Review Article

Thyroid disorders in pregnancy: Consensus statement of Indian Thyroid Society

ABSTRACT

Thyroid disease is the second most common endocrine disorder encountered in pregnant women with substantial maternal and fetal implications. Therefore, assessing thyroid status during pregnancy is essential for initiating treatment in newly diagnosed individuals and adjusting doses for those already under treatment. To initiate proper and timely treatment evidence-based recommendations are required for clinical decision-making in managing thyroid disorders in pregnant and postpartum women. Keeping this in mind, task force consisted of experts in the fields of endocrinology and thyroid disease was constituted and various published data and guidelines were explored to address screening, diagnosis, and management of hypothyroidism, thyrotoxicosis, GD, thyroid nodules, and post-partum thyroiditis and their related complications during pregnancy. This document provides much-required insights and useful, practical, and accurate guidance that aids a practicing clinician.

Keywords: Consensus statement, pregnancy, thyroid disorders

INTRODUCTION

Thyroid disease is the second most common endocrine disorder encountered in pregnant women after diabetes. It has a substantial impact on the physiology of pregnant women and has significant maternal and fetal implications.[1] Although it is frequently detected in pregnancy, it is usually diagnosed before conception.[2]

Normal changes in thyroid physiology during pregnancy involve increased thyroid hormones (THs), tetraiodothyronine (T4) and triiodothyronine (T3) production, increased iodine needs, increased levels of circulating human chorionic gonadotropin (hCG) that stimulate the thyroid-stimulating hormone (TSH) receptors and increased thyroid-binding globulin (TBG) concentration.[3] In healthy women, these physiological changes occur naturally. However, thyroid disorders can develop in many pregnant women due to pathological processes.[4] An Indian study estimated that thyroid disorders were prevalent in 24.1% of pregnant women.[5] Hypothyroidism during pregnancy is highly prevalent in India and other Asian countries.[6] Furthermore, thyroid peroxidase (TPO) antibodies (TPOAbs) or thyroglobulin antibodies are positive in up to 18% of all pregnant women.[4] An Indian epidemiological study reported

Access this article online	
Website: www.thetrp.net	Quick Response Code
DOI: 10.4103/trp.trp_17_22	

Rajesh Rajput, Sarita Bajaj[1], Sujoy Ghosh[2], Pramila Kalra[3], Arun S. Menon[4], Minni G. Pillai[5], Prasanna Kumar[6], Shashank Joshi[7], Krishna Seshadri[8], R. V. Jayakumar[9], Mohd Ashraf Ganie[10], Jabbar Puttiyaveettil[11], Sushil Gupta[12], Hema Girish Rao[13]

Consultant Endocrinologist, Former Senior Professor and Head, Department of Endocrinology, PGIMS, Rohtak, [1]Consultant Endocrinologist, Former Director-Professor and Head, Department of Medicine, MLN Medical College, Prayagraj, [2]Department of Endocrinology, Institute of Post Graduate Medical Education and Research, Kolkata, [3]Professor and Head, Department of Endocrinology, Ramaiah Medical College and Hospitals, [4]HOD and Senior Consultant Endocrinologist, Lisie Hospital, Kochi, Kerala, [5]Consultant Endocrinologist, Lakshmi Hospital, Kochi, Kerala, [6]Director and Consultant Endocrinologist, Centre for Diabetes and Endocrine Care- Bengaluru, [7]Consultant Endocrinologsit, Lilavati Hospital, Maharashtra, Mumbai, [8]Senior Consultant, Apollo Hospitals, Chennai, [9]Senior Consultant Endocrinologist, Aster Medicity Hospital, Kochi, [10]SKIMS, Srinagar, Jammu and Kashmir, India, [11]Professor of Endocrinology, Government Medical College, Trivandrum, [12]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, [13]Associate Professor of Surgery, St John's Medical College Hospital, Bangalore, India

Address for correspondence: Dr. Rajesh Rajput, MD, DM(Endocrinology), FRCP (Edin), FACE (USA), FICP, FIACM, FISH, FIMSA, FRSSDI, Former Senior Professor and Head, Department of Endocrinology, PGIMS, Rohtak-124001, Haryana, India.
E-mail: drrajeshrajput@outlook.com

How to cite this article: Rajput R, Bajaj S, Ghosh S, Kalra P, Menon AS, Pillai MG, *et al*. Thyroid disorders in pregnancy: Consensus statement of Indian Thyroid Society. Thyroid Res Pract 2021;18:89-110.

Received: 30-Oct-2022
Accepted: 04-Nov-2022 **Published:** 15-Feb-2023

the presence of positive TPOAbs in 40% of hypothyroid pregnant women.[7] Other thyroid conditions, such as Graves' disease (GD), thyrotoxicosis, and nodular disease are also occasionally detected in pregnancy.[4]

The production TH increases by around 50% during pregnancy, along with a similar increase in total daily iodine requirements.[1] The levels of THs in pregnancy show characteristic changes from the nonpregnant state and vary with each trimester.[8] THs are crucial during pregnancy to support the growth and development of the fetal brain and nervous system.[9] The fetus depends on the maternal THs throughout the 1st 10 to 12 weeks of pregnancy until the fetal-thyroid gland starts to function.[10] The maternal thyroid gland has to adapt to fulfill the increased demand for TH production during pregnancy.[9,11]

Pregnant women with thyroid autoimmunity (TAI) are at a higher risk of developing subclinical hypothyroidism (SCH) and overt hypothyroidism (OH) than women without TAI. The presence of antibodies could be a sign of subtle thyroid dysfunction and a failure of the thyroid to respond to the increased demand for THs during pregnancy.[12] Hypothyroidism is associated with miscarriage, preterm delivery, infertility, postpartum thyroiditis (PPT), placental abruption, and premature rupture of membranes, as well as adverse neonatal outcomes such as compromised motor and neuropsychological development,[13] attention deficit disorders, low brain-to-body mass ratio, and reduced brain weight.[14,15]

Therefore, assessing thyroid status during pregnancy is essential for initiating treatment in newly diagnosed individuals and adjusting doses for those already under treatment.[16] It is essential to establish trimester-specific reference intervals to define the typical ranges of TH concentrations throughout pregnancy to detect problems as pregnancy progresses.[8] Therefore, evidence-based recommendations are required for clinical decision-making in managing thyroid disorders in pregnant and postpartum women.

Objective

The aim was to update the recommendations for the management of women with thyroid dysfunction during pregnancy and the postpartum period.

Expert panel and consensus process

The task force consisted of experts in the fields of endocrinology and thyroid disease. Various published data and guidelines were explored to address screening, diagnosis, and management of hypothyroidism, thyrotoxicosis, GD, thyroid nodules, and PPT and their related complications during pregnancy. This document provides much-required insights and useful, practical, and accurate guidance that aids a practicing clinician. The guidelines were developed through a series of E-mails, conference calls, and face-to-face meetings. The task force prepared the initial draft with the help of a medical writer, and it was reviewed and commented on by members of the Indian Thyroid Society.

Methods

The sections and recommendations addressed in the guidelines were based on the feedback from task force members and previous trials and guidelines. The task force members followed a well-defined grading system (mentioned below) for the critical appraisal of evidence and grading strength of recommendations.

Level of evidence	Description
Level A	Data derived from multiple randomized trials or meta-analysis
Level B	Data derived from a single randomized trial or large nonrandomized trial
Level C	The consensus of opinion of experts or small studies, retrospective studies, or registries
Level D	Data derived from clinical experience
Class of recommendations	
Class I	Evidence and or general agreement that a given treatment or procedure is beneficial, useful, or effective. It is recommended
Class IIa	Evidence is in favor of efficacy/usefulness and should be considered
Class IIb	Efficacy/usefulness is less well established and recommendations may be considered
Class III	Evidence and or general agreement that a given treatment or procedure is not beneficial, useful, or effective and in some cases may cause harm. Not recommended

HYPOTHYROIDISM IN PREGNANCY

Overview of maternal hypothyroidism

Globally, the prevalence of hypothyroidism in pregnant women was reported to be 1.5%–4%, of which 0.3%–0.5% had overt, and the remaining had SCH. The prevalence of maternal hypothyroidism in Indian women ranged between 1.2% and 67.0%.[17] In a 2021 published meta-analysis of observational studies, it was found that the pooled estimate of the prevalence of hypothyroidism was 11.07%, that of SCH was 9.51%, and OH was 2.74% in pregnant women in India.[17]

A multicenter epidemiological study from 11 cities in 9 states of India demonstrated a very high prevalence of hypothyroidism. Using the trimester-specific TSH cutoffs as <2.5 mIU/L for the 1st and <3.0 mIU/L for the

2nd and 3rd trimesters, (as per older American Thyroid Association's [ATA] guidelines, now obsolete), 44.3%, 32.0%, and 34% of women were found to have hypothyroidism in the 1st, 2nd, and 3rd trimester, respectively. Whereas with the use of a cutoff TSH level of 4.5 mIU/L, 13.13% of pregnant women were observed to have hypothyroidism. TPOAbs were positive in 20.74% of all pregnant women and 40% of hypothyroid pregnant women.[7] A study conducted by Rajput *et al*. in 461 pregnant women with uncomplicated intrauterine singleton pregnancies in the 1st trimester showed that anti-TPOAbs were elevated in 27.8% of pregnant women. SCH (FT3, FT4 in normal range with TSH >2.5 mIU/L) was diagnosed in 21.5% of the women, and 39.4% of them were positive for anti-TPO ($P \leq 0.001$).[6]

Consensus statement
A high prevalence of hypothyroidism is observed in Indian pregnant women (with the use of trimester-specific TSH cutoffs), and a large proportion of pregnant women with SCH are positive for anti-TPO. (A/I)

Causes and factors affecting the prevalence of hypothyroidism during pregnancy

The leading cause of hypothyroidism in pregnancy is iodine deficiency, and the most common cause is autoimmune thyroiditis in iodine-sufficient areas.[17] The factors influencing thyroid functions during pregnancy are summarized in Table 1.

Consensus statement
Interpretation of the prevalence rates of hypothyroidism should be based on the trimester of pregnancy, ethnicity, iodine nutrition, anti-TPO positivity, and the reference range or cut-off level and analytical platform on which TSH is measured. (C/IIa)

Maternal and neonatal risks of hypothyroidism

Iodine deficiency and pregnancy complications

Since iodine is an essential micronutrient for the synthesis of THs (T3 and T4), it plays an important role in the normal growth and development of the brain and central nervous system of the fetus. Further, since the fetal thyroid does not develop until 13–15 weeks of gestation, it is dependent on the maternal THs. Hence, a lack of iodine in the maternal diet may result in iodine deficiency, and subsequently, an iodine-deficient fetus.[19]

Estimates have shown that, in India, nine million pregnant women and eight million newborns every year are at risk of iodine deficiency disorder. These figures are derived from a coverage evaluation survey 2009, which reported household-level coverage of adequately iodized salt, and the findings were extrapolated to total population estimates from census 2011.[19] A recent study among 250 pregnant Indian women in their 1st trimester showed that iodine deficiency was present in 11.8%, of which 59.25% had a mild deficiency, 33.33% moderate deficiency, and 7.4% severe deficiency.[20] When urine iodine levels were compared in the three trimesters among Indian pregnant women, the maximum deficiency was observed in the 1st trimester (39.5%), followed by the 3rd trimester (31.6%), and a dip was seen in the 2nd trimester (28.9%).[21]

Rajesh *et al.* evaluated the nutritional status of iodine among euthyroid pregnant women consuming iodized salt and carrying a healthy singleton uncomplicated intrauterine pregnancy. A decreasing trend was observed in the trimester-specific median urinary iodine (MUI) levels from 193.2 μg/L in the 1st to 111.8 μg/L in the 2nd to 97.65 μg/L in the 3rd trimester. Around 43.82%, 54.08%, and 62.24% of women in the 1st, 2nd, and 3rd trimesters had MUI levels below 150 μg/L. This study demonstrated that 53.68% of pregnant women had MUI levels in the iodine deficient range (MUI of <150 μg/L) as per the WHO guidelines.[22]

A recent study by Pramanik *et al*. did not report iodine deficiency in Indian pregnant women. The urinary iodine excretion (UIC; μg/L) in different trimesters was observed to be 205 ± 16.9, 176 ± 14.9, and 182 ± 16.7, respectively, and the mean UIC in nonpregnant women was 176 ± 15.7 μg/L. Hence, the researchers postulated that the Indian population may still be in the possible final stages of transition into the state of iodine sufficiency.[23]

Table 1: Factors that modify thyroid functions during pregnancy[18]

