Maternal thyroid deficiency and pregnancy complications: implications for population screening

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Abstract

***Objective*—To examine the relation between certain pregnancy complications and thyroid stimulating hormone (TSH) measurements in a cohort of pregnant women.**

***Methods*—TSH was measured in sera obtained from women during the second trimester as part of routine prenatal care. Information was then collected about vaginal bleeding, premature delivery, low birthweight, abruptio placentae, pregnancy induced hypertension, need for cesarean section, low Apgar scores, and fetal and neonatal death.**

***Results*—Among 9403 women with singleton pregnancies, TSH measurements were 6 mU/l or greater in 209 (2.2%). The rate of fetal death was significantly higher in those pregnancies (3.8%) than in the women with TSH less than 6 mU/l (0.9%, odds ratio 4.4, 95% confidence interval 1.9–9.5). Other pregnancy complications did not occur more frequently**

***Conclusion*—From the second trimester onward, the major adverse obstetrical outcome associated with raised TSH in the general population is an increased rate of fetal death. If thyroid replacement treatment avoided this problem this would be another reason to consider population screening.**

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Although clinically apparent maternal hypothyroidism during pregnancy has long been known to be associated with both maternal and fetal complications, most of the studies documenting those problems have focused on patients in specialty or high risk clinics. The present study assesses the impact of maternal hypothyroidism in a cohort of pregnant women being managed in primary care settings. In 1991, our group reported thyroid stimulating hormone (TSH) measurements in a cohort of 2000 pregnant women whose sera were being obtained for α-fetoprotein measurements at 15–18 weeks' gestation as part of routine care.[1] TSH measurements were at, or above, 6 mU/l in 49 of the women (2.4%). In six of these 49 women the thyroxine (T_4) and/or free T_4 measurements were sufficiently abnormal (more than two standard deviations below the average) for clinical manifestations to be anticipated. It was not possible to gather individual information about health status in this cohort, because all identifiers were removed from the serum samples before the thyroid measurements were performed. Given the frequency of thyroid deficiency identified in this pregnancy population, it was decided that its possible impact on late pregnancy and delivery should be evaluated. To accomplish this, it was necessary to study a second, larger cohort of pregnant women.

Materials and methods

The Foundation for Blood Research offers prenatal serum screening services for open neural tube defects and Down's syndrome to all primary care prenatal practices in Maine. The testing is generally performed between 15 and 18 weeks' gestation. Approximately two thirds of the women receiving prenatal care in Maine opt for those services.

Between July 1990 and June 1992 the order form for the prenatal screening test contained a supplementary consent form, asking women if they would agree to have thyroid function measurements performed, in addition to the prenatal screening test being ordered. Our Institutional Review Board approved the consent form and project. The study design called for limiting enrollment to women with singleton pregnancies having prenatal screening for neural tube defects and Down's syndrome. Approximately 20 900 women were eligible for prenatal screening, and samples and consent were received from 10 010. Of these, 170 were from women not being tested for screening purposes and another 369 consents were provided by women who had signed up a second time during the collection of a follow up sample. Thus, 9471 women were eligible for the study, and pregnancy outcome was available for 9403 (99.2%). Among the remaining 68 women, about three quarters were known to have moved to another state before delivery. The women provided selected information about their pregnancy—for example, gravidity, parity, vaginal bleeding, and smoking status, at the time of enrollment. Also included was a question about insulin dependent diabetes that was independently verified as part of another project.[2] Information about pregnancy outcome—for example, viability, length of gestation, birthweight, and Apgar score was obtained via a collaborative agreement with the state's Bureau of Vital Records. In the few instances where pregnancy outcome was not

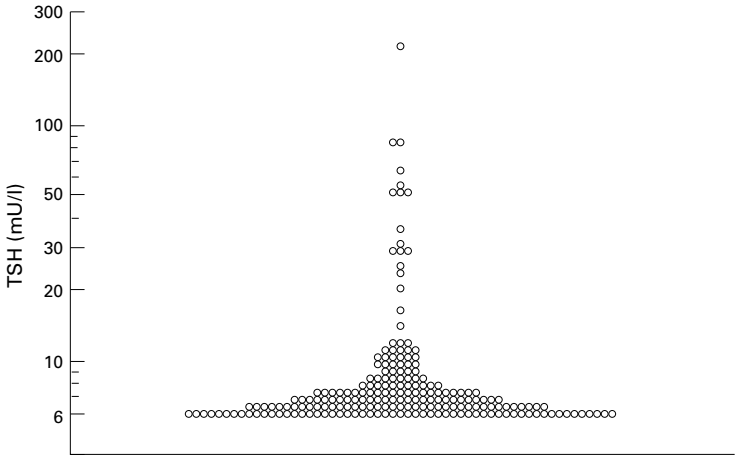

Figure 1 Individual TSH measurements for the 209 women with TSH measurements at or above 6.0 mU/l (approximately the 98th centile) are shown on a logarithmic scale.

