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Guidelines for Management of Thyroid Dysfunction During Pregnancy

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A Clinical Practice Guideline

Guidelines for Management of Thyroid Dysfunction During Pregnancy

An Initiative from Indian Thyroid Society
Endorsed by- Endocrine Society of India

Chairperson
Dr. R.V. Jayakumar, Prof of Endocrinology, AIMS, Cochin

Core committee members
- Dr. K.M. Prasanna Kumar, CEO-Bangalore Diabetes Hospital
- Dr. Mala Dharmalingam, Chief of Endocrinology-M.S. Ramaiah Hospital, Bangalore
- Dr. Sudip Chatterjee, Hon. Prof of Endocrinology, Vivekananda Institute of Medical Sciences, Kolkata
- Dr. Manoj Chadha, HOD of Endocrinology, Hinduja Hospital, Mumbai
- Dr. S.K. Wagnoo, Sr. Consultant Endocrinologist, Indraprasthaapollo Hospital, New Delhi
- Dr. A.G. Unnikrishnan, Prof. of Endocrinology, AIMS, Cochin
- Dr. P.K. Shah, Prof of OBGY, KEM Hospital, Mumbai
- Dr. Rakesh Sahay, Prof. of Endocrinology, Osmania Medical College, Hyderabad
- Dr. Anil Bhansali, HOD of Endocrinology, PGI-Chandigarh
- Dr. P.C. Mahapatra, Prof of OBGY, SCB Medical College, Cuttack
- Dr. Sanjay Anant Gupte, Director-Gupte Hospital, Pune
- Dr. Bipin Kumar Sethi, Sr. Consultant Endocrinologist, Care Hospital, Hyderabad

Method of development

A national task force was created, under the auspices of The Indian Thyroid Society, to review the available evidences in the field and develop evidence-based guidelines. Members of the task force included highly reputed and experienced endocrinologists and gynecologists.

This task force worked for a period of 6 months and reviewed most evidences available on the topic. They had multiple phone conversations and a meeting to evaluate the evidence and accordingly develop recommendations. Upon completion of the guidelines, it will be reviewed and approved by all of the participants as well as the extending committee.

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 trials 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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Elsevier Pharmaceutical Communications Division (South Asia)

Ajay Pratap Singh
Director

Jyotishman Boruah
Chief Coordinator and Manager Customer Relations

Dr. Pranab Sakhre
Medical Content Manager

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, 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 thyroxine binding globulin (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 baby is completely dependent on the mother for the production of thyroid hormone. By the end of the first trimester, the baby's thyroid begins to produce its own hormone. The baby, however, remains dependent on the mother for ingestion of adequate amounts of iodine, which is essential to make the thyroid hormones.[4]

The recommended nutrient intake for iodine in nonpregnant women is 150 µg/d and for pregnant and lactating women it is 250 µg/day.[5,6] 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.[5,7]

Maternal iodine deficiency also affects pregnancy outcomes and is associated with a higher incidence of miscarriage, stillbirths, abortions and congenital abnormalities.[2,8]

This guideline discusses the different aspects of thyroid disorders in pregnancy and its management. Each topic has clinical evidence followed by the recommendations of the committee. The level of evidence of 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.[9]

It is now well established that not only overt, but also subclinical thyroid dysfunction have significant adverse effects on pregnancy and fetal development. The adverse pregnancy outcomes include, miscarriage, pregnancy-induced hypertension and it's more severe form pre-eclampsia, as well as placental abruption, anaemia, 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.[10-15]

Kooistra et al 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 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.[16-18]

Iodine deficiency significantly raises the risk of still birth 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.[19,20]

Some of the causes of maternal and fetal hypothyroidism are[11,21];

- **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 thought to be the first trimester.[22]

Epidemiology

In general, the incidence of overt hypothyroidism during pregnancy ranges from 0.2 to 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.[2,3,12,23-27]

Gayathri et al analyzed the prevalence of subclinical hypothyroidism among 495 pregnant women attending Government hospitals in South India. Subclinical hypothyroidism was detected in 2.8% and of these thyroid antibodies were seen in 57.1% of cases. This study showed that the prevalence of subclinical hypothyroidism among Indian pregnant women is fairly high and they have high rates of thyroid antibody positivity.[23]

