CLINICAL STUDY

Effects of increased thyroxine dosage pre-conception on thyroid function during early pregnancy

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Abstract

Objective: To compare the effects of pregnancy on the serum free thyroxine (FT4) levels in two cohorts of primary hypothyroid women treated with different levothyroxine (L-T4) doses before gestation.

Design and method: Twenty-five women with compensated hypothyroidism of different aetiology (thyroidectomized and Hashimoto's thyroiditis) were enrolled in this prospective study. The women were receiving substitutive doses of L-T4 and were anticipating pregnancy. They were assigned to two groups: 14 patients (group I) were switched to partially suppressive treatment while 11 patients (group II) continued the same therapeutic regimen.

Results: Pre-conceptional thyroid function evaluation demonstrated significantly higher FT4 and lower TSH in group I ($P < 0.001$, for both hormones) and comparable free 3,5,3'-triiodothyronine (FT3) levels. The first post-conception thyroid function evaluation occurred at a median time of 6 (5–8) and 7 (5–9) weeks of gestation, for groups I and II respectively ($P < 0.05$); all women in group I showed adequate serum FT4 levels while three patients in group II showed low-normal FT4 levels and one case was below normal levels. Statistical analysis demonstrated significantly higher frequencies (0% vs 36.4%; $P < 0.05$) of low-normal FT4 levels in patients receiving substitutive doses of L-T4. None of the Hashimoto's-affected patients showed low or low-normal serum FT4 levels regardless of their therapeutic regimen.

Conclusion: Our results suggest that in hypothyroid women anticipating pregnancy (with serum TSH in the lower quartile of normal range), the pre-conception adjustment of L-T4 doses may result in adequate maternal thyroid function up to the first post-conception evaluation. The procedure seems safe and inexpensive; it may be a worthwhile treatment, at least in thyroidectomized women, in view of the well-known potential effects of even marginal maternal thyroid hypofunction on the subsequent IQ of the progeny.

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Introduction

Adequate maternal thyroid function during pregnancy is an important determinant of early fetal brain development; it plays a critical role for at least the first 12–14 weeks of gestation when fetal thyroxine supply comes exclusively from placental transfer of maternal hormones (1–3). The issue of the potential repercussions of maternal hypothyroidism on the neuropsychological development of the progeny has received increasing attention since large-scale studies have demonstrated a correlation between decreased maternal thyroid function and subsequent IQ of the unborn child (4). Recent reports demonstrating that even low-normal maternal serum FT4 levels can interfere with normal brain development have renewed interest in the topic and possible strategies for dealing with such conditions have been proposed (5–9). Mild thyroid failure during pregnancy is not a rare event

in the general population and it is estimated to occur very frequently in pregnant women with compensated hypothyroidism antedating pregnancy (10–12).

More than 10 years have passed since Mandel *et al.* (13) demonstrated that an increase in levothyroxine (L-T4) dosage is required in hypothyroid woman undergoing pregnancy; despite this, these patients still often refer to the endocrinologist for an adjustment of L-T4 doses after several weeks of gestation and in some cases a low-normal serum free thyroxine (FT4) level may already be detected (14, 15). Moreover, the prevalence of thyroid function impairment due to inadequate L-T4 levels during pregnancy has increased over the last few years because, in order to avoid several side-effects, current average replacement doses of L-T4 are lower than those given in the mid-1980s (14). Recently published reviews have discussed in depth the physiopathological mechanisms by which thyroid deficiency leads to neuropsychological impairment (16, 17). Three

major clinical conditions of impaired neuropsychological development of thyroïdal origin have been described: fetal thyroid impairment, maternal thyroid impairment or where both maternal and fetal glands are involved such as in iodine deficiency (18).

However, despite these exhaustive reviews, the major clinical guidelines commonly employed, while useful in clinical practice, are still lacking the possible preventive strategies. In other words, we now well know the maternal and fetal risks of maternal thyroid failure, as well as how to promptly treat an occasionally discovered maternal hypothyroidism, we could be ready now to evaluate new therapeutic strategies to prevent such adverse events. If we consider that pregnancy is always more a planned event rather than an unexpected pleasant surprise we could be on the right track. Therefore, the aim of this work has been to evaluate whether, in hypothyroid women hoping to become pregnant, a pre-conception shift from replacement to partially suppressive doses of L-T4 may prevent even marginal deficiency of maternal serum FT4 levels up to the first post-conception endocrinological evaluation.

