Hyperemesis Gravidarum: Literature Review

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ABSTRACT
Nausea and vomiting commonly occur in pregnant women. Hyperemesis gravidarum is a severe form of nausea and vomiting rarely occurring in pregnancy. Between 0.3% and 2% of all pregnant women suffer from hyperemesis gravidarum. The objective of this paper is to review current literature focusing on the definition, incidence, etiology, prognosis, and treatment of hyperemesis gravidarum. A MEDLINE search of the English literature from 1982 through 2001 utilized the keywords hyperemesis gravidarum, nausea, and pregnancy. Current data pertaining to the epidemiology, etiology, clinical presentation, various treatment modalities, and prognosis are presented. Review of the literature supports that hyperemesis gravidarum is a multifactorial disease. The cause is unknown. Various treatments are recommended although few studies have evaluated effectiveness. A case report of molar pregnancy presenting with hyperemesis gravidarum introduces this literature review.

HYDATIDIFORM MOLE PRESENTING WITH HYPEREMESIS GRAVIDARUM
Case Report
L.L. is a 20-year-old Hmong woman who presented with complaint of excessive vomiting over 1 week. She was a G1P0 female who presented at 19 3/7 weeks gestation based on dating. A urine pregnancy test at the local health care department was positive 10 weeks prior to presentation. She did not have any initial prenatal care.

Although she admitted to first trimester nausea and vomiting, her presenting symptoms were significantly worse. She denied any lightheadedness or weakness but had not been able to tolerate her normal oral intake.

She denied vaginal bleeding or discharge. She did not have any cramping, contractions, headaches, or visual changes. She had not felt fetal movement.

On physical examination she was a thin Hmong woman, alert and in no acute distress. Vital signs were as follows: weight 91 pounds (4 pound weight loss), blood pressure 132/80 mmHg, and pulse 84 bpm. She had signs of dehydration, with dry oral mucosa. Neck examination was normal. Auscultation of heart and lungs was normal. The abdominal examination was unremarkable for tenderness or fullness. The uterus was palpable just above the pubic symphysis.

Fetal heart tones were not audible with doppler. Transabdominal ultrasound was performed looking for evidence of fetal cardiac motion as well as dating secondary to a large discrepancy between size and dates.

The ultrasound was described as a “snowstorm” pattern, a characteristic appearance of molar pregnancy. (Figure 1) Laboratory data was obtained including a B-HCG (Beta-human chorionic gonadotropin) level of 526,483, and a TSH (thyroid stimulating hormone) of less than .06. A diagnosis of molar pregnancy was made.

The patient underwent a successful dilation and evacuation. Pathology reports supported a complete hydatidiform mole. She was monitored for resolution of her elevated B-HCG levels, which did return to normal within 2 months of her treatment. Follow-up TSH levels were also within normal limits. Chemotherapy may have been indicated if the B-HCG levels had reached a plateau or did not fall appropriately. She was instructed to avoid conception for at least 6 to 12 months. The hyperemesis in this patient resolved upon treatment of the hydatidiform mole by dilatation and evacuation.

BACKGROUND
Hydatidiform mole is characterized by proliferation of the trophoblast. Molar pregnancies can be complete (classic) or incomplete (partial). The importance of recognizing molar pregnancy is related to its potential for both gestational trophoblastic disease as well as chorio-
carcinoma. Molar pregnancies occur in approximately 1 in every 1500 pregnancies in the United States, 1 per 1000 pregnancies in the United Kingdom, and are several-fold more common in Asian and Latin American populations.1 The incidence is higher in both teenagers and women older than 35 years. The most common presentation is vaginal bleeding. Both hyperemesis gravidarum and preeclampsia can be presenting features.

Hyperemesis gravidarum is reported to occur in as many as 26% of molar pregnancies.2 Increases in the level of serum B-HCG may be the mechanism of hyperemesis gravidarum in molar pregnancy as molar tissue produces markedly elevated B-HCG levels.

