Antithyroperoxidase antibody and antithyroglobulin antibody positivity during the first trimester of pregnancy is a major risk for perinatal death

Männistö T, Vääräsmäki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, Bloigu A, Järvelin MR, Suvanto-Luukkonen E. Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. J Clin Endocrinol Metab 2009;94:772-9.

SUMMARY

BACKGROUND Undiagnosed or insufficiently treated thyroid dysfunction affects a considerable number of pregnant women. The suspected adverse outcome on the offspring is currently the subject of considerable concern and extensive discussion. There are, however, only a few large prospective studies evaluating the effect of maternal thyroid dysfunction on offspring. Moreover, the observations are inconsistent.

METHODS The prospective Northern Finland Birth Cohort comprises 99% of live births in the region of Northern Finland. The study comprises all births with a calculated term from July 1 through June 30, 1986, that was drawn from the two northernmost provinces of Finland, with 9362 mothers and 9479 children in the target population. This study included only 9247 singleton pregnancies from the present study of 9479 children who had been followed since the 12th gestational week. The first questionnaire on demographic, biologic, health behavioral, and socioeconomic characteristics of the mothers and families covered the period up to the 24th gestational week, when the mothers were enrolled in the study if they were still pregnant. A second questionnaire covered maternal health and health behavior during pregnancy and the perinatal period. The third questionnaire contained items about pregnancy complications and diseases, delivery, and neonatal outcome and was completed in the maternity hospitals by the attending midwives. All women gave birth at the hospital.

Data were collected on thyroid hormones, thyrotropin (TSH), free triiodothyronine (FT_3), free thyroxine (FT_4), and autoantibodies (thyroid peroxidase antibody [TPOAb] and thyroglobulin antibodies [TgAb]). The lower limits of detection were 0.0025 μIU/ml for TSH, 5.1 pmol/L for FT_4, 2.3 pmol/L for FT_3, 1.0 IU/ml for TPOAb, and 1.0 IU/ml, for TgAb. The mean (±SD) gestational age at sampling was 11±3.6 weeks, and only samples drawn before or at the 20th gestational week were accepted (98% of the samples).The study population was large enough to create reference values applicable to the study cohort and to take into account the effect of freezing and storage.

The subjects with thyroid dysfunction were divided into four groups with respect to thyroid hormone levels: group A (clinical hypothyroidism) with TSH over the 95th percentile and FT_4 under the 5th percentile (n = 54); group B (subclinical hypothyroidism) with TSH over the 95th percentile and FT_4 between the 5th and 95th percentiles (n = 224); group C (subclinical hyperthyroidism with TSH under the 5th percentile, FT_4 between the 5th and 95th percentile (n = 204); and group D (clinical hyperthyroidism) with TSH under the 5th percentile and FT_4 over the 95th percentile (n = 204). The reference group had TSH between the 5th and 95th percentiles and FT_4 between the 5th and 95th percentiles. Groups A to D were compared with the reference group.

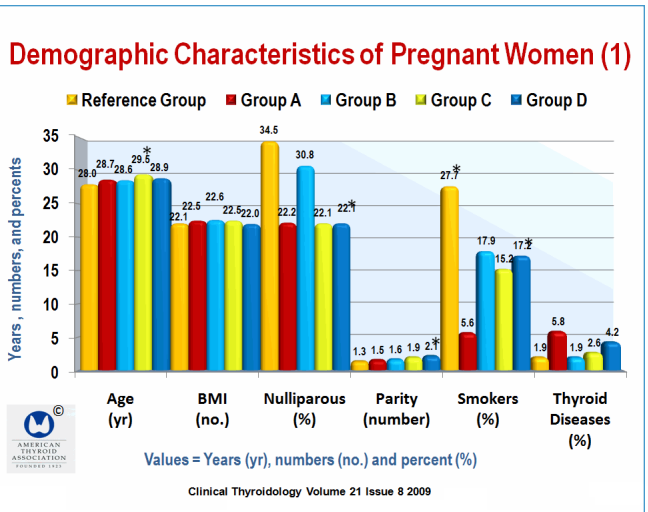

Figure 1. This figure shows the demographic characteristics of pregnant women. Values are means, numbers, or percents. The reference group had a TSH between the 5th and 95th percentiles and an FT_4 between the 5th and 95th percentiles; group A (clinical hypothyroidism) had a TSH over the 95th percentile, and FT_4 under the 5th percentile; group B (subclinical hypothyroidism) had a TSH over the 95th percentile, and FT_4 between the 5th and 95th percentiles; group C (subclinical hyperthyroidism) had a TSH under the 5th percentile and FT_4 between the 5th and 95th percentiles; group D (clinical hyperthyroidism) had a TSH under the 5th percentile, and FT_4 over the 95th percentile. *P<0.05 when comparing groups A to D together or separately with the reference group or comparing the antibody-positive group with the antibody-negative group. Body-mass index is the weight in kilograms divided by the square of the height in meters. Derived from Table 2 in Männistö et al.