Biochemical measurement	Population factors	Physiological factors in pregnancy	Individual factors
Thyroid immunoassay tests Upper limit cut-off values Macro TSH measurements by LC/MS/MS Pitfalls (clinical laboratories providing generic reference ranges for T4, T3, and TSH)	Geographical area ethnicity Regional iodine nutritional variations	Dynamism of thyroid function across gestation (gestational age) Increased thyroxine-binding globulin Secretion of human chorionic gonadotrophin Increased iodine excretion Expanded plasma volume Increased type 3-5 deiodinase activity from the placenta	Age BMI Smoking Iodine intake Thyroid autoimmunity Exposure to endocrine disruptors Drugs (amiodarone, glucocorticoids, iodinated antiseptics)

BMI: Body mass index, T4: Tetraiodothyronine, T3: Triiodothyronine, TSH: Thyroid-stimulating hormone, LC: Liquid chromatography, MS: Mass spectrometry

Iodine deficiency during pregnancy is likely to increase the risk of thyroid disorders. Low TH levels stimulate increased pituitary TSH production and result in maternal and fetal goiter, which exerts adverse effects on the cognitive function of offspring and leads to intellectual impairment, deaf-mutism, and motor rigidity. Severe iodine deficiency in pregnant women increases the rates of pregnancy loss, stillbirth, and perinatal and infant mortality.[4]

The current salt iodization Indian guideline (15 ppm of iodine at the consumer level) is designed to deliver 150 μg of iodine per day and this appears to be inadequate for pregnant women, whose dietary iodine requirement is 250 μg/day according to the WHO. Therefore, to cover this increased iodine demand of 250 μg/day during the pregnancy, the iodine content of salt needs to be higher. However, no iodine supplementations are recommended during pregnancy.[21] The ATA suggests that women consuming levothyroxine (LT4) regularly do not require supplemental iodine because the substrate is no longer needed for hormone formation.[4]

Consensus statement

- Indian pregnant women should ingest approximately 250 μg iodine daily. (A/I)
- Salt intake consisting of a minimum of 250 μg iodine daily should be consumed by pregnant women.
- Those on regular LT4 supplementation can be exempted from supplemental iodine. (A/I)

Thyroid peroxidase antibodies and pregnancy complications

Women who are positive for TPOAb are associated with an increased risk of developing hypothyroidism during pregnancy and adverse obstetric outcomes.[12] Estimates have shown that 18.9% of Indian pregnant women were detected as being TPOAb positive with euthyroid status.[24]

The prevalence rates vary widely with ethnicity, age, and analytical methods used to detect thyroid antibodies.[4] However, a fifth of euthyroid women with TPOAb will develop hypothyroidism in the course of pregnancy.[25] Pregnant women with a known level of anti-TPOAb (levels of more than 34 IU defined as a positive test), and TSH levels of 2.5–3.9 mIU/L in the 1st trimester and 3–4.1 mIU/L in the 2nd and 3rd trimesters, may be associated with pregnancy; however, benefits of treating the same remain questionable.[26]

Mothers who are positive for TPOAb have been reported to have an increased risk of preterm births. A study has also reported twice as many miscarriages for euthyroid pregnant women who were TPOAb positive (17·0%) compared with those who were TPOAb negative (8·4%, $P = 0·01$). TAI has been associated with postpartum depression and with depression during pregnancy, an increased risk of gestational diabetes, placental abruption, and premature rupture of membranes.[12]

Consensus statement

Women with positive TPOAb develop hypothyroidism during the course of pregnancy, and are at a high risk of miscarriages, preterm births, gestational diabetes, intrauterine growth retardation, placental abruption, premature rupture of membranes, and depression during pregnancy. However, treating the same has questionable benefits. (A/I)

Diagnosis of maternal hypothyroidism

Thyroid function assessment during pregnancy is challenging, as the physiologic changes (increase in TBG, placental deiodinase activity, UIC, and increase in hCG secretion) cause a downward shift of TSH reference intervals and make it difficult to interpret maternal thyroid function tests. Hence, if nonpregnant TSH reference intervals were applied to pregnant women, it would lead to underdiagnosis of hypothyroidism or overdiagnosis of hyperthyroidism.[18]

Determining the trimester-specific reference ranges for serum thyroid-stimulating hormone

The first diagnostic challenge for the clinician lies in deciding the reference range for serum TSH during pregnancy.[18]

Problems associated with serum thyroid-stimulating hormone determinations

The serum TSH gradually returns to within the prepregnancy range by the time of delivery as a result of a decrease in hCG stimulation during the 2nd–3rd trimesters.[18] Further, the downward shift in the TSH reference interval is greater in twin pregnancies, as hCG concentrations are higher in multiples than in singleton pregnancies.[4] TSH was suppressed (≤0.2 mU/L) in 67% of women with hCG concentrations >200,000 IU/L and in 100% of women if hCG concentrations were >400,000 IU/L.[27]

TAI is another variable contributing to thyroid dysfunction in pregnant women. Others include parity, smoking, age, and body mass index. Iron, endocrine disruptors, and the ethnicity of the pregnant women also need to be taken into consideration.[4,28]

1. The potential bias of the analytical platform on which the TSH level is measured is also a reason for influencing the TSH reference range. Around 10% of normal pregnant women would be diagnosed with SCH at 4–7 weeks of gestation, according to the analytical platforms marketed by commercial companies that provide reference TSH range. This can lead to misclassification and hence under or overtreatment.[29]

Need to develop reference ranges for serum thyroid-stimulating hormone

Rajput *et al.* in a study established trimester-specific reference ranges for TH during pregnancy in the Indian population after using rigorous exclusion criteria (any history of chronic illness, goiter on physical examination, thyroid illness in the past or present, consuming thyroid medications (current and past), family history of thyroid illness, presence of anti-TPO, and poor obstetrics history including 3 or more abortions). It was found that the mean TSH increased and the mean FT3 decreased significantly with the progression of the gestational period. FT4 decreased from the 1st to 3rd trimester, but the decrease was nonsignificant from the 2nd to 3rd trimester. The 2.5–97.5th percentiles for FT3, FT4, and TSH were 2.53–4.54 pg/ml, 0.88–1.78 ng/ml, and 0.37–3.69 μIU/ml in the 1st trimester, 2.0–4.73 pg/ml, 0.91–1.78 ng/ml and 0.54–4.47 μIU/ml in the 2nd trimester, and 2.01–4.01 pg/ml, 0.83–1.73 ng/ml, and 0.70–4.64 μIU/ml in the 3rd trimester of pregnancy.[30]

Researchers concluded that trimester-specific reference intervals for THs cannot be extrapolated due to the differences in ethnicity, maternal iodine status, laboratory assay method, and rigor for the selection of reference population. Thus, the establishment of reference intervals in each region is very important.[30]

When trimester-specific cutoff values for TSH as defined by Endocrine Society guidelines were applied in the study, the prevalence of SCH was reported to be 21.5% in the 1st trimester, 15.8% in the 2nd trimester, and 25.8% in the 3rd trimester of pregnancy. However, after applying the cutoffs of 2.5th and 97.5th percentile of TSH, the number of women with SCH decreased to 6.7%, 10.7%, and 8% in the 1st, 2nd, and 3rd trimester, respectively. Therefore, applying the endocrine society guidelines to the Indian study population would have misclassified the pregnant women as having SCH and would have led to an incorrect diagnosis.[30]

In a country like India, which has a heterogeneous population, reference intervals need to be developed for the individual regions of the country. Hence, it is necessary to develop trimester-specific reference intervals for thyroid function tests in pregnancy.[31]

The ATA 2017 guideline suggests that the TSH reference range should be pregnancy and trimester-specific and developed from a local population that is iodine sufficient, TPOAb negative, and free from any underlying thyroid disorder. In case of unavailability of locally derived reference ranges and when local assessments are not available, the lower reference range of TSH can be reduced in the 1st trimester of pregnancy by approximately 0.4 mU/L. The upper reference range is reduced by approximately 0.5 mU/L and this usually corresponds to a TSH upper reference limit of 4.0 mU/L. This reference limit should generally be applied beginning with the late 1st trimester, weeks 7–12, with a gradual return toward the nonpregnant range in the 2nd and 3rd trimesters.[4]

Consensus statement

- All patients seeking pregnancy or those during early pregnancy should undergo clinical evaluation and testing for serum TSH when risk factors for thyroid dysfunction are identified. (C/IIa)
- The establishment of trimester-specific reference intervals in each region is very important, as the intervals for thyroid hormones cannot be extrapolated due to differences in ethnicity, maternal iodine status, laboratory assay method, and rigor for selection of the reference population. (A/I)
- The TSH reference range should be pregnancy and trimester specific and developed from a local population that is iodine sufficient and free from any underlying thyroid disorder.
- In the case of unavailability of locally derived reference ranges, an upper reference limit of ~4.0 mU/L may be used during the late first trimester, with a gradual return towards the nonpregnant range in the second and third trimesters. (C/IIa)

Measurement of FT4 and total T4

Free T4 level measurement is usually recommended to confirm a diagnosis of OH or SCH if the TSH concentration is outside the pregnancy reference range. Since sera of pregnant women consist of higher concentrations of TBG and nonesterified fatty acids and lower concentrations of albumin relative versus nonpregnant women, serum FT4 measurement is generally not recommended as a first-line screening test, as it is prone to inaccuracy in the setting of pregnancy. High protein concentrations in serum samples tend to result in higher FT4 values, whereas low protein concentrations are likely to yield lower FT4 values when performed by indirect analog immunoassays.[4] The use of equilibrium dialysis or liquid chromatography/tandem mass spectrometry can be more accurate for the measurement of free T4 levels, but these tests are expensive and not readily available in the clinical practice.[18] Therefore, FT4, if measured in pregnant women, assay method-specific and trimester-specific pregnancy reference ranges should be applied.[4]

Consensus statement

- If the TSH concentration is outside the pregnancy reference range, T4 level measurement is recommended to confirm the diagnosis. (C/IIa)
- In the case of non-availability of reliable FT4 assay, total T4 multiplied by 1.5 can be used.

The ATA 2017 guideline has suggested that total T4 (TT4) measurement (with a pregnancy-adjusted reference range) is a highly reliable means of estimating hormone concentration during pregnancy. An accurate estimation of the FT4 concentrations can also be done by calculating an FT4 index.[4]

When trimester-specific reference intervals for TFTs were established in South Indian pregnant women, 0.08–2.24, 0.42–2.84, and 0.40–3.14 μIU/ml for TSH, 0.68–1.44, 0.59–1.21, and 0.53–1.15 ng/dl for FT4, and 2.08–3.48, 1.81–3.81, and 1.86–3.38 pg/ml for FT3 were reported.[32]

In the case of the nonavailability of a reliable FT4 assay, TT4 multiplied by 1.5 can be used as a reference for treatment during pregnancy.

Screening for thyroid autoantibodies

TAI increases the risk of hypothyroidism in pregnant women. The ATA suggests TSH concentrations be assessed every 4 weeks through to mid-pregnancy in women with known TAI.[4] TPOAb status may be assessed in pregnant women as this information is of prognostic value.[12]

Consensus statement

- In women with known TAI, the TSH concentrations should be assessed every 4 weeks through to mid-pregnancy.
- TPOAb status should be assessed in pregnant women with a TSH concentration of 2.5–10.0 mU/L. (C/IIa)

Treatment of hypothyroidism in pregnancy

Benefits of levothyroxine treatment

The first choice for the clinical treatment of SCH is LT4. LT4 decreases the level of TSH and gradually increases the levels of T3 and FT4.[32] As per a 2021 study, LT4 has a role in improving the hypothyroidism-induced metabolic disorder during pregnancy and promotes normalization of thyroid function-related hormones.[33] Timely and appropriate administration and adjustment of LT4 during pregnancy are important to normalize thyroid function, reduce the occurrence of complications, and achieve satisfactory pregnancy outcomes.[34]

A 2022 published systematic review and meta-analysis has shown that LT4 treatment in pregnant women with SCH significantly reduces the incidence of premature birth, miscarriage, postpartum hemorrhage, and low birth weight infants.[34]

Initiation of LT4 therapy in the 1st trimester was associated with a decreased risk of adverse obstetric events (preterm births, pregnancy loss, low birth weight, postpartum hemorrhage, preeclampsia, and gestational diabetes). In addition, the low rates of adverse events were reported in TPOAb-positive women when LT4 therapy was initiated in the 2nd trimester.[35] Another 2022 randomized controlled trial showed that treatment with LT4 decreased the risk of pregnancy loss and increased the live birth rate in recurrent pregnancy loss pregnant women who were positive for TPOAb and SCH. LT4 therapy is recommended for SCH and TPOAb-positive pregnant women with recurrent pregnancy loss.[36] According to ATA 2017, insufficient evidence exists to conclusively determine whether LT4 therapy decreases pregnancy loss risk in TPOAb-positive euthyroid women who are newly pregnant. However, the administration of LT4 to TPOAb-positive euthyroid pregnant women with a prior history of loss may be considered on an individual case-to-case basis given its potential benefits in comparison with its minimal risk, and in such cases, 25–50 μg of LT4 is a typical starting dose.

