

Pregnant women with high serum TSH levels without overt thyroid dysfunction have an increased risk of miscarriage

Benhadi N, Wiersinga WM, Reitsma JB, Vrijkotte TG, Bonsel GJ. Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death. *Eur J Endocrinol* 2009;160:985-91.

SUMMARY

BACKGROUND Thyroid hormones are critical for the development of the fetal brain during early postnatal life. One study has shown that thyrotropin (TSH) levels above 6 $\mu\text{IU/ml}$ are associated with a significantly higher rate of stillbirth, and from the second trimester onward, the main adverse obstetrical outcome is an increased of fetal death. In addition, women with high free thyroxine (FT_4) levels accompanied with normal or slightly elevated serum TSH levels have a higher rate of miscarriage. The purpose of this study was to examine the association between maternal serum TSH and FT_4 levels and the presence of thyroid peroxidase antibodies (TPOAb) in pregnancy, and the rate of subsequent fetal loss.

METHODS The study was performed using data from pregnant Dutch women without known thyroid disease who participated in the Amsterdam Born Children and their Development (ABCD) study in Amsterdam from March 2003 through January 2004. This is a collaborative effort of the Municipal Health Services and all hospitals and midwife practices in Amsterdam. The main aim of the ABCD study was to examine the differences in pregnancy outcomes by focusing on maternal ethnic background, lifestyle, and psychosocial conditions as they relate to pregnancy outcome and the baby's health. Of 12,377 pregnant Dutch women queried, 8266 (67%) agreed to participate in the study by filling out a questionnaire that included questions about social demographic characteristics and ethnic background. Other ethnic groups were excluded from the analysis because of

the significant differences in serum TSH and pregnancy outcome among various ethnic groups. In addition, 4267 women provided consent for blood collection during their first obstetrics visit, which on average took place during the 13th week of gestation. Miscarriage, fetal death, or neonatal death was determined from three overlapping sources: (1) the National Midwife Registry, (2) the National Obstetricians Registry, and (3) the National Neonatal Registry. Miscarriage was defined as fetal death occurring before 22 weeks of gestation. Fetal death was defined as death occurring from 22 weeks of gestation until delivery, and neonatal death from 0 to 7 days after delivery, including stillbirth and intrauterine deaths. Overt hyperthyroidism was defined as a TSH concentration less than 0.35 $\mu\text{IU/ml}$ with an FT_4 above the upper limit of normal (21.1 pmol/L). Overt hypothyroidism was defined as a TSH above 5.60 $\mu\text{IU/ml}$ with a FT_4 below the lower limit of normal (7.5 pmol/L).

RESULTS A total of 2497 women remained in the study after excluding 116 who had blood samples that were either unacceptable or had missing TSH values. The mean age ($\pm\text{SD}$) of the study group was 32 ± 4.0 years. This was the first pregnancy in 60% of the women and the second in 32%. A total of 230 women (9.2%) smoked during their pregnancy. The serum TSH was less than 3.4 $\mu\text{IU/ml}$ in 129 women (5%) and was 5.6 $\mu\text{IU/ml}$ or higher in 11 women (0.5%). Among 95 women (4%), the FT_4 concentration was less than 7.5 pmol/L, and none had an FT_4 value above 21.1 pmol/L. TPOAb was elevated (>80 kU/L) in 146 of 2497 women (5.8%). TSH and FT_4 concentrations were

