Approach to Hyperemesis gravidarum

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ABSTRACT:
Nausea and vomiting commonly known as morning sickness in pregnancy is extremely common. During pregnancy normal nausea and vomiting may be evolutionary protective mechanism as it may protect the pregnant woman and her embryo from harmful substances in food such as pathogenic microorganisms in meat products and toxins in plants, these effects are maximal during embryogenesis the most vulnerable period of pregnancy. Studies suggest that women who had nausea and vomiting were less likely to have miscarriages and stillbirth.

Hyperemesis gravidarum is rare but the most severe form of nausea and vomiting in pregnancy that may necessitate hospitalization. It is characterized by persistent nausea and vomiting associated with ketosis and weight loss (>5%) which may lead to volume depletion, electrolyte and acid base imbalances, nutritional deficiencies and even death.

KEYWORDS: pregnancy, Hyperemesis gravidarum, nausea and vomiting

INTRODUCTION:

Hyperemesis gravidarum is rare but the most severe form of nausea and vomiting in pregnancy. It accounts for 0.5% to 2% among pregnant women. It is extreme, persistent nausea vomiting during pregnancy which can lead to dehydration, weight loss and electrolyte imbalance (ketosis). This condition may lead to volume depletion, electrolyte and acid-base imbalances, nutritional deficiencies and even death.

Studies suggest that nausea and vomiting occur in 50-90% of pregnancies. The nausea and vomiting associated with pregnancy...
usually begins by 9-10 weeks of gestation, peaks at 11-13 weeks, and resolves in most cases by 12-14 week. In 1-10% of pregnancies, symptoms may continue beyond 20-22 weeks.

No specific line exists that separates Hyperemesis gravidarum from nausea and vomiting in pregnancy. Affected individuals can progress from mild or moderate nausea and vomiting to Hyperemesis gravidarum. While the cause of HG is likely multifactorial, currently, the most evidence exists for the placenta and appetite hormone GDF15 as playing an important role in the etiology of HG.

The International Statistical Classification of Disease and Related Health Problems, Tenth Revision, defines Hyperemesis gravidarum (HG) as persistent and excessive vomiting starting before the end of the 22nd week of gestation and further subdivides the condition into mild and severe, with severe being associated with metabolic disturbances such as carbohydrate depletion, dehydration, or electrolyte imbalance.

**ETIOLOGY:**

HG is most likely a multifactorial condition and has been associated with many risk factors. Genetic evidence also supports a role for the hormone receptors GFRAL and PGR, and for IGFBP7. Some studies suggest hyperthyroid disorder, psychiatric illness, previous molar disease, gastrointestinal disorders, pregestational diabetes and asthma increases risk of Hyperemesis gravidarum, whereas maternal smoking and maternal age older than 30 years decreases the risk. One observational study demonstrated that women with HG were more likely to have higher levels of pregnancy-associated plasma protein A (PAPP-A) and free human chorionic gonadotropin (hCG) in the first trimester. Infection with Helicobacter pylori may play a role in the development of HG in some women.

In some studies, woman from low to middle socioeconomic status, woman with lower levels of education, woman with previous pregnancies with nausea and vomiting, woman with first pregnancy and woman with previous intolerance to oral contraceptives are more commonly experience nausea and vomiting during pregnancy. Hyperemesis gravidarum is also more common with multiple gestation pregnancies.

Trophoblastic disease, greater body weight (obesity), nulliparity, previous pregnancy with Hyperemesis gravidarum are also risk factors of Hyperemesis gravidarum. In addition, rare mutations in genes coding for the serotonin receptor, thyroid-stimulating hormone receptor, and the ryanodine receptor 2 in families with HG suggest these receptors may also play a role in a subset of patients with familial HG.

**PATHOPHYSIOLOGY:**

There are certain theories proving the effects of Hyperemesis gravidarum rather than the causality.

