Hyperemesis, Hyperthyroidism, or Both?

William J. Crump, MD, and Laurie A. Aten, MD
Huntsville, Alabama

Nausea and vomiting are common during pregnancy and, when severe enough to require intervention, may develop into the syndrome known as hyperemesis gravidarum. When the diagnosis of hyperemesis is considered, a careful search for secondary causes is necessary. The list of secondary causes includes hyperthyroidism, a relatively uncommon condition during pregnancy. Because many of the signs and symptoms of hyperthyroidism are common, and thyroid function tests are more difficult to interpret during normal pregnancy, making the diagnosis of hyperemesis gravidarum is a challenge. The decision to treat or to await spontaneous resolution depends on the severity of the illness and the likelihood of the presence of true Graves' disease. The case summarized here demonstrates these issues, and includes treatment options for hyperemesis-associated hyperthyroidism.

Key words. Hyperemesis gravidarum; pregnancy complications; hyperthyroidism.
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Nausea and vomiting are very common in the first trimester of pregnancy, frequently beginning when the fetus is about 8 weeks of gestational age and ending by 14 weeks. Occurring during 70% of all pregnancies,[1] these symptoms are usually self-limited and require only simple palliative measures and watchful waiting. Hyperemesis gravidarum is a severe form of nausea and vomiting, resulting in weight loss and dehydration that often lasts throughout pregnancy. Well-known associations with hyperemesis include multiple gestations and trophoblastic disease, but the symptoms may also reveal the presence of another disease (Table 1).

Hyperthyroidism can present as hyperemesis. Furthermore, many of the usual signs of hyperthyroidism are common during normal pregnancy, and thyroid function tests may be difficult to interpret with certainty. Adding to the difficulty is the finding of transient hyperthyroidism in patients with hyperemesis that resolves spontaneously.[2] Thus, the diagnosis requires a high index of suspicion, and the decision to treat or wait is complex.

Case Summary

A 25-year-old woman, G2P1, presented for prenatal care at approximately 12 weeks of pregnancy. She had been referred by her usual family physician, who had recently stopped providing maternity care, because of a presumptive diagnosis of hyperemesis gravidarum. She already had required intravenous (IV) administration of fluids for dehydration during two previous visits to her usual family physician, was taking vitamin B_6, and had been hospitalized twice in the last 6 weeks for persistent vomiting and dehydration. Prior evaluation included a gallbladder ultrasonogram and a test of serum amylase level; the results of both were normal. During each hospital admission, the nausea and vomiting had resolved after approximately 12 hours of IV rehydration and no oral intake.

On presentation, the patient denied significant past illnesses; her family history was positive only for hypertension and coronary artery disease (the patient's father). During her first pregnancy 3 years ago she had experienced very little vomiting, but she had lost 10 pounds before subsequently gaining 30 pounds above her prepregnancy weight. Her first child had been born by uncomplicated spontaneous vaginal delivery at 40 weeks' gestation and weighed 6 lb 14 oz. An important finding in taking the patient's social history was that the vomiting began when she and her husband moved 30 miles away from her hometown, where she had lived her entire life.

At that first office visit, it was noted that she was 4

continued on page 453

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From the Department of Family Medicine, University of Alabama in Huntsville, Alabama. Requests for reprints should be addressed to William J. Crump, MD, Department of Family Medicine, University of Texas Medical Branch at Galveston, Galveston, TX 77555.

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continued from page 450

Table 1. Causes of Recurrent Vomiting in Pregnancy

Physiologic	Trophoblastic disease
Multiple gestation	Hyperthyroidism
Gastroenteritis	Peptic ulcer disease
Cholecystitis	Pancreatitis
Hepatitis	Appendicitis
Intestinal obstruction	Ketoacidosis

ft 9 in. tall and weighed 90 lb. She reported no vomiting for 7 days and a good appetite. She also denied tremor or palpitations. Her blood pressure was 100/60 mm Hg. In general, she was a pleasant, talkative, petite woman. Heart and lung examinations were unremarkable except for a 2/6 systolic ejection murmur. Reflexes were normoactive and there was no tachycardia. No fetal heart tones were heard by Doppler ultrasound, and bimanual examination revealed a 10-week-sized uterus, which correlated with an ultrasound estimate of 10 weeks that had been made the week before. By menstrual dates, however, the patient would have been 16 weeks pregnant. Initial prenatal laboratory tests were done, the results of which were normal. Appropriate prenatal care was discussed, including continuing to take vitamins.

The patient was seen at a scheduled visit 2 weeks later, at which time she gave a 4-day history of recurrent vomiting and inability to keep even liquids down during the previous 12 hours. Her weight had decreased 4 pounds, and her blood pressure, between episodes of emesis, was 114/74 mm Hg. She was admitted to the hospital, at which time her heart rate was 132 beats per minute and her blood pressure was 144/98 mm Hg. Examination was remarkable only for poor skin turgor and dry mucous membranes. Fetal heart tones were heard at 160 to 170 beats per minute. Admission laboratory tests were normal except for moderate ketonuria.

