Pregnant Women on Thyroxine Substitution Are Often Dysregulated in Early Pregnancy

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Background: Thyroid hormones are important for normal fetal development. Maternal hypothyroidism during early pregnancy is associated with impaired neuropsychological development of children and other adverse outcomes. The primary aim of this prospective study was to determine whether thyroxine-treated pregnant women with hypothyroidism are adequately thyroxine substituted in early pregnancy. A secondary aim was to determine if fetal loss differed between females with thyrotropin (TSH) values within and outside the reference range at their first TSH test, scheduled for 1–2 weeks after verification of pregnancy.

Methods: This was a prospective open-labeled study. During the years 1997–2002, 119 consecutive pregnancies in 101 females with thyroid diseases were followed at the Department of Endocrinology, Malmö University Hospital. At the first visit, 63 patients, median age 30 years (range 17–45 years), were on thyroxine substitution therapy for hypothyroidism. In these patients 83% were in their first trimester at the time of the initial test.

Results: Of the 63 patients on thyroxine substitution for hypothyroidism 32 (51%; Group A) patients had serum TSH values within the reference range at their initial test and 31 (49%; Group B) had serum TSH values outside the reference range. Twelve (19%) had TSH values of <0.40 mIU/L and 19 (30%) had TSH values of >4.0 mIU/L. The fetal loss was 2 of 32 (6%) in Group A compared to 9 of 31 (29%) in Group B ($p < 0.05$).

Conclusions: In 49% of pregnant women on thyroxine substitution, serum TSH values were outside the reference range when first tested, generally in the first trimester. Fetal loss was significantly greater in pregnant women with abnormal TSH values compared to those with normal TSH values. Thyroid function in pregnant women on thyroxine substitution should be monitored early in pregnancy and carefully followed during pregnancy. The thyroxine dose should be increased as needed early in pregnancy to avoid hypothyroidism.

Introduction

THYROID DYSFUNCTION in pregnant women can influence the outcome for mother and fetus at all stages of pregnancy as well as interfere with ovulation and fertility (1–3). Maternal hypothyroidism during early pregnancy is associated with impaired neuropsychological development of children and other adverse outcomes, including premature birth, preeclampsia, breech delivery, and increased fetal mortality (4–8). These complications are seen in overt hypothyroidism, which occurs in about 0.2% of pregnancies, as well as subclinical hypothyroidism, found in about 2.3% of pregnancies (9). Maternal overt hyperthyroidism is associated with fetal loss, fetal growth restriction, preeclampsia, and preterm delivery (1,10), whereas subclinical hyperthyroidism has not been specifically associated with adverse pregnancy outcomes in a study in which 1.7% of pregnancies were associated with subclinical maternal hypothyroidism (11). As the fetus is entirely dependent on maternal thyroid hormones for

its development until about 13 weeks of gestation, it is important to ensure adequate thyroxine substitution in pregnant women during the first trimester (2). The aim of this prospective study was to explore whether thyroxine-treated pregnant women with hypothyroidism are adequately thyroxine substituted in early pregnancy. A secondary aim was to determine if fetal loss differed between pregnant women with normal and abnormal plasma thyrotropin (TSH) values obtained in early pregnancy.

Material and Methods

The town of Malmö is generally considered to be iodine sufficient although iodine data from recent years are lacking. The study was approved by the Ethical Review Board of Lund University, Malmö/Lund, Sweden.

During the years 1997–2002, 119 consecutive pregnancies in 101 females with thyroid diseases were followed at the outpatient clinics, Department of Endocrinology, Malmö

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University Hospital. At the first visit 63 patients (median age, 30 years; range, 17–45 years) were on thyroxine substitution for hypothyroidism. The etiologies of their hypothyroidism was autoimmune thyroiditis (AIT) in 35, ablative treatment for Graves' thyrotoxicosis in 20 (postsurgical = 13, radioactive iodine = 7), and other causes in eight. Nine other patients had active hyperthyroidism. This was due to Graves' disease in seven and toxic multinodular goiter in two.

