

Hyperemesis Gravidarum

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- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
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Faculty

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Faculty Disclosure

Contributing faculty, Sandra Mesics, CNM, MSN, RN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for all nurses, especially those working in obstetrics and maternal/child nursing.

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Course Objective

Practitioners commonly treat nausea and vomiting in early pregnancy, regardless of whether the patient fits all the criteria of a diagnosis of hyperemesis gravidarum. The purpose of this course is to increase the awareness of hyperemesis gravidarum and present guidelines for nursing management of the condition.

Learning Objectives

Upon completion of this course, you should be able to:

1. Define hyperemesis gravidarum, and distinguish it from the normal nausea and vomiting of pregnancy.
2. List the potential effects of hyperemesis gravidarum on the fetus and mother.
3. Compare the various theories of etiology of hyperemesis gravidarum.
4. Identify the populations at risk for hyperemesis gravidarum.
5. Describe dietary interventions for treatment of hyperemesis gravidarum.
6. Describe pharmacologic agents used in the management of hyperemesis gravidarum.
7. Describe the role of intravenous therapy in treating hyperemesis gravidarum.
8. Outline nonpharmacologic interventions to treat hyperemesis gravidarum.
9. Explain the nursing assessment and related diagnosis and interventions for the patient with hyperemesis gravidarum.



Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Between 50% and 80% of pregnant patients experience nausea and vomiting beginning at about the 4th week and ending at about the 12th week of gestation [1; 2]. In fact, nausea and vomiting are considered a presumptive sign of pregnancy, and for 10% to 20% of pregnant patients, these symptoms may persist throughout the whole pregnancy. While nausea and vomiting are common occurrences, hyperemesis gravidarum is rare, occurring in 0.2% to 3.6% of all pregnancies [1; 2; 127].

In the United States, more than 280,000 emergency department visits were associated with a primary diagnosis of hyperemesis gravidarum or nausea/vomiting of pregnancy in 2014, with 4.5% of these patients being admitted to the hospital [128]. This represented a 28% increase in emergency department visits for hyperemesis gravidarum compared with 2006; however, admissions from the emergency department decreased by 42% over the same period [128]. The average emergency department costs associated with these diagnoses is about \$3,500 per visit totaling more than \$1 billion in emergency department visit costs only [128]. This is an increase of 110% compared with 2006 costs. Total costs per hyperemesis gravidarum patient were estimated to be \$47,351; however, costs can exceed \$88,000 per patient if the condition is poorly managed [3; 115]. These are in addition to the personal losses stemming from the disorder, including loss of desire to have more children, difficulty maintaining employment/career, inability to care for existing children, relationship difficulties, inability to have a intervention-free pregnancy, and persistent health effects to the mother and child following a long course of medications and treatment.

DEFINITION OF HYPEREMESIS GRAVIDARUM

There is some variation in the literature as to the exact definition of hyperemesis gravidarum. It has been described as intractable nausea and vomiting during pregnancy severe enough to require hospitalization [4; 115]. The condition appears during the first trimester and is unassociated with other medical conditions, such as cholestasis, hepatitis, pre-eclampsia, viral syndromes, Ménière disease, or influenza.

The most commonly accepted definition of hyperemesis gravidarum is a severe form of nausea and vomiting with weight loss greater than 5% of pre-pregnancy body weight, dehydration, acidosis from starvation, alkalosis from loss of hydrochloric acid, hypokalemia, ketosis, acetonuria, and ptyalism (excessive salivation) [4]. Many patients require hospitalization in order to control the symptoms [5; 115]. In most cases, the onset of symptoms is between 4 and 10 weeks' gestation and the symptoms usually subside by 20 weeks' gestation. Clinically, practitioners commonly treat nausea and vomiting in early pregnancy, regardless of whether the patient fits all the criteria of a diagnosis of hyperemesis gravidarum.



EVIDENCE-BASED
PRACTICE
RECOMMENDATION

According to the Royal College of Obstetricians and Gynaecologists, hyperemesis gravidarum can be diagnosed when there is protracted nausea and vomiting of pregnancy with the triad of more than 5% prepregnancy weight loss, dehydration, and electrolyte imbalance.