In first trimester hCG levels are comparatively high, hCG physiologically stimulates thyroid gland via TSH receptors.
It is often seen that women with Hyperemesis gravidarum have higher levels of hCG. The higher levels of hCG leads to transient hyperthyroidism. Studies suggest that in approximately 50-70% TSH is transiently suppressed and the free thyroxin is elevated without clinical signs of hyperthyroidism. In some women free T4 levels are found with elevated hCG levels, and the severity of nausea appears to be related to the degree of thyroid stimulation.

The presence of morning sickness is associated with gastric dysrhythmias. Gastric dysrhythmia is caused by elevated estrogen or progesterone levels, thyroid disorders, vagal and sympathetic tone and vasopressin secretion in response to intravascular volume perturbation, which are seen in early pregnancy.

In approximately 3% of pregnancies abnormal liver function are found without any pathology. In most of the cases of Hyperemesis gravidarum, there is serum transaminase elevation. In association with Hyperemesis gravidarum, liver disease is mainly caused by impaired mitochondrial fatty acid oxidation. Studies suggest that starvation leading to peripheral lipolysis and increased load of fatty acids in maternal fetal circulation leading to defective mitochondrial fatty acid oxidation causing Hyperemesis gravidarum and liver injury.

Some studies suggest higher levels of triglycerides, total cholesterol, and phospholipids in women with Hyperemesis gravidarum, along with abnormal hepatic functions.

Low carbohydrate reserve, deficiency of vitamin B6, B1 and protein may be the effects rather than the cause.

Helicobacter pylori has long been implicated in the pathogenesis of Hyperemesis gravidarum. Studies suggest that h. pylori is an independent risk factor for vomiting in pregnancy and future studies on eradication of h. pylori in pregnant women may be beneficial.

Changes in multiple organs:

As stated, liver enzymes are elevated, some centrilobular fatty changes is there. Renal functions are usually normal with some occasional fatty changes, which might be caused by acidosis. In heart there is subendocardial hemorrhage. There are small hemorrhages in the hypothalamic region giving the manifestation of Werneck’s encephalopathy, this may be related to vitamin B1 deficiency.

Recurrent emesis and nausea lead to inadequate intake of food resulting in glycogen depletion. Low carbohydrate leads to incomplete oxidation of fat and accumulation of ketone bodies in blood. Starvation leads to acidosis, loss of hydrochloric acid leads to alkalosis and hypokalemia, plasma sodium potassium and chlorides falls drastically due to heavy loss of water and salts in vomitus.

The biochemical changes not limit to fall in sodium, potassium and chlorides but rise in blood urea and uric acid is seen because of ketosis. Further patient suffers from hypoglycemia, hypoproteinemia and hypovitaminosis.
PREVALENCE:

Up to 90% of women experience nausea and vomiting during pregnancy. Approximately 25-30% of women experience only nausea, while vomiting may be seen in 28-52% of all pregnancies. The incidence of Hyperemesis gravidarum ranges from 0.2-5% depends on different diagnostic criteria. Hyperemesis gravidarum is more common among young, primiparous, non-smoker. Hyperemesis gravidarum is more prevalent in western industrialized nations, more in urban than rural areas, less common in African and some Asian populations. The risk of Hyperemesis gravidarum decreases with advanced maternal age.

MANAGEMENT:

Hyperemesis gravidarum is a self-limiting disorder. The treatment should be started as early as diagnosis sets in; initial treatment should begin with non-pharmacologic interventions.

On outpatient basis, continuous monitoring of weight and urinary ketones is necessary.

In some patients even decreasing activity and increasing rest improves nausea and vomiting in pregnancy. In case of severe fluid loss and dehydration, in patient care is necessary, to correct dehydration and electrolyte and metabolic imbalance.

In more severe cases of Hyperemesis gravidarum if maternal survival is threatened of if it is causing severe physical and psychological burden, termination of pregnancy is indicated.

The non-pharmacologic treatment consists of switching prenatal vitamins to folic acid supplements only. Using ginger supplementation orally four times a day helps in reducing nausea and vomiting. In some parts of the world acupressure wrist bands are also found to be effective.

