REVIEW

# Thyroid dysfunction in pregnancy

Khalid A El Baba[1]
Sami T Azar[2]

[1]Department of Internal Medicine, Division of Endocrinology, Bahrain Specialist Hospital, Manama, Bahrain; [2]Department of Internal Medicine, Division of Endocrinology, American University of Beirut-Medical Center, New York, NY, USA

**Abstract:** Timely treatment of thyroid disease during pregnancy is important in preventing adverse maternal and fetal outcomes. Thyroid abnormalities are very often subclinical in nature and not easily recognized without specific screening programs. Even mild maternal thyroid hormone deficiency may lead to neurodevelopment complications in the fetus. The main diagnostic indicator of thyroid disease is the measurement of serum thyroid-stimulating hormone and free thyroxine levels. Availability of gestation-age-specific thyroid-stimulating hormone thresholds is an important aid in the accurate diagnosis and treatment of thyroid dysfunction. Pregnancy-specific free thyroxine thresholds not presently available are also required. Large-scale intervention trials are urgently needed to assess the efficacy of preconception or early pregnancy screening for thyroid disorders. Accurate interpretation of both antepartum and postpartum levels of thyroid hormones is important in preventing pregnancy-related complication secondary to thyroid dysfunction. This article sheds light on the best ways of management of thyroid dysfunction during pregnancy in order to prevent any possible maternal or fetal complication.

**Keywords:** TSH, HCG, TBG

## Introduction

It is a very well known fact that thyroid diseases during pregnancy are related to maternal and fetal complications. In this article, the authors try to summarize the possible adverse outcomes of hypothyroidism and hyperthyroidism on the mother and fetus during gestation. They also shed light on the proper management of these conditions to avoid such complications.

## Physiology of maternal thyroid in pregnancy

The thyroid gland undergoes definite physiological changes during pregnancy. Moderate thyroid enlargement and increased vascularity occurs as a result of pregnancy hormone-induced glandular hyperplasia. Thyroid stimulation starts as early as the first trimester by human chorionic gonadotropin hormone (beta-HCG), which shares some structural homology with thyroid-stimulating hormone (TSH). There is also an estrogen-mediated increase in circulating levels of thyroid-binding globulin (TBG). Furthermore, there is a relative decline in the availability of iodide, secondary to the increased renal clearance and overall losses to fetus and placenta.[1]

Circulating TBG is known to increase 2–3-fold during pregnancy. Serum TBG increases a few weeks after conception and reaches a plateau during mid-gestation. The mechanism behind this increase involves increased hepatic synthesis and estrogen-mediated prolongation of TBG half-life from 15 minutes to 3 days.[2]

Correspondence: Sami T Azar
Department of Internal Medicine,
Division of Endocrinology and
Metabolism, American University of
Beirut-Medical Center, 8th floor,
3 Dag Hammarskjold Plaza, New York,
NY 10017, USA
Tel +961 3 234 250
Fax +961 1 365 189
Email sazar@aub.edu.lb

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Total thyroxine (T4) and total triiodothyronine (T3) concentrations increase sharply in early pregnancy and plateau early in the second trimester at concentrations 30%–100% greater than prepregnancy values, primarily following the rise in TBG. However changes in free T4 and T3 concentrations during pregnancy are controversial. Some authors have reported a decrease in free hormones, whereas others have reported no change or even an increase. Pregnant women in general have lower free-hormone concentrations at term than nonpregnant women.[3–5]

Beta-HCG has a mild thyrotropic activity and shares 85% sequence homology with TSH beta subunit. During the first trimester of pregnancy, beta-HCG is at its greatest concentration, while serum TSH drops. Thyroglobulin frequently increases during pregnancy reflecting an increased activity of the thyroid gland.[6]

## The physiology of fetal thyroid

The fetal thyroid gland begins concentrating iodine and synthesizing thyroid hormones after 12 weeks of gestation. Any requirement for thyroid hormones before this time is solely supplied by the mother. It is during the first trimester of pregnancy that the thyroid hormones are most important to fetal brain development. Still, significant fetal brain development continues considerably beyond the first trimester, making thyroid hormones important also later in gestation. Overt maternal thyroid failure during the first half of pregnancy has been associated with several pregnancy complications and intellectual impairment in the offspring. It is currently less clear whether milder forms of thyroid dysfunction have similar effects on pregnancy and infant outcomes.[7,8]

## Hypothyroidism

Untreated hypothyroidism is associated with pregnancy-induced hypertension, abruption, and postpartum hemorrhage plus an increase in frequency of low birth weight infants. Mild or subclinical hypothyroidism has been reported to increase the risk of impaired neurodevelopment in the offspring.[9–12] Hypothyroidism occurs in 2.5% of pregnancies; however, overt hypothyroidism only complicates 1–3 per 1000 pregnancies.[13] Symptoms of hypothyroidism can often be masked by the hypermetabolic state of pregnancy. During the early weeks of pregnancy, a fall in serum TSH and increase in free thyroxine (FT4) is observed that may confuse the diagnosis of hypothyroidism. The reference range for serum TSH in nonpregnant women is 0.45–4.5 mU/L, with more than 95% of individuals having a value below 2.5 mU/L. Gestation-age-specific TSH thresholds from large population-based studies seem to be the best way to increase diagnostic accuracy of hypothyroidism in pregnancy.[14]

