

## Levothyroxine liquid solution versus tablet form for replacement treatment in pregnant women

Carlo Cappelli<sup>1</sup>, Roberto Negro<sup>2</sup>, Ilenia Pirola<sup>1</sup>, Elena Gandossi<sup>1</sup>, Barbara Agosti<sup>1</sup>,  
Maurizio Castellano<sup>1</sup>.

1. Department of Clinical and Experimental Sciences, Endocrine and Metabolic Unit, University of Brescia, c/o 2<sup>a</sup> Medicina Spedali Civili di Brescia, Piazzale Spedali Civili no. 1, 25100 Brescia, Italy.
2. Division of Endocrinology, "V. Fazzi" Hospital. Piazza F. Muratore. 73100, Lecce (Italy).

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Corresponding author:  
C. Cappelli, MD  
Department of Clinical and Experimental Sciences, Endocrine and Metabolic Unit,  
University of Brescia.  
c/o 2<sup>a</sup> Medicina Spedali Civili di Brescia  
Piazzale Spedali Civili n°1  
25100 Brescia (Italy)  
tel. ++390303995251.  
e-mail: [cappelli@med.unibs.it](mailto:cappelli@med.unibs.it)

## **ABSTRACT**

**Objective:** To evaluate the need and the magnitude of Levothyroxine (LT4) increase in hypothyroid pregnant women on liquid compared to tablet formulations.

**Methods:** Patients were recruited by searching our 'thyroid patients' database. The selection criteria were as follows: a) pregnant women on treatment for hypothyroidism (both liquid or tablet LT4) who have given birth at our hospital between February 2012 and January 2014; b) TSH and FT4 level obtained at least three months before missed menstrual cycle, with a TSH value less than 2.5 mIU/L; c) TSH and FT4 obtained within 12 weeks of pregnancy, and each month subsequently.

**Results:** During pregnancy, 8/31 (25.5%) of the women had to increase the dosage of LT4. Of these, 7/17 (41.2%) were on LT4 replacement therapy with tablet, and 1/14 (7.1%) with liquid formulation ( $p=0.038$ ). Daily LT4 was significantly increased in liquid group only ( $52.9\pm 19.5$  vs  $67.5\pm 19.2$  mcg/day ( $p=0.013$ )). A logistic regression analysis showed that treatment with LT4 tablet was the only predictor of LT4 increase (OR 0.44, 95% CI 0.04-0.83;  $p=0.031$ ).

**Conclusion:** Pregnant women on optimal replacement therapy before pregnancy, require increase of LT4 dose more often if on tablet than liquid formulation.

## INTRODUCTION

Hypothyroidism in pregnancy is defined as TSH above the trimester-specific reference range and is subdivided in subclinical or overt, depending on FT4 values within or below the normal range, respectively. Current Guidelines suggest to adopt local trimester specific range for TSH, and in absence of this, to consider an upper limit of 2.5mIU/L in the first, 3.0 mIU/L in the second and 3.0-3.5 mIU/L in the third trimester [1-4]. The state of pregnancy requires an adaptation of thyroid function that results physiologically increased [5]. That is the reason why hypothyroid women on replacement treatment with Levothyroxine (LT4), usually require an increase of LT4 amount by 30-50% at the beginning of pregnancy [6]. The need and the magnitude of LT4 increase depend on the etiology of hypothyroidism and the pre-pregnancy TSH level [7, 8]. Traditionally, LT4 is administered in form of tablet, but soft gel capsule or liquid formulations are available in some European Countries. Recent studies have shown a better absorption of soft gel/liquid formulation than tablet, hesitating in more stable TSH values [9-11]. The aim of the study is to retrospectively evaluate the need and the magnitude of LT4 increase in hypothyroid pregnant women on liquid compared to tablet formulation.

## **SUBJECTS AND METHODS:**

Women were recruited by searching the database of patients treated and followed at the Thyroid Unit of the Department of Clinical and Experimental Science, University of Brescia. The search criteria were as follows: a) pregnant women on treatment for hypothyroidism (both liquid or tablet LT4) who have given birth at our hospital between February 2012 and January 2014; b) TSH and FT4 level obtained at least three months before missed menstrual cycle, with a TSH value less than 2.5 mIU/L; c) TSH and FT4 obtained within 12 weeks of pregnancy, and each month subsequently; d) detailed LT4 treatment; e) detailed other drugs therapy (if any). As per protocol adopted in our Institution, in case of TSH higher than the pregnancy specific reference range, LT4 was increased by 25µg/day at each visit. All women satisfying the above criteria were enrolled in this study and informed consent was obtained from all subjects. The study was approved by the Institutional Review Board. Serum concentrations of free thyroxine (FT4 normal range 8.0-19 pg/ml, analytical sensitivity 1 pg/ml; intra and inter-assay coefficient of variation, 2.4 and 6.8%, respectively); TSH (normal range: 0.2-4.2 mIU/L, analytical sensitivity 0.004 mIU/L; intra and inter-assay coefficient of variation, 2.5 and 5.7%, respectively) were measured by means of chemiluminescence immunoassay using an automated analyser (Immulite 2000, DPC Cirrus, Los Angeles, CA, USA), employing commercial kits (Diagnostic Products Corporation, Los Angeles, CA, USA). Blood thyroid stimulating hormone (b-TSH) on neonatal Guthrie cards was measured by automated fluoro-immunoassay (Autodelfia technology; Perkin-Elmer Life Science). The blood sample was collected between days 2-4 after birth in the newborn and the b-TSH cut-off values was 10 mIU/L.