The majority of patients with complete moles are diagnosed before 20 weeks of gestation.1 Cytogenic studies show that complete hydatidiform moles are female and that all 45 chromosomes are paternally derived, likely through dispermy.1 Partial hydatidiform moles are consistent with embryonic and fetal tissue and are usually triploid. Gestational choriocarcinoma may arise from a mole or normal conception. In the United States and Europe, choriocarcinoma is found in 1 in 50,000 pregnancies and the risk of choriocarcinoma after a complete hydatidiform mole is about 3%.1 Microscopic findings include marked edema and enlargement of the villi along with proliferation of the trophoblastic lining. Pathological specimens usually reveal hydric swelling and a typical “grape-like” appearance of the chorionic villi.

If molar pregnancy is suspected, a few tests aid in diagnosis, including quantitative B-HCG, TSH, and ultrasound. Likely results include abnormally elevated B-HCG, low TSH, and a “snowstorm” appearance on ultrasound.

Treatment should include dilation and evacuation of tissue with close tissue analysis for cell ploidy. Close monitoring of B-HCG levels after evacuation is extremely important to ensure that no trophoblastic tissue remains. Follow-up and monitoring along with prevention of pregnancy for 6 to 12 months are recommended.

Physicians should be aware of the possibility of molar pregnancy in all patients with hyperemesis gravidarum and be familiar with the appropriate management to monitor and prevent an often fatal trophoblastic neoplasm. A proper understanding of the proposed mechanism of nausea and vomiting in pregnancy and the knowledge that molar pregnancy can present as hyperemesis gravidarum are crucial to recognizing women at risk.

REVIEW OF CURRENT LITERATURE

Definition

Nausea and vomiting during pregnancy is a common experience affecting 50% to 90% of all women.3-7 Nausea and vomiting are usually limited to the first trimester, but 20% of women have symptoms that continue throughout pregnancy.3 The spectrum of nausea and vomiting in pregnancy can range from mild to severe and can involve persistent and excessive vomiting.

Hyperemesis gravidarum (HG) is the most severe form of nausea and vomiting in pregnancy and is characterized by intractable nausea and vomiting that leads to dehydration, electrolyte and metabolic disturbances, and nutritional deficiency that may require hospitalization.3,7-9 Hyperemesis gravidarum has also been defined as severe vomiting with onset at less than 16 weeks of estimated gestational age that causes 5% weight loss and considerable ketonuria.6,10-13

Incidence

Hyperemesis gravidarum has an incidence varying from 0.3% to 2% of all pregnancies.4-6,8,9,13-15 Although rare, its clinical and social impact can be immense. The socioeconomic impact of the complete spectrum of nausea and vomiting of pregnancy on time lost from either paid employment or household work is substantial. Deuchar noted 8.6 million hours of paid employment and 5.8 million hours of housework are lost each year because of this condition.3

Etiology

The cause of HG is not well understood but appears to have both physiologic and psychologic components. Estrogen, progesterone, adrenal, and pituitary hormones have been proposed as causes but currently there is no conclusive evidence implicating any of them.14
One popular theory is that nausea and vomiting of pregnancy is related to trophoblastic activity and gonadotropin production, possibly secondary to elevated serum human chorionic gonadotropin (hCG) levels. Schoeneck, in the early 1940s, noted that women with nausea and vomiting of pregnancy had higher concentrations of urinary hCG than asymptomatic pregnant women. A relationship to the level of hCG has been postulated because the incidence of hyperemesis gravidarum is higher in multiple gestation pregnancies as well as in molar disease where hCG levels are markedly elevated.

Serotonin has a role in emesis in humans as seen by its physiological effects in the central nervous system, gastrointestinal tract, and other sites. For this reason, serotonin has been implicated as a cause of HG. However, Borgeat et al found that hyperemesis gravidarum was not associated with an increase of serotonin secretion.