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.[12,24] 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.[24]

As all pregnant women have raised TBG levels, the serum T4 level cannot distinguish thyrotoxicosis from euthyroidism. The normal non-pregnant total

T4 range (5–12μg/dL) therefore should be multiplied 1.5 times, to obtain appropriate ranges for the second and third trimesters. Hence monitoring of maternal thyroid function requires measurement of serum total T4 level 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. No consensus has been reached on trimester-specific or laboratory specific normal values of serum fT4 in pregnancy. The Endocrine Society (USA) guidelines recommends "caution in the interpretation of serum fT4 levels during pregnancy and also that each laboratory should establish trimester-specific reference ranges for pregnant women."[28,30,31] Similarly, there are no clear reference ranges for serum levels of TSH in pregnancy. A caution is also required while interpreting TSH values. Several factors, including a negative feedback because of elevated T3 and T4, elevated circulating HCG concentrations influence the TSH levels.[24]

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 first trimester.[32] A TSH value of >4 mIU/L should alert the physician to the diagnosis.[27]

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. Levothyroxine (LT4) is the drug of choice.[22,27]

The average full replacement dose of LT4 in nonpregnant patients with overt hypothyroidism is 1.6-2.0 μg/kg/day.[28,33,34]

In pregnant women diagnosed with hypothyroidism same dose should be used with an adjustment of 25 - 50μg increment. TSH should be reassessed 4 to 6 weeks following a dose change, with a treatment goal of ≤2.5 mIU/L.[28,35-37]

Vaidya et al reviewed the strategy of 190 clinicians in the management of maternal hypothyroidism. They found that in pregnant women with newly diagnosed overt hypothyroidism, most clinicians initiated a full dose of LT4, whereas for women with preexisting hypothyroidism planning pregnancy, 50% recommended increasing the dose of LT4 as soon as pregnancy was confirmed.[38]

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 to 100 µg/day LT4. Free T4 and TSH levels should be tested every 4 to 6 weeks.[3,27,28,39-41]

Most researchers have recommended that if TSH levels are between 5-10mIU/L the average LT4 dosage should be increased by 25 to 50µg/d at a time, if TSH is between 10 to 20mIU/L dosage should be increased by 50 to 75µg/d at a time, whereas if TSH levels are >20mIU/L dosage should be increased by 75 to 100µg/d at a time. The target TSH levels should be ≤2.5 mIU/L in first trimester (or 3mIU/L in the second and third trimester).[27,30,41]

Patients with preexisting hypothyroidism should have their LT4 dose increased by 25 to 50µg/d as soon as pregnancy is diagnosed. 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.[27,30,41]

According to Kung et al pregnant patients with pre-existing hypothyroidism require a 40%-50% increase in their daily T4 dosage to maintain euthyroidism.[29]

A similar finding has been seen by Unnikrishnan et al who suggested a 25-47% increase in LT4dose during pregnancy.[27]

Post-delivery the patient should be reverted back to the pre-pregnant dosage and TSH levels should be rechecked after 6 weeks.[27,41]

Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at risk of developing hypothyroidism should be monitored for elevation of TSH above the normal range.[7,42-45]

Recommendations

1. Both maternal and fetal hypothyroidism is known to have serious adverse effects on the fetus Therefore maternal hypothyroidism should be avoided by early diagnosis at the first prenatal visit or at the time of diagnosis of pregnancy (I/B).
2. Diagnosis should be based on trimester specific TSH and low total T4 values (IIa/B).
3. In patients diagnosed with overt hypothyroidism during pregnancy start therapy with full replacement dose of LT4 (1.6-2.0 µg/kg/d) to normalize thyroid function tests as rapidly as possible (I/A).
4. Subclinical hypothyroidism has been shown to be associated with an adverse outcome for both the mother and offspring and hence should be treated with LT4. Free T4 and TSH levels should be tested every 6 weeks

and appropriate adjustments done to maintain the target TSH levels ≤2.5 mIU/L (or 3 mIU/L in the second and third trimester) (I/B).

