Chapter 1

Pregnancy and Thyroid Diseases

Ahmet Dundar[1]

Enes Karaman[2]

Abstract

Early diagnosis and effective treatment of thyroid diseases during pregnancy are the greatest priority. A delay in treatment can have severe adverse effects on the mother and unborn child.

Thyroid-stimulating hormone (TSH) and T4 levels are checked as the first test to evaluate thyroid function during pregnancy. TSH levels are elevated, and T4 levels are depleted in hypothyroidism. About 2.5% of pregnant women experience it. Hypothyroidism, if left untreated, can cause neurological issues and developmental delays. 0.1-0.4% of pregnant women have hyperthyroidism. Graves' disease accounts for 80-85% of cases in pregnant women. Functional adenoma, thyroiditis, and thyrotoxicosis factitia are additional causes of hyperthyroidism in pregnant women besides Graves' disease (use of high-dose thyroxine hormone). Abortion, pre-eclampsia, premature birth, retardation in the baby's normal development, and intrauterine fetal death are possible outcomes if a pregnant woman with hyperthyroidism is not treated effectively.

Levothyroxine (LT4), used in treating hypothyroidism in pregnant women, should be started as soon as possible. During the follow-up period, it is appropriate to measure TSH every 6-8 weeks after the initiation of treatment. TSH levels should be maintained between 0.5 and 2.5 mU/L during the first trimester of pregnancy and between 0.5 and 2.5 mU/L during the second and third trimesters.

Medical therapy is the first line of treatment for hyperthyroidism during pregnancy. The goal of treatment is to maintain a serum fT4 level close to the upper limit of average values using the smallest effective dose of antithyroid medication. Due to potential side effects, treatment with propylthiouracil is preferred among antithyroid drugs. Propylthiouracil can be started at 100–150 mg per day. With 4-6 weeks of follow-up, the serum fT4 level to be used in the follow-up should be checked.

1 Dr., Savur Prof. Dr. Aziz Sancar District State Hospital, Internal Medicine Clinic, drahmetdundar@hotmail.com, Orcid: 0000-0002-8106-7447

2 Dr., Savur Prof. Dr. Aziz Sancar District State Hospital, Gynecology, and Obstetrics Clinic, dr.eneskaraman@gmail.com, Orcid: 0000-0003-1459-0606

https://doi.org/10.58830/ozgur.pub91.c380

1. INTRODUCTION

While thyroid problems can negatively affect both mother and fetus during pregnancy, early diagnosis, follow-up, and therapy are crucial. Otherwise, a situation with severe consequences for the mother and baby may occur. Free T4 and TSH are utilized in normal pregnancy to evaluate thyroid function.

During pregnancy, the thyroid gland in women undergoes several physiological changes. Human chorionic gonadotropin (hCG), which rises in the first trimester, has a comparable action on TSH receptors and produces an increase in serum total thyroxine (T4) and tri-iodothyronine (T3) levels. Thyroid stimulating hormone levels in the serum fall (1). Serum levels of thyroxine-binding globulin (TBG) are also elevated in pregnant women with high estrogen levels. By binding to total thyroxine (T4) in the circulatory system, serum thyroxine-binding globulin decreases fT4 levels (2). As a result of these modifications, tT4, and tT3 levels continue to increase until the eleventh week of pregnancy, remain steady in the weeks that follow, and remain comparable until the conclusion of the third trimester (1,2). Iodine, a necessary component of thyroid production, increases renal excretion due to elevated GFR (glomerular filtration rate) in pregnant women. As a result of the use of thyroid hormones in physiological synthesis and the use of iodine in the mother's circulation in the fetus, there is also an increase in the need for iodine in pregnant women. Hence, during pregnancy, the serum amount of iodine falls (3). As a result, thyroxine (T4) levels in pregnant women decline, thyroid stimulating hormone (TSH) rises, and the growth of the thyroid gland becomes more noticeable in pregnant women. The risk of prenatal hypothyroidism increases in the fetus, which is more susceptible to the consequences of iodine deficiency (4,5).

