DOI: https://doi.org/10.53350/pjmhs22166998

ORIGINAL ARTICLE

An understanding of Thyroid Problems during Pregnancy

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ABSTRACT

Several questions persist, even though our considerate of the connections concerning thyroid function and pregnancy is growing. It is essential to utilize a TSH range for the trimester when evaluating thyroid function during pregnancy. Low TSH levels in the initial trimester should be regarded as natural rather than problematic. TSH levels should not exceed 2.5 mIU/L in the 1st trimester and 3.0 mIU/L in the 2nd and 3rd trimesters. The major form of treatment during the 1st trimester of prenatal period for women with overt hyperthyroidism is PTU therapy. Women with overt hyperthyroidism are highly advised to take anti-thyroid medication. The dosage of LT4 must be increased by 30% to 50% in women who have hypothyroidism and are currently taking it. Pregnant women who have recently been diagnosed with overt hypothyroidism are strongly advised to start on LT4 replacement therapy. Another factor that must be considered is the existence of subclinical hypothyroidism. People with isolated hypothyroxinemia don't need LT4 therapy, but it's recommended to protect their thyroids by getting enough iodine. Patients with persistent autoimmune thyroiditis who are euthyroid should not take LT4, although they should still be closely watched because hypothyroidism may set in. The unanswered questions in this area will be addressed by the decisive results of the research, which was just finished and is now being conducted. These uncertainties range from the presence of thyroid antibodies to the management of preclinical hypothyroidism and the usage of LT4 to treat isolated hypothyroxinemia.

INTRODUCTION

Pregnancy with thyroid dysfunction is very common. Even though their thyroid levels are normal, at least 2% to 4% of women suffer from thyroid dysfunction, and about 10% of women have autoimmune thyroid disease. In the past 20 years, the scientific community has made specific recommendations considering their improved considerate of the functioning of the thyroid gland in pregnancy as well as the link between thyroid dysfunction and unfavourable obstetrical and neonatal outcomes. This understanding has allowed for the development of this understanding. The preliminary recommendations were approved by the Endocrine Society, and they were issued in 2007. These guidelines are scheduled to be updated in just three years. The American Thyroid Association has also newly published its very specific set of recommendations for this year. Pregnancy impacts thyroid function, and natural thyroid disfunction (whether hyperthyroidism or hypothyroidism) is linked with a higher risk of undesirable consequences. This demonstrates how critical it is to educate people about the dangers of thyroid disease in pregnancy to reduce the danger of developing complications. Along with other medical professionals, such as obstetricians and endocrinologists, the pregnant woman and, in a roundabout way, the unborn child are two additional patients in this field. As a result, having the proper expertise is necessary for effective management.

In this publication, we sought to synthesize the results of earlier studies and turn them into practical recommendations that would improve clinical practice and be backed by strong data. The primary clinical concerns of diagnosis, treatment, and patient management served as a source of inspiration and guidance for the endocrinologist's decision-making processes. The treatment of thyroid disorder in pregnant females is a relatively new field that is still in its early stages of development and has a great deal of open research questions. It is hoped that ongoing research over the next few years will answer all the questions that are currently unanswered.

Thyroid test in pregnancy: The levels of circulating absolute T4 and thyroxine binding globulin (TBG) begin to rise between four and eight weeks following the conception of a child. Due to the thyrotropic commotion of human chorionic gonadotropin (HCG), which lowers serum TSH, the concentrations of thyroid-stimulating hormone (TSH) in the blood serum of pregnant females are lower than the concentrations of TSH in the serum of non-pregnant ladies throughout the first trimester of pregnancy (Negro, 2009). Despite increasing TBG and decreased albumin concentrations complicating pregnant women's blood FT4 measurements, numerous studies reveal a considerable drop in serum-free thyroxine (FT4) concentrations as the pregnancy continues. This is the case even though elevated TBG and lessened albumin concentrations may disturb the accuracy of immunoassay estimation (Kahric-Janicic et al., 2007; Soldin et al., 2004). Despite the common perception that FT4 concentrations tend to drop off as the pregnancy progresses, this is the case. According to these findings, the maximum amounts of TSH that should be present during the 1st, 2nd, and 3rd trimesters of pregnancy, respectively, should be 2.5 mIU/L, 3.0 mIU/L, and 5.0 mIU/L. In addition, the lowermost physiological limit may be 0.1 mIU/L during the 1st trimester, 0.2 mIU/L during the 2nd trimester, 0.3 mIU/L during the 3rd trimester, and so on (Haddow et al., 2004). These values vary depending on the stage of pregnancy. If these reference ranges that are specific to each trimester are not utilised, then it is quite possible that both hypothyroidism and hyperthyroidism will be understated (Stricker et al., 2007).