5. Patients with preexisting hypothyroidism in whom thyroid assessment cannot be done immediately should have their LT4 dose increased by 30% as soon as pregnancy is diagnosed. Patients should have their TSH levels assessed as soon as possible after conception and at 6 weeks interval till delivery (IIa/B).
6. Post-delivery the patient should be reverted back to the pre-pregnant dosage and TSH levels should be rechecked after 6 weeks (I/A).
7. Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at risk of developing hypothyroidism and should be monitored with TSH every trimester (IIb/C).

Maternal Hyperthyroidism

Overt hyperthyroidism during pregnancy may be referred to as suppressed (<0.1 mU/L) or undetectable (<0.01) serum TSH value and elevated thyroid hormone levels that exceed the normal range for pregnancy.[46,47]

The prevalence of hyperthyroidism in pregnancy has been found to be about 0.2% in different studies. The most common cause is Graves' disease (GD).[48-52]

Other uncommon etiologies of hyperthyroxinemia in pregnancy are;[53-55]

Intrinsic thyroid disease	Gestational thyrotoxicosis
▪ Toxic adenoma ▪ Subacute thyroiditis ▪ Iatrogenic hyperthyroidism ▪ Excessive thyroid hormone intake ▪ Factitious ▪ Therapeutic	▪ Nausea/vomiting ▪ Multiple gestations ▪ Hyperemesis gravidarum ▪ Hydatidiform mole

Maternal, fetal, and neonatal morbidity and mortality is 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.[15,49]

Signs and symptoms of Graves's hyperthyroidism 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. Goiter is almost always present. Careful examination of the eyes may reveal signs of exophthalmopathy.

Usually there is exacerbation of symptoms during the first trimester with reduced severity during the second half of pregnancy and symptoms may worsen again during the postpartum period.[56]

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 upto 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.[57-59]

A syndrome, referred to as `gestational transient thyrotoxicosis' (GTT), has to be differentiated from GD, 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 first trimester, often with hyperemesis. Usually classic hyperthyroid symptoms are absent or minimal, except for weight loss. Differentiation of GD from non autoimmune GTT is supported by evidence of diffuse goiter and autoimmunity like presence of anti-TSH receptor antibodies (TRAb).[4,54,60-62]

Fetal thyroid function

The fetus is dependent on the small supply of thyroxine (T4) from the mother until 10 to 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 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.[28,49,63,64]

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 GD has not been established before pregnancy, the disorder is not always readily suspected clinically, mainly because the symptoms and signs of mild to moderate hyperthyroidism may be mimicked by

the hypermetabolic state of normal pregnancy. Attention should be given to a history of autoimmune thyroid disease in close family relatives, the presence of a goiter and/or suggestive eye signs, and a variety of clinical manifestations such as heat intolerance, warm and moist skin, tachycardia, wide pulse pressure, weight loss and excessive vomiting in the early stages of pregnancy.[54]

Free thyroxine determination or calculation of the free thyroxine index (fT4I) (using total thyroxine levels and a test for assessing thyroxine binding globulin, 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 first 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 (anti-TPO) 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.[53]

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.

Anti-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 first trimester as they are negative in gestational hyperthyroidism. Because GD tends to undergo immunological remission after the late second 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's 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 second trimester. Most commonly, the thyroid-stimulating immunoglobulins (TRSAb) 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.[65-67]

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 goiter, fetal thyrotoxicosis should be suspected.[67,68-71]

Other findings associated with fetal hyperthyroidism include IUGR, craniosynostosis, premature skeletal maturation, cardiac failure, and hydrops.[35]

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.[68]

A minority of newborns from mothers with GD develop transient central hypothyroidism. In these cases the fT4 level may be elevated at birth, indicating fetal hyperthyroidism.[68,69]

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.[69]

Management of overt maternal hyperthyroidism

Antithyroid drugs (ATD)

The treatment of choice 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 to 6 weeks of therapy. PTU also blocks the conversion of T4 to T3. Many physicians recommend the use of PTU rather than methimazole (MMI) because methimazole may be teratogenic. There has 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. PTU is the preferred drug in the 1st trimester.[35,55,72-76]

Dosage and monitoring

The initial dose of ATD depends on the severity of the disease. PTU is usually initiated at 100-150 mg/8 h (or MMI 20mg or carbimazole 15mg 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 to 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. [35,55,72-76]

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.