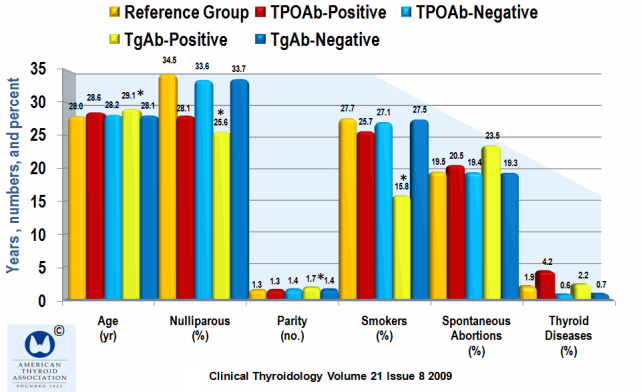

Figure 2. This figure shows demographic characteristics of pregnant women. *P<0.01. See Figure 1 for further legend details. Derived from Table 2 in Männistö et al.

Mothers were considered to be TPOAb- or TgAb-positive if the concentrations of the antibody were over the 95th percentile.

All data concerning the mothers and their obstetric histories were obtained from the questionnaires. The data on perinatal outcomes comprised gestational age, preterm delivery (birth at <37th gestational week); birth measurements (birth weight small for gestational age [SGA] and large for gestational age [LGA]; birth length, ponderal index [birth weight/birth length^3], and head circumference); Apgar scores; perinatal mortality (stillborns and early neonatal deaths <7 days after birth); neonatal deaths; malformations; and umbilical-cord length.

RESULTS The demographic data of the mothers in each group did not differ substantially from that in the whole cohort according to their thyroid hormone and antibody status. However, there were significant differences among those in the reference group and in groups A to D in maternal age, body-mass index, parity, smoking habits and the prevalence of previous thyroid disease. The mothers in group C were older; those in group B were heavier; and those in groups B, C, and D had higher parity; groups A, B, and C included fewer smokers, and groups A, B, and D more often had a history of thyroid disease than mothers in the reference group (Figure 1). TPOAb-positive women were older and had higher parity and fewer were smokers, as compared with the TgAb-negative mothers, and for these reasons the results were adjusted for maternity age and parity. Infants in group A had a higher mean ponderal index than infants of the reference group. Absolute and relative placental weights were higher in group A (Figure 2). There were no significant differences in any of the perinatal outcomes when group B was compared with the reference group (Figure 3).

The infants in group C less often had Apgar scores of 7 or less at 5 min than infants in the reference group (Figure 3) and had a risk of 0.4 for having low Apgar scores at 5 min when compared with the reference group (Figure 4). In group D, both absolute and relative placental weights as well as absolute birth weight and the number of LGA infants were higher than in the reference group (Figure 3).The infants in group D were at a 2.7-fold greater risk for being LGA as compared with infants in the reference group (Figure 4), but the risk was no longer significant after adjusting for maternal age and parity. Mothers who were TPOAb-positive more often had both low-birth-weight infants and LGA infants than did TPOAb-negative mothers (Figure 5). No differences were observed in the frequencies of SGA infants in groups A to D. Infants of TPOAb-positive mothers were at a 2-fold higher risk for being LGA and a 1.7-fold higher risk for low birth weight (Figure 4). The offspring of TPOAb- and TgAb-positive mothers had a 2- to 3-fold greater perinatal mortality than those of the antibody-negative mothers (Figures 4 and 5). In the TPOAb-positive group, four of seven perinatally deceased infants were born very preterm (before gestational week 28), and in the TgAb-positive group, three of six were born very preterm. Mothers who were TgAb-positive had an almost 2-fold risk for having children showing nonocephalic presentation at birth (Figures 4 and 5). An evaluation of the independent effect of maternal underweight (body-mass index ≤20) found that it was not associated with any

