Endocrine Disorders During Pregnancy

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Hypothyroidism and Pregnancy

Rajesh Rajput

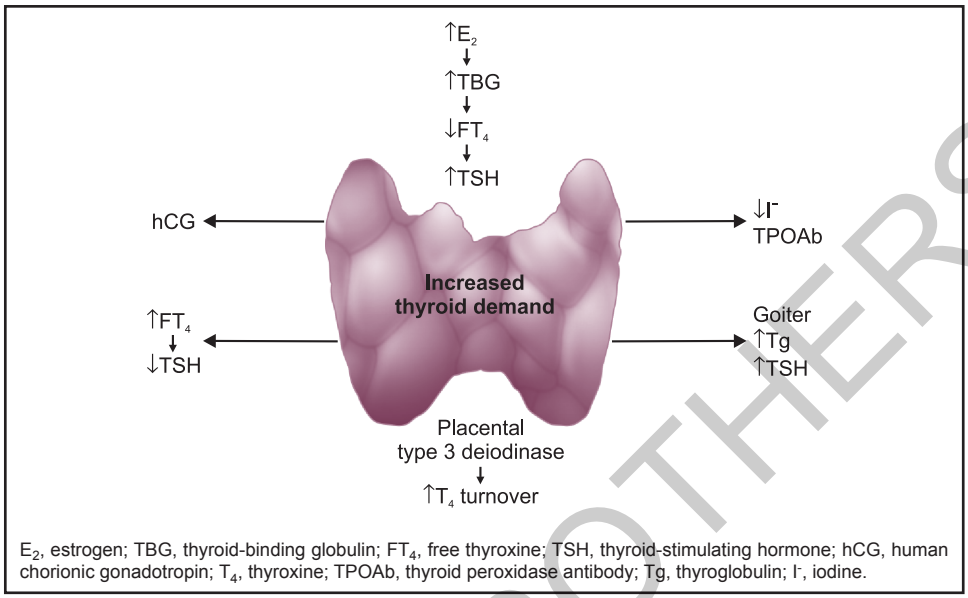
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INTRODUCTION

Hypothyroidism occurs commonly in the reproductive age group and is a well-recognized complication of pregnancy and puerperium. Various screening studies have shown that overt hypothyroidism is estimated to occur in 0.3–0.5% of pregnancies while subclinical hypothyroidism appears to occur in 2–3% of all pregnancies.[1] The etiology of hypothyroidism during pregnancy is not different from that in nonpregnant women. In iodine replete areas, Hashimoto's thyroiditis is the leading cause, while in iodine deficient areas, iodine deficiency itself is the most common cause of hypothyroidism. The various other less common causes include overtreatment of hyperthyroidism, concomitant use of various medications that alter the absorption of levothyroxine (LT_4), and various pituitary and hypothalamic disorders.[2,3]

NORMAL PHYSIOLOGY

Several alterations in thyroid physiology occur during various stages of pregnancy, which are completely reversible in the postpartum period. The most common alterations in thyroid physiology are increase in thyroid binding globulin (TBG), increase in glomerular filtration rate (GFR) resulting in increased iodide clearance, transplacental transfer of thyroxine (T_4) and iodine for normal fetal brain development, and increased placental degradation of thyroid hormones (Figure 4-1). As a result of these physiological adaptations, maternal thyroid hormone production increases and results in elevation of total triiodothyronine (T_3) and T_4 levels in normal pregnant women. If this compensation is inadequate or absent, it results in clinical or subclinical hypothyroidism during pregnancy.[2,3]



E_2, estrogen; TBG, thyroid-binding globulin; FT_4, free thyroxine; TSH, thyroid-stimulating hormone; hCG, human chorionic gonadotropin; T_4, thyroxine; TPOAb, thyroid peroxidase antibody; Tg, thyroglobulin; I^-, iodine.

Figure 4-1 Normal physiological alterations in thyroid functions during pregnancy.

