2019 RECOMMENDATIONS FOR THE MANAGEMENT OF

THYROID DYSFUNCTION IN PREGNANCY

PANELISTS FOR 2019 RECOMMENDATIONS FOR THE MANAGEMENT OF THYROID DYSFUNCTION IN PREGNANCY

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Method of Development

These recommendations are a joint collaboration between the Indian Thyroid Society (ITS) & Federation of Obstetric and Gynaecological Societies of India (FOGSI). These recommendations review the available evidences in the field by members of the task force which include eminent endocrinologists and gynecologists of National and International repute.

The current updation was chaired by Dr. Shashank R Joshi and presided by Dr. K M Prasanna Kumar and Dr. Nandita Palshetkar, with other eminent members of the Indian medical faculty participating from all corners of India.

The committee evaluated recommendations and evidence using the methodology of the United States Preventive Service Task Force (USPSTF), on the basis of the strength of evidence and magnitude of net benefit (benefits minus harms), as follows (treatments or medical advice are referred to as a "service.")

Level of Evidence	Description
Level A	Data derived from multiple randomized trials or meta-analyses
Level B	Data derived from a single randomized trial or large non-randomized trial
Level C	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 recommendation 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.

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Introduction

Pregnancy results in a number of important physiological and hormonal changes that alter thyroid function mainly due to the influence of two main hormones: human chorionic gonadotropin (HCG) and estrogen.[1] There is a change in the level of thyroxine-binding globulin (TBG), total thyroid-hormone level and thyroid stimulating hormone (TSH) during normal pregnancy.[2] The thyroid gland increases in size (by about 10-15%) during pregnancy and the half-life of TBG increases from 15 min to 3 days and concentration increases 3 times by 20 weeks.[3] For the first 10-12 weeks of pregnancy, the fetus is completely dependent on the mother for the production of thyroid hormone. By the end of the 1st trimester, the fetus's thyroid begins to produce its own hormone. The fetus, however, remains dependent on the mother for ingestion of adequate amounts of iodine, which is essential to make the thyroid hormones.[4]

World Health Organization has revised the reference of Median Urinary Iodine (MUI) for adequate iodine nutrition in pregnancy from 150 to 250 µg/L and the Recommended Dietary Allowance (RDA) for iodine in pregnancy from 200 to 250 µg/L.

Median Urinary Iodine (µg/L)	Iodine Intake
<150	Insufficient
150-249	Adequate
250-499	Above requirements
>500	Excessive

Over the past several years, it has been proven that maternal thyroid disorders influence the outcome of mother and fetus, during and also after pregnancy. About 2-5% of pregnant women suffer from any variety of thyroid disorder.[3]

Thyroid hormone is required for normal neuronal migration, myelination, synaptic transmission and plasticity during fetal and early postnatal life. Iodine deficiency during pregnancy can cause maternal and fetal hypothyroxinemia resulting in irreversible brain damage with mental retardation and neurologic abnormalities.[5,6]

Maternal iodine deficiency also affects pregnancy outcomes and is associated with a higher incidence of miscarriage, stillbirths, abortions and congenital abnormalities.[2,7]

The 2019 Recommendations for the Management of Thyroid Dysfunction in Pregnancy apprise the readers about the different aspects of thyroid disorders in pregnancy and their management. Each topic has clinical evidence followed by the recommendations of the committee. The level of evidence of recommendation is mentioned in a bracket against each recommendation. All recommendations are summarized at the end of the document.

MATERNAL HYPOTHYROIDISM

Maternal and Fetal Aspects

Hypothyroidism is a disorder commonly encountered in pregnancy. Overt hypothyroidism is defined as an increase in serum TSH (usually >10 mIU/L) associated with a decreased concentration of thyroxine, as a result of negative feedback. On the other hand, subclinical hypothyroidism is an increase in serum TSH (usually 4-10 mIU/L) associated with normal concentrations of serum thyroxine and triiodothyronine.[8]

It is now well established that not only overt, but also subclinical thyroid dysfunction has significant adverse effects on pregnancy and fetal development. The adverse pregnancy outcomes include, miscarriage, pregnancy-induced hypertension and its more severe form, pre-eclampsia, as well as placental abruption, anemia, postpartum hemorrhage and increased fetal mortality. These obstetric complications contribute to the overall increase in frequency of adverse neonatal outcomes, which include preterm birth, low birthweight, increased admission to neonatal intensive care and increased perinatal morbidity and mortality.[9-14]

Kooistra *et al.*[15] studied 108 neonates born to mothers with serum free thyroxine (fT4) levels below the 10th percentile at 12 weeks gestation. Compared with control subjects, these infants had decreased neonatal behavioral assessment scores at three weeks of age. Pop *et al.*[16] studied 220 healthy infants and found that having maternal serum fT4 levels below the 10th percentile at 12 weeks gestation was a significant risk for impaired psychomotor development at 10 months of age. A similar result was observed by Kasatkina *et al.*[17]

Iodine deficiency significantly raises the risk of still births and abortion amongst pregnant women and also leads to decreased availability

of iodine to the fetus. It retards neurologic development in the fetal stage and also impairs cognitive development thereby leading to learning disability and lowered achievement motivation in later stages of childhood.[18,19]

Some of the causes of maternal and fetal hypothyroidism are:[10,20]

- **Maternal (overt, subclinical)**
  - Autoimmunity
  - Post-thyroidectomy
- **Fetal**
  - Congenital
  - Thyroid-binding inhibitory immunoglobulin (TBII)
  - Antithyroid drugs
  - Prematurity
- **Maternal and Fetal**
  - Iodine deficiency (severe, mild/moderate)
  - TBII

Timely treatment of maternal hypothyroidism has shown to reduce the risk of neurodevelopmental deficits in the offspring. The stage of development during which the lack of T4 in the fetus is most detrimental for neurodevelopment, is assumed to be the 1st trimester.[21]

Epidemiology

In general, the incidence of overt hypothyroidism during pregnancy ranges from 0.2-2.5% and subclinical hypothyroidism from 2-7%, while thyroid antibodies are present in as high as 60% of women in the reproductive age group.[2,3,11,22-26]

Dhanwal *et al.*[27] concluded from an epidemiological study of 11 cities from 9 states in India that there is a high prevalence of hypothyroidism (13.13%) in India, majority being subclinical in pregnant women during the 1st trimester.

Diagnosis

It is difficult to diagnose hypothyroidism during pregnancy, due to nonspecific presenting features like asthenia, constipation, lethargy, etc., which may be masked by existing obstetric symptoms (increase in weight, altered appetite). Symptoms like cold intolerance and bradycardia are more specific.[11,23]

Because of the nonspecific nature of presentation, hypothyroidism needs to be diagnosed by thyroid function tests. An elevated TSH indicates primary hypothyroidism, and serum T4 levels will help to categorize this as either overt or subclinical hypothyroidism. Thyroid antibodies may be measured to confirm Hashimoto's thyroiditis, which is the most common cause of hypothyroidism in pregnancy.[23]

As all pregnant women have raised TBG levels, the serum T4 level cannot distinguish thyrotoxicosis from euthyroidism. The normal non-pregnant total T4 range (5–12 µg/dL) therefore should be multiplied 1.5 times, to obtain appropriate ranges for the 2nd and 3rd trimesters. Hence, monitoring of maternal thyroid function requires measurement of serum total T4 levels and a careful interpretation of TSH levels.[28,29]

Serum fT4 levels are frequently determined in order to bypass the changes in TBG serum levels. However, fT4 determined by commercial assays may be insensitive due to the changes in serum albumin and TBG leading to false readings in the presence of high TBG.

Due to ethnic differences and geographical variations in populations, 2011 American Thyroid Association (ATA) and 2012 Endocrine Society guidelines recommended that the normal range of TSH should be determined locally for each population. The recommended upper TSH value in the 1st trimester in both the 2011 and the 2012 guidelines was 2.50 mIU/L and 3.00 mIU/L in 2nd and 3rd trimester. In the latest 2017 ATA thyroid and pregnancy guidelines, 19 studies published upper normal TSH limits (defined as the 97.5th percentile) ranging from 2.15 mIU/L to 4.68 mIU/L. A universal TSH cutoff

distinguishing the upper range of normal from the lower range of abnormal does not exist.

The 2017 ATA thyroid and pregnancy guidelines recommended that an upper reference limit (URL) of 4.0 mIU/L can be used if internal or transferable pregnancy-specific reference ranges of TSH are not available. However, a review of the 19 studies referenced in the 2017 ATA thyroid and pregnancy guidelines revealed that only 5 of 19 of the papers cited, reported an upper limit of normal ≥4.0 mIU/L. Out of the five largest studies cited (each including more than 5000 pregnant women), only one reported an upper limit of normal exceeding 3.5 mIU/L.

A 2016 study by Rajput *et al.*[30] on the trimester-specific reference interval for thyroid hormones during pregnancy conducted at a tertiary care hospital in Haryana, India also concluded that existing results for trimester-specific reference intervals for thyroid hormones are inconsistent and cannot be extrapolated due to differences in ethnicity, maternal iodine status, laboratory assay method, and rigor for selection of reference population. Thus, the establishment of reference intervals in each region is of great importance.[30]

To ensure that most women with subclinical hypothyroidism are appropriately diagnosed, a 2018 editorial by Kalra *et al.*[31] concluded that recent 2017 recommendation of ATA of a revised URL for TSH of 4.0 mIU/L is high and should instead be 3.0 mIU/L in the 1st trimester and 3.5 in 2nd and 3rd trimester.

Due to heterogenicity in study methodology, ethnic differences and geographical variations in populations, there is a need for a nation-wide study. Until then, it is recommended to follow lower cut-off considering potential benefits of Levothyroxine in comparison with its minimal risk.

It is recommended that all pregnant women should be screened at 1st antenatal visit by measuring TSH levels. TSH cut-off should be

lower rather than keeping it on 4.0 mIU/L. However, the trimester specific TSH cut-off recommended are:

- *1st trimester: 2.5 mIU/L;*
- *2nd trimester: 3.0 mIU/L;*
- *3rd trimester: 3.0 mIU/L.*

The Endocrine Society (USA) guidelines recommend "caution in the interpretation of serum fT4 levels during pregnancy and also that each laboratory should establish trimester-specific reference ranges for pregnant women."[28,29,32] Similarly, there are no clear reference ranges for serum levels of TSH in pregnancy. Caution is also warranted while interpreting TSH values.

