Bangladesh Endocrine Society (BES)

Consensus Recommendations on Thyroid Disorders in Pregnancy 2022

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Consensus Recommendations on Thyroid Disorders in Pregnancy 2022

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MESSAGE

It's a great pleasure to know that Bangladesh Endocrine Society is going to publish guideline on management of thyroid disease in pregnancy.

Hormonal disease like thyroid disorder perhaps quite common problem in the society. Early and effective treatment can prevent morbidity. I am pleased to know that in Bangladesh we have a good number of qualified endocrinologists to deal with the problem. Disease occurring in pregnancy is a two edged sword, adversely affect both mother and child. So, definitely it demands special attention. I hope this guideline will help all the physicians of Bangladesh to manage thyroid disease effectively during pregnancy. My heartfelt thanks to Bangladesh Endocrine Society for their relentless effort in this regard.

It is a great significance that Government of Bangladesh has been paying great effort to combat non-communicable diseases. So it is our common interest to provide better health services for the people of Bangladesh. I believe Government of Bangladesh and Bangladesh Endocrine Society will act in collaboration to fulfill the unmet demand of health care services in the field of Endocrinology.

I wish every success of this effort to publish a guideline.

Md. Saiful Hassan Badal
Secretary
Medical Education & Family Welfare Division
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MESSAGE

Today 25 May 2022 is World Thyroid Day (WTD 2022) is dedicated to the global thyroid community, to our patients, physicians, and researchers who are committed to the care of thyroid patients and the treatment of thyroid diseases. The theme of the day is to create public awareness, standard treatment of the patient early diagnosis and prevention of all sorts of thyroid diseases specially hormonal abnormality and Thyroid cancers. I pay my best wishes on this WTD 2022 to all Endocrinologist of our Country.

I am delighted to express my heartfelt thanks and gratitude to the Thyroid Task force of Bangladesh Endocrine Society(BES) as they are going to disseminate "BES Thyroid Disorders in Pregnancy "guideline. I thanks all the contributors of the guideline.
Pregnancy and Thyroid disorders is a different entity than non pregnant thyroid disorders. Its screening, early diagnosis proper management is very essential to minimize over and under treatment and reduce feto-maternal complications. This guideline will definitely help the treating doctors(Endocrinologist, Gynecologist & obstetricians, Internists) for standard care of Hypothyroid, Hyperthyroid and Thyroid Nodules in pregnancy & peri-partum periods.

I hope all the physicians of the country including Endocrinologists' will be benefitted by practicing on this guideline. The patients of Thyroid disorders with Pregnancy will get standard of care. By the way BES is dedicated to serve the Endocrine community and the Nation as well.

I wish success of the task force specially with current coordinator Dr. Shahajada Selim, General Secretary BES with his team.

Prof. Dr. S M Ashrafuzzaman
Professor of Endocrinology
President, Bangladesh Endocrine Society (BES)

MESSAGE

Pregnancy has a profound impact on the thyroid gland and its function. During pregnancy, the thyroid gland increases in size by 10% in iodine replete countries but by 20% to 40% in areas of iodine deficiency. Production of the thyroid hormones, thyroxine (T4), and triiodothyronine (T3), increases by nearly 50%, in conjunction with a separate 50% increase in the daily iodine requirement. These physiological changes happen seamlessly in healthy women, but thyroid dysfunction can occur in many pregnant women because of pathologic processes. Furthermore, other thyroid illnesses such as nodular disease and thyroid cancer are occasionally detected during pregnancy and may require treatment. Together, the burden of thyroid disease affecting women, either before, during, or directly after pregnancy, is substantial.

For these reasons thyroid function is frequently assessed during the gestation period. However, accurate assessment of maternal (and fetal) thyroid function during pregnancy remains difficult, and interpretation of laboratory testing differs from the nonpregnant patient. Placental human chorionic gonadotropin (hCG) stimulates thyroid hormone secretion, often decreasing maternal thyrotropin (TSH) concentrations, especially in early pregnancy. But while such transiently suppressed maternal TSH concentrations are often observed and deemed safe, defining the upper reference limit for serum TSH in this population has remained controversial. Furthermore, up to 18% of all pregnant women are thyroid peroxidase antibody (TPOAb) or thyroglobulin antibody (TgAb) positive. Increasingly, data suggest that TPOAb positivity adversely modulates the impact of maternal thyroid status (especially hypothyroidism) on the pregnancy and the developing fetus. Thyroid antibody positivity separately increases the risk of thyroid dysfunction following delivery and during the postpartum period.

Studies have recently questioned the optimal treatment of hyperthyroidism during pregnancy. Clinical management of patients with Graves' disease (GD) is challenged by the understanding that maternal antibodies as well as antithyroid medication may differentially affect maternal and fetal thyroid function. Reports have also detailed the potential teratogenic effects of the antithyroid medications methimazole (MMI) and propylthiouracil (PTU). But while mild hyperthyroidism appears safe for the mother and fetus, moderate to severe hyperthyroidism can prove dangerous. Thus, when and how to treat affected mothers during pregnancy remains an important clinical question. Following delivery, mothers often choose to breastfeed. Separate questions surround the optimal approach to the treatment of hypo- and hyperthyroidism while lactating.

Given the prevalence and potential dangers detailed above, many have suggested universally evaluating thyroid function in all women either before or during pregnancy. Such a screening mandate, however, must take the cost, effectiveness, and practical nature of any such approach into account. To date, studies evaluating this question appear to demonstrate mixed conclusions. Several ongoing investigations will shed further light on this difficult question. Given the complexity surrounding thyroid physiology and thyroid illness during pregnancy and the postpartum period, how and when to evaluate for thyroid dysfunction and how and if to treat thyroid illness during this period remain challenging.

Considering the prevalence and impacts of thyroid disorders on mother and fetus physicians should equipped with good recommendations and, ethnic specific one. Bangladesh Endocrine Society (BES) is trying to respond to need of our physicians and people's better management of thyroid and other disorders. This guideline may not be the best evidence guideline but can provide uniformity to some extent. The thyroid task force of BES would be vigilant to find out the low falls of the guideline and update it in time.

Dr. Shahjada Selim
General Secretary
Coordinator of Thyroid Task Force
Bangladesh Endocrine Society (BES)

Contents

Preamble

The purpose of guidelines and recommendations is to summarize and assess available evidence to help the healthcare professionals in appropriate decision making in the management of an individual patient with a given condition. Bangladesh Endocrine Society (BES), as a professional body, has been publishing its recommendations for the last few years. As a part of it's continuing educational activities, BES formed a task force comprising of experts in this field to formulate the practical recommendations for the management of thyroid disorders during pregnancy. The members of this task force comprehensively reviewed the available evidences for the specific conditions. Search engines like Google Scholar, PubMed and Scopus were used, with keywords including "Thyroid disease and pregnancy, Hypothyroidism in pregnancy, Thyrotoxicosis in pregnancy, Thyroid nodules in pregnancy, Thyroid function tests in pregnancy, Pregnancy planning in thyroid diseases, Postpartum thyroid disorders" etc. Each section of the recommendation was drafted by one member, followed by rigorous review and modifications by other members. During selection of the articles, interventional studies were given highest preference, but due to scarcity of sufficient randomized trials in this field, observational studies, case studies and expert recommendations were also included. Therefore, this recommendation is a combination of expert opinions and narrative summary of the available evidences regarding management of pregnant females with thyroid diseases.

Section-1:
Screening of Thyroid Function in Pregnancy

Key Notes:

- ***Adverse pregnancy outcomes were noticed in undiagnosed thyroid hypofunction as well as inappropriate replacement of thyroxine replacement during peri-partum period. Abnormal Neuropsychiatric developments were also revealed in fetus and children***
- ***Different guidelines recommended screening of women during reproductive period in both high risk targeted cases and low risk group with pros and cons evidences.***
- ***There is growing debate on universal screening versus targeted cases with cost effective evidences***

Normal thyroid function is essential for successful maintenance of normal pregnancy as well as optimal fetal development. High prevalence of thyroid hypofunction was found in female in the community globally [1]. Overt hypothyroid and Subclinical hypothyroid was found significantly high in female during pregnancy in south Asia region also [2-4]. Thyroid disorder particularly hypothyroidism is frequently encountered and assumed more prevalent as they are mostly asymptomatic specially in subclinical stage during per-partum period with evidences of complications [5-8]. Significant adverse obstetrical and neuro-psychological development in children were observed in different studies [8-10]. Even marginal hypofunction is associated with fetal loss, preterm delivery, prematurity, cognitive dysfunction in child. In some studies maternal autoimmunity is found to be associated with potential fetal loss [11,12]. It is difficult to distinguished from features in normal pregnancy on clinical ground alone as most of the time dysfunction is asymptomatic. So, it is logical to screen thyroid function in early gestation or even planning in preconception care so that we can avoid adverse outcomes in both mother and fetus. In fact, thyroid disorders can be simply diagnosed with easily available and inexpensive blood tests.

