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Should Determination of Serum TPOAb and FT_4 Be Considered in the Evaluation of Thyroid Dysfunction in Pregnancy?

Jorge H. Mestman

Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, Edward Visser W, Visser W, de Muinck Keizer-Schrama SM, Hofman A, Alec Ross H, Hooijkaas H, Tiemeier H, Bongers-Schokking JJ, Jaddoe VW, Visser TJ, Steegers EA, Medici M, Peeters RP. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the Generation R Study. J Clin Endocrinol Metab. September 13, 2013 [Epub ahead of print].

SUMMARY

Background

Premature delivery is an important risk factor for child mortality and for psychiatric, metabolic, and cardiovascular disease later in life. In the majority of cases, the cause of prematurity cannot be identified. Currently, whether abnormal maternal thyroid function during pregnancy increases the risk for premature delivery remains controversial. The authors investigated the relation between maternal serum thyroid parameters and the risk of premature delivery in a large prospective, population-based study.

Methods

Serum TSH, FT_4, T_4, and TPO antibodies (TPOAb) were determined during early pregnancy in 5971 pregnant women from the Generation R Study, a population-based prospective study from fetal life onward in Rotterdam, The Netherlands. Data were available on maternal age, parity, smoking, socioeconomic status, ethnicity, maternal anthropometrics, and urinary iodine levels.

Results

Of all pregnant women, 5.0% had a premature delivery (<37 weeks of gestation), 4.4% had a spontaneous premature delivery, and 1.4% a very premature delivery (<34 weeks). High TSH levels and subclinical hypothyroidism were associated with premature delivery but not with spontaneous (in contrast with iatrogenic) premature delivery. Maternal hypothyroxinemia was associated with a 2.5-fold increased risk of premature delivery, a 3.4-fold increased risk of spontaneous premature delivery, and a 3.6-fold increased risk of very premature delivery. TPOAb positivity was associated with a 1.7-fold increased risk of premature delivery, a 2.1-fold increased risk of spontaneous premature delivery, and a 2.5-fold increased risk of very premature delivery. These effects remained similar after correction for TSH and FT_4 levels.

Conclusions

Hypothyroxinemia and TPOAb positivity are associated with an increased risk of premature delivery. The increased risk in TPOAb-positive women seems to be independent of thyroid function.

ANALYSIS AND COMMENTARY

Preterm delivery, defined as birth occurring at or before 37 weeks of gestation, is the leading cause of perinatal morbidity and mortality in the world and of serious diseases later in life (1). The Generation R Study (Rotterdam, The Netherlands) is a population-based prospective cohort study of subjects from fetal life until young adulthood (2). The study is designed

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to identify early environmental and genetic causes of normal and abnormal growth and development and health during fetal life, childhood, and adulthood. Past publications from the Generation R Study have described specific pregnancy and child neuropsychological outcomes. The present publication differs from previous studies in the literature by selecting patients according to the etiology of prematurity (spontaneous versus iatrogenic deliveries), excluding pregnancy comorbidities as cofactors in prematurity, and adjusting for other covariates, among them smoking, socioeconomic status, and ethnicity. The authors studied the independent effect on prematurity of thyroid dysfunction, autoimmunity (presence of TPOAb), and hypothyroxinemia. It is important that they measured iodine status, measuring urinary iodine concentration in a random subset of 1099 women at a mean gestational age of 12.9 weeks and finding that the population was iodine-sufficient. The prevalence of thyroid dysfunction in their population was similar to those reported in the literature, with a prevalence of TPOAb positivity of 5.6%. They also compared outcomes between TSH reference ranges according to their own population-based trimester-specific ranges and the reference range of <2.5 mU/L for the first trimester and <3.0 mU/L in the second and third trimesters of gestation as recommended by recent ATA and Endocrine Society Pregnancy Guidelines. Hypothyroxinemia was defined as a low serum FT_4 and normal serum TSH. Normal FT_4 levels are defined as levels within 2.5th to 97.5th percentiles.