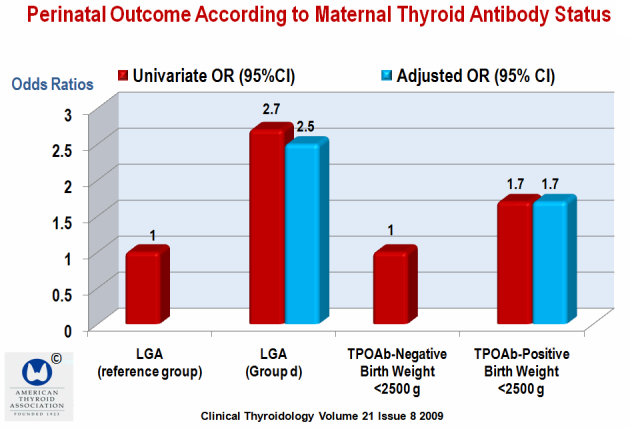

Figure 3. Odds ratios (ORs) with 95% confidence intervals (CIs) showing perinatal outcome of children grouped according to maternal thyroid hormone status. Derived from Table 4in Männistö et al. See legend in Figure 1 for further legend details. LGA is large growth weight for gestational age.

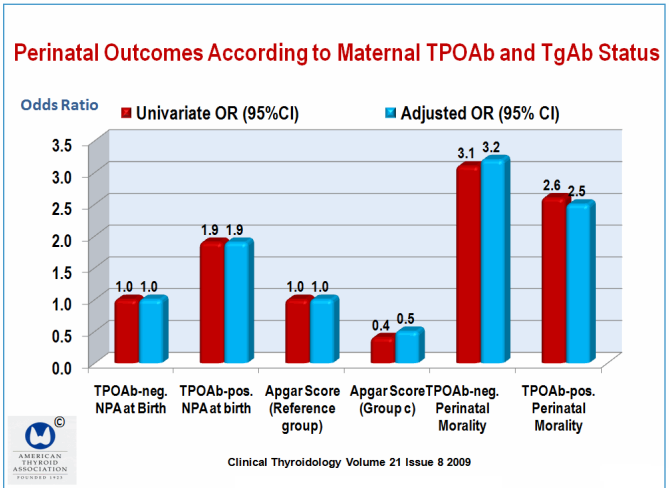

Figure 4. Estimated risks of perinatal outcomes with maternal antibody status. CI = confidence interval; NPA = noncephalic presentation; OR = odds ratio. Derived from Table 4 in Männistö et al.

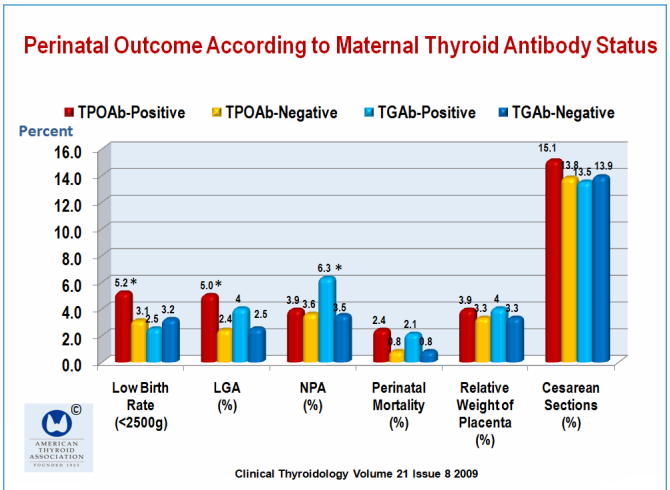

Figure 5. Prenatal outcome according to maternal thyroid antibody status. *P = 0.05 comparing TPOAb-positive and TPOAb-negative. Derived from Table 5 in Männistö et al. NPA = noncephalic presentation.

of the adverse perinatal outcomes (Figure 4). However, maternal overweight was a significant risk factor (odds ratio, 1.7 1.2 to 2.5) for LGA, but there was no association between maternal overweight and perinatal mortality and low birth weight. Thyroid hormone status appears to be less influential in this regard

CONCLUSION Antithyroperoxidase antibody and antithyroglobulin antibody positivity during the first trimester of pregnancy is a major risk for perinatal death, although thyroid-function status, as such, is not associated with this risk.