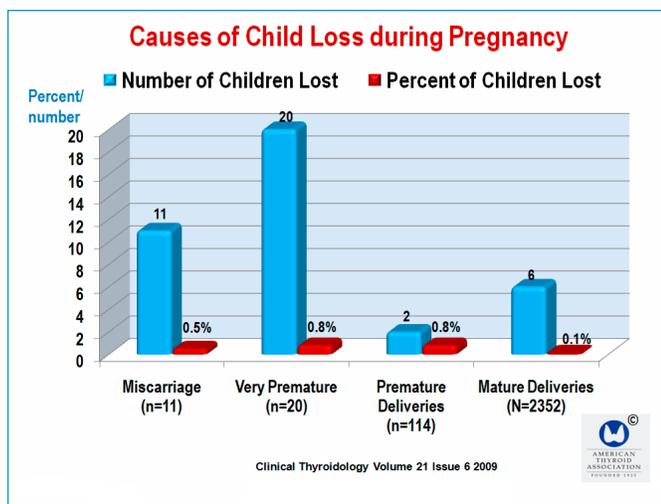


Figure 1. The rate of child loss is shown in this figure. Miscarriage was defined as death of the fetus occurring before 22 weeks of gestation. Fetal death and neonatal death were defined according to existing standards: fetal death = death occurring from 22 weeks of gestation until delivery; neonatal death = death from 0 to 7 days after delivery). Fetal death includes stillbirth and intrauterine deaths in this cohort. The numbers in parentheses in the horizontal axis are the number of events. (Derived from data in Table 2A of Benhadi et al.)

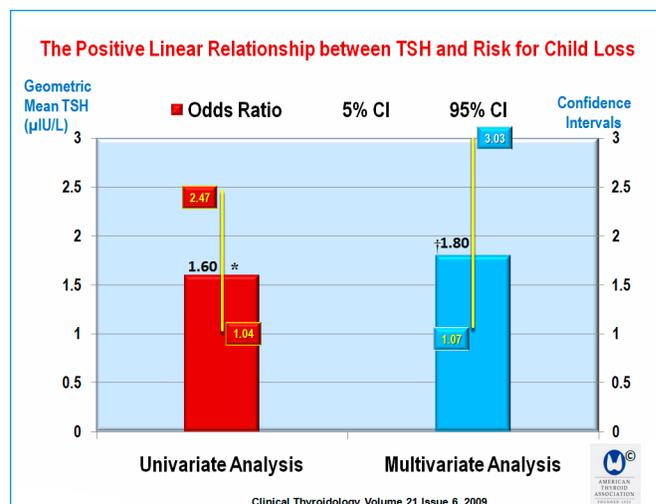
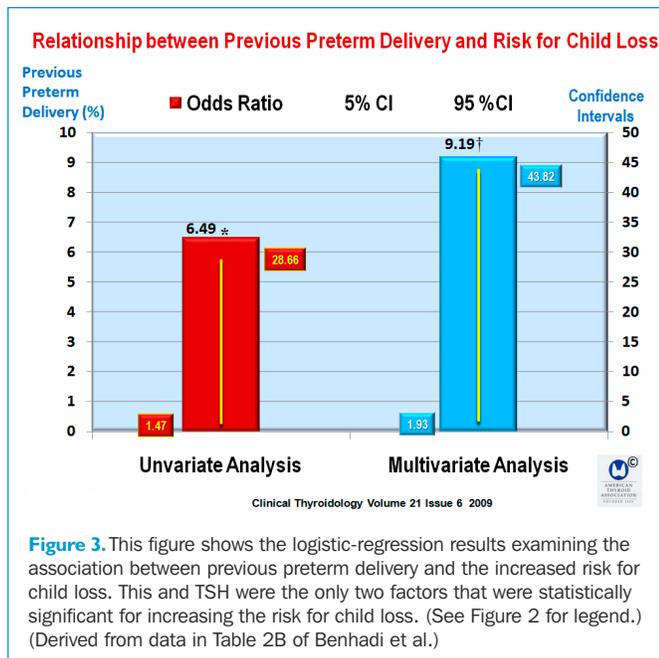


Figure 2. The log-transformed TSH level was related to child loss (OR, 1.60 for every doubling in TSH concentration; 95% CI, 1.04 to 2.47; *P = 0.033). After multivariate analysis, the effect of TSH had an OR of 1.80 (95% CI, 1.07 to 3.03; †P = 0.027 for OR). The yellow bars are 5% and 95% Confidence intervals. The small red and blue yellow boxes contain the confidence intervals. (Derived from data in Table 2A of Benhadi et al.)

negatively correlated (Pearson's $r = -0.375$, $P < 0.001$) and the TPOAb concentration was positively correlated with TSH ($r = 0.32$, $P < 0.001$) and negatively with FT_4 ($r = -0.065$, $P < 0.001$).

