Hyperthyroidism In Pregnancy-A Review

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ABSTRACT

The changes in thyroid gland physiology induced by pregnancy must be differentiated from hyperthyroidism. Hyperthyroidism during pregnancy is not very common with reported incidence of 0.05–3.0% with Graves’ disease accounting for 85% of cases. Gestational transient thyrotoxicosis is typically reported in women with hyperemesis gravidarum, and is mediated by high circulating concentrations of human chorionic gonadotropin. The exact diagnosis of the cause of hyperthyroidism in pregnancy should be determined as outcomes for both the mother and the child depend on the cause. Antithyroid drug therapy to treat hyperthyroidism in pregnant women is considered controversial because the usual drugs (methimazole or carbimazole) are considered safe, but has found to be teratogenic in some reports; and the alternative (propylthiouracil) is safe in terms of foetal side effects but can have some hepatotoxic potential. Propylthiouracil (PTU) is recommended as the first line drug for treatment of hyperthyroidism during the first trimester of pregnancy and should be changed to either methimazole or carbimazole after the completion first trimester. The maternal free T4 level should be maintained at the upper limit of the non-pregnant reference range. Fetal monitoring should be done with the fetal ultrasound at 18th to 22nd week in women who are TRAb positive. Antithyroid drugs are also recommended for hyperthyroidism in the postpartum period and for women who are breastfeeding.

Key-words: Gestational transient thyrotoxicosis, hyperemesis gravidarum, congenital malformations, thyrotoxic crisis.

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INTRODUCTION

Hyperthyroidism during pregnancy is not very common with reported incidence of 0.05–3.0% with Graves’ disease, accounting for 85% of cases. The hyperthyroidism may be difficult to diagnose in pregnant women as symptoms and signs such as nervousness, sweating, breathlessness, tachycardia is normally seen in most pregnancies. Pregnancy itself induces many changes in thyroid physiology. The increase in
estrogen level lead to an increase in the serum concentration of thyroid-binding globulin and as a result, serum total T4 and T3 rise up to around 50% above the upper limit of the reference range for non-pregnant women. There is also the direct effect of hCG on the thyroid gland to cause a small and transient increase in free T4 levels near the end of the first trimester, resulting in a partial TSH suppression. Because of the increase in thyroid hormone synthesis, the dietary iodine requirement to supply the thyroid gland also increases but there is enhanced urinary iodine loss due to an increase in glomerular filtration rate that is seen in pregnancy which in places with low iodine take can cause goiter in pregnancy.

**Causes of hyperthyroidism in pregnancy**

When signs and symptoms of hyperthyroidism are present in pregnant woman, the definite cause should be evaluated as it is important for management and outcomes for both the mother and the child. The causes of gestational thyrotoxicosis are as follows:

**A. Excessive TSH-receptor stimulation**
- Graves' disease
- Gestational transient thyrotoxicosis
- Familial gestational hyperthyroidism
- Gestational Trophoblastic disease
- TSH-producing pituitary adenoma

**B. Autonomous thyroid hormone secretion**
- Multinodular toxic goitre
- Solitary toxic thyroid adenoma

**C. Destruction of follicles with release of hormone**
- Subacute (granulomatous, de Quervain's) thyroiditis
- Painless (silent) thyroiditis
- Acute thyroiditis

**D. Extrathyroidal sources of thyroid hormone**
- Over treatment with thyroid hormone
- Factitious intake of thyroid hormone
- Functional thyroid cancer metastases
- Struma ovarii

**Maternal and fetal outcomes**

Hyperthyroidism in pregnancy can have severe outcomes for both mother and the fetus. Thirteen cases of heart failure out of 150 pregnant women with hyperthyroidism was observed in one study. Thyrotoxicosis crisis in the form of thyroid storm can also develop. Pregnancy-related complications, such as pre-eclampsia and premature delivery, are also seen. A tenfold higher frequency of low birth weight babies has been reported in pregnant women with poorly controlled hyperthyroidism. Due to transplacental passage of TRAbs, the fetus might also have hyperthyroidism and there is increased risk of intrauterine growth retardation, fetal tachycardia, goiter, advanced bone age, hydrops fetalis and even death. The data from 11 countries, including 249 cases of hyperthyroidism in pregnancy showed that fetal death or stillbirth had occurred in 5.6% of pregnant women with gestational thyrotoxicosis with or without treatment.
DIAGNOSIS

