Median maternal serum TSH concentration is increased and FT_4 is decreased in pregnancies resulting in miscarriage or fetal death during the second and third trimesters

Ashoor G, Maiz N, Rotas M, Jawdat F, Nicolaides KH. Maternal thyroid function at 11 to 13 weeks of gestation and subsequent fetal death. Thyroid 2010. doi:10.1089/thy.2010.0058

SUMMARY

BACKGROUND

Hypothyroidism is associated with a substantial risk for miscarriage. However, whether subclinical hypothyroidism has the same effect and is mediated by antithyroid antibodies is in question. This study is based on the hypothesis that maternal thyroid function in the first trimester is altered in pregnancies ending in miscarriage or fetal death

METHODS AND STUDY PATIENTS

This is a prospective screening study of adverse obstetric outcomes in women attending their first routine hospital visit during the 11th to 13th weeks of gestation. During this visit, maternal age, ethnic origin (white, black, South Asian, East Asian, and mixed) were recorded, including cigarette smoking during pregnancy, the method of conception (spontaneous or assisted), parity (parous or nulliparous if no delivery beyond 23 weeks), weight, height, and body-mass index (BMI). Ultrasonography was performed to confirm gestational age by measurement of the crown-to-rump length, to diagnose any major fetal abnormalities, and to measure fetal nuchal translucency thickness (a measurement of the size of the translucent space behind the neck of the fetus using ultrasound between 10 and 14 weeks of pregnancy), reflecting the amount of fluid that has accumulated under the skin of the fetus.

Nuchal translucency tends to be increased in chromosome disorders such as Turner syndrome and Down syndrome; however, this is strictly a screening test that provides information that requires further testing). Also measured were the maternal serum free beta subunit of human chorionic gonadotropin and pregnancy-associated plasma protein A as part of screening for chromosomal abnormalities by a combination of measurement of fetal nuchal translucency thickness and serum biochemistry, as well as serum concentrations of free triiodothyronine (FT_3), free thyroxine (FT_4), thyrotropin (TSH), antithyroperoxidase antibody (anti-TPOAb), and antithyroglobulin antibody (anti-TgAb) at 11 to 13 weeks' gestation. A total of 202 singleton pregnancies that subsequently resulted in miscarriage or fetal death comprise the fetal loss group.

These data were compared with the results of the authors' previous study of 4318 singleton pregnancies with no history of thyroid disease and without the development of preeclampsia that resulted in live birth after 34 weeks of phenotypically normal neonates with birth weight above the 5th centile. The study comprised 726 (16.8%) pregnancies in which the concentration of one or both antithyroid antibodies was ≥60 U/ml. Normal ranges for TSH, FT_3, and FT_4 were derived from the study of the 3592 pregnancies with no antithyroid antibodies. The minimum detectable concentrations were 0.3 pmol/L for FT_3, 1.3 pmol/L for FT_4, 0.003 mIU/L for TSH, and 15 U/ml 30 U/ml for anti-TPOAb. A serum concentration <60 U/ml for anti-TPOAb and anti TgAb was considered normal.

RESULTS

TSH, FT_3, and FT_4 Values in the Fetal Loss and Unaffected Groups (Figures 1 and 2)

The patients in this study were examined from December 2005 through May 2006. The gestational age distribution at the time of miscarriage or the diagnosis of fetal death in the fetal loss group is shown in *Figure 1*. The patient characteristics of the fetal loss and unaffected groups are compared in *Figure 2*. The median BMI was higher in the fetal loss group, as compared with the unaffected group, and there was a higher prevalence of black women, and women who conceived after receiving ovulation induction drugs in the fetal loss group.

Univariate Analysis (Figure 3)

This study converted the serum FT_3, FT_4, and TSH to multiples of the normal medians (MoMs) corrected for gestational age, maternal age, ethnic origin, and BMI.

Univariate analysis found that the TSH MoM was increased in the fetal loss group as compared with the unaffected group

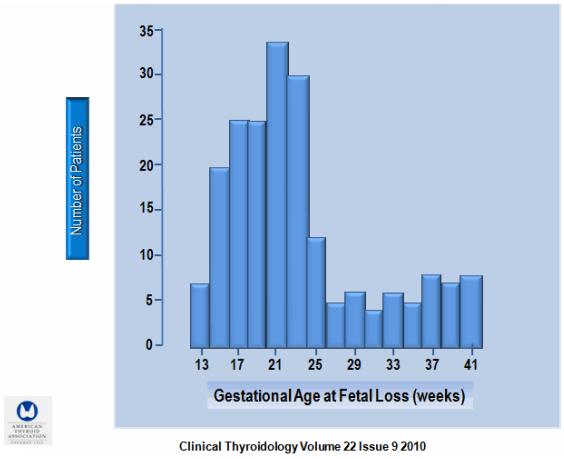

Figure 1. This figure shows the number of patients expressed as gestational age distribution of miscarriage or fetal death. This figure is adapted from Figure 1 of Ashoor et al.