Patients and methods

Patients were recorded either from the Surgery Unit or from the Endocrinology Unit of the Second University of Naples. All women lived in Naples or the surrounding area, a region known to be moderately iodine deficient, with the usual urinary iodine levels ranging from 40 to 100 µg/day (19). All of the women were under L-T4 replacement therapy for primary hypothyroidism of different aetiology. In detail, 21 women had undergone thyroidectomy for non-toxic multinodular goiter while nine women had a clinical and biochemical diagnosis of hypothyroid Hashimoto's thyroiditis. At every consultation, patients were asked if they were planning a pregnancy in the next 12 months. Thirty consecutive women anticipating pregnancy were enrolled and randomly assigned to two groups. The computerized randomization stratified patients to assure balance between the two groups with respect to age, parity and aetiology of hypothyroidism. All women were informed that their hypothyroidism would not negatively influence their future pregnancy as long as strict thyroid function surveillance was performed during gestation and all agreed to participate.

Group I comprised 15 women (11 thyroidectomized and 4 with Hashimoto's thyroiditis) in which the L-T4 dose was adjusted to maintain low-normal serum TSH levels. At the moment of the switch from substitutive to partially suppressive doses of L-T4, all women were asked to perform a serum 3,5,3'-triiodothyronine (FT3), FT4 and thyroid-stimulating hormone (TSH) evaluation at least 60 days from the L-T4 increase, in order to assess their thyroid status.

At this first evaluation of serum thyroid parameters, L-T4 had to be decreased in one woman for palpitations

and increased in three women who still showed a serum TSH level above 1.0 µU/ml (1.2, 1.2 and 1.9 µU/ml); the last of these patients turned out to be pregnant before the second evaluation, and was therefore excluded from group I.

Group II comprised 15 hypothyroid women (10 thyroidectomized and 5 with Hashimoto's thyroiditis) who had not modified their L-T4 doses since they had decided to become pregnant.

None of the patients from group I were lost to follow-up although one woman was shifted to group II. However, five women from group II missed evaluation during pregnancy; in detail, two patients were lost to follow-up, two patients decided not to become pregnant and one patient was seen at her 23rd week of gestation and was excluded from the study.

The whole post-conception study group contained 25 pregnant women under mildly suppressive or replacement L-T4 therapy for primary hypothyroidism antedating pregnancy.

Their median age was 27 (18–36) years with slight differences between the two groups: 26 (22–31) and 28 (18–36) years respectively. The mean parity status in the two groups was 0.7 ± 0.6 and 1.3 ± 0.9 for groups I and II respectively.

Thyroid hormones and TSH were assayed in all women at their first post-conception endocrinological consultation which occurred at a median time of 7 (5–9) weeks of gestation.

The exclusion criterion for all patients was a pregnancy dated more than 12 weeks at the moment of the first post-conception endocrinological consultation. All women enrolled met the above criteria.

Hormone assay

Serum FT3 and FT4 (normal range, 2.2–5.5 and 6.0–18.0 pg/ml respectively) were assayed by RIA with Lysophase kits (Technogenetics, Milan, Italy). Intra- and inter-assay variations and sensitivities were, respectively, 2.9%, 4.7% and 0.6 pg/ml for FT3 and 3.0%, 5.7% and 0.8 pg/ml for FT4. Serum TSH levels (normal range, 0.25–3.5 µU/ml) were investigated by an ultrasensitive assay kit (DiaSorin, Inc., Saluggia, Italy). Intra- and inter-assay variations were 3.9 and 5.4% respectively; sensitivity was 0.05 µU/ml. Quality control pools were present in each assay at low, medium and high concentrations for all hormones. Samples were assayed in duplicate for each hormone.

Statistical analysis

Statistical analyses were performed using SSPS software (SPSS, Inc., Evanston, IL, USA). Due to the non-parametric distribution, comparisons between groups were performed by Mann–Whitney *U*-test. Data are reported as median and ranges, unless otherwise stated. Frequencies of serum FT4 levels below the

25th centile of normal range and of pathological serum TSH levels were compared between groups by χ^2 test and Fischer's exact test. A *P* value < 0.05 was considered statistically significant.

Results

Clinical characteristics for all patients are shown in Table 1. The two groups were matched for age, parity status and aetiology of hypothyroidism while significant differences were found with regards to L-T4 dosage and to the week of gestation at the time of the first post-conception endocrinological consultation (*P* < 0.005 and *P* < 0.05 respectively). Women under partially suppressive L-T4 doses referred to the endocrinologist after a median of 6 (5–8) weeks of gestation compared with 7 (5–9) in group II.

The parameters of serum thyroid function were assayed in both groups before conception. Patients under a partially suppressive regimen showed significantly higher FT4 and lower TSH levels (*P* < 0.001 for both hormones) than women receiving replacement doses; the difference in FT3 levels did not reach statistical significance.

