CONTINUING MEDICAL EDUCATION

Understanding Hyperemesis Gravidarum

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Summary

Nausea and vomiting are common in early pregnancy affecting 70-80 percent of pregnant mothers. In a majority of women vomiting begins between 4-7 weeks of pregnancy. Nausea and vomiting are usually mild and self-limiting, however some of the mothers have a more profound course which lead to hyperemesis gravidarum. Careful clinical evaluation is necessary to exclude underlying medical illnesses or non pregnancy related causes of severe vomiting. Hyperemesis gravidarum poses health risk to both mother and baby, therefore prompt treatment should be initiated without delay. Non pharmacotherapy such as dietary modification and emotional support are useful. Pharmacotherapy with antiemetics, pyridoxine, methylprednisolone are effective and relatively safe. Severe hyperemesis with dehydration and electrolyte imbalance may need hospitalisation for electrolyte and fluid replacement.

Key Words: Hyperemesis gravidarum, Vomiting, Pregnancy

Introduction

Nausea and vomiting are very common symptoms in early pregnancy. This condition is commonly known as morning sickness, affecting up to 70-80 percent of pregnant mothers[1,2]. The usual onset of nausea and vomiting is around 4th to 7th week from the last menstrual period, peaking during 8th to 12th week. Majority of them will resolves by the 20th week of gestation[1,3].

Hyperemesis gravidarum is a severe form of nausea and vomiting which affects one in 200 pregnant mothers[3,4]. It is also the most common indication for hospital admission during early pregnancy[4]. This disorder has a higher prevalence among the low educational level, lower income group and those in part-time employment[2]. The common clinical features associated with hyperemesis gravidarum are persistent vomiting, dehydration, electrolyte imbalance, ketonuria, and weight loss of more than 5% of the body weight. The incidence of hyperemesis gravidarum increases with multiple gestation, molar pregnancy, trisomy gestation and hydrop fetalis[1,2]. If a mother presents with nausea and vomiting after 9th week of gestation or experiences vomiting throughout the pregnancy, other medical conditions should be excluded. (Table I)

Pathogenesis

The exact pathogenesis of hyperemesis gravidarum remains unknown, but a number of hypotheses have been postulated. Many studies have suggested that hormonal changes in pregnancy as a cause of hyperemesis gravidarum. Women with molar pregnancy and trisomy gestation are associated with elevated human chorionic gonadatropin (HCG) levels. These levels peak at about 8 weeks gestation with increasing symptoms of nausea and vomiting. However, HCG levels do not correlate well with the severity of hyperemesis. Elevated levels of circulating and urinary estrogen levels may be associated,

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although some studies indicate poor relationship between estrogen levels and hyperemesis gravidarum hence the role of estrogen in this condition remains unclear. Serum progesterone levels also peak in first trimester of pregnancy; progesterone alone or in combination with estrogen may cause gastric dysrhythmias by decreasing the gastric smooth muscles contractility. Serum prostaglandin E2 (PGE2) levels were found to be higher during symptomatic period of hyperemesis gravidarum. Placental PGE2 synthesis is stimulated by HCG, the latter usually peaking between 9th to 12 weeks of gestations, which may explain the symptoms of hyperemesis gravidarum[1,2]. HCG has a thyrotropic action and hyperemesis gravidarum is more common in pregnancies with high HCG and exhibiting transient self-limiting hyperthyroidism. Anti thyroid drugs in this situation is usually unnecessary [11].

Recent studies suggested that chronic *Helicobacter pylori* infection might play a role in hyperemesis. *H. pylori* seropositivity was present in up to 60% of pregnant mothers compared with 50% in the general population. However, the seropositivity did not correlate with gastrointestinal symptoms[1,2]. *H. pylori* infection has been found in cases of persistent vomiting in pregnancy not responding to supportive treatment. However, endoscopic diagnosis should be performed after initial non-invasive test are negative [12].