Consensus statement

- Timely and appropriate administration and adjustment of LT4 during pregnancy is important to normalize thyroid function as it has a role in improving the hypothyroidism-induced metabolic disorder during pregnancy, reducing the occurrence of complications, and achieving satisfactory pregnancy outcomes. (A/I)
- LT4 treatment in pregnant women positive for TPOAb and SCH reduces the risk of premature birth, miscarriage, recurrent pregnancy loss, postpartum hemorrhage, and low birth weight infants. (A/I)
- LT4 treatment to TPOAb-positive euthyroid pregnant women with a prior history of loss may be considered on an individual case-to-case basis given its potential benefits in comparison with its minimal risk, and in such cases, 25–50 μg of LT4 is a typical starting dose.

Dosage of levothyroxine during pregnancy

The ETA proposes a starting dose of LT4 as 1.20 μg/kg/day in newly diagnosed patients with SCH in pregnancy. TSH values should be checked every 4–6 weeks during the 1st trimester and once during the 2nd–3rd trimesters, and the thyroxine dose should be adjusted to maintain TSH to <2.5 mU/l or within the trimester-specific reference range.[37]

The ATA suggests a starting dose of 50 μg/d LT4 for the effective treatment of SCH women during pregnancy.[4] LT4

treatment is suggested for all pregnant women with TSH levels above the pregnancy-specific range. Pregnant women with TSH between 2.5 and 4 mU/l and anti-TPO positive may also be considered for LT4 depending on decision by the treating physician, endocrinologist, and gynecologists.[4]

As per a communication from the National Indian Patient-centered Thyroid Management group, thyroxine is reported to be safe during pregnancy and lactation for the mother and fetus and should not be stopped. The dose of thyroxine can be increased from 7 to 9 tablets a week after pregnancy is confirmed.[38] Therefore, all pregnant women already taking LT4 should increase the dosage by 25%–30%.

The administration of LT4 to TPOAb-positive euthyroid women undergoing assisted reproductive technology with ovulatory dysfunction may be considered; 25–50 µg of LT4 can be a typical starting dose.[4]

Other thyroid preparations such as T3 or desiccated thyroid should not be used in pregnancy.[4]

Adjustment of levothyroxine dose

As per the ATA, in hypothyroid women treated with LT4 who are planning pregnancy, serum TSH should be evaluated preconception, and the LT4 dose adjusted to achieve a TSH value between the lower reference limit and 2.5 mU/L.[4]

In hypothyroid patients receiving LT4 treatment with a suspected or confirmed pregnancy (positive home pregnancy test), the dose can be increased by ~20%–30%. Two additional tablets weekly of the patient's current daily LT4 dosage can be administered.[4]

A recent study conducted in 2022 showed that in hypothyroid pregnant women the median LT4 dosage prescribed before conception was 85.7 mcg/day, which increased by 14.3 mcg/day in the 1st trimester ($P = 0.001$), a 16.7% increase from preconception to the 1st trimester.[39]

Another study showed that in well-controlled hypothyroid women (TSH ≤2.5 mIU/L) who were monitored throughout pregnancy, LT4 dosage needed to be increased in 84% of the pregnancies.[40]

Following delivery, LT4 should be reduced to the patient's preconception dose. Additional thyroid function testing should be performed at approximately 6 weeks postpartum.[4]

Some women in whom LT4 is initiated during pregnancy may not require LT4 postpartum. Hence, LT4 can be discontinued in such women, especially when the LT4 dose is ≤50 µg/d. If LT4 is discontinued, serum TSH should be evaluated in approximately 6 weeks.[4] Alternatively, the LT4 dose should be reduced by 50% with the measurement of thyroid function tests at 6 weeks. If women remain euthyroid even on this reduced dose, then a trial of stopping LT4 can be taken.

Consensus statement

- In newly diagnosed patients with SCH in pregnancy, a starting dose of LT4 as 1.20 μg/kg/day can be considered. TSH values should be checked every 4-6 weeks during the 1st trimester and once during the 2nd and 3rd trimesters and the dose should be adjusted to maintain TSH to <2.5 mU/l or within the trimester-specific reference range. (C/IIa)
- LT4 treatment is suggested for all pregnant women positive for TPOAb and having TSH above the pregnancy-specific range. Pregnant women with TSH between 2.5–4 mU/l and anti-TPO positive may be considered for LT4 depending on decision by the treating physician, an endocrinologist, and obstetrician-gynecologist. (C/IIa)
- In hypothyroid women on LT4 treatment, preconception serum TSH should be evaluated in those who are planning pregnancy, and the dose should be adjusted to achieve a TSH value between the lower reference limit and 2.5 mU/L. (B/IIa)
- In hypothyroid patients with a suspected or confirmed pregnancy (positive home pregnancy test), the LT4 dose can be increased by ~20%–30%. (B/IIa)
- In women following delivery, LT4 should be reduced to the patient's preconception dose, and additional thyroid function testing should be performed at approximately 6 weeks post-partum. (C/IIa)
- Other thyroid preparations such as T3 or desiccated thyroid should not be used in pregnancy. (C/IIa)
- Iron/calcium supplements if prescribed to a pregnant woman, she should be advised to consumed it at least 4 hours after LT4 treatment.

Screening for thyroid hypofunction in pregnancy

Optimizing feto-maternal outcomes is the ultimate aim of maternal thyroid disease screening in pregnancy, so that therapeutic intervention can be implemented as early as possible when indicated in the course of fetal development.[25]

Universal versus targeted screening for hypothyroidism in pregnant women

Targeting "high-risk" women in the detection of thyroid abnormalities during pregnancy was observed to have over

six times the increased risk of developing OH or SCH during pregnancy.[41] A systematic review and meta-analysis showed that case-based screening missed up to 49% of pregnant women with thyroid dysfunction, and that early detection of thyroid dysfunction can minimize the adverse maternal and fetal outcomes.[42]

A recent 2020 study has shown that testing only high-risk pregnant women would miss approximately 40% of all hypothyroid patients. The targeted high-risk case-finding approach would also lead to misidentifying around 41.2% of women with SCH and 25% with OH since they belonged to the low-risk group. Further, 50% of women with positive autoantibodies and TSH >2.5 mIU/L in whom treatment with LT4 would be considered, would also be missed.[43] Targeted screening may fail to detect asymptomatic hypothyroid women before conception or during pregnancy.[18]

In a retrospective study, antenatal Indian women with SCH (serum TSH used as a screening tool; 1st trimester: <2.5 mIU/L, 2nd trimester: <3.0 mIU/L and 3rd trimester: <3.5 mIU/L) who were followed up until delivery were analyzed for maternal complications. The analysis showed that maternal complications such as anemia 8%, preeclampsia 17.3%, gestational diabetes 16.7%, fetal growth restriction 5.3%, oligohydramnios 8.7%, premature rupture of membranes 7%, placental abruption 1.33%, antiphospholipid antibody syndrome 1.33%, and low birth weight 17.3% were prevalent in these women with SCH. The authors strongly recommend universal screening for hypothyroidism for all antenatal women, especially in the 1st trimester to reduce the burden of adverse maternal and fetal outcomes.[44]

Universal screening for thyroid disease in pregnant women in the 1st trimester is reported to be cost-effective as compared to no screening. It also allows the diagnosis and treatment of clinical and SCH that may not be detected when only high-risk women are screened.[45]

A study conducted by Rajput *et al*. showed that maternal thyroid dysfunction has an immense impact on maternal and fetal outcomes. Therefore, quick identification of thyroid dysfunction and its timely treatment are essential. The authors supported the universal screening of pregnant women for thyroid dysfunction due to the high prevalence of thyroid dysfunction.[6]

All pregnant women should be screened at their 1st antenatal visit by measuring TSH levels, and ideally, screening should be carried out during prepregnancy evaluation or as soon as pregnancy is confirmed.[46]

Consensus statement

- Universal screening for hypothyroidism for all antenatal women, especially in the first trimester, should be preferred over targeted case-based screening.
- Case-based screening can miss a substantial proportion of pregnant women with SCH, and OH. Case-based screening can also miss women with positive autoantibodies with otherwise normal TFTs. These patients may need repeat testing both during and after pregnancy as they are at higher risk of hypothyroidism and postpartum thyroiditis.

Isolated hypothyroxinemia

Isolated hypothyroxinemia (IH) is defined as a serum thyroxine concentration below the 2.5th–5th percentile with a TSH concentration within the normal range. Analysis show that the biochemical criteria on the basis of which maternal hypothyroxinemia is diagnosed are quite variable. Therefore, the incidence rates of IH vary widely among the studies due to the differences in the diagnostic criteria or in the timing of its evaluation as well as in the iodine nutrition status of the population under examination.[4,47]

IH is associated with various adverse outcomes, such as lower intelligence quotient, language delay, worsened motor function, smaller head circumference, and an increased risk of autism in children born to mothers with this condition. An association with a higher risk of premature delivery is also reported. No studies have shown the benefit of LT4 administration in ameliorating the harmful effects in patients with IH. Therefore, the treatment of IH cannot be recommended at this time.[4]

Consensus statement

Based on Current evidences, treatment of isolated hypothyroxinemia is not recommended at present, and such women should be closely followed during gestation with repeat measurement of TFT.

THYROTOXICOSIS IN PREGNANCY

Thyrotoxicosis is a condition involving the excessive secretion of THs,[48] which is common among pregnant women.[49] In a cross-sectional study, Rajput *et al.* demonstrated a high prevalence of undetected thyroid disorders during pregnancy during the 1st trimester of pregnant women. A total of 0.4% of women had OH, while 3.3% of the women had sub-clinical hyperthyroidism.[6] GD affects 0.4%–1.0% of women in the preconception period and about 0.2% of pregnant women. It is the most frequent cause of overt, persistent hyperthyroidism among these women. The incidence of gestational thyrotoxicosis, a transient hCG-mediated

hyperthyroidism, in the 1st trimester of pregnancy may be highest in Asian populations and has been estimated at between 1% and 11%. Thyrotoxicosis is linked to negative results in both pregnant and nonpregnant patients when untreated and improperly managed.[49]

Causes of thyrotoxicosis

The most prevalent cause of thyrotoxicosis in pregnancy is gestational transient thyrotoxicosis (GTT), which results from the stimulation of the TSH receptor (TSHR) by hCG.[50] Toxic multinodular goiter and toxic adenoma are two less frequent nonautoimmune causes of hyperthyroidism in pregnancy. Some of the less frequent causes of thyrotoxicosis in pregnancy include subacute, painful, or painless thyroiditis with the passive release of THs from a damaged thyroid gland, whereas several other conditions such as TSH-secreting pituitary adenoma, struma ovarii, functional thyroid cancer metastases, or germline TSHR mutations are very rare.[4]

Consensus statement

- Thyrotoxicosis is most frequently caused by hyperthyroidism, less frequently by subacute, painful or painless thyroiditis with passive release of thyroid hormones from a damaged thyroid gland, and rarely by a TSH-secreting pituitary adenoma, struma ovarii, functional thyroid cancer metastases, or germline TSH receptor mutations. (C/I)
- The most frequent cause of thyrotoxicosis in the first trimester is GTT.

Diagnosis of thyrotoxicosis

Due to the overlapping clinical and biochemical characteristics of a typical pregnancy, thyrotoxicosis in pregnancy is difficult to diagnose. Normal total T3 and T4 levels are up to 1.5 times higher than the recommended range for women who are not pregnant. Although free T4 is a better indicator of true thyroid health, its amount varies throughout the pregnancy's three trimesters. A diagnosis of thyrotoxicosis is considered when we have elevated TH levels above the pregnancy range and a suppressed or undetectable TSH. In such situations, the presence of diffuse goiter, eye signs, and a high TSH-receptor antibody (TRAb) titer confirms GD [Figure 1].[51]

Thyrotoxicosis in pregnancy can cause anxiety, tremors, heat intolerance, palpitations, lack of weight gain or loss, goiter, tachycardia, and hyperreflexia. These signs and symptoms are the same as those observed in nonpregnant individuals. It is crucial to distinguish between GTT and intrinsic hyperthyroidism due to the differences in their courses and suggested treatments. Laboratory and imaging tests are crucial because of the overlap between aberrant signs, symptoms, and physical examination [Table 2].[50]

Initial evaluation of a suppressed serum thyroid stimulating hormone concentration during the first trimester of pregnancy

As a physiological reaction to the stimulating effect of hCG upon the TSHR, serum TSH may fall in the 1st trimester of a healthy pregnancy.[4]

- A high hCG level develops between 7 and 11 weeks of gestation
- By week 11 of pregnancy, about 5% of women may have a serum TSH <0.1 mU/L, and in rare situations, it may even be undetectable
- Along with serum and TT4 and T3 readings, any subnormal serum TSH value must be assessed
- In the presence of an excessively increased serum TT4/FT4 or T3, as well as a suppressed or undetectable serum TSH, the biochemical diagnosis of OH is made.