(<https://www.rcog.org.uk/media/y3fen1x1/gtg69-hyperemesis.pdf>. Last accessed August 21, 2023.)

Grade of Recommendation: D (Case reports or expert opinion)

EFFECTS OF HYPEREMESIS GRAVIDARUM

FETAL EFFECTS

It has been suggested that hyperemesis gravidarum may be associated with low infant birth weight, likely related to maternal nutritional (i.e., weight) maintenance [6; 7; 8]. Researchers have found a modest association between severe nausea and vomiting in pregnancy and intrauterine growth restriction and low infant birth weight [6]. A maternal weight loss of greater than 5% seems to be the critical factor in fetal growth restriction. However, even insufficient weight gain can have negative repercussions. A weight gain of less than 7 kg (15.4 pounds) during the duration of pregnancy is associated with low birth weight and preterm births [5; 7; 115; 119].

There also appears to be a correlation between severe hyperemesis during pregnancy and impaired insulin sensitivity in offspring [9]. In one study of healthy children (4 to 11 years of age) who were born at term to mothers who were admitted to hospital with severe hyperemesis gravidarum during their pregnancy, the offspring of the patients with hyperemesis had 20% lower insulin sensitivity compared to children of healthy individuals. Longer term follow-up studies are necessary to determine if this difference persists into adulthood.

One study found an increased risk for psychological and behavioral problems in adult offspring of pregnancies affected by hyperemesis [10]. Adult offspring exposed to hyperemesis in utero reported higher likelihood of depression, anxiety, and bipolar disorder diagnoses.

Various studies have linked a greater risk for birth defects, developmental delays, and serious health problems (e.g., type 2 diabetes, hypertension, high cholesterol, and cardiovascular disease) with maternal hyperemesis gravidarum [8; 11]. One small Japanese study found impaired fetal head growth was associated with lower maternal weight gain from the lowest body weight to weight at 20 weeks' gestation [129]. The authors hypothesize that this could affect fetal brain growth and development. Other potential fetal complications include [12]:

- Shorter length
- Undescended testes
- Testicular cancer
- Behavioral/emotional problems
- Integumentary abnormalities
- Neurodevelopmental sequelae
- Congenital heart disease
- Neural tube defects
- Hip dysplasia
- Perinatal death

Although it is clear that hyperemesis gravidarum is associated with adverse fetal effects, the exact causation is the subject of debate. Poor maternal health and fetal exposure to stress hormones are thought to play a role, but some have suggested that the fetal complications seen with hyperemesis gravidarum may be the result of maternal risk factors, not the condition itself. In one study, the researchers assert that individuals who develop hyperemesis gravidarum tend to have pre-existing conditions that could predispose their infants to complications, including younger age, lower socioeconomic status, primiparity, use of assisted reproductive technologies, substance abuse, non-Western descent, and chronic health conditions (e.g., diabetes, hypertension, mental illness) [13]. It is possible that the factors that place patients at risk for developing hyperemesis gravidarum are responsible for low infant birth weight and other negative fetal effects associated with the condition.

Despite the fact that hyperemesis gravidarum may be associated with poor fetal growth and outcome, a large, epidemiologic study found that the likelihood of miscarriage was 70% lower in those who experienced normal nausea and vomiting early in pregnancy [14]. More severe sickness was associated with a greater decrease in the risk of miscarriage. This finding supports the belief that normal nausea and vomiting in the first trimester of pregnancy may be protective against miscarriage [14; 15]. This may be a result of robust placental synthesis in a healthy pregnancy [92].

Hyperemesis is also associated with a reduced incidence of stillbirth, likely due to the increased rate of spontaneous and elective preterm deliveries among affected patients [119]. Evidence indicates that there are likely no severe long-term negative outcomes to children born from pregnancy affected by hyperemesis [120].

MATERNAL EFFECTS

Prior to the modern understanding of fluid and electrolyte balance, hyperemesis gravidarum could be a life-threatening event. In many cases, pregnancy termination was advocated. Today, while this condition is rarely fatal, several life-threatening complications may occur, commonly involving the central nervous system [16].