Several factors, including a negative feedback because of elevated T3 and T4 and elevated circulating HCG concentrations influence the TSH levels.[23] The normal values of TSH are lower in pregnancy than in non-pregnant adults and may be suppressed to the so-called thyrotoxic levels in normal pregnant women, especially in the 1st trimester.[33]

A February 2019 report published in the *International Journal of Gynecology & Obsterics* summarized that pregnancy impacts the functioning of the thyroid gland profoundly and is associated with a 10–40% increase in the size of the gland (iodine-replete areas show greater increase), a 50% increase in the production of thyroxine (T4) and triiodothyronine (T3), and a 50% increase in the daily requirement of iodine. These physiological changes can render a pregnant, iodine-deficient, euthyroid woman in the 1st trimester, hypothyroid during the later stages of pregnancy.[34]

The report further summarized that all patients found to have overt hypothyroidism should be treated with oral Levothyroxine (other preparations are not recommended) and both overt and subclinical hypothyroidism patients should be followed up with serum TSH levels every 4 weeks up to 16–20 weeks of gestation and then at least once between 26 and 32 weeks.[34]

Euthyroid women who are thyroid autoantibody positive also require the same monitoring during pregnancy as they have increased propensity to develop hypothyroidism during this period. During pregnancy, there is also a higher risk of overt and subclinical hypothyroidism in women who are positive for thyroid antibodies before conception. The presence of thyroid autoantibodies is relatively high in women of childbearing age. A nearly 2-fold increase in spontaneous pregnancy loss in euthyroid pregnant women tested for thyroid antibodies has been demonstrated in several studies, including a meta-analysis.[35]

There is evidence of the potential association of thyroid autoantibodies, particularly thyroid peroxidase antibodies (TPOAb), and increased risk of pregnancy loss and preterm delivery even in euthyroid women. Given the potential association of thyroid autoimmunity and adverse pregnancy outcomes, it is of prime importance to screen pregnant women for thyroid autoimmunity and to manage thyroid antibody in euthyroid women during pregnancy, when necessary.[36]

Management

Given the increased risk for adverse obstetrical and neonatal outcomes in untreated patients, it is prudent to treat all pregnant women who have hypothyroidism. Also, the 2017 guidelines of the American Thyroid Association stated that insufficient evidence exists to conclusively determine whether Levothyroxine therapy decreases pregnancy loss risk in TPOAb positive euthyroid women who are newly pregnant; the guidelines further recommended that administration of Levothyroxine to TPOAb positive euthyroid pregnant women with a history of loss may be considered given its potential benefits in comparison with its minimal risk.[37]

Levothyroxine, the synthetic form of thyroxine, is routinely used as the primary form of thyroid hormone replacement in the management of hypothyroidism, a condition that affects up to 7% of the general population.[38]

All of the most recent guidelines of major endocrine societies recommend Levothyroxine monotherapy for first line use in hypothyroidism.[39] Levothyroxine use is monitored with thyroid blood tests, the results of which depend partly on the stability of circulating thyroid hormone levels after oral ingestion. Fluctuating thyroid test results require more frequent adjustments in Levothyroxine dose. In turn, constantly adjusting a patient's Levothyroxine dose requires greater follow-up monitoring; thus, there has been substantial interest in ensuring that patients are given the appropriate instructions for taking their Levothyroxine, to allow the medication to be absorbed as consistently as possible.[40]

The need to adjust Levothyroxine dose manifests itself as early as at 4-8 weeks of gestation, therefore justifying the adjustment of Levothyroxine replacement to ensure that maternal euthyroidism is maintained during early gestation.[41]

Dosing of Levothyroxine

There are several possible explanations for an increased need for T4 during pregnancy including increment of absorption and distribution of thyroxine due to gravid uterus and mass of fetal placental unit and increase in serum concentration of TBG that is a consequence of an estrogen-induced increase in the glycosylation of TBG and leads to decreased hepatic clearance of this protein.[41] The average full replacement dose of Levothyroxine in nonpregnant patients with overt hypothyroidism is 1.6-2.0 µg/kg/day.[28,42-44]

Most researchers have recommended that:

- The target TSH levels should be ≤2.5 mIU/L in 1st trimester (or 3 mIU/L in the 2nd and 3rd trimester).[16,26,32]
- In women already taking Levothyroxine, 2 additional doses per week of the current Levothyroxine dose, given as one extra dose twice weekly with several days separation, may be started as soon as pregnancy is confirmed.
- Pregnant women with subclinical hypothyroidism (serum TSH concentration above the upper limit of the reference range

with a normal free T4) should be started with 50-100 µg/day of Levothyroxine. Free T4 and TSH levels should be tested every 6 weeks.[3,26,28,48-50]

- Patients with pre-existing hypothyroidism should have their Levothyroxine dose increased by 25-50 µg/day as soon as pregnancy is confirmed. Patients should have their TSH levels assessed as soon as possible after conception, and again at 8-12 weeks and at 20 weeks of gestation. The target TSH level should be ≤2.5 mIU/L.[26,32,50]
- According to Kung *et al.*[29] pregnant patients with pre-existing hypothyroidism require a 40-50% increase in their daily Levothyroxine dosage to maintain euthyroidism.
- A similar finding has been seen by Unnikrishnan *et al.*[26] who suggested a 25-47% increase in Levothyroxine dose during pregnancy.
- Post-delivery, the patient should be reverted back to the pre-pregnant dosage and TSH levels should be rechecked after 6 weeks.[26,50]

On the same lines, it is emphasized that women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy, are at risk of developing hypothyroidism and should be monitored for TSH at least once in every trimester, and at least up to the 2nd trimester. Levothyroxine therapy can be considered in euthyroid pregnant women with TPOAb positive with a history of pregnancy loss.[6,51-54]

Management of Subclinical Hypothyroidism in Pregnancy

Data on treatment outcomes in subclinical hypothyroid pregnant women are conflicting. A meta-analysis of 14 RCTs (*n*=1918 women) concluded that Levothyroxine supplementation significantly reduced the miscarriage rate, gestational diabetes, and gestational hypertension.[55]

On the other hand, a randomized trial (*n*=21,846) showed that treatment for hypothyroidism in pregnant women did not improve cognitive function in their children.[56]

In subclinical hypothyroidism, pregnant women with TSH level >10 mIU/L and women with TSH level 4-10 mIU/L with positive TPOAb status must always be treated. Pregnant women with TSH level 4-10 mIU/L with TPOAb negative status can be considered for treatment. There is scarcity of data on pregnant women with TSH levels 2.5-4 mIU/L and they may also be treated if they are TPOAb positive. TPOAb negative women with TSH <4.0 mIU/L do not require treatment. However, in these cases, the treatment decision varies as per clinician's experience and is still controversial. Evaluation of TPOAb status for deciding the treatment also depends on availability of the test and affordability by the patient.

Recommendations

Management of Hypothyroidism During Pregnancy and Postpartum

During Pregnancy

1. The trimester specific TSH cut-off recommended are: (IIa/B)
   - 1st trimester: 2.5 mIU/L;
   - 2nd trimester: 3.0 mIU/L;
   - 3rd trimester: 3.0 mIU/L.
2. For overt hypothyroidism, Levothyroxine dose to be 1.6-2.0 µg/kg/day. (I/B)
3. Maintain the target TSH levels ≤2.5 mIU/L. (I/B)
4. Patients with pre-existing hypothyroidism, in whom thyroid assessment cannot be done immediately, should have their Levothyroxine dose increased by 30% as soon as pregnancy is confirmed. Patients should have their TSH levels assessed as soon as possible after conception, and at 6 weeks interval till delivery. (I/A)

Monitoring

1. Regular TSH monitoring (approximately every 4-6 weeks until mid-gestation, and at least once nearing 28 weeks gestation) of patients with overt hypothyroidism and subclinical hypothyroidism should be done. (I/B)
2. TPOAb testing in pregnancy should be done only once. (IIa/B)

Postpartum

1. Postpartum, in patients with pre-existing hypothyroidism: Post-delivery, the patient should be reverted to the pre-pregnancy dosage and TSH levels should be rechecked after 6 weeks. (I/A)
2. Patients with newly diagnosed hypothyroidism in pregnancy: Some women in whom Levothyroxine is initiated during pregnancy, may not require Levothyroxine postpartum. Such women are candidates for discontinuing Levothyroxine, especially when the Levothyroxine dose is ≤50 µg/day. If Levothyroxine is discontinued, serum TSH should be evaluated in ~6 weeks. Women with thyroid autoimmunity need annual monitoring with TSH. (I/B)

Management of Subclinical Hypothyroidism in Pregnancy

- Patients with subclinical hypothyroidism to be started on 50-100 µg/day of Levothyroxine. (IIa/B)
- Levothyroxine therapy is recommended for:
  - Women with a TSH >10.0 mIU/L (I/C)
  - TPOAb positive women with a TSH between 4 mIU/L and 10.0 mIU/L (I/B)
- Levothyroxine therapy can be considered for:
  - TPOAb negative women with a TSH between 4 mIU/L and 10.0 mIU/L (IIa/B)
  - TPOAb positive women with a TSH between 2.5 mIU/L and 4 mIU/L (IIa/B)

MATERNAL HYPERTHYROIDISM

Thyroid disease is the second most common endocrine disorder after diabetes in pregnancy. Thyroid disease poses a substantial challenge on the physiology of pregnant women and has significant maternal and fetal implications. Research shows during pregnancy, the size of the thyroid gland increases by 10% in countries with adequate iodine stores and by approximately 20-40% in countries with iodine deficiency. During pregnancy, thyroid hormone production increases by around 50% along with a similar increase in total daily iodine requirements. Thyroid dysfunction in pregnant women including hypothyroidism and hyperthyroidism requires close monitoring and treatment as warranted. Occasionally, pregnancy may be complicated by thyroid nodules and thyroid cancer requiring further intervention.[37]

Overt hyperthyroidism during pregnancy may be referred to as suppressed (<0.1 mIU/L) or undetectable (<0.01) serum TSH value and elevated thyroid hormone levels that exceed the normal range for pregnancy.[57,58]

The prevalence of hyperthyroidism in pregnancy has been found to be about 0.2% in different studies. The most common cause is Graves' disease.[59-63]

Other uncommon etiologies of hyperthyroxinemia in pregnancy are:[64-66]

Intrinsic Thyroid Disease	Gestational Thyrotoxicosis
• Toxic adenoma • Subacute thyroiditis • Iatrogenic hyperthyroidism	• Nausea/vomiting • Multigravida • Hyperemesis gravidarum • Hydatidiform mole

Maternal, fetal, and neonatal morbidity and mortality are significantly higher in patients with uncontrolled hyperthyroidism. Maternal morbidity includes a higher incidence of toxemia, still birth, preeclampsia, premature delivery, placenta abruptio, congestive heart failure, and thyroid crisis. In some cases, anemia and infections may also be seen.[14,60]

Signs and symptoms of Graves' disease in pregnancy are similar to those in affected nonpregnant women. However, some of these symptoms may be synonymous with those seen in normal pregnancy such as heat intolerance, shortness of breath, insomnia, slightly elevated pulse rate, and decreased exercise tolerance. Goitre is almost always present. Careful examination of the eyes may reveal signs of exophthalmopathy.