1.1 Why to screen

Women with hypothyroid suffer an increased risk of adverse pregnancy outcomes in overt hypothyroidism, subclinical hypothyroidism, even isolated hypothyroxemia[5,6,7,8,9,010,11,12]. In addition off springs of hypothyroid mother were experienced to have neuro-psychological, cognitive dysfunction and congenital malformation [9,10].

1.2 Adverse events in mother

1.2.1 Preconception stage:

- Decreased fertility or unable to conceive
- Increased abortion or miscarriage
- During gestation period (failed to adequate thyroid level)

1.2.2 Conception period:

- Anemia, Congestive heart failure
- Pre-eclampsia
- Gestational hypertension
- Placenta abruption
- Preterm delivery
- Low birth weight
- Myopathy
- Miscarriage, still birth
- Postpartum hemorrhage

1.2.3 Postpartum period:

- Maternal thyroid dysfunction
- Hemorrhage

1.3 Fetal adverse event:

- Cognitive impairment
- Neurological abnormality
- Congenital anomalies
- Congenital hypothyroidism
- Hyperbilirubinemia

1.4 Whom to screen:

We can proceed to screen the women in reproductive age seeking for conception or at first anti-natal visit who are high risk to have thyroid dysfunctions. Most of the guideline advocate the women with following criteria can be offered for screening for thyroid dysfunction [8,13-18].

- Age more than 30 years
- Previous history of thyroid dysfunction
- Family history of hypothyroidism more in autoimmune
- Goiter
- History of other autoimmune diseases
- Prior history of thyroid surgery
- History of head and neck irradiation
- TPO antibodies positive
- Subfertility
- Repeated abortion or miscarriage
- Iodine deficiency zone
- History of iodine containing medication or iodine containing media
- Obese
- Type 1 DM
- Taking anti -thyroid drugs
- Previous delivery of infant with congenital thyroid hypofunction

1.5 When to screen:

There is continuing debate going on among the experts whether we should go for universal screening or target base high risk individuals in terms of benefit outcome and cost-effectiveness. There are lots of studies some are in favor and some are against universal screening. Most of the guidelines (AACE, ACOG, ATA, ISE) based on several studies advocate screening for target case of high risk group [8,15,16,17,18,19,20,21]. Many experts considering sub-clinical hypothyroidism, asymptomatic hypothyroidism, isolated hypothyroxemia and their outcome opined for universal screening. Target screening may miss 30% women in even low risk population. In another study 55% women may be missed hypothyroidism comparing case base screening approach rather than universal screening. Vaidya et al shown 42% respondent reported to screen all women, 43% reported to screen only targeted cases [16,17]. Some study has supported universal screening as cost effective considering pregnancy loss and adverse events[20,21]. ATA 2013 showed 74% respondent were in favor for universal screening. Polish, Chinese and Spanish endocrine community recommended universal screening [8,16,17].

1.6 Recommendations:

- Considering high prevalence of hypothyroidism both overt and sub-clinical hypothyroidism and iodine deficiency status of our population universal screening is recommended by 9-10 weeks of gestation or first antenatal check up.
- Preconception screening of undiagnosed case and education of previously treated case will help to identify subfertility, can avoid bad obstetrical cases and congenital anomalies of fetus.
- Preconception counselling and screening is recommended and appropriate iodine replacement and L- thyroxine replacement is needed to be ensured according to trimester specific level.

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Section-2:
Planning Pregnancy in Women with Thyroid Disorders

Key points:

- ***Evaluation of serum TSH concentration is recommended for all women seeking care for infertility.***
- ***Evaluation of thyroid autoimmunity by measuring antithyroid antibodies is recommended for all women seeking care for infertility, particularly for those, who previous pregnancy loss(s).***
- ***LT4 treatment is recommended for infertile women with overt hypothyroidism who desire pregnancy.***
- ***Subclinical hypothyroid women undergoing IVF or intracytoplasmic sperm injection (ICSI) should be treated with LT4. The goal of treatment is to achieve a TSH concentration <2.5 mU/L.***

2.1 Introduction:

Thyroid function is closely interlinked with obstetric health.1 Maternal and fetal outcomes can be improved if optimal thyroid function is maintained. Hence, there is a need to optimize thyroid function during the pre-conception period. This can be done by rational screening, appropriate management, and pragmatic counseling. Endocrine services are thus an integral part of preconception management. Conventional categorization of drugs with regards to their use in pregnancy is followed in this text, even though the United States Food and Drug Administration (US FDA) has recently discontinued this process [1].

Thyroid disorders are a common occurrence in women of reproductive age. These include hypothyroidism, hyperthyroidism and thyroid nodules. Thyroid health is impacted by iodine nutrition as well. Thyroid disorders, if untreated, may be associated with subfertility, bad obstetric history and suboptimal pregnancy outcomes [2]. Some forms of therapy, such as radioactive iodine and anti-thyroid drugs may have teratogenic potential.

2.2 Iodine Nutrition:

All women must be counseled to use iodized salt in the pre-conception, as well as other phases of life. Iodized salt contains >15 PPM of iodine (added as potassium iodate, KIO3) per 100g. Ten grams of salt contains 150 mcg of iodine, which is sufficient to meet physiological requirements. There is no need to add an iodine- containing multivitamin/ mineral preparation in the preconception phase. Selenium supplementation is not recommended during preconception or pregnancy.

American Thyroid Association recommends a minimum of 250 µg iodine daily and suggests that sustained iodine intake from diet and dietary supplements exceeding 500-1100 µg daily should be avoided due to concerns about the potential for fetal hypothyroidism [3,4].

2.3 Hypothyroidism:

Screening for thyroid disorders, using a sensitive and accurate TSH assay, is indicated for all women as part of preconception counseling. Thyroid antibody estimation (anti-thyroglobulin, thyroid peroxidase antibodies (TPOAb) is indicated only in select cases which pose a therapeutic dilemma [5].Women with history of postpartum thyroiditis or postpartum depression must be screened for thyroid status in preconception.

There is insufficient evidence to recommend for or against screening for thyroid antibodies in euthyroid women with bad obstetric history or in women undergoing in vitro fertilization (IVF). As there is no benefit in treatment of isolated maternal hypothyroxinemia, universal FT4 screening during preconception is not recommended. Thyroid ultrasonography and scan are not indicated as part of routine preconception workup.

While American Thyroid Association suggests that there is insufficient evidence to recommend for or against TSH preconception testing in women at high risk for hypothyroidism, they do recommend all pregnant women be verbally screened at the initial prenatal visit for any history of thyroid dysfunction and/or use of thyroid hormone (LT4) or anti-thyroid medications.

Keeping in view the high prevalence of subclinical hypothyroidism, continued prevalence of iodine deficiency, and lack of universal iodized salt use in South Asia, biochemical screening for thyroid disorders should be a mandatory part of pre-conception care [6]. It must also be noted that TSH estimation is more economical and easily available, as compared to TPOAb testing, in most South Asian countries.

Overt hypothyroidism and subclinical hypothyroidism should be managed with l-thyroxine (category A drug), and TSH levels optimized to $\leq$2.5mIU/l, prior to conception [4]. Lower preconception TSH values (within the nonpregnant reference range) reduce the risk of TSH elevation during the first trimester. Select TPOAb negative patients with mild subclinical hypothyroidism may be kept under close follow-up without LT4 supplementation. Such women should be monitored for progression to overt hypothyroidism with monthly serum TSH and FT4 until 16-20 weeks of gestation and at least once between 26 and 32 weeks of gestation.

Women who are already receiving L-thyroxine should be counselled to increase their dose of LT4 by approximately 25%-30% if they miss a menstrual cycle or note a positive home pregnancy test, and notify the obstetrician promptly. A simple way of ensuring this adjustment is to increase LT4 from once daily dosing to a total of nine doses per week (29% increase) [4].

2.4 Hyperthyroidism:

All antithyroid drugs are classified as category D in pregnancy. Hyperthyroidism should be managed and stabilized with methimazole or carbimazole, prior to conception. Patients should be switched to propylthiouracil as soon as pregnancy is diagnosed. Methimazole or carbimazole can be used as alternatives, but patients should be aware that there is a very low risk of congenital defects such as aplasia cutis and esophageal/choanal atresia [5]. Radioactive iodine, if indicated, should be administered at least six months prior to conception.

Radioactive iodine therapy has not been associated with deterioration in gonadal function or adverse outcomes in offsprings [6]. Pharmacologic doses of iodine exposure during preconception should be avoided, except in preparation for thyroid surgery for Graves' disease. While thyrotoxic women should be rendered euthyroid before attempting pregnancy, subclinical hyperthyroidism does not need pharmacological management in the preconception phase or in pregnancy.

2.5 Thyroid Nodules:

Thyroid nodules should be evaluated, diagnosed, and managed appropriately, prior to conception. Thyroid ultrasonography and fine needle aspiration cytology (FNAC) may be performed if thyroid nodular disease is detected during the preconception phase [7].