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.[35,55,72-75]

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 to 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.[35,72,74]

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 goiter, iodide use is not recommended.[55,67]

Surgery

Subtotal or total thyroidectomy is indicated when, for any reason, ATDs fail to control the hyperthyroid disease (over 300 mg of PTU or 40 mg/day methimazole/carbimazole). The appropriate time is the 2nd trimester. Ideally, surgery requires previous pharmacological treatment to normalize thyroid function.[35,55]

Radioactive iodine therapy

During pregnancy ^{131}I is contraindicated because of the possible teratogenic effects of radiation. After ^{131}I ablative therapy, effective contraception 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 first 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.[28,35,55,67,74]

Different clinical scenarios in management of maternal GD are;[55,74]

1) **Pregnancy in active GD:** Continuing with an ATD is recommended. To determine whether the fetus is at risk of having hyperthyroidism, TRAb titers should be assessed in the third trimester (preferably by bioassay) to confirm they are of the stimulating variety.

2) **New diagnosis of GD 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 GD:** In this event, medication should be restarted. When evaluating such patients, the normal physiological increase in T4 plasma concentrations during the first trimester should be borne in mind.

4) **Pregnancy after a previous ablative treatment (surgery or radioiodine):** In these cases, reassessment of TRAb levels at the beginning of pregnancy is recommended 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/8 h (to control fetal hyperthyroidism), as well as to continue LT4 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.[36]

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, goiter resolution) by ultrasound in 2 weeks and appropriate dose adjustment should be done.[53]

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, LT4 therapy may need to be increased if hypothyroxinemia develops while treating fetal hyperthyroidism with PTU.[68,72]

Recommendations

1. In case of subnormal serum TSH during pregnancy, hyperthyroidism must be distinguished from both normal physiology during pregnancy and hyperemesis gravidarum due to its adverse effects on the mother and fetus. Diagnosis of Grave's disease is supported by evidence of diffuse goiter and autoimmunity, like presence of anti-TSH receptor antibodies (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. PTU is the preferred drug in the 1st trimester. Maintain the maternal thyroid hormone levels for fT4 in the upper nonpregnant reference range (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 goiter 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). Second 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 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 Grave's disease continue treatment with an anti-thyroid drug. 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 Grave's 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 (>160bpm). If all other

causes of fetal tachycardia have been ruled out, start mother on methimazole/carbimazole to control fetal thyrotoxicosis and LT4 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 goiter, 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, goiter resolution) by ultrasound in 2 weeks and appropriate dose adjustment done (IIb/B).
14. Umbilical blood sampling should be considered only if the diagnosis of fetal thyroid disease is not reasonably certain from the clinical data and if the information gained would change the treatment (III/C).

Gestational Hyperemesis And Hyperthyroidism

Hyperemesis gravidarum (HG) occurs in 0.3%-2% of pregnant women, although populations with significantly higher rates have been reported. HG is defined as severe nausea and vomiting with a weight loss of ≥5%, dehydration and ketosis. Pregnant females with HG have high 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 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, goiter and thyroid antibodies are absent, and the T3 level is much less likely to be elevated 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 second trimester. The condition is usually self limiting and does not require specific antithyroid therapy. If hyperthyroidism and thyroid function abnormalities persist beyond 18 to 20 weeks of gestation, then mild Graves' disease is indicated and should be treated with antithyroid drugs.

Routine assessment of thyroid function is recommended in patients with hyperemesis gravidarum.[35,55,78-82]

Recommendations

1. Thyroid function tests should be measured in all patients with hyperemesis gravidarum 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 goiter 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 to 20 weeks of gestation (IIa/B).

Autoimmune Thyroid Disease In Pregnancy

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 abortion, typically defined as three or more spontaneous miscarriages, the cause of pregnancy termination remains unknown in approximately 50% of the women, despite extensive evaluation.[83]

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.[84,85]

Studies have found some correlation between pregnancy loss and thyroid autoantibodies. Stagnaro-Green et al screened 552 women in the 1st trimester of pregnancy for the presence of thyroid antibodies. They found a doubling of the miscarriage rate in women who were antibody positive in the first 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.[86,87]

In another study, Glinoer et al found that women with thyroid autoimmunity had a miscarriage rate which was almost four-fold compared with the controls (p= 0.005).[88]

Lejeune et al found that miscarriages associated with thyroid autoimmunity take place early and almost entirely within the first trimester of pregnancy.[89]

In another study Bagis et al 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.[90]

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

Some other studies have shown no association.

