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Review

Thyrotoxicosis of pregnancy☆

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ABSTRACT

Thyrotoxicosis presenting during pregnancy is a common clinical problem and can be challenging to differentiate between physiologic patterns of thyroid dysfunction during gestation and intrinsic hyperthyroidism. This review provides a summary of the differential diagnosis, clinical presentation, diagnostic options, potential adverse effects of maternal thyrotoxicosis to the fetus, and treatment recommendations for thyrotoxicosis arising in pregnancy.

Introduction

Metabolic disorders, including thyroid dysfunction, are among the most common pre-pregnancy diseases in pregnant women [1]. Thyrotoxicosis presenting in pregnancy can be particularly challenging, given the normal physiologic changes which occur and limitations of laboratory and radiologic testing during pregnancy. Early recognition, accurate diagnosis, and appropriate management of thyrotoxicosis during pregnancy are important for decreasing the risks of adverse maternal and fetal outcomes.

Differential diagnosis

Thyrotoxicosis during pregnancy is suggested by a suppressed serum thyroid stimulating hormone (TSH). Hyperthyroidism is thyrotoxicosis arising from the thyroid; subclinical hyperthyroidism is defined as a TSH concentration below the lower limit of the reference range and normal free or total thyroxine (T4) and triiodothyronine (T3) concentrations, whereas overt hyperthyroidism is defined as TSH concentration below the lower limit of the reference range and elevated concentrations of serum T4 and T3 [2]. The most common cause of thyrotoxicosis in pregnancy is gestational transient thyrotoxicosis (GTT), which occurs from the stimulatory action of human chorionic gonadotropin (HCG) on the TSH receptor. GTT is reported to have a prevalence of 2–3% in a European population [3]. However, this is variable, and in a study of 184 women in Singapore, the prevalence of GTT during the first trimester was much higher at 11% [4]. GTT is also more common in patients with a history of Graves' disease prior to pregnancy, in whom the prevalence can be as high as 25% [5]. The prevalence of overt thyrotoxicosis in pregnancy ranged from 0.2 to 0.7% in one large U.S. population sample [6].

Other etiologies to consider in the differential diagnosis of thyrotoxicosis during pregnancy include subtypes of overt hyperthyroidism, such as Graves' disease, toxic multinodular goiter, and toxic adenoma, as well as thyroiditis and exogenous thyroid hormone use [6,7]. In addition, a rare cause of thyrotoxicosis during pregnancy is trophoblastic disease. Molar pregnancies, which include complete and partial hydatidiform moles, result from abnormal genomic duplication associated with monospermic or dispermic fertilization and subsequent loss of the maternal nuclear genome [8]. The hyperthyroidism of trophoblastic disease is often subclinical in nature; the incidence of symptomatic hyperthyroidism is very rare and confined to small case series or case reports [9,10].

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Clinical presentation

The signs and symptoms of thyrotoxicosis in pregnancy are the same as those in nonpregnant patients and can include anxiety, tremor, heat intolerance, palpitations, weight loss or lack of weight gain, goiter, tachycardia, and hyperreflexia [11,12]. Distinguishing between GTT and intrinsic hyperthyroidism is important, given the differences in their course and recommended management. The duration and types of symptoms may help guide diagnostic decisions. The presence of goiter, ophthalmopathy, and persistence of disease can be suggestive of Graves' disease [13,14]. In contrast, GTT rarely manifests with signs and symptoms of overt hyperthyroidism, but is more commonly associated with the persistent vomiting of hyperemesis gravidarum [13,15]. The severity of hyperemesis correlates with the degree of hyperthyroidism and usually resolves by 18–19 weeks of gestation [13,16]. Symptomatic hyperthyroidism is also rare in trophoblastic disease, in which the more common manifestations are vaginal bleeding and a characteristic "snowstorm pattern" on ultrasound of the uterine contents [8].

Thus, although certain signs and symptoms can provide clues to the underlying etiology of thyrotoxicosis during pregnancy, they are not specific to any one disease. This significant overlap between abnormal signs, symptoms, and physical exam makes laboratory testing essential.

Diagnosis

Laboratory tests

TSH

Current guidelines by the American Thyroid Association, American Association of Clinical Endocrinologists, and the Endocrine Society recommend that trimester-specific TSH ranges be used in the evaluation of thyroid function during pregnancy, as established from data of pregnant women [17–19]. Recommended TSH ranges are 0.1–2.5 mIU/L, 0.2–3.0 mIU/L, and 0.3–3.0 mIU/L for the first, second, and third trimesters, respectively [17–19]. The lower end of TSH is not well-established in pregnancy, and normal values can be as low as 0.02 mIU/L [20,21].