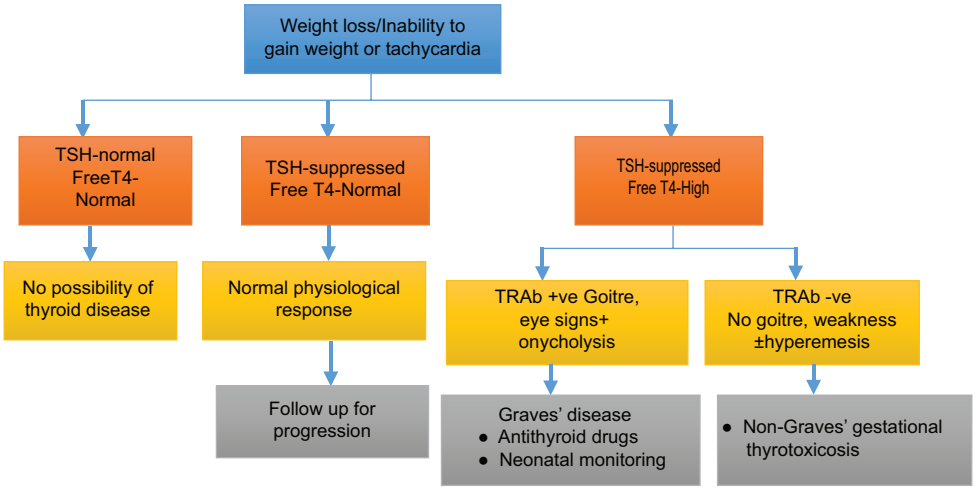

Figure 1: Workup of a patient with suspected hyperthyroidism during pregnancy.[51] TSH: Thyroid stimulating hormone; T4: Thyroxine; TRAb: Thyroid stimulating hormone receptor antibody

Table 2: Tests to diagnose thyrotoxicosis in pregnancy[50]

Tests	Uses
TSH	A serum TSH below 0.1 mU/L (in some cases even undetectable) may be present in women by week 11
Total T4, T3, and FTI	Serum total T4 and T3 levels >1.5 times the nonpregnant range should be used to diagnose thyrotoxicosis in the second and third trimesters of pregnancy Measurement of the FTI, which adjusts for the presence of binding proteins, has also been proposed as an alternate and perhaps more accurate test for diagnosing hyperthyroidism
TRAB	Measurement of serum TRAb is important in pregnant patients undergoing evaluation for thyrotoxicosis for both diagnostic and prognostic reasons Current guidelines recommend measuring TRAb at 20-24 weeks of gestation in patients with a past or present history of GD Serum TRAb titers can also be used to help differentiate between postpartum thyrotoxicosis secondary to destructive thyroiditis and GD TSH receptor antibody test should ideally be done on a chemiluminescence method or platform
HCG	HCG levels peak at 9-10 weeks of pregnancy and play a significant role in the preservation of the placenta. It contains an identical α-subunit to those found in TSH, LH, and FSH Biochemical evidence of hyperthyroidism is evident with serum HCG levels of 100,000-500,000 IU/L, and clinical hyperthyroidism can result when levels >500,000 IU/L are measured The gestational trophoblastic disease is associated with severely elevated serum HCG levels and is usually the first clue to suggest a molar pregnancy upon initial presentation
Imaging studies	Ultrasound: Thyroid ultrasonography, which measures thyroid volume and blood flow and can help distinguish GD from thyroiditis is a useful diagnostic tool in thyrotoxic pregnant women Thyroid nuclear medicine studies: Radioiodine uptake and scanning can result in negative prenatal outcomes, including those associated with radiation exposure to the developing fetus and fetal hypothyroidism. Thus, thyroid nuclear tests are not recommended during pregnancy

T4: Tetraiodothyronine, T3: Triiodothyronine, FTI: Free T4 index, TSH: Thyroid-stimulating hormone, TRAb: TSH receptor antibodies, HCG: Human chorionic gonadotropin, LH: Luteinizing hormone; FSH: Follicle stimulating hormone

Consensus statement

- A medical history, physical exam, and testing of the maternal blood FT4 or TT4 concentrations should be performed when a suppressed serum TSH is found in the first trimester (a serum TSH below 0.1 mU/L (in some cases, even undetectable) by week 11. (A/I)
- Serum total T4 and T3 levels more than 1.5 times the non-pregnant range should be used to diagnose thyrotoxicosis in the second and third trimesters of pregnancy.
- Measuring TRAb may be useful in determining the cause of thyrotoxicosis. (C/I)
- Radionuclide scintigraphy or radioiodine uptake determination should not be performed in pregnancy. (C/I)

Diagnostic clues regarding the etiology of thyrotoxicosis

When treating a patient with thyrotoxicosis, it is crucial to identify the disease's underlying etiology.[4] The most common cause of thyrotoxicosis in pregnancy is GTT. It is also commonly observed in patients who have had GD before pregnancy. Subtypes of OH, such as GD, toxic multinodular goiter, and toxic adenoma, as well as thyroiditis and exogenous TH use, should be considered in the differential diagnosis of thyrotoxicosis during pregnancy.[50]

Furthermore, trophoblastic disease is a rare cause of thyrotoxicosis during pregnancy. The hyperthyroidism associated with the trophoblastic disease is often subclinical; the occurrence of symptomatic hyperthyroidism is extremely rare and limited to small case series or case reports.[50] The diagnostic clues regarding the etiology of thyrotoxicosis in the peri-pregnancy setting are summarized in Table 3.

Consensus statement

- When treating a patient with thyrotoxicosis, it is crucial to identify the disease's underlying etiology. (C/IIa)
- Apart from the common cause, GTT, other causes to be considered in the differential diagnosis of thyrotoxicosis in pregnancy include overt hyperthyroidism subtypes such as GD, toxic multinodular goiter, and toxic adenoma, as well as thyroiditis. (C/I)

GESTATIONAL TRANSIENT THYROTOXICOSIS

Differential diagnosis between Graves' disease and gestational transient thyrotoxicosis

Differential diagnosis between GD and GTT during early pregnancy is very important. GTT is a transient nonautoimmune hyperthyroid condition that affects around 1%–5% of pregnant women and accounts for most cases of hyperthyroidism in pregnancy. Both conditions are associated with common clinical manifestations, but GTT does not require treatment with Antithyroid drugs (ATD) and has not been associated with adverse pregnancy outcomes. Hence, a careful history and physical examination are of utmost importance in establishing the etiology. GTT is diagnosed for the first time in early pregnancy and resolves by the end of the 1st or 2nd trimester of pregnancy. TSH is generally suppressed, T4 is elevated, and TRAb is absent. Other distinguishing characteristics between GTT and GD are elaborated in Table 4.[52]

Table 3: Diagnostic clues regarding the etiology of thyrotoxicosis in the peri-pregnancy setting[49]

	GTT	GD	Toxic nodular goiter	Postpartum thyroiditis
Presence of TRAb	No	Yes	No	No
Severity of thyrotoxic symptoms	Mild	Variable, may be severe	Variable	Mild
Stigmata of GD	None	May be present: Diffuse goiter, thyroid bruit, ophthalmopathy	None	None
Ratio of serum T3:T4	<20:1	>20:1	>20:1	<20:1
Radioactive iodine uptake/scan (contraindicated in pregnancy)	NA	Elevated uptake; diffuse pattern on scan	Normal to elevated uptake; focal uptake in autonomous nodule (s)	Low to absent uptake
Presence of/emesis nausea	Yes, may be severe	No	No	No

GD: Graves' disease, GTT: Gestational transient thyrotoxicosis, TSH: Thyroid-stimulating hormone, TRAb: TSH receptor antibodies, NA: Not available, T4: Tetraiodothyronine, T3: Triiodothyronine

Consensus statement

GD can be distinguished from GTT based on the presence of hyperthyroid symptoms prior to pregnancy, goiter, TSH-receptor antibodies, and the presence or absence of nausea/vomiting. (C/I)

Management of gestational transient thyrotoxicosis

The degree of symptoms determines how to treat women with GTT.[4]

- Controlling vomiting and treating dehydration with intravenous fluids is the standard of care for women with hyperemesis gravidarum
- Dehydration and irregular electrolytes must be managed with frequent physician visits in women with severe hyperemesis gravidarum
- Hospitalization is essential in severe cases
- Since serum T4 recovers to normal between 14 and 18 weeks of gestation, ATD medications are not recommended, and early pregnancy usage of ATDs increases the risk of birth abnormalities
- Small doses of β-blockers given over a brief period may be helpful in circumstances when symptomatic therapy is advised and close follow-up with a repeat investigation into the etiology of sickness should be carried out.[4]

Consensus statement

- The appropriate management of abnormal maternal thyroid tests attributable to GTT and/or hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed. (C/I)
- β-blockers may be considered for a brief period of time to providesymptomatic relief. (C/I)

GRAVES' DISEASE DURING PREGNANCY

GD is an autoimmune organ-specific disease wherein the TRAb stimulates the growth and function of the thyroid gland and is directed against the TSHR. GD is the most frequent cause of thyrotoxicosis in iodine-sufficient countries.[52,53] Estimates have shown that OH occurs in <1%, and GD in <0.5% of pregnant women.[52] Uncontrolled GD during pregnancy can lead to maternal, obstetrical, fetal, and neonatal complications. Therefore, accurate diagnosis and measures to maintain euthyroidism throughout pregnancy and the delivery of a healthy, euthyroid infant should be the goal.[52]

Table 4: Distinguishing characteristics between gestational transient thyrotoxicosis and Graves' disease

	GD	GTT
Hyperthyroid symptoms before pregnancy	+	−
Hyperthyroid symptoms during pregnancy	+	+/−
Nausea/vomiting	−/+	++
Goiter/ophthalmopathy	+	−
TRAb/TSI	+	−

GTT: Gestational transient thyrotoxicosis, TSH: Thyroid-stimulating hormone, TRAb: TSH receptor antibodies, TSI: Thyroid-stimulating immunoglobulin, GD: Graves' disease, +: Presence, −: Absence

Diagnosis of Graves' disease in pregnancy

The signs and symptoms of GD in pregnancy are similar to those of a nonpregnant GD patient. These include palpitations, tremors, heat intolerance, weight loss, and loose bowel movements. The signs include ophthalmopathy, goiter, and rarely, pretibial myxedema.[52] Some women with GD experience an exacerbation of symptoms in the 1st trimester of pregnancy, which may be due to a moderate increase in the incidence of GD in early pregnancy. The incidence of GD becomes very low by the 3rd trimester with a decrease in TRAb.[4] GD should be suspected in a hyperthyroid pregnant woman based on the following:

1. Having symptoms before pregnancy
2. A prior diagnosis of hyperthyroidism
3. A previous birth to an infant with thyroid dysfunction.

Thyroid function tests for women with Graves' disease during pregnancy

- GD is diagnosed with suppressed TSH, elevated FT4, and positive TRAb[52]
- Maternal serum TSH and TT4/FT4 are the initial

tests required for evaluation for hyperthyroidism in pregnancy.[52] These should be measured approximately every 2–4 weeks following the initiation of therapy, and every 4–6 weeks after achieving the target value[4]

- When trimester-specific FT4 values are not available, the use of reference range for nonpregnant patients is recommended. A TT4 measurement with a reference value of 1.5 times the nonpregnancy range may be used in the 2nd and 3rd trimesters[4]
  - A study was conducted to evaluate the reference interval for thyroid function in different trimesters of pregnancy (n = 600 women; 200 from each trimester) and evaluate the degree of elevation of TT4 versus nonpregnant women. The rise in mean TT4 in the 2nd trimester occurred by 25% versus the value at the 6th to 9th week, and by 35% versus the nonpregnant value. These findings are in contrast with the notion that TT4 rises maximally to 50% of its nonpregnant value after week 16 of pregnancy. The increase in TT4 is much less than what some guidelines suggest.[54]
- In cases where TSH is suppressed and T4 remains normal, as observed in the setting of exogenous T3 or autonomous functioning nodule, T3 is indicated in a clinically hyperthyroid patient[52]
- TRAb is ordered if tests are consistent with hyperthyroidism.[52]

Measurement of TSH-receptor antibody in women with Graves' disease during pregnancy

Serum TRAb levels should be determined in early pregnancy so that it can help in evaluating pregnancies at risk and be helpful in a mother who is still in need of ATD therapy to remain euthyroid. Repeat testing should occur at weeks 18–22 if maternal TRAb concentration is elevated in early pregnancy, whereas no further TRAb testing is needed if it is undetectable or low in early pregnancy. A repeat determination of TRAb is recommended at weeks 18–22 if the patient requires treatment with ATDs for GD through mid-pregnancy. A TRAb measurement should again be performed in late pregnancy (weeks 30–34) to evaluate the need for neonatal and postnatal monitoring if TRAb is elevated at weeks 18–22 or if the mother is taking ATD in the 3rd trimester.[4]

Indications for TRAb test in pregnant women with GD:[4]

- Mothers with untreated or ATD-treated hyperthyroidism in pregnancy
- Previous history of GD with past treatment with radioiodine or total thyroidectomy
- Previous history of delivering an infant with transient hyperthyroidism
- Known history of thyroidectomy for the treatment of hyperthyroidism in pregnancy.

