The dose of levothyroxine in pregnant women with hypothyroidism should be increased by 20-30% in the first trimester

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ABSTRACT

INTRODUCTION: Severe hypothyroidism in pregnancy is associated with maternal and foetal complications, and in less severe cases impaired neuropsychological foetal development is seen. The aim of the present study was to evaluate the efficiency of the clinical control suggested in the guidelines.

METHODS: This was a retrospective study of 93 consecutive pregnant women with hypothyroidism who were followed at Herlev Hospital in 2012. The thyroid function was evaluated upon confirmation of pregnancy and thereafter every fourth week. The aim of the treatment was a concentration of serum thyroid-stimulating hormone (S-TSH) less than 2.5 mU/l.

RESULTS: The frequency of an S-TSH of more than 4.1 mU/l was 39%. In 27% of all patients, a single measurement was made of a slight increase in S-TSH during the pregnancy, and only 12% had several increased S-TSH measurements exceeding 4.1 mU/l. Furthermore, 62% had a minimum of one S-TSH measurement above 2.5 mU/l. The pregnant women with increased S-TSH levels in the beginning of their pregnancy had a tendency to be overtreated later in their pregnancy.

CONCLUSION: Although a careful follow-up was performed, we found a high number of patients with a single occurrence of S-TSH outside of the recommended range during their first trimester. The high S-TSH values were registered during the first weeks of the pregnancy, but hereafter corrected, and the number of pregnancy complications recorded did not seem to differ from the number of complications in patients with a normal thyroid function. We recommend increased attention and monitoring of fertile women with hypothyroidism who are planning pregnancy.

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During pregnancy, changes related to thyroid function are seen. The production of thyroxine (T4) and triiodothyronine (T3) as well as the daily iodine requirement is increases by 50% [1].

Pregnancy is a stress test for the thyroid gland. Among women who are euthyroid prior to conception, a higher prevalence of hypothyroidism is seen in those with a limited thyroid reserve (induced by iodine deficiency or underlying Hashimoto's disease) than in patients with a normal thyroid reserve [1]; and primary hypothyroidism during pregnancy has an estimated prevalence of 2-3% [2]. Severe maternal hypothyroidism is associated with preeclampsia, gestational hypertension, cretinism, foetal death and spontaneous abortion [3], but subclinical hypothyroidism is also associated with impaired neuropsychological development of the child [4].

The foetus is entirely dependent on maternal thyroid hormones for its development until about 13 weeks of gestation, and it is important to ensure an adequate thyroxine substitution in pregnant women very early in the pregnancy [5]. Therefore, during pregnancy, an increased daily substitutive dosage of levothyroxine (L-T4) is required in hypothyroid patients in order to meet the maternal needs and secure a normal foetal development [6]. The increase of the L-T4 dosage is usually 30% in the first trimester, and there is an average increase of 48% by 16-20 weeks [7].

The aim of the present study was to evaluate the clinical control programme suggested in guidelines for patients with hypothyroidism during pregnancy. Furthermore, we set out to evaluate if it was possible to keep the thyroid function parameters within the recommended range by monitoring the patients every fourth week during pregnancy. The secondary aim was to investigate the number of pregnancy complications.

METHODS

This was a retrospective study of 93 consecutive pregnant women with hypothyroidism who were followed at the Outpatient Clinic of the Endocrinology Unit at Herlev Hospital, Denmark, during 2012. A list of all patients who had been diagnosed with hypothyroidism (International Classification of Diseases (ICD)-10: DE 03.1-9 and DE 89.0) and who had been seen in the outpatient clinic in 2012 were drawn from the electronic medical system. The medical records were reviewed, and a total of 95 of these patients were pregnant during 2012. The women who were not followed throughout the whole pregnancy and therefore had missing data were excluded from the study (n = 2). The study was approved by the Danish

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TABLE 1

Parity of the patients.

Parity	Patients, n
1	26
2	30
3	22
4	9
5	3
6	3

TABLE 2

Number of patients with a concentration of serum thyroid-stimulating hormone (S-TSH) > 2.5 mU/l and an S-TSH > 4.1 mU/l.

	n (N = 93)	%
S-TSH > 2.5 mU/l	58	62
S-TSH > 4.1 mU/l		
Single measurement	25	27
Several measurements	11	12
Total	36	39

Data Protection Agency (HEH-2014-048 I suite 02894). Blood tests for the hormone levels were drawn in the laboratory of the Clinical Biochemical Department, Herlev Hospital.

The mean age of the patients was 35.0 ± 4.7 standard deviation (SD). In all, 58 patients were known in the outpatient clinic before their pregnancy, and 38 were new referrals from the primary sector.

The parity of the women is shown in **Table 1**. The number in the table includes the current pregnancy and previous pregnancies (including any spontaneous abortions).