EFFECT OF HYPOTHYROIDISM ON PREGNANCY OUTCOMES

Untreated hypothyroidism in the mother may cause microcytic anemia, preeclampsia, placental abruption, postpartum hemorrhage, and miscarriage.[4] Subclinical hypothyroidism has also been associated with spontaneous abortion and preterm labor.[4,5]

FETAL AND NEONATAL CONSEQUENCES OF MATERNAL HYPOTHYROIDISM

Before fetal thyroid gland starts functioning, the fetus is solely dependent on maternal iodine and T_4 transfer across the placenta for normal neuropsychological development. If maternal hypothyroidism is not recognized early in pregnancy, it may result in serious consequences ranging from decrease in intelligent quotient (IQ) to frank mental retardation. Development of fetal brain with neuronal multiplication, migration, and architectural organization occurs during first and second trimesters and is almost exclusively dependent on maternal T_4 levels. The later phases of brain development like glial cell multiplication, migration, and myelinization occur largely during third trimester and during first 3 years of life. It is dependent on fetal and neonatal thyroid hormone synthesis. Therefore, severe maternal hypothyroidism developing early during

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pregnancy results in irreversible brain damage. Maternal hypothyroidism developing during later part of gestation results in less severe and also partially reversible brain damage.[6,7]

AUTOIMMUNE THYROID DISORDERS AND PREGNANCY

Pregnancy is characterized by elevation of progesterone and estradiol levels with overall increase in their ratio. The elevated progesterone decreases reactivity of both humoral and cellular arms of the immune system while estradiol exerts opposite effect. Apart from these hormonal alterations, several, not well elucidated, mechanisms result in partial immune tolerance during pregnancy which reverts back in the postpartum period. This results in an increased chance of thyroiditis during postpartum period.[8]

The presence of thyroid autoimmunity as characterized by elevated thyroid peroxidase antibody (TPOAb) levels in an otherwise euthyroid pregnant woman is found to be associated with adverse pregnancy consequences, including increased fetal loss in various studies. The reason behind this association is not clearly established, but various likely reasons include the following:

- Thyroid autoimmunity representing an underlying, more generalized immune imbalance that results in greater rejection of the fetus rather than elevated TPOAb levels causing it directly
- Lesser ability of diseased thyroid gland to adapt to physiological changes associated with pregnancy, resulting in reduced functional thyroid reserve despite apparently normal thyroid functions
- Women of advanced age becoming pregnant with underlying thyroid autoimmunity.[9]

Pregnant women who are otherwise positive for thyroid autoimmunity and had normal thyroid function tests initially, show gradual decline in parameters of thyroid functions despite apparent decrease in titers of TPOAb as gestation advances. As a result of this, as much as 50% of pregnant women have low normal or subnormal T_4 levels, indicating the need for timely detection and intervention in such women. Whether all these women should be treated with LT_4 is not clear at present, but if a pregnant woman is having thyroid-stimulating hormone (TSH) levels of more than 2.0 mIU/L with TPOAb more than 12500 U/mL before 20 weeks of gestation, the chances of progression to subclinical/overt hypothyroidism are very high before the end of pregnancy. Such cases should be closely followed up during their gestation and in the postpartum period.[10] Several recent clinical trials have shown beneficial effects of LT_4 on pregnancy outcomes in such women irrespective of their baseline thyroid status.[11]

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DIAGNOSIS

For diagnosing hypothyroidism during pregnancy, one should use trimester-specific cutoff for thyroid function tests and should order free T_3 and free T_4 rather than total T_3 and T_4 in view of increased TBG levels during pregnancy. If facility for measurement of free T_3 and free T_4 is not available, one should then adjust the increased thyroid hormone production during pregnancy by multiplying the normal nonpregnant range for total T_4 by a factor of 1.5 during pregnancy. Trimester specific cutoff is well established for TSH but not for serum free T_4 levels. The normal range for TSH during pregnancy is 0.1–2.5 mIU/L during first trimester and 0.2–3.0 mIU/L during second and third trimesters. In primary hypothyroidism, TSH levels are elevated and free T_4 should be low, while in secondary or tertiary hypothyroidism, TSH levels are low or normal in presence of low free T_4. Subclinical hypothyroidism is diagnosed in the presence of normal free T_4 and elevated TSH levels.[12]

