Original Article

Study for Optimal Dose Determination of Levothyroxine in Subclinical Hypothyroid Pregnant Patients: A Prospective Observational Study

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ABSTRACT

Introduction: Subclinical hypothyroidism in pregnancy is associated with early pregnancy loss, preterm birth, abruptio placentae, and postpartum thyroiditis. The aim of this study was to analyze the optimal dose of Levothyroxine given during 1st, 2nd, and 3rd trimester in pregnant women with subclinical hypothyroidism and to analyze whether there is significant change in dose of Levothyroxine when patients shift from one trimester to another.

Methodology: It was a prospective and observational study conducted among 90 subclinical hypothyroid pregnant women. Thyroid tests were repeated in each trimester in order to adjust Levothyroxine dosage. Paired t test was used for analysis of two groups of dependent quantitative data.

Results: This study showed that there was a significant increase in the mean dose of Levothyroxine required in the third trimester (65±16.639 μg) as compared to the first trimester (40.18±16.38 μg). There was also a significant difference in the mean dose of Levothyroxine required in the second trimester (44±20.761 μg) as compared to first trimester (40.18±16.38 μg).

Conclusion: Subclinical hypothyroid patients can be treated with low dose thyroxine without any associated side effects.

Keywords: Hypothyroidism, Pregnancy, Thyroxine.

INTRODUCTION

The butterfly shaped thyroid gland makes two hormones thyroxine (T4) and triidothyroxine (T3), which plays function is by negative feedback mechanism in which TSH concentrations are inversely related to T3, T4 concentrations.[1] There is an increase in total serum T4 and T3 concentrations and estrogen mediated thyroid binding globulin (TBG) but decrease in free T3 and T4 in pregnancy. Serum TSH decreases in first trimester due to hCG hormone which has thyrotropin like activity between 8 to 14 weeks of pregnancy.[2]

In the first half of pregnancy, before fetal thyroid maturation, this transfer of maternal thyroid hormone is particularly important for normal cognitive outcomes of babies. These concentrations then remain high until delivery. During pregnancy, women have lower serum TSH concentrations as compared to before pregnancy, and a TSH below the non pregnant lower limit of 0.4 mU/L is observed in as many as 15% of healthy women during the first trimester of pregnancy.[3]

Risk factors include personal or family history of thyroid dysfunction, advanced maternal age, diabetes, autoimmune disorders, and possibly morbid obesity. Many prospective and retrospective studies have demonstrated an increased risk of pregnancy complications associated with mildly elevated maternal TSH concentrations.[4,5] Although, subclinical hypothyroidism (SCH) is a biochemical diagnosis characterized by raised TSH with normal serum thyroid hormone levels, many patients have nonspecific symptoms. It can progress to overt hypothyroidism. Indian Thyroid Society (ITS) recommends screening of TSH levels in all pregnant women at the time of their first visit, ideally during pre-pregnancy evaluation or as soon as pregnancy is confirmed.[6]

There are a few observational studies suggesting a beneficial effect of Levothyroxine treatment in pregnant women with SCH.[7,8] The pregnancy and trimester specific reference levels for TSH are as follows:[9] 1st trimester - 0.1-2.5 mIU/l; 2nd tri-mester - 0.2-3 mIU/l; and 3rd trimester - 0.3-3 mIU/l. The present study was aimed to analyze the optimal dose of Levothyroxine in subclinical hypothyroid pregnant patients and to see the changes in dose when patient shifts from one trimester to another.

METHODS

This was a prospective observational study conducted on 90 patients attending the Department of Obstetrics and Gynecology at Narayana Multispeciality Hospital, Jaipur for a period of 8 months, after obtaining the approval of ethics committee of the hospital. An informed consent was taken from all the study participants. All pregnant women between 20 to 35 years of age, diagnosed with subclinical hypothyroidism first time in pregnancy, with normal BMI, and with no history of prior thyroid or any other medical or surgical disorders were included. Patients with hypothyroidism of autoimmune etiology, post radioiodine, thyroid cancer, postsurgery, post total thyroidectomy, central hypothyroidism, overt hypothyroidism, and pregnant women with obesity or with gestational hypertension or diabetes and with other co morbidities like chronic liver and kidney diseases, taking drugs known to alter thyroid level (e.g. Amphetamines, dopamine agonist, Amiodarone, Steroids) were excluded. Complete history was taken along with physical and obstetrical examination. Apart from recommended routine antenatal investigations (blood investigations and ultrasonography) blood for FT4, TSH was advised. American Thyroid Association Guidelines (2017)[9] recommends 2.5 µIU/l as the upper limit of TSH in the first trimester of pregnancy and <3 µIU/l in the second and third trimester, so in this study TSH value of 2.5 µIU/l was taken as cut-off to diagnose SCH in the first trimester. All the women having normal FT4 with TSH >2.5 µIU/l were diagnosed as subclinical hypothyroidism in this study. Blood samples were collected in OPD setting at least 6 hours after using Levothyroxin. Serum TSH and free T4 analysis was performed by chemiluminescence immunoassay method (Advia Centaur CP of Siemens). Serum creatinine and liver function test were also done to exclude renal and hepatic dysfunction. The pregnant women diagnosed with sub-clinical hypothyroidism were given appropriate dose of Levothyroxine (tablet Eltroxin) for their management. In the present study, drug brand Eltroxin from company is used to avoid drug variance in the study. Levothyroxine dosage was adjusted according to TSH levels measured. Thyroid tests were repeated in each trimester in order to adjust Levothyroxine dosage which is recorded.

