Review Article
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Hyperemesis gravidarum–a serious issue during pregnancy: in-depth clinical review and treatment modalities

Abstract

Hyperemesis gravidarum[1] is the medical condition of extreme, persistent nausea and vomiting during pregnancy. It is a serious complication of pregnancy that is characterized by intractable nausea, vomiting and dehydration. It is estimated to affect 0.5–2.0% of pregnant women.[2–4] Malnutrition and other serious complications, such as fluid or electrolyte imbalances may also result from this issue. This serious condition, if left unchecked, can lead to dehydration, weight loss, and electrolyte imbalances. Hyperemesis gravidarum differs from Morning Sickness.[5] Morning sickness is characterized by nausea, with or without vomiting. Morning sickness is most common during the first trimester, sometimes beginning as early as two weeks after conception and affects up to 90% of women.[6] Often, morning sickness is the first indication to a woman that she is pregnant. The cause of this nausea and vomiting during pregnancy, which usually subsides after the first trimester, is believed to be related to the rapidly rising blood level of a hormone called Human Chorionic Gonadotropin (HCG). HCG is released by the placenta.

Keywords: hyperemesis gravidarum, morning sickness, human chorionic gonadotropin (HCG), β-human chorionic gonadotropin (β-hCG), phocomelia, thalidomide, depression, anemia, hyponatremia, wernicke's encephalopathy, kidney failure, central pontine myelinolysis, coagulopathy, atrophy, mallory-weiss tears, hypoglycemia, jaundice, malnutrition, pneumomediastinum, rhabdomyolysis, deconditioning, DVT (deep vein thrombosis), pulmonary embolism, splenic avulsion, vasospasms of cerebral arteries, fetal growth retardation, hyperolfaction, ptyalism (hypersalivation)

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Abbreviations: HCG, human chorionic gonadotropin; B-hCG, B-human chorionic gonadotropin; DVT, deep vein thrombosis; TMP-SMX, trimethoprim and sulfamethoxazole; EBV, epstein barr virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase, PT, prothrombin time; CBC, complete blood cell; AFLP, acute fatty liver of pregnancy; DKA, diabetic ketoacidosis; GTD, gestational trophoblastic disease; BUN, blood urea nitrogen; NS, normal saline; OT, over-the-counter

Causes of hyperemesis gravidarum

There are numerous theories regarding the cause of Hyperemesis gravidarum, but the cause(s) remains controversial. It is thought that Hyperemesis gravidarum is due to a combination of factors which may vary between women and include: genetics,[2] obesity (a major factor), body chemistry and overall health.[7] One other factor is an adverse reaction to the hormonal changes of pregnancy, in particular, elevated levels of β-Human Chorionic Gonadotropin (β-hCG).[8,9] This theory would also explain why Hyperemesis gravidarum is most frequently encountered in the first trimester (often around 8–12weeks of gestation), as hCG levels are highest at that time and decline afterward. Another postulated cause of Hyperemesis gravidarum is an increase in the maternal levels of estrogens (which can have the effect of decreasing intestinal motility and gastric emptying time leading to nausea and/or vomiting).[1] However, Hyperemesis gravidarum is considered a rare complication of pregnancy. Unlike morning sickness, Hyperemesis gravidarum can cause severe weight loss from 10% upwards to 40% of one's pre-pregnancy weight. It can also be life-threatening if not treated due to severe electrolyte imbalances that occur from severe, continuous vomiting. Also, unlike morning sickness, Hyperemesis gravidarum can last throughout the pregnancy and usually comes with constant vomiting, but always with constant nausea. A small percentage of patients with Hyperemesis gravidarum rarely vomit, but the nausea still causes most (if not all) of the same issues that Hyperemesis gravidarum with vomiting does.

Signs and symptoms

When Hyperemesis gravidarum is severe or inadequately treated, regardless of the reason, it may result in the following symptoms:

i. Loss of 10 to 40% or more of pre-pregnancy body weight
ii. Dehydration, causing ketosis[10] and constipation
iii. Nutritional disorders such as Vitamin B_1 (Thiamine) deficiency, Vitamin B_6 (Pyridoxine) deficiency or Vitamin B_{12} (Cobalamin) deficiency
iv. Metabolic imbalances such as metabolic ketoacidosis[10] or thyrotoxicosis[11]
v. Physical and emotional stress of pregnancy on the body
vi. Difficulty with activities of daily living
vii. Symptoms can be aggravated by hunger, fatigue, prenatal vitamins (especially those containing iron) and diet.[12]

viii. Many sufferers of Hyperemesis gravidarum are extremely sensitive to odors in their environment; certain smells may exacerbate symptoms which is known as Hyperolfaction. Ptyalism or hypersalivation, is another symptom experienced by some women suffering from Hyperemesis gravidarum.

ix. Hyperemesis gravidarum tends to occur in the first trimester of pregnancy and lasts significantly longer than morning sickness. While most women will experience near-complete relief of morning sickness symptoms near the beginning of their second trimester. Some sufferers of Hyperemesis gravidarum will experience severe symptoms until they give birth to their baby, and sometimes even after giving birth.[13]

x. Unfortunately, many women that have experienced Hyperemesis gravidarum during any pregnancy are at a higher risk of experiencing it with subsequent pregnancies.

Pathophysiology

Although the pathophysiology of Hyperemesis gravidarum is poorly understood, the most commonly accepted theory suggests that levels of hCG are associated with it.[14] Leptin may also play a role according to recent (2006) joint research study out of Australia and New Zealand.[15] Possible pathophysiological processes involved are summarized in the following Figure 1.