Psychological factors associated with hyperemesis gravidarum is by far the oldest theory. Some researchers also postulated that psychological factors might be responsible for hyperemesis gravidarum. In one study, it was suggested that women with hyperemesis have hysteria, excessive dependence on their mothers and infantile personalities[1,5]. Psychoanalytic theories describe hyperemesis as a conversion or somatization disorder or inability of the mother to cope with excessive life stress. However these findings are not conclusive due to a lack of robust data to support these associations[5].

Persistent nausea and vomiting has been associated with food substances. Hyperemesis gravidarum is more common in populations where meat, fish, poultry and eggs are commonly consumed; in contrast nausea and vomiting is less common in cultures where plant foods such as corn are consumed. Olfactory sensitivity may play a role in pathogenesis of hyperemesis gravidarum[5].

Serotonin (5-hydroxytryptamine) receptors which are found in the central nervous system and gut may play a role in vomiting. Drugs like ondansetron, a 5-HT receptor blocker are commonly used against vomiting induced by chemotherapy. However, hyperemesis gravidarum has not been associated with increased serotonin secretion disputing a widespread use of 5-HT receptor blockers in hyperemesis gravidarum[13]. Therefore, the pathogenesis of hyperemesis gravidarum seems to be multifactorial. Women with vomiting in pregnancy are also found more commonly have history of oral contraceptive sickness, motion sickness, migraine, a positive family history of hyperemesis and carrying a female fetus.

Complications of Hyperemesis Gravidarum

Maternal Complications

Persistent severe vomiting of mother can lead to dehydration, electrolyte imbalance and ketosis. More serious conditions include esophageal tear or rupture, splenic avulsion, pneumothorax and peripheral neuropathy due to B6 and B12 deficiency [5,6]. Wernicke's encephalopathy has been associated with treatment of hyperemesis gravidarum with intravenous dextrose replacement without thiamine supplement. Central pontine myelinolysis associated with Wernicke's encephalopathy has been reported[5]. The incidence of maternal death due to hyperemesis gravidarum is rare. In Malaysia two cases of maternal death due to Hyperemesis gravidarum were reported between 1991-2000[6].

Fetal complications

Uncomplicated nausea and vomiting have been noted to have more favourable outcome of pregnancy than those without vomiting, these includes less cases of miscarriages, preterm deliveries and stillbirths. However uncontrolled hyperemesis gravidarum has been associated with fetal growth retardation and fetal death. In one report it was stated that up to 32% of infants whose mothers experienced weight loss due to hyperemesis were less than 10th percentile for the gestational weight at birth[1,5]. A low risk of central nervous system and skeletal malformations was noted in children born of mothers with hyperemesis gravidarum[2]. Hyperemesis gravidarum may also be a risk factor for testicular cancer in the male offspring [2].

Clinical Evaluation

History

Hyperemesis gravidarum more commonly occurs in primigravida. Most of these patients present at the maternal antenatal clinic or emergency department depending on the severity of the symptoms. When a multipara presents with hyperemesis gravidarum, they

may have had previous pregnancies complicated with a similar problem.

In history taking, the attending doctor must document clearly the period of amenorrhoea, symptoms of pregnancy, the time of onset of nausea and vomiting and history of any co-morbid disease. History of fever, chills and rigors, headache and visual disturbance are not seen in hyperemesis gravidarum. If these symptoms present, other acute medical or surgical conditions should be excluded.

Physical examination
The general condition of the mother including blood pressure, pulse, and hydrational status must be examined. Features suggestive of dehydration such as dry lips and tongue, decreased skin turgor and reduced urine output warrant admission to hospital and resuscitation. Besides the usual signs of pregnancy, one must examine the thyroid to look for goitre and to elicit clinical signs of thyrotoxicosis. Abdominal examination to look for uterine size is important. An uterus larger than gestational age and absence of fetal parts may suggest a molar pregnancy. The pregnancy is best confirmed by ultrasonography. Acute pyelonephritis and acute surgical condition such as appendicitis or renal colic must be excluded.