Females in Malmö are followed regularly during pregnancy at an antenatal care unit or at a specialist antenatal care center at the Department of Gynecology and Obstetrics. Patients with known or suspected thyroid diseases are referred to the Department of Endocrinology. The patients in this study were referred from the antenatal care unit, the specialist antenatal care center, or the primary care unit or were already regular patients at the Department of Endocrinology, Malmö University Hospital. In the latter group the patients had previously been instructed to contact the clinic as soon as they found out they were pregnant. They had their first visit and TSH test within 1–2 weeks after pregnancy was established. Patients were followed every 4 to 8 weeks during pregnancy at the outpatient endocrine clinic. Before each visit serum free thyroxine (FT₄; reference range, 9–22 pmol/L) and TSH (reference range, 0.4–4.0 mIU/L) concentrations were determined. In patients on thyroxine substitution, the dose was adjusted as needed, usually by 25–50 µg, to maintain the TSH concentration within the reference range and, during the first two trimesters, below 2 mIU/L. A low TSH value was accepted in the first trimester without changing the thyroxine dose.

TSH and FT₄ were measured on the Technicon Immuno 1[®] system (Bayer Inc., Pittsburgh, PA). Reference ranges were established in Sweden on nonpregnant subjects.

Statistical analysis

Statistical analysis of differences was determined by chi-square test. A *p* value of < 0.05 was considered significant.

Results

Patients on thyroxine substitution for hypothyroidism

Of the 63 patients on thyroxine substitution for hypothyroidism 32 (51%) had serum TSH values within the reference range at their first TSH test and therefore were assigned to Group A. Thirty-one (49%) had TSH tests outside the reference range and were therefore assigned to Group B. Figure 1 shows the distribution of TSH values in the 63 pregnant women on thyroxine substitution due to hypothyroidism. In 12 patients TSH was <0.40 mIU/L and in 9 of these, TSH was ≤0.1 mIU/L. In 19 patients TSH was >4.0 mIU/L and in 9 of these, TSH was >10 mIU/L. Forty-two (67%) of the patients had to increase their thyroxine dose during pregnancy. The median increase in the dose was by 50% (from 100 to 150 µg). The first blood sample was collected in first trimester in 52 of 63 (83%) patients, at the gestational week 8.5 (median range 3–13 weeks). In 34 of 52 patients the first dose change was performed at gestational week 11 (median range 3–32 weeks). The dose was increased on two to three occasions in 10 patients and the second and third changes made during gestational weeks 11–35. Fetal loss occurred in 2 of 32 (6%) patients in Group A as compared to 9 of 31 (29%) patients in Group B

FIG. 1. Serum thyrotropin (TSH) values at first laboratory control in 63 female pregnant patients on thyroxine substitution due to hypothyroidism.

(*p* < 0.05) (Fig. 2). In Group B, four of nine patients had a TSH value <0.4 mIU/L and five patients had a TSH value >4.0 mIU/L (Table 1).

Patients with hyperthyroidism

Fetal loss occurred in three of the nine patients with active hyperthyroidism, all having Graves' disease.

Discussion

In this prospective study we found that 30% of patients on thyroxine substitution had an elevated TSH concentration when first tested during pregnancy. This is in agreement with previous studies (6,12–15) and a very recent study of Vayida *et al.* (16) who found that nearly one quarter (22.9%) of hypothyroid women on thyroxine replacement had elevated

FIG. 2. Distribution of the outcomes of pregnancy in 63 women on L-thyroxine treatment as a function of their initial serum TSH (Group A = those with normal TSH, Group B = those with abnormal TSH). Open bars are data for pregnancies without fetal loss; solid bars are data for pregnancies with fetal loss. There was increased fetal loss (*p* < 0.05) in Group B (TSH values outside the reference range) compared to Group A (TSH within the reference range).

TABLE 1. SERUM THYROTROPIN AND FREE THYROXINE VALUES AT FIRST CONTROL IN PREGNANT WOMEN ON THYROXINE SUBSTITUTION DUE TO HYPOTHYROIDISM AND WITH FETAL LOSS

Patient	Age	Diagnosis	TSH ^a (mIU/L)	FT ₄ ^b (pM/L)	First control (week)	Fetal loss (week)
1	21	St post GD	<0.01	26	8	10
2	32	St post GD	<0.10	20	6	7
3	28	AIT	0.11	—	9	11
4	36	AIT	0.21	20	9	24
5	31	AIT	1.3	13	6	9
6	32	NoAIT	3		15	17
7	28	AIT	5.8	13	11	14
8	33	AIT	6		5	8
9	33	NoAIT	9.6	12	11	20
10	21	AIT	15	15	3	7
11	33	NoAIT	16	8	11	16

^areference range: 0.4–4.0 mIU/L.