The thyroid function was evaluated immediately upon confirmation of pregnancy and thereafter every fourth week. The concentration of serum thyroid-stimulating hormone (S-TSH) was determined in all 93 pregnant women. The aim of the treatment was an S-TSH below 2.5 mU/l. S-TSH was determined by the method Immulite 2500, chemiluminescent enzyme immunoassay. The S-TSH reference interval was 0.35-4.1 mU/l, which is in accordance with the manufacturer's reference interval.

All patients in the study, including those with a normal S-TSH, were screened for obstetric and foetal complications. These complications were not predefined; all complications stated in the medical record were registered.

Data were calculated as medians and ranges for the S-TSH values and L-T4 dosage. The χ^2-test was used to correlate S-TSH level and complications. The level of significance was set to $p < 0.05$.

Trial registration: ClinicalTrials.gov identifier: NCT02094079.

RESULTS

All 93 pregnant women were in replacement therapy with L-T4. Among these, 83 were in L-T4 replacement therapy before their pregnancy, and ten started L-T4 during their pregnancy. The dosage of the replacement therapy with L-T4 before the pregnancy was 39 to 236 microgram/daily, with a median dosage of 100 microgram/daily. The maximum L-T4 dosage during the pregnancy was 43 to 329 microgram/daily, with a median dosage of 164 microgram/daily. The median increase of L-T4 (100% corresponds to the pre-pregnancy dose) for the entire group was equal to 150% during pregnancy.

A total of 86 patients had autoimmune hypothyroidism, four had hypothyroidism after radioactive iodine treatment and three after thyroid surgery.

The number of patients who had an S-TSH above 4.1 mU/l measured (min. 4.1 and max. 35.0 mU/l) during the pregnancy was 36 (see **Table 2**). However, in 25 patients only one measurement with a slight increase in S-TSH was present. If the cut-off was lowered to 2.5 mU/l, the number increased to 58 pregnant women with a minimum of one measurement of elevated S-TSH (including patients with an S-TSH exceeding 4.1 mU/l). If the women who were referred to the clinic with hypothyroidism during pregnancy were excluded, the number of patients who had an S-TSH over 2.5 mU/l was 48, and 26 had an S-TSH above 4.1 mU/l (median 6.1, range 4.1-35.0). Only 11 women had several measurements of S-TSH over 4.1 mU/l, five of these had poor compliance despite increased care, and five were not monitored in the clinic before their pregnancy.

The patients with increased S-TSH levels in the beginning of their pregnancy had a tendency to be overtreated later in pregnancy. A total of 21 women were registered with at least one S-TSH measurement below 0.1 mU/l during their pregnancy. From this group, nine women had measured S-TSH values exceeding 4.1 mU/l from earlier in their pregnancy. Four of them were known to have a poor compliance, and one patient had pregnancy complications (stillbirth in week 33). No significant correlation between age and maximum S-TSH was found.

Complications were seen in 12 pregnancies (see **Table 3**). The individual S-TSH values are listed in Table 3. Comparing complications in patients with an increased S-TSH, we found that three of 36 (8%) patients with at least one S-TSH > 4.1 mU/l had a spontaneous abortion compared with one of 57 (2%) patients without any S-TSH measurement > 4.1 mU/l ($p = 0.32$). When including all registered complications, the number was six of 36 (17%) compared to six of 57 (11%) ($p = 0.59$). None

of the patients with complications had an S-TSH between 2.5 and 4.1 mU/l. The week of the pregnancy with an increased S-TSH and the time for the increase of L-T4 treatment are shown in **Figure 1**. The figure shows a comparison between these correlations in both groups of patients with an S-TSH above 2.5 mU/l and above 4.1 mU/l. The high S-TSH levels were most commonly measured between weeks five and fifteen. The S-TSH levels were stabilised during the second half of the pregnancy and no new increases were seen.

DISCUSSION

Hypothyroidism in young women is usually caused by autoimmune thyroiditis [8]. The condition is associated with a decrease in fertility, and an association between maternal hypothyroidism and pregnancy complications [9-11], as well as impairment of the neuropsychological function of the child [12, 13]. It was previously found that pregnant women in L-T4 replacement therapy, whose S-TSH values were abnormal when first tested, had a tendency towards increased foetal loss [14]. In an open-label study of hypothyroid patients, miscarriages were found in nine of 31 (29%) of patients with an S-TSH above 4.0 mU/l compared with two of 32 (6%) with an initial S-TSH below 4.0 mU/l [14]. Another new study of 1,013 pregnant L-T4-treated hypothyroid patients [15] showed an increased risk of miscarriage in women with an S-TSH of 4.51-10 mU/l with an odds ratio of 1.8 (95% confidence interval: 1.03-3.14), but no significant risk in patients with an S-TSH between 2.51 and 4.5 mU/l [15]. In our study, we found a similar non-significant trend towards an increased risk of miscarriage in patients with an S-TSH exceeding 4.1 mU/l. However, our study was too small for sufficient evaluation of the pregnancy complications, and the definition of those complications was broad.