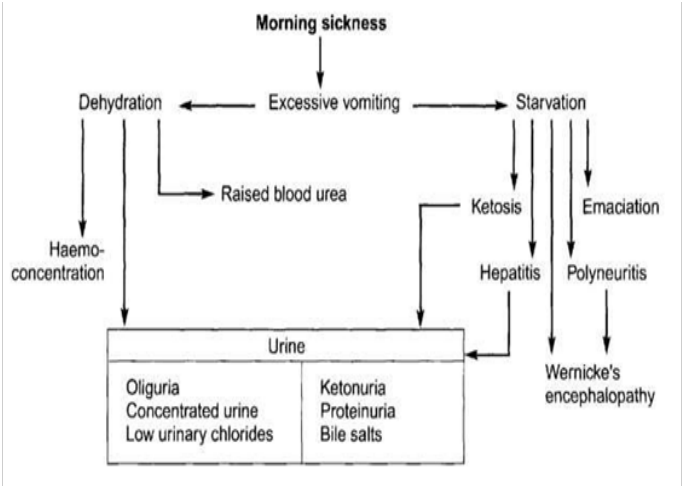

Figure 1 Pathophysiological processes.

Diagnosis

Hyperemesis gravidarum is a diagnosis of exclusion.[1] Hyperemesis gravidarum can be associated with serious maternal and fetal morbidity, such as Wernicke's encephalopathy, coagulopathy, peripheral neuropathy,[4] fetal growth retardation, and even maternal and fetal death. Women experiencing Hyperemesis gravidarum are often dehydrated and lose weight despite efforts to eat.[16,17] The onset of the nausea and vomiting in Hyperemesis gravidarum is typically before the twenty-second week of pregnancy.[1]

Differential diagnosis

The following is a simple list of all of the possible differential diagnoses that need to be kept in the back of the clinician's mind. This list is by no means all inclusive, it is based on the primary author's personal experience in Obstetrics and Gynecology. Although Hyperemesis gravidarum is usually easily established by taking a thorough history and physical exam, do not miss any of the following possible differentials:

Infections (usually accompanied by fever or associated symptoms)

Urinary tract infection

a) Common in females, more common during pregnancy due to voiding issues

b) Easily diagnosed in the office with Urine Dipstick

I. Confirm with sterile, midstream urine sample

II. Do not delay treatment as infection can travel to kidneys

III. Infection can be in any part of the urinary system

IV. Kidneys, Ureters, Bladder, Urethra.

V. Most infections involve the bladder and the urethra.

VI. Treat carefully, choose antibiotics based on safety to mother and fetus

Antibiotics generally considered safe during pregnancy:

A. Amoxicillin

B. Ampicillin

C. Clindamycin

D. Erythromycin

E. Penicillin

F. Nitrofurantoin

a. Do not use Tetracycline (including Doxycycline and Minocycline) under any circumstances

b. Tetracycline can damage a pregnant woman's liver

c. Tetracycline can also permanently discolor a baby's teeth.

d. Two antibiotics commonly used together to treat urinary tract infections, Trimethoprim and Sulfamethoxazole (TMP-SMX, also commonly sold as Bactrim) may be linked with an increased risk of birth defects – use with caution.

e. This is a common list of antibiotics used for UTI's – the authors take no responsibility for their use –please use your clinical judgement and experience.

Hepatitis

(1) Acute viral hepatitis is the most common cause of jaundice in pregnancy. The clinical course of most viral infections is not affected by pregnancy. Jaundice is a characteristic feature of liver disease. Clinical signs and symptoms are indistinguishable between the various forms of viral hepatitis. The differential diagnosis requires serologic testing for a virus-specific diagnosis. Diagnosis is by biochemical assessment of liver function.

(2) The differential diagnosis should include other forms of viral hepatitis

i. Mononucleosis and Epstein-Barr Virus (EBV)

ii. Autoimmune Disease

iii. Widespread Systemic Infection with Liver Failure.

a) Patients presenting with jaundice during pregnancy often require a workup to differentiate obstructive gall bladder or bile duct disease, severe preeclampsia, HELLP Syndrome (hemolysis, elevated liver enzyme levels, low platelet count), or acute fatty liver of pregnancy from viral hepatitis.

b) The most useful tests to diagnose hepatitis include laboratory evaluation of urine bilirubin and urobilinogen, total and direct serum bilirubin, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), alkaline phosphatase (ALP), prothrombin time (PT), total protein, albumin, complete blood cell (CBC) count and in severe cases, serum ammonia.

Bacterial meningitis

i. Bacterial meningitis is usually severe. Most people with meningitis recover however it can cause serious complications, such as brain damage, hearing loss, or learning disabilities.

ii. Meningitis infection may show up in a person by a sudden onset of fever, headache, and stiff neck. The patient may exhibit other symptoms, such as:

a. Nausea

b. Vomiting

c. Photophobia (Increased sensitivity to light)

d. Altered mental status

iii. Babies younger than 1 month old are at a higher risk for severe infections such as meningitis.

iv. In newborns and infants, the classic meningitis symptoms of fever, headache and neck stiffness may be absent or difficult to notice.

v. The infant may appear to be slow or inactive (lack of alertness), irritable, vomiting or feeding poorly. The infant may exhibit a bulging fontanelle or abnormal reflexes, which can also be signs of meningitis.

vi. There are several pathogens that can cause bacterial meningitis.

A. Leading causes of bacterial meningitis include:

a. Haemophilus influenzae (most often Type B, HiB)

b. Streptococcus pneumoniae

c. Group B Streptococcus

(i) Pregnant women who test positive for *Group B Streptococcus* can pass the bacteria to their baby, most often during labor and vaginal birth. A newborn infected with Group B Strep bacteria can develop meningitis or other life-threatening infections soon after birth.

d. Listeria monocytogenes

e. Neisseria meningitidis

vii. If meningitis is suspected, samples of blood or cerebrospinal fluid are collected and sent to the laboratory for testing.

viii. Do not delay treatment–use caution in the pregnant patient regarding which drugs are used to treat Bacterial Meningitis

ix. Bacterial Meningitis can cause spontaneous abortion of the fetus

Gastrointestinal disorders (usually accompanied by abdominal pain)

Gastroenteritis

a. Many different causes of gastroenteritis exist, including viruses or bacteria.

i. Gastroenteritis usually lasts only a couple of days, whether the patient is pregnant or not.

b. Dehydration can cause premature contractions, fatigue and dizziness.

1) Advise your patient to drink plenty of fluids including water, soda, tea, chicken soup or whatever she can take in without vomiting.

2) Symptoms that are very severe or persist for more than 2 or 3days may require IV Rehydration.