Usually there is exacerbation of symptoms during the 1st trimester with reduced severity during the second half of pregnancy and symptoms may worsen again during the postpartum period.[67]

Autoimmune thyroiditis occurs in up to 10% of women and can present with both a hyperthyroid phase of Hashimoto's thyroiditis and silent thyroiditis. Postpartum thyroiditis (PPT) occurs in up to 10% of all pregnancies and may have a hyperthyroid phase. It may begin between 6 weeks to 6 months after delivery, and occasionally, as long as 1 year later. It may also be triggered by a miscarriage occurring as early as 6 weeks. Because the hyperthyroid phase of thyroiditis is often followed by a hypothyroid phase, and because hypothyroidism is an important risk for abnormal fetal development, careful sequential monitoring is necessary to detect and treat the hypothyroid phase of this illness.[68-70]

Routine screening of all women for PPT is not justified. Women who have type 1 diabetes or are TPOAb positive during the 1st trimester or have postpartum depression should have their TSH monitored at 3- and 6-months postpartum.

A syndrome, referred to as 'gestational transient thyrotoxicosis' (GTT), has to be differentiated from Graves' disease, as the course of both conditions, the fetal risks associated with them, and the management and follow-up of both entities, are different. Patients usually present in the mid-to late-1st trimester, often with hyperemesis. Usually classic hyperthyroid symptoms are absent or minimal, except for weight loss. Differentiation of Graves' disease from non-autoimmune GTT is supported by evidence of diffuse goitre and autoimmunity like presence of TSH receptor antibodies (TRAb).[4,65,71-73]

- Gestational transient thyrotoxicosis should be differentiated from Graves' hyperthyroidism in pregnancy.
- In case of subnormal serum TSH during pregnancy, hyperthyroidism must be distinguished from both normal physiology during pregnancy and hyperemesis gravidarum (HG).
- Diagnosis of Graves' disease is supported by evidence of diffuse goitre and autoimmunity, like presence of TRAb.

Fetal Thyroid Function

The fetus is dependent on the small supply of thyroxine (T4) from the mother until 10-12 weeks of gestation. When the fetal thyroid gland starts secreting thyroid hormones by 20 weeks of gestation, the fetal thyroid gland becomes responsive to TSH from its own pituitary gland. TSH does not cross the placenta; however, clinically significant amounts of maternal T4 do cross the placenta. In neonates with congenital hypothyroidism, enough maternal thyroid hormone crosses the placenta to prevent stigmata of hypothyroidism at birth and to maintain umbilical cord blood thyroid hormone levels at near 50% of normal. Antithyroid drugs, such as methimazole and propylthiouracil, also cross the placenta and therefore serve as treatment for both maternal and fetal hyperthyroidism.[28,60,74,75]

Neonatal morbidity in maternal hyperthyroidism includes small for gestational age neonates, intrauterine growth retardation (IUGR), low birth weight (LBW) infants, and prematurity.

Globally, in mothers with a good control of hyperthyroidism, the relative risk of fetal complications is only increased two-fold, compared with a nine-fold relative risk increase for untreated hyperthyroid mothers.

Diagnosis

When the diagnosis of Graves' disease has not been established before pregnancy, the disorder is not always readily suspected clinically. Women with Graves' disease seeking future pregnancy should be counseled regarding the complexity of disease management during future gestation, birth defects with antithyroid drug use, risks and benefits of all treatment options, and the patient's desired timeline to conception.

Free thyroxine determination or calculation of the free thyroxine index (fT4I) (using total thyroxine levels and a test for assessing TBG, such as resin uptake) are routine tests in most clinical laboratories. Almost every patient with Graves' disease has elevated fT4 concentrations or fT4I.

A suppressed TSH value in the presence of a high fT4 or fT4I confirms the diagnosis of hyperthyroidism. In about 15% of normal pregnant women, a low or suppressed serum TSH is present in the 1st trimester of pregnancy. In some unusual situations, the serum fT4 may be in the upper limit of normal or be slightly elevated, in which case, the determination of fT3 and the fT3I will confirm diagnosis of hyperthyroidism. Thyroid peroxidase antibodies or thyroid antimicrosomal antibodies, markers of thyroid autoimmune disease, are elevated in most patients with Graves' disease and its determination is indicated in patients in whom the etiology of hyperthyroidism is in doubt.[64]

Upto 60% of women with hyperemesis gravidarum have a subnormal TSH and nearly 50% have an elevated fT4 concentration. Most patients with Graves' disease will have detectable TRAb.

TSH receptor antibodies are present in a majority of patients with Graves' disease. Measurement of TRAb may also help to distinguish Graves' disease from gestational thyrotoxicosis in the 1st trimester as they are negative in gestational hyperthyroidism. Because Graves' disease tends to undergo immunological remission after the late 2nd trimester, detection of TRAb may depend upon gestational age at measurement.[28]

Fetal Hyperthyroidism

Fetal or neonatal hyperthyroidism occurs in 1–5% of pregnancies with active or inactive Graves' disease. Fetal and neonatal hyperthyroidism is usually produced by transplacental passage of thyroid-stimulating immunoglobulins. The passage of immunoglobulins and the potential for fetal hyperthyroidism become clinically significant at the end of the 2nd trimester. Most commonly, the thyroid-stimulating immunoglobulins are a component of active maternal Graves' disease. However, such antibodies may continue to be produced after ablation of the thyroid by surgery, radioiodine therapy or by the immune mechanisms of Hashimoto's thyroiditis.[76-78]

Thyroid-stimulating immunoglobulin levels ≥35% and TSH receptor binding inhibitory immunoglobulin levels ≥40% have been associated with fetal thyrotoxicosis. If either antibody titer is suspiciously high, a careful fetal ultrasound examination should be performed. In the presence of fetal tachycardia (>160/min) and goitre, fetal thyrotoxicosis should be suspected.[78-82]

Other findings associated with fetal hyperthyroidism include IUGR, craniosynostosis, premature skeletal maturation, cardiac failure, and hydrops.[44]

The necessity of cordocentesis to confirm the diagnosis in the clinical setting of fetal tachycardia and a mother with either active or previously treated Graves' disease is controversial.[79] It can be considered if the diagnosis of fetal thyroid disease is not reasonably certain from the clinical data and fetal goitre is detected in women taking antithyroid drugs to help determine whether the fetus is hyperthyroid or hypothyroid.

A minority of newborns from mothers with Graves' disease develop transient central hypothyroidism. In these cases, the fT4 level may be elevated at birth, indicating fetal hyperthyroidism.[79,80]

In neonatal hyperthyroidism serum T3 and fT3 are higher, and serum TSH level is lower than the normal range of the same gestational age. The measurement of serum thyrotropin receptor antibodies can be important for the early differential diagnosis.[80]

Management of Overt Maternal Hyperthyroidism

Antithyroid drugs (ATD)

The treatment of choice for hyperthyroidism in pregnancy is antithyroid drugs (ATD) of which thionamides (propylthiouracil, methimazole, carbimazole) are the most commonly used. They inhibit thyroid hormone synthesis by blocking iodination of the tyrosine molecule. Because these drugs block the synthesis, but not the release of thyroid hormone, the clinical response to thionamides is not immediate. In fact, a clinical response to thionamides does not occur until colloid stores are depleted. Therefore, the time required to achieve control of the thyrotoxicosis is variable and depends on the amount of colloid stored in the thyroid gland. Commonly, the patient notices some initial clinical improvement after the first week of therapy and approaches euthyroidism by 4-6 weeks of therapy. Propylthiouracil (PTU) also blocks the conversion of T4 to T3. Many physicians recommend the use of PTU rather than methimazole (MMI) because MMI may be teratogenic. There have been numerous

case reports describing cutis aplasia and congenital abnormalities (choanal atresia, gastrointestinal, and facial) in pregnancies treated with methimazole. Although a causal relationship between methimazole and cutis aplasia or the spectrum of birth defects is not certain, the reports have led to the avoidance of methimazole in early pregnancy. However, if allergy or intolerance occurs with PTU therapy, it is recommended that carbimazole/methimazole be used as substitution therapy. Propylthiouracil is the preferred drug in the 1st trimester.[44,66,83-87]

- Propylthiouracil is recommended during the 1st trimester followed by a switch to methimazole/carbimazole beginning in the 2nd trimester.

Dosage and monitoring

The initial dose of ATD depends on the severity of the disease. Propylthiouracil is usually initiated at 100-150 mg/8h (or MMI 20 mg or carbimazole 15 mg in divided doses) guided by maternal T4 levels. To avoid fetal hypothyroidism, the lowest dose possible to keep maternal T4 in the high normal range should be used. Once ATDs are started, the patient should be monitored every 3-4 weeks during gestation and the dose adjusted accordingly. Monitoring consists of assessing maternal pulse, weight gain, thyroid size and measurements of total T4 (TT4) or fT4 and TSH with the recommended therapeutic target being TT4: 12-18 μg/dL (or fT4, 2-2.5 ng/dL). The recommended range for TSH in patients on ATDs has been suggested to be 0.1-0.4 mIU/L. Monitoring only by TSH is useful in late gestation when the disease is controlled.

After control of thyrotoxicosis, the dosage of PTU should be decreased to 50 mg four times a day. If the patient remains clinically euthyroid, the PTU dosage could be decreased to 150 mg/day and then, after 3 weeks, to 50 mg twice a day. Pregnant women with thyrotoxicosis should be maintained on as low a dosage of PTU as possible, preferably <100 mg/day.

The fetus should be monitored for signs of hypothyroidism by clinical examination for growth and fetal heart rate for baseline bradycardia.[44,66,83-87]

Antithyroid medications can be continued postpartum as there is minimal excretion of these drugs into breast milk. The American Academy of Pediatrics and WHO support the compatibility of breastfeeding and all antithyroid medications.

- In women on a low dose of MMI (<5–10 mg/day) or PTU (<100–200 mg/day), ATD may be stopped. Such patients should be monitored every 1-2 weeks to assess maternal and fetal thyroid status.
- Furtheron, in pregnant patients taking ATDs, TRAb testing is recommended. If patient requires treatment through mid-pregnancy, a repeat determination of TRAb is recommended again at weeks 18-22, and in late pregnancy.

