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Maternal Thyroid Function at 11–13 Weeks of Gestation in Women with Hypothyroidism Treated by Thyroxine

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Key Words
Hypothyroidism · Pregnancy · Thyroid-stimulating hormone · Thyroxine · Tri-iodothyronine · Antithyroid antibodies

Abstract
Objective: The aim of this study in pregnant women with hypothyroidism treated by levothyroxine is to examine the interrelations between thyroid-stimulating hormone (TSH), free thyroxine (FT_4) and free tri-iodothyronine (FT_3), and examine whether in such patients the treatment is adequate. ***Methods:*** This was a retrospective cross-sectional study. Maternal serum concentrations of FT_3, FT_4 and TSH were measured at 11–13 weeks in 164 singleton pregnancies from women with hypothyroidism before pregnancy receiving treatment with thyroxine. The values were compared to the results in 4,318 normal singleton pregnancies. ***Results:*** In the hypothyroid group, compared to the normal group, there was an increase in median TSH (1.990 vs. 1.007 MoM) and FT_4 (1.052 vs. 0.992 MoM) and decrease in FT_3 (0.901 vs. 0.991 MoM). Serum FT_4 was at or above the 2.5th centile in 158 (96.3%) cases but TSH was above the 97.5th centile in 48 (29.3%) and FT_3 was below the 2.5th centile in 49 (29.9%) cases. In both the hypothyroid and unaffected groups there were significant associations between TSH and FT_4, TSH and FT_3 and between FT_3 and FT_4. ***Conclusions:*** In a high proportion of pregnant women with hypothyroidism treated with levothyroxine there is evidence of persistent hypothyroidism because the treatment is inadequate in correcting the levels of FT_3.

Introduction

Pregnancy is associated with an approximate 50% increase in demand for thyroid hormones which is apparent within the first 16 weeks of gestation [1]. This increase is mainly attributed to the estrogen-driven doubling in thyroxine-binding globulin concentrations [2].

In women with preexisting hypothyroidism treated with levothyroxine the increased demands for thyroid hormones in pregnancy should be met by increasing the dose of the drug [1, 3]. Nevertheless, several studies have documented that in the first trimester of pregnancy, 30–

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50% of such women may be inadequately treated during this critical period for fetal development when the fetal brain is entirely dependent on maternal thyroid hormones [4–8].

The evidence for inadequate therapy is based on the biochemical finding of high serum thyroid-stimulating hormone (TSH) in the presence of normal free thyroxine (FT_4) [1]. However, assessment of thyroid function by TSH and FT_4 alone may be insufficient because it is free tri-iodothyronine (FT_3) which is ultimately responsible for the control of both metabolic activity and regulation of TSH production [9]. Under normal circumstances the daily relative production of T_3 to T_4 by the thyroid gland is about 1:9. While the whole source of circulating T_4 is the thyroid gland, 80% of circulating T_3 is derived from peripheral deiodination of T_4 [10–12]. In cases of hypothyroidism treated by the exogenous administration of levothyroxine, normalization of the serum levels of T_4 would not adequately address the deficiency in the production of T_3 by the thyroid gland. Whatever the dose of levothyroxine, the serum T_4 to T_3 ratio will always be elevated [9, 13]. In patients undergoing total thyroidectomy the dose of levothyroxine needed to maintain serum T_3 at its normal endogenous pre-thyroidectomy level results in elevated serum FT_4 concentration [14]. The symptoms of hypothyroidism in patients treated with levothyroxine are abolished only with a dose resulting in supernormal FT_4 and subnormal TSH [15, 16]. These results may essentially indicate that levothyroxine treatment is successful only when there is normalization of FT_3.

The aim of this study in pregnant women with hypothyroidism treated by levothyroxine is to examine the interrelations between FT_3, FT_4 and TSH and examine whether in such patients the treatment is adequate.

Materials and Methods

In women attending for their routine first hospital visit in pregnancy at 11^{+0}–13^{+6} weeks of gestation, we record maternal characteristics, including age, racial origin (White, Black, South Asian, East Asian and mixed), weight, height and body mass index (BMI). We then perform an ultrasound scan to confirm gestational age from the measurement of the fetal crown-rump length, to diagnose any major fetal abnormalities and to measure fetal nuchal translucency thickness. We also measure maternal serum free β-hCG and PAPP-A (Delfia Xpress Analyzer, PerkinElmer, Waltham, Mass., USA) as part of screening for chromosomal abnormalities by a combination of fetal nuchal translucency thickness and serum biochemistry [17, 18]. Additionally, blood is collected for research and the separated plasma and serum are stored at –80°C for subsequent biochemical analysis. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by King's College Hospital Ethics Committee.

