REVIEW ARTICLE

Levothyroxine Therapy: Its Effect on Subclinical Hypothyroidism

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Abstract

Thyroid hormones are necessary for the desired development and growth of the fetus. There is an essential correlation between thyroid dysfunction in mothers and cognition in children; maternal hypothyroidism also affects reproductive functions, including fertility, abortions, and preterm birth. Due to regular changes in the metabolism of thyroid hormone and thyroid function, trimester-wise thyroid-stimulating hormone (TSH) levels and free thyroxine should be estimated. However, due to variations in age, ethnicity, and iodine intake, it is restricted to one population, which can be misleading to diagnose a euthyroid woman as a patient of hypothyroidism. Therapeutic benefits of levothyroxine remain unclear; however, when an intervention was made during the first trimester, it indicated a reduction of abortions and preterm delivery in women. The harmful effects of treatment with levothyroxine include hypertension, diabetes in pregnancy, and preeclampsia. Intervention with levothyroxine in the second trimester is of no use in reducing cognitive impairment. Thus, routine screening of subclinical hypothyroidism should be performed in all pregnant women to prevent its complications. Intervention with levothyroxine depends on the TSH levels, which vary according to trimester. Hence, the benefits of levothyroxine therapy depend upon the timing of intervention, change in the requirement of thyroxine during pregnancy, and alteration of dose of levothyroxine as required following delivery.

Keywords: Levothyroxine, Pregnancy, Subclinical hypothyroidism.

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Introduction and Background

The importance of deficient thyroid hormone in the mother throughout the pregnancy and its effect on the development and growth of the child came to notice over two decades ago.[1] In subclinical hypothyroidism (also known as mild thyroid dysfunction), thyroid-stimulating hormone (TSH) ranges between 2.5 and 10 mU/L. Studies have shown that subclinical lower levels of the thyroid have adverse effects on the development of children.[2]

It is also seen that lower levels of thyroid hormone during the early phase of pregnancy harms the neurodevelopment of the child, which may improve when free t4 levels increase during further course of pregnancy. Mild thyroid dysfunction is also related to higher risks of premature delivery, abruption placenta, defective cognition in children, and admission to intensive care units.[3] These findings led institutions to imply screening and treatment for the same during pregnancy.[4] These can affect about 15% of the women, depending upon the free thyroxine thresholds used.[5] The American College of Obstetricians and Gynecologists has stated that screening is of little use without trials showing improvement in this outcome without levothyroxine therapy.[6] The controlled antenatal thyroid screening (CATS) study has shown that cognition in children whose mothers have been identified as having mild thyroid dysfunction and given levothyroxine therapy is not better than the children whose mothers were not placed before.[7]

Many studies have shown that subclinical hypothyroidism increases the risk of abortions, preterm birth, abruption placenta, diabetes in pregnancy, hypertension in pregnancy, intrauterine growth retardation, and low weight during childbirth.[8–10] Still, in many studies, no side effects of subclinical hypothyroidism have been seen.[11,12] These discoveries might be associated with different standards used for the diagnosis of subclinical hypothyroidism like the presence of antithyroid antibodies, which itself is a risk factor for side effects in pregnancy, differences in maternal age, which were used in studies, study of thyroid hormone levels in different trimesters, a similar discrepancy is seen in the association among maternal subclinical hypothyroidism and neurodevelopmental disorders in children like low intelligence, attention deficit hyperactivity disorder, and autism. The aim of this review is to evaluate the effects of levothyroxine therapy on subclinical hypothyroidism in pregnancy.

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Review

How to Identify Subclinical Hypothyroidism During Pregnancy?

Subclinical hypothyroidism is diagnosed by trimester-specific levels of free thyroxine, TSH, and total thyroxine.[13,14] Pregnancy severely changes the function of the thyroid gland and thyroid hormone metabolism; for that reason, normal reference levels for tests of the role of the thyroid differ in pregnant and non-pregnant females and trimesters. Human chorionic gonadotropin (HCG) shows similarity

Table 1: Ranges of thyroid-stimulating hormone (trimester-specific), free triiodothyronine, and free thyroxine (data for pregnant females)[15]

		Pregnant female		
Parameters in test for thyroid function	*General population*	*1st trimester*	*2nd trimester*	*3rd trimester*
TSH (mU/L)	0.3–4.5	0.009–3.177	0.05–3.442	0.11–3.53
Free thyroxine (pmol/L)	11–22	11.99–21.89	10.46–16.67	3.1–5.37
Free triiodothyronine (pmol/L)	3.1–6.8	3.63–6.55	3.29–5.45	8.96–17.23

TSH, thyroid-stimulating hormone

Table 2: Outcome of levothyroxine therapy for subclinical hypothyroidism during pregnancy