## **Statistics**

Statistical analysis was performed using SPSS 17.0 software (SPSS, Imnc, Evanston, IL, USA). Mann-Whitney U test was performed to evaluate TSH and FT4 distribution. Comparisons between groups and difference between proportions were calculated using ANOVA test for quantitative variables, as appropriate. A logistic analysis was performed to examine the influence of confounders on the hormonal thyroid profile. Two-tailed  $p < 0.05$  was considered significant. Data are presented as mean  $\pm$  standard deviation.

## Results

Between February 2012 and January 2014, 31 hypothyroid pregnant who satisfied the above mentioned criteria gave birth at our hospital. All the subjects were nulliparous, and suffered from Hashimoto's thyroiditis. Fourteen patients were in replacement therapy with liquid LT4 and 17 were on tablet. Baseline demographics and clinical characteristics are shown in Table I. No difference in age and body weight, were observed between patients on liquid and tablet treatment. All the patients assumed multivitamin pills containing iron and iodine. No difference was observed in thyroid function test before pregnancy between the tablet and the liquid group. Pre-pregnancy TSH and FT4 values were similarly distributed in the two groups. During pregnancy, 8/31 (25.5%) of the women had to increase the dosage of LT4. Of these, 3 women increased LT4 within 12 weeks, and 5 between 13-24 weeks. Among them, 7/17 (41.2%) were on LT4 replacement therapy with tablet, and 1/14 (7.1%) with liquid formulation ( $p=0.038$ ). The mean dose of LT4 from baseline to delivery was significantly increased only in women on tablet, as opposed to those on liquid therapy ( $52.9\pm 19.5$  vs  $67.5\pm 19.2$  mcg/day ( $p=0.013$ ), and  $53.6\pm 25.7$  vs  $55.4\pm 29.7$  mcg/day ( $p=0.34$ ), respectively).

There was no significant difference between women who needed to increase LT4 and those who did not (Table II). There was no significant difference in parameters of newborn from mothers who needed to increase LT4 and those who did not (Table III).

A logistic regression analysis taking into account age, pre-pregnancy and delivery weight, gestational weight gain, TSH values, showed that treatment with LT4 tablet was the only predictor of LT4 increase (OR 0.44, 95% CI 0.04-0.83;  $p=0.031$ ).

## Discussion

Either American or European Guidelines about treatment of thyroid disease in pregnancy suggest to treat hypothyroid women in order to keep TSH within trimester specific reference range [1-4]. Increased TSH levels are associated with adverse events like miscarriage, gestational hypertension and preeclampsia, gestational diabetes, intrauterine growth restriction, neonatal low birth weight, reduced intelligence quotient in the offspring [12, 13]. Given the well known variation in demand of thyroid hormones during pregnancy, a prospective study demonstrated that in hypothyroid women, an increase of two tablet per week is able to maintain TSH within the pregnancy reference range, then mimicking the physiological adaptation of an healthy thyroid to the pregnant state [14]; the need for an increase of LT4 dosage may be even higher than 30% in hypothyroidism induced by radioiodine or total thyroidectomy; other than the etiology of hypothyroidism, also the pre-pregnancy TSH level should be taken into account when deciding the variation dose: data suggest that increased LT4 dosage is necessary in 50% of cases when pre pregnancy TSH is 1.2-2.4 mIU/L versus 17% when TSH is lower than 1.2 mIU/L [7, 15, 16].

