



# The Relationship Between Levothyroxine and Gestational Weight Gain in Subclinical Hypothyroidism Compared to Euthyroid Individuals

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## Abstract

**Background:** Untreated subclinical hypothyroidism (SCH) can lead to complications during pregnancy. One significant concern associated with pregnancy is excessive weight gain. Given the link between hypothyroidism and obesity, we aimed to investigate the relationship between the dose of levothyroxine and gestational weight gain (GWG), for which we did not find any reports. Additionally, we measured the differences in GWG between women with and without SCH who were monitored until the end of their pregnancies.

**Methods:** Primiparous women ( $N=245$ ) were selected using cluster sampling and entered into a prospective cohort study. Subclinical hypothyroidism (SCH) was determined so that participants could be divided into two groups, with and without SCH, and followed until the end of pregnancy. Levothyroxine dose was used as an independent variable, and maternal weights at 6–10, 18, 26, 33, 36 weeks, and at term (37–41) were determined as dependent (outcome) variables. Thyroid-stimulating hormone (TSH) levels during the first trimester and pre-pregnancy body mass index (BMI) were also recorded as key influencing variables. Data were collected via interviews and prenatal records from community health centers. Ten specialists confirmed the face validity of the questionnaire. To enhance reliability, all interviewers received training under the same conditions. Additionally, since the information was recorded using fixed and standardized forms, the reliability of the data had already been established.

**Results:** After adjusting for time (weight measurement in different weeks of pregnancy) and pre-pregnancy BMI, the average dose of levothyroxine was found to be correlated with gestational weight gain (GWG) ( $\beta=0.036$ ,  $SE=0.016$ ,  $P=0.025$ ). Additionally, there were no significant differences in total GWG between individuals with subclinical hypothyroidism (SCH) and euthyroid concerning their levothyroxine use (yes or no) ( $\beta=0.812$ ,  $SE=0.997$ ,  $P=0.415$ ).

**Conclusion:** We found a positive correlation between levothyroxine dosage and weight gain during pregnancy, which is a valuable result. Additionally, total weight gain in participants with subclinical hypothyroidism treated with levothyroxine did not differ statistically from that of euthyroid subjects.

**Keywords:** Levothyroxine sodium, Thyroxine, Gestational weight gain

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## Introduction

Pregnancy leads to an increase in thyroid hormone production, which is essential for fetal development. As a result, women may develop or experience a worsening of hypothyroidism, including subclinical hypothyroidism (SCH). There is strong evidence that uncontrolled SCH can lead to complications such as miscarriage, pre-

eclampsia, and gestational diabetes. In such cases, treating the condition with levothyroxine to bring thyroid-stimulating hormone (TSH) levels within the normal range for pregnancy can help reduce the risk of these complications, particularly if TSH levels are elevated or if thyroperoxidase antibodies are present (1). SCH is defined as a TSH level between 2.5 and 10 mU/mL, accompanied



by normal free thyroxine (FT4) levels. This condition is typically treated with a dose of 1 microgram per kilogram of body weight per day of levothyroxine, without the need to assess the anti-thyroperoxidase (ATPO) concentration (2). Once pregnancy begins, an increase of 30% in levothyroxine dosage and monthly monitoring are necessary to maintain TSH within the normal range (2). Now, the question arises whether treatment with levothyroxine can affect gestational weight gain (GWG), considering that the effect of levothyroxine therapy on incidences of other maternal and neonatal outcomes in SCH has been reported (3, 4, 5).

This issue is important, given the significant association between excessive gestational weight gain and maternal and child complications (6), especially since there is also a significant correlation between weight gain and thyroid function (7). Also, the effect of nutritional and educational interventions on pregnancy weight gain in pregnant women with SCH who take levothyroxine compared to euthyroids is unknown. In addition, weight gain is one of the main variables in the effect of levothyroxine treatment on birth weight (8).

Despite the importance of the subject, there are very few studies on the effect of levothyroxine on weight gain during pregnancy. One study indicated that after levothyroxine treatment in women with SCH, the median (IQR) of GWG in the SCH group was significantly lower than that in the EU group (14.0 [11.0–16.0] vs. 15.0 [12.0–17.0];  $p=0.003$ ) (9). Also, another study indicated that women with gestational hypothyroidism experienced lower weight gain compared to controls after receiving levothyroxine therapy (10). On the other hand, other researchers have demonstrated that the total weight gain after taking levothyroxine is not significantly different from that of controls in participants with SCH (11) or in those with both subclinical hypothyroidism and overt hypothyroidism (OH) (12). In addition to its importance, the inconsistency in this small number of studies also highlights the need for further studies on the association between levothyroxine and GWG. Therefore, we decided to compare the average weight gain during pregnancy in women with SCH who took levothyroxine to that of euthyroid women. Moreover, in this area of research, one study suggested that administering levothyroxine in the first trimester is more likely to reduce adverse pregnancy complications in women with SCH (13). Hence, assessing the relationship between the dose of levothyroxine taken (in micrograms) and weight gain (in kilograms) at different weeks of pregnancy among women with SCH was another goal of this study.

