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A Case Report from Rural Kenya**

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Transient Hyperthyroidism of Hyperemesis Gravidarum: A Case Report from Rural Kenya

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Abstract

Purpose: The aim of the study was to assess the transient hyperthyroidism of hyperemesis gravidarum: A case report from rural Kenya.

Materials and Methods: This study adopted a desk methodology. A desk study research design is commonly known as secondary data collection. This is basically collecting data from existing resources preferably because of its low cost advantage as compared to a field research. Our current study looked into already published studies and reports as the data was easily accessed through online journals and libraries.

Findings: Hyperthyroidism complicates 0.2-0.4% of pregnancies. It may be diagnosed in the setting of hyperemesis gravidarum and can be pathological or transient. Untreated pathological hyperthyroidism has adverse maternal and fetal outcomes. Transient hyperthyroidism of hyperemesis gravidarum (THHG) affects up to 60% of women with hyperemesis, is self-limiting, and needs no antithyroid drug treatment. A diagnosis of THHG (rather than overt pathological hyperthyroidism) should be made when hyperthyroidism occurs in the setting of hyperemesis gravidarum and in the absence of

pre-pregnancy hyperthyroidism, clinical findings compatible with maternal hyperthyroidism, and a negative antithyroid autoimmune profile. THHG resolves by the end of the first trimester without adverse pregnancy outcomes. We present a case from a rural Kenyan hospital to highlight the clinical profile and management of THHG for the primary care physician.

Implications to Theory, Practice and Policy: Assessment of thyroid functions is indicated in hyperemesis gravidarum, where there are clinical features of hyperthyroidism. THHG is a self-limiting benign condition that may inappropriately lead to unnecessary drug treatment for pathological hyperthyroidism in pregnancy. A diagnosis of THHG should be made when a laboratory picture of hyperthyroidism occurs in the setting of hyperemesis gravidarum in the absence of pre-pregnancy hyperthyroidism, compatible physical findings, and a negative antithyroid autoantibody profile.

Keywords: *Hyperthyroidism Pregnancy, Hyperemesis Gravidarum, Transient Hyperthyroidism Hyperemesis Gravidarum, THHG, Kenya*

1.0 INTRODUCTION

Hyperemesis gravidarum is characterized by persistent and excessive vomiting in the first trimester of pregnancy and is associated with fluid and electrolyte losses, weight loss, and ketonuria/ketonemia ⁽¹⁾. The pathogenesis is multifactorial and includes a complex interplay of hormonal factors (e.g., high human chorionic gonadotropin [hCG] levels) ⁽²⁾, genetic predisposition (e.g., excessive production of *GDF15* and *IGFBP7*) ⁽³⁾, altered gastrointestinal motility ⁽⁴⁾, etc. Hyperemesis gravidarum is usually self-limiting, but secondary causes may lead to protracted presentations that may extend into the second trimester. These include molar pregnancy, multiple gestations, pyelonephritis, malaria, cholecystitis, hepatitis, and hyperthyroidism. Hyperthyroidism and hyperemesis gravidarum have many overlapping symptoms, e.g., vomiting, dehydration, tachycardia, loss of weight, and organ dysfunction ⁽⁵⁾. Hyperthyroidism is characterized by elevated free or unbound thyroxine (T4) and/or triiodothyronine (T3) with a correspondingly low or suppressed thyroid stimulating hormone (TSH). Total T3 and T4 measure both the bound and unbound/free T3 and T4, respectively, and their measured values mirror those of the free or unbound tests ⁽⁶⁾. Overt hyperthyroidism in pregnancy is most commonly due to Graves' disease and is estimated to occur in 0.2-0.4% of pregnancies ^(7, 8). Increased metabolic demands in normal pregnancy lead to changes in thyroid physiology that alter thyroid function tests. For example, estrogen-stimulated synthesis of thyroid-binding globulin (TBG) causes excess circulating levels of the latter, which in turn results in high levels of serum total T3 and total T4 concentrations. However, the biochemically active free T3 and free T4 levels are often within the normal limits ⁽⁹⁾. Furthermore, high serum concentrations of hCG levels during early pregnancy directly act on the TSH receptor to stimulate excess thyroid hormone production, which is often transient and subclinical. This is because hCG and TSH belong to the same family of glycoproteins and share a common alpha and beta subunit. The beta subunits of both hCG and TSH have significant homology, such that hCG has weak TSH activity ⁽¹⁰⁾. The hCG activates the TSH receptor and high thyroid binding globulin (TBG) levels in pregnancy lead to high serum levels of total T3 and T4. However, most of these findings are transient and occur commonly in the first trimester, often in association with hyperemesis gravidarum in women with no pre-pregnancy history of hyperthyroidism. This is transient hyperthyroidism of hyperemesis gravidarum (THHG), which affects up to 60% of women with hyperemesis gravidarum ^(11, 12). THHG is self-limiting and does not require drug treatment. On the other hand, untreated hyperthyroidism in pregnancy is associated with adverse maternal and fetal outcomes, including maternal hypertension (and preeclampsia), spontaneous abortions, fetal growth restriction, low birth weight, premature delivery, etc. ^(13, 14). True hyperthyroidism in pregnancy, usually due to Graves' disease, is associated with pre-pregnancy features of thyrotoxicosis and laboratory findings of antithyroid autoantibodies. These include anxiety, hand tremors, heat intolerance, oligomenorrhea, ophthalmoplegia, thyroid bruits, etc. ⁽¹⁵⁾.