Consensus statement

- GD is diagnosed with suppressed TSH, elevated TT4, and positive TRAb. (C/I)
- Maternal serum TSH and TT4 are the initial tests required for evaluation of hyperthyroidism in pregnancyand should be measured approximately every 2–4 weeks after initiation of therapyand every 4–6 weeks after achieving the target value. (C/I)
- Serum TRAb should be ordered if tests are consistent with hyperthyroidism. (C/I)
- Serum TRAb levels should be determined in early pregnancy so that it can help in evaluating pregnancies at risk. (C/I)
- TRAb should be repeated at 18–22 weeks, if the maternal TRAb concentration is elevated in early pregnancy. If elevated at 18–22 weeks, the TRAb should be repeated again during late pregnancy (weeks 30–34) or if the mother is taking ATD in the third trimester, to evaluate the need for neonatal and postnatal monitoring. (C/I)

Ultrasonography for diagnosis of fetal hyperthyroidism

Elevated TRAb, uncontrolled hyperthyroidism, and preeclampsia may be responsible for compromising fetal well-being. Ultrasound examinations can assist in the assessment of gestational age, fetal viability, amniotic fluid volume, fetal anatomy, and the detection of malformations. Ultrasonography (USG) can help in detecting signs of potential fetal hyperthyroidism such as fetal tachycardia (heart rate >170 bpm, persistent for over 10 min), intrauterine growth restriction (IUGR), presence of fetal goiter (the earliest sonographic sign of fetal thyroid dysfunction), accelerated bone maturation, signs of congestive heart failure, and fetal hydrops. An experienced obstetrician or maternal-fetal medicine specialist, neonatologist, and anesthesiologist are essential for the management of these patients. Overall, fetal hyperthyroidism can be diagnosed based on maternal history, interpretation of serum TRAb levels, and fetal USG.[4] The ATA also suggests cordocentesis in rare circumstances, which may be of use when fetal goiter is detected in women taking ATDs to help determine whether the fetus is hyperthyroid or hypothyroid.[4]

Consensus statement

- Fetal ultrasonography should be performed in all women with hyperthyroidism in pregnancy.(C/I)
- Ultrasound monitoring can assess heart rate, growth, amniotic fluid volume, and the presence of fetal goiter, and can hence be useful in detecting signs of potential fetal hyperthyroidism. (C/I)

Management of patients with Graves' disease during pregnancy

Preconception counselling should be initiated for the successful management of GD in pregnancy. Or the successful management of GD in pregnancy, preconception counseling should be initiated. Early recognition of the symptoms and utilization of a multidisciplinary approach is essential involving the maternal-fetal-medicine specialist, anesthesiologist, endocrinologist, neonatologist, and pediatric endocrinologist.[55] The treatment of GD in pregnancy is aimed at maintaining T3 and T4 levels in the upper quartile of pregnancy-specific rangers with strict monitoring of maternal thyroid function at appropriate intervals. GD is treated by reducing TH synthesis, using ATD, or by reducing the amount of thyroid tissue with RAI treatment or total thyroidectomy.[4,56]

Antithyroid drugs for patients with Graves' disease

Important ATDs are thionamides, such as propylthiouracil (PTU), carbimazole, and the active metabolite of the latter, methimazole (MMI). ATDs reduce TSH-R-Ab levels and improve rates of remission compared to no therapy.[4,56]

ATDs inhibit TH synthesis by reducing iodine organification and coupling monoiodotyrosine and diiodotyrosine. The thyroid function tests are normalized gradually over weeks with ATDs. The initial dose of ATD depends on the severity of the symptoms and the degree of hyperthyroxinemia.[4]

The starting dose of ATD should be gradually reduced (titration regimen) as thyrotoxicosis improves. Thyroid function tests are carried out every 3–4 weeks after starting treatment, and the dose is titrated based on TT4 and total T3 levels. Most patients reach euthyroidism within 3–4 weeks of treatment. For several months after therapy, TSH levels often remain suppressed, and a sensitive index of early treatment response is not available. The titration regimen is often preferred to minimize the dose of ATD.[57]

MMI in doses of 10–20 mg or PTU 100–200 mg daily should be started, and after 1 month, it is desirable to adjust the doses to maintain maternal T4 in the upper 1-3rd of each trimester-specific reference interval. T4 and TSH should be monitored at monthly intervals during pregnancy. Serum TSH levels of 0.1–2.0 mU/l are appropriate.[57] The equivalent potency of MMI to PTU is approximately 1:20, and since the half-life of PTU is shorter than that of MMI, PTU dosing should generally be split into two or three daily doses. MMI can generally be given in one daily dose. In rare cases of severe hyperthyroidism, twice or three-times daily dosing may be of benefit.[4]

Patients taking thionamide drugs usually develop side effects within the 1st months following the initiation or re-initiation of therapy. As the risk of hepatotoxicity was reported in patients exposed to PTU, it was advised to be limited only to the 1st trimester of pregnancy. Patients with MMI allergy or those with thyroid storm can be exceptions to the use of PTU, and hepatic enzyme monitoring during the administration of PTU may be considered. The use of ATDs such as MMI and PTU in pregnancy is also reported to be associated with potential teratogenic effects.[4]

Withdrawal or modifying antithyroid drugs in early pregnancy

GD patients treated with ATDs gradually enter into remission of the autoimmune abnormality when made euthyroid. It is suggested that ATD medication should be withdrawn from a woman with a confirmed pregnancy receiving ATD therapy for GD and who appears to be in remission, and repeated thyroid function testing during the 1st trimester of pregnancy should be performed. PTU is preferred over MMI (though PTU too has been reported to cause teratogenicity) due to a questionable lower risk of birth defects, if at all, ATD therapy is needed during the 1st trimester. It is advisable to stop ATDs early in gestation before the major teratogenic periods (gestational weeks 6–10). Testing for pregnancy is important in women receiving ATD within the 1st few days of missing their periods. In case of a positive pregnancy test, the woman should contact the clinician to withdraw or modify ATD therapy and to discuss thyroid function testing.[4]

Withdrawal of ATD in early pregnancy is associated with an increased risk of rapid relapse of hyperthyroidism and varies amongst patients.[4]

If the risk of relapse is high, PTU can be administered as the drug of choice instead of withdrawing the ATD medication.

Management of fetal goiter

In the early stages of fetal goiter, the mother with GD who is taking antithyroid medication, the first step is to decrease the dosage or discontinue the administration of the medication before planning intraamniotic treatment with LT4.[58] Upon confirmation of fetal hypothyroidism, replacement therapy with intraamniotic instillation of LT4 should be considered.

Hyperthyroidism requires maternal administering of PTU or MMI or, if already initiated, increasing the dose. Some cases may require small doses of replacement THs.[59]

Consensus statement

- For patients with GD, a starting dose of MMI 10–20 mg or PTU 100–200 mg daily should be considered, and should be gradually adjusted as thyrotoxicosis improves. The dose of ATDs during pregnancy should be lower.
- During the first 16 weeks of pregnancy, PTU is preferred.
- Thyroid function tests should be carried out every 3–4 weeks after starting treatment, and dose titration should be based on total T4 and total T3 levels. (C/I)
- If ATDs are used during the preconception period, it is mandatory to test for pregnancy within the first days of missing menstruation, and in cases of a positive pregnancy tests, a clinical should be consulted immediately for withdrawal or modification of the ATD therapy. (C/I)
- In cases of early fetal goiter, the dosage of ATD should be decreased or discontinued in the mother with GD. Intraamniotic LT4 instillation can be done after confirmation of fetal hypothyroidism. (C/I)

Indications and timing for thyroidectomy in the management of Graves' disease during pregnancy

During pregnancy, surgery is riskier than medical therapy, and hyperthyroidism can lead to complications. Surgery is also linked to an increased risk of spontaneous abortion or premature delivery.[56] Considerations for thyroidectomy in maternal hyperthyroidism:

- Subtotal thyroidectomy in patients with major or severe adverse reactions to ATD
- Subtotal thyroidectomy may be required if hyperthyroidism is uncontrolled due to lack of compliance, the requirement of high doses of ATDs to control the disease, and large goiter that may require high doses of drugs
- The optimal timing for surgery is in the 2nd trimester, as:
  - Organogenesis is complete
  - The uterus is relatively resistant to stimulating events
  - The rate of spontaneous miscarriage is reduced.

As thyroidectomy is followed by a gradual disappearance of TRAb, the withdrawal of ATD in the mother postprocedure may lead to isolated fetal hyperthyroidism. Therefore, careful fetal monitoring and evaluation of serum TRAb values before surgery are suggested to prevent the risk of isolated fetal hyperthyroidism. For patients who are nonresponsive to ATD therapy, β-blocking agents and a short course of potassium iodide solution (50–100 mg/d) can be used to prepare them for surgery.[56]

Consensus statement

- Thyroidectomy in pregnancy should be indicated in special situations, with the second trimester being the optimal time to conduct it. (C/I)
- Careful fetal monitoring throughout and post-procedureis essential to prevent the occurrence of isolated fetal hyperthyroidism if maternal TRAb concentration is high before thyroidectomy. (C/I)

Graves' disease in lactating women

The WHO recommends breastfeeding for up to 2 years and exclusive breastfeeding for the 1st 6 months. A hyperthyroid mother needs adequate treatment in the postpartum period and also long-term treatment may be required.[60]

In patients receiving an ATD at delivery, therapy should be continued after delivery even if breastfeeding is possible, as ATDs are shown to be safe. The ATDs are excreted in the breast milk in very small quantities, and experts recommend using the lowest effective dose possible <MMI 20 mg daily and PTU 300 mg total daily. The ATD should be taken after the mother has breastfed, but 131-iodine therapy is contraindicated in lactating mothers. Surgery is the preferred definitive therapy in lactating mothers.[55]

Breastfeeding is considered safe for patients with PTU ≤300 mg/day or MMI 20–30 mg/day and close monitoring of thyroid function. However, breastfed infants of mothers with thyroid dysfunction should be evaluated for normal growth and development and normal thyroid function.[60]

Consensus statement

ATDs are safe in lactating mothers, and should be prescribed in divided doses, to be taken immediately after a breastfeed. (C/I)

Resistant Graves' disease in pregnancy

Resistant GD in pregnancy is the inability to control TH levels after using the maximum permissible dose of ATD in pregnancy (30 mg/day of MMI or 40 mg/day CM or PTU 600 mg/day). Further, even β-blockers have to be continued for a prolonged period in these patients, which may increase the risk of IUGR, fetal bradycardia, and neonatal hypoglycemia. As the fetal thyroid gland is extremely sensitive to ATD, higher doses can lead to fetal hypothyroidism, and the ATD dose for a long duration may lead to ATD-induced embryopathy. Hence, the use of ATDs and β-blockers in larger doses for a longer period increase the risk of growth retardation, anomalies, and thyroid dysfunction in the fetus of mothers with resistant GD.[61]

Total thyroidectomy during the 2nd trimester of pregnancy can be considered an alternative to uncontrolled GD in pregnancy. Measures to be taken while deciding the procedure:[61]

- The patient should be prepared with high doses of β-blockers, steroids, and potassium iodide solution to avoid thyroid storms intra-and postoperatively
- The chances of maternal cardiac failure, cardiac rhythm disturbances, fetal distress, preterm labor, or fetal demise are to be kept in mind
- Postoperatively, patients should be followed up with T4 levels and replaced with THs once T4 levels sink below the normal range
- TSH should not be taken as a benchmark to follow-up for the initial few weeks as TSH may be suppressed due to the long-standing TH level or due to hCG levels
- The fetus need regular follow-up in patients who have undergone total thyroidectomy during the 2nd trimester, as the effects of TRAB continue for years after total thyroidectomy.

Mother and fetus require close monitoring in situations where surgery is deferred;[61]

- Maternal TFT (TSH, T4 or FT4, T3) should be repeated every 2 to 4 weeks, targeting the T4 and T3 levels in the upper reference range of normal
- Maternal cardiac status is to be assessed at each visit. Anemia needs prompt correction and avoidance of infection
- Fetal surveillance includes TRAb, serial monthly USG, and cardiotocography. TRAb samples are done at 18–20 weeks and later at 30–34 weeks. The presence of TRAb more than 3× upper limit of normal (ULN) indicates higher chances of fetal hyperthyroidism.