The literature is not consistent with regard to pregnancy outcomes in women affected by thyroid dysfunction in the presence or absence of autoimmunity. Among the several reasons for this discrepancy is the variation in gestational age at the time of the study, the definition of maternal and obstetrical complications, ethnicity, maternal comorbidities (among them diabetes, chronic hypertension, and obesity), thyroid test reference ranges, and the presence of thyroid autoimmunity. Serum TSH, FT_4, and TPOAb were not evaluated in all publications. A recent meta-analysis showed that TPOAb-positive euthyroid women have an increased risk of a delivery before 37 weeks of gestation, although the mechanism by which TPOAbs may cause premature births is poorly understood (3). An extensive analysis of 13 studies concluded that there is a compelling argument in support of a relationship between preterm delivery and thyroid abnormalities (4). In the present study, although iatrogenic spontaneous deliveries were associated with clinical and subclinical hypothyroidism, mild thyroid dysfunction in the absence of autoimmunity and maternal comorbidities was not associated with spontaneous prematurity. This is, to my knowledge, an original observation. Hypothyroxinemia (normal TSH with low FT_4) as a risk for premature delivery has been investigated by only three groups (5-7), with negative results. Hypothyroxinemia is reported in studies from countries with iodine deficiency. The cause and physiologic mechanisms of "hypothyroxinemia" in countries with sufficient iodine supply is not clear. Even the authors of the present study stated that low levels of FT_4 due to iodine deficiency may be transient and/or have different consequences than other causes of hypothyroxinemia, but they did not elaborate on the other causes of hypothyroxinemia. The authors concluded that hypothyroxinemia by itself, in the absence of autoimmunity and comorbidities among women, is a significant risk for both iatrogenic and spontaneous premature and very premature delivery. This is indeed an intriguing finding. As stated by Negro et al. (8), the critical questions about the diagnosis of hypothyroxinemia in pregnancy are: 1) the definition of what constitutes an FT_4 level below the 2.5th percentile is unclear because regional and iodine status reference ranges have not been established; 2) perhaps equally problematic is that the accuracy of commonly used FT_4 measurements during pregnancy is questionable ; and 3) research to date evaluating the effect of isolated hypothyroxinemia on maternal

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and fetal outcomes has yielded conflicting data. In the discussion, the authors suggested that "screening for TPOAb positivity and hypothyroxinemia could be considered, especially among women with other risk factors for premature delivery." Although I agree with the first suggestion for TPOAb determination along with serum TSH in pregnancy, I am cautious about the interpretation of serum TF4 because of the lack of population-based trimester-specific reference ranges and the lack of accuracy of commonly used commercial FT_4 kits (9).

References

1. Menon R. Spontaneous preterm birth, a clinical dilemma: etiologic, pathophysiologic and genetic heterogeneities and racial disparity. Acta Obstet Gynecol Scand 2008;87:590-600.
2. Jaddoe VW, van Duijn CM, Franco OH, et al. The Generation R Study: design and cohort update 2012. Eur J Epidemiol 2012;27:739-56. Epub October 20, 2012.
3. He X, Wang P, Wang Z, He X, Xu D, Wang B. Thyroid antibodies and risk of preterm delivery: a meta-analysis of prospective cohort studies. Eur J Endocrinol 2012;167:455-64. Epub ahead of print July 23, 2012.
4. Stagnaro-Green A. Maternal thyroid disease and preterm delivery. J Clin Endocrinol Metab 2009;94:21-5. Epub November 4, 2008.
5. Casey BM, Dashe JS, Spong CY, et al. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. Obstet Gynecol 2007;109:1129-35.
6. Haddow JE, Cleary-Goldman J, McClain MR, et al. Thyroperoxidase and thyroglobulin antibodies in early pregnancy and preterm delivery. Obstetrics Gynecol 2010;116:58-62.
7. Ashoor G, Maiz N, Rotas M, Jawdat F, Nicolaides KH. Maternal thyroid function at 11–13 weeks of gestation and spontaneous preterm delivery. Obstetrics Gynecol 2011;117:293-8.
8. Negro R, Soldin OP, Bregon M-J, Stagnaro Green A. Hypothyroxinemia and pregnancy. Endocr Pract 2011;17:422-9.
9. Lee RH, Spencer CA, Mestman JH, et al. Free T_4 immunoassays are flawed during pregnancy. Am J Obstet Gynecol 2009;200:260.e1-260.e6. Epub December 27, 2008.