Esplin et al tested for TG-and TPO-Ab 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.[91]

Rush-worth et al 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.[92]

De Carolis et al 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.[93]

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.

Benefit of intervention and treatment of autoimmune thyroid disease in otherwise euthyroid pregnant women is still not clear.[85]

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. At present time, routine screening and treatment of autoimmune thyroid disease in euthyroid pregnant women is not warranted (IIa/B).

Thyroid Nodules In Pregnancy

Pregnancy is associated with growth of pre-existing thyroid nodules as well as the growth of new nodules.[35,94] Among reproductive-age women, most palpated nodules of the thyroid are benign hyperplastic (or colloid) nodules; however, between 5% and 20% are true neoplasms, benign adenomas, or carcinomas.[95] Papillary thyroid cancer is the most common histologic type diagnosed and has an excellent long-term prognosis.[35] The approach to diagnosis in a pregnant woman with a palpable thyroid nodule is similar to that in the nonpregnant woman and includes a serum TSH and an ultrasound assessment of the neck and thyroid gland.[35,96]

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.[97]

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.[68,98]

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.[96-101]

If malignant, start suppressive therapy with LT4 (TSH to 0.1-1mIU/L) and consider surgery in the second trimester.[98,100,101]

If benign, no further evaluation is needed during pregnancy, except LT4 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.[97]

In all women with cytology indicative of papillary or follicular thyroid cancer, LT4 suppression therapy should be initiated to maintain the serum TSH in the range of 0.1 to 0.8 mIU/L and ≤2.5 mIU/L for patients with medullary thyroid cancer.[68]

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.[97]

Women who undergo surgical treatment during pregnancy require monitoring of thyroid function and need replacement LT4. In case of papillary microcarcinoma (<1cm) hemithyroidectomy is recommended.[102-103]

Postsurgically patients should be maintained on LT4 with monitoring of TSH and fT4 levels every 8 weeks.[74]

Postsurgical ^{131}I whole-body scintigraphy and radioiodine remnant ablation are contraindicated during pregnancy and lactation.[35]

Management of hyperthyroidism in pregnancy resulting from a hyperfunctioning solitary nodule or multinodular goiter consists of antithyroid medications, beta-adrenergic blockers, and thyroid surgery.[35]

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) (IIa/B).
2. If nodule is malignant or shows rapid growth consider surgery in the second trimester (IIa/B).
3. If the nodule is benign, no further evaluation is needed, except in the cases with elevated TSH, LT4 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, LT4 suppression therapy should be initiated to maintain the serum TSH in the range of 0.1 to 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 LT4 therapy with monitoring of TSH and free T4 levels every 6 weeks (IIa/C).
7. Postsurgical ^{131}I 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 to 16.7%.[104-107]

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).[108-111]

Women with a history of PPT have a dramatically increased risk of developing permanent hypothyroidism in the following 5–10 years.[97,104-106]

The presence of serum antibodies against thyroperoxidase during the first trimester is the best predictor of PPT development.[112]

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.[97-111]

Hyperthyroidism always predates hypothyroidism and occurs between 2 and 6 months postpartum.[97]

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 goiter and thyroid peroxidase antibodies are positive. However, the presence of exopthalmos, a bruit, or TSH receptor antibody 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.[97]

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 LT4 50 to 75µg/day and 25 to 50µg/day respectively. Asymptomatic women with a TSH between 4 and 10mIU/L and planning a subsequent pregnancy in the near future also require therapy.[113]

The duration of therapy with LT4 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 a weaning trial off of LT4 one year after the birth of the final child.[113]

Studies have failed to show a clear association between presence of PPT or thyroid antibodies and postpartum depression (PPD).[114-117]

The rationale behind a possible association between positive PPD 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.[118]

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 post partum (IIb/B).
2. Majority of women in the hyperthyroid phase do not require intervention (IIa/C).
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 LT4 (IIa/B).
5. The duration of therapy with LT4 should be approximately 1 year postpartum or until the woman completes her family. No clear association between presence of PPT or thyroid antibodies and postpartum depression has been established (IIb/B).
6. Women with postpartum depression should be screened for hypothyroidism and appropriately treated (IIb/C).