Sample size calculation: Using Raosoft sample size calculator with population size of 105, 5% margin of error and 95% confidence interval the sample size comes out to be 83 (≈ 90). Hence sample size of 90 patients was taken. The sample size n and margin of error E are given by:

$$X = Z(^{C}/100)^{2}r((100-r)$$

$$n = ^{NX}/((N-1)E^{2}+X)$$

$$E = Sqrt[^{(N-n)x}/_{n(N-1)}]$$

Where N is the population size, x is average, r is the fraction of responses that we are interested in, and Z (c/100) is the critical value for the confidence level c. Data expressed as mean±standard deviation and percentage (%) as applicable. Student paired t-test was used for analysis of two groups of dependent quantitative data. p value < 0.05 was considered statistically significant with 95% confidence intervals and 5% of margin of error.

RESULTS

The mean age of study participants was 26.66±3.57 years, mean weight was 64.57±7.03 kg, and mean body mass index (BMI) was 22.20±1.95 kg/m^2 (Table 1).

Table 1: Age, weight, and BMI of study participants (n=90)

Parameters	Mean±SD
Age (years)	26.67±3.58
Weight (kg)	64.58±7.04
BMI (kg/m^2)	22.2±1.95

The mean Levothyroxine dose used in the first trimester was 40.18±16.39 µg (Table 2). The minimum and maximum dose used being 25 and 75 µg (Table 5), respectively. The mean Levothyroxine dose used in the second trimester was 43.6±20.76 µg. The mean Levothyroxine dose used in the third trimester was 65±16.64 µg

(Table 2). The minimum and maximum dose used being 25 and 100µg, respectively (Table 5).

Table 2: Mean of dose (µg) of Levothyroxine in first, second, and third trimester (n=90)

Trimester	(Mean±SD)
First Trimester	40±16.39
Second Trimester	43.6±20.76
Third Trimester	65±16.64

Seventy four (82%) out of 90 patients in the second trimester were having normal TSH value (≤ 3 mIU/L) and the remaining sixteen patients (18%) were having abnormal TSH value (>3 mIU/L) (Table 3). Forty six (51%) out of 90 patients in the third trimester were having normal TSH value (≤ 3 mIU/L) and the remaining forty four four (49%) patients were having abnormal TSH value (> 3 mIU/L).

There was a significant increase in the mean dose of Levothyroxine required in the third trimester (65±16.64 µg) as compared to the first trimester (40.18±16.39 µg) as determined by paired T test. There was significant difference in the mean dose of Levothyroxine required in the second trimester (43.6±20.76 µg) as compared to first trimester (40.18±16.39 µg) as determined by paired t test. There was a significant difference in the mean dose of Levothyroxine required in the second trimester (43.6± 20.76 µg) and third trimester (65±16.64 µg) as p value is < 0.05. Trimester specific doses of (µg/kg body weight) Levothyroxine are shown in table 4. This was quite low as compared to non-pregnant overt hypothyroid patients.

Table 3: TSH level of study participants in second and third trimester

Serum TSH levels (mIU/l)	Number of patients	
	second trimester	third trimester
TSH < 3 in Second Trimester	74	46
TSH > 3 in Second Trimester	16	44