Wernicke encephalopathy results from a deficiency of thiamine (vitamin B₁) and is manifested by confusion, gait ataxia, ophthalmoplegia (paralysis of the eye muscles), or convulsions. Typically, thiamine is initially lost by prolonged vomiting. When intravenous fluid replacement containing dextrose is given, the body's metabolism of the dextrose quickly consumes the remaining thiamine. Therefore, the cause is usually not the hyperemesis itself but is instead due to fluid replacement without thiamine supplementation. Although the condition is very rare, it is associated with a high mortality rate (20%) [16; 130].

Other rare maternal complications of hyperemesis gravidarum include esophageal rupture, spontaneous pneumomediastinum (presence of air or gas in the mediastinum), vasospasm of cerebral arteries, rhabdomyolysis (disintegration of striated muscle fibers with excretion of myoglobin in the urine), peripheral neuropathy due to vitamin B₆ and B₁₂ deficiency, and coagulopathy due to vitamin K deficiency. Also, a rapid correction of severe hyponatremia (sodium deficiency) by intravenous infusion may rarely cause osmotic demyelination syndrome.

One study found a strong correlation between hyperemesis gravidarum and both pre-eclampsia and eclampsia [119]. It is hypothesized that hyper-

emesis and pre-eclampsia/eclampsia may share a common etiology, likely related to faulty immunology of pregnancy. Individuals with hyperemesis are also at increased risk for antepartum, intrapartum, and postpartum (12 weeks following birth) venous thromboembolism [119].

Hyperemesis gravidarum imposes a physical, emotional, and financial burden on patients and their families [17; 110]. Almost half of working women think that their job effectiveness is impaired by this problem, and 78% take time away from their employment [18]. Approximately 50% of patients with nausea and vomiting in pregnancy report that the condition has adverse effects on their spousal relationships, and more than half of affected women feel depressed. Some women may actually choose to terminate pregnancies affected by hyperemesis. One survey of individuals with hyperemesis found that 15% had at least one pregnancy termination as a result of the nausea and vomiting, with 6% reporting multiple terminations [19]. An additional 11% of those surveyed had considered terminating a pregnancy due to hyperemesis gravidarum. One study of 712 women with severe nausea and vomiting of pregnancy found that more than 25% had considered terminating the pregnancy and 75% considered not getting pregnant again [20].

Presence of hyperemesis gravidarum has been shown to significantly affect a patient's quality of life. In one study, those experiencing severe nausea and vomiting had deficits in the eight measured domains of quality of life, including physical functioning, role limitations (physical and emotional), bodily pain, general health, vitality, social functioning, and mental health [21; 110]. Possibly as an extension of the impact on quality of life, those with hyperemesis are at greater risk for emotional distress, depression, and anxiety [5; 110; 122; 124]. There is also an increase in post-traumatic stress disorder that can persist for over two years postpartum, regardless of the subjective birth experience [123]. Patients who experienced hyperemesis gravidarum describe it as one of their worst life experiences, with a perceived lack of support and suboptimal management [126].

THEORIES OF ETIOLOGY

No single cause for hyperemesis gravidarum has been found. Theories of causality include hypothyroidism/thyrotoxicosis, parathyroid dysfunction, gestational hormone influx, hepatic dysfunction, hypercholesterolemia, type 1 diabetes, infection, autonomic nervous system dysfunction, anemia, nutritional deficiencies, psychological factors, and genetics [4; 118; 119]. Each of these theories will be discussed in some detail. It is likely, however, that hyperemesis gravidarum is a multifactorial syndrome, with no single etiology being responsible.

HYPERTHYROIDISM/THYROTOXICOSIS

In normal pregnancy, the thyroid gland enlarges 50% and thyroxine (T_4) secretion increases due to increased levels of human chorionic gonadotropin (hCG) and human chorionic thyrotropin (hCT), which are secreted by the placenta. The hCG molecule is a glycoprotein molecule that contains the structural characteristics required for interaction with the thyroid-stimulating hormone (TSH) receptor and activation of the membrane adenylate cyclase that regulates thyroid cell function. The hCT molecule is also a glycoprotein molecule with properties similar to TSH; it increases the secretion of thyroid hormone and stimulates the incorporation of inorganic phosphate into the thyroid. The increase in thyroid hormone levels occurs in the first trimester and continues throughout pregnancy. Estrogen levels also increase during pregnancy. The increase in estrogen causes an increase in thyroxine-binding globulin (TBG) production in the liver. About 80% of thyroid hormones are bound to TBG, resulting in serum T_4 concentrations in the hyperthyroid range.