## Methods

Single primiparous women of Iranian origin, aged between 18 and 40 years, were enlisted for this prospective cohort study conducted in Isfahan, Iran, from May 22,

2022, to July 21, 2023. These women were chosen from the control group of a separate study (240037, IR.MUI.MED.REC.1400.206) (14). The recruitment took place at 15 community health centers located in various areas of Isfahan city to consider socioeconomic factors that may influence the outcomes. It is important to mention that pregnant women were directed by healthcare providers from different regions of the city to the specified community health centers, based on the mothers' preferences and the distance involved.

Considering the selection of participants from a prior study (240037), it was crucial that the participants not only fulfill the inclusion criteria but also possess information pertinent to the current study, such as TSH levels, levothyroxine dosage, and other relevant data. They were medically prescreened by midwives working at the community health centers. When necessary, assistance was also sought from the obstetricians and gynecologists at community health centers and private clinics to which the participants had been referred. The women were excluded if they had medical conditions affecting body weight, such as untreated thyroid disorders, type 1 or 2 diabetes, mental illnesses, substance addiction, nutritional problems and deficiencies, chronic diseases, kidney disease, anemias (including thalassemia minor), or were following a special diet. Additionally, women with a body mass index (BMI) greater than 35 were not included (15). The diagnosis and treatment criteria for SCH were based on the 2017 American Thyroid Association (ATA) guidelines by the obstetricians who were consulting the women or to whom the pregnant women had been referred. Also, if necessary, the participants were referred to an endocrinologist. Treatment with levothyroxine was initiated before or during the first trimester of the pregnancy.

We utilized G\*power 3.1.9, and a prior analysis for the *F*-test of repeated measures ANOVA with 6 measurements. Given that  $\alpha$  was considered 0.05,  $\beta$  was 0.80, the effect size was equal to 0.07, and with a correlation of 0.5, the sample size was estimated to be at least 220. Considering a potential 10% dropout rate, we included 245 individuals in the study.

Participants were first asked about demographic information (age, education, and occupation at the time of pregnancy, but not before) and reproductive characteristics (pre-pregnancy BMI). Also, the dose of levothyroxine taken at baseline and then at 26 weeks and at term (37–41 weeks of pregnancy) was asked, considering that eligible primiparous women were followed prospectively until delivery. Gestational age was also calculated from LMP (last menstrual period) and date of birth by the corresponding author. The face validity of the section and the entire questionnaire was verified by ten specialists in obstetrics, endocrinology, nutrition, and reproductive health. All interviews were conducted by the corresponding author under identical conditions and via

telephone conversation, thus ensuring their reliability.

Moreover, data were gathered regarding the presence or absence of SCH before or during pregnancy, first-trimester TSH levels, pre-pregnancy BMI, and maternal weight at weeks 6–10, 18, 26, 33, 36, and at term from the prenatal care files at community health centers and private offices. Since these files have a fixed and standardized format designed by the Ministry of Health, and have been completed by practicing and trained midwives (with a bachelor's or master's degree), their reliability is ensured. Weight measurements of participants were conducted by midwives employed at the aforementioned 15 community health centers. It is noted that before starting work, a coordination meeting was held to standardize the weight measurement process as much as possible. Weight was measured using digital scales available at community health centers. Total weight gain during pregnancy was calculated as the difference between the last recorded weight before delivery (preterm or term) and the pre-pregnancy weight.

#### **Ethical considerations**

The Ethics Committee of the Research and Technology Vice-Chancellor has approved the ethical code (IR.MUI.MED.REC.1400.206) for the main research, from which the information necessary for this study has been extracted.

#### **Statistical analysis**

Statistical analyses were conducted using SPSS version 27. Descriptive statistics were calculated to summarize the study variables, including frequencies and percentages for categorical variables and means with standard deviations for continuous variables. The normality of maternal weight at each gestational time point was assessed using Q-Q plots, and a small number of outlier observations were excluded from the analysis.