2.6 Recommendations:

- Evaluation of serum TSH concentration is recommended for all women seeking care for infertility.
- Evaluation of thyroid autoimmunity by measuring antithyroid antibodies is recommended for all women seeking care for infertility, particularly for those, who previous pregnancy loss(s).
- LT4 treatment is recommended for infertile women with overt hypothyroidism who desire pregnancy.
- Subclinical hypothyroid women undergoing IVF or intracytoplasmic sperm injection (ICSI) should be treated with LT4. The goal of treatment is to achieve a TSH concentration <2.5 mU/L.

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Section-3:
Interpretation of
Thyroid Function Tests in Pregnancy

Key points:

- ***Human Chorionic Gonadotropin (hCG) increases in pregnancy, directly stimulates TSH receptor and increases thyroid hormone production which results in reduced serum TSH level.***
- ***Estrogen rises in pregnancy and increases in thyroxine-binding globulin (TBG) concentrations which leads to increased total thyroxine (TT_4) and triiodothyronine (TT_3) levels in maternal serum, but the free thyroxine (FT4) and triiodothyronine (FT_3) fraction remains normal.***
- ***Increased maternal renal iodine excretion and fetal iodine supply cause relative maternal iodine deprivation and stimulation of maternal thyroid, which increases in size and increases production of T4 and T3 during pregnancy.***
- ***Reference ranges of TSH in 1st trimester: 0.1-3.0 mIU/L, in 2nd trimester: 0.2-4.0 mIU/L and in 3rd trimester: 0.3-4.0 mIU/L.***
- ***Interpretation of free thyroid hormone levels in pregnancy is more challenging. TT4 measurements are more reliable than FT4 measurements during pregnancy. In general normal TT4 reference ranges in pregnancy increases by approximately 5% per week, beginning at week 7. At approximately 16 weeks, TT4 (and TT3) levels during pregnancy are 1.5-fold higher than in nonpregnant women.***

3.1 Thyroid Physiology in Pregnancy:

Pregnancy is associated with significant but reversible physiological changes in maternal thyroid physiology which are important for interpretation of thyroid function tests.

The estrogen concentrations rise in pregnancy and induce increased hepatic synthesis of thyroxine-binding globulin (TBG) as well as enhanced sialylation of TBG, which decreases its metabolic clearance rate [1]. The result is increase in TBG concentrations which leads to increased total thyroxine (TT_4) and triiodothyronine (TT_3) levels in maternal serum (Fig.3.1) but the free thyroxine (FT4) and triiodothyronine (FT_3) fraction remains normal [1,2]. TBG level begins to increase by 7 week of gestation, reach a plateau around 16 week of gestation, and remain ~2 fold higher until term. Similarly, levels of total T4 and T3 rise from 7 week of gestation, increase ~50 percent during the first half of pregnancy, plateau at ~16-20 week of gestation, and then remain high until delivery [3,4].

The family of glycoprotein hormones, that include both human chorionic gonadotropin (hCG) and TSH, have a common alpha subunit and a unique beta subunit. There is also considerable homology between the beta subunits of hCG and TSH. As a result, hCG act as a weak TSH receptor agonist.[5] Placenta produces hCG in the first week after conception, the levels peak at week 10, then decrease and reach a plateau by week 20 [3].Increased levels of hCG directly stimulate the TSH receptor and increase thyroid hormone production which results in a reduced, and sometimes suppressed serum TSH.

The fetus dependents entirely on transplacental passage of maternal thyroid hormone in 1st trimester, but fetal thyroid hormone production begins around 12th week of gestation and is under control of the pituitary around 20th week [6]. Maternal glomerular filtration rate (GFR) increases in pregnancy, resulting in increased renal clearance of iodine [7]. In late gestation, transplacental passage of iodide and placental metabolism of thyroid hormones increase fetal iodine supply [8]. All these cause relative maternal iodine deprivation and stimulation of the maternal thyroid. In iodine-sufficient areas, the thyroid typically increases around 10% in size during pregnancy. But in iodine-deficient areas, the gland typically increases from 20% to 40% in size during pregnancy [9]. This leads to increased production of T4 and T3 during pregnancy.

3.2 Thyroid Function Tests in Pregnancy

TSH concentrations decreases transiently during the first trimester of pregnancy and increases thereafter (without attaining prepregnancy levels), with similar but inverse changes in serum FT4 and FT3 [10].

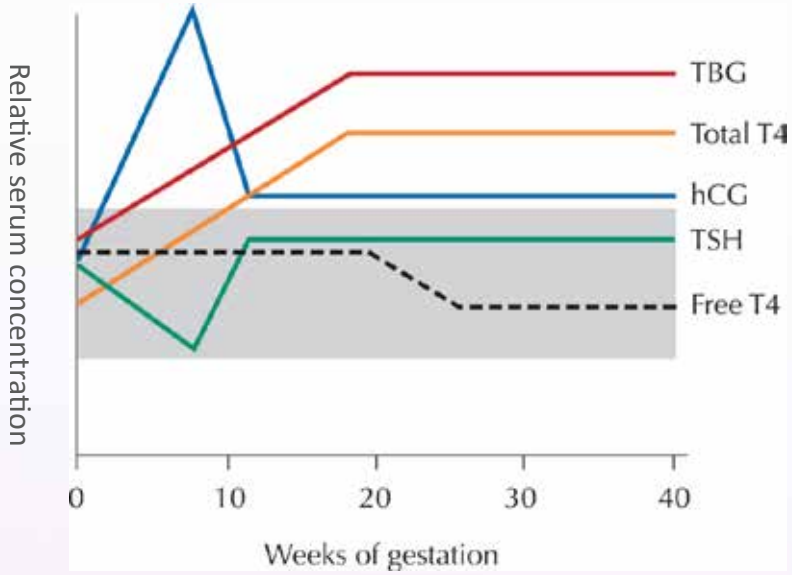

Fig.-3.1. The pattern of changes in serum concentrations of thyroid function studies and hCG according to gestational age. The shaded area represents the normal range of thyroid-binding globulin, total thyroxine, thyroid-stimulating hormone or free T4 in the nonpregnant woman. TBG, thyroid-binding globulin; T4, thyroxine; TSH, thyroid-stimulating hormone. Modified from Brent GA [2].

Thyroid function tests should be interpreted using population-based, trimester-specific reference ranges for TSH and assay method and trimester-specific reference ranges for serum free T4. Reference ranges should be defined in healthy TPOAb-negative pregnant women with optimal iodine intake and without thyroid illness [11].

A downward shift of both upper and lower TSH reference range is seen in pregnancy, lower limit by ~0.1-0.2 mIU/L and upper limit by ~0.5-1.0 mIU/L, with lowest decrease in 1st trimester and then gradually rise in 2nd and 3rd trimester, but still below the non-pregnant reference range [11]. But extent of this change varies significantly between different races and ethnic groups. Several reports and guidelines have been published recommending varied TSH cutoffs in different studies. The American Thyroid Association (ATA) 2011 guideline followed by Endocrine Society clinical practice guideline 2012 gave stricter TSH cutoffs as 0.1 to 2.5 mIU/L in first trimester, 0.2 to 3.0 mIU/L in second trimester and 0.3 to 3 mIU/L in third trimester [12,13]. Subsequently many reports, meta-analysis and systematic reviews were published which recommended higher cutoffs. The 97.5th percentile of TSH for the first trimester using different analytical method was found in two groups: according to the Architect, Beckman, and Immulite platform, it is about 3.0 mIU/L, while according to Centaur and Roche, it is close to 4 mIU/L [14]. Ethnicity may also have a significant effect on TSH and FT4 reference limits in pregnancy. On reviewing literature, ATA then revised the guidelines in 2017, recommending the upper cutoff limit 0.5 mIU/L less than the preconception TSH value or as 4.0 mIU/L when local population-specific reference range is not available.[11] Considering recent International and Indian data, Indian endocrinologists conclude that recent 2017 recommendation of ATA of a revised URL for TSH of 4.0 mU/L is high and should instead be 3.0 mU/L in the first trimester and 3.5 in second and third trimester till they are able to generate more nationally representative data for trimester-specific TSH values [15]. In Bangladesh, we have no representative data of TSH level in pregnancy.

In general, FT4 and FT3 levels increase slightly during 1st trimester and subsequently decrease as pregnancy progresses. But the interpretation of free thyroid hormone levels in pregnancy is more challenging. Most studies report a progressive decrease in measured free T4 during pregnancy [16-18]. However, direct free T4 measurements may be unreliable in some patients due to changes in binding proteins during pregnancy. Measurement of free T4 in the dialysate or ultrafiltrate of serum samples using liquid chromatography/tandem mass spectrometry appears to be the most reliable, and when this method is used, free T4 concentrations were shown to decrease modestly with advancing gestational age, particularly between the first and second trimester [19,20]. This assay is relatively expensive and not universally available. Other free T4 assays (and probably free T3 assays) frequently fail to meet performance standards in pregnant patients, owing to increases in TBG and decreases in albumin concentrations that cause the immunoassay to be unreliable [17]. To compensate, assay kits should provide different free T4 normal ranges for pregnant patients, usually lower than those of nonpregnant patient [4]. Considering this, all of the guidelines warned against the uncritical use of FT4 results in pregnancy.