Appendicitis

a. Acute appendicitis is the most common general surgical problem encountered during pregnancy. The diagnosis is challenging during pregnancy because of the relatively high prevalence of abdominal/gastrointestinal discomfort, anatomic changes related to the enlarged uterus and physiologic leukocytosis of pregnancy.

b. Appendiceal rupture occurs more frequently in pregnant women, especially in the third trimester, possibly because of the reluctance to operate on pregnant women delays diagnosis and treatment

I. Patient Presentation: In the "classic" presentation of appendicitis, the patient describes the onset of abdominal pain as the first symptom.

II. The pain is periumbilical initially and then migrates to the right lower quadrant as the inflammatory process progresses.

III. Anorexia, nausea and vomiting, if present, follow the onset of pain.

IV. Fever up to 101.0ºF (38.3ºC) and leukocytosis develop later.

c. Many pregnant patients have a nonclassical presentation, especially in late pregnancy, with symptoms such as heartburn, bowel irregularity, flatulence, malaise, or diarrhea.

d. If the appendix is retrocecal, patients often complain of a dull ache in the right lower quadrant rather than localized tenderness.

e. Rectal or vaginal examination in such patients is more likely to elicit pain than abdominal examination.

f. A pelvic appendix can cause tenderness below McBurney's Point; these patients often complain of urinary frequency and dysuria or rectal symptoms, such as tenesmus and diarrhea.

g. The most common symptom of appendicitis, i.e., right lower quadrant pain, occurs close to McBurney's point in the majority of pregnant women, regardless of the stage of pregnancy; however, the location of the appendix migrates a few centimeters cephalad

with the enlarging uterus, so in the third trimester, pain may localize to the mid or even the upper right side of the abdomen.

h. Surgery for appendicitis must be determined on a risk-to-benefit ratio. Consultation with a General Surgeon and Anesthesiologist is vital to ascertain the risk to the fetus from anesthesia compared to the risk of a ruptured appendix and subsequent peritonitis, which can kill both the mother and fetus.

Cholecystitis

I. Acute cholecystitis can be especially difficult to recognize in pregnancy.

a. Once diagnosed, the initial management plan should be conservative and include antibiotic therapy.

II. Subsequent management depends on the gestational age at diagnosis.

III. Surgical therapy, when indicated, should not be delayed and a planned intervention during the second trimester appears to offer a better outcome than surgery performed under emergent conditions.

Cholestasis of pregnancy

i. Cholestasis of pregnancy occurs in late pregnancy and triggers intense itching, usually on the hands and feet but often on many other parts of the body.

a. Cholestasis of pregnancy can make you intensely uncomfortable but poses no long-term risk to an expectant mother.

b. For the developing baby, however, cholestasis of pregnancy can be dangerous. Early delivery is recommended.

ii. The term "cholestasis" refers to any condition that impairs the flow of bile from the liver. Pregnancy is one of many possible causes of cholestasis. Other names for cholestasis of pregnancy include obstetric cholestasis and intrahepatic cholestasis of pregnancy.

Pancreatitis

a. Most cases of acute pancreatitis in pregnancy are caused by gallstone disease. It is thought with the weight and hormonal changes induced by pregnancy, gallstones are more likely to form and thus travel down the common bile duct to obstruct the pancreas duct outflow.

b. Another proposed mechanism for acute pancreatitis in pregnancy is high triglyceride levels.

1) Hormonal changes of pregnancy can predispose certain women to developing this condition. When the triglyceride levels become too high, oxygen cannot adequately travel to the pancreas via the bloodstream, and pancreatitis can ensue.

c. All of the other reasons for developing acute pancreatitis such as alcohol abuse, reaction to certain medications, trauma to the pancreatic duct can also lead to acute pancreatitis in pregnancy

d. Treatment of acute pancreatitis in pregnancy is similar to that of non-pregnant patients with some exceptions. Resting the digestive tract by not eating, pain control and aggressive fluids given through an IV line are essential.

e. If the reason is gallstone pancreatitis, removal of the gallbladder is deferred until after pregnancy. Often, a stent can be placed into the bile duct to temporize the situation until operative resection is needed.

1) If waiting until the end of pregnancy is not possible, surgical resection can generally be performed safely.

f. If the cause of acute pancreatitis is due to elevated triglycerides, certain medications and dietary modifications can be used to help prevent recurrent attacks.

I. If the attack occurs late in the third trimester, delivery is usually advocated, as this will cause an immediate decrease in the triglyceride levels.

g. Other causes of acute pancreatitis, such as traumatic ductal injury, need to be carefully assessed on an individual basis.

Acute Fatty Liver of Pregnancy (AFLP)

I. Acute fatty liver of pregnancy is a serious complication unique to pregnancy first described by Sheehan in 1940. It is characterized by micro vesicular steatosis in the liver. The foremost cause of AFLP is thought to be due to a mitochondrial dysfunction in the oxidation of fatty acids leading to an accumulation in hepatocytes. The infiltration of fatty acids causes acute liver insufficiency, which leads to most of the symptoms that present in this condition. If not diagnosed and treated promptly, AFLP can result in high maternal and neonatal morbidity and mortality.

II. AFLP is unique to pregnancy. There does not appear to be a predilection for any geographical area or race. It appears to occur more commonly in primiparous women than multiparous women

III. Due to advances in diagnostic strategies and supportive care, maternal mortality and perinatal morbidity of AFLP has declined. In the 1980s, Kaplan reported a mortality rate for both mother and fetus of about 85%. Maternal mortality is now estimated to be 12.5-18%, with a neonatal mortality rate of 7-66%.

IV. While laboratory abnormalities may persist after delivery, in rare cases patients may progress to hepatic failure with the need for liver transplantation.

V. Morbidity of the infant includes increased risk of cardiomyopathy, neuropathy, myopathy, non-ketotic hypoglycemia, hepatic failure and death associated with fatty acid oxidation defects in newborns.

VI. Delivery of the fetus, regardless of gestational age, is the only treatment for acute fatty liver of pregnancy (AFLP) once the diagnosis has been made.