TREATMENT

LT_4 is the drug of choice for treatment of subclinical and overt hypothyroidism during pregnancy. The dose of LT_4 depends on the severity of thyroid derangement and the timing of diagnosis. For newly diagnosed patient, it should be started in a dose of 2 μg/kg body weight, which is slightly higher than what is used in nonpregnant women. The drug has to be taken empty stomach, and at least 4 hours before any iron or calcium supplementation is taken by pregnant women. If these precautions are not taken, the absorption of LT_4 decreases by as much as 20–30% resulting in poor control of disease as well as injudicious increase in the dosage. The thyroid function should be rechecked after every 4 weeks to adjust the dosage, if needed. The objective is to keep TSH below 2.5 mIU/L during the first trimester and below 3.0 mIU/L during the second and third trimesters. For previously diagnosed hypothyroid women becoming pregnant, the need for LT_4 increases by as much as 30–50% during gestation as a result of number of physiological alterations already discussed. For such women, the dose of LT_4 should be increased depending on their baseline thyroid function test with the aim of maintaining TSH below 2.5 mIU/L during the first trimester and below 3.0 mIU/L during the second and third trimesters (Table 4-1).

TABLE 4-1

Levothyroxine Dosage for Various Baseline TSH Levels	
Baseline TSH levels (mIU/L)	*LT_4 Dosage (μg/day)*
TSH < 10	Increase by 50
TSH 10–20	Increase by 75
TSH > 20	Increase by 100

TSH, thyroid-stimulating hormone; LT_4, levothyroxine.

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Thyroid function test should be reassessed at least 4 weeks after any modification in the dosage. Once thyroid function is in the normal range for pregnancy, repeat thyroid function tests should be done every 6 weeks. The recommended mean intake of iodine during pregnancy and lactation is approximately 250 µg/day.[13-15]

American Thyroid Association Recommendations

In the year 2011, American Thyroid Association (ATA) issued its recommendations regarding the diagnosis and management of thyroid disorders during pregnancy, highlighting the role of thyroid function tests, thyrotoxicosis, hypothyroidism, iodine, thyroid antibodies, miscarriage/preterm delivery, thyroid nodules and cancer, postpartum thyroiditis, various recommendations for screening for thyroid diseases in pregnancy, and areas for future research.[16] The specific recommendations relating to hypothyroidism and pregnancy are summarized in table 4-2.

Indian Thyroid Society Recommendations

Recently, Indian Thyroid Society (ITS)[17] has also given its recommendations for diagnosis and management of hypothyroidism in pregnancy, and they are not very

TABLE 4-2

ATA Recommendations for Hypothyroidism During Pregnancy

- Oral LT_4 is indicated for women with overt hypothyroidism, which is associated with greater risks for fetal loss and premature birth and for those with subclinical hypothyroidism who are positive for TPOAb
- To treat maternal hypothyroidism, use of T_3, desiccated thyroid, or other thyroid preparations is strongly recommended against
- Women who are already receiving thyroid replacement therapy should increase their dose by 25–30% when they become pregnant
- Women with subclinical hypothyroidism initially untreated in pregnancy should be monitored for disease advancement to overt hypothyroidism. Serum TSH and free T_4 levels should be measured every 4 weeks, approximately, until 16–20 weeks of gestation, and at least once between 26 and 32 weeks of gestation
- In the first trimester, normal range for TSH level is 0.1–2.5 mIU/L; this level increases to 0.2–3.0 mIU/L in the second trimester and 0.3–3.0 mIU/L in the third trimester
- Serum levels of free T_4 during pregnancy should be measured with online solid-phase extraction liquid chromatography or tandem mass spectrometry on serum dialysate or ultrafiltrate
- Treatment is not needed for women with low isolated free T_4 levels.

ATA, American Thyroid Association; LT_4, levothyroxine; TPOAb, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone; T_4, thyroxine; T_3, triiodothyronine.

Source: Stagnaro-green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. Guidelines of American Thyroid Association for Diagnosis and Management of Thyroid disease during pregnancy and postpartum. *Thyroid.* 2011;21:1081-125.