Investigations
The most important immediate blood test is serum urea and electrolytes. Hypokalemia and hyponatremia are well known complications in severe hyperemesis gravidarum, which may lead to metabolic alkalosis. Urine test for specific gravity and ketone is done daily till negative for at least for 2 days[6]. Daily weight measurement and input-output records should be maintained. Other baseline investigations for pregnancy if have not been done must be included such as haemoglobin level, ABO grouping and Rhesus, VDRL and HIV serology test.

In cases where the diagnosis is unclear or symptoms persists for more than three days despite treatment, other blood tests may be helpful. These include thyroid function test, liver function test, serum amylase and a complete renal function test[5,6].

Treatment
The management of hyperemesis gravidarum depends on the severity of the symptoms. These range from explanation and emotional support, dietary modification, use of oral antiemetics to more aggressive treatment to correct fluid and electrolyte imbalances in the hospital.

Non pharmacological management
Mothers should be instructed to have frequent but small meals with high carbohydrates but low fat content. Food with offensive odours, which can induce nausea, must be avoided. Citrus drinks are better tolerated than plain water and can also be used for rinsing mouths[5,6]. Family members must be informed that the pregnant mother suffers from hyperemesis gravidarum may need to alter her meal times and dietary changes.

Ginger has been used by many cultures for the treatment of nausea and vomiting and it has been considered an effective anti-emetic. One European study demonstrated that ginger powder 1g per day was more effective as compared to placebo in reducing the symptoms of nausea and vomiting. However, it is a potent thromboxane synthethase inhibitor and has been reported to have an effect on sex steroid differentiation in the fetus. Until larger studies are conducted, its routine use is to be restricted[14,15].

A large number of patients will recover once they are removed from home environment, temporary leaving the home environment may help. Patient must be encouraged to rest when symptomatic. It is important that these mothers receive appropriate support from family members and nursing staff. Brushing teeth later rather than early morning may help in some patients although the exact reason remains unknown[6].

There are several studies have suggested that acupressure as a form of treatment. The most famous location for acupressure is the Pericardium 6 or Neiguan point. This point is situated at three fingerbreadths above the wrist on the volar surface. Significant reduction in symptoms of nausea and vomiting has been shown with pressure over this point[1,2,5,8].

Pharmacotherapy
In the initial period of severe vomiting anti-emetics should be administered by the parenteral route together with intravenous fluids. Keeping the gut empty for the first 24 hours is usually recommended in hyperemesis gravidarum. Later when vomiting stops and patient can tolerate orally, oral antiemetic can be prescribed.

Common antiemetics such as the Phenothiazine group of drugs (e.g. prochloperazine, promethazine and chlorpromazine) have been proven to reduce nausea and vomiting as compared to placebo[5,10]. Other antiemetics such as metochlorpromide improves gastric emptying and corrects gastric dysrhymias and odansetron have been used but limited safety data is available[5,6,8]. Antihistamines and anticholinergics such as meclizine and diphenhydramine have been used to control nausea and vomiting in pregnancy. These drugs are also more effective than placebo [4,5,6,10]. All these drugs cause sedation, therefore patients must be counselled to avoid driving and handling sharp objects.

Use of oral vitamin pyridoxine (B6) in a dosage of 25mg every eight hours was found to be effective in controlling nausea and vomiting. Randomised controlled trial has proven its efficacy without teratogenic effects [5,6,8,10]. Oral methyprednisolone 16 mg for three days followed by tapering over two weeks has been found to significantly reduce the number of readmissions for persistent and recurrent vomiting exceeding four weeks. It is generally considered safe in pregnancy but there is recent meta-analysis showing marginal increased risk of major malformation and 3-fold risk of oral cleft if steroids are used in first trimester [4,5,9,10]. The risk and benefits of steroid therapy must be clearly explained prior to initiating treatment.

