

EDITORS' CHOICE —
MATERNAL THYROID FUNCTION DURING GESTATION

Pregnant women with TSH levels higher than 2.5 IU/L during the end of gestation are at risk for breech presentation, and obstetrical complications.

Kuppens SM, Kooistra HA, Wijnen HA, Crawford S, Vader HL, Hasaart TH, Oei SG, Pop VJ. Maternal thyroid function during gestation is related to breech presentation at term. Clin Endocrinol (Oxf) 2009. doi: 10.1111/j.1365-2265.2009.03729.x

SUMMARY

BACKGROUND

Breech presentation at term is the most common abnormal fetal presentation, and it is associated with neonatal and maternal morbidity and mortality. There are many factors associated with breech presentation, including, among other causes, prematurity, low birth rate, primiparity, and smoking during pregnancy. The objective of this study was to evaluate the relationship between suboptimal maternal thyroid function during gestation and breech presentation at term.

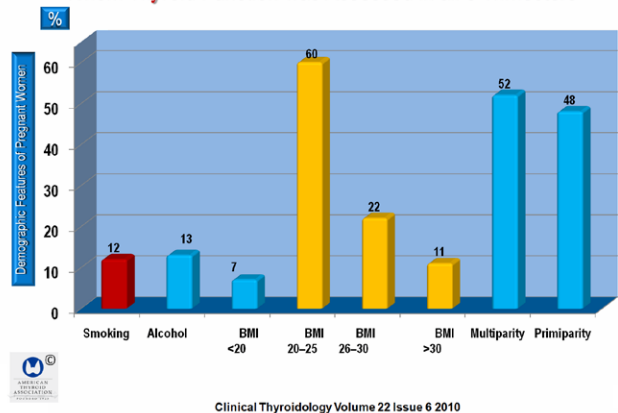
METHODS AND STUDY PATIENTS

Over a 2-year period, 1507 pregnant white Dutch women in five community midwifery practices, living in and around the city of Eindhoven, The Netherlands, were invited to participate in the study at the time of their first antenatal visit at 12 weeks of gestation. A total of 1190 women (79%) agreed to participate in the study. Nonresponders did not differ from the responders in age, parity, and educational level. Excluded from the study were 8 women who were taking thyroid medications for known clinical hyperthyroidism, 2 with hypothyroidism at screening, 8 who became pregnant after hormonal stimulation, and 5 with type 1 diabetes, leaving 1149 women who were eligible for further participation and had follow-up at 24 and 36 weeks of gestation. Because spontaneous change of fetal position at term was an outcome measure, four women with successful

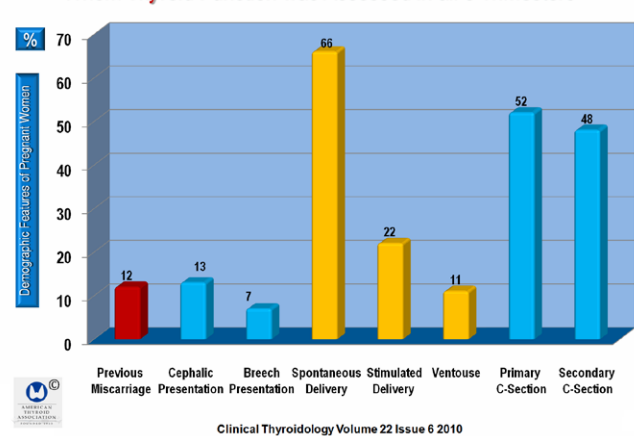
external cephalic version were excluded. Also excluded were 11 women with incomplete data and 4 whose babies were born with severe congenital abnormalities that were a possible determinant of fetal position.