Definition of subclinical hypothyroidism	*Intervention started at*	*Therapy outcome*
Normal free thyroxin and TSH > 2.5 mU/L	1st trimester	Drop in adverse pregnancy outcomes
Normal free thyroxine and TSH = 2.5–10 mU/L[16]	1st trimester	Drop in the incidence of premature birth and admission of neonates to neonatal units
TSH = 2.5–10 mU/L[17]	Not mentioned	The rate of pregnancy loss decreased

with TSH; there is a reverse relationship between TSH and HCG all through the pregnancy; the peak concentration of HCG is seen during trimester 1, later on its plateaus; hence, TSH is low during the 1st trimester and later on in the 2nd and 3rd trimester, it increases but does not reach pre-pregnant values. Therefore, the upper and lower ranges of normal thyroxine levels change with the trimester. As a result of an increase in the ranks of HCG, free thyroxine and triiodothyronine also increase during the first trimester.

Mild thyroid dysfunction is also defined as the appearance of increased levels of TSH with normal thyroxine and total thyroxine levels. Factors like serum TSH levels, trimester of pregnancy, and nutritional variation in regional iodine may lead to the development of hypothyroidism in pregnancy. Differences in iodine intake have a critical impact on the occurrence of subclinical hypothyroidism.

TSH levels increase with age; therefore, age is another factor contributing to the development of hypothyroidism during pregnancy.[18] Various societies such as the European Thyroid Society, American Thyroid Association, and Endocrine Society suggest upper limits of TSH as 2.5, 3, and 3–3.5 mU/L for 1st, the 2nd and 3rd trimesters.[19,20] Recently, the American Thyroid Association issued a new guideline stating common TSH values for all the trimesters, which is 4 mU/L.[13] Table 1 represents trimester-wise TSH, free triiodothyronine, and free thyroxine in the general population and pregnant females.

Benefits of Using Levothyroxine in Subclinical Hypothyroidism During Pregnancy

In a trial, the effect of levothyroxine on pregnant females with levels of TSH more than 2.5 mU/L was evaluated. The test was executed in trimester 1; levothyroxine was given to maintain TSH levels below 2.5 mU/L in the 1st trimester and below 3 mU/L in the 2nd and 3rd trimesters. Levothyroxine was shown to decrease adverse outcomes of the pregnancy like abortions, preterm birth, and abruption placenta occurring due to subclinical hypothyroidism.[21] It is also seen that levothyroxine therapy helps prevent complications like preterm birth and admission into the intensive care unit. Still, it is only helpful and beneficial in women having TSH levels above 4 mU/L.[16] The faster the treatment with levothyroxine is started, the more valuable it becomes; therapy with levothyroxine is initiated in the first trimester in females with TSH levels above 4 mU/L, and it showed a remarkable decrease in the occurrence of preterm births, though not seen in females having TSH levels between 2.5 and 4 mU/L.[16]

Hypothyroidism is a serious health issue and is the most common thyroid dysfunction during pregnancy. Even borderline hypothyroidism during pregnancy increases the risk of abortions, preterm birth, intrauterine deaths, and cognitive impairment in the newborn. Levothyroxine is safe and effective for preventing complications arising due to subclinical hypothyroidism in mother and child.

In a study, both the benefits and side effects of levothyroxine therapy in subclinical hypothyroidism have been studied. And 2.5–10 mU/L was the cut-off range for including pregnant females in this study. Levothyroxine therapy remarkably reduced the chances of loss in pregnancy by 38% but also increased the chances of a few complications of pregnancy, such as premature birth, diabetes in pregnancy, and preeclampsia. Levothyroxine is effective in women with levels of TSH between 4.1 and 10 mU/L and not found effective in women between 2.5 and 4 mU/L. The most crucial factor concerning the treatment of subclinical hypothyroidism is the level of TSH at which the intervention should be initiated. Table 2 shows the level of free thyroxine and TSH, when intervention should be created, and its outcome.

Subclinical hypothyroidism is linked with many complications of pregnancy.[22,23] Studies also show that women with thyroid peroxidase antibodies who were treated showed fewer chances of preterm birth than the women who were not treated;[24] however, no remarkable improvement in pregnancy and fetal outcomes, which are related to subclinical hypothyroidism, were seen.

The relationship between subclinical hypothyroidism and its Sid effect on maternal and fetal health remains controversial, but present guidelines support levothyroxine therapy in such patients, considering its safety; however, treatment options should be evaluated according to TSH levels.[16]

It must be taken into consideration that the increased requirement of thyroid hormone in subclinical hypothyroidism during pregnancy is solely gestational stimulation. Prepartum levothyroxine dosage should be started after delivery, and TSH levels should be checked after 6 weeks of delivery.[25]

The Outcome of Levothyroxine Therapy on a Child's Cognitive Function

The medical intervention was performed at the mid-gestational age, the treatment was adjusted according to the desired TSH levels, the cognitive function of children was evaluated at the age of 3 years, and no dissimilarity was seen among those whose mothers

were given therapy or were not treated during pregnancy. The intelligence quotient of children was assessed again at 9.5 years with no remarkable changes in values.[26] These might be happening because of the following reasons: (1) Delay in intervention, which skips the early phase of the development of the brain; (2) Borderline hypothyroidism in pregnancy; (3) Testing of I.Q. in offspring with improper indices;[27] and (4) No levothyroxine therapy to the mother.