Other adverse effects

The most common complication associated with thionamide therapy tends to occur within the first 4 weeks of therapy, affecting approximately 2% of patients. It includes a mild, occasionally purpuric, rash, pruritus, drug fever, and nausea. Agranulocytosis is an idiosyncratic reaction that occurs during treatment with thionamides and is rare, affecting approximately 0.5% of the treated population. A leukocyte count should be obtained before initiation of thionamide therapy.[44,66,83-87]

Beta-blockers

Beta-adrenergic blockers inhibit conversion of T4 to T3 and can be used as an adjunctive treatment to antithyroid medications to reduce tachycardia, palpitations, and tremors. Concerns have been raised, however, because the use of beta-blocking agents during pregnancy has been associated with adverse outcomes, including small placenta, IUGR, neonatal respiratory distress, impaired responses to anoxic

stress, and postnatal bradycardia, hypothermia, and hypoglycemia. Hence, beta-blockers have not been recommended for long term treatment of thyrotoxicosis during pregnancy. Propranolol 20–40 mg orally every 8-12 hours or atenolol, 50–100 mg/day may be used for the rapid control of thyrotoxicosis or while awaiting response to the antithyroid medications or surgery.[44,83,85]

Iodide

Low-dose iodide (6–40 mg/day of potassium iodide) has been used, leading to improvement in maternal thyroid function and normal neonatal outcome, but because of the risk of fetal goitre, iodide use is not recommended.[66,78]

Surgery

Subtotal or total thyroidectomy is indicated when, for any reason, ATDs fail to control the hyperthyroid disease even on large doses. The appropriate time is the 2nd trimester. Ideally, surgery requires previous pharmacological treatment to normalize thyroid function.[44,66]

Radioactive iodine therapy

During pregnancy ^{131}I is contraindicated because of the possible teratogenic effects of radiation. After ^{131}I ablative therapy, effective contraception postponing is recommended for at least 3 months, and some recommend postponing conception for 1 year. Inadvertent treatment nevertheless may occur, raising the question of what information should be given to the mother. This inadvertent exposure is most likely in the 1st trimester, the crucial period of organogenesis, when the patient does not yet realize that she is pregnant. However, the consequence of inadvertent administration of 5-10 mCi of ^{131}I to pregnant women shows that hypothyroidism occurs in only 3% of the fetuses. Exposure after 12 weeks can induce thyroid ablation, requiring intrauterine thyroid hormone replacement and lifelong therapy for hypothyroidism.[28,44,66,78,85]

Different clinical scenarios in management of maternal Graves' disease are:[61,80]

1) **Pregnancy in active Graves' disease:** Continuing with an ATD is recommended. To determine whether the fetus is at risk of having hyperthyroidism, TRAb titers should be assessed in the 3rd trimester (preferably by bioassay) to confirm they are of the stimulating variety.
2) **New diagnosis of Graves' disease during pregnancy:** Treatment should be started with an ATD as soon as the diagnosis is made.
3) **Relapse during early pregnancy in a woman with a past history of Graves' disease:** In this event, medication should be restarted. When evaluating such patients, the normal physiological increase in T4 plasma concentrations during the 1st trimester should be borne in mind.

Pregnancy after a previous ablative treatment (surgery or radioiodine): In these cases, reassessment of TRAb levels at the beginning of pregnancy is recommended and if elevated, repeat testing should occur at weeks 18-22 to determine the chance of fetal or postnatal hyper- or hypothyroidism, as maternal thyroid function is normal on T4 replacement therapy.

When positive TSHR-stimulating Ab is found, several precautionary measures should be initiated, as a hyperthyroid fetus in a euthyroid mother is possible. In this condition the fetal pulse must be monitored and should not be tachycardic (>160 bpm). If tachycardia is detected, it is reasonable to initiate PTU 100-200 mg/8h (to control fetal hyperthyroidism), as well as to continue Levothyroxine supplementation to maintain maternal euthyroidism.

Subclinical Hyperthyroidism

Patients with subclinical hyperthyroidism have a normal serum fT4 level and a serum TSH level below the reference range (0.1–0.45 mIU/L). Among pregnant women, the prevalence of this diagnosis is 1.7%. Studies have demonstrated that subclinical hyperthyroidism

is not associated with adverse pregnancy outcomes and does not warrant treatment.[45]

Management of Fetal Hyperthyroidism

Once fetal hyperthyroidism is diagnosed, treatment should be PTU 100–400 mg/day or methimazole 10–20 mg/day given to the mother. The fetus should be re-evaluated for clinical improvement (heart rate, goitre resolution) by ultrasound in 2 weeks and appropriate dose adjustment should be done.[64]

As soon as the fetal heart rate normalizes, ATD dose should be reduced systemically with frequent monitoring of fetal heart rate to maintain it in the normal range. For previously ablated hyperthyroid mothers, Levothyroxine therapy may need to be increased if hypothyroxinemia develops while treating fetal hyperthyroidism with PTU.[79,83]

Recommendations

1. In case of subnormal serum TSH during pregnancy, hyperthyroidism must be distinguished from both normal physiology during pregnancy, and HG due to its adverse effects on the mother and fetus. Diagnosis of Graves' disease is supported by evidence of diffuse goitre and autoimmunity, like presence of TRAb. (I/A)
2. For overt hyperthyroidism diagnosed during pregnancy, thionamides are the treatment of choice. Start treatment immediately with PTU, in case of allergy or intolerance, carbimazole/methimazole can be substituted. Propylthiouracil is the preferred drug in the 1st trimester. Maintain the maternal thyroid hormone levels for fT4 in the upper nonpregnant reference range (IIa/B). In women on a low dose of MMI (<5–10 mg/day) or PTU (<100–200 mg/day), ATD may be stopped. Such patients should be monitored every 1-2 weeks to assess maternal and fetal thyroid status. PTU is recommended during the 1st trimester followed by a switch to methimazole/carbimazole beginning in the 2nd trimester. (IIa/B)

3. Long term use of beta-blockers is associated with adverse effects; hence they are recommended only for the symptomatic control of thyrotoxicosis or while awaiting response to the antithyroid medications or surgery. Propranolol is the most commonly used beta-blocker. (IIa/B)
4. Iodides can lead to fetal goitre and should not be used. (IIa/C)
5. Surgery is indicated when ATDs fail to control the hyperthyroid disease (over 300 mg of PTU or 40 mg/day methimazole/ carbimazole). 2nd trimester is the safest time suggested for surgery. (I/B)
6. Use of ^{131}I is contraindicated because of the possible teratogenic effects of radiation. Effective contraception postponing is recommended for at least 3 months following therapy. There are no data for or against recommending termination of pregnancy after inadvertent ^{131}I exposure. (I/B)
7. In case of pregnancy in active Graves' disease, continue treatment with an ATD. To determine whether the fetus is at risk of having hyperthyroidism, TRAb titers could be assessed in the 3rd trimester if possible. (IIa/B)
8. Medication should be restarted in case of relapse during early pregnancy in a woman with a past history of Graves' disease. (IIb/C)
9. In case of pregnancy after a previous ablative treatment, reassessment of TRAb levels (if possible) at the beginning of pregnancy, is recommended to determine the chance of fetal or postnatal hyper- or hypothyroidism. (IIb/C)
10. If mother is euthyroid but positive for TRAb, there is a possibility of fetal thyrotoxicosis which should be assessed by FHR (>160/min). If all other causes of fetal tachycardia have been ruled out, start mother on methimazole/carbimazole to control fetal thyrotoxicosis and Levothyroxine to maintain maternal euthyroidism. (IIa/B)
11. Presence of subclinical hyperthyroidism (normal serum fT4 level and a low serum TSH level) in pregnant women does not warrant any treatment. (IIa/B)

12. Pregnant women with TRAb or those treated with ATD should have a fetal ultrasound to detect fetal thyroid dysfunction. This may include growth restriction, hydrops, presence of goitre, and cardiac failure. (IIa/B)
13. Once fetal hyperthyroidism is diagnosed, ATD therapy should be administered to the mother. The fetus should be re-evaluated for clinical improvement (heart rate, goitre resolution) by ultrasound in 2 weeks and appropriate dose adjustment done. (IIb/B)
14. Umbilical cord blood may be considered if the diagnosis of fetal thyroid disease is not reasonably certain from the clinical data and fetal goitre is detected in women taking antithyroid drugs to help determine whether the fetus is hyperthyroid or hypothyroid. (IIb/C)

HYPEREMESIS GRAVIDARUM AND HYPERTHYROIDISM

Hyperemesis gravidarum (HG) or pernicious vomiting of pregnancy, is a complication of pregnancy that affects various areas of the woman's health, including homeostasis, electrolytes, and kidney function, and may have adverse fetal consequences. Hyperemesis gravidarum occurs in 0.3-2% of pregnant women, although populations with significantly higher rates have been reported.

Pregnant females with HG have higher serum HCG values than healthy pregnant women. Since HCG has a structure similar to TSH; it can stimulate the thyroid when present in high concentrations in serum. Therefore, such patients might develop transient hyperthyroidism. This transient hyperthyroidism of hyperemesis gravidarum is noted in 50-70% of women who have hyperemesis. The typical symptoms and signs of hyperthyroidism are absent, and it usually can be distinguished from intrinsic thyroid disease in that, there is no history of hyperthyroid symptoms preceding pregnancy, goitre and thyroid antibodies are absent, and the T3 level is highly unlikely to be more than the thyroxine level. There rarely are symptoms of hyperthyroidism except for occasional tachycardia.

Differentiation from Graves' disease is usually possible because the hyperthyroidism tends to subside as symptoms of vomiting improve, usually by the beginning of the 2nd trimester. The condition is usually self-limiting and does not require specific antithyroid therapy. If hyperthyroidism and thyroid function abnormalities persist beyond 18-20 weeks of gestation, then mild Graves' disease is indicated and should be treated with antithyroid drugs.

It is recommended that gestational transient thyrotoxicosis should be differentiated from Graves' hyperthyroidism in pregnancy. In case of subnormal serum TSH during pregnancy, hyperthyroidism must

be distinguished from both normal physiology during pregnancy and HG. Diagnosis of Graves' disease is supported by evidence of diffuse goitre and autoimmunity, like presence of TRAb. Routine assessment of thyroid function is recommended in patients with HG.[44,66,88-92]

Hyperemesis gravidarum is usually self-limited and does not require antithyroid therapy, except in a few cases where thyroid function abnormalities persist beyond 18-20 weeks of gestation.