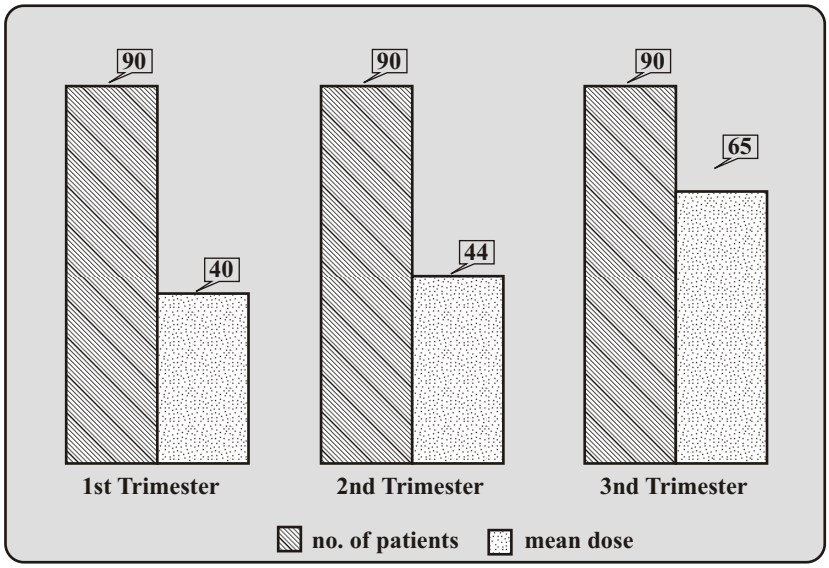

Figure 1 : Comparison of mean dose of Levothyroxine in all trimesters.

Table 4: Trimester specific doses of Levothyroxine (µg/kg body weight)

Trimester	Mean±SD
First trimester	0.63±0.27
Second trimester	0.66±0.30
Third trimester	1.01±0.40

Table 5: Minimum and maximum dose of Levothyroxine used in each trimester

Trimester	Minimum dose (µg/day)	Maximun dose (µg/day)
First	25	75
Second	25	100
Third	25	100

DISCUSSION

Thyroid dysfunction during pregnancy has been an important research area in clinical endocrinology due to the fact that thyroid dysfunction has immense impact on maternal and fetal outcomes.[10] Thyroid hormone is essential for the growing embryo during pregnancy for normal brain development and also to prevent complications during delivery and the postpartum period. In the first trimester, the baby gets it's thyroid hormone exclusively from the mother.

There is a approximately 50% increased production of thyroid hormones in pregnancy. Iodine requirement is also increased in pregnancy. The increased level of thyroid binding globulin, increase in plasma volume, and the influence of the mass of the fetal-placental unit are explanations for this increased requirement. To maintain adequate concentrations of thyroid hormone during pregnancy, T4 and triiodothyronine (T3) production are increased physiologically by the thyroid gland throughout a normal pregnancy but this compensation cannot happen in women with hypothyroidism. Thyroid gland in hypothyroid women is not able to respond either to thyrotropin or to chorionic gonadotropin, so the incremented requirement for thyroxine is not achieved and the serum thyrotropin concentration increases. Thus, pregnancy creates a challenge for the thyroid gland, particularly where thyroid reserve is limited or iodine deficiency is present.

In subclinical hypothyroidism, serum TSH levels are increased but free T4 levels remain within normal limit. Impact of subclinical hypothyroidism on pregnancy is a matter of debate. Many studies have shown that the children of the subclinical hypothyroid subjects did statistically less well on developmental tests. The children of women whose TSH levels were elevated during the mid trimester of pregnancy had a slight but significant reduction in intelligence quotient scores between 7 to 9 years of age when compared with infants of euthyroid women.[11]

National Guidelines for Screening of Hypothyroidism during Pregnancy, India 2014 December recommends to start thyroxine for all hypothyroid patients in pregnancy.[6] Thyroid function should be checked soon after starting therapy between 4 to 6 weeks and up titrate the dose to achieve TSH below 2.5 mIU/L as quickly as possible in first trimester.[12]

The mean Levothyroxine dose in a study[13] in the first trimester was 40.18±13.78 µg and in the third trimester was 58.25±18.57 µg. There was a significant increase in the mean dose of Levothyroxine required in the third trimester (58.25±18.57 µg) as compared to the first trimester (40.18 ±13.78 µg, $p = 0.0012$).

Abalovich et al[14] in their study suggested Levothyroxine doses in pregnant women with newly diagnosed hypothyroidism i.e. for subclinical hypothyroidism as 77.98 (µg/day) and 1.26 (µg/kg/day) and also 147.08 (µg/day) and 2.33 (µg/kg/day) for overt hypothyroidism. Duntas et al[15] showed that when commencing Levothyroxine therapy, initial dose requirements can vary greatly from small doses such as 2550 µg in an individual with mild or subclinical disease, where the therapy may be supplementing endogenous function, to larger doses of 88175 µg in cases of patients with negligible endogenous thyroid function. The Levothyroxine dose required to attain the TSH target levels varied significantly, depending on the baseline TSH levels.