The fetus needs the mother's transplacental thyroxine hormone in the first trimester of pregnancy (1). As a result, changes in thyroid functions that may occur in pregnant women may negatively impact not only the mother but also the normal physiological development of the fetus. Hypothyroidism, which occurs at a rate of 25 per 1000 in pregnant women, is caused by increased TSH value. Overt hypothyroidism is an increased TSH value and a decreasing fT4 level (6,7). The baby may experience neurological issues and developmental delay due to hypothyroidism (8,9). On the other hand, subclinical hypothyroidism is a state in which standard free T4 is accompanied by an increase in Thyroid Stimulating Hormone levels (10). Subclinical hypothyroidism occurs at a rate of 40–85 per 1000 in the general population but only 20–50 per 1000 in pregnant women (11). Subclinical hypothyroid-

ism, like hypothyroidism, has been linked to neuropsychological issues in newborns in the future, according to specific research (12,13).

In pregnant women, the prevalence of hyperthyroidism ranges from 0.1% to 0.4%. (14). Graves' disease is the most common cause of hyperthyroidism in pregnant women (15). The prevalence rate of Graves' illness ranges from 80 to 85%. Besides Graves' illness, functional adenoma, thyroiditis, and thyrotoxicosis factitia are other causes of hyperthyroidism in pregnant women (15). Abortion, pre-eclampsia, early birth, impairment in the baby's normal development, and intrauterine fetal mortality are risks for a pregnant woman with hyperthyroidism (1,14).

2. EVALUATION OF THYROID FUNCTIONS IN PREGNANCY

When evaluating thyroid functions in a pregnant woman, it is necessary to consider the periods of pregnancy. Because the physiological changes that occur differ according to the trimester of pregnancy, TSH measurement should be done first in all pregnancies. Values of 0.1-2.5 mU/L for the first trimester, 0.2-3.0 mU/L for the second trimester, and 0.3-3.0 mU/L for the third trimester can be used (16).

3. HYPOTHYROID IN PREGNANCY

3.1.Diagnosis

According to reports, the prevalence of hypothyroidism during pregnancy ranges from 0.3% to 0.5% for overt hypothyroidism and 2% to 4% for subclinical hypothyroidism. In areas where adequate iodine is consumed, autoimmune thyroid disease is the most prevalent cause of hypothyroidism during pregnancy (17,18).

The symptoms of hypothyroidism can be mimicked by pregnancy. Symptoms include cramping muscles, anxiety, constipation, weariness, and weight gain. Symptomatic similarities can make diagnosing hypothyroidism during pregnancy challenging. Thus, every pregnant woman should be asked to undergo thyroid screening (19,20).

A pregnant woman with increased TSH should also have her fT4 level evaluated. Reduced T4 levels accompanying high TSH (>2.5 mU/L) levels during pregnancy suggest overt hypothyroidism. A patient with a 2.5-10 mU/L TSH level and an average fT4 level is diagnosed with subclinical hypothyroidism.

3.2. Treatment

Pregnant women should receive treatment as soon as feasible for hypothyroidism. The aim is to make the pregnant woman's euthyroid as soon as possible (21). In treating hypothyroidism, levothyroxine (LT4) is commonly utilized. The physiological changes noted during pregnancy increase the need for thyroid hormone in pregnant women with hypothyroidism. There is an increase of 30-50% in the hormone output of the thyroid gland. Due to this requirement in pregnant women, mothers diagnosed with hypothyroidism should increase their Levothyroxine dosage. Given the lengthy half-life of thyroid hormones, increasing the daily dose by 25-30% would be prudent. Monitoring TSH at 6-8 weeks after commencing the treatment is suitable. TSH should be maintained for treatment between 0.5 and 2.5 mU/L. Serum Thyroid Binding Globulin-, T4, and T3 levels revert to pre-pregnancy levels 4-6 weeks after birth. The levothyroxine dose should be readjusted by looking at thyroid functions within 6-8 weeks following birth (22).

4. HYPERTHROID IN PREGNANCY

4.1.Diagnosis

With a rate of 1-4 in 1000 pregnancies, hyperthyroidism is present. The most common cause of hyperthyroidism during pregnancy is Graves' disease with a rate of 80-85%. Thyroiditis, functioning adenoma, and excess thyroid hormone are further causes. Toxic nodular goiter is less common (23). An increased fT4 level and a decreased TSH characterize overt hyperthyroidism.