Of the remaining 1130 women, 72 (6%) delivered prior to 37 weeks of gestation, but because breech position before term is

Characteristics of 1058 Pregnant Women ≥37 Weeks of Gestation in Whom Thyroid Function was Assessed in all 3 Trimesters



Characteristics of 1058 Pregnant Women ≥37 Weeks of Gestation in Whom Thyroid Function was Assessed in all 3 Trimesters



Characteristics of 1058 Pregnant Women ≥37 Weeks of Gestation in Whom Thyroid Function was Assessed in all 3 Trimesters

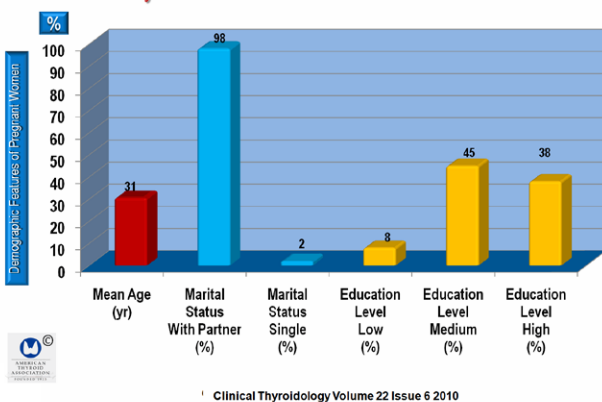


Figure 1. This figure shows the characteristics of 1058 term (≥37 weeks of gestation) pregnant women in whom thyroid parameters were assessed during all three trimesters. The data for figures 1 through 4 are derived from Table 1 of Kuppens et al.

Figures 2 and 3. These figures show the characteristics of 1058 term (≥37 weeks of gestation) pregnant women in whom thyroid parameters were assessed in all three trimesters. BMI = body-mass index, which is the weight in kilograms divided by the square of the height in meters.

not regarded as an abnormal fetal position, these women were also excluded from the study. The final sample comprised 1058 women who delivered at term (≥ 37 weeks of gestation) and in whom thyroid function was assessed in all three trimesters. None of the women in this group were treated for thyroid disease during gestation, but gestational diabetes developed in 8 of the 1058 women (0.8%).

ASSESSMENTS

Obstetric parameters Term was described in two ways: first from the date of the last menstrual period, and second from an ultrasound scan (US) in the first trimester. A second US was performed within 2 weeks to reassess gestational age if there was a discrepancy of more than 7 days in the two initial assessments. Gestational age was expressed as weeks and days. Fetal positions at birth were classified as cephalic or breech (i.e., complete or incomplete, or frank breech). During follow-up, possible confounders such as previous obstetrical history such as parity, previous cesarean section, demographic features, body-mass index, and lifestyle habits such as smoking and alcohol intake were assessed. The findings are shown in Figures 1 to 3.

Thyroid parameters (Figure 4)

Thyrotropin (TSH), free thyroxine (FT₄), and autoantibodies to thyroid peroxidase (TPO-Ab) were assessed at 12, 24, and 36 weeks of gestation. Women with serum TPO-Ab concentrations higher than 35 IU/ml at 12 weeks of gestation were regarded as TPO-Ab-positive.

RESULTS

During gestation, a decrease in mean FT₄ was accompanied by an increase in mean serum TSH. The number of women with elevated TPO-Ab concentrations decreased toward term. Figure 5 shows the differences in thyroid parameters between 58 women (5.5%) who presented with breech position at term versus the 100 remaining women who presented with a fetal cephalic position. At 36 weeks of gestation, women with breech fetuses had significantly higher serum TSH concentrations, as compared with those who had fetuses in a cephalic position

($P = 0.007$), whereas there no differences in TSH at 12 and 24 weeks of gestation. The FT₄ was not significantly related to breech presentation in any trimester. Likewise, the prevalence rates of TPO-Ab did not differ among the groups (Figure 5).

The 5th, 10th and 95th percentile cutoff points for serum TSH at 36 weeks were as follows: <5th percentile, <0.51 mIU/L ($n = 54$); 5th to 10th percentiles, 0.51 to 0.71 mIU/L ($n = 54$); 90th to 95th percentile, 2.50 to 2.89 mIU/L ($n = 49$); and 95th percentile, >2.89 mIU/L ($n = 59$). Figure 5 shows the percentage of women who presented with a breech presentation at delivery for each of the four percentile groups. The 90th and 95th percentile TSH groups at 36 weeks of gestation were 11% and 14% among the women who presented in fetal breech position at delivery, whereas there were no breech presentations in the lowest 5th percentile TSH group ($P = 0.02$).