Intravenous Fluids therapy

Persistent vomiting with ketonuria and dehydration warrants admission to hospital and intravenous fluid therapy. Patient should be kept nil orally for the first 24 hours. Normal saline and Hartmans' solution is the mainstay of intravenous fluid therapy. If Dextrose solution is used, it is advisable to give thiamine (B1) first to prevent Wernicke's encephalopathy [5]. Fluid therapy should be tailored to patient's hydrational status and serum electrolytes results. Potassium supplement is needed if patient has hypokalemia and the fluid regime is only normal saline [4,5].

Rarely, in severe cases where hyperemesis gravidarum leads to weight loss and malnutrition, parenteral nutrition is indicated. Consultation with gastroenterologist and perinatologist experienced in parenteral nutrition is necessary in these cases. Parenteral nutrition carry higher risk of complications such as infection, sepsis, pneumothorax and fatty infiltration of the placenta[1,5].

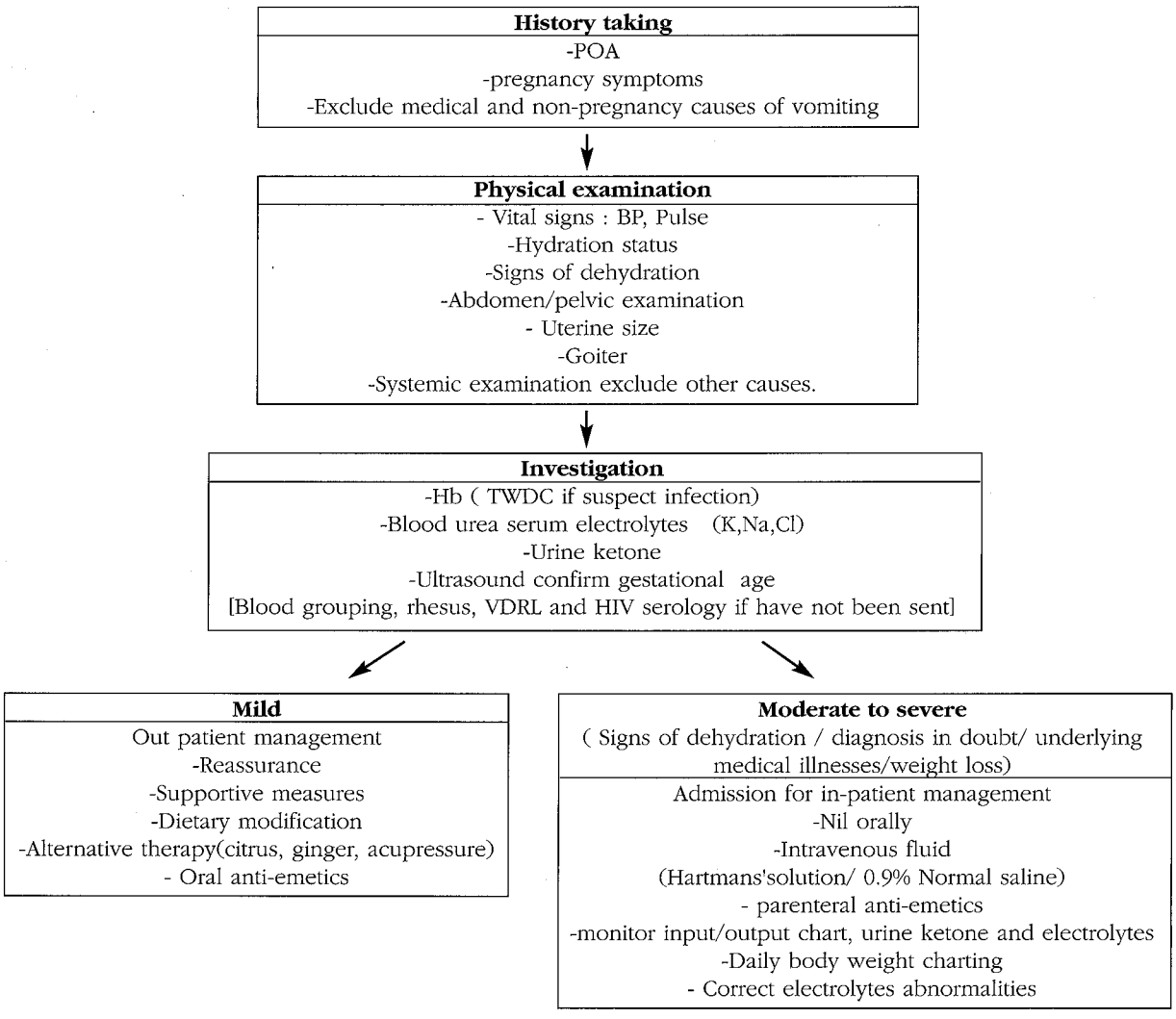
Table I: Differential diagnosis of prolonged or persistent vomiting in pregnancy