In contrast, subclinical hyperthyroidism is accompanied by normal fT4 levels despite a lowered TSH value. Diagnosing hyperthyroidism during pregnancy is a challenging illness. The clinical manifestations include tachycardia, heat intolerance, hand tremor, profuse perspiration, anxiety, weight loss, and irritability. These symptoms might also be noticed owing to pregnancy. The two most significant indicators of thyroid disease are the absence of weight gain despite an increase in hunger during pregnancy and a resting heart rate of more than 100 beats per minute (23). While these symptoms can be observed during a normal pregnancy, the diagnosis may be delayed. In addition, the fact that the reference values for thyroid function tests vary from trimester to trimester during pregnancy makes this diagnosis considerably more challenging.

Pregnancy and delivery may be impacted by hyperthyroidism. In these pregnancies, the risk of spontaneous abortion, pre-eclampsia, preterm birth, intrauterine growth retardation, low birth weight, and stillbirth also rose

(24). The connection between subclinical hyperthyroidism and worse obstetric outcomes could not be established (25). Physiological changes, observations, and tests in the first trimester of pregnancy may mimic thyrotoxicosis, in which case no treatment is necessary.

Gestational hyperthyroidism (hCG-induced temporary hyperthyroidism) and Graves' disease are the two most common causes of hyperthyroidism in regular thyroid function tests. Gestational hyperthyroidism is a disorder that occurs during the first trimester of pregnancy and is frequently asymptomatic and treated solely with TSH suppression. It is caused by an increase in hCG during early pregnancy, and no harmful pregnancy result is anticipated. Anti-thyroid medication treatment is not necessary.

Serum Tsh levels below 0.1 mU/L or below 0.01 mU/L indicate a diagnosis of hyperthyroidism. The fT4 level should be evaluated if the TSH level is less than 0.1 mU/L. If T4 levels are normal, T3 levels can be measured. If the free thyroid hormone levels and TSH are inconsistent with clinical symptoms, the total T4 level should be determined. The thyrotropin receptor antibody (TRAb) test is 95% positive in Graves' disease. It can be used when a clinical diagnosis cannot be made for a patient. If there are classic clinical indications of the disease (ophthalmopathy) and/or TRAb positive, the diagnosis of Graves' disease is manageable.

4.2. Treatment

To prevent maternal, fetal, and neonatal problems, hyperthyroidism must be treated during pregnancy. Graves' disease might spontaneously remit in the second and third trimesters of pregnancy. In the majority of individuals, the anti-thyroid medication can be discontinued. Medical treatment is the initial method of choice for treating hyperthyroidism during pregnancy. The goal of treatment is to reduce the serum fT4 level to the upper limit of the reference values as quickly as feasible and to maintain it at this level with the lowest dose of anti-thyroid medication therapy.

Anti-thyroid medications cross the placenta. Because methimazole in pregnancy has been linked to embryopathy and cutis ablation, propylthiouracil treatment is suggested. -Blocker therapy can manage symptoms during pregnancy at low doses for brief periods. It should only be used for a few weeks. Prolonged use may result in miscarriage and fetal growth retardation, and use during late pregnancy may result in newborn hypoglycemia, apnea, and bradycardia. During pregnancy, PTU can be administered at a dose of 100 to 150 mg per day. Dose adjustments should be made to maintain the serum fT4 level at or near its maximum. High doses of anti-thy-

roid medications might cause fetal hypothyroidism and dose goiter. Serum fT4 levels should be maintained near the standard upper limit, and patients should be monitored at frequent intervals (26). The serum fT4 level should be tested every 4 to 6 weeks for the whole pregnancy. TSH serum levels return to normal within 6-8 weeks (26). Since it is known that the serum TSH level may remain suppressed for a long time, TSH should not be used as a foundation for follow-up. Even if the patient achieves euthyroid status, anti-thyroid medications should not be removed until 32-34 weeks have passed due to the danger of relapse (27). It is advised to check AST, ALT, and hemoglobin with thyroid hormones. With treatment with thionamide group medicines, transient leukopenia can occur at a rate of 10%. It typically does not necessitate discontinuing medication therapy. Agranulocytosis occurs in roughly 0.2% of patients. Drug therapy must be stopped for agranulocytosis. Agranulocytosis appears suddenly. It is independent of drug dose. Hence, recurrent leukocyte counts are unnecessary during treatment (27). The end of the second trimester is the ideal time for a thyroidectomy. Although it is the most predictable time, there is a risk of premature birth ranging from 4.5 to 5.5%. Thyroid surgery is contraindicated in the first trimester due to the risk of teratogenicity and fetal loss from the anesthesia used, and in the third trimester due to the risk of premature birth (29). Throughout pregnancy, radioactive iodine reaches the placenta and destroys fetal thyroid tissue. Pregnancy is categorically prohibited from using it (28).