Neonatal care:[61]

- Neonatal thyroid function should be assessed in all newborn babies
- Every neonate should be tested for TSH, FT4, and TRAb
- FT4 and TSH should be evaluated starting at 2–3 days of life and repeated every week until the disappearance of TRAb and TFT normalization
- Neonates with normal TFT with significant elevation of TRAb should be closely monitored, as TRAb-mediated effects in neonates may occur as late as 40 days. In such situations, TFT should be repeated within 2 weeks. Any clinical or biochemical evidence of thyrotoxicosis mandates ATD in neonates
- All babies with abnormal TFTs should be referred to endocrinologists and urgently reviewed by specialists.

Consensus statement

- In cases of resistant GD, total thyroidectomy during the second trimester of pregnancy can be considered, and if the procedure is deferred, the mother and fetus require close monitoring, in terms of assessment of maternal TFT (TSH, total T4, or total T3), cardiac status, fetal surveillance (TRAb, serial monthly USG, and cardiotocography). (C/I)
- Every neonate should be tested for TSH, total T4, and TRAb, and those with normal TFT and significant elevation of TRAb should be closely monitored. Any clinical or biochemical evidence of thyrotoxicosis mandates ATD in neonates. (C/I)

Balancing maternal and fetal thyroid function in Graves' disease in Pregnancy

The following is suggested for balancing maternal and fetal thyroid function:[4,62]

1. As ATD therapies including MMI, PTU, and carbimazole can cross the placenta, it can modulate fetal thyroid function and is reported to be more potent in the fetus than in the mother. Hence, the goal of ATD treatment should be directed to maintaining maternal TT4/FT4 values at or just above the pregnancy-specific ULN to avoid overtreating the fetus and deleterious fetal impact
2. ATD therapy can be discontinued in ~ 20%–30% of patients in the last trimester of gestation. TSH within the reference range indicates that the ATD dose has to be reduced to avoid fetal overtreatment. ATD can be successfully withdrawn when maternal TRAb disappears in late pregnancy
3. The ATD dose should be reduced in the second half of pregnancy to protect the fetus. A balance in ATD dosing with careful clinical evaluation of the fetus and the mother is needed since an increase in dose to normalize maternal serum TT3 will cause elevated serum TSH in the infants at birth
4. Women should be informed about this risk of relapse of hyperthyroidism postdelivery and should be monitored appropriately. Low-dose ATD can be administered during the postpartum period to prevent relapse
5. The combination of LT4 and an ATD (block-replace therapy) administered to the mother has not been shown to improve GD remission rates and may cause fetal goiter and hypothyroidism. The reason is, the placenta is permeable to ATD but not to the LT4 given to the mother, and the fetal thyroid is relatively more sensitive to the effect of ATDs than the maternal thyroid. The only indication for such combination therapy during pregnancy is in the treatment of isolated fetal hyperthyroidism; ATD to treat the fetal hyperthyroidism and LT4 to keep the mother euthyroid.

THYROID NODULES DURING PREGNANCY

Pregnancy represents a stimulatory environment for thyroid follicular cells. Physiological effects of pregnancy such as stimulatory effects of hCG, sustained activation of the signaling cascade mediated by the TSHR, iodine deficiency, and excess are associated with an increased prevalence of thyroid nodules.[18,63] The prevalence of thyroid nodules during pregnancy in areas with mild to moderate iodine deficiency varies between 3% and 21% and increases with increasing parity. The cancer rate of thyroid nodules diagnosed in pregnancy has been reported to be between 12% and 43%.[64] All women with a thyroid nodule should have a TSH measurement performed. TSH assessment can detect an autonomously functioning nodule when TSH is suppressed. When suppressed TSH is identified beyond 16 weeks of gestation, further evaluation may be delayed until after pregnancy when TSH can be accurately repeated.[4] The ATA suggests that for women with suppressed serum TSH levels that persist beyond 16 weeks of gestation, FNA of a clinically relevant thyroid nodule may be deferred until after pregnancy. At that time, if serum TSH remains suppressed, a radionuclide scan to evaluate nodule function can be performed if not breastfeeding.[4]

Consensus statement

- During suspicion of thyroid nodules in pregnancy, physical examination is suggested to confirm palpable abnormality, neck lymph nodes and signs of compression of local adjacent structures. (C/IIa)
- Historical aspects such as childhood radiation exposure, family history of thyroid cancer, hereditary syndromes carrying the risk, and history of symptoms should be considered. (C/IIa)
- Ultrasonographic evaluation should be performed as it can identify the size and location of a thyroid nodule and also evaluate features associated with malignancy. It canalso help in guiding which thyroid nodules should undergo FNAB. (C/I)
- Fine needle aspiration biopsy (FNAB) can be performed for nodules ≥1 cm with a sonographic appearance highly suspicious of malignancy, whereas for nodules with lower risk, FNAB is recommended only at larger sizes (1.5–2.5 cm). (C/I)
- TSH measurement should be performed in all women with a thyroid nodule, as the test can detect an autonomously functioning nodule when TSH is suppressed. If suppressed serum TSH levels persist beyond 16 weeks of gestation, FNAB of the thyroid nodule can be deferred until after pregnancy. (C/I)
- LT4 suppressive therapy is not recommended for cytologically benign thyroid nodules. (C/I)
- As the diagnostic performance of molecular tests may change due to thyroid gestational stimulation, application of molecular testing for cytologically indeterminate nodules in pregnant women is not recommended. (C/I)
- In case of newly diagnosed thyroid carcinoma, surgery can be considered during the 2nd trimester if there is substantial growth of nodules by 24 weeks gestation. Stable nodules during midgestation does not require immediate surgery, and can be performed post-delivery. (C/I)
- Thyroid hormone therapy can be initiated to lower serum TSH levels and maintain target TSH levels for the remainder of gestation if surgery is not performed in case of differentiated thyroid cancer diagnosis during gestation. (C/I)
- In pregnant women with previously treated thyroid cancer, careful monitoring of thyroid function tests and smaller levothyroxine increase in dose is required. If any change in dose is done, treatment adequacy should be evaluated every 4 weeks. (C/I)

POSTPARTUM THYROIDITIS

PPT is a destructive autoimmune illness that occurs in the 1st year following delivery in women with no prior history of thyroid disease. PPT can result in either transient or permanent thyroid dysfunction.[65] It comprises thyrotoxicosis followed by hypothyroidism; while 1/3rd of patients may manifest both phases, the others may be either only thyrotoxic or hypothyroid.[51]

Pregnant women with positive TPOAbs early in pregnancy have a 30%–52% chance of having PPT. Women who test positive for TPOAbs during their 3rd trimester have an 80% likelihood of getting PPT. The following are three clinical manifestations of PPT:[65]

1. Transient hyperthyroidism (32% of patients)
2. Transient hypothyroidism (43% of patients)
3. Transient hyperthyroidism followed by hypothyroidism and then recovery, which is the classic form of PPT (25% of patients).

Symptoms associated with postpartum thyroiditis

Most women with PPT are asymptomatic or just minimally symptomatic throughout the thyrotoxic phase of the illness, the reason being that the increase in THs is normally moderate and that T4 levels are often higher than T3 levels. However, in prospective investigations, palpitations, weariness, and irritability were among the reported symptoms. The hypothyroid phase of PPT can cause symptoms such as paresthesias, dry skin, tiredness, and cold intolerance, and these are manifested more frequently. According to one study, people with PPT and TPOAb had higher symptoms than people without TPOAb.[4]

Diagnosis of postpartum thyroiditis

Distinguishing between thyrotoxicosis caused by PPT and that by GD is challenging. This is a crucial distinctionbecause the two disease entities have markedly different clinical courses and require different therapeutic approaches. The first appearance of symptoms can reveal some etiological information.[4]

Distinguishing characteristics between Graves' disease and other postpartum thyrotoxic conditions

Distinguishing characteristics of the postpartum thyrotoxicosis causes are elaborated in Table 5.

Consensus statement

- The thyrotoxic phase of PPT is usually asymptomatic, whereas the hypothyroid phase of PPT can cause symptoms such as paresthesias, dry skin, tiredness, and cold intolerance (C/I)
- Symptoms, presence or absence of TSH receptor antibodies and T4:T3 ratio can help distinguish PPT from GD or other thyrotoxicosis conditions. (C/I)

Management of postpartum thyroiditis

Management of thyrotoxic and hypothyroid phases of PPT is summarized in Figure 2.[4]

Duration of treatment

The guiding concepts for the use of LT4 are to keep women who are trying to get pregnant or who are pregnant in a euthyroid state. By 12 months postpartum, it is possible to begin tapering LT4 doses to assess whether the hypothyroid phase of PPT was temporary or permanent. Tapering should be done gradually, and TSH levels should be checked every 6–8 weeks. If LT4 is initiated for PPT, discontinuation of therapy should be attempted after 12 months. Tapering of LT4 should be avoided when a woman is actively attempting pregnancy or is pregnant.[4]

Consensus statement

- ATDs are not recommended for the treatment of the thyrotoxic phase of PPT. (C/I)
- Following the resolution of the thyrotoxic phase of PPT, serum TSH should be measured in approximately 4–8 weeks (or if new symptoms develop) to screen for the hypothyroid phase. (C/I)
- LT4 should be considered in women who have symptomatic PPT-induced hypothyroidism. Their TSH level should be assessed every 4 to 8 weeks until thyroid function is normalized if no therapy is initiated. Additionally, hypothyroid women who are planning a pregnancy or who are breastfeeding should begin taking LT4. (C/I)
- If LT4 is initiated for PPT, discontinuation of therapy should be attempted after 12 months. (C/I)
- Women with a prior history of PPT should have TSH testing annually to evaluate the development of permanent hypothyroidism. (C/I)

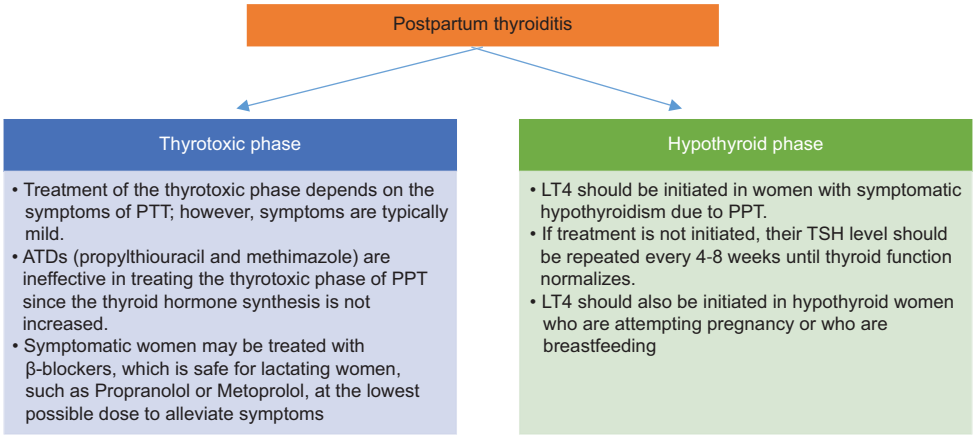

Figure 2: Management of postpartum thyroiditis.[4] TSH: Thyroid stimulating hormone; PPT: Postpartum thyroiditis

Table 5: Characteristics of causes of postpartum thyrotoxicosis[66]

Characteristic	GD	Postpartum thyroiditis	Painless sporadic thyroiditis	Painful subacute thyroiditis
Frequency	Common	Most common	Rare	Rare
Etiology	Autoimmune	Autoimmune	Autoimmune	Autoimmune
Erythrocyte sedimentation rate	Normal	Normal	Normal	High
Radioiodine uptake	High	Low	Low	Low
T3/thyroxine ratio	High	Low	Low	Variable
Thyroid peroxidase antibodies	High	High	High	Low or absent
Thyrotropin receptor-stimulating antibodies	Present	Absent	Absent	Absent

GD: Graves' disease, T3: Triiodothyronine

EXECUTIVE SUMMARY OF CONSENSUS STATEMENT

Hypothyroidism in pregnancy

- A high prevalence of hypothyroidism is observed in Indian pregnant women (with the use of trimester-specific TSH cutoffs), and a large proportion of pregnant women with SCH are positive for anti-TPO (A/I)
- Interpretation of the prevalence rates of hypothyroidism should be based on the trimester of pregnancy, ethnicity, iodine nutrition, anti-TPO positivity, and the reference range or cut-off level and analytical platform on which TSH is measured (C/IIa).

Hypothyroidism and complications

- Indian pregnant women should ingest approximately 250 μg iodine daily (A/I)
- Salt intake consisting of a minimum of 250 μg iodine daily should be consumed by pregnant women
- Those on regular LT4 supplementation can be exempted from supplemental iodine (A/I)
- Women with positive TPOAb develop hypothyroidism during pregnancy and are at a high risk of miscarriages, preterm births, gestational diabetes, intrauterine growth retardation, placental abruption, premature rupture of membranes, and depression during pregnancy. However, treating everyone the same has questionable benefits (A/I).

