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CO-occurring exposure to perchlorate, nitrate and thiocyanate alters thyroid function in healthy pregnant women

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ABSTRACT

Background: Adequate maternal thyroid function during pregnancy is necessary for normal fetal brain development, making pregnancy a critical window of vulnerability to thyroid disrupting insults. Sodium/iodide symporter (NIS) inhibitors, namely perchlorate, nitrate, and thiocyanate, have been shown individually to competitively inhibit uptake of iodine by the thyroid. Several epidemiologic studies examined the association between these individual exposures and thyroid function. Few studies have examined the effect of this chemical mixture on thyroid function during pregnancy

Objectives: We examined the cross sectional association between urinary perchlorate, thiocyanate and nitrate concentrations and thyroid function among healthy pregnant women living in New York City using weighted quantile sum (WQS) regression.

Methods: We measured thyroid stimulating hormone (TSH) and free thyroxine (FreeT4) in blood samples; perchlorate, thiocyanate, nitrate and iodide in urine samples collected from 284 pregnant women at 12 ($\pm$2.8) weeks gestation. We examined associations between urinary analyte concentrations and TSH or FreeT4 using linear regression or WQS adjusting for gestational age, urinary iodide and creatinine.

Results: Individual analyte concentrations in urine were significantly correlated (Spearman's r 0.4–0.5, $p < 0.001$). Linear regression analyses did not suggest associations between individual concentrations and thyroid function. The WQS revealed a significant positive association between the weighted sum of urinary concentrations of the three analytes and increased TSH. Perchlorate had the largest weight in the index, indicating the largest contribution to the WQS.

Conclusions: Co-exposure to perchlorate, nitrate and thiocyanate may alter maternal thyroid function, specifically TSH, during pregnancy.

1. Introduction

Pregnancy represents a period of unique vulnerability to the adverse effects of thyroid disrupting chemicals. During pregnancy, maternal thyroid function increases to meet the needs of both mother and developing fetus. Physiologic changes associated with pregnancy require the maternal thyroid gland to increase production of thyroid hormones by 40–100% (Stagnaro-Green, 2011). Until the fetal thyroid matures towards the end of gestation, the developing fetus relies on maternal thyroid hormones to guide normal brain development (Burrow et al., 1994). Maternal thyroid insufficiency during gestation has been associated with adverse neurodevelopmental health outcomes in offspring. Frank hypothyroidism (serum thyrotropin concentrations $\geq$ 99.7th percentile) during early pregnancy is associated with adverse outcomes ranging from delayed cognitive function and low intelligence scores to cretinism (i.e. severely stunted physical and mental growth) in offspring (Haddow et al., 1999). More subtle changes in maternal thyroid function during critical windows of development may also predict poor psychomotor and cognitive outcomes in children (Pop et al., 1999). Because thyroid hormone is important for the synchrony of brain development, and fetal thyroid hormone production is not sufficient until late in pregnancy, pregnant women may be more vulnerable to the thyroid disrupting effects of some environmental chemicals (Howdeshell,

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2002). Indeed, among the small number of mothers who were hypothyroid or hypothyroxinemic during pregnancy ($n=44$), high perchlorate exposure was associated with increased odds of offspring IQ being in the lowest 10% at 3 years of age (Taylor et al., 2014). In the current paper, we investigate exposure to thyroid disrupting compounds and estimate the contribution of perchlorate, nitrate and thiocyanate to adverse changes in maternal thyroid function among healthy pregnant women.

Perchlorate, nitrate and thiocyanate are environmental chemicals known to inhibit iodine uptake at the sodium iodide symporter (NIS) located in the basolateral membrane of thyroid follicular cells (Cao et al., 2010; NRC, 2005; Steinmaus et al., 2007; Tran et al., 2008; Ward et al., 2010; Wolff, 1998). Iodine uptake at the NIS is essential for thyroid hormone synthesis and inadequate iodine is the major cause for disturbance in the hypothalamus-pituitary-thyroid (HPT) axis leading to hypothyroidism (IOM, 2001; Yen, 2001; Zimmermann, 2009). Human exposure to these chemicals occurs mainly through diet and drinking water (Blount and Valentin-Blasini, 2006; Dasgupta et al., 2006; Huber et al., 2011; Lau et al., 2013; Murray et al., 2008). Cigarette smoke is likely the major source of thiocyanate exposure for the non-occupationally exposed population (ATSDR, 2006). Diet may be an important source of exposure to thiocyanate among non-smokers as it is also found naturally in Brassica genus vegetables, such as cauliflower, broccoli, kale and Brussel sprouts (Han and Kwon, 2009). Perchlorate, both a naturally occurring and man-made chemical used to produce rocket fuel, fireworks, and explosives, is widespread in the U. S. (Blount et al., 2007; Dasgupta et al., 2006; Steinmaus et al., 2013) and worldwide (Dyke et al., 2007; Ozpinar et al., 2014; Taylor et al., 2014; Zhang et al., 2010). Large-scale studies of the U.S. population suggest environmental perchlorate exposure is associated with altered thyroid function, namely decreased free thyroxine (free T4) and increased thyroid stimulating hormone (TSH) (Blount et al., 2006; Steinmaus et al., 2010; Suh et al., 2013). In one recent study of pregnant woman, exposure to perchlorate during pregnancy has been associated with changes in maternal thyroid function (Charatcharoenwitthay et al., 2014), though other population studies including pregnant women do not show demonstrate similar associations (Pearce et al., 2011; Taylor et al., 2014). Nitrate and thiocyanate were detected in nearly all spot urine samples collected from NHANES 2001–2002 participants (Suh et al., 2013). Levels of exposure to nitrate and thiocyanate are much higher than perchlorate, though experimental studies suggest nitrate and thiocyanate are less potent inhibitors of NIS activity than perchlorate (Tonacchera et al., 2004). Exposure to nitrate or thiocyanate has been associated with decreased thyroid function in human populations (Blount et al., 2006; Brauer et al., 2006; Tajtakova et al., 2006).