Case Presentation

Presenting Illness and Physical Examination

A 37-year-old mother of four (para 4+1, gravida 6), a businesswoman from Narok, Kenya, presented to us with a 4-day history of incessant vomiting at about 8 weeks estimated gestational age of pregnancy by ultrasound (she forgot the date of her last normal monthly menstrual periods). She reported 6-10 episodes of emesis daily, predominantly postprandial, and could not retain oral food. She had associated lethargy and on-off orthostatic dizziness but no history of diarrhea,

abdominal pains, vaginal discharge, or bleeding; no history of fevers or chills; and no recent travel to a malaria-endemic zone. She had been well prior to the current pregnancy and denied any history of palpitations, nervousness, sweaty palms, hand tremors, heat intolerance, or anterior neck swelling. She had normal, regular monthly menstrual periods. Her obstetric history was remarkable for first-trimester hospitalizations for excessive vomiting in two of the pregnancies. Otherwise, she had full-term vaginal deliveries for all the living children. The last pregnancy (3 years ago) resulted in a miscarriage at about the 10th week of gestation (unclear etiology).

Clinically, she was severely dehydrated with a sitting BP of 105/70 mmHg and a standing BP of 92/58 mmHg (consistent with orthostatic hypotension), a pulse rate of 114 bpm, afebrile, and a random blood glucose of 90 mg/dl. She weighed 65kg, with a reported pre-pregnancy weight of about 68-69 kg. Her physical exam was remarkable for features of severe dehydration and mild epigastric tenderness in a non-distended abdomen. She had no goiter, no features of ophthalmopathy (no proptosis, lid lag, etc.), no finger clubbing, finger acropachy, or hand tremors, and no pedal edema (to suggest pretibial myxedema). The rest of the exam was unremarkable.

Diagnostic Workup and Management

Her urine pregnancy test was positive, while the urine dipstick showed ketonuria of 3+. She had a normal complete blood count and serum creatinine, but a slightly low serum sodium of 133 mmol/l (135-145) and a potassium of 3.1 mmol/l (3.5-5.5). Her tests for malaria and HIV were negative, while her complete antenatal profile was unremarkable. An abdominopelvic ultrasound showed a single live intrauterine pregnancy at an average gestation of 8 weeks +/- 14 days, with an unremarkable rest of the visceral organs reported. A clinical diagnosis of hyperemesis gravidarum at 8 weeks of gestation was made, and she was treated with volume replacement (using intravenous fluid enriched with vitamin B complex solution) and antiemetics (starting with metoclopramide and eventually adding promethazine and ondansetron in 2 subsequent re-admissions with the same diagnosis).

Thyroid Function Testing and Management

A screening serum TSH was done to exclude hyperthyroidism in pregnancy as a possible cause for the hyperemesis during a second admission in view of persistent tachycardia of 120-130 bpm. The TSH was <0.1 mIU/L (reference 0.5-5 mIU/L)); she had an elevated total T4 of 4.76 nmol/L (1.2-3.1) and a total T3 of 192 nmol/L (68-181). It was too expensive to do free T3 and T4 levels. Because these findings were consistent with hyperthyroidism, she was re-evaluated for possible treatment of hyperthyroidism in pregnancy at 10 weeks, with propylthiouracil (PTU). However, her pre-pregnancy history, symptom profile, and initial physical examination did not show any features of hyperthyroidism. The elevated thyroid hormones were occurring in the context of hyperemesis. For these reasons, an alternative diagnosis of transient hyperthyroidism of hyperemesis gravidarum (THHG) was made. She had been scheduled to start PTU, but this was stopped. The hyperemesis gravidarum completely resolved by 14 weeks of gestation, and the thyroid profile had normalized by then without drug treatment. She is currently at 20 weeks of gestation and attends an antenatal clinic elsewhere with a normal thyroid profile.

Discussion

Our patient met the definition criteria for hyperemesis gravidarum with the additional risk factor of hyperemesis gravidarum in two previous pregnancies. She had persistent and excessive vomiting in the first trimester of pregnancy associated with fluid and electrolyte losses, weight loss

of about 5 kg, and ketonuria on the urine dipstick ⁽¹⁾. A focused history, physical examination, laboratory testing, and an abdominopelvic and obstetric ultrasound ruled out secondary causes of excessive vomiting in early pregnancy, including malaria, molar pregnancy, pyelonephritis, and cholecystitis ⁽¹⁶⁾. The finding of laboratory features of hyperthyroidism during evaluation of hyperemesis gravidarum necessitated a nuanced method of differentiating between THHG (which does not need antithyroid drug treatment) and overt hyperthyroidism (which should be treated with antithyroid drugs). The interpretation of thyroid profile in pregnancy is trimester-specific, and several laboratories have nomograms to aid diagnosis ⁽¹⁷⁾.