VII. Mode of delivery is dependent on the following several factors:

Fetal status: Many fetuses demonstrate evidence of asphyxia and hypoxia; therefore, close monitoring of fetal status is necessary, along with the ability to expedite delivery should fetal compromise be evident.

Maternal coagulation status: Due to coagulation abnormalities that can accompany AFLP, patients may need to have replacement of their coagulation factors should cesarean delivery be necessary.

Likelihood of success with induction of labor: If delivery cannot be safely accomplished within 24hours from the time of diagnosis, then a Caesarean Section is mandatory.

Management of severe hypoglycemia: Necessary to avoid coma and

death. Patients require at least a 5% Dextrose solution to maintain blood glucose levels. Blood glucose should be monitored closely until hepatic function returns and the patient tolerates a regular diet.

Renal function: can also be affected by several factors, including maternal hemorrhage, which can lead to acute tubular necrosis and hepatorenal syndrome. Fluid balance should be closely monitored, as patients may develop pulmonary edema due to low plasma oncotic pressures

Peptic ulcer

a) Peptic ulcer disease developing during pregnancy is relatively rare. Certainly, gastroesophageal reflux symptomatology and Hyperemesis gravidarum are the primary pregnancy-associated upper gastrointestinal tract illnesses. The symptoms of dyspepsia accompanies all three diagnoses and makes it difficult to determine whether peptic ulcer is playing a role in the patient's symptomatology.

b) Patients with a previous history of complicated peptic ulcer diatheses should be suspected of having recurrent ulcer disease and treated accordingly. Endoscopy is not to be feared if needed to confirm a diagnosis of peptic ulcer disease or to aid in the diagnosis of the patient with upper gastrointestinal tract hemorrhage.

1 There is thought to be some improvement in peptic ulcer disease with pregnancy, which may be secondary to lower gastric acid output and increased protective mucus production associated with elevated progesterone levels.

a. This may afford some level of protection against this disease process in pregnant women.

2 Patients who are smokers and have a previous history of peptic ulcer disease are at highest risk for ulcer disease during pregnancy.

c) Multiple agents have been found to be relatively safe and effective for ulcer healing, with H2 Antagonists the mainstay of therapy during pregnancy.

Small bowel obstruction

(i) The most common cause of bowel obstruction in pregnancy is adhesions secondary to prior surgery or illness (Figure 2). In one study, 77% of the 66cases presented with known obstruction due to adhesions from previous abdominal surgery, pelvic surgery, or pelvic inflammatory conditions.

(ii) A previous caesarean birth can be a contributing factor. Bowel obstruction may occur during the fourth to fifth months of pregnancy when the uterus rises into the abdomen but most often occurs in the third trimester or postpartum.

(iii) When an obstruction occurs, there is significant risk for severe morbidity or mortality for both mother and fetus, treatment needs to occur as soon as possible.

a Delays due to errors in diagnosis, delayed diagnosis, or reluctance to operate during pregnancy all add to increased risk.

b The maternal mortality rate in one study was 4 deaths in 66 women diagnosed with obstruction (Figure 2).

Metabolic

Thyrotoxicosis (Hyperthyroidism)[14]

Graves-basedow disease: named after the Irish Physician (Robert Graves) and the German Physician (Karl von Basedow) who described several cases in 1835 and 1840. It was actually first described by Parry a few years earlier. In Europe the disease is known as Basedows' Disease. In all countries it is also known as "Thyrotoxicosis". The disease has a genetic component, although not every member of the afflicted families will suffer this condition. It is more common in females than in males.

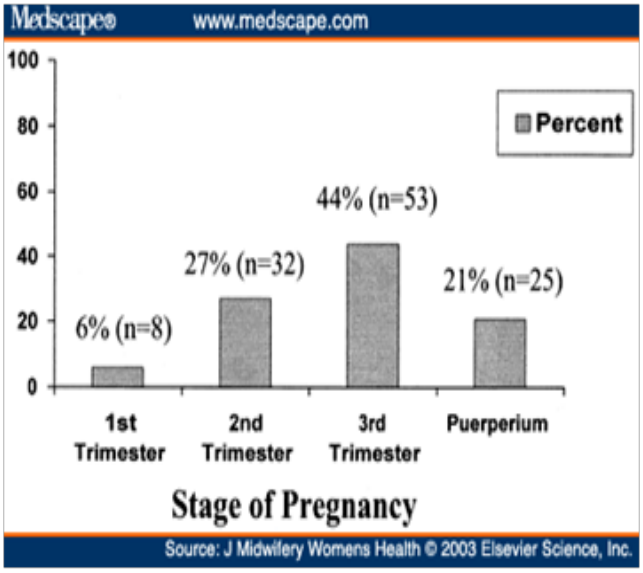

Figure 2 Stage of pregnancy.

Thyroid stimulating antibody: Graves' disease is an autoimmune disorder. It is caused by an abnormal protein called the thyroid stimulating antibody. This antibody stimulates the thyroid gland to produce large amounts of thyroid hormone in an uncontrolled manner. In normal people, the production of the thyroid stimulating antibody (and other abnormal antibodies) is prevented by a surveillance system. This system consists of certain blood cells called suppressor and helper lymphocytes, Killer Cells and other constituents. Measurement of the thyroid stimulating antibody present in the blood of patients with Graves' disease is not usually necessary, in order to establish the diagnosis.

Clinical Features: The signs and symptoms of Graves' hyperthyroidism are due to the effects of excess amounts of thyroid hormone on body function and metabolism. Common symptoms include weight loss, nervousness, irritability, intolerance to hot weather, excessive sweating, shakiness, and muscle weakness. Other signs include a rapid pulse, loss of body fat, loss of muscle bulk, thyroid enlargement (goiter), fine tremors of the fingers and hot, moist, velvety skin.[18] Clinically evident eye signs (ophthalmopathy) occur in patients with Graves' disease. Fortunately only approximately 5% are severe. The eyes, which bulge from their sockets can be red and watery and the lids are swollen. Often the eyes do not move normally because the swollen eye muscles are unable to work precisely and patients can experience double vision. Some patients with Graves' hyperthyroidism may have slightly bulging eyes because of spasm of the muscle of the lids, giving them a staring appearance.