To examine the association between levothyroxine (LT4) dosage and maternal weight gain (in both term and preterm pregnancies), linear regression models were fitted using the generalized estimating equation (GEE) approach to account for repeated measures over time. Separate models were constructed to evaluate the relationship between weight gain and LT4 dosage as a continuous variable, LT4 use as a binary variable (yes/no), and timing of LT4 initiation (before vs. during pregnancy). All models were adjusted for time and pre-pregnancy body mass index (BMI). Maternal age was initially included as a covariate but was excluded from the final models due to lack of statistical significance and to improve model parsimony.

Maternal weight was measured at consistent gestational timepoints (6–10, 18, 26, 33, 36 weeks, and at delivery) for all participants. Deliveries before 37 weeks were classified as preterm, and those at or beyond 37 weeks as term.

To account for variability in gestational age at delivery, analyses were conducted both in the overall sample and separately among women with term deliveries. Gestational age at delivery was also tested as a covariate in the models; however, it was not statistically significant and did not alter the effect estimates, and was therefore excluded from the final models.

#### **Results**

Most companies had a bachelor's degree or were studying for a bachelor's degree and their occupation was housewife. The mean and standard deviation of age was 27.25 (4.70). Seventy-six (31%) of the pregnant women were taking levothyroxine tablets, while the mean dose among them was 49.46 (35.24) micrograms and among all participants was 16.39 (30.92) micrograms (Table 1).

The relationship between LT4 dose and maternal weight during pregnancy (once by considering the last recorded weight in term and pre-term deliveries, and once by considering the last recorded weight in only term deliveries) by controlling time (different weeks of pregnancy weight measurement) and pre-pregnancy BMI has been measured (Table 2). Both models have led to the same results. For example, in the first model, based on the results at the 0.05 level, a significant relationship between levothyroxine dose and the maternal weight was observed ( $\beta=0.036$ ,  $SE=0.016$ ,  $P=0.025$ ). So that for every one microgram increase in levothyroxine dose, the maternal weight increased by an average of 36 grams when we considered term and pre-term birth, and by 37 grams after excluding pre-term birth. In this model, the relationship between time and maternal weight ( $\beta=2.77$ ,  $SE=0.065$ ,  $P<0.001$ ), also pre-pregnancy BMI and maternal weight ( $\beta=2.28$ ,  $SE=0.117$ ,  $P<0.001$ ) both were positive and significant (Table 2). It means that at each measurement time, on average, the participants' mean weights increased by 2.774 and 2.796 kilograms. Also, for each unit of increase in pre-pregnancy BMI, the weights increased by 2.279 and 2.281 kilograms on average (Table 2).

It should be noted that the  $\beta$  coefficient (0.036) may appear small at first glance, but it corresponds to a 36\*25 grams increase in maternal weight for every 25 micrograms increase in LT4 dose. Given that LT4 dosage in our sample ranged up to 164 micrograms, this effect translates to a potential increase of nearly 5.9 kg in maternal weight across the observed dose spectrum. Therefore, the effect size is not only statistically significant, but also clinically meaningful; especially in the context of cumulative dosing over the course of pregnancy.

Separate linear regression models have been fitted to the data at each measurement time and the results are placed in the supplement file. Based on the results, it can be seen that the relationship between levothyroxine dose and the maternal weight was significant from the 18th week onwards (Table 1 supplementary file).

**Table 1.** Descriptive statistics of demographic and clinical variables

	Demographic and clinical variables										
	Age	Pre-pregnancy BMI	Dose LT4	Total GWG including term and pre-term deliveries	Total GWG without pre-term deliveries	Maternal weight					
						10 wk	18 wk	26 wk	33 wk	36 wk	Term
Mean (SD)	27.25 (4.70)	24.29 (4.21)	16.39 (30.92)	14.20 (5.03)	14.35 (4.86)	64.94 (12.08)	66.58 (11.66)	70.95 (12.57)	74.15 (12.04)	76.29 (13.01)	78.17 (12.44)

GWG: Gestational weight gain

**Table 2.** The association between dosage of levothyroxine and maternal weight gain considering time and pre-pregnancy BMI by linear regression using GEE method

	Parameter	B	Std. Error	95% Wald Confidence Interval		Sig.
				Lower	Upper	
Maternal weight in term and pre-term deliveries	(Intercept)	6.321	2.7124	1.005	11.638	0.020
	Time	2.774	0.0651	2.647	2.902	<0.001
	LT4 dose	0.036	0.0160	0.005	0.067	0.025
	Pre-pregnancy BMI	2.279	0.1172	2.050	2.509	<0.001
Maternal weight in term deliveries	(Intercept)	6.209	2.6908	0.935	11.483	0.021
	Time	2.796	0.0679	2.663	2.929	<0.001
	LT4 dose	0.037	0.0159	0.006	0.068	0.020
	Pre-pregnancy BMI	2.281	0.1164	2.053	2.509	<0.001