Iodine Requirement In Pregnancy

During pregnancy, the requirement for iodine increases than the usual recommended intake of 150µg/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.[6,119-121]

Women who are iodine sufficient are little impacted, but those with who have a restricted or deficient iodine intake are markedly affected.[122-123]

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 goiter formation in mother and fetus.[118,124-127]

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.[121]

In areas with a severe iodine deficiency, correcting the iodine lack has proved highly beneficial to prevent mental deficiency disorders in infants and children.[125]

According to The International Council for Control of Iodine Deficiency Disorders (ICCIDD) and the Technical Consultation, the recommended nutrient intake (RNI) for iodine during pregnancy is 250µg/day. A daily intake of >500µg day is not necessary, as it would not provide any additional benefit and may be associated with impaired thyroid function.[6,121]

The intake during lactation should also be about 250µg/day as iodine is efficiently concentrated by the mammary gland.[28,128,129]

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.121

Population group	MUI concentration (µg/L)	Iodine intake
Pregnant women	▪ Toxic adenoma ▪ <150 ▪ 150–249 ▪ 250–499 ▪ ≥500	▪ Insufficient ▪ Adequate ▪ More than adequate ▪ No added health benefit expected
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.[121]

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 programmes 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.[5,125]

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 400mg of iodine as iodized oil.[28,121,130]

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 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.[131]

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;[131]

- How well-defined the disorder is and is the frequency sufficient enough to warrant screening?
- Is a simple, safe and cost-effective screening test available?
- Are available interventions safe and effective?
- 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.[132]

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 LT4 in appropriate women would be beneficial. In addition there is evidence that such a strategy would be cost-effective.[131-134]

However, the most recent published recommendations from the Endocrine Society of America do not endorse universal screening. Instead, a targeted approach has been suggested in which screening would be offered to high risk cases.[131,135,136]

Vaidya et al found that targeted testing of a previously defined high-risk group failed to detect 28% of pregnant women with a TSH > 4.2mIU/L.[13] In another study Li et al found that this strategy missed 36% of women with TSH > 4.0mIU/L.[137]

Negro et al screened low-risk women and found 28% of patients with thyroid dysfunction.[138]

These studies demand further information on screening of even low risk patients. The current clinical epidemiological evidence does not justify universal screening though the association of thyroid abnormalities and untoward maternal and fetal outcomes cannot be ignored. Hence, at present targeted screening in high-risk populations is recommended. Many researchers have also advocated aggressive case finding for subclinical thyroid disease during pregnancy, although systematic screening is not recommended.[13,35,131,132]

The high risk groups are;

- Women with a history of hyperthyroid or hypothyroid disease, post-partum 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 goiter
- 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 prepregnancy 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.[3,132]

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).[55]

Currently a study is being carried out by Lazarus et al, the Controlled Antenatal Thyroid Screening Study (CATS), which will directly test the value of screening for thyroid disease and treating women with serum TSH elevations.

It is sufficiently powered to determine conclusively the benefit of early identification and intervention. Until these data are available targeted case finding should be carried out.[136]

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 anti-TPO antibodies (IIa/C);
   - Personal history of thyroid or other autoimmune disorders or a family history of thyroid disease
   - Women with goiter
   - Women with a history of miscarriage or preterm delivery
   - Women with Type 1 diabetes
3. Maternal thyroid dysfunction is by itself not an indication for termination of pregnancy (IIa/B).
4. In cases with positive anti-TPO antibodies, but normal TSH there is no evidence for administering LT4 therapy or immunosuppressant's (corticosteroids) (IIa/C).
5. There is no contraindication for breastfeeding in women on antithyroid drugs (IA).