A recent study shows that children who were born to women not treated with levothyroxine had lower school performance and intelligence quotient than the children who were born to treated mothers.[28] This is usually produced as evidence that children born to mothers with subclinical hypothyroidism are at higher risk of developing cognitive dysfunction. Studies also show children born to mothers with hypothyroidism during pregnancy that was identified before 12 weeks of gestation are at lower risk of developing any cognitive impairment.[29,30] These studies showed that progeny would benefit from the treatment of mothers with subclinical hypothyroidism, and thus resulted in adaptation by many institutes routine screening and treatment of pregnant females to prevent the development of cognitive dysfunction in progeny.[4] The thyroid gland of the fetus is formed at 12 weeks of gestation and becomes excessively functional later.[31] The fetus is dependent on the maternal thyroid hormone. Fetal brain development requires thyroid hormone derived both from the mother and fetus.

Levothyroxine increases chances of developing attention deficit hyperactivity disorder and abnormal behavior.[7] Some studies also show that in pregnant females with subclinical hypothyroidism, even if the free thyroxine level is average and TSH alone is elevated, the intelligence of the progeny may be severely affected.[28,32] The levothyroxine therapy was started, and targeted levels of TSH were achieved in 2nd trimester of pregnancy, as soon as the steps of organ formation were finished. Also, there is a caution against overdosage of levothyroxine, which might lead to other complications like attention deficit hyperactivity disorder and abnormal behavior,[33] hence, the dose of therapy should be monitored. It came under observation that both low and high maternal free thyroxine during early pregnancy were associated with low intelligence quotient in children.[33]

When to Start Levothyroxine Therapy?

Variable results are shown by levothyroxine therapy for subclinical hypothyroidism; the recommendations launched by various organizations and societies vary. It has been suggested to treat non-pregnant women if the TSH level is above 2–2.5 mU/L, especially in TPoAb-positive patients, and irrespective of TPoAb status, treat every pregnant female identified as a case of subclinical hypothyroidism during pregnancy.[34] Likewise, the European Thyroid Association recommended treating all women identified as subclinical hypothyroidism before and during pregnancy and continuing TSH levels at the desired trimester-wise range.[16] In women diagnosed with subclinical hypothyroidism and who are under treatment for the same before the pregnancy itself, the levothyroxine dose should be doubled at the onset of pregnancy.[35] It is followed by giving two extra doses weekly, to be started as soon as possible to avoid the development of symptoms of hypothyroidism.[13] Gradual increase in the dose of levothyroxine is most accepted to achieve desired TSH levels during pregnancy.[36]

The cause of hypothyroidism is an essential factor in levothyroxine therapy; patients with overt hypothyroidism require higher doses of levothyroxine as compared with people with hypothyroidism due to autoimmune dysfunction. Suppressed TSH levels in patients with thyroid cancer, minimal levothyroxine doses are needed to increase levels during pregnancy. Pregnant women having levels of TSH in the middle of 2.5 mU/L and upper standard limit and who are TPoAb negative do not require treatment. A summary of all the articles included in this review is listed in the Table 1.

Conclusion

Benefits of using levothyroxine in subclinical hypothyroidism is controversial. It has both benefits as well as side effects, where it decreases chances of preterm delivery, abortions, intrauterine growth restriction, and low birth level; it increases the chances of development of attention deficit hyperactivity disorder and abnormal behavior. Whether levothyroxine should be started or not depends upon serum TSH levels, which vary according to trimester. Levothyroxine therapy is beneficial at TSH levels between 4.1 and 10 mU/L and non-beneficial between 2.5 and 4 mU/L. Due to the severe negative effect of levothyroxine on maternal and fetal health, over dosage of levothyroxine should be strictly under surveillance. Initiation of levothyroxine therapy in the 2nd trimester is not useful in preventing cognitive impairment in child, whereas, if started in the 1st trimester, it can help to reduce the adverse outcome. Due to prevention of some of the pregnancy-related complications, levothyroxine is used for treating subclinical hypothyroidism during pregnancy considering its safety; the sooner it is started, the better outcome it gives.

If a woman conceives, levothyroxine dosage should be doubled, two extra doses are given weekly, gradual increase in dose of levothyroxine is proven to be helpful. After delivery, pre-pregnant dosage should be resumed and serum TSH level should be checked after 6 weeks of delivery.

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