Overt hypothyroidism: Overt hypothyroidism is diagnosed when low FT4 levels are seen in conjunction with elevated TSH values (OH). In areas of the world where an acceptable amount of iodine is consumed, autoimmune thyroiditis is the most common reason of overactive thyroid (OH), even though iodine insufficiency is the leading reason of OH globally. Other causes include pituitary or hypothalamic disorder, immunoglobulin binding to the TSH receptor, congenital hypothyroidism, previous thyroid surgery, radioiodine therapy, using lithium, and taking anti-thyroid medicine (blocking its activity). It is believed that the frequency of OH falls anywhere between 0.2% and 1.0% (Vaidya et al., 2007).

It is hardly a stretch to say that serious adverse effects are associated with untreated OH. One of the most well-known negative effects of hypothyroidism is a lesser intelligence quotient (IQ) among children who were born to mothers who had the condition. This was initially observed by (Haddow et al. 1999). In this retroactive analysis, the investigators picked 62 pregnant ladies to participate based on their having serum TSH levels that were exceeding the 98th centile for all pregnant ladies (n = 14, 25216) and having small FT4 values. Their children were given IQ tests using the Wechsler Intelligence Scale for Children, 3rd edition, while they were between the ages of 7-9 years old. The results exhibited that there was a difference of 4 points between their children and the control group (P 1/4 0.06). Compared to euthyroid control offspring, 15% of children born to hypothyroid moms had IQs of 85 or lower. During their pregnancies, levothyroxine was not administered to 48 of the 62 women with

thyroid deficiencies. These 48 children had full-scale IQ values that were, on average, 7 points lesser than the control, and 19% of them had IQs of 85 or below. Comparing the IQs of 48 youngsters to those of controls yielded these results.

OH, has been linked with a range of obstetrical complications, involving those listed above. The increased chance of spontaneous abortion, stillbirth, and death in the newborn are among the most important consequences. Two more common complications of OH are preterm birth and foetal distress. Additionally, some studies have shown a higher risk of gestational hypertension, placental abruption, and postpartum haemorrhage (Krassas et al., 2010).

Despite the grave nature of the outcomes associated with OH, only few of these cases are the focus of an intervention that is up to the requirements of evidence-based medicine. According to Abalovich et al. (2002), when substitutive treatment is adequate, early foetal death is significantly decreased from 31% to 8%. This demonstrates the importance of restoring normal thyroid function, which is accomplished in pregnant hypothyroid women by LT4 medication. The study found that when hypothyroidism is properly handled, early foetal loss is reduced.

Tan et al. (2006) investigated a sample of treated hypothyroid moms during the primary stages of gestation and discovered that there was no surge in obstetrical or new-born snags. In a latest study, Negro et al. (2010) looked at harmful outcomes in ladies with overt and subclinical hypothyroidism. They discovered that those with thyroid disfunction who were not treated had a considerably elevated rate of problems than those who were. This was the case irrespective of whether the women had overt or subclinical hypothyroidism.

Levothyroxine is generally considered to be the extremely efficient treatment for hypothyroidism (LT4). Women who have been hypothyroid in the past and have been given a diagnosis are encouraged to adjust their dosage to obtain a pre-gestation TSH level of less than 2.5 mIU/L (Abalovich et al., 2007). The level of TSH should be maintained at a constant level throughout the 1st trimester, and during the 2nd and 3rd trimesters, it should not surpass 3.0 mIU/L. To accomplish this goal, the initial dosage of LT4 should be increased by 30–50% during the beginning of pregnancy. The amount needed to achieve this goal will vary depending on the cause of the hypothyroidism (Yasa et al., 2010). Theoretically, an increase in hypothyroidism caused by Hashimoto's thyroiditis (Alexander et al., 2004) requires less of an increase in residual functional reserve than an increase caused by thyroidectomy does. The greatest increase in dosage is required during the first trimester of pregnancy, although it is possible that additional increases will also be necessary throughout the second and third trimesters. Importantly, it has not been established that having subclinical hyperthyroidism (which may result from excessive thyroxine replacement) is connected to lower pregnancy outcomes; hence, having this condition may be preferred to having insufficient thyroxine replacement.