Free T4

The variability and lack of standardization of the serum free thyroxine (FT4) analog (direct) immunoassay, which is that available in most commercial laboratories, limits its utility in the diagnosis and management of hyperthyroidism during pregnancy. In a Danish study of two cohorts of pregnant women living in the same region, measurements of FT4 concentrations by two different immunoassays were widely variable across all gestational age groups; up to 100% of FT4 levels in one cohort were outside the reference range of the other [22]. Similar variability is seen when using different immunoassays for measuring FT4 concentrations on the same serum sample [23].

Such variability makes it difficult to establish pregnancy-specific reference ranges for serum FT4 levels. Other techniques for assaying FT4 levels, such as equilibrium dialysis and tandem mass spectrometry [24], are more accurate, but not widely available and usually more costly.

Total T4, T3, and free T4 index

Given the lack of standardization of the FT4 assay and variability of its results, serum total thyroxine (T4) and triiodothyronine (T3) levels are alternative options for assessing thyroid function. Pregnancy is associated with increased thyroid binding globulin (TBG) levels, due to the effect of estrogen on glycosylation of TBG, and therefore, increased total T4 concentrations. During the first trimester, total T4 levels increase by approximately 50% due to this physiologic effect [3]; the normal upper limit of serum total T4 concentrations is set at 1.5 times that of the non-pregnant normal upper limit [17,18,25,26]. The proposal for the use of total thyroid hormone levels is not without controversy, as variations in TBG concentrations and the lack of well-established pregnancy reference range for serum total T4 levels are disadvantages [27]. In a study of more than 17,000 women without thyroid disease, after establishing normative values for serum total T4 levels, there was an 88% agreement in identifying subclinical hypothyroidism (SCH) when using either the free T4 immunoassay or total T4 assay [28].

Measurement of the free T4 index (FTI), which adjusts for the presence of binding proteins, has also been proposed as an alternate and perhaps more accurate test for diagnosing hyperthyroidism [17]. However, trimester-specific reference ranges for FTI have only been established in one study of 152 antibody-negative pregnant women without known thyroid disease in Iran, a region considered to be generally iodine sufficient [29].

TSH receptor antibodies

In pregnant patients undergoing evaluation for thyrotoxicosis, measurement of serum TSH receptor antibodies (TRAb) is important for both diagnostic and prognostic reasons. The presence of antibodies, when evaluated concurrently with clinical findings, can help differentiate Graves' disease from GTT [13]. In addition, TRAb is able to cross the placental barrier to result in potentially adverse outcomes, such as neonatal hyperthyroidism and hypothyroidism [30,31]. The fetal thyroid gland begins to respond to the action of TRAb at approximately 20 weeks of gestation, corresponding to the decline of maternal TRAb titers due to gestational immune modulation [32,33]. Serum TRAb measurements, when indicated, can be used to guide the potential risk of fetal Graves' disease and provide important management decisions *in utero*.

According to guidelines by the European Thyroid Association, the decision to measure serum TRAb titers should depend on risk stratification determined by current and past treatment of Graves' disease [34]. As the risk of complications is low in euthyroid women with Graves' disease who are not receiving antithyroid medication and have no history of radioiodine treatment or thyroidectomy, measuring serum TRAb levels is not indicated in such patients. In women who are taking antithyroid medication, it is recommended to measure serum TRAb concentrations in the third trimester, and if there is history of radioiodine treatment, early in pregnancy, regardless of thyroid function status [34]. Current guidelines by the American Thyroid Association and the Endocrine Society recommend measuring TRAb at 20–24 weeks of gestation in patients with past or present history of Graves' disease [17,18]. Serum TRAb titers can also be used to help differentiate between postpartum thyrotoxicosis secondary to destructive thyroiditis and Graves' disease [35].

HCG

HCG plays an important role in the maintenance of the placenta, with serum levels peaking at 9–10 weeks of pregnancy. It is composed of an α-subunit that is identical with that of TSH, LH, and FSH. Due to its weak binding to the TSH receptor, serum HCG concentrations have a thyrotrophic effect that results in the TSH suppression seen in women with GTT [36,37]. Hyperemesis gravidarum is more common in women with GTT, and serum HCG levels not only correlate with the degree of biochemical thyroid function, but also with the severity of hyperthyroidism by laboratory assessment [38]. Biochemical evidence of hyperthyroidism can be seen with serum HCG levels of 100,000–500,000 IU/L, and clinical hyperthyroidism can result when levels greater than 500,000 IU/L are measured [9,39]. Severely

elevated serum HCG levels are observed in gestational trophoblastic disease and usually are the first clue to suggest a molar pregnancy upon initial presentation [9,36].