Condition	Disease
Infections	Acute pyelonephritis
	Acute gastroenteritis
	Viral fever
	Encephalitis
	Viral Hepatitis
	Malaria
Metabolic disorders	Diabetic ketoacidosis
	Hyperthyroidism
	Hyperparathyroidism
	Hypercalcemia
	Uraemia
	Addison's disease
Gastrointestinal disorders	Pancreatitis
	Appendicitis
	Peptic ulcer disease
	Billiary tract disease
Neurological disorders	Benign intracranial hypertension
	Tumour
	Severe migraine
	Vestibular disease
Others	Drugs induced

Table II: Common pharmacotherapy for hyperemesis gravidarum and the recommended dosage

Drugs	Dosage
Chlorpromazine	10-25 mg 8-12 hourly
Prochlorperazine	5-10 mg 6-8 hourly
Promethazine	12-25mg 6-8 hourly
MeclizineHcl 25mg +pyridoxine Hcl 50mg	1-2 tabs 8-12 hourly
Diphenhydramine	25mg 8 hourly
Ondansetron	8mg 8-12 hourly
Metoclopramide	5-10mg 8 hourly
Pyridoxine	25-50mg 8 hourly
methylprednisolone	16mg 8 hourly then tapering in 2 weeks

Figure 1: Summary of plan of management in hyperemesis gravidarum



Conclusion

Hyperemesis gravidarum is a multifactorial neurohormornal disorder of early pregnancy. It can lead to potential complications to both mother and fetus if it is not controlled. Important acute medical and surgical conditions, which present with vomiting must be excluded before making the diagnosis of hyperemesis gravidarum. A complete history, physical examination and investigations are important to establish the diagnosis. Prompt treatment is essential to prevent complications. Pharmacotherapy complement with non-pharmacological treatment successfully controlling most symptoms of hyperemesis gravidarum.

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Multiple Choice Questions (MCQs)
T= True F=False

1. Which of the following are recognised risk factors for hyperemesis gravidarum?
A. History of hyperemesis in previous pregnancy.
B. Positive family history.
C. Hypothyroidism.
D. Gestational trophoblastic disease.
E. Twin pregnancy.

2. Clinical features of hyperemesis gravidarum include:
A. Throbbing headache.
B. Fever with chills and rigors.
C. Ketonuria.
D. Metabolic alkalosis.
E. Blurring of vision.

3. The following are useful non pharmacotherapy management of hyperemesis gravidarum.
A. Frequent small meals intake.
B. High fat diet.
C. Citrus drinks.
D. Ginger root powder.
E. Acupressure.

4. The following drugs are effective in the treatment of hyperemesis gravidarum.
A. Metoclopramide
B. Pyridoxine.
C. Cetirizine.
D. Prochlorperazine.
E. Potassium chloride.

5. Differential diagnoses of persistent vomiting in pregnancy during second trimester include:
A. Acute pyelonephritis.
B. Peptic ulcer disease.
C. Viral infection.
D. Gastroenteritis.
E. Benign intracranial hypertension.