If overt hypothyroidism is discovered in pregnancy, it is recommended to administer 150 mg of levothyroxine daily for a limited days before lowering the dose in accordance with the serum TSH and FT4 levels. This will help to reestablish euthyroidism as instantly as feasible so that the pregnancy can continue as normally as possible. This strategy is essential in the 1st trimester because it lowers the danger of miscarriage and ensures that there is sufficient thyroxine for regular brain development in the foetus. When the level of LT4 has returned to its level before the pregnancy, which should happen after delivery, an evaluation of the thyroid's function should be performed (Caixas et al., 1999).

Subclinical hypothyroidism: It is thought to be a symptom of subclinical hypothyroidism when FT4 levels are standard, but TSH amounts are excessive (SH). SH is without a doubt the thyroid dysfunction that is observed during pregnancy more frequently than any other. The prevalence of SH varies from study to study due to factors such as the definition of SH, participants' ethnicity, the amount of iodine they consumed, and the research technique. In most cases, the prevalence falls somewhere in the range of 1.5 to 4.0% (Vaidya et al., 2007).

In a manner analogous to that of OH, SH is linked with a variety of obstetrical impediments. The outcomes of several studies are not readily visible, which may be the consequence of variations (and limits) in the study design as well as an insufficient number of participants. When doing study into the complications that are linked to thyroid disease, one of the most prevalent problems that researchers encounter is an inadequate population sample. The loss of a pregnancy is one of the most prevalent obstetric worries related to SH. In addition to the findings of Abalovich et al (2002) study, Benhadi et al. (2009) found that there is a certain linear link between pregnancy loss and elevated TSH levels. The researchers found that the rate of child loss increases by sixty percent for every augmenting in the concentration of TSH. When Ashoor et al. (2010) compared the thyroid function of 4318 healthy pregnancies to 202 singleton pregnancies that later ended in miscarriage or foetal death, she discovered that those who experienced foetal loss had higher median TSH multiples of the standard median (MoM) levels, lower FT4 MoM levels, and a higher frequency of TSH levels above the 97.5th percentile (5.9% vs. 2.5%) and FT4 levels lower the 2.5th percentile. Negro et al. (2010) described a elevated rate of pregnancy failure in thyroid antibody-negative ladies with TSH levels between 2.5 and 5.0 mIU/L equated to women whose TSH values were less than 2.5 mIU/L during the first trimester of pregnancy. This rate was 6.1 versus 3.6%, respectively. Definitively, Allan et al. (2000) discovered that the rate of foetal death was substantially greater in pregnant ladies with TSH levels higher than 6.0 mIU/L equated to controls (3.8% vs. 0.9%). There are a variety of additional complications that have been related to SH, including pre-eclampsia, prenatal hypertension, impulsive delivery, minimal birth mass, placental breaking off, and postpartum haemorrhage. Obstetrical issues should also be taken into consideration; however, the findings of 3 substantial research that studied the link between the two had contradictory conclusions. While Casey et al. (2005) found a considerable correlation between SH and complications, Cleary-Goldman et al. (2008) discovered a correlation between complications and hypothyroxinemia and autoimmunity, and (Mannisto et al., 2009) found a correlation between complications and thyroid autoimmunity regardless of how well the thyroid was functioning.

In addition, two studies on the effects of interventions have been published. In the first trial, which Negro et al. (2006), there were around one thousand pregnant women who participated Their TSH levels fluctuated from 0.3 to 4.2 mIU/L, and they all had positive thyroperoxidase antibodies. One of the groups was given treatment with levothyroxine, whereas the other group did not get any kind of medication. There was also a 3rd group of euthyroid antibody-negative girls who worked as the control group in this study. Despite the study's limitations, it was observed that administering treatment to women who tested positive for antibodies resulted in a reduction in the rate of premature births and miscarriages. The second prospective investigation examined two techniques of diagnosing and treating thyroid problems. Universal screening, case-finding. For the study, they were successful in recruiting two groups of women who suffered from thyroid dysfunction (SH accounting for most cases). Of these women, one group was given LT4 medication, while the other group was not. Patients were given LT4 medication if their TSH levels were above 3.0 mIU/L in the 2nd and 3rd trimesters, as well as above 2.5 mIU/L in the 1st trimester. When obstetrical and neonatal snags (as a composite outcome) were considered, the research found that non-treated ladies had a substantially higher rate of difficulties than treated and healthy women did. This was the same regardless of whether the women had previously given birth (TPOAb negative). Soon, Lazarus JH will publish yet another study that is of critical significance. The research project known as "CATS" (Controlled Antenatal Thyroid Screening) examined