In the present study that evaluated LT4 treatment in hypothyroid patients on liquid or tablet formulation we observed that, despite similar pre-pregnancy TSH levels (mean and distribution) the liquid-treated group require to increase the LT4 dose in a minority of cases. A possible explanation for this result may rely on the different characteristic of absorption demonstrated by the two formulations. Indeed, the gastric pH is one of the most important factors that influence the absorption of LT4, in an inversely proportional manner: the absorption capacity decreases with the increase of pH [17, 18]. Centanni et al. have demonstrated that patients with impaired acid secretion require an increase dose of thyroxine, confirming that normal acid gastric secretion is necessary for effective absorption of oral LT4 [19]. It is well known that during pregnancy gastric emptying and

small intestine motility are reduced by 30-50% due to elevation of progesterone (20-22). In addition, these changes alter bioavailability parameters like maximum concentration (C<sub>max</sub>) and time to maximum concentration (T<sub>max</sub>) of orally administered medication. The decrease in C<sub>max</sub> and increase in T<sub>max</sub> particularly affect medication taken daily as a single dose [23]. Another relevant modification during pregnancy is represented by an increase in gastric pH, due to a reduction of H<sup>+</sup> secretion and an increase in mucus production, which may increase the ionization of weak acids, tending to reduce their absorption more than that of weak bases [20, 21]. Many recent reports have clearly demonstrated that liquid LT4 formulation circumvents these problems, in patients taking proton pump inhibitors, those suffering from gastric related T4 malabsorption, those assuming T4 with coffee or fed by enteral tube, and also those submitted to bariatric surgery [24-28]. As our pregnant patients on tablet required to increase LT4 more often than those on liquid, it is possible that the usual increase in exogenous LT4 requirement may be partly due to altered LT4 tablet absorption and not exclusively to pregnancy-related thyroid hormone increased demand. A major concern is represented by the alcohol content (243mg) that is present in vials of liquid formulation. As a matter of fact, current guidelines recommend abstinence from alcohol for women planning pregnancy, at conception, and during pregnancy [29, 30]. A recent meta-analysis did not find a significant increase in risk of low birth weight and small for gestational age for alcohol daily intake lower than 10 g, and risk of preterm birth for a daily intake lower than 18 g [31]. Our study as well did not find any difference between in characteristics of newborn from mother on liquid and tablet formulation.

In conclusion, although limited by the retrospective collection of data, and the small number of patients, results show that hypothyroid pregnant women on optimal replacement therapy before pregnancy, require increase of LT4 dose more often if on tablet than liquid formulation. Randomized prospective studies are necessary to confirm



this preliminary finding, that may have relevant clinical implications in the treatment of hypothyroidism in pregnancy.

**Declaration of interest:**

C. Cappelli, R. Negro, I. Pirola, E. Gandossi, B. Agosti and M. Castellano have no conflicts of interest to declare.

**Author contributions:**

C. Cappelli, R. Negro and I. Pirola designed the purpose of this study. E. Gandossi and B. Agosti did the literature search and selection, and wrote the manuscript. C. Cappelli, R. Negro, I. Pirola, E. Gandossi, A. B. Agosti and M. Castellano collaborated equally in the literature search and selection, and in the paper revision.

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**Table I.** Baseline demographics and clinical characteristics of women before pregnancy

	<b>Hypothyroid women on liquid LT4 (14 patients)</b>	<b>Hypothyroid women on tablet LT4 (17 patients)</b>	<b>p value</b>
<b>Age (yrs)</b>	28±3.8	27.3±3.5	0.599
<b>Weight (kg)</b>	59.5±2.8	58.8±4.2	0.609
<b>LT4 dosage (mcg)</b>	53.6±25.7	52.9±19.5	0.939
<b>TSH (mUI/L)</b>	1.6±0.8	1.4±0.8	0.592
<b>fT4 (pg/mL)</b>	10.9±1.4	10.3±1.3	0.308



**Table II.** Age and body weight of women who needed to increase LT4 and those who did not.

	<b>Women who needed to increase LT4 dosage (8 patients)</b>	<b>Women with no need to increase LT4 dosage (23 patients)</b>	<b>p value</b>
<b>Age (yrs)</b>	26.1±3.1	28.1±3.7	0.183
<b>Weight pre-pregnancy (kg)</b>	57.8±3.9	59.6±3.4	0.212
<b>Weight at delivery (kg)</b>	69.9±4.2	71.1±3.7	0.433
<b>Increase of weight during pregnancy (%)</b>	21.1±2.2	19.4±2.5	0.102

**Table III.** Clinical parameters of newborn from mothers who needed to increase LT4 and those who did not.

	<b>Newborn from mother who has increased the LT4 dosage (8 neonates)</b>	<b>Newborn from mother who has not increased the LT4 dosage (23 neonates)</b>	<b>p value</b>
<b>Male/Female</b>	2/6	8/15	0.483
<b>Gestational age (weeks)</b>	40.1±0.8	39.3±0.9	0.055
<b>Head circumference (cm)</b>	35.2±1.1	35.4±1.8	0.771
<b>Weight (g)</b>	3631±0.36	3.683±0.29	0.687
<b>Length (cm)</b>	50.6±3.3	51.1±2.8	0.681
<b>Apgar score 1<sup>st</sup> minute</b>	8.4±1.3	8.3±1.2	0.844
<b>b-TSH (mU/L)</b>	6.8±2.1	6.8±1.3	0.969