Published in WWW.ENDOTEXT.ORG © 2019

HYPERTHYROIDISM IN PREGNANCY

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Updated February 9, 2019

CLINICAL RECOGNITION

Hyperthyroidism occurs in approximately 0.2-1.0% of all pregnancies. Most cases are due to Graves' disease. The clinical recognition of Graves' disease may prove challenging in pregnancy since the features of normal pregnancy overlap with symptoms of hyperthyroidism. Specific features which may point to Graves' hyperthyroidism include the presence of a diffuse goiter, ophthalmopathy, or pre-tibial myxedema (Table 1).

Table 1. Features of Graves' Disease
Past history of autoimmune thyroid disease
Family history of autoimmune thyroid disease
Features of hyperthyroidism such as weight loss and heat intolerance
Diffuse goiter
Ophthalmopathy
Pre-tibial myxedema
Proximal myopathy
Nail changes: onycholysis

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Hyperthyroidism is diagnosed on the basis of elevated trimester specific serum levels of free thyroxine (FT4) or free triiodothyronine (FT3) (or comparable measures of total thyroxine or FTI) and low thyroid stimulating hormone (TSH). In subclinical hyperthyroidism FT4 and FT3 are normal but TSH is low or suppressed to undetectable levels. Treatment is generally not required for subclinical hyperthyroidism in pregnancy. In fact, most instances of a low TSH in early pregnancy are not pathological and are due to TSH suppressive effects of β-human chorionic gonadotrophin (β-HCG). Detection of thyroid stimulating hormone receptor antibodies (TRAbs) in serum is diagnostically helpful in distinguishing Graves' disease from other pathological and non-pathological causes of a low TSH. Most cases of hyperthyroidism in pregnancy are due to Graves' disease. Other causes include single or multiple toxic nodules and thyroiditis (Table 2).

Table 2. Causes of Hyperthyroidism in Pregnancy
Graves' disease

Gestational thyrotoxicosis
Single toxic nodule
Toxic multinodular goiter
Subacute thyroiditis
Silent thyroiditis
Thyrotoxicosis factitial

It is important to distinguish hyperthyroidism in pregnancy from gestational transient thyrotoxicosis (GTT) which occurs as a result of the thyroid stimulatory actions of β–HCG. GTT is more common than Graves' disease being diagnosed in about 1-3% of all pregnancies. It may be associated with hyperemesis gravidarum, choriocarcinoma, or hydatiform mole and in rare instances may result from functional mutations which increase TSH receptor hypersensitivity to β-HCG. GTT is typically mild in presentation, self-limiting and rarely requires specific treatment with antithyroid medications (Table 3). While GTT may be difficult to distinguish from Graves' disease, features such as goiter, ophthalmopathy, or pretibial myxedema are suggestive of Graves' disease.

Table 3. Clinical Differences Between Graves' Disease in Pregnancy and Gestational Transient Thyrotoxicosis

Graves' Disease	**Gestational Thyrotoxicosis**
Past history of thyroid autoimmunity	No past history of thyroid autoimmunity
Family history of thyroid autoimmunity	No family history of thyroid autoimmunity
May exhibit overt hyperthyroid features	May present with hyperemesis, dehydration and electrolyte imbalance
Goiter may be present	No goiter
Ophthalmopathy may be present	No ophthalmopathy
TRAb positive	TRAb negative
TPOAb positive	TPOAb negative

Thyroid Stimulating Hormone Receptor Antibodies (TRAbs)

Measurement of TRAbs is useful for monitoring for the risk of fetal and neonatal hyperthyroidism (Table 4). The management of such patients can be considered in three categories.

Table 4. Measurement of Thyroid Stimulating Hormone Receptor Antibodies (TRAbs)
Patients with active hyperthyroidism
Patients previously treated with radioiodine or surgery
Patients with high TRAb levels require serial fetal monitoring with ultrasonography

PATIENTS IN REMISSION FROM HYPERTHYROIDISM

Patients who have successfully completed treatment for hyperthyroidism who become pregnant while in remission require close monitoring since there is a risk of relapse in pregnancy. Such patients may continue to harbor TRAbs with the risk of transplacental transfer. This risk is lowest for patients who were treated with antithyroid drugs and it is recommended that TRAbs are checked in early pregnancy in patients who were treated with surgery or radioiodine. If TRAbs are positive in early pregnancy, then fetal monitoring is indicated with repeated measurement of TRAbs at 18-22 weeks, and again at 30-34 weeks if TRAbs continue to be positive. TRAb levels

>5 IU/L or more than 3 times the upper limit of normal is an indication for close fetal or neonatal monitoring due to the high risk of fetal/neonatal hyperthyroidism from transplacental TRAb transfer.

PATIENTS CURRENTLY UNDERGOING TREATMENT FOR HYPERTHYROIDISM

Women who conceive while on antithyroid treatment should have TRAbs level checked in early pregnancy and again at 18-22 weeks, and at 30-34 weeks if TRAbs continue to be positive. Women of child bearing age with Graves' disease should be counselled against becoming pregnant until a euthyroid state is achieved.