Recommendations

1. Thyroid function tests should be measured in all patients with HG, as such patients are at risk of developing transient hyperthyroidism. (IIa/B)
2. Distinguishing features from intrinsic thyroid disease are the absence of typical symptoms and signs of hyperthyroidism, no prior history of hyperthyroid symptoms preceding pregnancy, absence of goitre and thyroid antibodies. (IIa/B)
3. The condition is usually self-limited and does not require antithyroid therapy, except in a few cases where thyroid function abnormalities persists beyond 18-20 weeks of gestation. (I/B)

AUTOIMMUNE THYROID DISEASE IN PREGNANCY

Thyroid autoimmunity refers to the presence of antibodies to thyroperoxidase or thyroglobulin, or TRAbs or a combination of these, and is present in up to 18% of pregnant women. Thyroid antibodies in pregnant women with normal functioning thyroids (i.e., euthyroid) have been associated with several complications, including miscarriage and premature delivery.[93]

Approximately one third of all pregnancies end in spontaneous miscarriage. Although majority of pregnancy loss occurs prior to the first missed menses, and therefore, prior to the mother being aware that she is pregnant, approximately one tenth of all spontaneous abortions are clinically apparent. Miscarriages can have diverse etiology including genetic anomalies, hormonal abnormalities, anticardiolipin antibodies, and uterine factors (such as fibroids). In women with recurrent abortions, typically defined as three or more spontaneous miscarriages, the cause of pregnancy termination remains unknown in approximately 50% of the women, despite extensive evaluation.[94]

The risk for miscarriage and preterm delivery is increased when the levels of TSH are higher than normal (0.1–4.5 mIU/L). Ever since the publication of the initial reports in 1990s, linking pregnancy loss to thyroid autoimmunity, a rich literature has unfolded to confirm this relationship.[95,96]

Studies have found some correlation between pregnancy loss and thyroid auto-antibodies. Stagnaro-Green *et al.*[97] screened 552 women in the 1st trimester of pregnancy for the presence of thyroid antibodies.[97] They found a doubling of the miscarriage rate in women who were antibody positive in the 1st trimester as compared to antibody negative women (17% *vs*. 8.4%, p=0.011). The finding of an increased miscarriage rate was independent of demographic

data, thyroid hormonal status, thyroid antibody titer and cardiolipin antibodies.[97,98]

A study by Lepoutre *et al.*[99] evaluated the rationale behind universal thyroid function screening in women and the potential benefits of thyroxine treatment in particular cases during early pregnancy. The analysis of obstetric complications revealed a significant difference in miscarriage rates in TPOAb positive women treated at the first prenatal visit as compared with the nontreated group, with no miscarriages being observed in the treated TPOAb positive women. In contrast, 4 TPOAb positive women with a TSH value >1 mIU/L had an early miscarriage before initiating Levothyroxine therapy. There is therefore potential benefit of universal screening and Levothyroxine treatment for autoimmune thyroid disease during pregnancy.

In another study, Glinoer *et al.*[100] found that women with thyroid autoimmunity had a miscarriage rate which was almost four-fold compared with the controls (p=0.005).

Lejeune *et al.*[101] found that miscarriages associated with thyroid autoimmunity take place early and almost entirely within the 1st trimester of pregnancy.

In another study Bagis *et al.*[102] performed a prospective study in women who were recruited in the 12th week of gestation and followed until 1-year postpartum. Women who were thyroid antibody positive comprised 12.4% of the total group. Fifty percent of the women who were antibody positive had a history of prior miscarriage, as compared to 14.1% in women who were thyroid antibody negative. Furthermore, women with miscarriage who were antibody positive had a significantly higher TSH, and lower free T4, as compared with the control group.

In the study of Pratt *et al.*[103] 45 women with recurrent abortions were evaluated for the presence of thyroid autoantibodies as well as for 15 non-organ-specific autoantibodies. The women with habitual miscarriages had a higher incidence of thyroid autoantibodies

as compared to the controls (31% *vs.* 19%). In a follow-up study in which pregnancy outcome was evaluated in 42 euthyroid women with a history of three or more consecutive 1st trimester abortions, 31% had thyroid autoantibodies. The presence of thyroid autoantibodies before conception carried a significantly increased risk of miscarriage, because 8 of 13 thyroid autoantibody positive women and only 4 of 29 thyroid autoantibody negative women miscarried (62% *vs.* 14%, p=0.003).[104]

Though these studies showed an association between thyroid antibodies and miscarriage in an unselected population, causality could not be established. Thyroid antibodies may simply serve as a marker for autoimmune disease.

Some other studies have shown no association.

Esplin *et al.*[105] tested for TG- and TPOAb in 74 nonpregnant patients historically remarkable for recurrent miscarriage. Twenty-nine percent of recurrent miscarriage patients and 37% of the control group were positive for one or both of the antibodies tested (p>0.05). All were euthyroid. The authors concluded that those with a history of recurrent miscarriage were no more likely than the control population to test positive for antithyroid antibodies.

Rushworth *et al.*[106] examined the prevalence of thyroid autoantibodies in 870 patients with the diagnosis of recurrent miscarriage. In the euthyroid, antibody positive group, the subsequent pregnancy success rate was 58%, as it was for the antibody negative group. It was concluded that the risk of subsequent pregnancy loss in women with recurrent miscarriage was unaffected by their thyroid antibody status.

De Carolis *et al.*[107] evaluated the presence of antithyroid antibodies in 203 non-pregnant women with antiphospholipid antibody syndrome (APLAs) and recurrent miscarriage; 162 non-pregnant women affected with recurrent miscarriage and thyroid autoimmunity alone

served as controls. Pregnancy outcome (spontaneous pregnancies and live births) in women with APLA alone was better than in those with APLA and antithyroid antibodies. The authors concluded that their results support an investigation for antithyroid antibodies in APLA patients with recurrent miscarriages.

These studies demonstrated an association between thyroid antibodies and miscarriage in euthyroid women with recurrent miscarriage. It should however be noted, however, that the strength of the association is not as robust as is the relationship between thyroid antibodies and miscarriage in an unselected population.

On the pretext that euthyroid pregnant women who are positive for TPOAb develop impaired thyroid function, which is associated with an increased risk of miscarriage and premature deliveries, Negro *et al.*[108] conducted a study, to determine whether these women suffer from a higher rate of obstetrical complications and whether Levothyroxine treatment exerts beneficial effects. The study concluded substitutive treatment with Levothyroxine is able to lower the chance of miscarriage and premature delivery.

Another study by Nazarpour *et al.*[109] aimed to assess whether pregnant women with autoimmune thyroid disease, but without overt thyroid dysfunction are affected by higher rates of adverse pregnancy outcomes. The study further aimed to explore whether Levothyroxine treatment improves the pregnancy outcome of affected women. Results displayed a lower rate of preterm deliveries, and the study concluded that treatment with Levothyroxine decreases the risk of preterm delivery in women who are positive for TPOAb.

Thus, although limited in nature, these data suggest a potential benefit to administration of Levothyroxine in TPOAb positive, euthyroid pregnant women with a prior history of loss. The underlying mechanism is, however, uncertain.

Recommendations

1. The data on the association of thyroid antibodies and recurrent pregnancy loss or preterm birth are conflicting and a statistically significant association has not been shown in large studies. (IIb/B)
2. Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy, are at risk of developing hypothyroidism and should be monitored for TSH at least once in every trimester, at least upto 2nd trimester. (I/A)
3. Levothyroxine therapy can be considered in euthyroid pregnant women with TPOAb positive and history of pregnancy loss. (IIb/C)

THYROID NODULES IN PREGNANCY

Pregnancy is associated with growth of pre-existing thyroid nodules as well as the growth of new nodules.[44,110] Among reproductive-age women, most palpated nodules of the thyroid are benign hyperplastic (or colloid) nodules; however, between 5–20% are true neoplasms, benign adenomas, or carcinomas.[101] Papillary thyroid cancer is the most common histologic type diagnosed and has an excellent long-term prognosis.[44] The approach to diagnosis in a pregnant woman with a palpable thyroid nodule is similar to that in the non-pregnant woman and includes a serum TSH and an ultrasound assessment of the neck and thyroid gland.[44,111,112]

Management is based on the stage of pregnancy at which it is detected and on the TSH level.

If the TSH is suppressed, no further evaluation (except to rule out hyperthyroidism) is indicated for a nodule detected in any trimester of pregnancy.[113]

Given the very slow evolution of nodular thyroid disease, in most cases, the postponement of surgery until after delivery is a very reasonable and acceptable management option.[79,114]

Fine-needle aspiration of thyroid nodules during pregnancy is recommended to exclude cancer if it is increasing in size, suspicious (microcalcifications, hypoechoic, increased vascularity, infiltrative margins), or >1 cm.[112-116]

If malignant, start suppressive therapy with Levothyroxine (TSH to 0.1-1 mIU/L) and consider surgery in the 2nd trimester.[114,116,117]

If benign, no further evaluation is needed during pregnancy, except Levothyroxine to normalize the TSH. If malignancy is suspected, ultrasonography (USG) of the neck is recommended to look for suggestive sonographic features and for assessment of nodule size and for any suspicious lymph nodes.[113]

Papini *et al.*[118] showed that 12 months suppressive therapy with Levothyroxine on 51 patients with thyroid nodules contributed to size reduction in 45% of patients compared to 26% in the control group.

In another study by Lima *et al.*[119] in 1997 on 54 patients with one-year Levothyroxine treatment, it was found that none of the patients had significant reduction in nodule size.

Zelmanovitz *et al.*[120] assessed 45 patients with thyroid nodules and concluded, that after one year of follow-up, with suppressive treatment with Levothyroxine, reduction in nodule size was seen in 17% of patients, and there was also prevention of nodule growth in 10% of the cases.

Larijani *et al.*[121] examined 62 patients in a double blind clinical trial in 1999, and observed that, after 24 months follow-up, 6 subjects in Levothyroxine, and 4 subjects in placebo group had >50% reduction in nodule size.

In 2002, in a randomized double blind study by Wemeau *et al.*[122] in 123 patients with thyroid nodules, >50% decrease in nodule volume was shown after 18 months follow up in 26% and 16% in Levothyroxine and placebo groups, respectively. However, the TSH level reached to 0.73 ± 0.8 mIU/L in Levothyroxine group.

In 2006, Tsai *et al.*[123] exhibited that from 30 patients receiving Levothyroxine for 6 months, 11 cases were reported to have more than 50% reduction in their thyroid nodule volume after reaching the mean TSH to 0.08 ± 0.02 mIU/L.

In all women with cytology indicative of papillary or follicular thyroid cancer, Levothyroxine suppression therapy should be initiated to maintain the serum TSH in the range of 0.1-0.8 mIU/L and $\leq$2.5 mIU/L for patients with medullary thyroid cancer.[79]

Nodule size should be determined by repeated USG every trimester. If size is stable, repeat biopsy should be performed only after delivery.