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different from ATA recommendations. ITS recommends that diagnosis should be based on trimester-specific TSH and low total T_4. Patients diagnosed with overt hypothyroidism during pregnancy should start the therapy with full replacement dose of LT_4 (1.6–2.0 μg/kg/day) to normalize thyroid function tests as rapidly as possible. Monitoring of treatment should be done by measuring free T_4 and TSH levels every 6 weeks. Subclinical hypothyroidism has been shown to be associated with an adverse outcome for both the mother and offspring and, hence, should be treated with LT_4. The appropriate adjustments in LT_4 dosage should be done to maintain the target TSH levels at less than 2.5 mIU/L in first trimester and 3 mIU/L in the second and third trimesters. Women with preexisting hypothyroidism in whom thyroid assessment cannot be done immediately should have their LT_4 dose increased by 30%, as soon as pregnancy is diagnosed. Post-delivery, the patient should be reverted back to the prepregnant dosage and TSH levels should be rechecked after 6 weeks. Even the women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at an increased risk of developing hypothyroidism and should be monitored for TSH every trimester.

SCREENING OF ALL PREGNANT WOMEN FOR HYPOTHYROIDISM

Despite the fact that several studies have suggested brain developmental abnormalities ranging from mild decrease in IQ to mental retardation in children born to women who had subclinical to overt hypothyroidism during pregnancy, there is no general consensus related to the screening of all women for hypothyroidism during pregnancy. However, few groups/associations recommend checking a woman's TSH value either before becoming pregnant, or as soon as pregnancy is confirmed. This holds true for women who are at higher risk for thyroid disease like those with previous treatment for hyperthyroidism, a positive family history of thyroid disease, and those with goiter. Evidently, women having hypothyroidism should undergo a TSH test once pregnancy is confirmed, as the requirements of thyroid hormone surging during pregnancy often leads to an essential increase in the LT_4 dose. If TSH is normal, further monitoring is not typically required.[16,18]

Controversy still surrounds whether or not to screen for postpartum thyroiditis in all women.[16] The American Congress of Obstetricians and Gynecologists (ACOG) does not recommend postpartum thyroid screening. The ATA states that this decision of screening in women of childbearing age should be made mutually between the physician and the patient. The American Association of Clinical Endocrinologists (AACE) recommends that in the pregnant women who are known to have high titers of TPOAb, postpartum screening should be done. In the middle of these controversies, it is recommended to do selective screening based on risk profile of postpartum women,

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TABLE 4-3

Women at High Risk for Postpartum Thyroiditis
• Women with type 1 diabetes mellitus or other autoimmune disorders
• Women with a strong family history of autoimmune thyroid disease
• TPOAb-positive
• Prior episode of postpartum thyroiditis
• Postpartum depression
• Women with prior miscarriage.

TPOAb, thyroid peroxidase antibody.

as mentioned in table 4-3. Screening should include TPOAb titers and TSH levels. In euthyroid women and those who are TPOAb-negative, there is no requirement of further follow-up. Women who are TPOAb-positive should undergo a serum TSH examination at 6 and 9 months postpartum.

POSTPARTUM THYROIDITIS

Postpartum thyroiditis occurs in women within first year after the delivery of the baby. It occurs in approximately 5–10% of women, but the incidence can be greater in certain high-risk women as mentioned in table 4-3.[16,19]

Following the partial immunosuppression of pregnancy, there occurs an immunological rebound, which aggravates an underlying autoimmune thyroiditis, thus, leading to postpartum thyroiditis. It may present as transient hyperthyroidism, transient hypothyroidism, or transient hyperthyroidism followed by transient hypothyroidism. The postpartum thyroiditis comprises of thyrotoxicosis followed by hypothyroidism, but it is not evident that all women go through both the phases; while 1/3rd of patients manifest both phases, other patients will manifest only a thyrotoxic or hypothyroid phase.[20]