Thyroid hormones: have a wide variety of effects on the body and the signs and symptoms reflect these.

All the metabolic processes are "speeded up". Pulse rate is rapid (over 100 bpm) and occasionally irregular (atrial fibrillation) Bowel function is increased (diarrhea) Sweat glands work excessively, cau-

sing the patient to often complain of hyperhidrosis. The nervous system is also stimulated so that the patient becomes irritable and nervous. Despite an increase in appetite, the patient usually loses weight because food intake cannot keep up with the increased breakdown of body proteins. The end result is a thin, hot, nervous patient with bulging eyes and goiter - a classical clinical situation quickly recognized by any medical practitioner who has previously seen such a patient.

Treatment: Graves' hyperthyroidism is caused by a genetically determined abnormality of the immune system, therefore the problem is complex and there is at present no specific treatment for the underlying abnormality. Since the end result of this problem is an over stimulation of thyroid function, treatment of the symptoms requires blocking thyroid hormone production with antithyroid drugs, destroying the thyroid cells with radioactive iodine or surgically removing the thyroid gland (thyroidectomy).

Radioactive iodine: Although radioactive iodine is by far the simplest and most convenient treatment, its use in younger adults and children has previously been a matter of concern because of the possible harmful effects of radiation. Radioactive iodine has been used for over 40years and there is no known evidence of any harmful effects. In North America most thyroid specialists would recommend its use in most patients with Graves' disease over the age of 20-25 because it has a higher chance of long-term success (resolution of hyperthyroidism) than antithyroid drugs. Its use in adolescents is increasing. However, it occasionally aggravates the eye sight and preventive treatment with corticosteroids is sometimes warranted. Radioactive iodine is usually given in the form of a capsule. The dose is calculated from the size of the goiter and the 24hour iodine uptake obtained by performing a "Thyroid Uptake Test." Because radioactive iodine takes several weeks to take its full effect, antithyroid tablets are sometimes given until such time as the full effect occurs.

Antithyroid drugs: Antithyroid drugs (such as Propylthiouracil and Methimazole) are commonly used in children and adults under the age of 20-25. It may also be used at any age so as to bring about remissions, or prior to ablation therapy. There are two main drawbacks with this type of treatment: Patients must take tablets for many months or years, the recommended period of time for the treatment is 12 to 18 months;Once treatment is stopped, there is only about a 50% chance that the disease will not flare up again. Therefore most patients require additional treatments. In addition, a very small percentage suffer side effects that very rarely can be severe (liver problems, low white blood cell count). Because of the recent evidence of side effects of Propylthiouracil on liver function, especially in children, the FDA has issued a warning for its use. Propylthiouracil is still the treatment of choice during pregnancy since there is unclear evidence about Methimazole side effects in the fetus (aplasia cutis, choanal atresia). It is preferable to treat the hyperthyroidism before considering pregnancy. Another medication that can be given to treat the symptoms of hyperthyroidism is Propranolol or other beta-blockers. This drug blocks the effects of excess thyroid hormones on the heart, blood vessels, and nervous system, but has no direct effect on the thyroid gland. It is contraindicated in patients with asthma.

Addison's disease

Women with diagnosed and undiagnosed autoimmune Addison's disease are at increased risk for preterm birth, low birth weight and other unfavorable pregnancy outcomes, according to results of a Swedish population-based cohort study.[19] In addition, women with autoimmune Addison's disease had a reduced parity compared with other women. Risks for congenital malformations or infant death were not associated with diagnosed or undiagnosed autoimmune Addison's disease.

Diabetic ketoacidosis (DKA)[20]

The occurrence of diabetic ketoacidosis in pregnancy compromises both the fetus and the mother. It usually occurs in the later stages of pregnancy and is also seen in newly presenting Type 1 Diabetic Patients. Despite improvement in its incidence rates and outcomes over the years, it still remains a major clinical problem since it tends to occur at lower blood glucose levels and more rapidly than in non-pregnant patients often causing delay in the diagnosis. Diabetic ketoacidosis (DKA) is an acute medical emergency associated with fetal loss rates in excess of 50%. Maternal mortality rates are generally less than 1%. DKA in pregnancy most commonly occurs in women with pregestational, insulin dependent diabetes who are poorly controlled or in women newly diagnosed with insulin dependent diabetes. DKA may be provoked by an exposure to a stress such as infection, surgery, or labor.

Hyperparathyroidism

a. Hyperparathyroidism (parathyroid disease with high calcium) occurring during pregnancy is a very serious problem. Hyperparathyroidism during pregnancy puts both the mother's and child's life at risk, and the chance for life-long calcium problems for the child exists. Hyperparathyroidism during pregnancy is treated with mom's surgery during the late first or early second trimester.

b. Hyperparathyroidism during pregnancy is very rare. However, this can be a very serious problem for both mother and child. It must be addressed in the correct fashion for the best results and the obstetrician and the surgeon must communicate so that both the mother and the child do well.

Potential Risks of Hyperparathyroidism During Pregnancy:

1. Increased risk of hypertension (pre-eclampsia and eclampsia) in the mother (about 20 times more common).
2. Risk of miscarriage can be as high as 85 percent.
3. Risk of permanent hypoparathyroidism in baby (failure of the parathyroid glands to form).
4. Risk of heart rhythm problems during labor/delivery.
5. Risk of premature birth.
6. Risk of seizures in the baby during first few days of life (due to LOW levels of calcium).
    a) This is one of the true emergencies with hyperparathyroidism. Do not fool around here! Bring in a neonatologist if possible to assist you with the infant.

Other drugs

Antibiotics: Antibiotics were discussed earlier in this report. The main reason to mention it here again briefly, is to NEVER give unnecessary antibiotics and to carefully choose which one is being prescribed if an antibiotic is absolutely necessary.