While [Table 2](#) investigates the dose-dependent association of LT4 with maternal weight gain, [Table 3](#) presents a comparison based on LT4 use as a binary exposure (user vs. non-user). The average GWG in SCH and euthyroid subjects [two groups of levothyroxine use (yes, no)], after adjusting for time and pre-pregnancy BMI was not significantly different ( $\beta=0.812$ ,  $SE=0.997$ ,  $P$ -values=0.415) ([Table 3](#)). Although the association did not reach statistical significance, the wide confidence intervals indicate uncertainty in the effect estimate, suggesting that the study may not have been adequately powered to detect small or moderate associations.

Controlling for pre-pregnancy BMI, no difference in weight gain was observed between the two groups at any of the measured times ([Supplementary file, Figure 1](#)).

Additionally, there was no significant difference in weight gain between those who started levothyroxine before pregnancy and those who took levothyroxine during pregnancy ([Supplementary file, Figure 2](#)). This comparison was also not significantly different after adjusting for time, pre-pregnancy BMI, and LT4 dose ([Table 4](#)).

Since a linear correlation was observed between levothyroxine dose and TSH ( $r=0.482$ ,  $P<0.001$ ), there was no need to investigate the relationship between levothyroxine dose and pregnancy weight gain considering TSH value in the first trimester.

## Discussion

In the present study, the dose of levothyroxine taken in micrograms in women with SCH was significantly associated with weight gain in kg, which was not different

for term and preterm deliveries. This association was observed in all the measured times except 6–10 weeks of pregnancy, because in weeks 6–10, all cases of subclinical hypothyroidism are not yet identified and treated, but the information is needed as baseline information for assessment ([supplementary file, Table S1](#)).

Similarly, a retrospective review of 882 patient charts across three age groups (18–44, 45–65, and over 65 years) found that the dosage of levothyroxine required to achieve euthyroidism was influenced more by actual body weight and the presence of antibodies than by age or menopausal status (16). Furthermore, some studies have reported a positive relationship between BMI and TSH levels. This relationship persisted even after controlling for factors such as age, menopause, and smoking. It was observed that for each unit increase in the logarithm of TSH, men gained an average of 1.1 kg and women gained 2.3 kg (17). Likewise, other studies have shown that weight loss is associated with reduced TSH levels (18).

In the context of pregnancy, researchers have asserted that treating newly diagnosed SCH with a weight-based strategy during pregnancy improves the chances of achieving TSH levels below 2.5 mIU/L more effectively than a fixed-dose approach (19). Additionally, one study indicated that changes in TSH levels within the reference range during the first trimester are correlated with weight gain and physical activity levels in the same trimester. Consequently, TSH concentration may either correlate with weight gain or be influenced by it (20).

The second result was that there was no significant difference in GWG in the two groups of users and non-users of levothyroxine, after controlling for the time of

**Table 3.** Comparison of maternal weight gain in women with SCH and euthyroid state, considering time and pre-pregnancy BMI, by linear regression using GEE method

Parameter	B	Std. Error	95% Wald Confidence Interval		Sig.
			Lower	Upper	
(Intercept)	6.393	2.7299	1.042	11.744	0.019
[LT4=Yes]	0.812	0.9965	-1.141	2.765	0.415
[LT4=No]	0 <sup>a</sup>	.	.	.	.
Time	2.778	0.0654	2.650	2.906	<0.001
Pre-pregnancy BMI	2.289	0.1173	2.059	2.519	<0.001

Dependent Variable: Maternal weight

Model: (Intercept), LT4 [(qualitative variable (Yes, No)), Time (quantitative variable), Pre-pregnancy BMI (quantitative variable).

a. Set to zero because this parameter is redundant.