PATIENTS WHO DEVELOP HYPERTHYROIDISM DURING PREGNANCY

Patients who develop hyperthyroidism for the first-time during pregnancy are at particular risk of adverse fetal and maternal adverse effects and should be controlled promptly and monitored carefully. TRAB levels should also be checked in late pregnancy to assess the risk of neonatal hyperthyroidism.

PATHOPHYSIOLOGY

Uncontrolled hyperthyroidism is associated with adverse feto-maternal effects including pre-eclampsia, maternal congestive cardiac failure, miscarriages, premature birth, still-birth, and low birth weight. Furthermore, neonates of hyperthyroid mothers with Graves' disease are at risk of developing fetal hyperthyroidism and goiter due to the transplacental transfer of TRAbs. Fetal hypothyroidism may also develop due to transplacental transfer of maternal antithyroid drugs or in rare instances from transplacental transfer of maternal blocking TRAbs.

THERAPY

The natural course of Graves' disease in pregnancy should be borne in mind during therapy. Due to the immune tolerant state of pregnancy there is a tendency for Graves' disease to remit towards the latter stages of gestation.

Anti-Thyroid Drugs

Anti-thyroid drugs are the treatment of choice for hyperthyroidism in pregnancy (Table 5). The lowest effective dose should be used. Treatment should be monitored with FT4 and TSH. These should be measured every 2-4 weeks initially and then 4-6 weekly once thyroid hormone levels are stabilized. FT4 levels should be maintained at or just above the upper limit of the trimester specific reference range.

Dose reductions or even cessation of therapy with careful monitoring may be necessary in late pregnancy. The thionamides, propylthiouracil (PTU), methimazole (MMI), and its pro-drug derivative, carbimazole are the antithyroid drugs of choice. Both propylthiouracil and methimazole exhibit similar placental transfer kinetics, have similar effects on fetal and neonatal thyroid function, and are equally safe in lactation. Methimazole has greater efficacy than propylthiouracil and is associated with better compliance since it can be administered once daily whereas propylthiouracil needs to be taken twice or thrice daily. More so a growing number of reports have highlighted the association of propylthiouracil with fatal liver failure. However, methimazole is associated, rarely,

with the occurrence of aplasia cutis and methimazole embryopathy in the neonate. Although this risk is slight it is most likely with methimazole administration in early pregnancy during embryogenesis. For the above reasons it is recommended that propylthiouracil is used in the first trimester and that consideration should be given to switching to methimazole in later pregnancy.

Table 5. Guidelines for Anti-Thyroid Drugs (ATD) in Pregnancy
PTU is recommended in first trimester
Consider switching to MMI from second trimester
Use lowest effective dose of ATD
Consider reducing dose or stopping ATD in later pregnancy
Monitor treatment with FT4 and TSH: Initially 2-4 weekly, later 4-6 weekly.
Aim for FT4 at or just above the upper end reference range

Beta-blocking agents such as propranolol may be used to control severe adrenergic symptoms but should be discontinued once symptoms begin to improve, usually within 2-4 weeks. The combination of thionamides with levothyroxine i.e. block and replace therapy is not recommended in pregnancy as this may lead to fetal hypothyroidism due to disproportionately greater transplacental transfer of antithyroid drugs than levothyroxine. Radioactive iodine is absolutely contraindicated in pregnancy. Adverse effects of radioiodine on fetal thyroid function include fetal hypothyroidism and this is more likely in later pregnancy since the fetal thyroid only starts to actively concentrate iodide from about 12 weeks gestation.

Surgery

Thyroidectomy is an option in patients with significant problems with compliance or severe adverse reactions to antithyroid medications. Surgery is best undertaken in the second trimester of pregnancy.

FOLLOW UP

Newborn

Following delivery, the infant of hyperthyroid mothers should be monitored for thyroid dysfunction. Transient neonatal hyperthyroidism due to transplacental transfer of maternal TRAbs is seen in 1-5% of neonates of mothers with Graves' disease. The presentation may be more obvious after the first few days of life since TRAbs are cleared from the neonatal circulation at a slower rate than maternal antithyroid drugs.

Mothers

Mothers with a past history of hyperthyroidism require regular thyroid function tests after delivery since Graves' disease may relapse in the postpartum period. Anti-thyroid drugs are safe in lactation and if indicated should be used at the lowest effective dose, preferably administered after breast feeds in divided doses. Women with risk factors for autoimmune thyroid dysfunction may develop postpartum thyroiditis (PPT). This occurs in 5-9% of pregnancies and is characterized by a transient hyperthyroid phase followed by a hypothyroid phase before return to euthyroidism. The hyperthyroid phase will usually not require treatment but levothyroxine may be given to

symptomatic women in the hypothyroid phase. Long term follow-up is necessary due to the risk of permanent hypothyroidism.

GUIDELINES

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