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ORIGINAL STUDY

Marginal Iodine Status and High Rate of Subclinical Hypothyroidism in Washington DC Women Planning Conception

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Introduction: Subclinical hypothyroidism during pregnancy has been associated with adverse maternal and fetal outcomes. A subset of pregnant women in the United States have been shown to have mild iodine deficiency. No study has evaluated the thyroid and iodine status of women who are planning to become pregnant in the near future.
Methods: Thyroid function tests, thyroid antibodies, and urine iodine levels were evaluated in women presenting for preconception screening and counseling. A thyrotropin (TSH) level above 3.0 mIU/L was considered abnormal.
Results: One hundred and forty one women enrolled in the study. The median TSH level was 1.70 mIU/L (range 0.43–5.3 mIU/L). Sixteen women (11%) had a TSH above the upper limit of normal (>3.0 mIU/L). Eleven women (8%) were positive for TPO-Ab and 21 women (15%) for TgAb. Twenty-three women (16%) were positive for at least one thyroid antibody (TPOAb and/or TgAb). Median serum TSH concentrations were higher in women with detectable antithyroid antibodies than in women who were antibody negative (2.2 mIU/L vs. 1.7 mIU/L; $p = 0.005$). The median urinary iodine concentration was 100.5 μg (range 19–843 μg/L).
Discussion: The present cohort exhibited the lowest median urinary iodine concentration levels to date reported in the United States for women in their childbearing years. One out of every nine women (11%) had thyroid function tests consistent with subclinical hypothyroidism.

Introduction

The impact of thyroid disease on pregnancy has been an area of increasing research attention over the last two decades. The impact of subclinical hypothyroidism (SCH) on adverse pregnancy outcomes is an important area of focus. Observational studies have demonstrated an association of SCH with increased rates of miscarriage, gestational diabetes, and preterm delivery (1–3). Prospective studies in women with subclinical hypothyroidism during pregnancy have yielded mixed results; Lazarus *et al.* (4) found that treating pregnant women with subclinical hypothyroidism (SCH) had no benefit on the intelligence quotient (IQ) of the offspring, whereas Negro *et al.* (5) documented a decrease in adverse maternal/fetal events when pregnant women with SCH were treated. The prevalence of SCH in pregnancy is also a topic of intense interest. While the prevalence was reported as 2–3% for decades, recent studies have revealed a prevalence as high as 15% (6). The increased prevalence rates may in part reflect the revised definition of the normal thyrotropin (TSH) range in the first trimester that is now defined with an upper limit of normal at 2.5 mIU/L (7,8).

Iodine in pregnancy is another key area of enhanced research focus. An obligatory nutrient, iodine is essential to thyroid hormone synthesis. Worldwide, iodine deficiency is the leading preventable cause of intellectual impairments, and in its severest form during pregnancy it results in cretinism. The United States, although iodine replete since the 1940s, has experienced a marked decline in iodine levels as documented in the National Health and Nutrition Examination Surveys series (9), with recent data suggesting that mild iodine deficiency exists in a subset of Americans. At greatest risk are pregnant women and women of childbearing age, who as a group have the lowest median iodine levels (10–12). During pregnancy, iodine requirements increase by 50%. Iodine deficiency presents specific risks to the developing fetus, as adequate iodine is necessary for normal neurocognitive development. Recent studies have demonstrated a link

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between mild iodine deficiency during pregnancy and decreased IQ (13,14) in offspring.

Given the potential impact of subclinical hypothyroidism on pregnancy, as well as the effect of mild iodine deficiency during pregnancy on the neuropsychological development of the fetus, we decided to evaluate thyroid function and iodine status in a cohort of women presenting for preconception screening and counseling. As this cohort of women was planning on becoming pregnant soon after their appointment, they represent a baseline of thyroid and iodine status for the prepregnant women. Given that both thyroid hormone and iodine requirements increase markedly with gestation, the presence of mild iodine deficiency, or a high prevalence of subclinical hypothyroidism, would identify a cohort of women who might benefit from screening and intervention prior to pregnancy.

Methods

Women presenting for prenatal screening to the obstetrics practice of the Medical Faculty Associates of the George Washington University School of Medicine and who were planning to become pregnant in the near future were invited to participate in the study. Exclusion criteria were as follows: women under 18 years of age, ongoing treatment for hypothyroidism or hyperthyroidism, prior treatment with I-131 radioactive iodine, or ongoing therapy with steroids, amiodarone, or lithium. The study was approved by the institutional review board and all women gave written informed consent. All women completed a questionnaire that included pregnancy history and demographic information. Thyroid function tests and urine iodine levels were obtained on all women at the time of the preconception visit.