Recently, Helicobacter pylori infection has been implicated as a possible cause of HG. In a prospective study, Helicobacter serum IgG concentrations in patients with HG were compared with those in asymptomatic gravidas matched for week of gestation. Positive IgG concentrations were found in 95/105 hyperemesis gravidarum patients compared with 60/129 controls. The authors conclude that infection with H. pylori may cause HG. A question that remains unanswered is whether an increased incidence of nausea and vomiting may lead to the elevated levels of H. pylori found in these pregnant patients.

A psychosomatic etiology has been proposed for HG. Zechnich and Hammer reported, “pregnant women have been shown to have a significantly higher level of anxiety than nonpregnant women and are known to be readily influenced by suggestion and by reassurance.” Other authors have suggested that HG has been linked to stress and emotional tension and is found more commonly among “immature, dependent, hysterical, depressed, or anxious” women, although this has not been studied. Other mechanisms that have been proposed for HG include changes in gastrointestinal tract motility, thyroid dysfunction, hypofunction of the anterior pituitary and adrenal cortex, and abnormalities of the corpus luteum.

Associated Risks
Various risk factors have been theorized to be associated with HG. These include increased body weight, multiple gestations, trophoblastic disease, H in a prior pregnancy, and nulliparity. In contrast, a decreased risk of HG has been associated with advanced maternal age and cigarette smoking. Also, metabolic disorders associated with HG could possibly contribute to an increased risk, including hyperthyroidism, hyperparathyroidism, altered lipid metabolism, and liver dysfunction.

Hyperthyroidism has been found to be associated with HG. In fact, decreased thyroid stimulating hormone (TSH) has been found in patients with HG while levels of free T3 and free T4 have remained within normal limits. It is thought that there may be a condition known as transient hyperthyroidism of hyperemesis gravidarum (THHG), which is a self-limiting hyperthyroidism occurring in the context of HG. Diagnosis of THHG rests on the following four criteria: (1) abnormal thyroid function tests developing in the context of hyperemesis gravidarum, (2) no evidence of pre-pregnancy hyperthyroidism, (3) absence of physical examination findings consistent with hyperthyroidism, and (4) negative thyroid antibody titers.

Another associated risk factor for hyperemesis gravidarum may be a previous diagnosis of an eating disorder. Studies have found that occurrence of HG is greater in women with eating disorders, such as bulimia, than in controls.

Diagnosis
The diagnosis of HG rests in careful observation of the signs and symptoms of pregnant patients with excessive vomiting. Symptoms of HG typically present during the first trimester of pregnancy, usually beginning between the 4th and 10th weeks of gestation, peaking between the 8th and 12th week, and resolving by the 20th week. In only the rare case, symptoms persist into the second half of gestation. Patients usually present with signs of dehydration, ketosis, electrolyte and acid-base disturbances. Weight loss of greater than 5% of body weight may occur.

Work-up must always start with confirmation of a viable, intrauterine pregnancy. When HG is diagnosed, the associated conditions of multiple gestations and hydatidiform mole should be excluded. Molar pregnancies and associated cancers can present with FH G in up to 30% of cases.

The diagnosis of HG should exclude other causes of vomiting, such as gastroenteritis, cholecystitis, acute pancreatitis, gastric outlet obstruction, pyelonephritis, primary hyperthyroidism, primary hyperparathyroidism, or liver dysfunction.

Laboratory tests to help with diagnosis and treatment may include electrolytes, liver function tests, amylase, lipase, thyroid function tests, B-H C G, creati-
nine, blood urea nitrogen, urinalysis, and CBC. Ultrasound examination should be considered to rule out multiple gestation and molar pregnancy. Laboratory findings at presentation of H G may include increased ketones and increased specific gravity in urine with an associated increase in blood urea nitrogen. Also, the hematocrit may be elevated indicating a contracted fluid volume. Electrolytes values that may be associated with H G include decreased sodium, potassium, and chloride, and possibly increased liver function tests.