It is well established that overt hypothyroidism in pregnancy should be treated, the recommended Levothyroxine doses ranging from 1.20-2.33 µg/kg/day during pregnancy, depending on the severity of hypothyroidism but when it comes to the subject of subclinical hypothyroidism, there are no clear guidelines about dose of Levothyroxine. American thyroid guidelines mention about target TSH levels in pregnancy, but the doses of Levothyroxine needed to attain these levels are not specified.[9]

With regard to the safety of LT4, over treatment results in

iatrogenic hyperthyroidism which occurs more often during pregnancy. hCG stimulates the maternal thyroid as previously discussed, but in contrast to TSH, hCG production is not regulated via negative feedback from FT4. Therefore high doses of LT4 during pregnancy may lead to high FT4 levels, particularly when treatment starts before the hCG peak at 10 weeks. High thyroid function has also been associated with preeclampsia and decreased birth weight of newborn.[4,16] Overzealously treated patients are at high risk for accelerated bone loss as well as the risk of osteoporosis and vertebral fractures.[17]

For women who are diagnosed with SCH during pregnancy, there is no official recommendation regarding the starting dose of Levothyroxine and there is a necessity to both update and promulgate novel guidelines in regard to Levothyroxine treatment during pregnancy because early treatment with Levothyroxine may reduce associated risk.[15] Based upon this discussion, it is clear that in hypothyroid patients, treatment should be started as soon as possible with appropriate dose of Levothyroxine to prevent maternal morbidity as well as mental retardation in newborns.

This study was designed in order to assess what percentage of thyroxine treated pregnant women with well-controlled hypothyroidism needed to increase their drug dosage during pregnancy and how much the drug should be increased. In our study, for total 90 patients of subclinical hypothyroidism in first trimester of pregnancy, levothyroxine was started as per serum TSH values. Out of 90 patients, 74 patients were euthyroid and 16 patients had serum TSH value more than 3 mIU/L. Levothyroxine dose was increased according to serum TSH level. The mean Levothyroxine dose used in the first trimester was 40.18± 16.39 µg /kg and in the second trimester was 43.6±20.76 µg. 46 out of 90 patients in the third trimester were having normal TSH value (< 3 mIU/L) and the remaining 44 patients were having abnormal TSH value (> 3 mIU/L). The mean Levothyroxine dose used in the third trimester was 65±16.64 µg. There was a significant increase in the mean dose of levothyroxine in third trimester (65±16.64 µg) as compared to the first trimester (40.18±16.39 µg). Minimum and maximum dose used is also low as compared to patients of overt hypothyroidism.

In overt hypothyroidism, patient is a diagnosed case of hypothyroidism before conception and needs a high dose of Levothyroxine. Subclinical hypothyroidism first diagnosed in pregnancy need less dose of thyroxine as compared to overt hypothyroid patients. In the present study, mean dose of thyroxine and trimester specific doses are less as compared to dose of overt hypothyroid patients. Trimester specific doses of Levothyroxine are as follows- (Levothyroxine in mcg/ body weight in kg): first trimester 0.63±0.27, second trimester 0.66±0.30, and third trimester 1.01±0.40. Subclinical hypothyroidism manifests due to low thyroid reserve and increased demand of hormones by fetus. Most of the subclinical patients do not require thyroxine in post-partum period. Also high dose of thyroxine has its own side effects like IUGR babies, preeclampsia, osteoporosis, and weight loss in mother.[18] So, as per observations in our present study, subclinical hypothyroid patients can be treated with low dose thyroxine without any associated side effects and also there is significant change in mean dose of levothyroxine when patient shift from one trimester to another.

Untreated maternal hypothyroidism has adverse effects on both the mother and fetus, but it can potentially be prevented by adequate Levothyroxine replacement. Subclinical hypothyroidism in pregnancy manifests due to less reserve of thyroid hormones in mother. During pregnancy, hypothyroidism should be treated aggressively, to normalize thyroid levels as soon as possible to have fewer side effects on maternal or developing fetus.

There are no clear cut guidelines about initial starting dose of Levothyroxine in subclinical hypothyroid pregnant patients; this study gives us a vision about initial dose of levothyroxine as pregnancy proceeds. Significant improvement in the thyroid function as indicated by higher proportion of patients achieving normal TSH values with significant increase in the mean Levothyroxine dose used during the course of treatment gives us guideline about the initial starting doses of Levothyroxine.

CONCLUSION

Our study has shown that when patient move from first to second trimester then there is significant change in Levothyroxine dose. Subclinical hypothyroid patients can be treated with low dose thyroxine without any risk of associated side effects. There is significant increase in dosage of thyroid hormone in third trimester of pregnancy

which is due to increased demand by fetus. This implies that serum TSH should be repeated in third trimester for every pregnant hypothyroid patient to optimize the dose of thyroxine.

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