pregnant ladies beginning as soon as the sixteenth week of their pregnancies. Women whose amounts of TSH were greater than 97.5 percentiles or whose levels of free thyroxine (FT4) were lower than 2.5 percentiles were split into 2 groups; one of these groups was given LT4. The primary takeaways from the research were the average IQ of children aged 3.5 years old as well as the percentage of children who had IQs of 85 or higher.

In September 2010, during the International Thyroid Congress in Paris, initial data showed no IQ difference between the two groups. When secondary outcomes, such as on-treatment analyses, were considered, the proportion of untreated kids with IQs below 85 was higher (15.6% vs. 9.2%, p = 0.009). This was corroborated by the lack of a significant difference between the groups. There have only been two prospective studies that have shown that treating SH pregnant women can lessen the risk of complications, and there have been no further prospective randomised trials that have either validated or disproved these results. In this scenario, it might be reasonable to consider treating SH with levothyroxine.

Thyroid autoimmunity: The presence of positive thyroid antibodies is the autoimmune illness that is far and away the most common and accounts for ten percent of all tests conducted on women of reproductive age. Stagnaro-Green et al. (1990) published the first research that demonstrated a relationship between miscarriage and the presence of thyroid antibodies in their study. Through the examination of the progression of 550 pregnancies, the researchers made the unintended discovery that persons who tested positive for Tg-Ab or TPOAb had a 2 times higher rate of miscarriage compared to those who tested negative for these antibodies (17% versus 8.4%). There have been a significant number of cohort and case-control studies recently made public. Cohort studies looked at women who had experienced repeated miscarriages, infertility, and those who did not fall into any of these categories. Women who had infertility and recurrent miscarriages were also the focus of case-control studies. A rationalized meta-analysis that included 31 studies discovered that ladies who have thyroid antibodies possess a 1.8-fold bigger risk of having a miscarriage, according to the findings of cohort studies, and a 4-times bigger risk of miscarriages, rendering to the findings of case-control studies (12,126 individuals). Ladies who had thyroid antibodies had TSH levels that were 0.51 mIU/L higher, and they were 0.87 years older than women who did not have thyroid antibodies (Thangaratinam et al., 2011). However, this difference was not statistically significant. There have been reports containing contradictory information regarding the potential link between thyroid autoimmunity and the loss of a pregnancy in women who are undergoing IVF treatment (Poppe et al., 2003). A meta-analysis of four studies that included patients undergoing in vitro fertilisation found that antithyroid antibodies were connected to a greater incidence of miscarriage (RR (Relative risk ratio) 1.99; 95% CI (confidence interval): 1.42-2.79) (Toulis et al., 2010). Glinoer et al. (1994) published the first study about the connection between thyroid autoimmunity and premature delivery, numerous studies have been published on this subject, also with contradictory findings. These studies have been published in a variety of academic journals. It was discovered by Ghafoor et al. (2006) that women who have thyroid antibodies had a fourfold greater risk of delivering birth prematurely. On the other hand, Iijima et al. (1997) did not find a significant connection between the two. In the larger study conducted by Haddow et al. (2014) which included over 10,000 patients (OR (Odd ratio): 1.18), the association was found to be positive. Despite its lack of significance, the link was found to exist. Finally, two separate meta-analyses concluded that an autoimmune thyroid condition is related with an elevated risk of preterm birth that is approximately 1.5–2 times higher (Negro, 2011). Despite research providing inconsistent findings due to changes in participant count, ethnicity, antibody dosage, and study design, an updated meta-analysis reveals that there is a relationship between thyroid autoimmunity, miscarriage, and early birth (the majority of which are retrospective). One of the possible causes for these correlations could be a diminished functional reserve, and another could be an unfavorable environment for the auto-immune system. Two new areas of research have surfaced in recent years: the intravenous administration of immunoglobulins and the injection of LT4 (IVIG). Negro et al. (2006) conducted a study in which euthyroid patients who tested positive for anti-TPO took levothyroxine and participated in a prospective, randomized, interventional trial. TPOAb positivity was found in 11.7 percent of the 984 participants who were included in the study during the first trimester of pregnancy. Patients diagnosed with thyroid autoimmunity were split into two groups; one of the groups got treatment with levothyroxine. When compared with the untreated group, the treated group saw a considerably reduced rate of premature birth (22.4% against 7%, p 0.05), as well as a significantly lower rate of miscarriage (3.5% versus 13.8%). According to the findings of (Negro et al., 2005) study, using levothyroxine could be beneficial for women who are undergoing assisted reproductive technology and who have thyroid antibodies (ART). There was no discernible difference in the number of miscarriages that occurred between the levothyroxine-treated group and the placebo group because only a limited number of patients were enrolled. Four brief, non-randomized studies have been published on the use of IVIG for the prevention of recurrent pregnancy loss in women who have anti-thyroid antibodies. These studies have been conducted on pregnant women. One study compared levothyroxine to IVIG and found that the levothyroxine-treated group had a greater rate of term delivery (92% vs 0% p 14 0.001) Another study found that there was a highly significant improvement in live birth compared with the control group (92% vs 0% p 14 0.001) Both of these findings were based on comparing the treated group to the control group. The present data on the efficacy of IVIG in reducing the rate of miscarriage are not very clear because the trials were only conducted with a small number of participants and there was no randomization. The findings of the levothyroxine or IVIG studies should be considered preliminary. Even though they yielded promising results, it is not possible to draw any definitive conclusions due to the limitations of the studies and the small number of patients that were recruited for each of the studies (Stricker et al., 2000; Vaquero et al., 2000; Kiprov et al., 1996).