The median TSH concentration in women without serum TPOAb was $1.17 \mu\text{IU/ml}$ (interquartile range [IQR], 0.80 to 1.70), and it was $2.16 \mu\text{IU/ml}$ (IQR, 1.27 to 3.38) in women with serum TPOAb. The median FT_4 concentrations were 9.59 pmol/L (IQR, 8.81 to 10.43) and 9.00 pmol/L (IQR, 8.16 to 10.17), respectively. The difference between the TPOAb-positive and TPOAb-negative women was significant for both TSH and FT_4 ($P < 0.001$).



A total of 11 women had a miscarriage (0.5%). There were 20 very premature deliveries (<32 weeks) (0.8%), 114 premature deliveries (32 to 36 weeks) (4.6%), and 2325 mature deliveries (>36 weeks) (93%). The infant died in 8 (0.3%), 2 (0.8%), and 6 (0.1%) cases, respectively (Figure 1). In all, there were 27 miscarriages, fetal deaths, or neonatal deaths. Five women were excluded from the analysis because their pregnancies were terminated for various reasons.

There was a positive linear relationship between the log-transformed TSH values and the risk for subsequent child loss. In univariate analysis, the TSH concentration was related to child loss (odds ratio [OR], 1.60 for every doubling in TSH concentration; 95% confidence interval [CI], 1.04 to 2.47; $P = 0.033$) (Figure 2). The effect of TSH had an OR of 1.80 (95% CI, 1.07 to 3.03; $P = 0.027$) after adjustment for smoking, parity, age, diabetes mellitus, hypertension, previous stillbirth/miscarriage, or previous preterm delivery and TPOAb positivity. The authors emphasized that while the increased relative risk was substantial, the absolute risks were small. For example, for a mother with a serum TSH level of $0.54 \mu\text{IU/ml}$ (10th percentile of the study population) the estimated absolute risk would be 0.8%, while the expected risk for a woman with a TSH of $3.12 \mu\text{IU/ml}$ (90th percentile) would be 2.2%. The relationship between serum FT_4 concentrations and child loss was not statistically significant. Of the other factors included in the analysis, a previous preterm delivery was the only factor other than TSH that was significantly associated with child loss (Figure 3).

CONCLUSIONS Pregnant women with high TSH levels without overt thyroid dysfunction and previous preterm delivery are independent factors that increase the risk of miscarriage; however, maternal FT_4 concentrations are not associated with fetal loss.

COMMENTARY

Severe maternal thyroxine deficiency is well known to be associated with poor obstetric outcomes. In 1991, Klein et al. (1) reported that 49 of 2000 consecutive woman (2.5%) living in Maine who were being tested for α -fetoprotein concentration had serum TSH concentrations above $6 \mu\text{IU/ml}$ during gestational weeks 15 to 18. Six of these women had elevated TSH concentrations, ranging from 6.9 to $54 \mu\text{IU/ml}$, with serum T_4 concentrations that were more than 2 SD below average, underscoring the high prevalence of hypothyroidism in pregnant women. In 2000, Allan et al. (2) found that among 9403 women with singleton pregnancies, TSH measurements were $6 \mu\text{IU/ml}$ or higher in 209 women (2.2%). The fetal death rate in these women was significantly higher (3.8%) than that in women with TSH levels less than $6 \mu\text{IU/ml}$ (0.9%; OR, 4.4; 95% CI, 1.9 to 9.5). Still, other pregnancy complications did not occur

more frequently. Klein et al. concluded that the major adverse obstetrical outcome of an elevated serum TSH concentration from the second trimester onward is an increased rate of fetal death. Benhadi et al. found that the risk for child loss not only increased with higher TSH levels, but occurred even when maternal FT_4 concentrations were normal. The large sample size in this study demonstrates the risk for child loss with higher TSH concentrations alone, and raises the idea that pregnancy outcome might be improved by levothyroxine treatment.

The Concise Review in this issue of Clinical Thyroidology by Dr. Alex Stagnaro-Green puts the study by Benhadi et al. in perspective, including the idea of levothyroxine therapy.

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References

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