Prognosis

The effect of nausea and vomiting of pregnancy on maternal and neonatal outcome has been controversial. Several studies suggest that nausea and vomiting of pregnancy is a favorable prognostic sign with a decreased risk of miscarriage, stillbirth, fetal mortality, preterm delivery, low birth weight, perinatal mortality, or growth retardation. Thus the outcome of nausea and vomiting in pregnancy is considered excellent with no adverse fetal outcome.3

Though nausea and vomiting are positively associated with favorable pregnancy outcomes and lower risks of spontaneous abortions, it is unclear if H G is associated with positive pregnancy outcomes.23 Studies on patients suffering from H G show conflicting results, with some reporting adverse effects on neonatal outcome and others reported a rather beneficial association with pregnancy outcome.4 A retrospective analysis reviewed 193 women who developed H G among 13,053 pregnant patients.23 There were no differences in pregnancy outcomes including mean birth weight, mean gestational age, deliveries less than 37 weeks, Apgar scores, perinatal mortality, or incidence of fetal anomalies in patients with and without H G.23 This result was also seen in another study that found that H G does not seem to have an adverse effect on the fetus.3 There was no significant difference in infants’ gestational weight or birth weight and no proportion of stillbirth or spontaneous abortion. In fact, there was found to be a significantly decreased risk of fetal loss among women with nausea and vomiting of pregnancy or H G versus women who do not vomit during pregnancy (4.9 percent instead of 8.6 percent).

Severe and untreated H G was found to be associated with a poor outcome. In one particular study, the hyperemetic pregnant patients were at severe nutritional risk as the mean dietary intake of most nutrients fell below 50% of the recommended dietary allowances and differed significantly from that of controls.12 More than 60% of patients had suboptimal biochemical stores of thiamine, riboflavin, vitamin B6, vitamin A, and retinol-binding protein.

In selected cases where greater than 5% weight loss and long-term malnourishment were of concern, adverse pregnancy outcomes have been reported including low birth weight, antepartum hemorrhage, preterm delivery, and an association with fetal anomalies.6,23 Poor outcome seems to be related to a lack of symptom control and inability to correct electrolyte abnormalities.3

Prolonged vomiting also carries the risk of Wernicke’s encephalopathy secondary to thiamine (vitamin B1) deficiency. Also, hyponatremia and its rapid reversal may cause fatal central pontine myelinosis.24

Treatment

The main treatment of H G is supportive care. Initially, a diagnosis of an intrauterine viable pregnancy must be made, and associated conditions such as multiple gestation and hydatidiform mole must be ruled out.

Various lifestyle and diet changes can help patients tolerate oral intake. Patients should try to avoid unpleasant odors; eat a bland, dry, carbohydrate diet; eat small, frequent meals; and separate solid and liquid foods by at least 2 hours.

Immediate correction of fluid and electrolyte deficits and acid-base disorders must be accomplished.25 If this cannot be done using oral therapy, intravenous fluids may be considered. The patient should initially have nothing by mouth until deficits are corrected. Once this is done, an attempt may be made to restart oral intake using the recommend diet. One study found that treatment with intravenous rehydration led to cessation of vomiting and increase tolerance to oral intake within 24 hours in H G patients.13

In cases that are refractory to intravenous fluid treatment, parenteral nutrition and even feeding tubes have been necessary. Nutritional support is reserved for patients who continue to have intractable symptoms and weight loss despite appropriate therapy. Without nutritional support, the mother and hence the fetus are at significant nutritional risk.3 Hsu and colleagues report successful use of nasogastric tube feeding in the management of H G. As compared with total parenteral nutrition. Tube feeding is less invasive, carries fewer risks, provides nutrition more physiologically, and is easier to use.8

In a retrospective study of 166 patients with hyperemesis, 27(16.3%) were treated with parenteral therapy. Patients treated with parenteral therapy have a marked increase in serious complications, such as venous thrombosis, cellulitis, line sepsis, bacterial endocarditis, and pneumonia, although exact incidence was not re-
ported. These data suggest that consideration should be given to less invasive methods of nutritional support.\textsuperscript{26}

The safety of antiemetic therapy is questionable, especially during the first trimester. Examples of antiemetics used for treatment of HG include doxylamine (Unisom), metoclopramide (Reglan), promethazine (Phenergan), prochlorperazine (Compazine), trimethobenzamide (Tigan), dimenhydrinate (Dramamine), droperidol (Inapsine), diphenhydramine (Benadryl), and ondansetron (Zofran). All the aforementioned medications are FDA class B (presumed safety based on animal studies) or class C (uncertain safety as animal studies show an adverse effect and no human studies have been performed).