On the other hand, measurement of TT4 and the calculated FT4 index do show the expected inverse relationship with TSH [17]. This finding suggests that TT4 measurement may be superior to FT4 measurement in pregnancy. As mentioned before, TT4 concentration increase from 7–16 weeks of gestation, ultimately reaching ~50% above the prepregnancy level and then sustained through pregnancy. So, a clinically acceptable upper reference range determination can be calculated by increasing the nonpregnant limit 50% higher. But, this limit can only be used after 16 weeks of gestation. If a T4 measurement is required before that time (i.e., 7–16 weeks of pregnancy), a calculation can be made for the upper reference range based on increasing the nonpregnant upper reference limit by 5% per week, beginning with 7 week. For example, at 11 weeks of gestation (4 weeks beyond week 7), the upper reference range for T4 is increased by 20% (4× 5%) [3].

The ATA recommended the measurement of TT4 and calculation of FT4 index (FTI) as preferable to FT4 immunoassays although some have argued that this is misguided and regressive. The Endocrine Society guidelines also suggested either FTI or TT4 (multiplying the non-pregnant range by 1.5 for the second and third trimesters), while the European guidelines recommended either TT4 or FT4 measurement with locally established trimester-specific reference ranges.

Trimester specific reference ranges for FT4 are not available in our country. TT4 measurements are superior and more reliable than FT4 measurements especially during 2nd and 3rd trimester of pregnancy.

1.3 Recommendations:

- Until specific reference range is not available for Bangladeshi population, we recommend the following trimester-specific reference ranges for TSH. [Strong recommendation, moderate quality evidence]
    - First trimester: 0.1-3.0 mIU/L
    - Second trimester: 0.2-4.0 mIU/L
    - Third trimester: 0.3-4.0 mIU/L
- Measure TT4 (and TT3) during pregnancy until trimester specific reference assay is established.
- The reference range for TT4 increases by approximately 5% per week, beginning at week 7.
- At approximately 16 weeks, TT4 (and TT3) levels during pregnancy are 1.5-fold higher than in nonpregnant women. [strong recommendation, moderate quality evidence]

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Section-4:
Management of Hypothyroidism in Pregnancy

Key Points:

- ***Primary hypothyroidism is generally defined as the presence of elevated TSH and decreased serum FT4 concentration during gestation, with both concentrations outside the (trimester-specific) reference ranges.***
- ***Overt maternal hypothyroidism has consistently been shown to be associated with an increased risk of adverse pregnancy complications.***
- ***The recommended treatment of maternal hypothyroidism is administration of oral LT4.***
- ***It is reasonable to target a TSH in the lower half of the trimester-specific reference range. When this is not available, it is reasonable to target maternal TSH concentrations below 2.5mU/L.***

Primary maternal hypothyroidism is defined as the increase in serum TSH level during pregnancy. Depending on the free T4 levels, it is further classified as overt hypothyroidism (OH; free T4 levels decreased) or subclinical hypothyroidism (SCH; normal FT4 levels). Central hypothyroidism (low FT4 but low normal or low TSH) is very rare. Primary hypothyroidism is generally defined as the presence of elevated TSH and decreased serum FT4 concentration during gestation, with both concentrations outside the (trimester-specific) reference ranges. In very rare cases, it is important to exclude other causes of abnormal thyroid function such as TSH-secreting pituitary tumors, thyroid hormone resistance or central hypothyroidism with biologically inactive TSH [1,2].

When iodine nutrition is adequate, the most frequent cause of hypothyroidism is autoimmune thyroid disease (Hashimoto's thyroiditis). Therefore, not surprisingly, thyroid autoantibodies can be detected in approximately 30%–60% of pregnant women with an elevated TSH concentration [3].

When available, population and trimester-specific reference ranges for serum TSH during pregnancy should be established. Reference ranges should be defined in healthy TPOAb-negative pregnant women with optimal iodine intake and without thyroid illness. If pregnancy-specific TSH reference ranges are not available, an upper reference limit of 4.0mU/L may be used [4].

Overt maternal hypothyroidism has consistently been shown to be associated with an increased risk of adverse pregnancy complications as well as detrimental effects upon fetal neurocognitive development. Specific adverse outcomes associated with overt maternal hypothyroidism include increased risks of premature birth, low birth weight, pregnancy loss, and lower offspring IQ and gestational hypertension [5,6].

Pregnant women with TSH concentrations >2.5 mU/L should be evaluated for TPOAb status [7].

Subclinical hypothyroidism in pregnancy should be approached as follows [7,8,9]:

TSH level	TPOAb	LT4 therapy
>10 mU/L	Positive	Recommended
	Negative	Recommended
4-10.0 mU/L	Positive	Recommended
	Negative	Can be considered
2.5-4 mU/L	Positive	Can be considered
	Negative	Not recommended

The recommended treatment of maternal hypothyroidism is administration of oral LT4.Inparalleltothetreatmentofhypothyroidisminageneral population, it is reasonable to target a TSH in the lower half of the trimester-specific reference range. When this is not available, it is reasonable to target maternal TSH concentrations below 2.5mU/L [10].

Women with overt and subclinical hypothyroidism (treated or untreated) or those at risk for hypothyroidism (e.g., patients who are euthyroid but TPOAb or TgAb positive, post-hemithyroidectomy, or treated with radioactive iodine) should be monitored with a serum TSH measurement approximately every 4 weeks until mid-gestation and at least once near 30 weeks gestation [11].

In hypothyroid women treated with LT4 who are planning pregnancy, serum TSH should be evaluated preconception, and LT4 dose adjusted to achieve a TSH value between the lower reference limit and 2.5mU/L. Hypothyroid patients receiving LT4 treatment with a suspected or confirmed pregnancy (e.g., positive home pregnancy test) should urgently notify their caregiver for prompt testing and usually need to increase dose of LT4 by 20%–30%. Following delivery, thyroid function testing should be performed at approximately 6 weeks postpartum with adjustment of dose if needed [12,13].

4.1 Recommendations:

- Treatment of maternal hypothyroidism is administration of oral LT4.
- As trimester-specific reference range of TSH is not established in Bangladesh, it is reasonable to target maternal TSH concentrations below 2.5mU/L.

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Section-5:
Hyperthyroidism in Pregnancy

Key Points:

- ***TSH value should be evaluated in conjunction with either TT4 and TT3 with TT4 and TT3 reference value adjusted at 1.5 times the non-pregnant range or FT4 trimester-specific normal reference ranges (if available).***
- ***Overt hyperthyroidism is confirmed in the presence of a suppressed or undetectable serum TSH and inappropriately elevated serum TT4/FT4, or TT3level.***
- ***Gestational Transient thyrotoxicosis is more frequent than Graves's disease and should be treated symptomatically. Radionuclide scintigraphy or radioiodine uptake are not recommended. Management is symptomatic. Antithyroid drugs (ATDs) are not indicated. Beta-blockers (propranolol or metoprolol) can be considered over a limited time period. Follow-up should be done with repeat investigation.***
- ***Management of Graves' disease (GD) during pregnancy is challenging. Hyperthyroid patient who desires future pregnancy may be offered ablative therapy using 131I, thyroid surgery, or medical therapy***
- ***Due to potential teratogenic effects, use of antithyroid medications carbimazole/methimazole and propylthiouracil need trimester specific consideration.***
- ***A balance in ATD dosing with careful clinical evaluation of the fetus and the mother is needed. If possible, ATDs should be avoided in the first trimester of pregnancy, but when necessary PTU is generally favored.***
- ***If subtotal thyroidectomy is considered, it should be done during second trimester.***
- ***All newborns of mothers with Graves' disease (except those with negative TRAb and not requiring ATD) should be evaluated for thyroid dysfunction and treated if necessary.***

5.1 Introduction:

The most common cause of hyperthyroidism in women of childbearing age is autoimmune Graves' Disease (GD) occurring before pregnancy in 0.4%–1.0 % of women and in approximately 0.2% during pregnancy [1].Poorly controlled thyrotoxicosis is associated with adverse maternal and fetal outcome. Thyroid stimulating antibody, TRAb can cross placenta and adversely affect fetal thyroid function. Due to reversible changes of maternal thyroid hormone physiology and production of placental human chorionic gonadotropin (hCG) which has potential effect on thyroid gland, assessment and interpretation of thyroid function tests is challenging during pregnancy.