Iron supplements

When a woman is pregnant, she will need about twice the amount of iron as she normally did before becoming pregnant. The body uses

iron to make extra blood for your baby. Unfortunately, about 50% of pregnant women do not get enough of this important mineral. Eating iron-rich foods and taking extra iron (approximately 30 mg. per day) will be sufficient. The human body uses iron during pregnancy to make extra hemoglobin for the mother and the fetus. Iron also helps move oxygen from the mother's lungs to the rest of the mother's and fetus's body. Getting enough iron can prevent a condition of too few red blood cells that can make you feel tired, called iron deficiency anemia. Having anemia can cause your baby to be born too small or too early.

Prenatal Vitamins

Advise your patient to eat a healthy diet during pregnancy, which can lessen the effects of morning sickness and *Hyperemesis gravidarum*. Prescribe your patient with a good Prenatal Vitamin, numerous ones are available depending on where you live. Prescription Prenatal Vitamins are preferred in lieu of OTC Vitamins as the prescription vitamins are specifically formulated for pregnant patients.

A good, well-formulated Prenatal Vitamin will contain at least the following:

a) 400micrograms (mcg) of folic acid.

b) 400IU of vitamin D.

c) 200 to 300milligrams (mg) of calcium.

d) 70mg of vitamin C.

e) 3mg of thiamine.

f) 2mg of riboflavin.

g) 20mg of niacin.

h) 6 mcg of vitamin B_{12}.

i) 10mg of vitamin E

j) 15mg of zinc

k) 17mg of iron

l) 150mcg of iodine

Prenatal vitamins contain many vitamins and minerals. All of them contain folic acid, iron, iodine, and calcium which are especially important during pregnancy. Folic acid helps prevent neural tube birth defects, which affect the brain and spinal cord.

Gestational trophoblastic diseases (rule out with urine β-hCG)

Molar pregnancy

A. A Molar Pregnancy is an abnormal form of pregnancy in which a non-viable fertilized egg implants in the uterus and will fail to come to term. A molar pregnancy is a gestational trophoblastic disease which grows into a mass in the uterus that has swollen chorionic villi. These villi grow in clusters that resemble grapes. Even though it isn't an embryo, this growth triggers symptoms of pregnancy.

B. A molar pregnancy should be treated right away. This will make sure that all of the tissue is removed. This tissue can cause serious problems in some women.

C. About 1 out of 1,500 women with early pregnancy symptoms has a molar pregnancy.

D. Molar pregnancy is thought to be caused by a problem with the genetic information of an egg or sperm. There are two types of molar pregnancy - complete and partial.

Complete molar pregnancy: An egg with no genetic information is fertilized by a sperm. It does not develop into a fetus but continues to grow as a lump of abnormal tissue that looks a bit like a cluster of grapes and can fill the uterus.

Partial molar pregnancy: An egg is fertilized by two sperm. The placenta becomes the molar growth. Any fetal tissue that forms is likely to have severe defects. A Molar Pregnancy causes the same early symptoms that a normal pregnancy does, such as a missed period or morning sickness. But a molar pregnancy usually causes other symptoms too, which may include:

I. Bleeding from the vagina.

II. A uterus that is larger than normal.

III. Severe nausea and vomiting.

IV. Signs of hyperthyroidism. These include feeling nervous or tired, having a fast or irregular heartbeat, and sweating a lot.

V. An uncomfortable feeling in the pelvis.

VI. Vaginal discharge of tissue that is shaped like grapes. This is usually a sign of a "miscarriage" of a molar pregnancy.

VII. Most of these symptoms can also occur with a normal pregnancy, a multiple pregnancy, or a miscarriage.

Choriocarcinoma

A malignant, trophoblastic cancer, usually of the placenta. It is characterized by early hematogenous spread to the lungs. It belongs to the malignant end of the spectrum in gestational trophoblastic disease (GTD). It is also classified as a germ cell tumor and may arise in the testis or ovary.

Choriocarcinoma of the placenta during pregnancy is preceded by:

I. Hydatidiform Mole (50% of cases)

II. Spontaneous Abortion (20% of cases)

III. Ectopic Pregnancy (2% of cases)

IV. Normal Term Pregnancy (20-30% of cases)

V. Hyperemesis gravidarum

a) Rarely, choriocarcinoma occurs in primary locations other than the placenta. Very rarely, it occurs in the testicles and elements of choriocarcinoma in a mixed testicular tumor have no prognostic importance.

(i) Although trophoblastic components are common components of mixed germ cell tumors, pure choriocarcinoma of the adult testis is rare.

(ii) Pure choriocarcinoma of the testis represents the most aggressive pathologic variant of germ cell tumors in adults, characteristically with early hematogenous and lymphatic metastatic spread.

(iii) Because of early spread and inherent resistance to anticancer drugs, patients have poor prognosis.

(iv) Choriocarcinomas can also occur in the ovaries with an equally poor prognosis.

Clinical investigations

Common investigations include blood urea nitrogen (BUN) and electrolytes, liver function tests, urinalysis and thyroid function tests. Hematological investigations include hematocrit levels, which are usually raised in Hyperemesis gravidarum. An ultrasound scan may be needed to know gestational status and to exclude molar or partial molar pregnancy.

Management of hyperemesis gravidarum patient

Dry bland food and oral rehydration are first-line treatments. Due to the potential for severe dehydration and other complications, Hyperemesis gravidarum is treated as an emergency. If conservative dietary measures fail, more extensive treatment such as the use of antiemetic medications and intravenous rehydration may be required. If oral nutrition is insufficient, intravenous nutritional support may be needed. For women who require hospital admission, thromboembolic stockings or low-molecular-weight heparin may also be used as measures to prevent the formation of a blood clot.

Intravenous fluids

IV hydration often includes supplementation of electrolytes as persistent vomiting frequently leads to not only a fluid deficiency, which can cause a patient to go into shock with a dropping blood pressure and an increased pulse rate but also severe electrolyte and vitamin deficiency. Unfortunately, most patients do not seek treatment in the hospital or office until they are in trouble – so action must be taken quickly. Supplementation for lost thiamine (Vitamin B_1) must be considered to reduce the risk of Wernicke's Encephalopathy, Vitamins A and B are depleted within two weeks and so extended malnutrition indicates a need for evaluation and supplementation. In addition, electrolyte levels should be monitored and supplemented; of particular concern are sodium and potassium.

