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Thyroid antagonists and thyroid indicators in U.S. pregnant women in the Vanguard Study of the National Children's Study

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ABSTRACT

The sodium iodide-symporter (NIS) mediates uptake of iodide into thyroid follicular cells. This key step in thyroid hormone synthesis is inhibited by perchlorate, thiocyanate (SCN) and nitrate (NO_3) anions. When these exposures occur during pregnancy the resulting decreases in thyroid hormones may adversely affect neurodevelopment of the human fetus. Our objectives were to describe and examine the relationship of these anions to the serum thyroid indicators, thyroid stimulating hormone (TSH) and free thyroxine (FT4), in third trimester women from the initial Vanguard Study of the National Children's Study (NCS); and to compare urine perchlorate results with those in pregnant women from the National Health and Nutritional Examination Survey (NHANES).

Urinary perchlorate, SCN, NO_3, and iodine, serum TSH, FT4, and cotinine were measured and a food frequency questionnaire (FFQ) was administered to pregnant women enrolled in the initial Vanguard Study. We used multiple regression models of FT4 and TSH that included perchlorate equivalent concentration (PEC, which estimates combined inhibitory effects of the anions perchlorate, SCN, and NO_3 on the NIS). We used multiple regression to model predictors of each urinary anion, using FFQ results, drinking water source, season of year, smoking status, and demographic characteristics. Descriptive statistics were calculated for pregnant women in NHANES 2001–2012.

The geometric mean (GM) for urinary perchlorate was 4.04 μg/L, for TSH 1.46 mIU/L, and the arithmetic mean for FT4 1.11 ng/dL in 359 NCS women. In 330 women with completed FFQs, consumption of leafy greens, winter season, and Hispanic ethnicity were significant predictors of higher urinary perchlorate, which differed significantly by study site and primary drinking water source, and bottled water was associated with higher urinary perchlorate compared to filtered tap water. Leafy greens consumption was associated with higher urinary NO_3 and higher urinary SCN. There was no association between urinary perchlorate or PEC and TSH or FT4, even for women with urinary iodine < 100 μg/L. GM urinary perchlorate concentrations in the full sample ($n=494$) of third trimester NCS women (4.03 μg/L) were similar to pregnant women in NHANES (3.58 μg/L).

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1. Introduction

The perchlorate anion is an oxidizing agent, and its ammonium salt has been used in rocket and missile propellant systems, fireworks, matches, and for several other industrial uses (Trumpolt et al., 2005). Perchlorate is formed in the atmosphere and can accumulate in the soils of arid regions (Dasgupta et al., 2005). Human exposure sources include contaminated drinking water and consumption of foods containing perchlorate; mainly, milk and high surface area plants such as leafy green vegetables (Murray et al., 2008; Sanchez et al., 2009). Human health concerns are related to the ability of perchlorate to competitively inhibit iodide uptake by the sodium-iodide symporter (NIS) of the thyroid gland (Dohan and Carrasco, 2003; Tonacchera et al., 2004). So effective is it for blocking iodide uptake that high dose potassium perchlorate (up to 1000 mg per day) historically was used to treat hyperthyroidism (Crooks and Wayne, 1960). Current concerns about potential anti-thyroid effects

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of environmental perchlorate exposure focus largely on pregnant women. During fetal development, adequate thyroid hormone is essential for neurological development, and until 20 weeks gestation, the fetus is dependent on maternal thyroid hormone (Pearce, 2012). At the same time, adequate maternal iodine intake is essential for thyroid hormone production. Iodine intake is considered to be adequate in a population of pregnant women with a urinary median iodine concentration of 150–249 μg/L (World Health Organization (WHO), 2008). Perchlorate absorbed into the body easily passes through the placenta, and fetal exposure parallels maternal exposure (Blount et al., 2009).

The U.S. Environmental Protection Agency (EPA) has begun to develop a drinking water standard for perchlorate (U.S. EPA, 2011), but the majority of the U.S. population exposure to perchlorate derives from dietary sources. Huber et al. (2011) used National Health and Nutrition Examination Survey (NHANES) data and estimated that approximately 80% of urinary perchlorate was derived from dietary sources. Others also have shown diet as the primary perchlorate exposure source for U.S. residents, based on tap water perchlorate concentrations (Mendez et al., 2010), dietary analysis (Murray, et al. 2008), and analysis of tap water and exposure data from NHANES (Blount et al., 2010; Lau et al., 2013; Yang et al., 2012).