In this study we measured the maternal serum concentrations of FT_3, FT_4, TSH, anti-TPO and anti-Tg at 11–13 weeks in 164 singleton pregnancies from women who reported that they had hypothyroidism before pregnancy and they were receiving treatment with thyroxine. The values were compared to the results of our previous study in 4,318 singleton pregnancies with no history of thyroid disease, which did not develop preeclampsia and resulted in live birth after 34 weeks of phenotypically normal neonates with birth weight above the 5th centile [19]. In that study there were 726 (16.8%) pregnancies in which the concentration of one or both antithyroid antibodies was 60 U/ml or more. Normal ranges for TSH, FT_3 and FT_4 were derived from the study of the 3,592 pregnancies with no antithyroid antibodies [19]. All blood samples were collected between March 2006 and October 2008.

Sample Analysis

The maternal serum concentrations of FT_3, FT_4, TSH, anti-TPO and anti-Tg were measured by immunoassay using direct, chemiluminometric technology (Siemens Advia Centaur Assays, Siemens Healthcare Diagnostics Ltd, Surrey, UK). The minimum detectable concentrations of FT_3, FT_4, TSH, anti-TPO and anti-Tg were 0.3 pmol/l, 1.3 pmol/l, 0.003 mIU/l, 15 U/ml and 30 U/ml, respectively. The intra-assay coefficients of variation were 3.08, 2.35, and 2.47% at FT_3 concentrations of 2.9, 6.6, and 14.2 pmol/l, respectively; 4.69, 2.31, and 2.22% at FT_4 concentrations of 6.1, 13.9, and 39.9 pmol/l, respectively; 2,48, 2.44, and 2.41% at TSH concentrations of 0.74, 5.65, and 18.98 mIU/l, respectively; 7.93, 4.54 and 6.26% at anti-TPO concentrations of 1.70, 10.01, and 14.95 U/ml, respectively, and 5.5 and 2.9% at anti-Tg concentrations of 62 and 333 U/ml, respectively. If the serum concentration of anti-TPO and anti-Tg was <60 U/ml, which was the manufacturer's reference limit, the patients were considered to be antibody negative.

Statistical Analysis

The characteristics of the hypothyroid group with the group used for the construction of normal ranges were compared by Mann-Whitney test for continuous variables and Fisher's exact test or χ^2 test for categorical variables. The measured concentrations of FT_3, FT_4 and TSH were converted to multiples of the expected normal median (MoM) corrected for gestational age and maternal age, racial origin and BMI. We reported previously that serum TSH increases whereas FT_3 and FT_4 decreases with gestational age and all three are lower in Black than in White women, serum FT_3 and FT_4 decrease but TSH does not change significantly with maternal age and serum TSH and FT_3 increase whereas FT_4 decreases with BMI [19]. The hypothyroid and normal groups were compared for median TSH MoM, FT_3 MoM and FT_4 MoM using the Mann-Whitney test and for the proportion of cases with serum TSH above the 97.5th centile and serum FT_3 and FT_4 below the 2.5th centile by the χ^2 test. In the hypothyroid group, regression analysis was also used to determine the significance of the interrelations between TSH MoM, FT_3 MoM and FT_4 MoM.

The statistical software package SPSS 16.0 (SPSS, Inc., Chicago, Ill., USA) was used for the data analyses.

Table 1. Maternal demographic characteristics in the hypothyroid and unaffected groups

Maternal variables	Unaffected (n = 3,592)	Hypothyroid (n = 164)
Maternal age, years (median, IQR)	32.2 (28.0–36.0)	35.4 (23.6–42.9)*
BMI, median (IQR)	24.7 (22.2–27.9)	24.9 (19.2–41.0)
Racial origin		
White, n (%)	2,543 (70.8)	134 (81.7)**
Black, n (%)	708 (19.7)	12 (7.3)
Indian or Pakistani, n (%)	148 (4.1)	11 (6.7)
Chinese or Japanese, n (%)	57 (1.6)	4 (2.4)
Mixed, n (%)	136 (3.8)	3 (1.8)
Parity		
Nulliparous, n (%)	1,684 (46.9)	64 (39.0)
Parous, n (%)	1,908 (53.1)	100 (61.0)
Cigarette smoker, n (%)	322 (9.0)	10 (6.1)
Conception by ovulation drugs	101 (2.8)	11 (6.7)*

Comparison between the hypothyorid and unaffected groups was conducted by χ^2 or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. * $p < 0.001$. ** $p < 0.0001$.