5.2 Causes of Thyrotoxicosis in Pregnancy: [2]

- Gestational Transient thyrotoxicosis: More frequent than GD.
- Grave's Disease (GD): common autoimmune cause.
- Toxic multinodular goiter (TMG): non-autoimmune cause, less common than GD.
- Toxic adenoma: non-autoimmune cause, less common than TMG.
- Subacute painful or painless thyroiditis: less common causes.
- Overtreatment with or factitious intake of thyroid hormone: A special cause of thyrotoxicosis.
- Other rare causes: TSH-secreting pituitary adenoma [3]; Struma ovarii [4]; hCG-induced thyrotoxicosis include multiple gestation, hydatidiform mole, and choriocarcinoma [5,6]; Functional thyroid cancer metastases, or germline TSH receptor mutations [7]; A TSH receptor mutation leading to functional hypersensitivity to hCG [8].

5.3 Maternal &Fetal Outcome:

5.3.1 Maternal Outcome:

Poorly controlled thyrotoxicosis may may result into pregnancy induced hypertension, thyroid storm, maternal congestive heart failure [9].

5.3.2 Fetal Outcome:

Uncontrolled thyrotoxicosis may lead to intrauterine growth retardation, low birth weight, prematurity, stillbirth, pregnancy loss and neonate may develop seizure disorders and neurobehavioral disorders in later life [10]. Regarding thyroid health, fetal risks in women with previous or current Graves' hyperthyroidism include (a) fetal hyperthyroidism, (b) neonatal hyperthyroidism, (c) fetal hypothyroidism, (d) neonatal hypothyroidism, and (e) central hypothyroidism. The above potential complications depend on several factors: (a) poor control of hyperthyroidism throughout pregnancy may induce transient central hypothyroidism [11, 12] (b) excessive amounts of ATDs may be responsible for fetal and neonatal hypothyroidism [13] and (c) high levels of thyroid stimulating antibodies in the second half of pregnancy may induce fetal and neonatal hyperthyroidism [14-17].

5.4 Evaluation of Thyroid Function in Pregnancy for Hyperthyroidism: [2,18]

- TSH value should be evaluated in conjunction with either TT4 and TT3 with TT4 and TT3 reference value adjusted at 1.5 times the non-pregnant range or FT4 trimester-specific normal reference ranges (if available).
- When a suppressed serum TSH is detected in the first trimester (less than the reference range), a medical history, physical examination, and measurement of maternal serum FT4 or TT4 concentrations should be performed. Measurement of TRAb (if available) and maternal TT3 may prove helpful in clarifying the etiology of thyrotoxicosis.
- Radionuclide scintigraphy or radioiodine uptake determination should not be performed in pregnancy.
- Overt hyperthyroidism is confirmed in the presence of a suppressed or undetectable serum TSH and inappropriately elevated serum TT4/FT4, or TT3.

5.5 Gestational Transient Thyrotoxicosis (GTT):

In early pregnancy, the differential diagnosis in majority of cases is between Graves' hyperthyroidism and gestational transient thyrotoxicosis [19, 20]. GTT is characterized by elevated FT4 and suppressed serum TSH and is diagnosed in about 1–3% of pregnancies [2]. Frequency of gestational transient thyrotoxicosis depends on the geographic area and is secondary to elevated hCG levels in 1st half of pregnancy[19, 20]. GTT is often associated with hyperemesis gravidarum which is manifested as severe nausea and vomiting that results in weight loss, dehydration, and ketonuria in early pregnancy. Findings with no prior history of thyroid disease, no stigmata of GD (goiter, orbitopathy), self-limited mild disorder, and symptoms of emesis favor the diagnosis of gestational transient thyrotoxicosis. Serum hCG is higher on average in gestational transient thyrotoxicosis than in patients with GD, but overlap is considerable [21]. No study has demonstrated usefulness of thyroid ultrasonography for differentiating between gestational transient thyrotoxicosis and GD.

5.6 Management of Gestational Transient Thyrotoxicosis:

Management depends on severity of symptoms. Antithyroid drugs (ATDs) are not indicated. Serum T4 returns to normal by 14–18 weeks gestation when HCG level decreases. Supportive treatment like, control of vomiting by antiemetics and treatment of dehydration with intravenous fluids and monitoring of electrolyte abnormalities are mainstay. In some cases, hospitalization is required. Beta-blockers can be considered over a limited time period (propranolol or metoprolol). Follow-up should be done with repeat investigation [2].

5.7 Management Graves' hyperthyroidism during pregnancy:

Thionamide ATDs (MMI, carbimazole [CM], and PTU) are the mainstays of treatment for hyperthyroidism during pregnancy. The initial dose of ATD depends on the severity of the symptoms and the degree of hyperthyroxinemia [2].

5.7.1 Initial doses of ATDs use during pregnancy in GD:

- CM, 10-40mg/d [2, 18]
- MMI, 5–30mg/d (typical dose in average patient 10–20mg) [2, 18]
- PTU, 100–600mg/d (typical PTU dose in average patient 200–400mg/d) [2, 18]
- The equivalent potency of CM to PTU is approximately 1:12 [22-24]. Half-life of PTU is shorter than that of CM, so PTU dosing should generally be split into two or three daily doses. CM/MMI can generally be given in once daily dose. In cases of severe hyperthyroidism, twice or three times daily dosing may be of benefit [25, 26]

5.7.2 Adverse Side effects of ATDs:

- Minor Allergic reactions such as skin rash (3-5%) [27]
- Rare but severe effects are Agranulocytosis (0.15%) [28, 29] and liver failure.
- Most side effects develop within the first months following initiation [27] or re-initiation [30] of therapy.
- Hepatotoxicity develops in patients exposed to PTU [31, 32], souse of PTU to the first trimester of pregnancy [33]
- Monitoring hepatic enzymes during administration of PTU may be considered.

5.7.3 Potential teratogenic effects of ATD:

CM/MMI had been associated with aplasia cutis [34], dysmorphic facies [35], choanal or esophageal atresia; various types of abdominal wall defects including umbilicocele; and eye, urinary system, and ventricular septal defects [36][37][38]. PTU-associated birth defects like face and neck cysts and urinary tract abnormalities appear less severe than CM/MMI-associated birth defects but occur with similar incidence [2].

5.7.4 ATD options during different trimesters:

- Many patients receiving ATD therapy for GD may gradually enter remission when made euthyroid. If ATD s are withdrawn, patients may go into relapse. The risk of rapid relapse of hyperthyroidism after medication withdrawal in early pregnancy varies among patients. An approach is that when pregnancy is diagnosed in a woman with GD receiving on a low dose of ATD (CM/MMI (5 mg) or PTU (100–200 mg/d) and clinical and biochemical findings appears to be in remission, approach is to consider is to withdrawal of all ATD medication and to repeat thyroid function testing. Cessation of medication has to be recommended early in gestation (6-10 weeks) before the major teratogenic periods. Following cessation, maternal thyroid

function testing (TSH, and FT4 or TT4) and clinical examination should be performed every 1–2 weeks during first trimester and 2–4 weeks during the second and third trimester. At each assessment, the decision to continue conservative management (withholding antithyroid medication) should be guided both by the clinical and the biochemical assessment of maternal thyroid status.[2].The risk of rapid relapse of hyperthyroidism after medication withdrawal in early pregnancy is high in patients who have been treated for a short period (<6months),who have suppressed or low serum TSH while on medication pre-pregnancy, who require >5–10mg of MMI per day to stay euthyroid, who have active orbitopathy or large goiter, and those who have high levels of TRAb [39].

- In high-risk cases, medication should not be withdrawn, and PTU should be administered as the drug of choice. PTU is recommended through 16 weeks of pregnancy. Pregnant women receiving CM/MMI ideally should be switched to PTU (if available) as early as possible. CM/MMI may also be prescribed if PTU is not available or if a patient cannot tolerate or has an adverse response to PTU. Patients started on propylthiouracil (if available) during the first trimester be switched to CM/methimazole at the beginning of the second trimester. When required, beta-adrenergic blockers should be used for limited period (~2-6 wk).
- Combination regimen of LT4 and an ATD should not be used in pregnancy, except in the rare situation of isolated fetal hyperthyroidism caused by maternal TRAb production who previously received ablative therapy for GD [40-41]. The ATD will pass the placenta and treat the fetal hyperthyroidism, whereas the LT4 is necessary to keep the mother euthyroid [2].

5.7.5 Principles of thyroid testing and monitoring ATD therapy during pregnancy:

Thyroid stimulating antibodies, ATDs and most maternal thyroid hormones effectively cross the placenta and modulates fetal thyroid function. All ATDs tend to be more potent in the fetus than in the mother. Thus, when the mother is made euthyroid, the fetus is often overtreated [42]. To avoid this, the aim is to maintain maternal TT4/ FT4, TT3 values at, or just above the pregnancy-specific upper limit of normal with smallest possible dose of ATDs [2]. Maternal TT4/FT4 and TSH (in cases of severe hyperthyroidism, also serum TT3/FT3) should be measured every 2–4 weeks following initiation of therapy, and every 4–6 weeks after achieving the target level [43-45].