Imaging studies

Ultrasound

Although clinical presentation, serum thyroid function tests, and serum thyroid antibody titers are usually sufficient for diagnosis, thyroid ultrasonography to assess thyroid volume and blood flow can be a helpful tool for differentiating Graves' disease from thyroiditis in the thyrotoxic pregnant woman [35,40]. If fetal Graves' disease is suspected, fetal thyroid ultrasonography can be used to assess for a goiter and additionally, accelerated bone maturation and sustained fetal tachycardia as signs suggestive of fetal hyperthyroidism [41,42].

Thyroid nuclear medicine studies

Radioiodine uptake and scanning can lead to adverse fetal outcomes, including those adverse effects associated with radiation exposure to the developing fetus, as well as fetal hypothyroidism. Thus, thyroid nuclear studies are contraindicated in pregnancy [43].

Adverse pregnancy outcomes of maternal hyperthyroidism

Mother and fetus

Overt hyperthyroidism (thyrotoxicosis arising from the thyroid gland) during pregnancy can lead to poor maternal and fetal outcomes. Maternal complications of pregnancy associated with hyperthyroidism include pre-term delivery, miscarriage, hypertension, and heart failure [44,45].

In a recent report of 223,512 pregnancies from the U.S. Consortium of Safe Labor, hyperthyroidism during pregnancy was associated with 1.4-fold increased odds of induction of labor, a 1.8–3.6-fold increased risk of preeclampsia, a 1.8-fold increased risk of preterm births, and nearly a 4-fold increased risk of maternal admissions to the intensive care unit following delivery, which included mothers diagnosed with heart failure [6]. Although this study did not include data regarding treatment of the maternal hyperthyroidism, these complications are likely even more frequent in women with poorly-managed hyperthyroidism. Severe complications of hyperthyroidism during pregnancy, such as maternal heart failure, are associated with a lack of prenatal care or nonadherence with antithyroid medications [45].

The fetal and neonatal complications of maternal hyperthyroidism include goiter formation and hyperthyroidism, which can lead to intrauterine growth restriction and failure to thrive in the neonate [46]. In a pregnant woman with Graves' disease fetal hyperthyroidism can result from placental transfer of TRAb that stimulate the fetal thyroid gland [31,42,47]. One report estimates that the frequency of fetal hyperthyroidism ranges from 1 to 5% in women with Graves' disease during pregnancy [48]. In particular, a significantly elevated serum TRAb concentration late in pregnancy is associated with an increased risk of hyperthyroidism in the newborn [47]. Based on this association, some clinicians measure maternal TRAb or Thyroid Stimulating Immunoglobulin levels in the third trimester of pregnancy to identify those at increased risk of neonatal Graves' disease. More specifically, guidelines recommend measuring TRAb levels at 20–24 weeks gestation [17,18]. Although more rare, fetal or neonatal hypothyroidism is also a known complication that can arise from shifting in the balance between thyroid stimulating and thyroid blocking antibodies [49]. Fetal hypothyroidism can also result from the transplacental passage of antithyroid drugs [50]. Central hypothyroidism is seen in some infants of mothers with elevated thyroid hormone levels during pregnancy [51].

Childhood outcomes

The adverse effects of hyperthyroidism during pregnancy on long term outcomes are less clear. In a prospective cohort study that assessed variations in serum thyroid function during pregnancy, maternal overt hyperthyroidism in early pregnancy was not associated with childhood body composition and adverse cardiovascular outcomes [52]. In another study that evaluated maternal thyroid dysfunction and associated attention deficit hyperactivity disorder (ADHD) and autism spectrum (ASD) disorders, there were no associations of these diseases and treated maternal hyperthyroidism during pregnancy, compared to women with no preexisting thyroid dysfunction [53].

Treatment

Thionamides

Current guidelines by the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endocrine Society recommend the use of propylthiouracil (PTU) in the first trimester of pregnancy, and consideration to switch to methimazole after the first trimester [17,18,54]. These recommendations are based on concerns of rare congenital abnormalities associated with methimazole use during embryogenesis. In breastfeeding mothers, antithyroid drugs (ATD) are considered safe and can be used in moderate doses. The recommendation is to administer ATD in divided doses immediately following each feeding and for the breastfeeding infant to be monitored for potential development of thyroid dysfunction [18].