In case of enlargement, surgery may be considered, irrespective of the trimester.[113]

Women who undergo surgical treatment during pregnancy require monitoring of thyroid function and need replacement Levothyroxine. In case of papillary microcarcinoma (<1 cm), hemithyroidectomy is recommended.[124,125]

Postsurgically, patients should be maintained on Levothyroxine with monitoring of TSH and fT4 levels every 8 weeks.[85]

Postsurgical whole-body scintigraphy and radioiodine remnant ablation are contraindicated during pregnancy and lactation.[44]

Management of hyperthyroidism in pregnancy resulting from a hyperfunctioning solitary nodule or multinodular goitre consists of antithyroid medications, beta-adrenergic blockers, and thyroid surgery.[44]

Recommendations

1. A pregnant woman with a palpable thyroid nodule should be evaluated by measuring serum TSH and an ultrasound assessment of the neck and thyroid gland and FNAC (fine-needle aspiration cytology). (IIa/B)
2. If nodule is malignant or shows rapid growth, consider surgery in the 2nd trimester. (IIa/B)
3. If the nodule is benign, no further evaluation is needed, (except in the cases with elevated TSH), Levothyroxine is given to normalize the TSH and follow-up with USG of the neck. (IIa/B)
4. In case of papillary or follicular thyroid cancer, Levothyroxine suppression therapy should be initiated to maintain the serum TSH in the range of 0.1-0.8 mIU/L and <2.5 mIU/L for patients with medullary thyroid cancer. (IIb/C)

5. If the size of the nodule is stable, repeat biopsy should be performed only after delivery. (IIa/B)
6. Postsurgically, patients should be maintained on Levothyroxine therapy with monitoring of TSH and free T4 levels every 6 weeks. (IIa/C)
7. Postsurgical whole-body scintigraphy and radioiodine remnant ablation are contraindicated during pregnancy and lactation. (I/B)

POSTPARTUM THYROIDITIS

Postpartum thyroiditis (PPT) is the occurrence of hyperthyroidism, hypothyroidism, and/or hyperthyroidism followed by hypothyroidism in the first year postpartum in women without overt thyroid disease before pregnancy. It is the most common endocrinological disease experienced by women with prevalence, ranging from 1.1-16.7%.[126-129]

In type 1 diabetes mellitus, the prevalence of PPT has been found to be 10–25% (three- to four-fold higher than in non-diabetic women).[130-133]

Women with a history of PPT have a dramatically increased risk of developing permanent hypothyroidism in the following 5–10 years.[113,126-128]

The presence of serum antibodies against thyroperoxidase during the 1st trimester is the best predictor of PPT development.[134]

The association of PPT with thyroid antibodies, distinct T-cell abnormalities, and a pathological picture consistent with thyroiditis, combine to provide strong evidence for the immunological basis of PPT.[113-133]

Hyperthyroidism always predates hypothyroidism and occurs 2-6 months postpartum.[113]

In a patient presenting with hyperthyroidism postpartum, the commonest differential diagnosis is PPT and Graves' disease. In both disorders, there is a suppressed TSH and elevated fT4 and T3 levels, occurs shortly after delivery, and goitre and TPOAb are positive. However, the presence of exophthalmos, a bruit, or TRAb positivity is typically diagnostic of Graves' disease. But, from an epidemiological standpoint, the most likely etiology of postpartum hyperthyroidism is PPT as its prevalence is 20-fold greater than

Graves' disease. In cases with mild hyperthyroidism postpartum, it is reasonable to repeat the thyroid function tests 4–6 weeks prior to scanning. If by this time there is resolution of hyperthyroidism, it would be consistent with the transient hyperthyroidism of PPT and would obviate the need for thyroid scanning.

On the other hand, patients presenting with hypothyroidism postpartum, with positive thyroid antibody is pathognomonic for PPT.[113]

Symptoms of PPT include the typical symptoms of hyperthyroidism and hypothyroidism. The majority of women in the hyperthyroid phase of PPT do not require intervention as it is mild and rarely exceeds a couple of months. Symptomatic cases are managed with a short course of beta-blockers titrated based on symptom severity. It is controversial whether to treat women in the hypothyroid phase of PPT.

- Women with a TSH of 4-10 mIU/L and who are asymptomatic, require no treatment.
- Women with a TSH of >10 mIU/L and those who are symptomatic with a TSH between 4 and 10 mIU/L, should be treated with Levothyroxine 50-75 µg/day and 25 to 50 µg/day respectively.
- Asymptomatic women with a TSH between 4 and 10 mIU/L and planning a subsequent pregnancy in the near future, also require therapy.[113]

The duration of therapy with Levothyroxine is controversial. Either attempt to discontinue treatment approximately 1 year postpartum following the occurrence of PPT, or maintain therapy until the woman completes her family and begin weaning Levothyroxine one year after the birth of the final child.[135]

Risk for postpartum depression and alexithymia showed a direct borderline statistically significant correlation with serum TPOAb, suggesting that these mood disorders could be neurobehavioral consequences of an autoimmune attack (because of the TPOAb

circulation in the CSF and of their possible cross-reaction with cerebral autoantigens).[136]

The PPT is more likely to occur in pregnant thyroid autoantibodies positive women compared to negative women.[137] Most PPT women develop thyroid dysfunction during the first 6 months postpartum with initial mild symptoms of hyperthyroidism (heat intolerance, palpitations, weight loss, and fatigue) and a subsequent hypothyroid phase, frequently associated with depression.[138] Approximately 50% of PPT women return euthyroid by 12 months postpartum.

Kuijpens *et al.*[139] studied prospectively 310 women during gestation and up to 36 weeks postpartum. The presence of TPOAb was independently associated with depression at 12-week gestation and at 4- and 12-weeks postpartum (odds ratios between 2.4 and 3.8) in a prospective study on 310 unselected women.

In a follow-up study, Harris *et al.*[140] showed a significantly greater depression incidence in 110 thyroid autoantibodies positive women (47%) compared with 132 negative women (32%) regardless of thyroid dysfunction.

In another study, lower levels of serum FT3 were associated with increased incidence of mood disorders in the first postpartum week; only TPOAb and TgAb were significantly higher in women at risk for postpartum depression compared to women not at risk, using EPDS cutoff values of $\geq$13 or $\geq$14.[141] The presence of thyroid autoantibodies or higher TSH levels during the postpartum period may be related to depressive symptoms or dysphoric mood. Pregnant TPOAb positive women were shown to have higher depressive symptoms during pregnancy, and higher depression, anger, and total mood disturbance, postpartum, regardless of the development of PPT.[142]

Sylvén *et al.*[143] found an association between the TSH level over the clinical cutoff of 4.0 mIU/L and the increased risk for depressive symptoms at 6 months postpartum in a Swedish population-based cohort (OR 11.30, 95% CI 1.93–66.11).

The rationale behind a possible association between positive postpartum depression and PPT is that hypothyroidism is associated with depression outside of the postpartum period, and that hypothyroidism appears to decrease 5-hydroxytrytamine neurotransmission which reverses with thyroid hormone replacement.[144]

Recommendations

1. Routine screening of all women for PPT is not justified. Women who have type 1 diabetes or are TPO positive during the 1st trimester should have their TSH monitored at 3- and 6-months postpartum. (IIb/B)
2. Majority of women in the hyperthyroid phase do not require intervention. (I/A)
3. Symptomatic cases should be managed with a short course of beta-blockers. (IIa/B)
4. Symptomatic women with a TSH of >10 mIU/L or between 4 and 10 mIU/L, as well as asymptomatic women with a TSH between 4 and 10 mIU/L and planning pregnancy in the near future should be treated with Levothyroxine. (IIa/B)
5. Women with postpartum depression should be screened for hypothyroidism and appropriately treated. (IIb/C)
6. Women with a prior history of PPT should have TSH testing annually to evaluate for the development of permanent hypothyroidism. (I/A)

IODINE REQUIREMENT IN PREGNANCY

During pregnancy, when iodine is necessary also for the production of fetal thyroid hormones (as the fetal thyroid begins to function around the twelfth week of gestation), women need to increase their iodine intake by about 50%[145] as against the usual recommended intake of 150 µg/day. It is due to an increased need for thyroxine by the mother, transfer of maternal T4 and iodine from the mother to the fetus and also an increase in the renal clearance of iodine during pregnancy as a consequence of an increased glomerular filtration rate. This leads to increased activity of the thyroid gland, which is evidenced by an elevation in thyroid iodide clearance and thyroid enlargement.[146-149]

Women who are iodine sufficient are little impacted, but those with a restricted or deficient iodine intake are markedly affected.[150,151]

Iodine deficiency results in low maternal circulating thyroid hormone concentrations, a reduced placental transfer of thyroxine, thereby leading to maternal hypothyroxinemia, enhanced thyroidal stimulation and ultimately goitre formation in mother and fetus.[144,152-155]

The most serious adverse effect of iodine deficiency is damage to the fetus. Iodine treatment of pregnant women in areas of severe deficiency reduces fetal and perinatal mortality and improves motor and cognitive performance of the offspring. Severe iodine deficiency *in utero* causes a condition characterized by gross mental retardation along with varying degrees of short stature, deaf mutism, and spasticity that is termed cretinism.[156]

In iodine sufficient mothers, defined by the WHO technical consultation group as regions where universal salt iodization (USI) has been effective for at least 2 years, with salt adequately iodized and consumed by more than 90% of the population, the iodine

needs are covered by their diet, and the iodine stored in the thyroid gland is sufficient to ensure adequate hormone synthesis and secretion during pregnancy.[149]

In areas with a severe iodine deficiency, correcting the iodine lack has proved highly beneficial to prevent mental deficiency disorders in infants and children.[153]

According to The International Council for Control of Iodine Deficiency Disorders (ICCIDD) and Technical Consultation, the recommended nutrient intake (RNI) for iodine during pregnancy is 250 µg/day. A daily intake of >500 µg day is not necessary, as it would not provide any additional benefit and may be associated with impaired thyroid function.[146,149]

The intake during lactation should also be about 250 µg/day as iodine is efficiently concentrated by the mammary gland.[28,157,158]

The Consultation proposed that the median urinary iodine (MUI) concentration was the best indicator to use in population surveys to assess the iodine nutrition of pregnant and lactating women. Interpretation can be done as shown below.[149]

Population group	MUI concentration (µg/L)	Iodine intake
Pregnant women	• <150 • 150-249 • 250-499 • ≥500	• Insufficient • Adequate • More than adequate • Excessive
Lactating women	• <100 • ≥100	• Insufficient • Adequate

Systematic neonatal screening for congenital hypothyroidism in iodine-deficient regions is done by detection of TSH concentration in blood. An elevated level of TSH reflects an insufficient supply of maternal and/or fetal thyroid hormone to the developing brain and indicates a risk of irreversible brain damage.[149]

The many actions undertaken to eradicate severe iodine deficiency have allowed preventing the occurrence of mental retardation in millions of young infants throughout the world. In most public health programs dealing with the correction of iodine deficiency disorders, iodized salt has been used as the preferred strategy in order to convey the iodine supplements to the household.[5,153]

In countries without an efficient USI program, complementary approaches are required to reach the RNI of iodine. Such approaches include the use of oral iodine supplements in the form of potassium iodide [KI (100–200 µg/day)] or the inclusion of KI (125–150 µg/day) in multivitamin tablets specifically designed for pregnancy or a single annual oral dose of 400 mg of iodine as iodized oil.[28,149,159]

Recommendations

1. Iodine sufficient mothers have adequate iodine stored in the thyroid gland to ensure adequate hormone synthesis and secretion and do not require routine iodine supplementation. (IIa/A)
2. Iodized salt has been used as the preferred strategy for correction of iodine deficiency disorders. (IIa/A)

SCREENING FOR THYROID DYSFUNCTION DURING PREGNANCY

Thyroid disorders are common in pregnancy and there has been an increasing appreciation of the incidence of thyroid dysfunction during pregnancy as well as the resultant adverse maternal and fetal effects.[160]

Medical screening is the systematic application of a test or inquiry to identify individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action.