Table 1 below is adapted from Caffrey J. T. and details the pattern of thyroid hormones in normal pregnancy, THHG, and Graves' disease ⁽¹⁶⁾.

Table 1: Patterns of Thyroid Profile and Thyroid Autoantibodies in Normal Pregnancy, Transient Hyperthyroidism of Hyperemesis Gravidarum (THHG), and Graves' Disease ⁽¹⁶⁾.

Thyroid Function Tests	Normal Pregnancy	THHG	Graves' Disease
Thyroid-stimulating hormone	Normal	Low or normal	Low
Thyroid-binding globulin	High	High	Normal or high
Total thyroxine	High	High	High
Free thyroxine	Normal	High or normal	High
Total triiodothyronine	High	High	High
Free triiodothyronine	Normal	High or normal	High
Thyroid autoantibodies			
Antithyroid peroxidase	Negative	Negative	Positive
Antithyroid-stimulating hormone receptor	Negative	Negative	Positive

Since it is impossible to differentiate pathological hyperthyroidism from THHG on the basis of a thyroid profile alone, additional parameters are necessary ⁽¹⁶⁾. These include: 1) Absence of symptoms of hyperthyroidism before pregnancy. Graves' disease is the most likely cause of hyperthyroidism in women of reproductive age, and often predates pregnancy. This presents with nervousness, palpitations, sweaty palms, oligomenorrhea, hand tremors, and heat intolerance. 2) Absence of physical examination findings consistent with hyperthyroidism. These include thyroid ophthalmopathy (e.g., lid lag, lid retraction, proptosis, etc.), goiter, proximal myopathy, thyroid acropachy (with finger clubbing and onycholysis), pretibial myxedema, etc. 3) Onset of an abnormal thyroid profile in the setting of hyperemesis gravidarum. Abnormal thyroid function tests that predate hyperemesis gravidarum or persist beyond its resolution should lead to a search for alternative diagnoses. THHG, by definition, occurs only in the context of hyperemesis gravidarum. 4) Negative thyroid autoantibody tests. Graves' disease (which is an autoimmune disease) is characterized by positive antithyroid peroxidase and anti-TSH receptor antibody tests. These tests are negative in patients with THHG. Based on these parameters, our patient clearly had THHG. We were not able to do serum thyroid autoantibodies due to their prohibitive costs.

THHG is a self-limiting condition. There is no specific drug treatment required other than supportive care for hyperemesis gravidarum. There is no evidence of adverse outcomes in women with THHG who are not given antithyroid medications ⁽¹⁸⁾. Antithyroid drugs (thionamides),

methimazole (carbimazole), and propylthiouracil are indicated in overt hyperthyroidism but are associated with some risk of teratogenicity as they both cross the placenta. Beta blockers, e.g., propranolol or metoprolol, may be used to control sympathetic symptoms, while thyroidectomy may rarely be used in women who cannot tolerate thionamides. The American College of Obstetrics and Gynecology has guidelines on the safe use of thionamides in pregnancy⁽¹⁹⁾. Since hCG levels physiologically decline in the second trimester, both hyperemesis gravidarum and the thyroid abnormalities of THHG resolve by the 15th week of gestation^(16,18). Thyroid function tests can be closely monitored until they return to normal. For our patient, the hyperemesis gravidarum resolved by the 15th week of gestation with normalization of the thyroid profile without antithyroid drug treatment. She remains stable on follow up.

2.0 CONCLUSION AND RECOMMENDATION

Assessment of thyroid functions is indicated in hyperemesis gravidarum, where there are clinical features of hyperthyroidism. THHG is a self-limiting benign condition that may inappropriately lead to unnecessary drug treatment for pathological hyperthyroidism in pregnancy. A diagnosis of THHG should be made when a laboratory picture of hyperthyroidism occurs in the setting of hyperemesis gravidarum in the absence of pre-pregnancy hyperthyroidism, compatible physical findings, and a negative antithyroid autoantibody profile. Monitoring of the clinical status of the patient with serial thyroid function tests is adequate since the thyroid profile normalizes by the end of the first trimester. There have not been any reports of adverse pregnancy outcomes with this approach.

Implications of the Study

This study has highlighted a logical approach to differentiating transient hyperthyroidism of hyperemesis gravidarum (THHG) and hyperthyroidism in hyperemesis gravidarum (and in general pregnancy) in order to avoid using antithyroid drugs to treat the benign self-limiting THHG and reserve thionamides for the treatment of overt/pathological hyperthyroidism in pregnancy. Primary care physicians should make this distinction within the scope of their routine clinical care.

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Ethical Consideration

Informed consent was obtained from the patient for this case.

Conflict of Interest

The authors declare no conflict of interest.

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