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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