The requirements for a justifiable screening test for thyroid dysfunction are:[136]

1. How well-defined the disorder is and is the frequency sufficient enough to warrant screening?
2. Is a simple, safe and cost-effective screening test available?
3. Are available interventions safe and effective?
4. Are the tests and interventions acceptable to patient and physician?

The thyroid abnormalities during gestation described in above sections suggest that screening for thyroid dysfunction in relation to pregnancy should be strongly considered. However, because of the low incidence of hyperthyroidism in pregnancy, the current cost of this strategy makes it an impractical approach.[161]

The strength of evidence relating maternal hypothyroidism (even subclinical hypothyroidism) to low IQ in children, strongly suggests that screening for thyroid function in early gestation and treatment with Levothyroxine in appropriate women would be beneficial. In addition, there is evidence that such a strategy would be cost-effective.[160-163]

The 2011 American Thyroid Association pregnancy guidelines and the 2012 Endocrine Society pregnancy guidelines significantly expanded the definition of "high risk" women from that used in earlier editions to include women >30 years of age. This expanded definition of high risk encompassed many more women in populations with a high mean maternal pregnancy age.

In a 2012 study by Potlukova *et al.*[164] with a mean maternal age at pregnancy of 31 years, the addition of age 30 or older as a risk factor increased the proportion of women correctly identified in a case-finding strategy from 55.3 to 85.6%. However, in a Chinese population with mean maternal age at pregnancy of 26.6 years, testing using only high-risk criteria missed 82.4% of women with subclinical hypothyroidism, 28.6% of women with overt hyperthyroidism, and 74.6% of women with antithyroid antibodies.[165] Member surveys of professional societies have shown that 42.7% of responders in Latin America and 43% in Europe perform universal screening,[166] whereas only 21% of the Asia-Oceania Thyroid Association members do so,[167] and 74% of American Thyroid Association members support such an approach.[168]

In the 2014 European Thyroid Association guidelines, the majority of authors recommended universal screening because of the beneficial effects of treatment for overt hypothyroidism, and the fact that the targeted approach may miss a large percentage of women with subclinical hypothyroidism.[169] The Spanish Society of Endocrinology and Nutrition[170] have expressed support for universal screening in early pregnancy or preconception. The Indian National Guidelines recommend testing only high-risk women.[171,172] Finally, the American Society for Reproductive Medicine recommends TSH testing in all infertile women attempting pregnancy and in high-risk women in early pregnancy.[173]

Many researchers have also advocated aggressive case finding for subclinical thyroid disease during pregnancy, although systematic screening is not recommended.[12,44,160,161]

The high-risk groups are:

- Women with a history of hyperthyroid or hypothyroid disease, postpartum thyroiditis, or thyroid lobectomy
- Personal history of thyroid or other autoimmune disorders or a family history of thyroid disease
- Women who have symptoms or clinical signs suggestive of hypothyroidism or hyperthyroidism
- Women with goitre
- Women with a history of miscarriage or preterm delivery
- Previous neck irradiation or thyroid surgery
- Women with type 1 diabetes

Choosing Screening Tests

Ideally, screening should be carried out during pre-pregnancy evaluation or as soon as pregnancy is confirmed. A disadvantage of screening during confirmed pregnancy is that by the time testing is possible, damage may already have occurred. Screening should be limited to detection of TSH level only and if necessary fT3 and fT4 may be tested.[3,161]

Routine ultrasound and thyroid antibodies may be considered when nodular disease is suspected not only to characterize nodules and evaluate their growth characteristics but also to help establish a clinical diagnosis of Graves' disease (by excluding nodules) or Hashimoto's thyroiditis (based on typical heterogeneous patterning).[66]

Recommendations

1. All pregnant females should be screened at 1st antenatal visit by measuring TSH levels. (IIa/B)
2. For the following high-risk groups screening should also include TPOAb: (IIa/C)
   i. Personal history of thyroid or other autoimmune disorders or a family history of thyroid disease
   ii. Women with goitre
   iii. Women with a history of miscarriage or preterm delivery
   iv. Women with type 1 diabetes
3. Maternal thyroid dysfunction is by itself not an indication for termination of pregnancy. (IIa/B)
4. There is no contraindication for breastfeeding in women on ATD. (I/A)

THYROID DISORDERS AND INFERTILITY

Infertility is defined as the failure to achieve a clinical pregnancy after 12 or more months of regular unprotected sexual intercourse. Infertility is due to female factors in about 35% of cases, due to male factors in 30% of cases, and due to both female and male factors in 20% of cases. In approximately 15% of cases, the cause of infertility is unknown.[174]

Thyroid hormones have profound effects on reproduction and pregnancy. Thyroid dysfunction is implicated in a broad spectrum of reproductive disorders, ranging from abnormal sexual development to menstrual irregularities and infertility. Undiagnosed and untreated thyroid disease can be a cause for infertility as well as sub-fertility. Both these conditions have important medical, economical, and psychological implications in our society.[175]

Thyroid dysfunction can affect fertility in various ways resulting in anovulatory cycles, luteal phase defect, high prolactin (PRL) levels, and sex hormone imbalances. Therefore, normal thyroid function is necessary for fertility, pregnancy, and to sustain a healthy pregnancy, even in the earliest days after conception.

Thyroid evaluation should be done in any woman who wants to get pregnant and has a family history of thyroid problems or irregular menstrual cycles or has had more than two miscarriages or is unable to conceive after 1 year of unprotected intercourse.[176] The comprehensive thyroid evaluation should include T3, T4, TSH, and thyroid autoimmune testing such as TPOAb, thyroglobulin/antithyroglobulin antibodies, and thyroid stimulating immunoglobulin.[177]

Prevalence

Prevalence of hypothyroidism in the reproductive age group is 2–4% and has been shown to be the cause of infertility and habitual abortion.[178]

Diagnosis

Hypothyroidism can be easily detected by assessing TSH levels in the blood. The 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum also recommend the evaluation of serum TSH concentration for all women seeking care for infertility.[37]

A slight increase in TSH levels with normal T3 and T4 indicates subclinical hypothyroidism whereas high TSH levels accompanied by low T3 and T4 levels indicate clinical hypothyroidism.[179] Subclinical hypothyroidism is more common. It can cause anovulation directly or by causing elevation in prolactin (PRL). It is extremely important to diagnose and treat the subclinical hypothyroidism for pregnancy and to maintain it unless there are other independent risk factors.

Many infertile women with hypothyroidism have associated hyperprolactinemia due to increased production of thyrotropin releasing hormone (TRH) in ovulatory dysfunction.[180] Hyperprolactinemia adversely affects fertility potential by impairing gonadotropin-releasing hormone pulsatility and thereby ovarian function. Gynecologists mostly check TSH and PRL levels in every infertile female, regardless of their menstrual rhythm.

Management Approach

Thyroid dysfunction is a common cause of infertility which can be easily managed by correcting the appropriate levels of thyroid hormones.

Hormone therapy with thyroxine is the choice of treatment in established hypothyroidism. It normalizes the menstrual cycle, PRL levels and improves the fertility rate as shown in studies. With simple oral treatment for hypothyroidism, 76.6% infertile women with hypothyroidism conceived after 6 weeks to 1 year of therapy.[181]

It has been recommended that in the presence of raised PRL, the treatment should be first given to correct the hypothyroidism before

evaluating other causes of raised PRL. Measurement of TSH and PRL is routinely done as a part of infertility workup.[181]

Normal TSH levels are the pre-requisite for fertilization. The decision to initiate thyroid replacement therapy in subclinical hypothyroidism at early stage is justified in infertile women. Variations in TSH levels in the narrower range or borderline cases, i.e. 4–5, 5–6, and >6.0 μIU/ml, should not be ignored in infertile women which are otherwise asymptomatic for clinical hypothyroidism.[182] This group of infertile women, if only carefully diagnosed and treated for hypothyroidism, can benefit a lot rather than going for unnecessary battery of hormone assays and costly invasive procedures.

Levothyroxine: Place in Therapy

Infertile women with overt hypothyroidism should be treated with an adequate dose of Levothyroxine, especially before infertility treatment.[183] Levothyroxine treatment in patients with subclinical hypothyroidism improved embryo quality and enhanced embryo implantation after *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI). Raber *et al.*[184] conducted a research about Levothyroxine therapy to infertile subclinical hypothyroid patients based on a thyroxine-releasing hormone stimulation test, and they also observed a higher conception rate than in previously reported studies.

Subclinical hypothyroidism in patients undergoing IVF/ICSI has a deleterious effect on embryo quality and embryo implantation and these conditions can be corrected by Levothyroxine supplementation from the first day of controlled ovarian stimulation for IVF/ICSI. Lower embryo quality and embryo implantation rate in the control group may result from elevated TSH as well as reduced fT4 concentrations.[185]

A similar set of meta-analyses[186] included three trials with data on 220 patients and results showed Levothyroxine treatment resulted in a significantly higher delivery rate and significantly lowered

miscarriage rate providing clinical evidence that Levothyroxine supplementation should be recommended to improve clinical pregnancy outcome in women with subclinical hypothyroidism and/or thyroid autoimmunity undergoing assisted reproduction techniques.

On the same lines, a recent systematic and meta-analysis was conducted to determine whether Levothyroxine supplementation would improve pregnancy outcomes among infertile women with subclinical hypothyroidism and/or thyroid autoimmunity who underwent IVF/ICSI. This 2018 study showed patients receiving Levothyroxine supplementation had a significantly decreased miscarriage rate relative to those receiving a placebo or no treatment. The study thus concluded that given its potential to reduce the miscarriage rate, Levothyroxine supplementation is recommended for infertile women with subclinical hypothyroidism and/or thyroid autoimmunity who are undergoing IVF/ICSI.[187]

In conclusion, Levothyroxine treatment can improve embryo quality, implantation rate, and live birth rate in infertile women with subclinical hypothyroidism undergoing IVF/ICSI. Both TPOAb and thyroglobulin antibodies levels are associated with an increased risk of miscarriage, and this negative impact can be overcome by Levothyroxine treatment. Not only this, the 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum also state that Levothyroxine treatment is recommended for infertile women with overt hypothyroidism who desire pregnancy.[37]

Therefore, Levothyroxine treatment should be considered in subclinical hypothyroid patients planning IVF/ICSI, and pregnant women after IVF/ICSI should be treated with an adequate dose of Levothyroxine throughout the pregnancy period.