Table 1 Demographic characteristics of pregnant women with raised TSH measurements, in comparison to the general pregnancy population

	Women not consenting	*Women giving consent TSH category (mU/l)*		
		<6	*6–9.99*	*≥10*
Number of pregnancies	10857	9194	172	37
Mean maternal age (years)	26.5	26.9	28.0	29.7 (p<0.001)
Mean gestational age at screening (days)	119	121	121	121
Mean maternal weight (kg)	68.49	68.49	70.3	72.57 (p<0.05)
Mean maternal weight gain (kg)	14.06	14.06	14.51	12.24
More than high school education (%)	42	45	50	55
Smoke cigarettes (%)	26	23	17	15 (p<0.03)
Insulin dependent diabetes (%)	0.3	0.4	0.6	2.7

found in either the birth or death records, the information was collected from the health care provider who cared for the woman. Earlier publications by us have verified the reliability of this method of collecting both second trimester and pregnancy outcome data.[3 4]

The serum TSH measurements were performed at the New England Newborn Screening Program in Boston on sera from all enrolled pregnancies within one month of receipt. The women's physicians were notified if the TSH measurement was greater than 10 mU/l. Additional thyroid function measurements were performed at the Beth Israel Deaconess Medical Center at a later date on all serum samples with TSH measurements ⩾ 6 mU/l (the definition of thyroid deficiency for the current study) and on sera from the pregnancies enrolled immediately before and after each of those samples. Details of the assays used for the various measurements have been published elsewhere.[1]

Statistical significance was taken at the 0.05 value. Categorical variables were compared using the χ^2 test or, when there were few observations, Fisher's exact test. Exact confidence intervals were estimated using Cornfield's approximation. All statistical analyses were performed using software from either BMDP[5] or True Epistat.[6]

Results

Figure 1 displays TSH measurements in the 209 women (2.2%) whose values were ⩾ 6 mU/l. TSH measurements were 10 mU/l or higher in 37 of the women (0.4%). Table 1 shows that women with TSH measurements of 10 mU/L or higher were, on average, 2.8 years older and 4.08 kg heavier than women whose TSH measurements were not raised; fewer of them smoked cigarettes. Two of the 209 women had insulin dependent diabetes. It should be noted that the women declining involvement in the study were quite similar to women with TSH measurements less than 6 mU/l. Table 2 shows detailed thyroid function studies which were performed in all of the pregnancies with elevated TSH measurements and in a subset of the pregnancies with values less than 6 mU/l (see Methods). Mean T_4, free T_4, and T_4/thyroxine binding globulin (TBG) ratios all become progressively lower, as TSH measurements increase. In addition, the percent of women with thyroid antibodies increases.

Table 3 shows that most of the complications of pregnancy and delivery occur at similar rates among women with raised TSH measurements and the rest of the study population; average gestational ages at delivery and birthweights are also similar. Among the 9194 women whose TSH measurements were not raised, there were 83 fetal deaths (0.9%) as opposed to eight fetal deaths among the 209 women with TSH measurements at or above 6 mU/l (3.8%, odds ratio 4.4, 95% confidence interval 1.9 to 9.5). The rate of fetal death is further stratified by degree of TSH increase in table 3. None of the fetal or neonatal deaths among women with raised TSH measurements occurred in the women who also had insulin dependent diabetes.

Information could be obtained regarding the thyroid status of the 16 women with the highest TSH measurements (at or above 20 mU/l). Two had undergone thyroidectomies previously for "cancer" and four for Graves disease,

Table 2 Measurements of thyroid function in maternal sera during the second trimester, stratified by TSH measurement

	TSH category (mU/l)			
	*<6**	*6–9.99*	*≥10*	*p-value†*
Number of pregnancies	418	172	37	
Mean T_4 (nmol/l)	145 (108–192)	138	120	<0.001
Mean free T_4 (pmol/l)	11.8 (7.6–15.3)	11.0	9.6	<0.001
Thyroxine binding globulin (nmol/l)	770 (530–1060)	760	800	NS
T_4/TBG (molar ratio)	0.19 (0.13–0.25)	0.18	0.15	<0.001
Thyroid antibodies (% positive)	9 (28/304)	55 (66/119)	80 (24/30)	<0.001‡

*Two pregnancies with TSH measurements <6 mU/l were randomly selected for each sample with an raised TSH measurement. Numbers in parenthesis are the observed 5th and 95th centiles.
†P value for comparison between groups with TSH <6 and ⩾10 mU/l.
‡P value for comparison between group with TSH <6 and both TSH 6–9.99 and TSH ⩾10 mU/l.