Diagnosis

- All patients seeking pregnancy, or those during early pregnancy should undergo a clinical evaluation and testing for serum TSH, and when risk factors for thyroid dysfunction are identified (C/IIa)
- The establishment of trimester-specific reference intervals in each region is very important, as the intervals for THs cannot be extrapolated due to differences in ethnicity, maternal iodine status, laboratory assay method, and rigor for the selection of the reference population (A/I)
- The TSH reference range should be pregnancy and trimester-specific and developed from a local population that is iodine sufficient and free from any underlying thyroid disorder
- In the case of unavailability of locally derived reference ranges, an upper reference limit of ~4.0 mU/L may be used during the late 1st trimester, with a gradual return towards the nonpregnant range in the 2nd and 3rd trimesters (C/IIa)
- If the TSH concentration is outside the pregnancy reference range, T4 level measurement is recommended to confirm the diagnosis (C/IIa)
- In the case of the nonavailability of a reliable FT4 assay, total T4 multiplied by 1.5 can be used
- In women with known TAI, the TSH concentrations should be assessed every 4 weeks through to mid-pregnancy
- TPOAb status should be assessed in pregnant women with a TSH concentration of 2.5–10.0 mU/L (C/IIa).

Treatment

- Timely and appropriate administration and adjustment of LT4 during pregnancy are important to normalize thyroid function as it has a role in improving the hypothyroidism-induced metabolic disorder during pregnancy, reducing the occurrence of complications, and achieving satisfactory pregnancy outcomes (A/I)
- LT4 treatment in pregnant women positive for TPOAb and SCH reduces the risk of premature birth, miscarriage, recurrent pregnancy loss, postpartum hemorrhage, and low birth weight infants (A/I)
- LT4 treatment for TPOAb-positive euthyroid pregnant women with a prior history of loss may be considered on an individual case-to-case basis is given its potential benefits in comparison with its minimal risk and in such cases, 25–50 μg of LT4 is a typical starting dose
- In newly diagnosed patients with SCH in pregnancy, a starting dose of LT4 of 1.20 μg/kg/day can be considered. TSH values should be checked every 4–6 weeks during the 1st trimester and once during the 2nd and 3rd trimesters, and the dose should be adjusted to maintain TSH to <2.5 mU/l or within the trimester-specific reference range (C/IIa)
- LT4 treatment is suggested for all pregnant women positive for TPOAb and having TSH above the pregnancy-specific range. Also, pregnant women with TSH between 2.5–4 mU/l and anti-TPO positive may be considered for LT4 depending on the decision by the treating Physician, an Endocrinologist, and Obstetrician-Gynecologist (C/IIa)
- In hypothyroid women on LT4 treatment, preconception serum TSH should be evaluated in those who are planning pregnancy, and the dose should be adjusted to achieve a TSH value between the lower reference limit and 2.5 mU/L (B/IIa).
- In hypothyroid patients with a suspected or confirmed pregnancy (positive home pregnancy test), the LT4 dose can be increased by ~20%–30% (B/IIa)
- In women following delivery, LT4 should be reduced to the patient's preconception dose, and additional thyroid function testing should be performed at approximately 6 weeks postpartum (C/IIa)
- Other thyroid preparations such as T3 or desiccated thyroid should not be used in pregnancy (C/IIa)
- Iron/calcium supplements, if prescribed to pregnant women, should be advised to be consumed at least 4 h after LT4 treatment.

Screening

- Universal screening for hypothyroidism for all antenatal women, especially in the 1st trimester, should be preferred over targeted case-based screening
- Case-based screening can miss a substantial proportion of pregnant women with SCH and OH. Case-based screening can also miss women with positive autoantibodies with otherwise normal TFTs. These patients may need repeat testing both during and after pregnancy as they are at higher risk of hypothyroidism and postpartum thyroiditis.

Isolated hypothyroxinemia

- Based on current evidence, treatment of IH is not recommended at present, and such women should be closely followed during gestation with repeat measurement of TFT.

THYROTOXICOSIS IN PREGNANCY

- Thyrotoxicosis is most frequently caused by hyperthyroidism, less frequently by subacute, painful or painless thyroiditis with the passive release of THs from a damaged thyroid gland, and rarely by a TSH-secreting pituitary adenoma, struma ovarii, functional thyroid cancer metastases, or germline TSHR mutations (C/I)
- The most frequent cause of thyrotoxicosis in the 1st trimester is GTT
- A medical history, physical exam, and testing of the maternal blood FT4 or TT4 concentrations should be performed when a suppressed serum TSH is found in the 1st trimester (a serum TSH below 0.1 mU/L (in some cases, even undetectable) by week 11 (A/I)
- Serum total T4 and T3 levels more than 1.5 times the nonpregnant range should be used to diagnose thyrotoxicosis in the 2nd and 3rd trimesters of pregnancy
- Measuring TRAb may be useful in determining the cause of thyrotoxicosis (C/I)
- Radionuclide scintigraphy or radioiodine uptake determination should not be performed in pregnancy (C/I)
- When treating a patient with thyrotoxicosis, it is crucial to identify the disease's underlying etiology (C/IIa)
- Apart from the common cause, GTT, other causes to be considered in the differential diagnosis of thyrotoxicosis in pregnancy include overt hyperthyroidism subtypes such as GD, toxic multinodular goiter, and toxic adenoma, as well as thyroiditis (C/I).

Gestational transient thyrotoxicosis

Diagnosis

- GD can be distinguished from GTT based on the presence of hyperthyroid symptoms before pregnancy, goiter, TSH-receptor antibodies, and the presence or absence of nausea/vomiting (C/I).

Treatment

- The appropriate management of abnormal maternal thyroid tests attributable to GTT and/or hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed (C/I)
- β-blockers may be considered for a brief period to providesymptomatic relief (C/I).

Graves hyperthyroidism during pregnancy

Diagnosis

- GD is diagnosed with suppressed TSH, elevated TT4, and positive TRAb (C/I)
- Maternal serum TSH and TT4 are the initial tests required for evaluation of hyperthyroidism in pregnancy and should be measured approximately every 2–4 weeks after initiation of therapy and every 4–6 weeks after achieving the target value (C/I)
- Serum TRAb should be ordered if tests are consistent with hyperthyroidism (C/I)
- Serum TRAb levels should be determined in early pregnancy so that it can help in evaluating pregnancies at risk (C/I)
- TRAb should be repeated at 18–22 weeks if the maternal TRAb concentration is elevated in early pregnancy. If elevated at 18–22 weeks, the TRAb should be repeated during late pregnancy (weeks 30–34) or if the mother is taking ATD in the 3rd trimester, to evaluate the need for neonatal and postnatal monitoring (C/I)
- Fetal USG should be performed in all women with hyperthyroidism in pregnancy (C/I)
- Ultrasound monitoring can assess heart rate, growth, amniotic fluid volume, and the presence of fetal goiter, hence can be useful in detecting signs of potential fetal hyperthyroidism (C/I).

Treatment

- For patients with GD, a starting dose of MMI 10–20 mg or PTU 100–200 mg daily should be considered and should be gradually adjusted as thyrotoxicosis improves. The dose of ATDs during pregnancy should be lower
- During the 1st 16 weeks of pregnancy, PTU is preferred
- Thyroid function tests should be carried out every 3–4 weeks after starting treatment, and dose titration should be based on total T4 and total T3 levels (C/I)
- If ATDs are used during the preconception period, it is mandatory to test for pregnancy within the 1st days of missing menstruation, and in cases of positive pregnancy tests, a clinical should be consulted immediately for withdrawal or modification of the ATD therapy (C/I)
- In cases of early fetal goiter, the dosage of ATD should

be decreased or discontinued in the mother with GD. Intraamniotic LT4 instillation can be done after confirmation of fetal hypothyroidism (C/I).

Surgery

- Thyroidectomy in pregnancy should be indicated in special situations, with the 2nd trimester being the optimal time to conduct it (C/I)
- Careful fetal monitoring throughout and postprocedure is essential to prevent the occurrence of isolated fetal hyperthyroidism if maternal TRAb concentration is high before thyroidectomy (C/I).

In lactating mothers

- ATDs are safe for lactating mothers and should be prescribed in divided doses to be taken immediately after breast feeding (C/I).

In resistant Graves' disease

- In cases of resistant GD, total thyroidectomy during the 2nd trimester of pregnancy can be considered, and if the procedure is deferred, the mother and fetus require close monitoring in terms of assessment of maternal TFT (TSH, total T4, or total T3), cardiac status, fetal surveillance (TRAb, serial monthly USG, and cardiotocography) (C/I)
- Every neonate should be tested for TSH, total T4, and TRAb, and those with normal TFT and significant elevation of TRAb should be closely monitored. Any clinical or biochemical evidence of thyrotoxicosis mandates ATD in neonates (C/I).

Thyroid nodules during pregnancy

Diagnosis and management

- During the suspicion of thyroid nodules in pregnancy, a physical examination is suggested to confirm palpable abnormality, neck lymph nodes, and signs of compression of local adjacent structures (C/IIa)
- Historical aspects such as childhood radiation exposure, family history of thyroid cancer, hereditary syndromes carrying the risk, and history of symptoms should be considered (C/IIa)
- Ultrasonographic evaluation should be performed as it can identify the size and location of a thyroid nodule and also evaluate the features associated with malignancy. It can also help in guiding which thyroid nodules should undergo fine-needle aspiration biopsy (FNAB) (C/I)
- FNAB can be performed for nodules ≥1 cm with a sonographic appearance highly suspicious of malignancy, whereas for nodules with lower risk, FNAB is recommended only at larger sizes (1.5–2.5 cm) (C/I)
- TSH measurement should be performed in all women with a thyroid nodule, as the test can detect an autonomously functioning nodule when TSH is suppressed. If suppressed serum TSH levels persist beyond 16 weeks of gestation, FNAB of the thyroid nodule can be deferred until after pregnancy (C/I)
- LT4 suppressive therapy is not recommended for cytologically benign thyroid nodules (C/I)
- As the diagnostic performance of molecular tests may change due to thyroid gestational stimulation, the application of molecular testing for cytologically indeterminate nodules in pregnant women is not recommended (C/I)
- In the case of newly diagnosed thyroid carcinoma, surgery can be considered during the 2nd trimester if there is a substantial growth of nodules by 24 weeks of gestation. Stable nodules during midgestation do not require immediate surgery and can be performed postdelivery (C/I)
- TH therapy can be initiated to lower serum TSH levels and maintain target TSH levels for the remainder of gestation if surgery is not performed in the case of a differentiated thyroid cancer diagnosis during gestation (C/I)
- In pregnant women with previously treated thyroid cancer, careful monitoring of thyroid function tests and a smaller LT4 increase in dose is required. If any change in dose is made, treatment adequacy should be evaluated every 4 weeks (C/I).

Postpartum thyroiditis

- The thyrotoxic phase of PPT is usually asymptomatic, whereas the hypothyroid phase of PPT can cause symptoms such as paresthesias, dry skin, tiredness, and cold intolerance (C/I)
- Symptoms, presence or absence of TSHR antibodies and T4:T3 ratio can help distinguish PPT from GD or other thyrotoxicosis conditions (C/I)
- ATDs are not recommended for the treatment of the thyrotoxic phase of PPT (C/I)
- Following the resolution of the thyrotoxic phase of PPT, serum TSH should be measured in approximately 4–8 weeks (or if new symptoms develop) to screen for the hypothyroid phase (C/I)
- LT4 should be considered in women who have symptomatic PPT-induced hypothyroidism. Their TSH level should be assessed every 4–8 weeks until thyroid function is normalized if no therapy is initiated. Additionally, hypothyroid women who are planning a pregnancy or who are breastfeeding should begin taking LT4 (C/I)
- If LT4 is initiated for PPT, discontinuation of therapy

should be attempted after 12 months (C/I)

- Women with a prior history of PPT should have TSH testing annually to evaluate the development of permanent hypothyroidism (C/I).