Results

The patient characteristics of the hypothyroid group with the group used for the construction of normal ranges are compared in table 1. In the hypothyroid group, compared to the unaffected group, the maternal age was higher, there was a higher prevalence of White women and a higher prevalence of women who conceived after the use of ovulation induction drugs.

In the hypothyroid group, compared to the normal group, the median TSH MoM and FT_4 MoM were increased, whereas the median FT_3 MoM was decreased (table 2). The serum TSH was above the 97th centile in 48 (29.3%) of the 164 cases, the FT_3 was below the 2.5th centile in 49 (29.9%) cases and the FT_4 was below the 2.5th centile in 6 (3.7%) cases (fig. 1). In all cases of low FT_4 the serum TSH was above the 97.5th centile. In 25 (52.1%) of the cases with low FT_3 the serum TSH was above the 97.5th centile. On the basis of their serum TSH, FT_4 and FT_3 levels the 164 patients fell into one of five groups. In the first group there were 93 (56.7%) patients with serum TSH below the 97.5th centile and both FT_4 and FT_3 above the 2.5th centiles. In the second group there were 6 (3.7%) patients with TSH above the 97.5th centile and both FT_4 and FT_3 below the 2.5th centiles. In the third group of 20 (12.2%) cases, TSH was above the 97.5th centile, FT_3 was below the 2.5th centile and FT_4 was above the 2.5th centile. In the fourth group there were 22 (13.4%) cases with TSH above the 97.5th centile and both FT_4 and FT_3 above the 2.5th centiles. In the fifth group of 23 (14.0%) cases, FT_3 was below the 2.5th centile, TSH was below the 97.5th centile and FT_4 was above the 2.5th centile.

In both the hypothyroid and unaffected groups there were significant associations between TSH and FT_4, TSH and FT_3 and between FT_3 and FT_4 (table 3; fig. 2).

Antithyroid Antibodies

In our previous screening study of 4,318 pregnancies, 726 (16.8%) were positive for one or both antithyroid antibodies. In this study of pregnancies with hypothyroidism treated with thyroxine the prevalence of antithyroid antibody positivity was increased to 73.2% (table 4).

Discussion

This study has assessed thyroid function at the first obstetric visit at 11–13 weeks of gestation in women with known hypothyroidism diagnosed before pregnancy and receiving levothyroxine. In the hypothyroid group, compared to the unaffected group, there was a higher incidence of White women and the median maternal age was increased. These results are compatible with those of previous studies in non-pregnant individuals [20–22]. The finding that in the hypothyroid group there was a higher incidence of women who conceived after the use of ovulation induction drugs is compatible with the knowledge that hypothyroidism is associated with impaired ovulation [23, 24]. In the hypothyroid group the prevalence of antithyroid antibodies was substantially higher than in normal pregnancies. This is not surprising because in developed countries autoimmune thyroiditis is the most common cause of hypothyroidism, especially in women of childbearing age [25].

In the women with hypothyroidism treated with levothyroxine there was a good inter-correlation between serum FT_4, FT_3 and TSH but the median FT_4 and TSH were increased, whereas the median FT_3 was decreased. On the basis of their individual results, about 55% of the patients were biochemically euthyroid with normal serum TSH and normal or high FT_4 and FT_3. In the remaining 45% at least one of the three biochemical tests was suggestive of persistent hypothyroidism. There was a small group with low FT_4 and FT_3 and high TSH. In a much larger group, serum FT_4 was normal or increased but ei-