In a retrospective study comparing treatment of pre-existing Graves' disease in the first trimester with PTU, methimazole, and no treatment, the relative risk of major congenital malformations was significantly higher in the methimazole group [55]. Congenital malformations included aplasia cutis, omphalocele, symptomatic omphalomesenteric duct anomaly and esophageal atresia. Although there was a 2-fold increase in the odds of a congenital malformation with methimazole treatment, the risk did not seem to be dose-dependent. Similar findings were reported in a recent large cohort study using a Danish nationwide registry. In this study early pregnancy exposure was defined as start of antithyroid treatment from 6 months before pregnancy start to the end of the 10th gestational week. Both methimazole/carbimazole (MMI/CMZ) and PTU exposure in early pregnancy were associated with 1.39 fold increased risk of birth defects, with no significant difference in the overall prevalence of birth defects between the two treatment groups. However, MMI/CMZ was associated with birth defects in more organ systems compared to PTU, and a nearly 22-fold increased risk of choanal atresia, esophageal atresia, omphalocele, omphalomesenteric duct anomalies, or aplasia cutis compared to nonexposed group. Furthermore, switching from MMI to PTU during pregnancy did not decrease the risk of birth defects [56].

The potential reasons for the observed differences in fetal congenital malformation rates regarding the use of specific thionamides is not clear. This does not seem to be related to differential rates of placental passage, as one study reported that transplancental cross-over was similar between methimazole and PTU using an in-vitro assay of a perfused human term placental lobule [57]. The small increased relative risks of neonatal complications associated with methimazole may instead be related to the direct action of each medication, and additional research is needed to further understand this.

The choice of a thionamide in the treatment of maternal hyperthyroidism during pregnancy involves balancing the risks of adverse fetal outcomes with adverse maternal outcomes. Adverse maternal outcomes can include drug rash, pruritus, and very rarely hepatotoxicity [58]. While PTU is more hepatotoxic to the mother

and fetus, it has a greater safety profile regarding neonatal congenital malformations.

Subtotal thyroidectomy

Thyroidectomy as a definitive treatment option for maternal hyperthyroidism during pregnancy is recommended for patients who are unable to tolerate antithyroid medications, require large doses of these medications, or are nonadherent and have severe, uncontrolled hyperthyroidism [18]. Thyroid surgery during the second trimester is thought to be the safest option, although thyroid surgery during any time in pregnancy may confer an increased risk of maternal complications, including higher rate of hypoparathyroidism, recurrent laryngeal nerve injury, and general surgical complications [59].

Radioiodine therapy

Use of radioiodine (I-131) treatment during pregnancy is contraindicated, but can be an option prior to pregnancy. An important consideration for patients treated with either radioiodine therapy or thyroidectomy prior to pregnancy is the continued risk of persistently elevated TRAb titers during pregnancy. In a prospective randomized study, hyperthyroid patients treated with radioiodine continued to have elevated serum TRAb titers one year following treatment, while those who received antithyroid medication or thyroid surgery had shorter durations of positive serum TRAb concentrations [60]. In another retrospective study, use of radioiodine therapy prior to pregnancy was associated with a lower incidence of postpartum thyrotoxicosis, which was thought to be due to histological changes (various degrees of fibrosis) in the thyroid gland after radioiodine therapy and possible decrease in the responsiveness of the remaining cells [61]. Women should be counseled to avoid pregnancy for six months following radioiodine therapy [18].

Conclusions

Thyrotoxicosis of pregnancy can present unique diagnostic challenges and, if untreated, is associated with increased risks of adverse maternal, fetal, and neonatal complications. The clinical presentation, serum thyroid function test results, and serum TRAb titers can help differentiate the etiology of thyrotoxicosis. However, assessment and monitoring with serum thyroid function tests can be difficult, as there is significant overlap between test results arising from normal pregnancy physiology and intrinsic hyperthyroidism. Propylthiouracil is the preferred thionamide for treatment of hyperthyroidism in the first trimester. Radioiodine is contraindicated, and surgery, if indicated, should be performed during the second trimester. Appropriate treatment of maternal hyperthyroidism during pregnancy and close monitoring of mother and fetus are essential for optimizing outcomes. Treatment should be targeted to achieve serum TSH concentrations within established pregnancy-specific reference ranges.

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