As perchlorate, nitrate and thiocyanate are ubiquitous in the environment and potentially act through the same mechanism of action, it is useful to account for the effects of exposure to the mixture of these chemicals on thyroid function (De Groef et al., 2006; Tarone et al., 2010). An in vitro study considering the effects of exposure to a mixture of these three compounds suggests they interact in a simple additive fashion (Tonacchera et al., 2004). Such model predictions from in vitro studies can place perspective on health risks associated with environmental exposure to trace amounts of these compounds in humans, but similar dosing studies are not ethical in humans, thus we rely on data from epidemiologic studies. In the epidemiologic literature, analytical methods which typically evaluate associations with individual chemicals may not be appropriate to examine the effect of exposure to a chemical mixture on maternal thyroid function due to (1) correlated exposures, (2) low level exposures (particularly multiple compounds below an individual observable effect level, but which in combination produce an observable effect), and (3) differences in potency (i.e. chemicals with the highest body burdens are not necessarily the most potent/toxic) (Gennings et al., 2013). Weighted quantile sum (WQS) regression is an approach recently proposed to examine mixture effects in epidemiologic studies. This method can be used to estimate the total exposure burden due to a mixture of correlated contaminants and identify influential compounds in the mixture.

The objective of this cross sectional study was to assess the relationships between perchlorate, thiocyanate and nitrate concentrations and maternal thyroid function among healthy pregnant women enrolled in the New York City area between 2009–2010. We compare traditional regression approaches to weighted quantile sum (WQS) regression to examine the associations between exposure to a mixture of these compounds and maternal thyroid function.

2. Methods

2.1. Study design

The study sample comprises healthy pregnant women aged 16–35 years participating in the Endocrine Disruption in Pregnant Women: Thyroid Disruption and Infant Development Study. Enrollment took place in two prenatal clinics in New York City between September 2009 and December 2010. Eligible subjects consisted of pregnant women with singleton pregnancies seeking prenatal care before approximately 12 weeks gestational age (based on reported date of last menstrual period and the earliest ultrasound), who were free of clinical thyroid disorders, were not taking any thyroid medication, and reported no history of thyroid cancer. Subjects were also excluded if they had medical complications (including chronic hypertension, diabetes, or epilepsy), or reported use of street drugs and/or alcohol during pregnancy. Baseline data collected on mothers enrolled into the study included demographic characteristics, measures of social circumstances (marital status, home ownership, income, education, medical insurance coverage), number of previous pregnancies, infections during the current pregnancy, and pre-pregnancy weight and height. The Institutional Review Board (IRB) of Columbia University approved this study protocol. Written informed consent was obtained from all subjects. The Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA) involvement was limited to analyzing coded specimens and interpreting results.

2.2. Biological sampling data

During a routine prenatal visit conducted during the first half of pregnancy, blood and spot urine samples were collected from all participants. A single 7.5 mL serum separator tube was drawn for testing of thyroid hormones (TSH and Free T4). Following venipuncture, blood was clotted at room temperature for 30–45 min, centrifuged for 10 min, then stored cold (2–8 °C) until shipment to the Collaborative Studies Clinical Laboratory, Minneapolis, Minnesota. TSH and Free T4 were measured using a chemiluminescent immunoassay (Vitros Immunoassay System, OrthoClinical Diagnostics, Rochester, New York).

Aliquots of urine were shipped on dry ice to the Division of Laboratory Sciences at the Centers for Disease Control and Prevention for measurement of perchlorate, thiocyanate, nitrate, and iodide using ion chromatography tandem mass spectrometry (Blount and Valentin-Blasini, 2006, 2007). Urinary creatinine was measured using an automated colorimetric method (COBAS Creatinine plus assay, Roche Diagnostics Corporation, Indianapolis, Indiana). Reported results for all CDC assays met the division's quality control and quality assurance performance criteria for accuracy and precision (Caudill et al., 2008).