If trimester-specific FT4 values are not available, use of the reference range for non-pregnant patients is recommended or TT4 measurement with reference value 1.5 times the non-pregnancy range may be used during second and third trimesters. [2,18].

Discontinuation of ATD therapy is feasible in 20-30% of patients in the last trimester of gestation. Disappearance of maternal TRAb in late pregnancy indicates a high likelihood of successful ATD withdrawal [46]. Maternal serum TSH well within the reference range is a sign that the ATD dose has to be reduced to avoid fetal overtreatment [2]. Sometimes, in GD, serum TT3 may remain elevated even if TT4/FT4 becomes normal or even low [40]An increase in ATD dose to normalize maternal serum TT3 will cause elevated serum TSH in theinfants at birth, therefore a balance in ATD dosing with careful clinical evaluation of the fetus and the mother is needed [45].

5.7.6 Thyroidectomy during Pregnancy:

Subtotal thyroidectomy may be indicated during pregnancy as therapy for maternal Graves' disease if: 1) a patient has a severe adverse reaction or contraindication to ATD therapy; 2) persistently high doses of ATD are required (over 30 mg/d of MMI or 50 mg/d CM or 450 mg/d of PTU); or 3) a patient is non-adherent to ATD therapy and has uncontrolled hyperthyroidism [18]. Optimal timing of surgery is in the second trimester[18].Pre-operative preparation for

5.8 TRAb measurement of a pregnant woman with Graves' hyperthyroidism:

TRAb is measurable in around 95% of patients with active Graves' hyperthyroidism, and levels may remain high following ablation therapy. High levels of thyroid stimulating antibodies in the second half of pregnancy may induce fetal and neonatal hyperthyroidism. A value >5 IU/L or 3 times the upper normal limit of normal in mother is an indication for establishing close follow-up of the fetus.[50]

5.9 Fetal monitoring in women with Graves' hyperthyroidism:

Fetal well-being may be compromised in the presence of elevated TRAb, uncontrolled hyperthyroidism, and pre-eclampsia [51, 52].Ultrasonographic surveillance should be performed in women having uncontrolled hyperthyroidism in the second half of pregnancy or with high TRAb levels detected at any time during pregnancy (greater than 3 times the upper limit of normal)[2]. Signs of potential fetal hyperthyroidism thatmay be detected by ultrasonography include fetal tachycardia (heart rate >170 bpm, persistent for over 10 minutes), intrauterine growth restriction, presence of fetal goiter (the earliest sonographic sign), accelerated bone maturation, signs of congestive heart failure, and fetal hydrops[52].All newborns of mothers with Graves' disease (except those with negative TRAb and not requiring ATD) should be evaluated by a medical care provider for thyroid dysfunction and treated if necessary [18].

5.10 Hyperthyroidism caused by Autonomous Thyroid Nodule(s) in Pregnancy:
Autonomous nodules causing hyperthyroidism develops insidiously and usually less severe than in GD. ATDs should be kept low dose with the goal of maternal FT4 or TT4 concentration at the upper limit or moderately above the reference range. Surgical removal of autonomous nodule(s) should be considered if signs of fetal hypothyroidism develop. Generally, surgical removal should be considered before conception in women with hyperthyroidism seeking future pregnancy.[18]

5.11 Subclinical hyperthyroidism:
There is no evidence that treatment of this condition improves pregnancy outcome. Rather, treatment can adversely affect fetal outcome [18,53].

5.12 ATDs during Lactation:
A small but detectable amount of both PTU and CM/MMI are transferred into breast milk. Due to potential for hepatic necrosis in either mother or child from maternal PTU use (maximum 450 mg/day), CM (up to 20 mg/day) is the preferred ATD in nursing mothers [54].

5.13 Conclusion:
Mild hyperthyroidism appears safe, however, moderate to severe hyperthyroidism is associated with poor maternal and fetal outcome. Gestational Transient thyrotoxicosis is more frequent than Graves's disease and need symptomatic treatment. Management of Graves' disease (GD) during pregnancy is challenging as maternal antibodies may affect maternal and fetal thyroid function. Potential teratogenic effects of the antithyroid medications carbimazole/methimazole and propylthiouracil (PTU) have also been reported. Evaluation of thyroid function test during pregnancy is also challenging. Thus, when and how to treat affected mothers with hyperthyroidism during pregnancy remains a significant clinical problem.

5.14 Recommendations:

- TSH value should be evaluated in conjunction with TT4 and TT3. TT4 and TT3 reference value should be adjusted at 1.5 times the non-pregnant range or FT4 trimester-specific normal reference ranges (if available).
- Overt hyperthyroidism is confirmed in the presence of a suppressed or undetectable serum TSH and inappropriately elevated serum TT4/FT4, or TT3level.
- Due to potential teratogenic effects, use of antithyroid medications carbimazole/methimazole and propylthiouracil need trimester specific consideration.
- If possible, ATDs should be avoided in the first trimester of pregnancy, but when necessary PTU is generally favored.
- If subtotal thyroidectomy is considered, it should be done during second trimester.
- All newborns of mothers with Graves' disease (except those with negative TRAb and not requiring ATD) should be evaluated for thyroid dysfunction and treated if necessary.

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Section-6:
Management of Thyroid Nodule in Pregnancy

Key points:

- ***Thyroid nodules are common in pregnancy and tends to increase in volume and number throughout the pregnancy period.***
- ***Nodules should be evaluated clinically along with thyroid function tests and ultrasound.***
- ***FNAC of thyroid nodule can be done in any trimester if indicated.***
- ***Radionuclide scanning and radioiodine therapy are absolutely contraindicated during pregnancy***
- ***Benign nodules do not require surgery during pregnancy.***
- ***Papillary thyroid carcinoma should be followed up sonologically. If substantial growth occurs, or there is cervical lymphadenopathy, thyroidectomy should be done in second trimester.***

Prevalence of thyroid nodules in pregnancy is 3 -21% and increases with increasing parity [1-3]. Throughout the pregnancy period, nodules tend to increase in volume and number. [1,3] Chance of developing nodule increases with increasing maternal age [1,3]. Prevalence of thyroid cancer in pregnancy varies between 12% to 43%, although the studies were not population based; rather they were performed in referral centers [4-6].

6.1 Evaluation of a pregnant lady with thyroid nodule:

6.1.1 History [7-11]:

- Family history of thyroid disorder, including medullary thyroid carcinoma, MEN-2 etc.
- History of childhood cancers, irradiation involving head & neck
- Childhood exposure to ionizing radiation

6.1.2 Physical examination:

Thorough examination of the thyroid and neck, including cervical lymph nodes [12].

6.1.3 Ultrasound:

Thyroid ultrasound should be done in all patients with thyroid nodules, to determine their sonographic features and pattern, monitor growth, and evaluate cervical lymph nodes [13].

6.1.4 Thyroid function tests:

TSH should be tested in all pregnant women with a thyroid nodule [14,15].

6.1.5 Fine-needle aspiration cytology:

FNAC from a suspicious nodule is safe in pregnancy and may be performed in any trimester [16-25]. FNAC is generally recommended for newly detected nodules in pregnant women with a nonsuppressed TSH. Indications of FNAC is based upon the nodule's sonographic pattern as outlined in Table 6.1 [13]. For women with suppressed serum TSH levels persisting after 16 weeks gestation, FNAC of a clinically relevant thyroid nodule may be deferred until after pregnancy [13].

6.1.6 Radionuclide scanning:

Iodine 131 and Technetium pertechnetate scanning are contraindicated in pregnancy because all maternal radionuclides are associated with a fetal irradiation resulting from both placental transfer and external irradiation from maternal organs [26].

6.2 Management:

Levothyroxine treatment is not effective in decreasing the size or arresting the growth of thyroid nodules during pregnancy. Therefore, suppressive therapy by levothyroxine for thyroid nodules is not recommended during pregnancy [13].

6.2.1 Benign nodules:

Nodules that were benign on FNA but show rapid growth or ultrasound changes suspicious for malignancy should be evaluated with a repeat FNA and be considered for surgical intervention. In the absence of rapid growth, nodules with biopsies that are benign do not require surgery during pregnancy [27]. Pregnant women with cytologically benign thyroid nodules do not require special surveillance strategies during pregnancy [13].

Thus, in instances in which surgery during pregnancy is indicated or desired, it should be performed in the second trimester in order to minimize complications to both the mother and fetus (altered organogenesis and spontaneous abortion in the first trimester, preterm labor and delivery in the third trimester), preferably by an experienced thyroid surgeon [28]. The risk of post-thyroidectomy maternal hypothyroidism and hypoparathyroidism should also be considered.