Gestational Thyroid Function, TSH, and FT₄ in All Three Trimesters

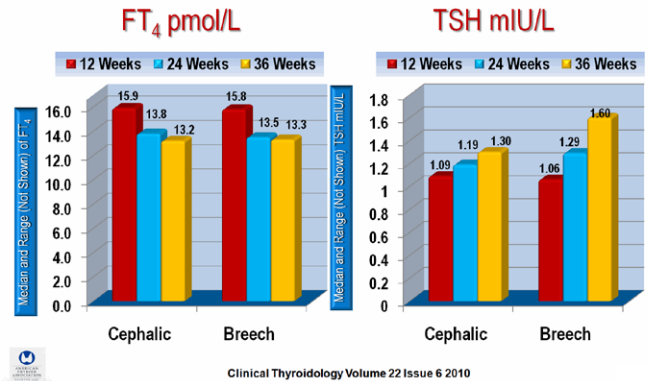


Figure 5. This figure shows the thyroid FT₄ and TSH levels during 12, 24, and 36 weeks of gestation in women who had cephalic presentation or breech presentation. The data for this figure were derived from Table 2 of Kuppens et.al.

Gestational Thyroid Function in All Three Trimesters

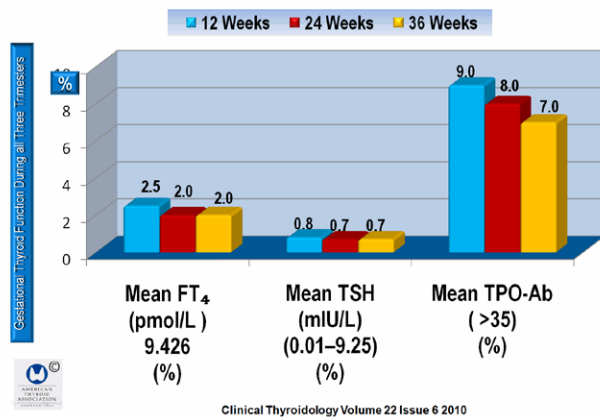


Figure 4. This figure shows the thyroid tests, FT₄ (in pmol/L), and TSH (in mIU/L) results at 12, 25, and 36 weeks of gestation.

Logistic-Regression analysis Depended Variable is Breech Presentation at Term

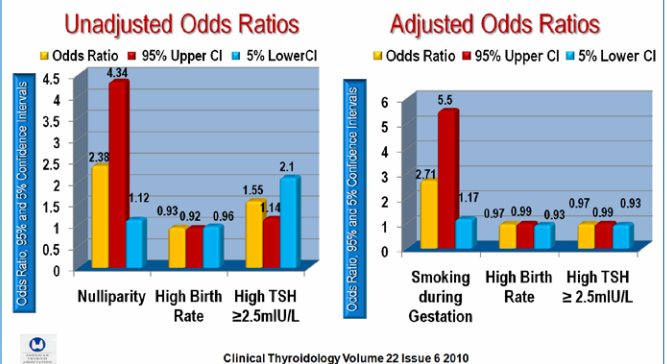


Figure 6. This figure shows the results of logistic-regression analysis in which the dependent variable is breech presentation at term. The figure shows the odds ratio and 95% and 5% confidence intervals (CI). The data for this figure were derived from Table 3 in Kuppens et.al.

The prevalence of breech presentation in the subgroup of women with a TSH ≥ 2.5 mIU/L (≥ 90 th percentile) was 11% (12 of 108), as compared with 4.8% in the women with TSH < 2.5 mIU/L ($P = 0.006$). When similar categories for FT₄ were assessed, there was no relationship between FT₄ and breech presentation.

Odds Ratios (Figure 6)

Figure 6 shows the unadjusted odds ratios (ORs) using logistic-regression analysis (OR 95% confidence interval [95thCI]). Breech position at birth is the dependent, and nulliparity, birth weight, and high TSH (> 2.5 mIU/L) at 36 weeks of gestation, were all significantly related to breech presentation.