The Endocrine Society recommends that thyroid function tests and thyrotropin receptor antibodies should be measured in patients with hyperemesis gravidarum and clinical features of hyperthyroidism.

(<https://academic.oup.com/jcem/article/97/8/2543/2823170>. Last accessed August 21, 2023.)

Strength of Recommendation/Level of Evidence:

2 | ++OO (Weak recommendation based on low-quality evidence)

During pregnancy, thyroid hormone economy adapts to the rise in TBG concentration. During the first trimester, there is a gradual rise in serum protein-bound iodine, which is dependent on the increase in estrogen levels. There is also a small increase in free T_4 and a decrease in TSH during early pregnancy [22]. This suggests that thyroid hormones are stimulated by something other than TSH.

The normal rise in serum T_4 that occurs in pregnancy may be due to the effects of hCG. As TSH and hCG share the same common α -subunit, it has been suggested that hyperemesis may be due to elevated hCG levels [23; 24].

An in vitro study of thyroid activity in five hyperemesis patients did not find support for the hypothesis that hCG stimulates thyroid activity [25]. Wilson et al. studied thyroid hormone levels in 10 patients with hyperemesis gravidarum and found that while individual patients were found to have some abnormal thyroid function tests, the group as a whole showed no differences in thyroid hormone levels than that of healthy first trimester pregnant patients [26]. Levels of hCG were also normal in the patients with hyperemesis. The authors suggest that hyperemesis gravidarum may be caused by some circulating stimulator not yet identified. Some experts have hypothesized that there is a circulating hormone or hormone-like substance that may stimulate the thyroid gland and render it temporarily unresponsive to the control of the pituitary [4]. When this substance subsides in later pregnancy, both the hyperemesis gravidarum and the hyperthyroidism resolve.

There is an increased risk of transient hyperthyroidism in hyperemesis patients [27]. A study of 67 patients with diagnosed hyperemesis gravidarum found that 66% had biochemical hyperthyroidism [23]. The signs and symptoms of hyperthyroidism include nausea, vomiting, diarrhea, increased sweating, heat intolerance, irritability, hyperkinesia, fatigue, goiter, tachycardia, and weight loss. In addition, pregnant patients with hyperthyroidism may have a greater mean arterial pressure and pulse [28]. Laboratory results show marked elevation of thyroid hormones and suppression of thyroid-stimulating hormone [23].

There is some debate in the literature regarding whether the severity of the nausea and vomiting in pregnancy is related to the degree of hyperthyroidism. While some investigations found a significant association between the severity of vomiting and the degree of hyperthyroidism, other studies showed no correlation [23; 29]. Goodwin, Montoro, and Mestman speculate that vomiting might induce thyroid stimulation but add that there is no evidence to support such an effect [23]. They believe that the source of the hyperthyroidism is linked to the cause of the vomiting, but it is not causative in and of itself. Accordingly, the degree of thyroid stimulation correlates significantly with hCG levels [23]. They also found that in hyperemesis gravidarum, hyperthyroidism did not persist after resolution of vomiting. In all cases, the hyperthyroidism was self-limiting and resolved within 1 to 10 weeks.

Kimura et al. measured triiodothyronine (T_3), T_4 , TSH, hCG, and thyroid-stimulating activity (TSA) in 51 pregnant women [30]. The women were divided into three groups: those without emesis, those with emesis, and those with hyperemesis. While the researchers found no significant difference in the hCG levels among the three groups, they found that T_4 levels were significantly higher in the emesis and hyperemesis groups than in the nonemesis group.

Also, TSA levels were unexpectedly high in the group with hyperemesis. The study found that clinical symptoms of thyrotoxicosis were found to be correlated to levels of T_4 ; the patients with thyrotoxicosis were found to have T_4 levels twice the upper limit of normal. The authors suggest a new diagnosis of “gestational thyrotoxicosis” because the symptoms are different than classical Graves disease and resolve in the second half of pregnancy [30].