6.2.2 Atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), suspicious for follicular neoplasm (SFN), or suspicious for malignancy (SUSP):

The chances of malignancy associated with these cytologic diagnoses are variable (6-48% for AUS/FLUS, 14-34% for SFN, and 53-87% for SUSP). [29] As prognosis for DTC diagnosed during pregnancy is not adversely affected by performing surgery post partum, it is reasonable to defer surgery until following delivery. Levothyroxine suppressive therapy during pregnancy is not recommended, as majority of these women will have benign nodules. If there is clinical suspicion of an aggressive behavior in cytologically indeterminate nodules, surgery may be performed during pregnancy. Molecular testing is not recommended for this type of nodules during pregnancy [13].

6.2.3 Thyroid carcinoma:

Papillary thyroid carcinoma detected in early pregnancy should be monitored sonographically. If it grows substantially before 24–26 weeks gestation, or if cytologically malignant cervical lymph nodes are present, surgery should be considered during pregnancy. However, if the disease remains stable by mid-gestation, or if it is diagnosed in the second half of pregnancy, surgery may be deferred until after delivery [13].

The impact of pregnancy on women with newly diagnosed medullary carcinoma or anaplastic cancer is unknown. However, a delay in treatment is likely to adversely affect outcome. Therefore, surgery should be strongly considered, following assessment of all clinical factors [13].

Based on studies which have demonstrated a lack of maternal or neonatal complications from subclinical hyperthyroidism, it is reasonable to assume that the preconception degree of patient at initial high risk for recurrence, TSH suppression at or below 0.1 mU/L is recommended. If the patient then demonstrates an excellent response to therapy at one year with an undetectable suppressed serum Tg and negative imaging, the TSH target may rise to the lower half of the reference range [13].

Thyroid function should be evaluated as soon as pregnancy is confirmed. The adequacy of LT4 treatment should be checked 4 weeks after any LT4 dose change. The same laboratory should be utilized to monitor TSH and Tg levels before, during, and after pregnancy. Pregnant women with thyroid cancer should be managed at the same TSH goal as determined preconception. TSH should be monitored approximately every 4 weeks until 16–20 weeks of gestation, and at least once between 26 and 32 weeks of gestation [13].

6.2.4 Papillary thyroid microcarcinoma:

Ultrasound monitoring of the maternal thyroid should be performed each trimester during pregnancy in women diagnosed with PTMC who are under active surveillance [13].

6.2.5 Pregnant women with previously treated differentiated thyroid carcinoma (DTC):

Ultrasound and Tg monitoring during pregnancy is not required in women with a history of previously treated DTC with undetectable serum Tg levels (in the absence of Tg autoantibodies) classified as having no biochemical or structural evidence of disease prior to pregnancy. Ultrasound and Tg monitoring should be performed during pregnancy in women diagnosed with well-differentiated thyroid cancer and a biochemically or structurally incomplete response to therapy, or in patients known to have active recurrent or residual disease [13].

Table-6.1: Ultrasound patterns and recommendation for FNAC for a thyroid nodule [13]

Pattern	Ultrasound features	Cutoff for FNAC (Largest dimension)
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: • Irregular margins (infiltrative, microlobulated), • Microcalcifications, • Taller than wide shape, • Rim calcifications with small extrusive soft tissue component, • Evidence of extrathyroidal extension	Recommend at >1 cm

Intermediate suspicion	Hypoechoic solid nodule with smooth margins without microcalcifications, extrathyroidal extension, or taller than wide shape	Recommend at >1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or extrathyroidal extension, or taller than wide shape.	Recommend at >1.5 cm
Very low suspicion	Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate or high suspicion patterns	Consider at >2 cm; OR observe without FNAC
Benign	Purely cystic nodules (no solid component)	No biopsy

Table-6.2: Indications for surgery of a thyroid nodule in the second trimester of pregnancy [30]

Appearance	Characteristic
Microscopic pathology	Aggressive histology
Gross pathology	Locally advanced disease
Presence of metastatic structural disease	Cervical lymph node metastases
Clinical course	Significant nodule growth (>50% in volume or >20% in diameter in two dimensions)
Complications	Severe compressive symptoms

6.3 Recommendations:

- In pregnant women with thyroid nodule and suppressed TSH levels beyond 16 weeks gestation, FNAC can be deferred until after pregnancy.
- Newly detected thyroid nodules with nonsuppressed TSH level usually needs FNAC (According to table 6.1).
- Radionuclide scanning or radioiodine uptake determination are contraindicated during pregnancy. .
- Pregnant women with cytologically indeterminate (AUS/FLUS, SFN, or SUSP) nodules do not routinely require surgery while pregnant. But if the nodule is clinically suspected to behave aggressively, then surgery may be considered.
- During pregnancy, if there is clinical suspicion of an aggressive behavior in cytologically indeterminate nodules, surgery may be considered.
- PTC detected in early pregnancy should be monitored by ultrasound. If it grows substantially before second trimester, or if malignant cervical lymph nodes are present, surgery should be considered.
- TSH goal for pregnant women with thyroid cancer is the same as preconception DTC goals.
- Pregnancy should be deferred for at least 6 months after receiving radioactive iodine treatment.

Intermediate suspicion	Hypoechoic solid nodule with smooth margins without microcalcifications, extrathyroidal extension, or taller than wide shape	Recommend at >1 cm
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Section-7:
Thyroid Emergencies during Pregnancy

Key points:

- ***Thyroid emergencies in the form of thyrotoxic crisis and myxedema coma are very rare during pregnancy***
- ***Thyroid emergencies can develop on exposure to precipitating triggers or among patients with preexisting thyroid dysfunction or noncompliance with medical treatment.***
- ***Management of thyroid storm and myxedema coma requires both medical and supportive therapies and should be treated in an intensive care unit (ICU) setting.***
- ***Both myxedema coma and thyroid storm during pregnancy are associated with increased mortality and must be recognized and treated promptly***.

7.1 Introduction:

Treatment of overt maternal hyperthyroidism and overt hypothyroidism clearly improves obstetric and fetal outcomes. These endocrine conditions can turn into an emergency if left ignored or untreated. This includes thyroid storm and myxoedema coma.Treatment of myxedema coma and thyroid storm is multifaceted and should be managed by the interdisciplinary team approach in an ICU setup.

7.2 Thyrotoxic crisis (Thyroid storm):

The incidence of hyperthyroidism in pregnancy is about 0.2% and mostly subclinical [1]. Approximately 90-95% of pregnant women with hyperthyroidism are manifestations of Grave's disease [2].Thyroid storm is a rare serious complication in hyperthyroidism patients (1-2% of cases of hyperthyroidism). Thyroid storm is the major risk to pregnant women with thyrotoxicosis. It often occurs in patients with undertreated or undiagnosed hyperthyroidism. This life-threatening condition is more likely to occur with another precipitating factor such as labor and delivery, surgical delivery, infection, or trauma. During pregnancy it is an Endocrine emergency characterized by is extreme hypermetabolic state and associated with a high risk of maternal heart failure and cause of non-obstetric maternal death. As many as 20% to 30% of cases can end in maternal and fetal mortality [1].

Diagnosis is based on a combination of signs and symptoms: fever, tachycardia out of proportion to the fever, altered mental status (nervousness, restlessness, confusion, seizures), vomiting, diarrhea, and cardiac arrhythmia [3]. An inciting event (e.g., surgery, infection, labor, delivery) may be identified. Untreated thyroid storm can result in shock, stupor, and coma. Serum-free triiodothyronine (FT_3), FT_4, and TSH levels help confirm the diagnosis, but treatment should not be delayed for test results.

Principle of thyroid storm management in pregnancy are reducing the synthesis and secretion of thyroid hormones (propylthiouracil or methimazole; saturated solution of potassium iodide or sodium iodide), decreasing the peripheral effects of thyroid hormone, inhibiting the conversion of T4 to T3 (dexamethasone and phenobarbital), General supportive measures, such as oxygen, antipyretics, and appropriate monitoring, are also important. The underlying cause of thyroid storm if identified should be treated. Other management include therapy to prevent systemic decompensation, trigger disease therapy, pregnancy management and supportive therapy [4].

Depending on gestational age, fetal status should be evaluated with ultrasound examination, nonstress testing, or a biophysical profile. Unless at term or necessary, delivery during thyroid storm should be avoided.

The immediate treatment of heart failure and the correction of precipitating pregnancy factors usually results in good outcome. Long-term follow-up confirmed that thyrotoxic cardiac dysfunction is reversible with successful antithyroid therapy [5].

7.3 Myxedema coma:

Myxedema coma is an extreme complication of uncontrolled hypothyroidism.It is usually seen in elderly women with undiagnosed hypothyroidism and is rare among young. It is very rare among pregnant women with less than 40 cases reported [6]. It is a potentially fatal complication of uncontrolled hypothyroidism manifesting as progressive mental deterioration like lethargy, stupor, delirium, or coma and multiple organ abnormalities. Diagnosis of this rare phenomenon is hampered by its insidious onset. It usually occurs when precipitating factors like infection, illness, drugs, labour and delivery etc weaken the compensatory responses. Although the prognosis of patients with myxedema coma is difficult to determine, the poor predictors of outcome, as reported in the literature, include bradycardia, persistent hypothermia, altered level of consciousness, a high APACHE II score at presentation, hypotension and need for mechanical ventilation. Despite appropriate treatment, mortality ranges between 30 to 50 percent; more so in pregnancy.