**Table 4.** Comparison of gained weights between women who started levothyroxine before pregnancy and those who took levothyroxine during pregnancy

Parameter	B	Std. Error	95% Wald Confidence Interval		Sig.
			Lower	Upper	
(Intercept)	6.604	5.6597	-4.489	17.697	0.243
Time	2.811	0.1271	2.562	3.060	<0.001
Pre-pregnancy BMI	2.180	0.2297	1.730	2.630	<0.001
Pre-pregnancy hypothyroidism	-0.936	2.2020	-5.251	3.380	0.671
Pregnancy hypothyroidism	0 <sup>a</sup>	.	.	.	.
LT4 dose	0.068	0.0341	0.001	0.135	0.047

Dependent Variable: Weight gain

Model: (Intercept), Pre-pregnancy BMI, Time, Time of getting SCH, Dose LT4

a. Set to zero because this parameter is redundant.

measurement and pre-pregnancy BMI (Supplementary file, Figure S1, Tables S2, S3 and Table 3). As can be seen in Tables 2 and 3 of the supplementary file, the mean weight of the participants increased by 2.840 kg in the group that took levothyroxine and by 2.747 kg in the group not receiving levothyroxine. For each unit increase in pre-pregnancy BMI, weight gain increased by 2.132 kg in the group receiving levothyroxine and by 2.371 kg in the group without levothyroxine, with no statistically significant difference between the two groups. Therefore, we concluded that weight gain was the same in groups with and without SCH.

Similarly, a study of 457 pregnant women with SCH, 148 of whom received levothyroxine, showed that weight gain in SCH was similar to that of the group that did not receive levothyroxine (11). Also, among 920 Lebanese pregnant women in a retrospective cohort, 157 women with hypothyroidism (probably subclinical and overt) were compared with 763 controls, and at the end of pregnancy, no significant difference was observed in terms of GWG and BMI in the two groups (21).

In contrast, in a study of 165 pregnant women with SCH and  $4.0 \text{ mIU/L} \leq \text{TSH} < 10 \text{ mIU/L}$  treated with levothyroxine, there was still a high incidence of adverse pregnancy outcomes, including insufficient GWG, while the researchers did not provide any explanation for this finding (9).

However, another retrospective study reported that treatment of subclinical or overt hypothyroidism in

the second trimester was associated with lower and greater than normal weight gain in SCH. In fact, they concluded that the relationship between weight gain and thyroid, especially in the second trimester of pregnancy, is either expected or unexpected (22). Other researchers also reported that thyroid hormones regulate appetite, manage temperature, access energy-rich substrates, and increase basal metabolic rate. Thus, thyroid dysfunction causes obesity, and BMI is positively related to  $\text{fT}_3$  and TSH levels. However, there is a lack of consistency in data regarding weight gain or loss after treatment for hypothyroid and hyperthyroid patients. Furthermore, changes in thyroid hormones do not correspond with weight gain or loss (23, 24).

The effect or relationship between levothyroxine and weight gain during pregnancy has rarely been studied. Therefore, we will discuss the results and reasons in the non-pregnant state. No significant effect of levothyroxine on weight has been reported in obese subjects, the elderly, adult women, and children with SCH with TSH less than  $10 \text{ mIU/L}$  (25). In contrast, one study found that epicardial adipose tissue (EAT) thickness was reduced in a predominantly male elderly population after levothyroxine treatment (26). According to the available evidence, SCH and obesity cannot cause each other, because according to studies, TSH levels return to normal with weight loss (25), and the European Thyroid Association has not provided evidence on the beneficial effects of levothyroxine on body weight in obese people

with SCH and TSH < 10 mIU/mL (24). One explanation is that changing the dose of levothyroxine in hypothyroid patients with normal TSH levels does not affect energy expenditure or body composition. This is to the extent that patients prefer to take high doses of levothyroxine, but research results do not support levothyroxine dose adjustment based on changes in body weight or body composition (27). Likewise, another study reported that changes in TSH concentration within the normal range in healthy and hypothyroid women had no significant effect on clinical symptoms (except fatigue) and resting energy expenditure (28).

We found no other studies examining the association between levothyroxine use and gestational weight gain in SCH. Also, this association was prospectively assessed over six measurements. Moreover, the effect of TSH on the dependent variable was considered at 6 to 10 weeks of gestation. Other strengths included having strict inclusion criteria and comparing SCHs with fully matched euthyroid pregnant women. However, the sample size is small, and it is recommended that larger population-based studies be designed on the present topic.

## Conclusion

The current study found a positive correlation between levothyroxine dosage and weight gain during pregnancy. Furthermore, the total weight gain among pregnant women with subclinical hypothyroidism (SCH) being treated with levothyroxine was not statistically different from that of euthyroid subjects. However, in order to draw a more accurate conclusion, more population-based studies with larger sample sizes are needed.

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## Competing Interests

None.

## Ethical Approval

This survey was approved by the Ethics Committee of the Vice Chancellor for Research and Technology, Isfahan University of

Medical Sciences, Isfahan, Iran (IR.ARI.MUI.REC.1400.206).

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## Supplementary File

Supplementary file contains Table S1, S2 and Figure S1.

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