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Serum FT_4 Values in the Upper Normal Range in the First Trimester of Pregnancy Are Associated with Lower Birth Weight

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SUMMARY

Background

Maternal hyperthyroidism during pregnancy is associated with an increased risk of low birth weight, resulting in a predisposition to neonatal morbidity and mortality. The objective of the authors was to study the effects on birth weight of early pregnancy maternal serum thyroid parameters within the normal range, as well as the relation between umbilical-cord thyroid parameters and birth weight.

Methods

In early pregnancy, serum TSH, FT_4, and thyroid peroxidase antibody levels were determined in 4464 pregnant women. Cord serum TSH and FT_4 levels were determined in 2724 newborns. Small size for gestational age at birth (SGA) was defined as a gestational age–adjusted birth weight below the 2.5th percentile. The associations between normal-range maternal and cord thyroid parameters, birth weight, and SGA were studied using regression analyses.

Results

In mothers with normal-range FT_4 and TSH levels, higher maternal FT_4 levels were associated with lower birth weight (P = 1.6x10–5), as well as with a slightly increased risk of SGA newborns (odds ratio, 1.09; 95% confidence interval, 1.01 to 1.17; P = 0.03). Birth weight was positively associated with both cord TSH (P = 0.007) and cord FT_4 levels (P = 9.2x10–13).

Conclusions

The authors showed that maternal high-normal FT_4 levels in early pregnancy are associated with lower birth weight and an increased risk for the delivery of SGA newborns. In addition, birth weight is positively associated with cord TSH and FT_4 levels. The authors postulated that even mild variation in thyroid function within the normal range can have important consequences for the fetus.

ANALYSIS AND COMMENTARY

In the past two decades, several population studies reported an association between euthyroid autoimmune disease, mild thyroid dysfunction (including isolated maternal hypothyroxinemia), and abnormal pregnancy outcome (mainly, but not limited to miscarriages, prematurity, and impaired neurodevelopment in the offspring). Not all the studies are consistent, with the same type and frequency of complications. Several major factors may have contributed to this, among them, iodine status in a given population, lack of thyroid-test trimester-specific reference intervals for each population, and exclusion of complications intrinsic to pregnancy, such as gestational diabetes

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and pregnancy-induced hypertension. Therefore, it may be hypothesized that screening for thyroid disease before pregnancy, or very early in pregnancy, and proper maternal treatment might prevent such abnormal outcomes. Unfortunately, this is a controversial topic among clinicians caring for these patients, with no definite answers in spite of recent guidelines published by The Endocrine Society and the American Thyroid Association (1,2). The provocative findings of the current study may result in more discussion and confusion about interpretation and significance of high "normal" FT_4 values in the first trimester of pregnancy. The current publication is part of the Generation R Study, a population-based cohort from early fetal life onward in Rotterdam, the Netherlands (3). For the study, serum TSH, FT_4, and TPOAb were obtained in the first trimester of pregnancy in 4464 women who delivered between April 2002 and January 2006, after exclusion of women with known comorbidities. Based on the 2.5th and 97.5th percentiles, maternal reference ranges were 0.03 to 4.04 mU/L for TSH and 10.4 to 22.0 pmol/L for FT_4. Fetal growth was estimated by ultrasound measurements in midpregnancy (gestational age, 20 weeks) and late pregnancy (gestational age, 30 weeks). Cord serum TSH and FT_4 levels were available in 2724 of their newborns. Outcome information on birth weight was obtained from medical records completed by community midwives and obstetricians. Accepted definitions for small-for-gestational-age (SGA), premature, and low-birth-weight (LBW) infants were used.

Serum FT_4 concentrations in the upper quintile of normal (between 17.01 and 22.00 pmol/L) were associated with reduced growth (SGA) in the fetus (116 g lower birth weight) and a 2.8-fold increased odds for infants weighing less than 2500 g (LBW) as compared with FT_4 concentrations in the lowest quintile (between 10.38 and 12.80 pmol/L). An interesting finding based on fetal ultrasonography was the lower birth weight detected only in late pregnancy, pointing, perhaps, to a specific complication of pregnancy such as pregnancy-induced hypertension as the reason for this finding.

One potential factor that was not discussed by the authors is the relation between initial TSH and FT_4 values, although they stated, "Trends toward lower maternal TSH levels and lower birth weight and estimated fetal weights were observed but did not reach statistical significance." One unexplained finding was the absence of complications in the mothers with euthyroid chronic thyroiditis, 5.5% of their population. As discussed by Mannisto in the accompanying editorial (4), we are not yet ready to redefine normal levels for FT_4 in pregnancy or to measure FT_4 levels in all pregnant women. "Although an association between both early and late pregnancy high-normal free T_4 and lower birth size has been demonstrated, we are far from showing causality or a strength of association that merits action."

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