Aggressive replacement of thyroid hormone in hypothyroid pregnant women, is recommended regardless of the degree of thyroid function, to minimize the time the fetus is exposed to a hypothyroid environment [7]. Pregnancy itself and poor compliance of the patient is the most frequent cause of lack of response to oral thyroid supplementation [8]. During pregnancy use of other drugs as antacids, sucralfate, antiepiletics, calcium carbonate and dietary interference may cause lack of availability of the required dose of thyroxine [9].

Thyroid hormone therapy is the cornerstone of management of patients with myxedema coma [10]. Both oral and intravenous T4 and T3 are used. If injectable preparation is not available oral administration of Thyroxine through Ryles tube has proved to be equally effective with a drawback that gastric atony may prevent absorption and put the patient at risk for aspiration. The treatment of myxedema coma is not only replacement of thyroid hormone but also, supportive care, and identification of coexistent acute processes and their treatment.

7.4 Recommendations:

- Compliance to thyroid treatment is very important as noncompliance may lead to thyroid emergencies**.**
- Development of thyroid emergencies during pregnancy requires ICU management with multidisciplinary approach

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Section-8:
Postpartum Issues

Key points:

- ***Postpartum thyroiditis and Graves' disease are common causes of thyrotoxicosis in the puerperium, and should be differentiated.***
- ***Hypothyroidism is a common presentation of postpartum thyroiditis.***
- ***Antithyroid drugs should not be given to patients with postpartum thyroiditis.***
- ***Antithyroid drugs are safe in lactation, but lowest possible dose should be used in Graves' disease.***
- ***Hypothyroidism impairs lactation and should be treated.***
- ***^{131}I use is contraindicated during lactation.***

8.1 Introduction:

The endocrinology of puerperium includes physiological and anatomical adjustments to expulsion of the feto-placental unit and onset of lactation [1]. The common thyroid disorders in the postpartum period are Graves' disease and postpartum thyroiditis [2]. There is also the issue of the impact of thyroid dysfunction, its diagnosis and treatment on lactation. Each of these topics will be discussed here.

8.2 Postpartum thyroiditis:

Postpartum thyroiditis occurs within one year after delivery in women who were previously euthyroid [3]. The prevalence of postpartum thyroiditis is approximately 5%, and higher in women with autoimmune disorders [4]. It can also occur after spontaneous or induced abortion. The classical course is transient hyperthyroidism (usually begins 2 to 6 months after delivery and lasts 2 to 8 weeks), followed by hypothyroidism (begins 3-12 months after delivery) and then recovery (within 1 year postpartum). Only 20-30% women present with the classical course, 25% present with only thyrotoxicosis and 50% present with hypothyroidism. Recovery is usual; however 10-20% becomes permanently hypothyroid [5].

The thyrotoxic phase may be asymptomatic or present with features of mild toxicosis. Investigations show raised thyroid hormones (FT4>FT3), low TSH and low radioiodine uptake [5,6,7,8]. It is important to differentiate this phase from Graves' disease (Table 8.1). The hypothyroid phase presents with typical features of hypothyroidism and diffuse, painless goiter. It is often confused with postpartum depression. Thyroid function tests show low FT4 and raised TSH. Anti-thyroid peroxidase antibody is present in high titres [6,8].

Treatment of thyrotoxicosis is not required for asymptomatic women. Monitoring of thyroid function is recommended every 4-8 weeks. Symptomatic women should be prescribed propranolol 40 to 120 mg daily in 3 divided doses until FT3 and FT4 are normal. Propranolol has the least concentration in breast milk. 25-50 mg daily atenolol or metoprolol can also be given. The lowest possible dose to alleviate symptoms should be used. Antithyroid drugs are not required. FT4 and TSH should be measured 4-8 weeks later to screen for hypothyroidism [10]. In case of hypothyroidism, treatment is unnecessary for asymptomatic women with TSH below 10 mU/L unless they are planning another pregnancy soon. However thyroid function should be monitored until it normalizes. Thyroxine supplementation is recommended for asymptomatic women with TSH above 10 mU/L and symptomatic women. Thyroxine supplementation should be given at a dose of 1.7 mcg/kg/day to normalize TSH level for 6 to 12 months. After 6-12 months, the dose should be reduced to half and reassessed after 6 weeks. If no there is abnormality of thyroid function then thyroxin can be stopped and reassessed in another 6 weeks.

If thyroid function tests are abnormal, thyroxin should be continued. In women with very elevated initial TSH values (>50 or 100 mU/L), and high titre antibody, thyroid hormone should be continued indefinitely. Thyroxine should not be stopped if the woman is pregnant, attempting pregnancy, or breastfeeding. For women who have fully recovered from postpartum thyroiditis, the TSH should be measured annually, particularly within 5 to 10 years after the initial diagnosis [9].

8.3 Graves' disease:

Graves' disease is another common thyroid disorder in pregnancy. It can be new onset Graves', relapse or ongoing disease. Patients present with features of toxicosis, which may be severe. There may be diffuse goiter with bruit and other features pathognomic of Graves' disease such as ophthalmopathy. Thyroid hormones are elevated (FT3>FT4), TSH low, TSH receptor antibodies are usually present and radioactive iodine uptake is high [10].

Treatment consists of antithyroid medication. Low to moderate doses of either carbimazole (upto 30 mg/d) or propylthiouracil (up to 450 mg/d) can be given as both are safe in breastfeeding [11]. The drugs should be taken in divided doses following a feed. Since small amounts of both drugs are secreted in breast milk, the lowest possible dose should be given. When the maternal dose of carbimazole is >30 mg daily, infants should have thyroid function tests assessed after one and three months [9]. Although carbimazole is secreted more in breast milk compared to propylthiouracil [12], the former is preferred as propylthiouracil is associated with hepatotoxicity [2]. In addition, there was no difference in the thyroid function of the breastfed infants [12]. Propranolol can also be given with carbimazole if necessary [9].

Women with ongoing Graves' disease have an increased likelihood of worsening of symptoms in the postpartum period. Therefore FT4 and TSH should be measured 6 weeks postpartum. If thyroid function tests are abnormal, dose of carbimazole should be adjusted and thyroid function reviewed after 6 weeks [13]. If thyroid function tests are normal, they can be repeated every 4 months. Women with Graves' disease who are in remission have an increased risk of relapse during this period, especially 4 to 8 months after delivery. Therefore, thyroid function (FT3, FT4, TSH) should be monitored [14].

Table-8.1. Features differentiating thyrotoxic phase of postpartum thyroiditis from Graves' disease [2,10]

	Postpartum thyroiditis (thyrotoxic phase)	Graves' disease (new/relapse)
Timing of onset	Within 3 months of delivery	After 6 months of delivery
Severity of clinical features	Mild	Usually severe
Goiter	Small	Usually larger May have bruit
Ophthalmopathy	Absent	May be present
FT3 and FT4	Mild elevation FT4>FT3 Usually normalizes in 3-4 weeks	Higher levels FT3>FT4 Persistently abnormal
TRAb	Negative	May be positive
Thyroid USG with Doppler flow	Low flow	High flow
99mTc scan*	Low uptake	High uptake

*Use of 99mTc requires breast feeding to be avoided on the day of the scan.

8.4 Lactation and thyroid dysfunction

Hypothyroidism can impair lactation [15] and treating this has shown to improve lactation [16]. Therefore, both subclinical and overt hypothyroidism should be treated in lactating women [9]. Moreover, women with poor lactation and no other cause should be screened for hypothyroidism [9]. The effect of hyperthyroidism on lactation is not clear. Therefore there is no recommendation of treating hyperthyroidism for the sole purpose of improving lactation [9].

8.5 Lactation and radiopharmaceuticals

Diagnostic tests as well as therapy with ^{131}I is absolutely contraindicated during lactation as it has a long half-life and may result in fetal hypothyroidism. If absolutely necessary, ^{123}I and Tc-99m pertechnetate can be used for diagnosis. However, breastfeeding should be avoided and breast milk pumped and discarded for 3–4 days after testing with ^{123}I and 1 day after Tc-99m pertechnetate [17].

8.6 Recommendations:

- It is important to differentiate between postpartum thyroiditis and Graves' disease in the puerperium as their treatment differs.
- Thyroiditis should not be treated with antithyroid drugs. Patients should be given only symptomatic treatment.
- Lowest possible dose of antithyroid drugs should be used in the treatment of Graves' disease in a lactating mother.
- Do not use radioactive iodine for therapeutic purpose during lactation. Its use should also be avoided in the diagnosis of thyroid disorders.

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