In patients diagnosed with Graves' disease during pregnancy, TRAb measurement should be performed at the time of diagnosis; if it is high, pregnant women should be constantly monitored, and the third-trimester antibody level should be assessed. A thorough fetal examination and ultrasonography (USG) should be undertaken in pregnant women who are found to be overweight. Owing to the placental transmission of antibodies, inhibiting antibodies may cause fetal hypothyroidism, and increasing antibodies may cause newborn hyperthyroidism (1-2%). In the postpartum period, the risk of recurrence and postpartum thyroiditis in the mother is significantly higher than average (30,31).

5. THYROID NODULES IN PREGNANCY

Thyroid nodules are widespread in the community. Sonographic imaging can detect thyroid nodules at 20–76%. These nodules, however, have a 5% malignancy rate (32-34). Due to the physiological changes during pregnancy, the size of the thyroid gland and its nodules increase. In pregnant and non-pregnant women, the suspicion of thyroid cancer is increased

by the rapid expansion of the nodule, compression symptoms, a history of radiotherapy to the head and neck, and a family history of thyroid cancer (33-35). Ultrasonography should be used to find nodules. Examining the characteristics of the nodule is necessary. Regardless of the gestational week, a thyroid fine-needle aspiration biopsy (FNAB) should be performed if the nodule has worrisome signs such as uneven borders, hypoechogenicity, increased intra-nodular blood supply, and microcalcification and if the nodule size is 10 mm or greater (36,37).

10% of thyroid malignancies are detected during pregnancy or within the first year of life. Papillary microcarcinoma is the most prevalent histological subtype (38). A study conducted in California during 1991-1999 revealed that the prevalence of thyroid cancer was 14.4/100.000 in pregnancy. The most prevalent kind of papillary cancer was discovered (39). The patient and the fetus are at considerable risk when thyroid cancer is diagnosed during pregnancy. In terms of thyroid cancer monitoring and treatment, a balance must be struck so as not to jeopardize the mother's health, and obstetrics must also consider maternal and newborn health. Sonographic follow-up is advised for each trimester if thyroid cancer is discovered in a thyroid nodule by thyroid fine-needle aspiration biopsy in the early stages of pregnancy and the disease is localized to the thyroid gland. If the size is stable, the surgery can be conducted after delivery. If the occurrence of extrathyroidal extension and/or metastatic LAP in the neck region, it is recommended that early surgery be performed during pregnancy. If an ultrasonographic follow-up reveals a considerable thyroid gland enlargement, thyroid surgery may be indicated. Surgery should wait until after delivery if thyroid cancer is discovered in the second trimester of pregnancy. If surgery is to be postponed following birth, thyroid hormone suppression medication may be considered, and levothyroxine therapy is initiated to maintain the TSH level between 0.1 and 0.5 mU/L. Even if surgery is to be performed, levothyroxine treatment should begin following the procedure. Similarly, TSH levels should be maintained between 0.1 and 0.5 mU/L. The outlook is identical to that of non-pregnant women.

RESOURCES

1. Glinoer D, de Nayer P, Bourdoux P, Lemone M, Robyn C, van Steirteghem A, Kinthaert J, Lejeune B.Regulation of maternal thyroid during pregnancy.J Clin Endocrinol Metab 1990;71(2):27
2. Ain KB, Mori Y, Refetoff S. Reduced clearance rate of thyroxine- binding globulin (TBG) with increased sialylation: A mechanism for estrogen-induced elevation of serum TBG concentration. J Clin Endocrinol Metab 1987;65(4):689- 96
3. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 1997;18(3):404-33.
4. Brent GA. Maternal hypothyroidism: recognition and management. Thyroid 1999;9(7):661-5.
5. Brent GA. Maternal thyroid functions: interpretation of thyroid function tests in pregnancy. Clin Obstet Gynecol 1997;40(1):3-15.
6. Pop VJ, Kuijpens JL, Van Baar AL, et al. Low maternal free thyroxine concentrations during early pregnacy are associated with impaired psychomotor development in early infancy. Clin Endocrinol (Oxf) 1999;50(2):149-55.
7. Andersen S, Bruun NH, Pedersen KM, Laurberg P. Biologic variation is important for interpretation of thyroid function tests. Thyroid 2003;13(11):1069-78.
8. . Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A, Mitchell ML. Prevalance of thyroid defiency in pregnant women. Clin Endocrinol (Oxf) 1991;35(1):41-6.
9. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG. Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol 2005;105(2):239-45.
10. Casey BM. Subclinical hypothyoridism and pregnancy. Obstet Gynecol Surv 2006;61(6):415-20;.
11. 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(8):549-55.
12. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf) 2003;59(3):282-8.
13. Burrow GN. The management of thyrotoxicosis in pregnancy. N Engl J Med 1985;313(9):562-5.
14. Neale D, Burrow G. Thyroid disease in pregnancy. Obstet Gynecol Clin North Am 2004;31(4):893-905.