The patient was given nothing by mouth, and received IV fluids and parenteral antiemetics. A repeat ultrasonogram of the gallbladder was normal, and the 18-test chemistry panel (SMAC-18), amylase, and serum ketone levels were negative. Urine culture showed no growth, and the erythrocyte sedimentation rate was 25 mm/h. A conference was held, during which family members expressed concern over the patient's anxiety about her and her husband's recent move. It was noted that she had temporarily moved into her mother's home. A psychologist was consulted for further evaluation of family dynamics and to provide instruction to the patient in relaxation techniques to assist in management of nausea.

A thyroid panel was ordered by a resident who remembered that thyroid disease could cause vomiting. The tests revealed a free thyroxine index (FTI) of 9.3 (normal 1.1 to 4.6); an FTI of 9.5 was obtained on repeat testing. Consultation was obtained from an obstetrician, who suggested treating with very low doses of propylthiouracil and increasing the dose until the vomiting stopped. Careful reexamination of the neck revealed a normal-sized thyroid with no nodularity. The patient's free thyroxine (T_4) level was greater than 51 pmol/L (4 ng/dL); the upper normal limit is 30 pmol/L (2.3 ng/dL). The thyroid-stimulating hormone (TSH) level was less than 0.1 mU/L (0.1 μU/mL); normal is 0.6 to 5. Both levels were consistent with hyperthyroidism.

The risks of propylthiouracil treatment, which include fetal hypothyroidism and maternal bone marrow suppression, as compared with the benefits of adequate maternal nutrition were discussed with the patient and her family. The decision was made jointly to begin treatment, and propylthiouracil, 100 mg three times daily by mouth, was begun. Twenty-four hours later the patient was able to eat with minimal nausea. Two days later she took in 2200 kcal/d, and 3 days later began maintaining 3400 to 4000 kcal/d. The FTI peaked at 12, and 7 days after beginning the propylthiouracil, the FTI was down to 7.4. The patient's heart rate after walking 10 steps at a slow pace was 140 to 160 beats per minute the day after propylthiouracil was begun, compared with 100 beats per minute at discharge 7 days later. At discharge, propylthiouracil, 50 mg three times daily, was prescribed, and the patient was instructed to follow a high-calorie, high-protein diet.

An ultrasonogram at 18 weeks' gestational age showed no abnormalities, and fetal weight and fundal height had increased. At 20 weeks, the FTI normalized and the propylthiouracil was stopped. The patient continued to gain weight, and there was no recurrence of nausea. Through the remainder of the pregnancy, the FTI remained in the normal range. The patient gave birth spontaneously at 39 weeks after 4 hours of active labor. The female infant weighed 5 lb 14 oz at birth and had Apgar scores of 8 and 9. The pathology report on the placenta showed no molar degeneration or hydropic changes. The patient was discharged on the second postpartum day, feeling quite well.

The patient was seen in the office 2 weeks postpartum. It was noted that she had returned to live with her husband in their new home. She subsequently reported that thyroid determinations on her baby were normal, and her baby's physician told her that all was well. At 8 weeks postpartum, the patient was maintaining her weight, and her FTI level was normal. She was seen subsequently over the next 2 years and there was no recurrence.

Discussion

The cause of typical nausea and vomiting during pregnancy is not well understood. One theory suggests that rapidly rising levels of steroid hormones and human chorionic gonadotropin (hCG) are involved. The occurrence of vomiting during pregnancy actually decreases the risk of miscarriage, and is the only significant association with any pregnancy outcome that has been found.[3]

The atypical condition of hyperemesis gravidarum occurs in 3.5 pregnancies per 1000. Patients with hyperemesis have been found to have normal levels of hCG, progesterone, and estrogen. Also, the adrenal cortex and anterior pituitary glands of these women function adequately.[4,5] Initial treatment should be symptomatic. The patient's eating pattern should be modified to include frequent small meals, and crackers should be kept at the bedside for eating before standing up. Also behavioral modification such as use of relaxation techniques can be effective. An assessment of family dynamics with careful consideration of anxiety-provoking situations is important early in the management.

Since the doxylamine and pyridoxine combination (Bendectin) has been removed from the market, antinauseant medications for pregnancy are limited. Low doses of pyridoxine have been used for many years, and a recent placebo-controlled trial demonstrated the effectiveness of 25 mg every 8 hours.[6] An over-the-counter medication, Emetrol, sometimes helps, and promethazine (FDA category C) or prochlorperazine (not categorized) can be used for more severe cases, although product information on these latter two drugs state that they should be used only if the potential benefits justify the potential risk to the fetus. Since hyperemesis can cause dehydration, these patients often have at least one severe episode that requires intravenous rehydration. This can often be accomplished on an outpatient basis, especially if started before the patient becomes severely dehydrated, but occasionally hospitalization is required. It is at this point that a careful consideration of the illnesses listed in Table 1 is wise.