Although antiemetics are frequently used, there have been several randomized studies for their use in the treatment of HG. Ylikorkala et al found no benefit of intramuscular adrenocorticotropic hormone with respect to placebo.\textsuperscript{27} Sullivan et al found no benefit of ondansetron (Zofran) compared with promethazine (Phenergan).\textsuperscript{27-29} In a study by Nageotte et al, results showed that patients treated with a droperidol-diphenhydramine protocol compared with other antiemetics had significantly shorter hospitalizations and fewer readmissions.\textsuperscript{9}

Oral corticosteroid use has been studied in the treatment of HG and may be beneficial.\textsuperscript{3} The mechanism by which corticosteroids suppress the severe vomiting is probably a direct effect on the vomiting center in the brain.\textsuperscript{30} A study by Carlan reported 25 patients who were randomized into two groups, one that received methylprednisolone and one that received placebo. Results showed that a short course of methylprednisolone in patients with HG decreased the likelihood of a recurrence of vomiting.\textsuperscript{31} A nother randomized, double-blind controlled study by Safari et al comparing promethazine showed oral methylprednisolone to be more effective.\textsuperscript{27}

Vitamin B6 has been postulated to have a beneficial effect on HG treatment. Unfortunately, studies have not shown a proven medical benefit.\textsuperscript{3} Ginger has also been used in HG treatment. A double-blind, randomized, crossover trial by Fischer-Ramussen et al reported that daily doses of 1 g of ginger extract during a 4-day period was better than placebo in reducing or eliminating symptoms in women with HG.\textsuperscript{27,28} Unfortunately, no other follow-up studies have been done and safety has not yet been established.

An alternative treatment that holds little if no risk to the mother and fetus involves acupuncture to help avoid nausea. A review of 12 randomized placebo-controlled studies found that P6 acupuncture point stimulation (located on the anterior forearm, 3 fingerbreadths proximal to the wrist) seems to be an effective antiemetic technique. But there did not appear to be any apparent medical benefit from the use of P6 acupuncture in the treatment of nausea and vomiting of pregnancy.\textsuperscript{32}

Due to a proposed psychosomatic component of hyperemesis, an attempt to find benefit from brief, non-intensive psychotherapy was performed by Zechnich and Hammer.\textsuperscript{20} The case report involved a patient with HG who was treated with psychotherapy. The authors suggest that hypnosis and brief psychotherapy are effective in HG treatment.

**Prevention**

Prevention of hyperemesis has been studied using oral multivitamin therapy. A randomized double-blind controlled trial of peri-conceptional multivitamin supplementation found a significant reduction in the occurrence of HG, 3% in the supplemented group versus 6.6% in the unsupplemented group.\textsuperscript{33} There was a significant decrease in the rate of moderate nausea and vomiting.

**CONCLUSION**

Hyperemesis gravidarum occurs rarely in the spectrum of nausea and vomiting of pregnancy but can have substantial effects on the mother and fetus if left untreated. After confirming a viable pregnancy and ruling out hyperthyroidism, initial management should be conservative, including reassurance of the transient nature of the symptoms and the good prognosis, in addition to dietary modifications. Pharmacological therapy is reserved for patients with persistent symptoms and is appropriate after discussion of the risks and benefits with consideration of informed consent. Alternative treatments including psychotherapy and other non-pharmacological modalities are of less proven effect but are potentially safe, thus providing additional therapeutic options. In refractory cases, nutritional supplementation becomes life-saving for both the mother and the fetus.\textsuperscript{3} Timely diagnosis and appropriate management of HG will reduce health risks and complications in both the mother and the fetus.

**REFERENCES**

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