In an article by Haddow et al, thyrotropin (TSH) was measured in stored serum samples collected from 25,216 pregnant women. A total of 47 women with serum thyrotropin concentrations at or above the 99.7th percentile of the values for all the pregnant women and 15 women with values between the 98th and 99.6th percentiles, inclusive, in combination with low thyroxine levels, and 124 matched women with normal values were located. Their 7–9-year-old children, none of whom had hypothyroidism as newborns, underwent 15 tests relating to intelligence, attention, language, reading ability, school performance, and visual–motor performance. The children of the 62 women with high serum thyrotropin (hypothyroid group) concentrations performed slightly less well on all 15 tests. Their full-scale IQ scores on the Wechsler Intelligence Scale for Children, third edition, averaged 4 points lower than those of the children of the 124 matched control women ($P = 0.06$, not significant). Of these 62 women with thyroid deficiency, 48 were not treated for the condition during the pregnancy. The full-scale IQ scores of their children averaged 7 points, significantly lower than those of the 124 matched control children ($P = 0.005$). The authors conclude that "undiagnosed hypothyroidism in pregnant women may adversely affect their fetuses; therefore screening for thyroid deficiency during pregnancy is warranted."[12]

Subclinical maternal hypothyroidism may be associated with poor pregnancy outcomes such as placental abruption, preterm birth, and low birth weight infants. Pregnancies in women with subclinical hypothyroidism were three times more likely to be complicated by placental abruption. Preterm birth, defined as delivery at or before 34 weeks of gestation, was almost 2-fold higher in women with subclinical hypothyroidism. Reports suggesting increased fetal wastage or subsequent neurodevelopmental complications in the offspring of women with mild hypothyroidism have prompted recommendations that levothyroxine be prescribed to restore the TSH level to the reference range. However, there are still no published intervention trials specifically assessing the efficacy of such treatment to improve neuropsychological performance in the offspring of women with subclinical hypothyroidism. Routine screening and treatment of subclinical hypothyroidism during pregnancy is not yet strictly recommended. National endocrinology organizations have greatly emphasized the need for large clinical trials to address this issue.[1,11,15]

## Management

Treatment should be initiated as soon as the diagnosis of overt hypothyroidism is made. The starting dose of levothyroxine is 0.10–0.15 mg/day (1–2 μg/kg/day) and should be adjusted every 4 weeks to keep the TSH at the lower end of normal. Women who are on levothyroxine at the beginning of pregnancy should have their dose increased by approximately 30% as soon as pregnancy is confirmed and have their TSH and free T4 levels checked every 8 weeks. Levothyroxine replacement requirements most likely will increase as the pregnancy progresses. This increase can be secondary to the increased demand for T4 with the progression of pregnancy as well as its inadequate intestinal absorption caused by accompanied ferrous sulfate replacement in most pregnant ladies. Thus levothyroxine and ferrous sulfate dosages should be spaced at least 4 hours apart.[16]

## Follow-up after delivery

After delivery, levothyroxine therapy should be returned to the prepregnancy dose, and the TSH checked 6–8 weeks postpartum. Breastfeeding is not contraindicated in women treated for hypothyroidism. Levothyroxine is excreted into breast milk, but levels are too low to alter thyroid function in the infant or to interfere with neonatal thyroid screening programs. Periodic monitoring with an annual serum TSH concentration for the mothers is generally recommended.

## Hyperthyroidism

Hyperthyroidism is less common than hypothyroidism, as it occurs in only 0.2% of pregnancies. Some of the signs and symptoms of hyperthyroidism may mimic the normal physiological changes of pregnancy. Severe maternal hyperthyroidism is associated with increased risk of stillbirth, preterm delivery, intrauterine growth restriction, preeclampsia, and heart failure. Thyrotoxicosis at conception also increases the risk for spontaneous abortion.[17]

The most common cause of hyperthyroidism in pregnancy is Graves' disease, which constitutes up to 95% of the cases. Other causes include gestational trophoblastic disease, toxic multinodular goiter or solitary toxic adenoma, and viral thyroiditis. In Graves' disease, there does not seem to be any clinical correlation between the levels of antibody activity and disease severity. These antibodies, however, can cross the placenta and cause neonatal Graves' disease.