Pregnancy also causes natural changes in maternal thyroid function. During the first 12 weeks of pregnancy there is a gradual rise in serum protein-bound iodine, which is dependent on the increase in estrogen levels.[7] There is a small increase in free T_4 and a decrease in TSH during early pregnancy.[2] Although the data are somewhat conflicting, a recent study found that the degree of increase in free T_4 and hCG and decrease in TSH correlated with the severity of morning sickness in normal pregnancies.[2] These data suggest that the thyroid is physically activated in early pregnancy, possibly by hCG or a related substance that may also induce nausea and vomiting.

The incidence of persistent hyperthyroidism, typically Graves' disease, in pregnancy is estimated to be from 0.2% to 0.6%.[8,9] The signs and symptoms of hyperthyroidism include tachycardia, diarrhea, nausea and vomiting, hyperkinesia, fatigue, irritability, and weight loss. Results of laboratory testing of a hyperthyroid patient will show persistent marked elevation of thyroid hormones and suppression of TSH, which must be differentiated from the transient and mild changes of normal pregnancy. Those patients who are euthyroid at delivery generally have good outcomes. There is, however, an increased incidence of morbidity including maternal heart failure and overall perinatal mortality as well as premature labor in those who remain thyrotoxic at delivery.[9] This syndrome may decrease in severity during the second half of pregnancy, but is persistent until treated. Symptoms often worsen in the postpartum period (Table 2).[10]

There is an increased incidence of transient hyperthyroidism in hyperemesis patients.[11] In one study, increased T_4 levels in 73% of 32 patients with hyperemesis were found.[4] These patients have all the hallmarks of autonomous gland function with a blunted TSH response to thyrotropin-releasing hormone, and a relative block of T_4 to triiodothyronine (T_3) conversion.[4] However, untreated, the hyperthyroxinemia associated with hyperemesis normalizes over several weeks (Table 2), but the symptoms of the most severe hyperemesis resolve quickly with propylthiouracil treatment.[12]

Initial treatment decisions are based on laboratory results and clinical assessment that includes occult signs of hyperthyroidism, especially weight loss and cardiac symptoms (including marked tachycardia and cardiac failure). The decision for treatment or watchful waiting is made based on those presenting symptoms that would endanger the health of the mother or fetus. Those requiring treatment can be given propylthiouracil, the drug of choice, 300 to 800 mg/d. The dose is best titrated by the FTI or free T_4 level. The risk of treatment includes impaired neonatal thyroid function (dose related) and maternal bone marrow suppression. Methimazole is not generally used in pregnancy because of its association with clinical scalp defects such as aplasia cutis. Propranolol is generally used only in thyroid storm. Surgical treatment of the enlarged thyroid gland is rarely indicated during pregnancy. Iodine is contraindicated in pregnancy because of possible induction of fetal hypothyroidism and goiter. As in this case, after careful consideration of risks vs benefits of treatment, an informed decision must be made by the patient and her family.

Early in the course of the hyperthyroxinemia, it may not be possible to differentiate transient from persistent disease. Failure of the abnormality to recur after cessation of treatment confirms that it is transient. Some forms of

continued on page 456

continued from page 454

Table 2. Hyperthyroidism in Women of Childbearng Age

Characteristics of Hyperthyroid Symptoms	Graves' Disease	Subacute Granulomatous Thyroiditis	Subacute Lymphocytic Thyroiditis	Hyperemesis-associated Hyperthyroidism
Symptoms prominent in first trimester	+	0	0	+
Symptoms decrease in second half of gestation	+	0	0	+
Recurrence in postpartum period common	+	0	+	0
Spontaneous remission common	0	+	+	+
Subsequent brief hypothyroid period common	0	+	+	0
Tender gland	0	+	0	0
Antithyroid treatment required	Usually	Rarely	Rarely	Sometimes

thyroiditis progress from hyperthyroid states through euthyroidism and ultimately to hypothyroidism, and only continued postpartum surveillance can prove which category of thyroid disease is present. The similarities and differences among various types of hyperthyroidism are summarized in Table 2.

Patients who do not require medical intervention should have their thyroid function followed for at least 1 year. Those requiring treatment need to be followed and treated until a euthyroid nonpregnant state has occurred, either spontaneously or by medication or surgery. Then annual thyroid evaluations should be done indefinitely.

In summary, this case illustrates a relatively uncommon complication of hyperemesis. It is interesting to speculate whether the resolution of weight loss and dehydration in this case would have occurred without propylthiouracil treatment, but the treatment decision was welcomed by the patient and her family, and the good outcome was gratifying.

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