Pharmacologic treatment consists of oral and parenteral therapy based on symptoms, severity of dehydration and response to therapy.

First line of oral therapy – this includes combination of vitamin B6 (Pyridoxin) and doxylamine. The American college of obstetrics and gynecology has classified pyridoxine and doxylamine therapy into three regiments:

1st 10 to 25 mg of pyridoxine and 12.5 to 25 mg of doxylamine three to four times a day.

2nd 10 mg of pyridoxine and 10 mg of doxylamine four times a day.

3rd 20 mg of pyridoxine and 20 mg of doxylamine two times a day.

Second line oral therapy – it consists of antihistaminic and dopamine antagonists.

- Dimenhydrinate – 25 to 50 mg four to six hourly.
- Diphenhydramine – 25 to 50 mg four to six hourly.
- Prochlorperazine – 5 mg twelve hourly.
- Promethazine – 12.5 to 25 mg four to six hourly.
- Triflupromazine – 10 mg 8-12 hourly intramuscular injection.
- Trifluoperazine – 1 mg 12 hourly intramuscular injection.
- Metoclopramide – it stimulates gastric and intestinal motility without stimulating the secretions

Nutrition supplementation including vitamin B1, vitamin B6, vitamin C, and vitamin B12.

**Hospitalization** – if the patient continues to be symptomatic and no response to oral therapy is achieved immediate hospital admission and intravenous fluid is recommended.

The in-patient care consists of –
- Maintenance of hydration
- Control vomiting
- Correct metabolic disturbance
- Correct fluid and electrolyte imbalance
- Prevent serious complications

**Care of pregnancy**

There needs to stop oral fluids in recurrent vomiting, and start intravenous fluids with 3 liters per day, divided into two parts, the first half is 5% dextrose and second half is ringer lactate. As per amount of fluid loss and urine output in 24 hours, extra amount of crystalloids is to be added. This regiments equals dehydration, ketoacidosis, water and electrolyte imbalance. Along with this, serum electrolytes should be estimated and corrected accordingly.

Corticosteroids like hydrocortisone and methylprednisolone can also be used in case with hypotension and intractable vomiting.

**COMPLICATIONS:**
- Maternal complications including esophageal rupture or perforation
- Pneumothorax and pneumomediastinum
- Wernicke encephalopathy or blindness
- Hepatic disease
- Seizures, coma or death.
- Other complications include renal failure, pancreatitis, dep vein thrombosis, pulmonary embolism, central pontine myelinolysis, rhabdomyolysis, vitamin K deficiency and coagulopathy, and septic avulsion.
- Complications associated with central hyperalimentation include sepsis, fungemia, tamponade, local infection, venous thrombosis, fatty infiltration of placenta, and transaminitis.
- Fetus usually remains unaffected once the problem is resolved. Fetal risks may be due to low birth weight.

**CONCLUSION:**

*Hyperemesis gravidarum* is rare but one of life-threatening disorder of pregnancy depends on degree of severity, and time of diagnosis. *Hyperemesis gravidarum* is typically the cause of psychologic stress also. This also leads to sleep disturbance, hyper olfaction, dysgeusia, decreased gustatory discernment, depression, anxiety, irritability, mood changes, decreased concentration. It is a self-limiting disorder in most of the cases when diagnosed early and with proper care and right education. But in severe cases even in-patient care with fluid replacement and electrolyte correction is necessary. Some other conditions need to be
excluded before jumping directly to *Hyperemesis gravidarum*, like drug toxicity, gastroparesis, migraines, ovarian torsion, pseudotumor cerebri, psychological disorder, vestibular lesions, appendicitis, acute pancreatitis, biliary disease, diabetic ketoacidosis, hepatitis. Complete lab investigations and ultrasonography is to be done for confirmation of diagnosis. Early diagnosis, proper care, timely use of pharmacologic therapy is the necessary way to reduce risk of life-threatening complications to both mother and fetus.

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