Some patients benefit from what is colloquially called a "Banana Bag", often used in malnourished alcoholics. The vitamins and supplements are sometimes available in 5 to 10cc. ampules which are added to a liter of whatever fluid the physician chooses for rehydrating the Hyperemesis gravidarum patient. Again, the clinical judgement and patient presentation are most important when utilizing any IV fluids for rehydration therapy. If pre-made ampules of vitamins or pre-made banana bags are not available in your hospital, the typical composition of a banana bag is 1 liter of Sodium Chloride 0.9% (NS-Normal Saline) with:

i. Thiamine 100mg

ii. Folic acid 1mg

iii. MVI 1 amp (Multivitamin for infusion, 1ampule)

iv. Magnesium sulfate 3g

The solution is typically infused over four to eight hours or as per physician's orders which should be based on patient status. Oftentimes you can piggyback 250cc. of D5W or Ringer's Lactate Solution onto the banana bag infusion set. All these IV fluids act differently but are very efficacious in helping the patient feel better. The primary author of this report will use Ringer's Lactate Solution in place of the Normal Saline 0.9% in making up a banana bag. He has had excellent results in severe cases of Hyperemesis gravidarum.

One liter of Ringer's lactate solution contains:

a) 130mEq of sodium ion=130mmol/L

b) 109mEq of chloride ion=109mmol/L

c) 28mEq of lactate=28mmol/L

d) 4mEq of potassium ion=4mmol/L

e) 3mEq of calcium ion=1.5mmol/L

Ringer's Lactate has an osmolarity of 273mOsm/L. The lactate is metabolized into bicarbonate by the liver, which can help correct metabolic acidosis, which can occur to a severe extent in *Hyperemesis gravidarum*. Ringer's Lactate solution alkalinizes via its consumption in the citric acid cycle, the generation of a molecule of carbon dioxide which is then excreted by the lungs. They increase the strong ion difference in solution, leading to proton consumption and an overall alkalinizing effect. After IV rehydration is completed, patients in general should be advised to transition to frequent small liquid or bland meals. After rehydration, treatment focuses on managing symptoms to allow normal intake of food. However, cycles of hydration and dehydration can occur, making continuing care necessary. Home care is available in the form of a PICC line for hydration and Total Parenteral Nutrition (TPN).[21] Home treatment is often less expensive than long-term or repeated hospitalizations.

Medications

A number of antiemetics are effective and safe in pregnancy including: pyridoxine/doxylamine, antihistamines (such as diphenhydramine), and phenothiazines (such as promethazine).[22] With respect to effectiveness, it is unknown if one is superior to another[22] and there is even limited evidence of significant effect at all of pharmacological therapy in hyperemesis gravidarum.[22]

While pyridoxine/doxylamine, a combination of Vitamin B_6 and Unisom/doxylamine (an Over-the-Counter {OTC} sleeping aid/antihistamine), is effective in nausea and vomiting of pregnancy,[23] some have questioned its effectiveness in Hyperemesis gravidarum.[24] The primary author of this report has had great success with the pyridoxine/doxylamine combination, for both morning sickness and Hyperemesis gravidarum. He has delivered well over 500 babies and has recommended it prophylactically for his patients to buy these two OTC drugs and have them on hand. Patients have reported mostly positive results, some even stating that at the first sign of nausea, they take the combination right away, usually with relief being obtained within 30minutes. Patients report taking 10 to 25mg. of Vitamin B_6 along with 5 to 25mg. of Doxylamine. It appears that the dosing is patient dependent. The primary author of this article does not recommend any other medications due to inadequate, high quality research available and too high of a risk for fetal defects.

Some researchers state that Ondansetron may be beneficial, however, there are some concerns regarding an association with cleft palate[25] and there is little high quality data.[22] Metoclopramide is also used and relatively well tolerated. Evidence for the use of corticosteroids is weak; there is some evidence that corticosteroid use in pregnant women may slightly increase the risk of oral facial clefts in the infant and may suppress fetal adrenal activity.[1,24] However, hydrocortisone and prednisolone are inactivated in the placenta and may be used in the treatment of hyperemesis gravidarum.[1]

Nutritional support

Women not responding to IV rehydration and medication may require nutritional support. Patients might receive parenteral nutrition (intravenous feeding via a PICC Line - Peripherally Inserted Central Catheter) or enteral nutrition (via a nasogastric tube or a nasojejunal tube). There is only limited evidence from trials to support the use of vitamin B_6 to improve outcome. Hyperalimentation may be necessary in certain cases to help maintain volume requirements and allow weight gain.[26] A physician might also prescribe Vitamin B_1 (to prevent Wernicke's Encephalopathy) and Folic Acid supplementation.[27]

Medicines

There is tentative, unsubstantiated evidence that seems to be circulating on the Internet that ginger, either in raw, pickled (the type used on sushi) or lozenge (candy) form may be useful to relieve the symptoms of Hyperemesis gravidarum. However, according to current scientific studies, the efficacy of ginger is not clear.[21] Safety concerns have also been raised regarding its unpredictable anticoagulant[22] properties which could have an adverse effects on the mother or fetus. These authors do not advise the ingestion of any ginger or ginger-based products during pregnancy. Acupuncture, both traditional needle acupuncture and Acupressure Point P6 on the wrist (Pericardium 6 or Nei Guan Point) have been found to be totally ineffective for Hyperemesis gravidarum.[28]

Complications pregnant woman

If Hyperemesis gravidarum is inadequately treated, Anemia, Hyponatremia, Wernicke's Encephalopathy, Kidney Failure, Central Pontine Myelinolysis, Coagulopathy, Atrophy, Mallory-Weiss Tears, Hypoglycemia, Jaundice, Malnutrition, Pneumomediastinum, Rhabdomyolysis, Deconditioning, DVT (Deep Vein Thrombosis), Pulmonary Embolism, Splenic Avulsion, or Vasospasms of Cerebral Arteries are possible serious consequences.[2] Depression is a common secondary complication of Hyperemesis Gravidarum and emotional support can be beneficial.[27]