COMMENTARY

The authors of this study found only four prospective cohort studies in which the effect of thyroid hormone status on perinatal outcome has been investigated. Allen et al. (1), in a study of 9403 women with singleton pregnancies, found 209 with serum TSH concentrations of 6 µIU/ml or higher (2.2%). The fetal death rate (3.8%) was significantly higher in the pregnancies with high serum TSH levels than in the women with a serum TSH less than 6 mU/L (0.9%; odds ratio, 4.4). The authors concluded that, from the second trimester onward, the major adverse obstetrical outcome associated with an elevated TSH in the general population is an increased rate of fetal death. The authors suggested that if thyroid-replacement treatment avoided this problem this would be another reason to consider population screening.

In a study by Casey et al. (2) of 25,756 women who underwent thyroid screening and delivered a singleton infant, 17,298 (67%) women enrolled for prenatal care at 20 weeks of gestation or less, and 404 (2.3%) of this group had subclinical hypothyroidism. The study found that pregnancies in women with subclinical hypothyroidism were 3-fold more likely to be complicated by placental abruption (relative risk, 3.0). Preterm birth, defined as delivery at or before 34 weeks of gestation, was almost 2-fold higher in women with subclinical hypothyroidism (relative risk, 1.8). Casey et al. speculated that the previously reported reduction in intelligence quotient of offspring of women with subclinical hypothyroidism may be related to the effects of prematurity.

In another study, Matalon et al. (3) investigated the results of pregnancy in women with hypothyroidism, comparing outcomes of singleton pregnancies of patients with and without hypothyroidism. During the study period, they found that among 139,168 singleton deliveries, 0.8% (n = 1102) were in patients with hypothyroidism. Multivariate analysis found that the following risk factors were significantly associated with hypothyroidism: fertility treatments, recurrent abortions, diabetes mellitus, previous cesarean section and advanced maternal age. There were no significant differences in pregnancy complications, such as placental abruption, preterm deliveries or postpartum hemorrhage, between the euthyroid and hypothyroid groups; however, patients with hypothyroidism had higher rates of cesarean deliveries (20.1% vs. 11.5%, P<0.001). This association remained significant even after controlling for confounders, such as diabetes mellitus, previous cesarean section, fertility treatments, recurrent abortions, and advanced maternal age. When hypothyroidism was diagnosed and treated before pregnancy, there were no significant differences in perinatal outcomes, including birth weight <2500 g (10.4% in the hypothyroidism group vs. 9.5% in the euthyroid control group [P = 0.159]) and Apgar score <7 at 5 minutes (0.8% vs. 0.6%, P = 0.312). Perinatal mortality (1.4% vs. 1.3%; P = 0.95) did not differ between the two groups. The authors concluded that appropriate treatment of maternal hypothyroidism with levothyroxine is not associated with adverse perinatal outcome.

Männistö et al. found that maternal thyroid autoantibody positivity but not thyroid hormone status at the end of the first trimester was associated with elevated perinatal mortality. Mothers who were positive for TgAb who had large for gestational age (LGA) children, whereas mothers who were also positive for TPOAb more often had both low-birth-weight infants and LGA infants than occurred in TPOAb-negative mothers. Still, no differences were observed in the frequencies of SGA infants between the groups with and without TPOAb. Infants of TPOAb-positive mothers had a 2-fold risk for being LGA and a 1.7-fold risk for low birth weight. Moreover, the offspring of TPOAb- and TgAb-positive mothers had a 2- to 3-fold higher risk of perinatal mortality than those of mothers who were antibody-negative. A study by Negro et al. (4) found that TPO-Ab positivity was significantly related to preterm delivery, the rate of which decreased with levothyroxine treatment. These findings, as well as those reported by Casey et al. (2), suggest that an increased rate of preterm delivery among TPO-Ab-positive women may be related to impaired thyroid function. The mothers with high TSH combined with low FT_4 levels also showed a slight tendency to have an increased rate of preterm delivery, but this was not the case when FT_4 levels were normal. Männistö et al. suggest that antibodies could possibly explain this because 50% of the mothers with high TSH and low FT_4 levels were antibody-positive. Männistö et al. suggest that thyroid dysfunction cannot be confirmed in their study and that the role of autoimmunity and thyroid autoantibodies in preterm deliveries requires further research.

This is an important study that likely will generate more studies of this important issue.

— Ernest L. Mazzaferri, MD, MACP

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