Isolated hypothyroxinemia: Isolated hypothyroxinemia in pregnancy is defined as a TSH level that falls within the normal range but an FT4 result that is lower than the 2.5th percentile. Consuming insufficient amounts of iodine is the primary factor in iodine deficiency (IH). The National Health and Nutrition Examination Survey 2003–2004 found that the population in the United States had an average urine iodine concentration (UIC) of 160 µg/L, but that 11.3% of the population had low UIC levels of less than 50 µg/L. This information was gleaned from the population's urine samples. Among addition, the level of UI in all women of reproductive age (whether they were pregnant) was 139 µg/L, and only 15.1% of women had a level of UI that was lower than 50 µg/L (Cladwell et al., 2011). Iodine deficiency in Europe can manifest itself in a wide variety of ways, but it continues to be a significant problem in the public health of many countries, particularly those that do not mandate the consumption of iodine supplements. As part of the Controlled Antenatal 40 Study, iodine status was determined for a total of 261 hypothyroid/hypothyroxinemic and 526 euthyroid women from Turin (Italy), as well as 374 hypothyroid/hypothyroxinemic and 480 euthyroid women from Cardiff (Wales). The median urine iodine level was quite low in Cardiff (98 g/L) and Turin (52 g/L), respectively (Pearce et al., 2012).

The incidence of IH was shown to vary greatly from study to study, ranging anywhere from 1.3% to 25.4% according to the data from these studies (Karassas et al., 2010). These discrepancies are largely due to the amount of iodine mothers consume daily, but the precision of the FT4 dose method is also a problem. FT4 immunoassays are essentially FT4 estimate tests that do not directly detect FT4 and are known to be sensitive to changes in

binding proteins, which take occur during pregnancy. These tests are now commercially available and can be purchased. A study of different methods revealed that some methods generated results that were higher than their non-pregnant reference values, but albumin-dependent immunoassays had a large negative bias with up to fifty percent of subnormal values (Kahric-Janicic et al., 2007; Soldin et al., 2004; Roti et al., 1991). Because of all these factors, it is imperative that one always exercise extreme caution before interpreting the incidence rate of IH (Anckaert et al., 20110; Soldin et al., 2011).