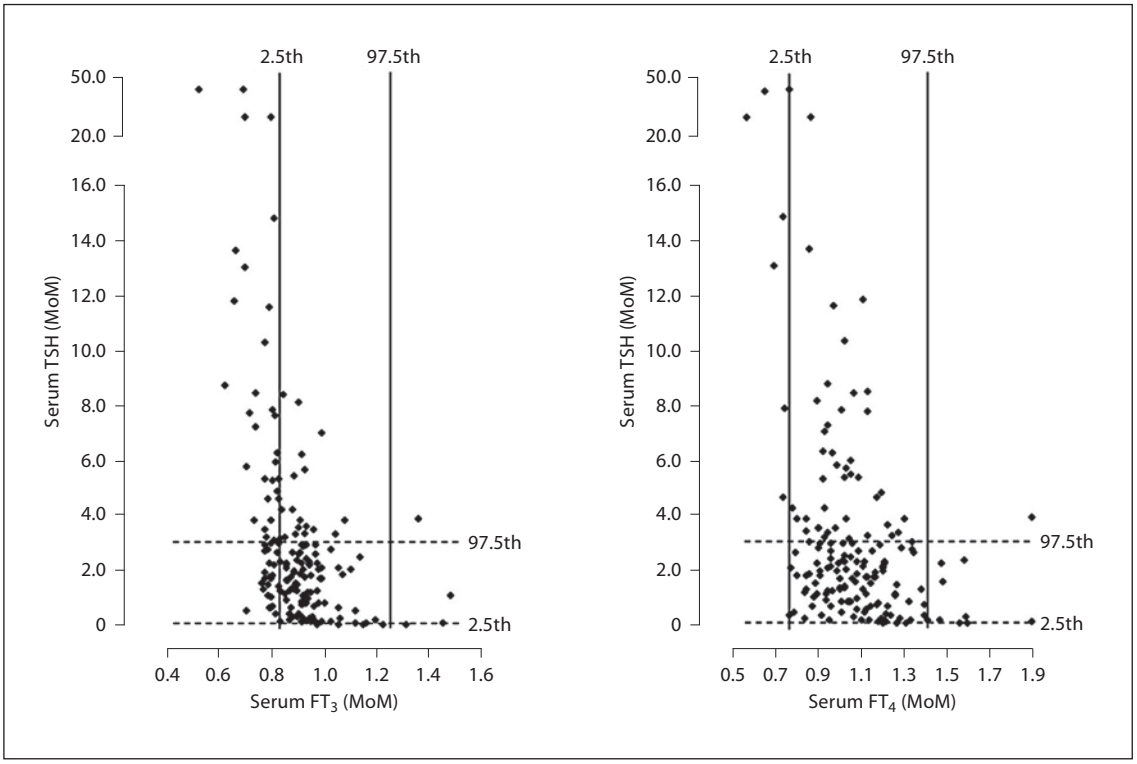

Fig. 1. Relationship between maternal serum TSH, FT_3 and FT_4 and in MoM at 11–13 weeks of gestation in pregnancies with preexisting hypothyroidism treated with levothyroxine. The vertical lines represent the 2.5th and 97.5th centiles of the normal ranges for FT_3 and FT_4, and the interrupted horizontal lines the 2.5th and 97.5th centiles for TSH.

Table 2. Maternal serum TSH, FT_4 and FT_3 values in the hypothyroid and unaffected groups

		Unaffected (n = 3,592)	Hypothyroid (n = 164)
TSH	MoM (median, IQR)	1.007 (0.608–1.511)	1.990 (0.793–3.467)**
	mIU/l (median, IQR)	1.096 (0.670–1.665)	2.435 (0.942–3.982)**
	MoM >97.5th centile (%)	89 (2.5)	48 (29.3)**
	MoM <2.5th centile (%)	89 (2.5)	5 (3.0)
FT_4	MoM (median, IQR)	0.992 (0.908–1.086)	1.052 (0.938–1.202)**
	pmol/l (median, IQR)	14.9 (13.6–16.3)	15.8 (14.0–17.9)**
	MoM >97.5th centile (%)	89 (2.5)	13 (7.9)**
	MoM <2.5th centile (%)	89 (2.5)	6 (3.7)
FT_3	MoM (median, IQR)	0.991 (0.935–1.059)	0.901 (0.818–0.957)**
	pmol/l (median, IQR)	4.6 (4.4–5.0)	4.2 (3.8–4.5)**
	MoM >97.5th centile (%)	89 (2.5)	4 (2.4)
	MoM <2.5th centile (%)	89 (2.5)	49 (29.9)**

Comparison between the hypothyroid and unaffected groups was conducted by χ^2 or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. ** $p < 0.0001$.