The thyrotoxic phase usually occurs 1–4 months postpartum, lasts for 1–3 months, and is associated with symptoms, including anxiety, palpitations, insomnia, fatigue, weight loss, and irritability. In majority of women, all the above cited symptoms are often attributed to the postpartum phase and the anxiety of having a new baby. Thus, the thyrotoxic phase of postpartum thyroiditis is often missed. Commonly, women present in the hypothyroid phase, which characteristically occurs 4–8 months postpartum and may last for up to 9–12 months. Typical symptoms include fatigue, weight gain, constipation, dry skin, depression, and poor exercise tolerance. The thyroid function returns to normal within 12–18 months of the onset of symptoms in most of the women.[21]

The choice of treatment primarily depends on the phase of thyroiditis and degree of symptoms exhibited by the patient. β-blockers are administered to decrease palpitations

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TABLE 4-4

Recommendations of ITS for Evaluation and Management of Postpartum Thyroiditis

- Routine screening of all women for postpartum thyroiditis is not justified. Women who have type 1 diabetes mellitus or are TPO-positive during the first trimester, should have their TSH monitored at 3 and 6 months postpartum
- Majority of women in the hyperthyroid phase do not require intervention
- Symptomatic cases should be managed with a short course of β-blockers
- Symptomatic women with a TSH >10 mIU/L or between 4 and 10 mIU/L, as well as, asymptomatic women with a TSH between 4 and 10 mIU/L and planning pregnancy in the near future, should be treated with LT_4
- The duration of therapy with LT_4 should be approximately, 1 year postpartum or until the woman completes her family. No clear association between presence of postpartum thyroiditis or thyroid antibodies and postpartum depression has been established
- Women with postpartum depression should be screened for hypothyroidism and treated appropriately.

ITS, Indian Thyroid Society; TPO, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone; LT_4, levothyroxine.

Source: Guidelines for Management of Thyroid Dysfunction During Pregnancy. An Initiative from Indian Thyroid Society. Endorsed by- Endocrine Society of India. 2012; *with permission*.

and others symptoms accompanying hyperthyroidism in women who present with thyrotoxicosis. The medication is tapered off as the symptoms improve, since the thyrotoxic phase is transient. Among β-blockers, propranolol is recommended by the Food and Drug Administration (FDA) as a safe drug to be used during lactation. Antithyroid medications are not indicated for the thyrotoxic phase since the thyroid gland *per se* is not overactive. LT_4 is the choice of treatment for the hypothyroid phase for thyroid hormone replacement. In case of mild hypothyroidism and if the patient has few, if any, symptoms, no therapy may be necessary. If thyroid hormone therapy has begun, treatment should be continued for approximately 6–12 months and then tapered to see if the patient requires thyroid hormone permanently, since approximately 80% of patients regain normal thyroid function and do not require a need for chronic therapy. However, approximately 20% of patients who go into a hypothyroid phase will remain hypothyroid and will require continuation of LT_4 therapy. In women where LT_4 is stopped, serum TSH should be monitored annually for early detection of future hypothyroidism.[19,21] Recommendations given by Indian Thyroid Society[17] for postpartum thyroiditis are summarized in table 4-4.

CONCLUSION

Hypothyroidism is one of the well-known complications of pregnancy and puerperal period. If untreated, it may complicate the normal course of pregnancy by various

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maternal and fetal conditions like preeclampsia, placental abruption, miscarriage, etc. in the mother; fetal growth and development may also be affected. Thus, adequate screening and early initiation of LT_4 according to the severity of the condition is recommended.

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Endocrine Disorders During Pregnancy

This book incorporates the expertise of renowned authors who have distilled an enormous body of knowledge, presenting it in a concise and lucid manner to keep pace with the progress in the field.

Key Features

- Enhances understanding of the pathophysiological processes and fundamental mechanisms underlying the various disease processes
- Thyroid disorders and role of iodine during pregnancy is well emphasized. Parathyroid and bone disorders during pregnancy, and the enigma of vitamin D is appropriately brought out
- Challenges in diagnosis and management of pituitary and adrenal disorders are discussed
- Separate discussions on GDM, PCOS, and obesity in pregnancy have also been made
- Exciting evidence has been put forth favoring the relationship between fetal origins and the epidemic of noncommunicable diseases

Serves the purpose of a quick reference both for learning as well as delivering evidence-based clinical care, which is easy to read with a beautifully illustrated text.

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