An analysis of population-based prenatal screening for overt hypothyroidism

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OBJECTIVE: The purpose of the study was to evaluate pregnancy outcomes of hypothyroidism that were identified in a population-based prenatal screening program.

STUDY DESIGN: This is a secondary analysis of a prospective prenatal population-based study in which serum thyroid analytes were obtained from November 2000 to April 2003. Initial screening thresholds were intentionally inclusive (thyroid-stimulating hormone [TSH], >3.0 mU/L; free thyroxine, <0.9 ng/dL); those who screened positive were referred for confirmatory testing in a hospital-based laboratory. Hypothyroidism was identified and treated if TSH level was >4.5 mU/L and if fT4 level was <0.76 ng/dL. Perinatal outcomes in these women and those who screened positive but unconfirmed to have hypothyroidism were compared with women with euthyroidism. Outcomes were then analyzed according to initial TSH levels.

RESULTS: A total of 26,518 women completed initial screening: 24,584 women (93%) were euthyroid, and 284 women (1%) had abnormal initial values that suggested hypothyroidism. Of those referred, 232 women (82%) underwent repeat testing, and 47 women (0.2% initially screened) were confirmed to have hypothyroidism. Perinatal outcomes of women with treated overt hypothyroidism were similar to women with euthyroidism. Higher rates of pregnancy-related hypertension were identified in the 182 women with unconfirmed hypothyroidism when compared with women with euthyroidism ($P < .001$); however, this association was seen only in women with initial TSH >4.5 mU/L (adjusted odds ratio, 2.53; 95% confidence interval, 1.4—4.5).

CONCLUSION: The identification and treatment of overt hypothyroidism results in pregnancy outcomes similar to women with euthyroidism. Unconfirmed screening results suggestive of hypothyroidism portend pregnancy risks similar to women with subclinical hypothyroidism, specifically preeclampsia; however, this increased risk was seen only in women with initial TSH levels of >4.5 mU/L and suggests that this is a more clinically relevant threshold than 3.0 mU/L.

Key words: overt hypothyroidism, screening, subclinical hypothyroidism

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There is a general consensus that untreated overt hypothyroidism has deleterious fetal effects and increased adverse pregnancy outcomes.[1-5] Over the last 2 decades, there have been several studies that have also linked subclinical hypothyroidism with adverse pregnancy outcomes such as preterm birth, placental abruption, and fetal death.[5,6] There have been several reports that suggest maternal subclinical hypothyroidism may be associated with neurodevelopmental delay in exposed offspring.[3,4,7] These findings have led some, but not all, organizations to recommend universal prenatal population-based screening for thyroid dysfunction in an attempt to mitigate some of these adverse outcomes.[7,8] To further confound this controversy, there are presently no universally accepted values to define normal thyroid function in pregnant women. For example, in some of these earlier studies, *overt hypothyroidism* was defined by levels of thyroid-stimulating hormone (TSH) of >6 mU/L or even >10 mu/L with free thyroxine (fT4) levels between 0.66 ng/dL and 0.91 ng/dL,[3-5] whereas subclinical hypothyroidism was diagnosed when the TSH level was 4.5-10 mU/L along with a normal fT4 level. More recently, however, a tighter range has been proposed to define normal thyroid function, with an upper limit of TSH level of 2.5 mU/L based on values that were derived from nonpregnant adults with euthyroidism.[9] Although these latter values likely would identify more women with overt hypothyroidism, they would also label more women with the diagnosis of subclinical hypothyroidism.

Because of the direct impact of these issues on both women and infants and the indirect effects of population-based screening in a large health care system, we designed the present investigation with 3 principal aims. First, we sought to determine the frequency of overt hypothyroidism that would be discovered in a population-based screening program. Second, we wanted to investigate the pregnancy outcomes of women who had been treated for overt hypothyroidism. Third, we wanted to determine whether women with TSH screening values at the lower ends of accepted thresholds were at greater risk for adverse pregnancy outcomes when compared with women with euthyroidism.

Materials and Methods

This was a secondary analysis of a prospective prenatal population-based study

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of thyroid analytes at Parkland Hospital from November 2000 to April 2003. Details of patient identification and study design have been described previously.[6,10] Briefly, all women seeking prenatal care at our institution underwent routine laboratory blood testing at their first visit. With the approval of the Institutional Review Board of the University of Texas Southwestern Medical Center and Parkland Hospital, excess serum from the rubella screening sample was stored for thyroid analyte testing per research protocol. Chemiluminescent immunoassays were used to measure TSH and fT4 concentrations (Immulite 2000 Analyzer; Diagnostic Products Corporation, Los Angeles, CA) in a research laboratory. TSH values outside of the referent ranges (TSH >3.0 or <0.2 mU/L) prompted a reflex assay for fT4 levels. FT4 values outside the referent range (fT4 <0.9 or >2.0 ng/dL) were considered abnormal. These referent ranges were developed during our previous studies; the analytical sensitivity and coefficients of variation were published previously.[6]