15. Ecker JC, Musci TJ. Thyriod function and disease in pregnancy. Curr Prob Obstet Gynecol Fertil 2000; 23(1): 109- 22.
16. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W; American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum.Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum.Thyroid. 2011;21:1081-125.
17. Delshad H, Azizi F. Thyroid and pregnancy. J Med Council Iran. 2008;26;392-408.
18. Negro R, Mestman JH. Thyroid disease in pregnancy. Best Pract Res Clin Endocrinol Metab 2001;25:927-943.
19. Cunningham F, Leveno KJ, Bloom SL, et al. Williams Obstetrics. 23 rd Ed. McGrraw-Hill Companies;2010.
20. Negro R, Formoso G, Mangieri T, et al. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab. 2006;91:2587-2591.
21. Casey BM, Leveno KJ. Thyroid disease in pregnancy. Obstet Gynecol 2006;108(5):1283-92.
22. Wier FA, Farley CL. Clinical controversies in screening women for thyroid disorders during pregnancy. J Midwifery Womens Health 2006;51(3):152-8.
23. Neale D, Burrow G. (2004). Thyroid disease in pregnancy. Obstet Gynecol Clin North Am; 31(4):893- 905.
24. Lazarus JH.Thyroid function in pregnancy.Br Med Bull 2011;97:137-48.
25. Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ, Cunningham FG. Subclinical hyperthyroidism and pregnancy outcomes.Obstet Gynecol 2006;107:337- 41.
26. Casey BM, Leveno KJ. Thyroid disease in pregnancy. Obstet Gynecol 2006;108(5):1283-92.
27. Mestman JH. Hyperthyroidism in pregnancy. Best Prac Res Clin Endocrin Metabol 2004;18(2):267-88.
28. Lin CH, Tapscott SJ, Olson JM. Congenital hypothyroidism (cretinism) in neuroD2-deficient mice. Mol Cell Biol 2006;26(11):4311-5.
29. Lao TT, Thyroid disorder in pregnancy. Curr Opinion Obstet Gynecol 2005;17(2):123-7.
30. Papendieck P, Chiesa A, Prieto L, et al. Thyroid disorders of neonates born to mothers with graves disease. J Pediatr Endocrinol Metab 2009;22:547-553.
31. McKenzie JM, Zakarija M. Fetal and neonatal hyperthyroidism and hypothyroidism due to maternal TSH receptor antibodies. Thyroid 1992;2:155-159.

32. Singer PA, Cooper DS, Daniels GH, et al. Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. American Thyroid Association. Arch Intern Med 1996;156:2165-2172.
33. Hegedus L. Clinical practice. The thyroid nodüle. N Engl J Med 2004;351:1764-1771.
34. Gharib H, Papini E, Paschke R, et al. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract 2010;16(Suppl 1):1-43
35. Kung AW, Chau MT, Lao TT, et al. The effect of pregnancy on thyroid nodule formation. J Clin Endocrinol Metab 2002;87:1010-1014
36. Burch HB. Evaluation and management of the solid thyroid nodüle. Endocrinol Metab Clin North Am 1995;24:663- 710.
37. Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with nodules and differentiated thyroid cancer. Thyroid 2006;16:10.
38. SEER Cancer Statistics Review, 1975-2010 (portal en internet). National Cancer Institute.Bethesda, MD. Updated November 2012 [viewed April 2013]. Available from: http:// seer.cancer.gov/csr/1975-2010.
39. Smith LH, Danielsen B, Allen ME, Cress R. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. Am J Obstet Gynecol 2003;189:1128-1135.