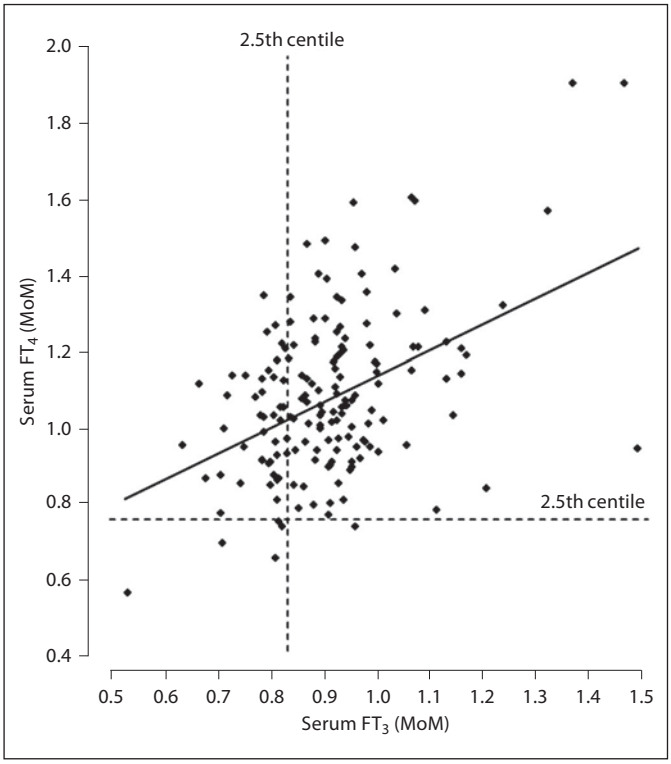

Fig. 2. Relationship between maternal serum FT_3 and FT_4, and in MoM at 11–13 weeks of gestation in pregnancies with preexisting hypothyroidism treated with levothyroxine. The interrupted lines represent the 2.5th centiles of the normal ranges for FT_3 and FT_4.

Table 3. Correlations between serum TSH, FT_3 and FT_4 values in the hypothyroid and unaffected groups

Correlations	Unaffected		Hypothyroid	
	r	p	r	p
TSH with FT_3	–0.182	<0.0001	–0.550	<0.0001
TSH with FT_4	–0.245	<0.0001	–0.474	<0.0001
FT_3 with FT_4	0.476	<0.0001	–0.452	<0.0001

ther TSH was high and/or FT_3 was low. These findings raise the question as to whether the objective in the treatment of hypothyroidism in pregnancy should be to normalize TSH or FT_4 or FT_3.

In non-pregnant individuals with overt hypothyroidism, levothyroxine treatment is successful in abolishing their symptoms only with a dose resulting in supernormal FT_4 and subnormal TSH [15, 16]. These results may essentially indicate that the treatment is only successful when there is normalization of FT_3. Many of the symptoms of hypothyroidism, such as fatigue, constipation, weight gain, hair loss, dry skin and carpal tunnel syndrome, are common in normal pregnancy making it impossible to rely on such symptoms for monitoring success of treatment. In the management of pregnant women with hypothyroidism it is recommended that the same approach should be used as in non-pregnant individuals where the objective of treatment is normalization of TSH [26]. However, such recommendation is not based on scientific evidence that in women with hypothyroidism treated with levothyroxine and normal serum FT_4 pregnancy outcome is better in those with normal TSH than in those with high TSH. Indeed, there is an inherent contradiction in the recommendation for the need to normalize TSH because the same professional body recommends against screening for subclinical hypothyroidism (high TSH with normal FT_4) since there is no evidence that identification and treatment of women with this condition improves maternal or infant outcomes [27].

Our study was a retrospective cross-sectional one of patients examined in a university hospital clinic. We did not aim to examine the relation between our findings and the dose of levothyroxine, patient compliance, expertise of treating physicians or the interval between ingestion of the drug and blood sampling. The findings provide a snapshot view of thyroid profile in early pregnancy in women with hypothyroidism treated with levothyroxine. We found that although the level of serum FT_4 was invari-

Table 4. Prevalence of antithyroid antibody positivity in the pregnancies with hypothyroidism treated with thyroxine in comparison with pregnancies with no known thyroid disease

Pregnancy	n	Antibody positive			
		anti-TPO	anti-Tg	both	either
Hypothyroid	164	107 (65.2%)*	97 (59.1%)*	84 (51.2%)*	120 (73.2%)*
Unaffected	4,318	441 (10.2%)	593 (13.7%)	308 (7.1%)	726 (16.8%)

* $p < 0.0001$.

ably normal or increased in a high proportion of cases, there was high TSH and low FT_3, high TSH and normal FT_3 or normal TSH and low FT_3. Consequently, if the objective in the treatment of hypothyroidism in pregnancy is to normalize the levels of the biologically active FT_3, it is not useful to monitor the levels of FT_4 but it is essential to measure the levels of both TSH and FT_3.

Recommendations on whether the objective in the treatment of hypothyroidism in pregnancy is to normalize TSH and/or FT_3 rather than FT_4 should ultimately be based on the results of major prospective studies examining the differential incidence of adverse pregnancy outcomes in the groups with low FT_3 and normal TSH and FT_4 and in those with high TSH and normal FT_4 and FT_3 compared to those in which all three biochemical markers are normal.

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