Serum thyroid hormones and TSH assayed during pregnancy demonstrated significantly higher (*P* < 0.005) serum FT4 levels while no differences were found with regards to serum FT3 and TSH in the two groups.

However, the extreme heterogeneity of behaviour suggested that every patient should be considered separately rather than as a part of a group, therefore frequencies of inadequate maternal serum hormonal levels were compared with regards to different therapeutic strategy.

The analysis of post-conception serum FT4 levels showed significantly higher rates of FT4 serum levels below the 25th centile of the normal range (0% vs 36.4% for partially suppressive and replacement doses of L-T4 respectively; *P* < 0.05). The only case of FT4

being below the normal range was observed among women receiving substitutive L-T4 doses (Fig. 1). Pathological serum TSH levels above 3.5 μ U/ml were found in 2/14 and 4/11 pregnant women from groups I and II (14.3% and 36.4% respectively) (Fig. 2).

The possible role of the aetiology of hypothyroidism in determining low-normal levels of serum FT4 during gestation was also investigated. None of the Hashimoto's-affected patients showed low or low-normal serum FT4 levels regardless of their therapeutic regimen (Fig. 3), while in one case the pre-gestation L-T4 posology lead to mild hyperthyroidism during pregnancy (before pregnancy: FT4, 16.0 pg/ml and TSH, 0.32 μ U/ml; during pregnancy: FT4, 16.8 pg/ml and TSH 0.05, μ U/ml). This discrepancy between thyroidectomized and Hashimoto's-affected women is also suggested when pathological TSH levels are taken into account. In fact, the six patients showing above-normal (4.4 μ U/ml; range, 3.7–7.2 μ U/ml) serum TSH levels were all thyroidectomized while the only case showing a pregnancy-induced lowered serum TSH was a Hashimoto's-affected patient (Fig. 4).

Discussion

This study was designed with the aim of evaluating the potential benefit of L-T4 dose adjustment in hypothyroid women anticipating pregnancy for prevention of even marginal thyroid deficiency up to the first post-conception endocrinological evaluation. The issue of adequate L-T4 replacement therapy in pregnant women has received increasing attention following clinical trials demonstrating how low or even low-normal maternal FT4 serum levels play a crucial role in determining the subsequent neuropsychological development of the progeny (4, 5). The timing of the increase in L-T4 requirement during pregnancy is still controversial. In fact infant development appears not to be adversely affected when FT4 concentration increases during pregnancy in women who were

Table 1 Clinical and biochemical parameters of all women in relation to different L-T4 dose assumption.

Variable	Group I	Group II	<i>P</i> value
No. of patients	14	11	
Age (years)	26 (22–31)	28 (18–36)	NS
Ablation/Hashimoto's	11/3	7/4	NS
Parity	1 (0–2)	1 (0–3)	NS
L-T4 dosage (μ g per g day)	1.78 (1.37–2.18)	1.43 (1.1–1.62)	< 0.005
Last pre-conception evaluation (months)	5 (2–8)	4 (2–7)	NS
First post-conception evaluation (weeks of gestation)	6 (5–8)	7 (5–9)	< 0.05
Before pregnancy			
Serum FT3 (pg/ml)	2.4 (1.9–3.6)	2.0 (1.8–3.4)	NS
Serum FT4 (pg/ml)	15.2 (12.6–16.8)	11.7 (9.6–14.7)	< 0.001
Serum TSH (μ U/ml)	0.48 (0.32–0.70)	1.84 (1.23–2.71)	< 0.001
During pregnancy			
Serum FT3 (pg/ml)	2.3 (2.0–3.6)	2.1 (1.8–3.0)	NS
Serum FT4 (pg/ml)	12.8 (9.2–16.0)	10.5 (5.2–12.5)	< 0.01
Serum TSH (μ U/ml)	1.33 (0.05–4.90)	2.40 (0.5–7.2)	NS

Figure 1 Serum FT4 levels before and during pregnancy in primary hypothyroid women under mild suppressive (○) or replacement (●) levothyroxine treatment.