Perchlorate is widespread in the U.S. population, with virtually 100% of participants in the NHANES having detectable urinary concentrations (Blount et al., 2007; CDC, 2015). The ubiquitous exposure to perchlorate, in combination with decreasing iodine intake, especially in women of child-bearing ages (Caldwell et al., 2013), has given impetus to examine the relationship among thyroid function, perchlorate exposure, and urinary iodine. Results have been inconsistent. U.S. women with marginal iodine intake (urinary iodine < 100 μg/L) and higher urinary perchlorate had lower thyroxine and higher thyroid stimulating hormone (TSH) values compared to women with urinary iodine ≥ 100 μg/L (Blount et al., 2006). Prenatal perchlorate exposure increased the risk for elevated TSH in the newborn (Steinmaus et al., 2010) and was associated with lower IQ in childhood (Taylor et al., 2014). However, no association was found between urinary perchlorate and TSH or free thyroxine (FT4) in California women who had experienced perchlorate contamination of drinking water (Gold et al., 2013). Most studies in pregnant women have not found an association between measures of thyroid function (e.g. TSH, FT4, or thyroglobulin) and urinary perchlorate concentrations measured in the first or second trimesters, regardless of urinary iodine status (Pearce et al., 2010, 2011, 2012; Tellez et al., 2005). However, others have found that urinary perchlorate was a significant predictor for increased TSH and decreased FT4 (Charatcharoenwitthaya et al., 2014; Steinmaus et al., 2015).

The anions thiocyanate (SCN) and nitrate (NO_3) also inhibit the NIS and are virtually ubiquitous exposures because of their presence in green leafy vegetables and other foods (Clements, 1960; Hord et al., 2009). Cruciferous vegetables, including cabbage, kale, broccoli, and cauliflower, are rich in SCN (Clements, 1960). Cyanide in tobacco smoke also contributes significantly to urinary SCN in smokers (Buratti et al., 1997). Higher concentrations of these anions may act together: increased urine SCN (from smoking) and perchlorate interacted to reduce serum thyroxine in women with lower urine iodine concentrations (< 100 μg/L) (Steinmaus et al., 2013). The perchlorate equivalent concentration (PEC) has been proposed as a tool to estimate combined inhibitory effects of perchlorate, SCN, and NO_3 on the NIS, (Bruce et al., 2013; Tonacchera et al., 2004) and to examine the combined effects of these anions on thyroid function. However, the PEC was weakly predictive of thyroxine and no other measures of thyroid function, and PEC was not predictive of thyroid indicators in women with inadequate iodine intake (Bruce et al., 2013).

Two sources of variability may contribute to the inconsistent results of studies that examined effects of perchlorate or PEC on thyroid hormones in pregnancy. First pertains to the physiologic changes in FT4 and TSH, particularly in early pregnancy (first-to-early second trimester). FT4 concentrations typically increase by as much as 50% in the first trimester, and TSH decreases because of increasing human chorionic gonadotropin (hCG) produced by the placenta (Stagnaro-Green et al., 2011). Second is that widely used immunologic assays for FT4 can be unreliable and subject to biases related to protein bound T4 and related proteins (Sapin et al., 2003). We sought to reduce these sources of variability by limiting our sample to third trimester women and by measuring serum FT4 in a method that uses equilibrium dialysis to separate free from protein-bound T4.

In this analysis, we evaluated perchlorate and a combined effect of the NIS inhibitors (as PEC) on FT4 and TSH, and also examined determinants of urinary perchlorate, SCN, and NO_3 in third trimester women enrolled in the Vanguard Study of the NCS. We also present urinary perchlorate results from similar-aged pregnant women in NHANES 2001–2012 for comparison.

2. Methods

2.1. Study populations

The NCS Vanguard Study was a feasibility study to test the proposed recruitment, enrollment, and study visit assessment methodologies for a planned large-scale epidemiological cohort study of children and their parents. As described by Baker et al. (2014), 1399 women were enrolled in the NCS initial Vanguard Study from 2009—2010 from seven locations: Queens County, New York; Duplin County, North Carolina; Salt Lake County, Utah; Orange County, California; Montgomery County, Pennsylvania; Waukesha County, Wisconsin; and a composite location of four adjacent counties in South Dakota and Minnesota. During pregnancy, women had up to two visits that included an extensive interview, a physical examination, and collection of blood and urine specimens and environmental samples. This study reports a sample of third trimester pregnant women enrolled in the Vanguard Study and measurements made as part of a pilot study conducted with the Centers for Disease Control and Prevention (Mortensen and Hirschfeld, 2012).

NHANES has been conducted annually since 1999, releases data in two year cycles, and provides an ongoing assessment of the health, nutrition, health-related behaviors, and environmental chemical exposures in the U.S. population (Centers for Disease Control and Prevention (CDC), 2013). Using a stratified, multistage, probability cluster design, NHANES obtains a representative sample of the non-institutionalized U.S. population. Additional information is available at: http://www.cdc.gov/nchs/nhanes/about_nhanes.htm. Each year, approximately 5000 residents randomly selected in 15 counties across the U.S. are asked to participate through an advance letter, providing information that the household has been selected as part of the NHANES sample. A field interviewer conducts screening and enrollment, and completes the household interview at the home. Subsequent interviews, physical examination, and biological specimen collections are conducted at the Mobile Examination Center (MEC). The average participation rate for data collected at the MEC is approximately 80% (Centers for Disease Control and Prevention and National Center for Health Statistics (NCHS), 2013). Informed consent was obtained from all NHANES participants prior to collecting, data or specimens, and the analysis presented here used only de-identified data that were publicly available.

We used NHANES 2001–2012 urine perchlorate results for pregnant women ages 16–44 years to obtain a large number of