Recommendations

1. Evaluation of serum TSH concentration is recommended for all women seeking care for infertility. (IIa/B)
2. Levothyroxine treatment is recommended for infertile women with overt hypothyroidism. (I/B)
3. Levothyroxine may be considered in subclinical hypothyroidism women who are attempting natural conception given its potential benefits in comparison to its minimal risk. (IIb/C)
4. Subclinical hypothyroidism women undergoing IVF or ICSI should be treated with Levothyroxine. The goal of treatment is to achieve a TSH concentration <2.5 mIU/L. (I/B)
5. Levothyroxine may be considered in euthyroid thyroid autoantibody positive women who are undergoing assisted reproductive treatment given its potential benefits in comparison to its minimal risk. (IIb/C)

SUMMARY OF RECOMMENDATIONS

Maternal Hypothyroidism

1. During pregnancy, the trimester specific TSH cut-off recommended are: (IIa/B)
   - 1st trimester: 2.5 mIU/L;
   - 2nd trimester: 3.0 mIU/L;
   - 3rd trimester: 3.0 mIU/L.
2. For overt hypothyroidism, Levothyroxine dose to be 1.6-2.0 µg/kg/day. (I/B)
3. Maintain the target TSH levels ≤2.5 mIU/L. (I/B)
4. Patients with pre-existing hypothyroidism, in whom thyroid assessment cannot be done immediately, should have their Levothyroxine dose increased by 30% as soon as pregnancy is confirmed. Patients should have their TSH levels assessed as soon as possible after conception, and at 6 weeks interval till delivery. (I/A)
5. Regular TSH monitoring (approximately every 4-6 weeks until mid-gestation, and at least once nearing 28 weeks gestation) of patients with overt hypothyroidism and subclinical hypothyroidism should be done. (I/B)
6. TPOAb testing in pregnancy should be done only once. (IIa/B)
7. Postpartum, in patients with pre-existing hypothyroidism: Post-delivery, the patient should be reverted to the pre-pregnancy dosage and TSH levels should be rechecked after 6 weeks. (I/A)
8. Patients with newly diagnosed hypothyroidism in pregnancy: Some women in whom Levothyroxine is initiated during pregnancy, may not require Levothyroxine postpartum. Such women are candidates for discontinuing Levothyroxine,

especially when the Levothyroxine dose is ≤50 µg/day. If Levothyroxine is discontinued, serum TSH should be evaluated in ~6 weeks. Women with thyroid autoimmunity need annual monitoring with TSH. (I/B)

9. Patients with subclinical hypothyroidism to be started on 50-100 µg/day of Levothyroxine. (IIa/B)
10. Levothyroxine therapy is recommended for:
    - Women with a TSH >10.0 mIU/L. (I/C)
    - TPOAb positive women with a TSH between 4 mIU/L and 10.0 mIU/L. (I/B)
11. Levothyroxine therapy can be considered for:
    - TPOAb negative women with a TSH between 4 mIU/L and 10.0 mIU/L. (IIa/B)
    - TPOAb positive women with a TSH between 2.5 mIU/L and 4 mIU/L. (IIa/B)

Maternal Hyperthyroidism

12. In case of subnormal serum TSH during pregnancy, hyperthyroidism must be distinguished from both normal physiology during pregnancy and HG due to its adverse effects on the mother and fetus. Diagnosis of Graves' disease is supported by evidence of diffuse goitre and autoimmunity, like presence of TRAb. (I/A)
13. For overt hyperthyroidism diagnosed during pregnancy, thionamides are the treatment of choice. Start treatment immediately with PTU, in case of allergy or intolerance, carbimazole/methimazole can be substituted. Propylthiouracil is the preferred drug in the 1st trimester. Maintain the maternal thyroid hormone levels for fT4 in the upper nonpregnant reference range (IIa/B). In women on a low dose of MMI (<5–10 mg/day) or PTU (<100–200 mg/day), ATD may be stopped. Such patients should be monitored every 1-2 weeks to assess maternal and fetal thyroid status. PTU is recommended

during the 1st trimester followed by a switch to methimazole/carbimazole beginning in the 2nd trimester. (IIa/B)

14. Long term use of beta-blockers is associated with adverse effects; hence they are recommended only for the symptomatic control of thyrotoxicosis or while awaiting response to the antithyroid medications or surgery. Propranolol is the most commonly used beta-blocker. (IIa/B)
15. Iodides can lead to fetal goitre and should not be used. (IIa/C)
16. Surgery is indicated when ATDs fail to control the hyperthyroid disease (over 300 mg of PTU or 40 mg/day methimazole/carbimazole). 2nd trimester is the safest time suggested for surgery. (I/B)
17. Use of ^{131}I is contraindicated because of the possible teratogenic effects of radiation. Effective contraception postponing is recommended for at least 3 months following therapy. There are no data for or against recommending termination of pregnancy after inadvertent ^{131}I exposure. (I/B)
18. In case of pregnancy in active Graves' disease, continue treatment with an ATD. To determine whether the fetus is at risk of having hyperthyroidism, TRAb titers could be assessed in the 3rd trimester if possible. (IIa/B)
19. Medication should be restarted in case of relapse during early pregnancy in a woman with a past history of Graves' disease. (IIb/C)
20. In case of pregnancy after a previous ablative treatment, reassessment of TRAb levels (if possible) at the beginning of pregnancy, is recommended to determine the chance of fetal or postnatal hyper- or hypothyroidism. (IIb/C)
21. If mother is euthyroid but positive for TRAb, there is a possibility of fetal thyrotoxicosis which should be assessed by FHR (>160/min). If all other causes of fetal tachycardia have been ruled out, start mother on methimazole/carbimazole to control

fetal thyrotoxicosis and Levothyroxine to maintain maternal euthyroidism. (IIa/B)

22. Presence of subclinical hyperthyroidism (normal serum fT4 level and a low serum TSH level) in pregnant women does not warrant any treatment but it warrants follow-up testing for the same and antibodies. (IIa/B)
23. Pregnant women with TRAb or those treated with ATD should have a fetal ultrasound to detect fetal thyroid dysfunction. This may include growth restriction, hydrops, presence of goitre, and cardiac failure. (IIa/B)
24. Once fetal hyperthyroidism is diagnosed, ATD therapy should be administered to the mother. The fetus should be re-evaluated for clinical improvement (heart rate, goitre resolution) by ultrasound in 2 weeks and appropriate dose adjustment done. (IIb/B)
25. Umbilical cord blood may be considered if the diagnosis of fetal thyroid disease is not reasonably certain from the clinical data and fetal goitre is detected in women taking antithyroid drugs to help determine whether the fetus is hyperthyroid or hypothyroid. (IIb/C)

Hyperemesis Gravidarum and Hyperthyroidism

26. Thyroid function tests should be measured in all patients with HG, as such patients are at risk of developing transient hyperthyroidism. (IIa/B)
27. Distinguishing features from intrinsic thyroid disease are the absence of typical symptoms and signs of hyperthyroidism, no prior history of hyper-thyroid symptoms preceding pregnancy, absence of goitre and thyroid antibodies. (IIa/B)
28. The condition is usually self-limited and does not require antithyroid therapy, except in a few cases where thyroid function abnormalities persists beyond 18-20 weeks of gestation. (I/B)

Autoimmune Thyroid Disease in Pregnancy

29. The data on the association of thyroid antibodies and recurrent pregnancy loss or preterm birth are conflicting and a statistically significant association has not been shown in large studies. (IIb/B)
30. Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy, are at risk of developing hypothyroidism and should be monitored for TSH at least once in every trimester, at least upto 2nd trimester. (I/A)
31. Levothyroxine therapy can be considered in euthyroid pregnant women with TPOAb positive and history of pregnancy loss. (IIb/C)

Thyroid Nodules in Pregnancy

32. A pregnant woman with a palpable thyroid nodule should be evaluated by measuring serum TSH and an ultrasound assessment of the neck and thyroid gland and FNAC (fine-needle aspiration cytology). (IIa/B)
33. If nodule is malignant or shows rapid growth, consider surgery in the 2nd trimester. (IIa/B)
34. If the nodule is benign, no further evaluation is needed, (except in the cases with elevated TSH), Levothyroxine is given to normalize the TSH and follow-up with USG of the neck. (IIa/B)
35. In case of papillary or follicular thyroid cancer, Levothyroxine suppression therapy should be initiated to maintain the serum TSH in the range of 0.1-0.8 mIU/L and <2.5 mIU/L for patients with medullary thyroid cancer. (IIb/C)
36. If the size of the nodule is stable, repeat biopsy should be performed only after delivery. (IIa/B)
37. Postsurgically, patients should be maintained on Levothyroxine therapy with monitoring of TSH and free T4 levels every 6 weeks. (IIa/C)

38. Postsurgical whole-body scintigraphy and radioiodine remnant ablation are contraindicated during pregnancy and lactation. (I/B)

Postpartum Thyroiditis

39. Routine screening of all women for PPT is not justified. Women who have type 1 diabetes or are TPO positive during the 1st trimester should have their TSH monitored at 3- and 6-months postpartum. (IIb/B)
40. Majority of women in the hyperthyroid phase do not require intervention. (I/A)
41. Symptomatic cases should be managed with a short course of beta-blockers. (IIa/B)
42. Symptomatic women with a TSH of >10 mIU/L or between 4 and 10 mIU/L, as well as asymptomatic women with a TSH between 4 and 10 mIU/L and planning pregnancy in the near future should be treated with Levothyroxine. (IIa/B)
43. Women with postpartum depression should be screened for hypothyroidism and appropriately treated. (IIb/C)
44. Women with a prior history of PPT should have TSH testing annually to evaluate for the development of permanent hypothyroidism. (I/A)

Iodine Requirement in Pregnancy

45. Iodine sufficient mothers have adequate iodine stored in the thyroid gland to ensure adequate hormone synthesis and secretion and do not require routine iodine supplementation. (IIa/A)
46. Iodized salt has been used as the preferred strategy for correction of iodine deficiency disorders. (IIa/A)

Screening for Thyroid Dysfunction During Pregnancy

47. All pregnant females should be screened at 1st antenatal visit by measuring TSH levels. (IIa/B)

48. For the following high-risk groups screening should also include TPOAb: (IIa/C)
    i. Personal history of thyroid or other autoimmune disorders or a family history of thyroid disease
    ii. Women with goitre
    iii. Women with a history of miscarriage or preterm delivery
    iv. Women with type 1 diabetes
49. Maternal thyroid dysfunction is by itself not an indication for termination of pregnancy. (IIa/B)
50. There is no contraindication for breastfeeding in women on ATD. (I/A)

Thyroid Disorders and Infertility

51. Evaluation of serum TSH concentration is recommended for all women seeking care for infertility. (IIa/B)
52. Levothyroxine treatment is recommended for infertile women with overt hypothyroidism. (I/B)
53. Levothyroxine may be considered in subclinical hypothyroidism women who are attempting natural conception given its potential benefits in comparison to its minimal risk. (IIb/C)
54. Subclinical hypothyroidism women undergoing IVF or ICSI should be treated with Levothyroxine. The goal of treatment is to achieve a TSH concentration <2.5 mIU/L. (I/B)
55. Levothyroxine may be considered in euthyroid thyroid autoantibody positive women who are undergoing assisted reproductive treatment given its potential benefits in comparison to its minimal risk. (IIb/C)

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