The common differential diagnosis of hyperthyroidism in early pregnancy is Graves' disease and gestational transient thyrotoxicosis. In Graves' disease the cause of hyperthyroidism is the presence of TSH receptor stimulating antibodies, whereas high concentrations of hCG stimulating the TSH receptor cause gestational transient thyrotoxicosis. Sometimes it can be difficult to distinguish between Graves' and gestational transient thyrotoxicosis. The presence of orbitopathy, large diffuse goiter increased T3/T4 ratio and positive Thyroid receptor antibodies (TRAb) are typically seen in Graves' disease. Gestational transient thyrotoxicosis is commonly observed with hyperemesis and sometimes multiple gestations. Due to recurrent episodes of vomiting, caloric under nutrition is present, which might result in normal levels and/or raised serum T4 or free T4 levels. Gestational trophoblastic disease, including molar pregnancy or choriocarcinoma cause biochemical hyperthyroidism due to very high serum hCG concentrations and can be diagnosed by ultrasonography. Thyroid nodules either solitary or multiple can secrete thyroid hormone autonomously causing hyperthyroidism and are predominantly observed in women older than 40 years living in areas of low iodine intake.

Laboratory testing

As previously mentioned, features of thyrotoxicosis might overlap with those of pregnancy, but the presence of specific features like a goitre, orbitopathy, tachycardia, heart failure, unexplained weight loss, increased sweating or heat intolerance should lead to thyroid function testing which comprise of measurement of serum TSH, T4 or free T4, and T3 or free T3. However, in pregnancy, laboratory reference ranges can differ from non-pregnant states and also they vary in all three trimesters. In the initial stage of pregnancy, serum TSH concentrations tend to decrease due to increased serum hCG. TSH concentrations below the non-pregnant reference range can be seen in up to 10% of normal pregnant women, therefore high serum free T4 and free T3 estimates are needed to diagnose hyperthyroidism or if total T4 levels are measured they should be above 150% of the upper level of normal pregnancy value. TRAb testing can be used to differentiate Graves' disease from other causes. It can also be helpful to assess the risk of fetal hyperthyroidism in a pregnant woman with Graves' disease or those women who had been treated previously with either radioablative therapy or surgery and are now euthyroid by doing it in mid pregnancy. TRAb testing every 2 months during pregnancy can also measure disease activity to help with adjustment of dosage of antithyroid drugs and to avoid fetal hypothyroidism caused by over treatment.

TREATMENT

There is no clear evidence of benefit of antithyroid therapy in pregnant women
with gestational transient thyrotoxicosis and hyperemesis. The studies show that females with hyperemesis, with no or mild hyperthyroidism, suppressed TSH, and small elevated free T4, remit spontaneously, but antithyroid therapy may be considered in women with clear signs of hyperthyroidism and elevated free T4 and free T3, or total T3 above the normal pregnancy range. For treatment of Graves’ disease or autonomous nodules, antithyroid drugs should be started to maintain the maternal thyroid hormone levels for free T4 at the upper limit of the non-pregnant reference range. The mode of action of antithyroid drugs is to inhibit synthesis of thyroid hormones. They are also shown to have immunosuppressive action in thyroid gland causing a decrease in the circulating TRAbs. Besides, propylthiouracil (PTU) inhibits the conversion of T4 to the active hormone T3. Propylthiouracil (PTU) is recommended as the first line drug for treatment of hyperthyroidism during the first trimester of pregnancy as Methimazole (MMI) or carbimazole have been shown to be associated with some reports with specific congenital abnormalities that can occur in organogenesis in first trimester. It includes scalp defects (aplasia cutis congenita) and a more serious methimazole (or carbimazole) embryopathy comprising of choanal atresia, tracheo-oesophageal fistula, omphalocele, hypothyelia, and athelia (failure of the nipples to develop), developmental delays, and a distinctive facial phenotype. Since, the rare but life threatening side effect of PTU is severe liver toxicity, it is recommended that PTU should be changed to either methimazole or carbimazole after the completion first trimester. The initiating dose of PTU is between 100 mg and 300 mg per day in three divided doses. Methimazole can be started from 5 mg to 30 mg, whereas dose in carbimazole range between 10 mg and 40 mg per day; both are given as a single daily dose. Generally, Thyroid function should be assessed at 2- to 4 week interval after initiating therapy and dose can be adjusted accordingly.

