

Diagnosis of Subclinical Hypothyroidism Early in Pregnancy Is a Risk Factor for the Development of Severe Preeclampsia

Wilson KL, Casey BM, McIntire DD, Halvorson LM, Cunningham FG. Subclinical thyroid disease and the incidence of hypertension in pregnancy. *Obstet Gynecol* 2012;119:315-20.

SUMMARY ●●●●●●●●●●●●●●●●●●●●

Background

Thyroid hormones have a number of actions on cardiovascular physiology and blood-pressure regulation, which are mediated by genomic mechanisms that cause ventricular remodeling or by direct effects. In most cases, cardiovascular aberrations follow long-term exposure to excessive or decreased hormone levels. Some evidence shows that subclinical hypothyroidism in some, usually older, patients can cause hypertension, heart failure, and atherosclerotic vascular disease; subclinical hypothyroidism has been proved to cause endothelial-cell dysfunction characterized by diminished nitric oxide production with impaired vasorelaxation. Pregnant women with untreated overt hypothyroidism are at risk for the development of preeclampsia, placental abruption, and heart failure. The objective of the authors was to investigate the relationship between hypertensive disorders and subclinical thyroid dysfunction in a large cohort of women who presented for prenatal care before 20 weeks of gestation.

Methods

This is a secondary analysis of a prospectively collected database initially designed to estimate normative values for thyroid hormone analyses in a large population of pregnant women at Parkland Hospital, University of Texas Southwestern Medical Center in Dallas. Serum TSH and FT₄ were obtained before 20 weeks of gestation. Women identified as having both abnormal serum TSH and FT₄ values were excluded from the study. Normal values were considered to be those that comprised the range from the 2.5th to the 97.5th percentile for the entire cohort and were calculated to be a TSH of 0.03 to 4.13 mU/L and an FT₄ of 0.9 to 2.0 ng/dl. Pregnancy

outcomes were retrieved from the computerized perinatal database. Three groups of women were included for the study: euthyroid, subclinical hyperthyroid and subclinical hypothyroid. Hypertensive disorders were compared for the three cohorts described. Hypertensive disorders were defined and classified as followed: (1) gestational hypertension: persistent blood pressures of 140/90 mm Hg or more, occurring after 20 weeks of gestation, without evidence of proteinuria; (2) mild preeclampsia: women with hypertension who also had proteinuria, as determined by urine dipstick analysis from a catheterized specimen; and (3) severe preeclampsia: women with hypertension who had at least two of the following: proteinuria determined by dipstick analysis from a catheterized urine sample, blood pressure higher than 160/110 mm Hg, persistent headache, visual disturbances, right upper quadrant or epigastric pain, serum creatinine 1.2 mg/ml or more, serum aspartate transaminase levels more than twice the upper limit of normal, or thrombocytopenia less than 100,000/ml. Multivariable analyses were included to adjust for the effect modifiers of maternal age and weight as continuous measures, and categorical effects of race and parity.

Results

During the 30-month study, a total of 24,883 women who delivered singleton neonates weighing more than 500 g were included in this study. Of these, 23,771 (95.5%) had TSH values within the normal range and were considered to be euthyroid; 528 (2.1%) had TSH levels more than 4.13 mU/L with normal FT₄ levels (subclinical hypothyroidism). The remaining 584 (2.3%) had TSH levels less than 0.03 mU/L along with normal FT₄ levels (subclinical hyperthyroidism). Parity was the same in the three

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groups. Almost 80% of women were classified as Hispanic. The incidences of pregnancy-associated hypertensive disorders as well as mild and severe preeclampsia were compared between the three study cohorts. In general, as the serum TSH level increased in the entire population, the incidence of hypertensive disorders increased concomitantly (P for trend, 0.004). Women with subclinical hyperthyroidism who had the lowest TSH levels had an incidence of hypertensive disorders of 6.2%, as compared with 8.5% of euthyroid women and 10.9% of subclinical hypothyroid women. These differences when unadjusted were significant (P = 0.016); when adjusted for maternal age, race, parity, and weight using logistic regression, the only remaining significant association was in the cohort of women with subclinical hypothyroidism who were at increased

risk for severe preeclampsia (adjusted odds ratio, 1.6; 95% confidence interval, 1.1 to 2.4; P = 0.031).

Conclusions

Women with subclinical hypothyroidism identified during pregnancy have an increased risk for severe preeclampsia as compared with euthyroid women. The authors are of the opinion that their findings are more biologically significant than clinically relevant and that their observations add to accruing data that subclinical hypothyroidism, a relatively common finding in women of childbearing age, may be associated with some adverse perinatal outcomes. Nonetheless, the authors remain convinced that routine prenatal screening for thyroid disorders should not be implemented until clear benefit is established.

ANALYSIS AND COMMENTARY ● ● ● ● ●

In their initial 2005 analysis of pregnancy outcome in women with subclinical hypothyroidism, these authors found that hypertensive disorders were not recognized as a complication. As in many other studies since then, the potential role of autoimmunity was not routinely considered; in the majority of studies, only one thyroid determination was obtained in each patient, status of iodine sufficiency was not mentioned, serum TSH and FT₄ reference ranges differ between studies, and other factors such as body-mass index, age, and ethnicity were not always included in the final analysis. Therefore, it is understandable that there is no consensus on the significance of subclinical thyroid disease and the obstetric, medical, and neonatal complications, which brings more fire to the heated argument among physicians and medical societies concerning universal versus selective screening in the obstetric population. Several issues are of clinical significance in the Wilson et al. study. The definition and diagnosis of subclinical hyperthyroidism is complicated by the fact that undetectable serum TSH values are found in some normal pregnant women in the first half of pregnancy; the majority of them do not have thyroid pathology and their serum TSH normalizes with the

progression of pregnancy. Many of them may suffer from mild morning sickness or more severe hyperemesis gravidarum, known to be associated with dehydration and low blood pressure. Severe preeclampsia as a complication of hypothyroidism was reported in early publications by their group and others (2, 3), including some women with subclinical disease. The authors' conclusion that their "findings are of more biological significance than clinically relevant" is arguable. The authors discussed some of the published studies implicating subclinical hypothyroidism with cardiovascular effects and "causing endothelial cell dysfunction" (4). They did not discuss the beneficial effect of thyroid hormone therapy in the management of subclinical hypothyroidism in relation to the course of gestational hypertension; in one study published almost 20 years ago (3), normalization of serum TSH at delivery significantly decreased the development of gestational hypertension. Therefore, it appears that their findings have clinical significance and that treatment of women with subclinical hypothyroidism is clinically indicated as recommended by the recent guidelines of the ATA (5) and the Endocrine Society (6)

— Jorge H. Mestman, MD

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