Thyroid function tests were performed as follows: Serum TSH (third generation, reference range 0.3–3.0 mIU/L) and free thyroxine (FT4) (reference range 0.8–2.0 ng/dL) were measured using the Elecsys 2010 instrument (Roche Diagnostics). The TSH interassay coefficient of variability over 8 months was 6.1% at 0.04 mIU/L and 3.6% at 1.5 mIU/L. Thyroglobulin autoantibodies (TgAb) and thyroid peroxidase autoantibodies (TPOAb) were measured using radioimmunoassays (Kronus).

Spot urinary iodine concentrations were measured spectrophotometrically by a modification of the method of Benotti *et al.* (15) in the Iodine and Thyroid Function Laboratory at Boston University School of Medicine, an Ensuring the Quality of Urinary Iodine Procedures (EQUIP) certified iodine measurement laboratory. Iodine concentrations from all samples were measured at least twice. In cases where the initial two measurements were not within 15% of each other, a third or a fourth measurement was obtained and the average of all measurements was used. The interassay coefficient of variation for this assay in our laboratory ranges from 2.7% to 7%.

Results

Study population

One hundred and forty-one women participated in the study. The demographic distribution of the 141 women was as follows; 57% Caucasian, 27% African American, 8% Hispanic, 6% Asian, and 2% other. The mean age of the 141 participants was 31.7 ± 4.6 years. Fifty-two per cent of the women were nulliparous, whereas 27% and 10% had either one or two prior pregnancies respectively. There was a 3% incidence of prior preterm delivery. One-fifth of the women (19%) had a prior spontaneous abortion and 15% had previously undergone an elective pregnancy termination.

Thyroid function tests and thyroid antibodies

The median TSH level was 1.70 mIU/L (range 0.43–5.3 mIU/L). Sixteen women (11%) had a TSH above the upper limit of normal (>3.0 mIU/L) for the nonpregnant state. None of the 141 women had a suppressed TSH. Eleven women (8%) were positive for TPO-Ab and 21 women (15%) for TgAb. Twenty-three women (16%) were positive for at least one of the two antibodies.

Median serum TSH concentrations were higher in women with detectable anti-thyroid antibodies than in women who were antibody negative (2.2 mIU/L vs. 1.7 mIU/L; $p = 0.005$) Mean FT4 levels did not differ between antibody positive and negative women (1.15 vs. 1.11 ng/dL, $p = 0.7$).

The presence of anti-thyroid antibodies was not associated with having a history of miscarriage ($p = 0.6$) and showed borderline significance with preterm delivery ($p = 0.07$).

In multivariable models, age, and anti-thyroid antibody positivity were positively associated with serum TSH values, whereas urinary iodine concentration, parity, history of preterm delivery, history of miscarriage, race/ethnicity, and prenatal multivitamin use were not predictive of TSH.

Urinary iodine levels

The median urinary iodine concentration was 100.5 μg (range 19–843 μg/L). Approximately half of the study population (47%) reported taking prenatal vitamins, although the iodine content of those supplements was not ascertained. The length of time the women were on prenatal vitamins prior to the office visit was unknown. Median urinary iodine concentrations did not differ significantly between women who did and did not take prenatal multivitamins (108 μg/L vs. 93 μg/L, $p = 0.4$).

Relationship between urinary iodine and thyroid function tests

There were no significant correlations between urinary iodine concentrations and TSH ($r = -0.03$, $p = 0.7$) or fT4 ($r = 0.09$, $p = 0.2$).

Discussion

To our knowledge, this is the first study to assess the urinary iodine concentration and thyroid function tests of women living in the United States who were seeking preconception screening. Recent data demonstrating both a low median urinary iodine concentration (UIC) in pregnant women and a high prevalence of subclinical hypothyroidism in the first trimester provided the underlying rationale for the present study. The study had two major findings. The first finding is that the present cohort exhibited a marginal median urinary iodine concentration—: the lowest median UIC level to date reported in nonpregnant women living in the United States in their childbearing years. Secondly, one out of every nine women in this study (11%) had thyroid function tests consistent with subclinical hypothyroidism.

Iodine is an essential micronutrient utilized by the thyroid gland to produce thyroid hormone. Adequate iodine is essential during pregnancy in order to ensure normal neurodevelopment. Mild maternal iodine deficiency has been associated with a decrease in the intelligence quotient of the offspring (13,14) and a higher incidence of attention deficit disorder. Severe iodine deficiency may result in spontaneous abortion or cretinism. Iodine intake must increase by 50% during pregnancy in order to respond to an increase in the maternal production of thyroid hormones, an increase in renal iodine clearance, and to allow for fetal production of thyroid hormones. The World Health Organization defines adequate iodine intake during pregnancy as a median UIC for the population between 150 and 249 μg/L (16). A median UIC for a pregnant population below 150 μg/L reflects inadequate iodine intake.