Table 3 Selected demographic data and rates of complications involving pregnancy and delivery, according to TSH measurement

	TSH measurement (mU/l)		
	<6	*6–9.99*	*≥10*
Number of pregnancies	9194	172	37
Vaginal bleeding (%)	11	10	11
Mean gestational age at delivery (weeks)	40.2	40.3	40.2
Mean birthweight (grams)	3448	3451	3498
Abruptio placentae (%)	0.7	1.2	0
Pregnancy induced hypertension (%)	3.9	4.7	2.7
Cesarean section (%)	22	24	16
Apgar <3 @ 5 minutes (%)	0.4	0	2.7
Apgar <6 @ 5 minutes (%)	1.5	2.9	2.7
Fetal deaths† (%)	0.9	2.9	8.1 (p<0.001)*
Neonatal deaths‡ (%)	0.4	0.0	2.7

*Only comparison to reach statistical significance compared to value for group <6 mU/l.
†Includes all in utero deaths between the time of enrollment and term.
‡Includes all deaths occurring after a live birth, up to 1 month of age.

one woman had congenital hypothyroidism, five were reported to have idiopathic acquired hypothyroidism. The remaining four were diagnosed as a result of the TSH measurement obtained for this study. Of the 12 with previously recognised disease, one admitted to non-compliance, and their physicians suspected the others of non-compliance.

Discussion

This is the first large, population based study of complications in pregnancies with raised TSH measurements. Our finding that 2.2% of 9403 unselected pregnant women have a TSH measurement at, or above, 6 mU/l is similar to the frequency in our previous study (2.4% of 2000 pregnancies) and that of Glinoer (2.2% of 1900 pregnancies).[1 7] Neither of these earlier studies linked TSH measurements with pregnancy complications or outcome in the entire cohort. Other studies suggested that adverse events such as fetal death, premature birth, low birthweight, placental abruption, and pregnancy induced hypertension[8–11] occur more often in women with clinically diagnosed hypothyroidism. These observations, however, have been limited to women attending high risk or specialty clinics and may not reflect findings in the general population. Of the adverse events that were examined in the present cohort, only fetal death occurred more often in the women with raised TSH measurements. In previous studies, the frequency of fetal death in the presence of maternal hypothyroidism ranged from 1.5 to 10%.[7 9–13] However, none of these was a cohort study. Our study only included fetal deaths after 16–18 weeks' gestation, and this might explain why our rate among women with raised TSH measurements was towards the lower end of the reported range (3.8%).

Although the proportion of TSH associated late fetal deaths appears not to be great (3.8% of 2.2% of all pregnancies in the general population), it may be avoidable. Glinoer[7] reported four miscarriages among the 41 women with raised TSH measurements in his study of 1900 consecutive pregnant women. In that study, follow up was limited to women with elevated TSH measurements. He performed screening at the first prenatal visit, and all of the fetal deaths occurred before he could introduce treatment. In 1990, Stagnaro-Green and associates[13] examined the relation between thyroid antibodies and fetal death in a cohort of 522 women enrolled before 13 weeks' gestation; 108 of these women were classified as having positive antibody studies (21%). Among this group, the fetal death rate was 17%, as opposed to 8% in the antibody negative women. Five of the 17 deaths among the antibody positive women occurred in association with TSH increases. The authors speculated that thyroid antibodies might serve as a marker for other autoimmune conditions that might, in turn, be responsible for the fetal death. In the present study, TSH measurements alone were used to stratify the rate of fetal death. It was also shown, however, that thyroid antibodies were present in a much greater proportion of women with raised TSH measurements. For that reason, it is not possible to attribute causality to either marker with confidence. Although it is not certain that adequate treatment of hypothyroidism can avoid this complication, it is apparent that there is room for improvement in monitoring and treating maternal hypothyroidism. One possibility is that adequate treatment may, if introduced early enough, reduce fetal deaths in women with raised TSH measurements.

In a previous report, we documented an association between untreated hypothyroidism during pregnancy and lower IQ in the offspring.[14] That study also found that an average of five years elapsed before a clinical diagnosis of hypothyroidism could be made. In a few instances, the diagnosis was not made until 10 years later.[15] The current finding that raised TSH measurements are associated with an increased rate of fetal death adds another dimension to the argument that routine TSH screening should be evaluated as a way to potentially improve pregnancy outcome and maternal well being.

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