Summary of Recommnedations

Maternal Hypothyroidism

Recommendations

1. Both maternal and fetal hypothyroidism is known to have serious adverse effects on the fetus Therefore maternal hypothyroidism should be avoided by early diagnosis at the first prenatal visit or at the time of diagnosis of pregnancy (I/B).
2. Diagnosis should be based on trimester specific TSH and low total T4 values (IIa/B).
3. In patients diagnosed with overt hypothyroidism during pregnancy start therapy with full replacement dose of LT4 (1.6-2.0 µg/kg/d) to normalize thyroid function tests as rapidly as possible (I/A).
4. Subclinical hypothyroidism has been shown to be associated with an adverse outcome for both the mother and offspring and hence should be treated with LT4. Free T4 and TSH levels should be tested every 6 weeks and appropriate adjustments done to maintain the target TSH levels ≤2.5 mIU/L (or 3 mIU/L in the second and third trimester) (I/B).
5. Patients with preexisting hypothyroidism in whom thyroid assessment cannot be done immediately should have their LT4 dose increased by 30% as soon as pregnancy is diagnosed. Patients should have their TSH levels assessed as soon as possible after conception and at 6 weeks interval till delivery (IIa/B).
6. Post-delivery the patient should be reverted back to the pre-pregnant dosage and TSH levels should be rechecked after 6 weeks (I/A).
7. Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at risk of developing hypothyroidism and should be monitored with TSH every trimester (IIb/C).

Maternal Hyperthyroidism

Recommendations

1. In case of subnormal serum TSH during pregnancy, hyperthyroidism must

be distinguished from both normal physiology during pregnancy and hyperemesis gravidarum due to its adverse effects on the mother and fetus. Diagnosis of Grave's disease is supported by evidence of diffuse goiter and autoimmunity, like presence of anti-TSH receptor antibodies (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. PTU is the preferred drug in the 1st trimester. Maintain the maternal thyroid hormone levels for fT4 in the upper nonpregnant reference range (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 goiter 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). Second 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 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 Grave's disease continue treatment with an anti-thyroid drug. 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 Grave's 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 (>160bpm). If all other causes of fetal tachycardia have been ruled out, start mother on methimazole/carbimazole to control fetal thyrotoxicosis and LT4 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 goiter, 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, goiter resolution) by ultrasound in 2 weeks and appropriate dose adjustment done (IIb/B).
14. Umbilical blood sampling should be considered only if the diagnosis of fetal thyroid disease is not reasonably certain from the clinical data and if the information gained would change the treatment (III/C).

Gestational Hyperemesis And Hyperthyroidism

Recommendations

1. Thyroid function tests should be measured in all patients with hyperemesis gravidarum 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 goiter 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 to 20 weeks of gestation (IIa/B).

Autoimmune Thyroid Disease In Pregnancy

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. At present time, routine screening and treatment of autoimmune thyroid disease in euthyroid pregnant women is not warranted (IIa/B).

Thyroid Nodules In Pregnancy

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) (IIa/B).
2. If nodule is malignant or shows rapid growth consider surgery in the second trimester (IIa/B).
3. If the nodule is benign, no further evaluation is needed, except in the cases with elevated TSH, LT4 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, LT4 suppression therapy should be initiated to maintain the serum TSH in the range of 0.1 to 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 LT4 therapy with monitoring of TSH and free T4 levels every 6 weeks (IIa/C).
7. Postsurgical ^{131}I whole-body scintigraphy and radioiodine remnant ablation are contraindicated during pregnancy and lactation (I/B).

Postpartum Thyroiditis

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 post partum (IIb/B).
2. Majority of women in the hyperthyroid phase do not require intervention (IIa/C).
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 LT4 (IIa/B).
5. The duration of therapy with LT4 should be approximately 1 year postpartum or until the woman completes her family. No clear association between presence of PPT or thyroid antibodies and postpartum depression

has been established (IIb/B).

6. Women with postpartum depression should be screened for hypothyroidism and appropriately treated (IIb/C).

Iodine Requirement In Pregnancy

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 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

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 anti-TPO antibodies (IIa/C);
   - Personal history of thyroid or other autoimmune disorders or a family history of thyroid disease
   - Women with goiter
   - Women with a history of miscarriage or preterm delivery
   - Women with Type 1 diabetes
3. Maternal thyroid dysfunction is by itself not an indication for termination of pregnancy (IIa/B).
4. In cases with positive anti-TPO antibodies, but normal TSH there is no evidence for administering LT4 therapy or immunosuppressant's (corticosteroids) (IIa/C).
5. There is no contraindication for breastfeeding in women on antithyroid drugs (IA).

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