and that the FT_3 MoM and FT_4 MoM were decreased. Linear regression analysis of the fetal loss group found that there was no significant association between the gestational age at fetal loss and TSH MoM (P = 0.654), FT_3 MoM (P = 0.411), and FT_4 MoM (P = 0.917). In the fetal loss group, TSH was above the 97th centile of the normal range in 12 cases (5.9%) and the serum FT_4 was below the 2.5th centile in 10 (5%). In 5 of the 10 cases with low FT_4, serum TSH was high.

Multiple Logistic-Regression Analysis (Figures 4 and 5)

Multiple logistic-regression analysis showed significant contributions to the prediction of fetal loss from the following factors: black ethnic origin (odds ratio [OR], 4.102; 95% confidence interval [CI], 3.003 to 5.603; P<0.001); use of ovulation drugs (OR, 8.238; 95% CI, 5.210 to 13.028; P<0.001); BMI (OR, 1.028; 95% CI, 1.000 to1.057; P = 0.05); and log FT_4 MoM (OR, 0.011; 95% CI, 1.000 to 1.057; P<0.001); but not TSH MoM (P = 0.208). However, if FT_4 MoM is not included, then TSH MoM becomes statistically significant. The authors suggest that this is the result of the good correlation between FT_4 MoM and TSH MoM. The associations between TSH and FT_3, TSH, and FT_4 are shown in *Figures 4 and 5*.

Prevalence of Antithyroid Antibodies (Figure 6)

In a previous screening study by the authors, 726 of the 4318 pregnancies (16.8%), were positive for both antithyroid antibodies, but in this study of pregnancies complicated by fetal loss, the prevalence of antithyroid antibody positivity was not significant *(Figure 6)*.

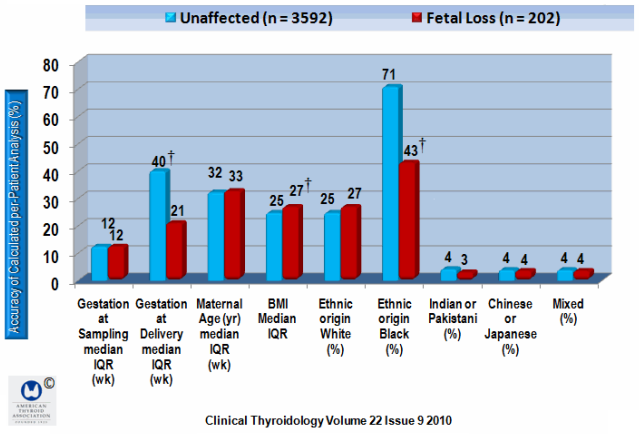

Figure 2. This figure shows the comparison the fetal loss group and the unaffected group. †P<0.001 comparing the two groups. IQR = interquartile range; MoM = multiple of the median. The data for this figure are derived from Table 1 of Ashoor et al.

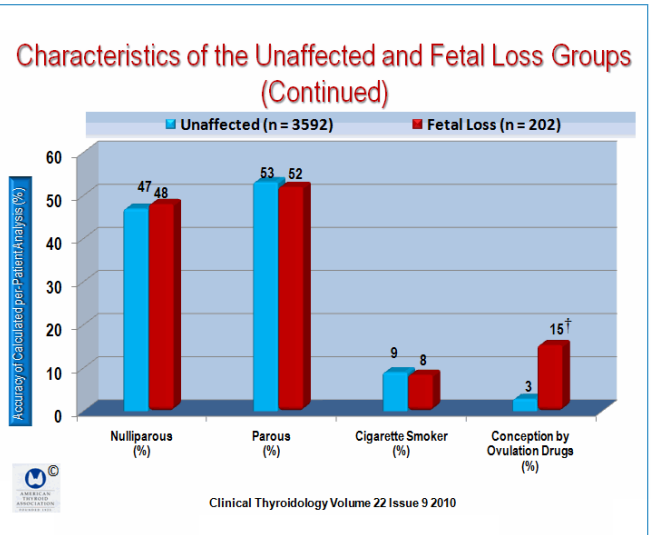

Figure 3. This is a continuation of *Figure 2*, showing the effects of ethnic origin, Parity, cigarette smoking, and the effect of conception by ovulation drugs (%)