^breference range: 9–22 pmol/L.

AIT, autoimmune thyroiditis; St post GD, status post Graves' disease; NoAIT, hypothyroidism without AIT; FT₄, free thyroxine.

TSH concentrations at their first antenatal visit. These findings are probably due to thyroid hormone requirements increasing very early in pregnancy, typically before the first obstetrical visit (15). In contrast, 20% of our patients on thyroxine substitution had a low TSH concentration at their first visit, also similar to the findings (22.8%) of Vayida *et al.* (16). It has previously been suggested (15) and recently discussed by the Endocrine Society (3) that all women on thyroxine substitution should increase their thyroxine dose immediately on confirmation of pregnancy. However, our findings indicate that routinely increasing the thyroxine dose may result in oversubstitution in a substantial portion of these pregnant women. Moreover, 33% of our patients did not have to increase the thyroxine dose during pregnancy.

During pregnancy thyroid physiology undergoes several well-established changes including an approximate doubling of thyroxine-binding globulin concentrations and an increase in plasma volume (17,18), both contributing to an increase in the total thyroxine pool. In addition, there is the presence of Type III deiodinase activity in the placenta which degrades thyroid hormones. Finally gut thyroxine absorption may be decreased, with or without iron supplements that pregnant women often take. All of these factors are probably responsible for increased requirements for levothyroxine in hypothyroid pregnant women (19). Our observation that 67% of patients on thyroxine substitution at first visit had to increase the thyroxine dose during pregnancy was in accordance with previous studies (14,15,19). The requirement for an increase in thyroxine dose was 50% (median), similar to previous studies (14,20–21). In a majority of our patients the first blood sample was collected in the first trimester as was our goal. In these patients the first dose adjustment was made in week 11 (median, range week 3–32). This is in agreement with a previous study where the median onset of dose modification occurred at 8 weeks and some women required an increased dose in week 5 (15). A large body of evidence strongly suggests that thyroid hormone is an important factor contributing to normal fetal development (3). Early in pregnancy transfer

of maternal thyroxine to the fetus is a requirement for the fetus; fetal production of thyroid hormones does not become efficient until mid-gestation (2). Therefore thyroid function in pregnant women on thyroxine substitution should be monitored early in pregnancy (i.e., as soon as pregnancy has been confirmed) to ensure adequate fetal supplies and should also be carefully followed during pregnancy.

Our finding of increased fetal loss in women having abnormal serum TSH when first tested is evidence that abnormal maternal thyroid status increases the risk of obstetrical complications. Interestingly we noted that four of the nine patients with fetal loss had a TSH value <0.4 mIU/L. In another study, however, subclinical hyperthyroidism was not associated with adverse outcome of pregnancy (11). Our findings of this association, however, need to be confirmed in a larger series of patients. Although several studies have reported that obstetrical and fetal complications occur with increased frequency in pregnant women with hypothyroidism (2,9), there are few reports regarding the outcome of pregnancy in women with treated hypothyroidism. Abalovich *et al.* (6) demonstrated that adequate thyroxine treatment was very important for pregnancy outcome both in overt and subclinical hypothyroidism. With inadequate thyroxine treatment, pregnancy ended with abortion in 60% and 71% of women with overt and subclinical hypothyroidism, respectively, with an increased prevalence of preterm deliveries. Conversely, the frequency of abortions in hypothyroid pregnant women receiving adequate treatment was very low and in general they went to term without complications (6).

In summary, in 49% of pregnant women on thyroxine substitution for hypothyroidism, serum TSH values were abnormal when first tested and fetal loss was increased in this setting. Thyroid function in pregnant women on thyroxine substitution should be monitored early in pregnancy (i.e., as soon as pregnancy has been confirmed) and carefully followed during pregnancy. The thyroxine dose should be increased if TSH is elevated early in pregnancy as this is likely to decrease the risk of obstetrical complications. Further studies on the relationship between maternal subclinical thyrotoxicosis and adverse fetal outcome are needed.

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Disclosure Statement

No competing financial interests exist.

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