Infant

The effects of Hyperemesis gravidarum on the fetus are mainly due to electrolyte imbalances caused by Hyperemesis gravidarum in the mother.[27] Infants of women with severe Hyperemesis gravidarum who gain less than 7kg. (15.4 lbs.) during pregnancy tend to be of lower birth weight, small for gestational age and born before 37weeks gestation.[5] In contrast, infants of women with Hyperemesis gravidarum who have a pregnancy weight gain of more than 7 kg. appear similar to infants from uncomplicated pregnancies.[4] There is no significant difference in the neonatal death rate in infants born to mothers with Hyperemesis gravidarum compared to infants born to mothers who do not have Hyperemesis gravidarum.[2]

Epidemiology

Severe, debilitating vomiting is a common condition in Hyperemesis gravidarum affecting about 50% of pregnant women, with another 25% suffering from nausea.[5] However, the incidence of Hyperemesis gravidarum is only 0.5–2.0%.[2–4] After preterm labor, Hyperemesis gravidarum is the second most common reason for hospital admission during the first half of pregnancy.[1] Factors such as infection with Helicobacter pylori, a rise in thyroid hormone production, low age, low body mass index prior to pregnancy, multiple pregnancies, molar pregnancies, and a past history of Hyperemesis gravidarum have been associated with the development of Hyperemesis gravidarum.[1]

Historical severe medication failures

Thalidomide (Immunoprin) is an immunomodulatory drug and the prototype of the thalidomide class of drugs. It was prescribed for treatment of Hyperemesis gravidarum worldwide, especially in Europe. The United States FDA refused to approve the drug when it was released in 1957 and confirmed the decision in 1962. Eventually other countries recognized that thalidomide is extremely teratogenic and is a direct causative agent of phocomelia in neonates. In the late 1950s and early 1960s, more than 10,000 children in 46 countries were born with deformities such as phocomelia as a direct consequence of thalidomide use.[29] Thalidomide was first developed by the German Drug Company of Chemie Grünenthal in 1957 under the name of Contergan. It was primarily prescribed as a sedative or hypnotic, Chemie Grünenthal also claimed thalidomide could be used to cure "anxiety, insomnia, gastritis, and tension"[30] and hence its use for Hyperemesis gravidarum–which turned out to be a grave mistake.

Thalidomide is still used for a number of conditions including Erythema Nodosum Leprosum–(an ancient infectious disease caused by *Mycobacterium leprae* that affects the skin and peripheral nerves), Multiple Myeloma (in combination with dexamethasone), a variety of other cancers, for some symptoms of HIV/AIDS, Sarcoidosis, Crohn's Disease, Graft-versus-Host Disease, Rheumatoid Arthritis and a number of skin conditions that have not responded to usual treatment [31,32] (Figure 3).

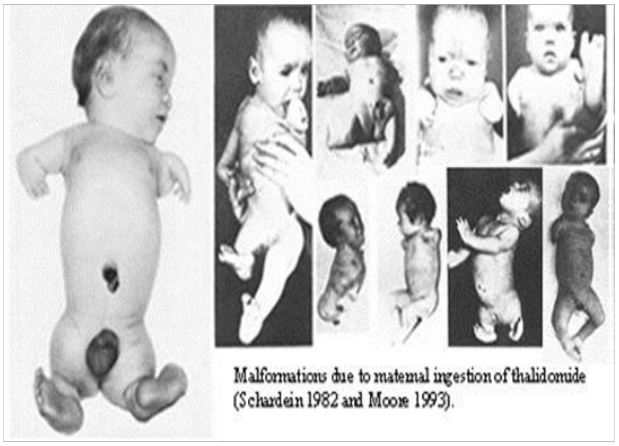

Figure 3 Maleformations due to maternal ingestion of thalidomide (Schardein 1982 and Moore 1992).

Prior to putting ANY female patient of child-bearing age on thalidomide for any of these conditions, the prescribing physician must make sure the patient is not pregnant and she must be strongly warned against becoming pregnant while on this drug. Thalidomide is classified by the U.S. Food and Drug Administration (www.fda.com) as a Pregnancy Category X Drug and according to the FDA. "Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits."

Phocomelia is an extremely rare congenital skeletal disorder that characteristically affects the limbs and was directly linked to mothers taking thalidomide for morning sickness or hyperemesis gravidarum. It can affect either the upper limbs, lower limbs or both, usually expressing this disorder with severe shortening of upper limb bones. Phocomelia can also present as severe, various abnormalities to the face, limbs, ears, nose, vessels and many other underdevelopments.

Under no circumstances should a pregnant woman be given thalidomide.

Conclusion

Hyperemesis gravidarum is from the Greek hyper-, meaning excessive and emesis, meaning vomiting and the Latin gravidarum, the feminine genitive plural form of an adjective. Here it is used as a noun, meaning "pregnant [woman]". Therefore, Hyperemesis gravidarum means "excessive vomiting of pregnant women".

Hyperemesis gravidarum is a serious, life-threatening condition that occurs during pregnancy. It is treatable, mostly by supportive means, vitamins, IV Fluids, bland diet and family support. Do not let a patient with suspected Hyperemesis gravidarum leave your office without developing a treatment plan. Remember these patients can "crash" rapidly from shock, fluid loss, electrolyte imbalance and all the other issues listed in this extensive review of Hyperemesis gravidarum.

A great portion of this document was dedicated to the differential diagnoses as we do not want you to miss something, thinking it is Hyperemesis gravidarum as many disease processes can mimic Hyperemesis gravidarum. If you even slightly suspect Hyperemesis gravidarum, treat it and worry about your differential investigation at a later time. Patients have been known to suffer from Hyperemesis gravidarum for weeks prior to seeking treatment and by the time they get to see you in the emergency room, you may have a massive problem on your hands. Be aggressive in your treatment – however it is best to avoid Hyperemesis gravidarum altogether if possible by being proactive when your patient comes in for her first Obstetrical Visit. Give your patient a simplified version of what she needs to watch for, whether it is her first baby or her sixth baby. Never assume the patient knows what to do. Educate your patient (and yourself) to avoid any future complications. Remember, our goal and only goal in Obstetrics is to have a healthy mother and baby go home.

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Conflict of interest

The author declares no conflict of interest.

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