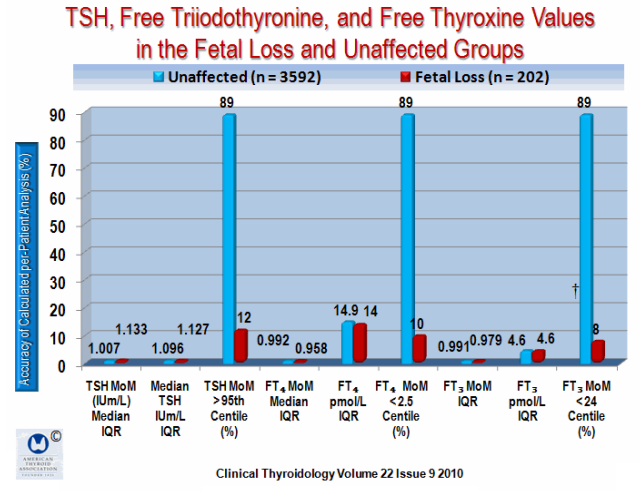

Figure 4. This figure shows TSH, FT_4, and FT_3 values in the fetal loss and unaffected groups. †P<0.05 and ‡P<0.0001, comparing the unaffected (n = 3592) and fetal loss groups (n = 202). The data for this figure are derived from Table 2 of Ashoor et al.

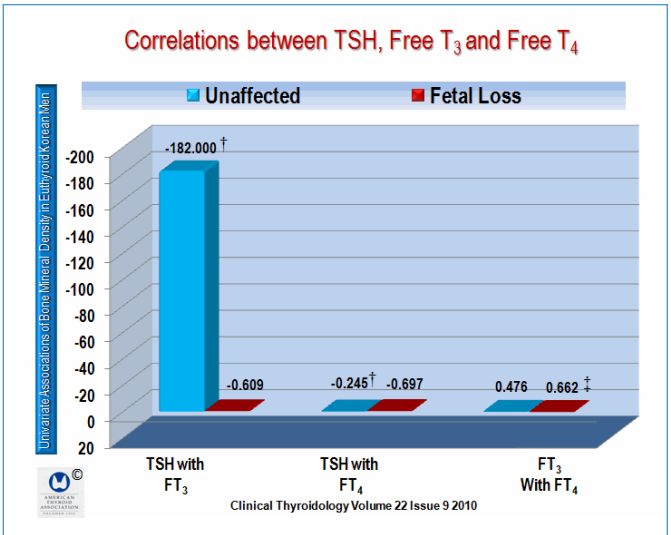

Figure 5. This figure shows the correlation between TSH, FT_3, and FT_4, in the unaffected and fetal loss groups. ‡P<0.01 and †P<0.0001 comparing TSH with FT_3, TSH with FT_4 and FT_3 with FT_4 in the unaffected and fetal loss groups. The data for this figure are derived from Table 4 of Ashoor et al.

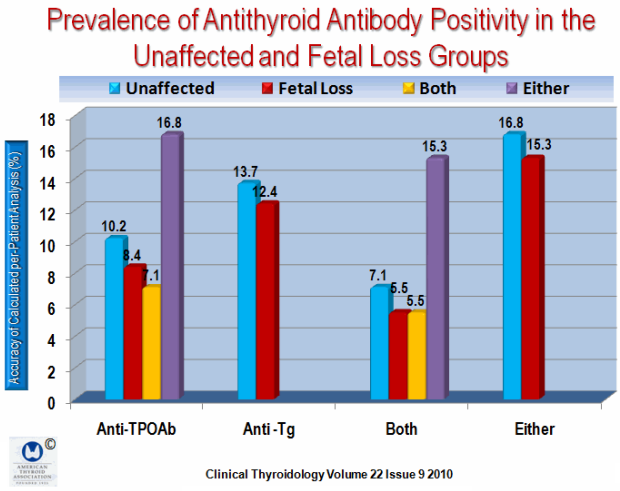

Figure 6. This figure shows the prevalence of antithyroid antibody positivity in the unaffected and fetal loss groups. The data for this figure are derived from Table 4 of Ashoor et al.

CONCLUSION

Median maternal serum TSH concentration is increased and FT_4 is decreased in pregnancies resulting in miscarriage or fetal death during the second and third trimesters, whereas there are no significant differences in FT_3 or the prevalence of antithyroid antibody positivity. Moreover, the fetal loss group had more women of black ethnic origin, a higher median maternal BMI, and more pregnancies conceived after ovulation as compared with the normal outcome group.

COMMENTARY

This study demonstrated that the median TSH MoM was increased, and the median FT_3 and FT_4 MoMs were decreased in the fetal loss group, as compared with the unaffected groups. Linear regression analysis in the fetal loss group found no significant association between the gestation at fetal loss and the TSH MoM and the FT_3 and FT_4 MoMs. In the fetal loss group, serum TSH was above the 97.5th centile of the normal range in 12 cases (5.9%) and the serum FT_4 was below the 2.5th centile in 10 (5%) with low serum FT_4 and high TSH.