Gestational transient hyperthyroidism (GTH) is associated with hyperemesis gravidarum, commonly presenting with elevated levels of FT4 and suppressed levels of TSH. This change is believed to be related to beta-HCG stimulation of the thyroid gland. GTH occurs in the first trimester in women who do not have a history of autoimmune disease. The thyroid gland is usually not enlarged. The resolution of symptoms parallels the decline in beta-HCG levels. Patients rarely need treatment, but beta blockers can be used for symptomatic relief.[19,20]

Subclinical hyperthyroidism is defined as a serum TSH concentration below the lower limit of reference range, with free T4 and free T3 concentrations within normal reference range. It affects up to 1.7% of pregnant women. Long-term adverse consequences may include osteoporosis, cardiovascular morbidity, and progression to overt thyrotoxicosis. However, subclinical hyperthyroidism in pregnancy has not been found to be associated with adverse outcomes. Thus, currently there is insufficient evidence in support of treating pregnant women with subclinical hyperthyroidism. The potential for long-term adverse sequelae in the mothers suggests that these women may benefit from periodic surveillance later in life.[1,11]

## Management

The goal of treatment of hyperthyroidism during pregnancy is to keep the patient euthyroid, with the FT4 level in the upper limit of normal range so as not to cause fetal or neonatal hypothyroidism. Propylthiouracil (PTU) is the drug of choice, but methimazole is also frequently used. Both are thionamides, which act by inhibiting the iodination of thyroglobulin and preventing thyroglobulin synthesis by competing with iodine for the enzyme peroxidase. PTU is given in a dose of 100–150 mg/8 hours (300–450 mg/day). It may take 2–4 weeks from the start of treatment to see a clinical change. Free T4 levels should be monitored monthly. After achieving an euthyroid state, the dosage of PTU should be tapered to minimize fetal exposure to thionamides. If PTU or methimazole are contraindicated, beta blockers may be used to control the adrenergic symptoms of thyrotoxicosis, particularly tachycardia. In addition, beta blockers block the peripheral conversion of T4 to T3. Propranolol in a dose of 20–40 mg 2–3 times a day is commonly used. In acute cases, intravenous esmolol (up to 200 g/kg/minute) may be used to maintain a heart rate of less than 90 beats/min. Surgery should be reserved for the most severe cases. Radioactive iodine is an absolute contraindication in pregnancy. It is also important to continue medications throughout the postpartum period, as exacerbation of Graves' disease is common during this time. PTU and methimazole are considered compatible with breastfeeding.[11,17,18]

## Conclusion

It is well documented that thyroid disorders are associated with maternal and fetal complications during gestation. This present paper has discussed the possible ways to prevent and manage these outcomes to assure a safe and proper ending to pregnancy.

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Casey B, Leveno K. Thyroid disease in pregnancy. *Obstet Gynecol*. 2006; 108(5):1283–1292.
2. Skjoldebrand L, Brundin J, Carlstrom A, Pettersson T. Thyroid associated components in serum during normal pregnancy. *Acta Endocrinol*. 1982; 100(4):504–511.
3. Kurtz A, Dwyer K, Ekins R. Serum free thyroxine in pregnancy. *Br Med J*. 1979;2(6189):550–551.
4. Boss AM, Kingstone D. Further observations on serum free thyroxine concentrations during pregnancy. *Br Med J (Clin Res Ed)*. 1981;283:584.
5. Hopton MR, Ashwell K, Scott IV, Harrop JS. Serum free thyroxine concentration and free thyroid hormone indices in normal pregnancy. *Clin Endocrinol*. 1983;18:431–437.
6. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev*. 1997; 18(3):404–433.
7. de Escobar GM, Obregón MJ, del Rey FE. Maternal thyroid hormones early in pregnancy and fetal brain development. *Best Pract Res Clin Endocrinol Metab*. 2004;18:225–248.
8. Kilby MD. Thyroid hormones and fetal brain development. *Clin Endocrinol*. 2003;59:280–281.
9. Glinoer D, Fernandez-Soto ML, Bourdoux P, et al. Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. *J Clin Endocrinol Metab*. 1991;73:421–427.
10. Glinoer D, Riahi M, Grun JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. *J Clin Endocrinol Metab*. 1994;79:197–204.
11. Abalovich M, Amino N, Barbour LA, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2007;92(8 Suppl): S1–S47.
12. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med*. 1999;341:549–555.
13. Allan WC, Haddow JE, Palomaki GE, et al. Maternal thyroid deficiency and pregnancy complications: implications for population screening. *J Med Screen*. 2000;7:127–130.
14. Dashe JS, Casey BM, Wells CE, et al. Thyroid-stimulating hormone in singleton and twin pregnancy: importance of gestational age-specific reference ranges. *Obstet Gynecol*. 2005;106(4):753–757.
15. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid*. 2002;12:63–68.
16. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med*. 2004;351:241–249.
17. Weetman A. Graves' disease. *N Engl J Med*. 2000;343:1236–1248.
18. Luton D, Le Gac I, Vuillard E, et al. Management of Graves' disease during pregnancy: the key role of fetal thyroid gland monitoring. *J Clin Endocrinol Metab*. 2005;90:6093–6098.
19. Albaar MT, Adam JM. Gestational transient thyrotoxicosis. *Acta Med Indones*. 2009;41(2):99–104.
20. Goodwin TM, Montoro M, Mestman JH, Pekary AE, Hershman JM. The role of chorionic gonadotropin in transient hyperthyroidism of hyperemesis gravidarum. *J Clin Endocrinol Metab*. 1992;75:1333–1337.