In 1971, the National Health and Nutrition Examination Surveys (NHANES) began monitoring the iodine status of the American public. A marked decline in the median UIC of the general population was seen when comparing NHANES I (1971–1974), with a median UIC of 320 μg/L, to NHANES III (1988–1994), which reported a median UIC of 145 μg/L (9). The median UIC in the general population has remained stable over the last 20 years with a level of 164 μg/L in NHANES 2007–2008, and 144 μg/L in NHANES 2009–2010 (10). However, pregnant women have experienced a more precipitous decline. The median UIC in NHANES I for pregnant women was 327 μg/L, with a decline to 141 μg/L in NHANES III, and 129 μg/L in NHANES 2009–2010. In a prospective study of pregnant women, Bath *et al.* examined the relationship between maternal UIC and IQ of the offspring at the age of 8 years (13). The median UIC reported was 91.1 μg/L. Bath *et al.* found that women with median UIC levels below 150 μg/g had a significant increase in the percentage of children with a verbal IQ, reading comprehension, and reading accuracy in the lowest quartile. Scores on all three outcome variables declined as the median UIC went from above 150 μg/g, to 50–150 μg/g, to below 50 μg/g.

The median UIC reported in the present study of 100.5 μg/L, while just within the optimal range of 100–200 μg/L for nonpregnant women, is the lowest reported value for women of childbearing age to date in the United States. This was seen despite the fact that 47% of the women reported taking prenatal vitamins. This likely reflects the lack of iodine in about 50% of the types of prenatal vitamins currently marketed in the United States (17).

Subclinical hypothyroidism during pregnancy has been associated with multiple adverse outcomes including spontaneous abortion, gestational hypertension, gestational diabetes, decreased IQ in the offspring, and preterm delivery (1–3,18), although a few studies have found no such association (19). In 2015 Yoshioka *et al.* reported that 84% of 69 infertile women with subclinical hypothyroidism conceived within one year of being placed on levothyroxine (20). The reported prevalence of subclinical hypothyroidism during pregnancy has traditionally ranged between 2% and 3% (7). Recent studies, however, have documented a much higher prevalence, which is in part a consequence of redefining the upper limit of TSH at 2.5 mIU/L during the first trimester of pregnancy. Specifically, Blatt *et al.*, in a retrospective analysis of women who had thyroid function tests performed during pregnancy, reported that 15.5% of pregnant women in the United States had subclinical hypothyroidism (defined as a TSH > 2.50 mIU/L in the first trimester, a TSH > 2.75 mIU/L in the second trimester, and a TSH > 2.91 mIU/L in the third trimester) (6). The present study yielded similar results, with a rate of subclinical hypothyroidism of 11%. The conclusion is that a high rate of subclinical hypothyroidism exists prior to pregnancy in women of childbearing age. This could be of importance given that prior research by Negro *et al.* have reported an increased rate of miscarriage in thyroid antibody negative women with a TSH between 2.5–5.0 mIU/L (1). Similarly, Benhadi *et al.* have shown an increase in the combination of miscarriage, fetal death, and neonatal death as TSH increased within the normal range (21). An alternative interpretation, however, is that the TSH cutoffs used in these studies may be too stringent. For example, Li *et al.* evaluated 4800 pregnant Chinese women in the first trimester of pregnancy and found the median TSH value at the 97.5th percentile varied between 4.04 mIU/L and 6.28 mIU/L depending on the week of gestation (22).

Limitations of this study include the selected population studied. In many centers it is not likely that women will present for preconception testing and counseling, and up to 50% of pregnancies in the United States are unplanned (23). The cross-sectional nature of the study also limits its applicability. Therefore it may not be appropriate to generalize the results of this study to all women.

In conclusion, the present study reveals marginally adequate iodine nutrition in women presenting to their physician for preconception counseling and a high rate of prepregnancy subclinical hypothyroidism. The UIC findings strengthen the evidence for the mandatory inclusion of iodine in prenatal vitamins in the United States and the importance of beginning prenatal vitamins prior to conception. This is consistent with recommendations from the American Thyroid Association (7), the Endocrine Society (8), the International Council of Iodine Deficiency Disorders (16), the Teratology Society (24), the American Pediatrics Association (25), and recent editorials on the topic (12,26). Prospective studies are needed to determine whether women with high-normal or mildly elevated serum TSH values prior to conception are at increased risk for gestational hypothyroidism, whether unselected U.S. women have an adequate iodine status preconception, and whether thyroid function screening preconception improves obstetrical and neurodevelopmental outcomes.

Author Disclosure Statement

No competing financial interests exist.

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