Multiple logistic-regression analysis showed that there were significant contributions to fetal loss, including black ethnic origin, use of ovulation drugs, BMI, and log FT_4 MoM but not TSH MoM. However if the regression of FT_4 MoM was not included, the TSH MoM became statistically significant. Thus, more women of black ethnic origin, median maternal BMI, and pregnancies conceived after ovulation all were contributors to fetal loss as compared with the normal outcome group.

Ashoor et al. identified a study by Willinger et al. (1) that reached comparable conclusions. The Willinger study comprised 5,138,122 singleton gestations from the National Center of Health Statistics perinatal mortality and birth files, from 2001 through 2002. The main results were that black women have a 2.2-fold increased risk of stillbirth as compared with white women. The disparity between black and white women in the stillbirth hazard at 20 to 23 weeks was 2.75, decreasing to 1.57 at 39 to 40 weeks. Higher education reduced the hazard for whites more than for blacks and Hispanics. Medical, pregnancy, and labor complications accounted for 30% of the hazard in blacks and 20% in whites and Hispanics. The study found that congenital anomalies and small size for gestational age contributed more to preterm stillbirth risk among whites than blacks. Moreover, pregnancy and labor conditions contributed more to preterm stillbirth risk among blacks than among whites. The authors concluded that the excess stillbirth risk for blacks was greatest in preterm deliveries and that factors contributing to stillbirth risk vary by race and gestational age.

Another finding of the Ashoor study was that BMI was higher in the fetal loss group. Metwally et al. (2) performed a systematic review of all the relevant articles on MEDLINE from 1964 through 2006 and in EMBASE from 1974 through September 2006. The main outcomes were pregnancy loss at <20 weeks of gestation. Sixteen studies were included in the meta-analysis. Patients with a BMI (the weight in kilograms divided by the square of the height in meters) ≥25 had significantly higher odds of a miscarriage, regardless of the method of conception (odds ratio [OR], 1.67; 95% confidence interval [CI], 1.25 to 2.25). Subgroup analysis from a limited number of studies suggested that this group of women may also have greater odds of miscarriage after oocyte donation (OR, 1.52; 95% CI, 1.10 to 2.09) and ovulation induction (OR, 5.11; 95% CI, 1.76 to 14.83). There was no evidence for increased odds of miscarriage after in vitro fertilization–intracytoplasmic sperm injection. The authors concluded that although there is evidence that obesity increases the general risk of miscarriage, there is insufficient evidence to describe the effect of obesity on miscarriage in specific groups such as those conceiving after assisted conception.

Ashoor et al. also noted that there is a scarcity of studies on the outcome of pregnancies conceived after the use of ovulation-induction drugs without in vitro fertilization. The authors question whether pregnancies conceived through assisted reproductive technology (ART) are at increased risk for fetal loss; is the results are inconclusive and studies on maternal-age ART-type and gestational age-specific risk are limited.

One study that Ashoor cites is by Farr et al. (3), who mention that approximately 30% of pregnancies in the United States end in

miscarriage or stillbirth. Farr et al. question whether the notion that pregnancies conceived through ART are at an increased risk of fetal loss is conclusive, and that data on maternal age, the type of ART, and gestational age-specific risk of loss are limited. Farr et al. studied 148,494 ART pregnancies conceived from 1999 through 2002 and found that the Kaplan–Meier estimate of total risk of pregnancy loss was 29% but ranged from 22% to 63% depending on patient age and the ART procedure. The study found that by 6 weeks' gestation, almost 60% of the pregnancy losses had occurred. The risk of pregnancy loss ranged from 10% to 45% at 6 weeks' gestation and from 2% to 7% at the first trimester and was <2% after 20 weeks' gestation.

Ashoor emphasizes that there are multiple causes of miscarriage and fetal death during the second and third trimesters, but their study demonstrates that previously undiagnosed hypothyroidism at 11 to 13 weeks' gestation may be a contributing factor to approximately 5% of fetal losses. They question whether subclinical hypothyroidism and appropriate therapy can prevent fetal loss and the cost-effectiveness of this strategy remains to be determined.

— Ernest L. Mazzaferri, MD, MACP

Reference List

1. Willinger M, Ko CW, Reddy UM.Racial disparities in stillbirth risk across gestation in the United States. Am J Obstet Gynecol 2009;201:469-8.

2. Metwally M, Ong KJ, Ledger WL, Li TC.Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. Fertil Steril 2008;90:714-26.

3. Farr SL, Schieve LA, Jamieson DJ.Pregnancy loss among pregnancies conceived through assisted reproductive technology, United States, 1999-2002. Am J Epidemiol 2007;165:1380-8.