Figure 6 also shows the results of adjusted OR using multiple-logistic-regression analysis. Breech presentation at birth, is the dependent variable. High TSH levels at 36 weeks of gestation, nulliparity, birth weight, and smoking status were all significantly related to breech presentation. Elevated TPO-Ab levels were not related to breech presentation.

A total of 17 of the 108 women (16%) with high TSH levels at 36 weeks of gestation had a history of parental thyroid disease, as compared with 66 women (6.6%) in the group with low TSH levels ($P = 0.001$). Likewise, of the 108 women with high TSH levels at 36 weeks of gestation, 20 (18%) had elevated TPO-Ab at 12 weeks, as compared with 66 (7%) in those with TSH < 2.5 IU/ml ($P = 0.001$). Lastly, of the 83 women with a history of parental thyroid disease, 20% had elevated serum TPO-Ab at 12 weeks of gestation, as compared with 8% of the women with no history of thyroid disease ($P = 0.001$). None of the women with gestational diabetes had an elevated TSH level at 36 weeks of gestation.

CONCLUSION

Women with TSH levels > 2.5 IU/ml during the end of gestation are at risk for breech presentation, and thus for obstetrical complications.

COMMENTARY

This is one of the first studies to identify a relationship between maternal thyroid function and fetal position at birth. The authors of this study published a previous prospective cohort study of pregnant women aimed at evaluating the relation between breech position at term (> 37 weeks of gestation) and low maternal FT₄ levels (1). The main outcomes of the study were that breech presentation at term delivery was independently related to FT₄ levels < 10 th centile at 12 weeks of gestation (OR, 4.7; 95% CI, 1.1 to 19), but was not related to an FT₄ level below the 10th centile at 12 weeks of gestation, and was also related to primiparity (OR, 4.7; 95% CI, 1.3 to 15). The study did not find a relationship between serum TSH levels and breech presentation. The conclusion of the study was that women with hypothyroxinemia (FT₄ at the lowest 10th centile) during early gestation without overt thyroid dysfunction are at risk for fetal breech presentation at term (> 37 weeks of gestation).

The present study, which is much larger, found that that breech position at birth is related to maternal thyroid hormone status during pregnancy. Indeed, not only was breech delivery almost 2.5-fold more common in women with TSH levels ≥ 2.5 mIU/L, regression analysis confirmed that elevated maternal TSH at 36 weeks of gestation is a key predictor for breech presentation. In addition, high TSH levels were significantly associated with

increased TPO-Ab levels and a parental history of thyroid disease. In sharp contrast, none of the women with TSH levels below the 5th percentile presented with breech position at term. The study also found no group differences for FT₄ levels at 12, 24, and 36 months of gestation.

This is a remarkably important study, as breech presentation at term is the most common abnormal fetal presentation and is associated with neonatal and maternal morbidity and mortality (2). There is considerable evidence of a relationship between subclinical thyroid dysfunction and impaired obstetrical outcome (3,4).

The authors of this study suggest that research is needed to detect the most appropriate tool for screening of maternal thyroid function during gestation.

This is a timely study that complements that of Yassa et al. (5), which precedes this study in this issue of CT. Together, they underscore the importance of carefully screening women at the time of pregnancy and meticulously performing follow-up and adjusting levothyroxine in pregnant women known to have hypothyroidism.

— Ernest L. Mazzaferri, MD, MACP

References

1. Pop VJ, Brouwers EP, Wijnen H, et al. Low concentrations of maternal thyroxin during early gestation: a risk factor of breech presentation? *BJOG* 2004;111:925-930.
2. Hickok DE, Gordon DC, Milberg JA, et al. The frequency of breech presentation by gestational age at birth: a large population-based study. *Am J Obstet Gynecol* 1992;166(3):851-2.
3. Casey BM, Dashe JS, Wells CE, et al. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 2005; 105:239-45.
4. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, et al. Maternal thyroid hypofunction and pregnancy outcome. *Obstet Gynecol* 2008; 112:85-92.
5. Yassa L, Marqusee E, Fawcett R, Alexander EK. Thyroid Hormone Early Adjustment in Pregnancy (The THERAPY) Trial. *J Clin Endocrinol Metab* 2010; May 12 [Epub ahead of print].