The side effects include minor reactions such as pruritic rash, gastrointestinal upset, or fever, which occur in 5–10% of patients. Major drug reactions such as ANCA positive vasculitis, agranulocytosis, and hepatotoxicity are rare. The prevalence of agranulocytosis is 0.3–0.5%, and is considered to be dose-related in few reports. Routine monitoring of white blood cell counts or liver function tests are not recommended because they have not been shown to prevent toxic events, although it is reasonable to monitor liver function every 3–4 weeks in the patient who is on PTU. β-blocking drugs can also be used to control the symptoms for short term and in lower doses if possible because when used chronically, they are found to have increased chances for small for gestational age babies. Propranolol in doses of 20-40 mg every 8 hours or metoprolol 100 mg once or twice a day is recommended to ameliorate adrenergic symptoms. Surgery as a treatment is
indicated only when there is a severe adverse reaction to oral drugs or the patient is symptomatic despite high doses of antithyroid drugs. Subtotal thyroidectomy is the surgery of choice and should be performed in the second trimester.\textsuperscript{16}

**Fetal aspects of maternal hyperthyroidism**

In women who are TRAb positive with level more than two to three fold than the normal, fetal thyroid should be screened for during the fetal ultrasound at 18th to 22nd week and repeated every 4-6 week or as clinically indicated.\textsuperscript{19} The signs of abnormal fetal thyroid function are goiter, intrauterine growth restriction, hydrops fetalis, advanced bone age, fetal tachycardia. Umbilical blood sampling for thyroid hormone levels is recommended only if the diagnosis of fetal thyroid disease is dubious from the clinical and sonographic findings.\textsuperscript{16} All newborns of mothers with Graves' disease except those with negative TRAb and not requiring ATD) should be advised thyroid function testing and treated if necessary.

**Thyroid storm in pregnancy**

Thyroid storm is the rare decompensated state of thyrotoxicosis which during pregnant state can be precipitated by infection, pre-eclampsia, labour or caesarean section. It is important to diagnose because it can be life threatening problem for both woman and baby. The symptoms and signs include fever, tachycardia or tachy-arrhythmias, alteration in mental status, heart failure, nausea, vomiting, severe diarrhoea, and sometimes liver dysfunction.\textsuperscript{25} The treatment of thyroid storm in pregnancy comprises of supportive measures with intravenous fluids, oxygen, and vitals monitoring. Fever should be treated with paracetamol. Tachyarrhythmias are controlled with β-blocking drugs. The propranolol can be given 60–80 mg every 4–6 hourly or intravenous esmolol is started at a dose of 250–500 µg/wt followed by a continuous infusion of 50–100 µg/kg per min. The antithyroid drug therapy is given in large doses (methimazole 20–30 mg every 4–6 hourly or propylthiouracil 400 mg every 6 h). Propylthiouracil is preferred for thyroid storm because of its ability to inhibit T4 to T3 conversion. The oral potassium iodide (potassium iodide tablets or a saturated solution of potassium iodide or Lugol solution) can be added after starting antithyroid drugs to inhibit release of thyroid hormones from the gland. Some studies have shown the benefits of using high-dose glucocorticoid therapy, which includes either hydrocortisone 50–100 mg every 8 h or dexamethasone 2–4 mg every 8 hourly) as steroid like PTU blocks peripheral T4 to T3 conversion.\textsuperscript{26}

**Treatment of hyperthyroidism in the postpartum period and during lactation**

Antithyroid drugs are recommended for hyperthyroidism in the postpartum period and for women who are breastfeeding. The American Academy of Pediatrics has approved both propylthiouracil and methimazole for used
by lactating mothers, and doses of less than 20 mg of methimazole are safe though PTU should not be given as first line. PTU is indicated only when there is methimazole-intolerance at maximum dose up to 300-450 mg per day. No adverse effects have been reported in breastfed infants so far.

In conclusion, the management of hyperthyroidism during pregnancy and lactation requires attention and should be carefully planned to best treat the mother and also prevent any adverse effects on the mother or the fetus.

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CD002863.

