of clinic visits and urine samples per subject ranged from 1 to 12 (mean ± standard deviation: 4 ± 3), and 84 (79%) subjects provided multiple samples throughout their pregnancy. There was an average of 20 days (±16) between samples among women who completed multiple study visits.

2.3. Quantification of urinary iodide and NIS inhibitors

Perchlorate, thiocyanate, nitrate, and iodide were analyzed by isotope dilution and ion chromatography/tandem mass spectroscopy (IC–MS/MS) using previously published methods with minor modifications [24]. Briefly, 0.250 mL of urine samples were diluted to 1.0 mL with aqueous internal standard solution containing stable isotope labeled perchlorate ($Cl^{18}O_4^-$), thiocyanate ($SC^{15}N^-$), nitrate ($^{15}NO_3^-$), and iodide (^{129}I). Urinary creatinine was measured based on enzymatic reaction using the Roche Creatinine Plus assay (Roche Product Application #11775685216v19).

Samples were vortex mixed and queued for injection (25 μL). Each analytical batch consisted of a blank, calibration standards, and four quality control (QC) samples (two QC low and two QC high). Analyte quantification was based on the peak area ratio of the analyte to stable isotope-labeled internal standard. The assay limit of detection was 0.05 ng/mL for perchlorate, 20 ng/mL for thiocyanate, and 700 ng/mL for nitrate. Reported results met the accuracy and precision guidelines of the quality assurance/quality control program of the Division of Laboratory Sciences, National Center for Environmental Health, CDC [25,26].

We also calculated a perchlorate equivalence concentration (PEC) for each urine sample by summing the product of the molar concentrations of each NIS inhibitor and its respective potency factor. The PEC calculation is based on evidence that thiocyanate and nitrate possess only 1/15 and 1/240, respectively, of the potency of perchlorate to inhibit iodide transport at the NIS [5]. Perchlorate, thiocyanate, nitrate, and iodide levels are reported as creatinine-adjusted concentrations, whereas PEC was calculated using molar concentrations.