Women with abnormal thyroid analyte test results relative to these referent values were considered suggestive of either overt hypo- or hyperthyroidism and were referred for further evaluation in the Obstetric Complications Clinic. On arrival, repeated confirmatory thyroid analyte testing was performed by the hospital-based laboratory. Women who were identified during this subsequent testing to have a confirmatory TSH levels >4.5 mU/L and fT4 <0.76 ng/dL were identified to have overt hypothyroidism and were treated with thyroxine replacement according to the guidelines of the American College of Obstetricians and Gynecologists.[11]

For the current study, we included women who were screened during their initial prenatal visit as described earlier, at any gestational age, and who delivered a singleton infant at Parkland Hospital who weighed at least 500 g. Gestational age at screening was established with the use of the obstetric estimate of gestational age recorded at delivery; the median gestational age for all initial screening was in the first one-half of pregnancy. The screening thresholds for initial analyte testing in the research laboratory were the same that were used during the original study by Casey et al[6]: TSH >3.0 mU/L and fT4 <0.9 ng/dL. In concert, the hospital-based confirmatory threshold values were also consistent with those from the 2005 report, TSH >4.5 mU/L and fT4 < 0.76 ng/dL for the diagnosis and treatment of overt hypothyroidism. Women who were identified to have overt thyrotoxicosis were excluded from this analysis.

Our service maintains a computerized database of selected obstetric and neonatal outcomes for all women who deliver at Parkland in which nurses who attend each delivery complete an obstetric data sheet. Before electronic storage, research nurses assess the data for consistency and completeness. Infant outcome data were abstracted from discharge records and entered into a separate infant database. Results from thyroid-related analyte serum levels determined in the aforementioned manner were stored electronically and linked to the aforementioned perinatal and infant databases. This analysis was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas.

Maternal and perinatal outcomes were compared among 3 cohorts: (1) women identified to be euthyroid on initial screening, (2) women confirmed to have overt hypothyroidism and given treatment during pregnancy, and (3) women who screened positive by the research laboratory but who were not confirmed to have overt hypothyroidism after referral and repeat testing by the hospital laboratory. Logistic regression was used to adjust for any differences that were accountable to age, race, parity, and body mass index. After this last analysis, we sought to determine whether lowered screening TSH values were clinically relevant. To do so, for this third cohort of women who screened positive but were not confirmed to have overt hypothyroidism, we analyzed pregnancy outcomes after stratifying their initial screening TSH values to either a TSH level of 3-4.5 mU/L or a level >4.5mU/L.

Outcomes of interest included gestational age at delivery, cesarean delivery rate, incidence of diabetes mellitus, gestational hypertension, and severe preeclampsia. *Gestational hypertension* was defined as persistent blood pressures of ≥140/90 mm Hg that occurred at ≥20 weeks of gestation, without evidence of proteinuria. Mild preeclampsia was diagnosed in hypertensive women who had 1+ proteinuria determined by urine dipstick analysis from a catheterized sample as per protocol of our institution. Severe preeclampsia was diagnosed in hypertensive women with any of the following: ≥2+ proteinuria on a dipstick from a catheterized specimen, blood pressure higher than 160/110 mm Hg, persistent headache, visual disturbances, right upper quadrant or epigastric pain, serum creatinine ≥1.2 mg/mL, serum aspartate transaminase levels more than twice the upper limit of normal, or thrombocytopenia <100,000/mL.

Pearson's χ^2 Student *t* tests were used for univariate 2-group comparisons. Logistic regression was applied to examine the significance of gestational hypertension, severe preeclampsia, and eclampsia that were adjusted for any differences accountable to age, race, parity, and body mass index. Statistical computations were performed with SAS software (version 9.3; SAS Institute, Cary, NC). A 2-tailed probability value of $< .05$ was deemed statistically significant.

Results

During the study period from November 2000 to April 2003, a total of 26,197 women underwent thyroid analyte screening by the research laboratory. As shown in Figure 1, a total of 24,584 women (93.8%) were identified to have euthyroidism; 284 women (1%) were identified to have abnormal values that suggested hypothyroidism. Of these 284 women who were referred for evaluation, 232 women (82%) continued prenatal care at our institution and attended repeat testing. As also shown in Figure 1, 47 of these 232 women were confirmed by the hospital laboratory to have overt hypothyroidism with both an abnormal TSH level (>4.5 mU/L) and free T4 level (<0.76 ng/dL). Put another way, 2 per 1000 women who initially were screened were identified to have overt