Figure 3 Serum FT4 levels before and during pregnancy in primary hypothyroid women in relation to the different aetiology of hypothyroidism and regardless of the therapeutic regimen.

found hypothyroxinaemic during early gestation (20); on the other hand, a recent study demonstrated that increased requirements for L-T4 during pregnancy in hypothyroid women occur earlier than previously thought (21). Our results indicate that the switch from a replacement to a partially suppressive L-T4 regimen performed once patients have decided to be pregnant results in adequate serum FT4 levels up to the first post-conception endocrinological consultation. In fact, all patients treated with mildly suppressive doses of L-T4 showed serum FT4 levels above the 25th centile of normal range while four of the 11 patients (36.4%) under replacement doses showed low-normal FT4 levels with one patient showing a serum FT4 below the normal range. Despite a more than double frequency of raised TSH concentration in

the replacement-treated women, statistical significance was not reached. However, lack of statistical significance may be at least in part dependent upon the small sample size of our study group as well as the different prevalence of thyroidectomized vs Hashimoto's-affected patients (27.3% and 57.1%) in groups I and II respectively.

Such results should not encourage delaying the first post-conception hormone evaluation; this should always be performed as soon as possible since previous studies have demonstrated that even patients under a suppressive L-T4 regimen before pregnancy may turn severely hypothyroid in later stages of gestation (22, 23). In other words, women under partially suppressive therapy, even when euthyroid at the first post-conception hormonal evaluation, must be

Figure 2 Serum TSH levels before and during pregnancy in primary hypothyroid women under mild suppressive (○) or replacement (●) levothyroxine treatment.

Figure 4 Serum TSH levels before and during pregnancy in primary hypothyroid women in relation to the different aetiology of hypothyroidism and regardless of the therapeutic regimen.

re-evaluated in later stages of pregnancy.

All women undergoing partially suppressive therapy attended the post-conception endocrinological evaluation within the first 12 weeks of pregnancy while a 20% drop-out rate (3/15) was observed among group II patients. Furthermore, a significantly shorter time to first post-conception thyroid function evaluation was found in women undergoing partially suppressive therapy. It may be proposed that such findings are not mere coincidences, in fact, it could be that switching from a substitutive to a partially suppressive regimen – more than the information received about the necessity for careful thyroid function surveillance throughout pregnancy, both for the mother and the fetus – has made these women more aware of their condition. Hypothyroid women are on life-long L-T4 therapy and, as commonly observed in clinical practice, after an initial phase of great concern for their condition, patients tend over the years to underestimate the importance of periodic thyroid function evaluation. With this in mind, it can reasonably be proposed that while the recent therapeutic modification has renewed concern in group I patients, patients in group II have delayed post-conception hormonal evaluation.

Another finding that should be discussed is the differential behaviour of Hashimoto's-affected hypothyroid women when compared with thyroidectomized patients. None of the Hashimoto's patients showed serum FT4 levels below the 25th centile of normal range at the first post-conception endocrinological consultation regardless of their therapeutic regimen. Previous reports evaluating the repercussions of pregnancy in hypothyroidism of different aetiology have demonstrated that thyroidectomized women require a greater percentage increase of pre-pregnancy L-T4 dose in order to meet the new equilibrium (13, 24, 25). Our results further confirm this observation and suggest that thyroidectomized or radioablated women displaying a higher risk of inadequacy of pre-pregnancy replacement doses, could be those who would most benefit from this therapeutic protocol. On the other hand, performing partially suppressive L-T4 treatment, although safe, seems not to be mandatory in hypothyroid women who are planning a pregnancy and who still have a certain degree of thyroid reserve. The safety of mildly suppressive L-T4 treatment has been increasingly questioned and, even if for clearly higher FT4 levels, a direct toxic effect of excess thyroid hormones on the fetus has been recently demonstrated in pregnant women with thyroid hormone resistance showing higher miscarriage rates (26–28). In this study, pre-gestation serum TSH levels were maintained within values slightly above the standard mildly suppressive therapy and none of our patients reported any symptoms possibly related to L-T4 excess, suggesting that the increase from a median L-T4 dose of 1.43 µg/kg per day to 1.78 µg/kg per day, performed for a very limited period of time (median 5 months) and

in young subjects, can be considered relatively safe. In conclusion, on the basis of our results a slight increase in L-T4 dose could be proposed, with the aim of maintaining a serum TSH level in the lower quarter of normal range in primary hypothyroid women anticipating pregnancy in the near future. Such dose adjustment may not be sufficient for the entire period of gestation, but seems clinically useful for the prevention of even marginal and temporary limited thyroid hypofunction from conception to first post-conception endocrinological evaluation. Our results may be regarded as rather preliminary, larger-scale studies will probably provide more statistically proven conclusions; nevertheless some firm conclusions may be proposed. In fact, the L-T4 dose adjustment seemed to increase the patient's concern about the necessity of an early post-conception thyroid function evaluation; this suggests that, at least in thyroidectomized women, the proposed protocol is simple, safe and inexpensive and may prove extremely worthwhile in view of the well-known potential repercussions of maternal thyroid hypofunction on the subsequent IQ of the progeny.

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