The intention of our study was to evaluate the effect of a pregnancy control programme recommended in modern guidelines. Guidelines have the following recommendations [1]:

– The goal of L-T4 treatment is to normalise maternal S-TSH values within the trimester-specific pregnancy reference range (first trimester, 0.1-2.5 mU/l; second trimester, 0.2-3.0 mU/l; third trimester, 0.3-3.0 mU/l).
– Women with subclinical hypothyroidism in pregnancy who are not initially treated should be monitored for progression to overt hypothyroidism with S-TSH and free thyroxine(FT4) approximately every four weeks until 16-20 weeks of gestation and at least once between 26 and 32 weeks of gestation.
– In pregnant patients with treated hypothyroidism, maternal S-TSH should be monitored approximately every fourth week during the first half of the pregnancy.

Although a careful follow-up was carried out, we did not reach the above-mentioned goals, and we had a high number of patients with S-TSH outside the recommended range during the first trimester. The number of patients with an S-TSH exceeding 4.1 mU/l was 36 (39%) in our study, and the number exceeding 2.5 mU/l was 58

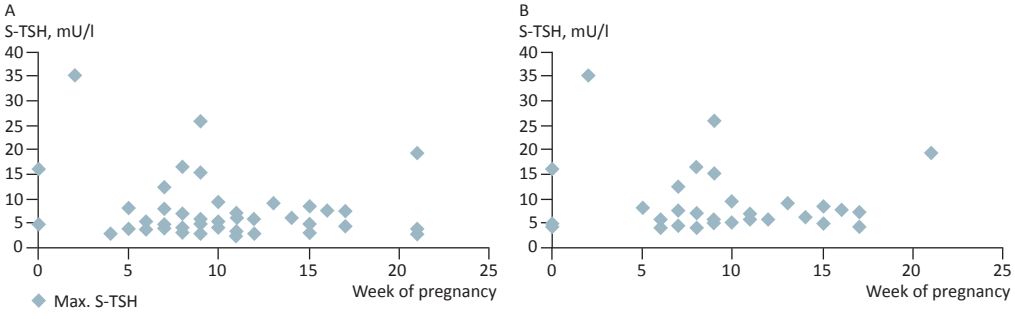
TABLE 3

Complications during pregnancy.

Type of complication	Patients, n	S-TSH measurement, n (actual S-TSH)
Spontaneous abortion	1 in week 20	1 > 4 mU/l (4.95 mU/l)
	1 in week 11	0 > 2.5 mU/l
	1 in week 7	1 > 4 mU/l (5.28 mU/l)
	1 in week 11	1 > 4 mU/l (7.00 mU/l)
Preterm delivery	1 in week 33 and 1 in week 35	1 > 4 mU/l (7.00 mU/l)
Asphyxia	2	1 > 4 mU/l (4.10 mU/l)
Stillbirth	1	1 > 4 mU/l (16 mU/l)
		1 > 2.5 mU/l (3.7 mU/l)
Oesophageal atresia	1	0 > 2.5 mU/l
Preeclampsia	1	0 > 2.5 mU/l
Premature rupture of membranes	1	1 > 4 mU/l (4.45 mU/l)

S-TSH = concentration of serum thyroid-stimulating hormone.

FIGURE 1



Comparison between the correlations of the maximum concentration of serum thyroid-stimulating hormone (S-TSH) measurements of > 2.5 mU/l (**A**) and > 4.1 mU/l (**B**) respectively, and the week of pregnancy when the dosage of the substitutive levothyroxine treatment was increased.

The replacement therapy with levothyroxine should be increased early during pregnancy.

(62%). This is in accordance with similar studies performed in Sweden [16] which described that 50% of women who were on L-T4 treatment at conception had an elevated S-TSH level at thyroid testing according to The Endocrine Society Guidelines in a follow-up on 5,254 pregnant Swedish women. However, for most of our patients who had an S-TSH above 4.1 mU/l, this was a single, isolated occurrence. Only 11 patients (12%) had several measurements of S-TSH exceeding 4.1 mU/l, five of them had poor compliance and five were not monitored in the outpatient clinic before their pregnancy. The high S-TSH values were registered during the first weeks of the pregnancy. After corrections in the substitutive therapy with L-T4, during the next weeks and later in gestation, S-TSH was normalised, and pregnancy complications did not seem to differ from the complications seen in patients with a normal thyroid function.

CONCLUSION

The thyroid function of hypothyroid women should be monitored upon confirmation of conception and closely followed during pregnancy [3]. The L-T4 dosage should be increased early during pregnancy. A 20-30% increase of L-T4 dosage may be considered. For patients who are followed in the primary sector, we suggest that the increase of the L-T4 dosage should be started by the general practitioner before the first visit in an endocrinological outpatient clinic in order to secure optimal S-TSH levels during the pregnancy. Increased attention and monitoring of fertile women with hypothyroidism who are planning pregnancy is important to optimise S-TSH levels before conception.

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