A substantial reduction in thyroid hormone during the early stages of fetal development might cause irreversible brain damage. The negative effects of iodine shortage and maternal hypothyroxinemia on fetal brain development are likely due to a decrease in the amount of thyroxine transmitted from the mother to the growing fetus before fetal thyroid function begins. During the first trimester, when the fetus is completely reliant on maternal T4, the fetal T4 concentrations are roughly one-third of those of the mother's, even though the fetal T4 concentrations are approximately one hundred times lower than the T4 concentrations in the mother's serum (Morreale et al., 2000).

In two separate studies, Pop et al. (1999, 2003) investigated whether there was a correlation between the FT4 readings of pregnant mothers and the psychomotor development of their children. Children born to mothers who were infected with IH had worse scores on the Bayley Psychomotor Developmental Index (PDI), as well as lower scores in terms of mental and motor development. The investigations also revealed that reduced FT4 levels in the mother during the latter stages of pregnancy had no influence on the neurodevelopment of the child.

These findings are supported by those of Vermiglio et al. (2004) who found that children whose mothers had hypothyroxinemic levels had greater rates of attention deficit hyperactivity disorder as well as worse IQ scores than controls.

A recent study that was conducted in China indicated that the cognitive and motor scores of children born to mothers who had subclinical hypothyroidism, hypothyroxinemia, and high TPOAb titers at 16–20 weeks of gestation had significantly lower mean scores than those of children born to controls. Independently, lower motor scores and lower IQ evaluations in the children were associated with elevated levels of maternal TPOAb titers, decreased levels of maternal serum TT4, and increased levels of maternal serum TSH (Li et al., 2010).

Henrichs et al. (2010) investigated the connection between a mother's low thyroid hormone levels and her child's cognitive ability when the child was young. According to the authors' analysis of a cohort consisting of 3659 infants and their mothers, maternal TSH was not associated with cognitive outcomes, but an increase in maternal FT4 was associated with a decreased risk of expressive language delay at 30 months. This was determined by looking at the correlation between the two variables. In addition, there was a correlation between mild and severe maternal hypothyroxinemia and an increased risk of expressive language delay at the ages of 18 and 30 months. The presence of severe maternal hypothyroxinemia was also associated with an increased likelihood of nonverbal cognitive impairment. According to the research, hypothyroidism, which is mostly brought on by an insufficient intake of iodine, has a harmful impact on the development of the brain in embryos. Long-term follow-up investigations are required to ascertain whether this neurological delay persists into later life. Two investigations that were carried out in Spain demonstrated both the negative consequences of an iodine shortage as well as the helpful advantages of an appropriate iodine supplementation that was started early in the pregnancy. Berbel et al. (2009) observed that a delay of 6–10 weeks in iodine supplementation (200 µg of potassium iodide) enhanced the risk of neurodevelopmental delay in the offspring of hypothyroxinemic mothers who were pregnant at the beginning of their pregnancies. Velasco et al. (2009) When compared to newborns whose mothers had not received iodine supplementation, the cognitive development of infants aged 3 to 18 months whose mothers had received 300 mg of potassium iodide during the first trimester of pregnancy (133 cases) was found to be significantly higher than that of infants whose mothers had not received the supplement (61 controls). Even though the collected data were not controlled for confounding factors and the study was not a randomized controlled trial, the results showed that children whose mothers had received an iodine supplement had a better psychometric assessment than controls. This was the case even though the study was not a randomized controlled trial. Awaiting the findings of the CATS, TSH, and TABLET trials, which should shed light on both the benefits and drawbacks of thyroxine therapy whenever they are published.

CONCLUSION

Untreated thyroid abnormalities are associated with an increased risk of unfavorable events, such as an increased chance of having a miscarriage, giving birth prematurely, or developing gestational hypertension. This is a commonly accepted fact. It is common for women of reproductive age to suffer from thyroid issues. In addition, autoimmune of the thyroid in general appears to be connected to complications such as miscarriage and premature delivery. It has not been conclusively determined whether a subclinical condition, more especially subclinical hypothyroidism, is a risk factor for undesirable outcomes. This is not the case with subclinical disease, as substantial data reveals clearly that overt dysfunctions (such as hyper- or hypothyroidism) have negative consequences on pregnancy. However, subclinical disease does have negative impacts. It is not yet clear whether or whether a replacement medication would be effective in treating a variety of additional illnesses, such as isolated hypothyroxinemia and thyroid autoimmunity in euthyroidism.

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