REFERENCES

1. Singh S, Sandhu S. Thyroid Disease and Pregnancy. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538485/. [Last assessed on 2022 Sep 01].
2. Girling J, Marineau M. Thyroid and other endocrine disorders in pregnancy. Obstet Gynec Reprod Med 2010;20:265-71.
3. Vaidya B, Chan SY. Thyroid physiology and thyroid diseases in pregnancy. In: Vitti P, Hegedüs L, editors. Thyroid Diseases. Endocrinology. Ch. 23. Cham: Springer; 2018. p. 673-708.
4. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, *et al.* 2017 guidelines of the American thyroid association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 2017;27:315-89.
5. Bajaj S, Chawla T, Gupta P, Chaurasia A. Mehrotra R. Thyroid dysfunction in pregnancy – A tertiary care centre experience. Endocrinol Metab 2016;6:3-7.
6. Rajput R, Goel V, Nanda S, Rajput M, Seth S. Prevalence of thyroid dysfunction among women during the first trimester of pregnancy at a tertiary care hospital in Haryana. Indian J Endocrinol Metab 2015;19:416-9.
7. Dhanwal DK, Bajaj S, Rajput R, Subramaniam KA, Chowdhury S, Bhandari R, *et al.* Prevalence of hypothyroidism in pregnancy: An epidemiological study from 11 cities in 9 states of India. Indian J Endocrinol Metab 2016;20:387-90.
8. Soldin OP. Thyroid function testing in pregnancy and thyroid disease: Trimester-specific reference intervals. Ther Drug Monit 2006;28:8-11.
9. Springer D, Jiskra J, Limanova Z, Zima T, Potlukova E. Thyroid in pregnancy: From physiology to screening. Crit Rev Clin Lab Sci 2017;54:102-16.
10. Salmeen K, Kurbisch IJ. Thyroid physiology during pregnancy, postpartum, and lactation. In: Kovac C, Deal C, editors. Maternal-Fetal and Neonatal Endocrinology Physiology, Pathophysiology, and Clinical Management. 1st ed., Ch. 4. Academic Press United Kingdom: Elsevier; 2020. p. 53-60.
11. Alemu A, Terefe B, Abebe M, Biadgo B. Thyroid hormone dysfunction during pregnancy: A review. Int J Reprod Biomed 2016;14:677-86.
12. De Leo S, Pearce EN. Autoimmune thyroid disease during pregnancy. Lancet Diabetes Endocrinol 2018;6:575-86.
13. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, *et al.* Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. Clin Endocrinol (Oxf) 2010;72:825-9.
14. Wilson RE, Salihu HM, Groer MW, Dagne G, O'Rourke K, Mbah AK. Impact of maternal thyroperoxidase status on fetal body and brain size. J Thyroid Res 2014;2014:872410.
15. LaFranchi SH, Haddow JE, Hollowell JG. Is thyroid inadequacy during gestation a risk factor for adverse pregnancy and developmental outcomes? Thyroid 2005;15:60-71.
16. Zhang D, Cai K, Wang G, Xu S, Mao X, Zheng A, *et al.* Trimester-specific reference ranges for thyroid hormones in pregnant women. Medicine (Baltimore) 2019;98:e14245.
17. Yadav V, Dabar D, Goel AD, Bairwa M, Sood A, Prasad P, *et al.* Prevalence of hypothyroidism in pregnant women in India: A meta-analysis of observational studies. J Thyroid Res 2021;2021:5515831.
18. Azizi F, Tehrani FR. Thyroid Diseases in Pregnancy. 1st ed. Switzerland: Springer Nature; 2022.
19. Prashant T, Yashwant R, Malvika M. Systematic review on association between iodine level during pregnancy and its outcomes. Int J Health Sci Res 2018;8:269-79.
20. Tayade SA, Chhabra S. Iodine status and its determinants in subpopulation of pregnant women in rural Central India. Int J Reprod Contracept Obstet Gynecol 2018;7:665-70.
21. Jauharia S, Agarwala M, Ali W, Singh VK, Tasleem M. Status of iodine in rural pregnant women of different trimesters in Lucknow-A cross-sectional study. Clin Epidemiol Glob Health 2020;8:1195-203.
22. Rajput R, Yadav L, Nanda S, Yadav R. Trimester specific nutritional status of iodine among euthyroid pregnant women. Thyroid Disord Ther 2017;6:208.
23. Pramanik S, Mukhopadhyay P, Bhattacharjee K, Bhattacharjee R, Mukherjee B, Mondal SA, *et al.* Trimester-specific reference intervals for thyroid function parameters in Indian pregnant women during final phase of transition to iodine sufficiency. Indian J Endocrinol Metab 2020;24:160-4.
24. Rajput R, Yadav T, Seth S, Nanda S. Prevalence of thyroid peroxidase antibody and pregnancy outcome in euthyroid autoimmune positive pregnant women from a tertiary care center in Haryana. Indian J Endocrinol Metab 2017;21:577-80.
25. Taylor PN, Zouras S, Min T, Nagarahaj K, Lazarus JH, Okosieme O. Thyroid screening in early pregnancy: Pros and cons. Front Endocrinol (Lausanne) 2018;9:626.
26. Mir F, Chiti H, Mazloomzadeh S. Short-term adverse pregnancy outcomes in women with subclinical hypothyroidism: A comparative approach of Iranian and American guidelines. J Thyroid Res 2022;2022:9315250.
27. Lockwood CM, Grenache DG, Gronowski AM. Serum human chorionic gonadotropin concentrations greater than 400,000 IU/L are invariably associated with suppressed serum thyrotropin concentrations. Thyroid 2009;19:863-8.
28. Veltri F, Poppe K. Variables contributing to thyroid (Dys) function in pregnant women: More than thyroid antibodies? Eur Thyroid J 2018;7:120-8.
29. Yuen LY, Chan MH, Sahota DS, Lit LC, Ho CS, Ma RC, *et al.* Development of gestational age-specific thyroid function test reference intervals in four analytic platforms through multilevel modeling. Thyroid 2020;30:598-608.
30. Rajput R, Singh B, Goel V, Verma A, Seth S, Nanda S. Trimester-specific reference interval for thyroid hormones during pregnancy at a tertiary care hospital in Haryana, India. Indian J Endocrinol Metab 2016;20:810-5.
31. Lakhani OJ, Patil M. Trimester-specific reference interval for thyroid function test in pregnancy: A review of data from Asia and Africa. Thyroid Res Pract 2018;15:103-4.
32. Rani KS, Tirupati S, Sarathi V, Kumar DK. Trimester-specific reference ranges for thyroid function tests in South Indian women. Thyroid Res Pract 2018;15:117-21.
33. Ding Z, Liu Y, Maraka S, Abdelouahab N, Huang HF, Fraser WD, *et al.* Pregnancy and neonatal outcomes with levothyroxine treatment in women with subclinical hypothyroidism based on new diagnostic criteria: A systematic review and meta-analysis. Front Endocrinol (Lausanne) 2021;12:797423.
34. Geng X, Chen Y, Wang W, Ma J, Wu W, Li N, *et al.* Systematic review and meta-analysis of the efficacy and pregnancy outcomes of levothyroxine sodium tablet administration in pregnant women complicated with hypothyroidism. Ann Palliat Med 2022;11:1441-52.
35. Zhao L, Jiang G, Tian X, Zhang X, Zhu T, Chen B, *et al.* Initiation timing effect of levothyroxine treatment on subclinical hypothyroidism in pregnancy. Gynecol Endocrinol 2018;34:845-8.
36. Leng T, Li X, Zhang H. Levothyroxine treatment for subclinical hypothyroidism improves the rate of live births in pregnant women with recurrent pregnancy loss: A randomized clinical trial. Gynecol Endocrinol 2022;38:488-94.

37. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur Thyroid J 2014;3:76-94.
38. Kalra S, Unnikrishnan AG, Tiwaskar M, Sahay R, Saboo B, Negalur V, *et al.* Medication counseling for thyroxine. Indian J Endocrinol Metab 2017;21:630-1.
39. Kiran Z, Khalid W, Sheikh A, Islam N. Levothyroxine dosages during pregnancy among hypothyroid women. An experience from a tertiary care center of Karachi, Pakistan, based on data from Maternal Hypothyroidism on Pregnancy Outcomes Study (MHPO-5). BMC Res Notes 2022;15:92.
40. Kashi Z, Bahar A, Akha O, Hassanzade S, Esmaeilisaraji L, Hamzehgardeshi Z. Levothyroxine dosage requirement during pregnancy in well-controlled hypothyroid women: A longitudinal study. Glob J Health Sci 2015;8:227-33.
41. Mirghani Dirar A, Kalhan A. Hypothyroidism during pregnancy: Controversy over screening and intervention. World J Obstet Gynecol 2018;7:1-16.
42. Jouyandeh Z, Hasani-Ranjbar S, Qorbani M, Larijani B. Universal screening versus selective case-based screening for thyroid disorders in pregnancy. Endocrine 2015;48:116-23.
43. Berbara TM, Morais NS, Saraiva DA, Corcino CM, Schtscherbyna A, Moreira KL, *et al.* Selective case finding versus universal screening for detecting hypothyroidism in the first trimester of pregnancy: A comparative evaluation of a group of pregnant women from Rio de Janeiro. Arch Endocrinol Metab 2020;64:159-64.
44. Priyadharshini VM, Panicker S. Universal screening for hypothyroidism in pregnancy: Is it necessary? Int J Reprod Contracept Obstet Gynecol 2019;8:2683-86.
45. Donnay Candil S, Balsa Barro JA, Álvarez Hernández J, Crespo Palomo C, Pérez-Alcántara F, Polanco Sánchez C. Cost-effectiveness analysis of universal screening for thyroid disease in pregnant women in Spain. Endocrinol Nutr 2015;62:322-30.
46. Kalra S, Baruah MP, Unnikrishnan AG. Hypothyroidism in pregnancy: From unanswered questions to questionable answers. Indian J Endocrinol Metab 2013;17:200-2.
47. Moleti M, Trimarchi F, Vermiglio F. Doubts and concerns about isolated maternal hypothyroxinemia. J Thyroid Res 2011;2011:463029.
48. Andersen SL, Knøsgaard L. Management of thyrotoxicosis during pregnancy. Best Pract Res Clin Endocrinol Metab 2020;34:101414.
49. Pearce EN. Management of thyrotoxicosis: Preconception, pregnancy, and the postpartum period. Endocr Pract 2019;25:62-8.
50. Labadzhyan A, Brent GA, Hershman JM, Leung AM. Thyrotoxicosis of pregnancy. J Clin Transl Endocrinol 2014;1:140-4.
51. Bajaj S, Rajput R, Jacob JJ. Endocrine Disorders During Pregnancy. New Delhi: Jaypee Brothers Medical Publisher (P) Ltd; 2013.
52. Nguyen CT, Mestman JH. Graves' hyperthyroidism in pregnancy. Curr Opin Endocrinol Diabetes Obes 2019;26:232-40.
53. Botushanov NP, Botushanov AN, Dimitrova A. Chapter 13 Graves' disease and pregnancy. In: Gensure R. editor. Graves' disease. Tufts Medical Center, United States of America. IntechOpen. 2021: 312. Available on: https://www.intechopen.com/chapters/76619. DOI: 10.5772/intechopen.97640. [Last assessed on 2023 Jan 27].
54. Pramanik S, Mukhopadhyay P, Ghosh S. Total T4 rise in pregnancy: A relook? Thyroid Res 2020;13:14.
55. Nguyen CT, Mestman JH. A look at Graves' hyperthyroidism in pregnancy. Ann Thyroid 2018;3:28.
56. Azizi F, Amouzegar A. Management of hyperthyroidism during pregnancy and lactation. Eur J Endocrinol 2011;164:871-6.
57. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European thyroid association guideline for the management of Graves' hyperthyroidism. Eur Thyroid J 2018;7:167-86.
58. Illouz F, Luton D, Polak M, Besançon A, Bournaud C. Graves' disease and pregnancy. Ann Endocrinol (Paris) 2018;79:636-46.
59. Sanz-Cortés M, Fernández S, Puerto B. Fetal thyroid masses and fetal goiter. In: D'Alton M, Feltovich H, Gratacos E, Odibo A, Platt BT, eds. Obstetric Imaging: Fetal Diagnosis and Care. 2nd ed. New York, NY: Elsevier, 2017; 338-345.e1.
60. Dumitrascu MC, Nenciu AE, Florica S, Nenciu CG, Petca A, Petca RC, *et al.* Hyperthyroidism management during pregnancy and lactation (Review). Exp Ther Med 2021;22:960.
61. Das DV, Baro A. Guidance to the maternal, fetal and neonatal management of resistance Grave's disease in pregnancy. Acta Endocrinol (Buchar) 2021;17:517-20.
62. Laurberg P, Bournaud C, Karmisholt J, Orgiazzi J. Management of Graves' hyperthyroidism in pregnancy: Focus on both maternal and foetal thyroid function, and caution against surgical thyroidectomy in pregnancy. Eur J Endocrinol 2009;160:1-8.
63. Rowe CW, Boelaert K. Thyroid Nodules and Thyroid Cancer Prior To, During, and Following Pregnancy. [Updated 2022 Apr 26]. In: Feingold KR, Anawalt B, Blackman MR, *et al*., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Available on: https://www.ncbi.nlm.nih.gov/books/NBK580017/. [Last assessed on 2023 Jan 27].
64. Jiskra J, Horáček J, Špitálníková S, Paleček J, Límanová Z, Krátký J, *et al.* Thyroid nodules and thyroid cancer in women with positive thyroid screening in pregnancy: A double-centric, retrospective, cohort study. Eur Thyroid J 2022;11:e210011.
65. Naji Rad S, Deluxe L. Postpartum thyroiditis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557646/.
66. Azizi F, Braverman LE. Management of postpartum thyrotoxicosis. Curr Opin Endocrinol Diabetes Obes 2005;12:471-6.