A similarly designed, yet somewhat conflicting study conducted by El Orabi et al. measured T_3 , T_4 , TSH, hCG, serum leptin, and antithyroid peroxidase (anti-TPO) antibodies in 50 pregnant women [31]. The women were divided into three groups, as in the previous study. T_4 levels were significantly higher in the hyperemesis group, but although the T_4 levels were elevated, they were judged as within acceptable limits. Additionally, the hyperemesis group showed no abnormal thyroid function or signs of thyrotoxicosis. Levels of hCG were similar between groups. The researchers suspect that hyperemesis gravidarum pathogenesis may be attributed to serum leptin [31]. However, the small sample sizes of these studies raise questions regarding widespread applicability of the results.

GESTATIONAL HORMONES

Human chorionic gonadotropin has been suspected as the cause of hyperemesis gravidarum based chiefly on the observation that its peak concentration in pregnancy coincides with the peak of nausea and vomiting [32]. Another suggestion for the causative role of hCG in persistent nausea and vomiting is the association between increased hCG concentrations and hyperemesis gravidarum in cases of twin and molar pregnancies.

In a study of 57 women with hyperemesis gravidarum, Goodwin et al. found that, when compared with a control group of non-hyperemesis patients, the hyperemesis patients had significantly higher levels of hCG [33]. The level of hCG correlated with the degree of thyroid stimulation and the degree of emesis. The researchers believe that hCG is the causative factor for both hyperemesis and

hyperthyroidism in pregnancy. This conflicts with the findings of Kimura and El Orabi, who found no difference in hCG levels between emesis and non-emesis groups [30; 31].

Apart from higher levels of hCG, estradiol is elevated in hyperemesis pregnancies compared with controls [11]. Several studies have found a higher female-to-male sex ratio in the offspring of pregnancies complicated by hyperemesis, with 55% of the offspring of these pregnancies being female compared with 49% of control pregnancies [34]. One study found that although hyperemesis appears to be more common and more severe in the presence of a female fetus, pregnancies with male fetuses appear to be more susceptible to the adverse effects of hyperemesis gravidarum on outcome [35].

Another hormone possibly responsible for hyperemesis gravidarum is 17-hydroxyprogesterone, a steroid hormone produced by the corpus luteum during pregnancy [4]. However, one study found that the rising levels of progesterone in pregnancy act to suppress nausea and vomiting by inhibiting prostaglandin E-2, which is released from decidual cells and macrophages of the decidua basalis [36].

It has been postulated that the position of the corpus luteum affects nausea and vomiting during pregnancy [37]. Theoretically, a corpus luteum arising from the right ovary results in a high concentration of sex steroids draining directly into the inferior vena cava and portal system, overwhelming the liver and causing hyperemesis.

HEPATIC DYSFUNCTION

In pregnancy, there are few changes in liver morphology, but there are alterations in liver function. During the first trimester, serum albumin and protein concentration fall, although intravascular protein is increased due to the increase in plasma volume. Most globulin fractions rise during pregnancy due to placental hormone production, and the albumin-globulin ratio decreases because of the dilution of albumin.

Hepatic dysfunction has been reported in patients with hyperemesis gravidarum [38]. Liver enzyme abnormalities have been documented in 25% of cases of hyperemesis gravidarum, as well as hyperbilirubinemia and retention of bromsulphalein sodium [39]. It is postulated that because the liver is the major site of inactivation of steroid hormones, hyperemesis may be due to either the liver's inability to or delay in inactivating the increased hormonal load during pregnancy. Hyperestrogenism can induce vomiting, which can lead to dehydration and inadequate nutrition, thus producing liver enzyme abnormalities.

Goodwin, Montoro, and Mestman examined both thyroid function and liver function in 67 patients with hyperemesis gravidarum and found that the patients with hyperthyroidism and hyperemesis were significantly more likely to have abnormalities in electrolyte levels and liver function studies [23]. Conversely, patients with the most severe alterations in these parameters demonstrated the greatest degree of biochemical hyperthyroidism. In a separate study, it was found that 72.7% of women with hyperthyroidism had irregular electrolyte levels compared with only 27.3% of euthyroid women [40]. Those with hyperthyroidism were also found to have abnormal liver enzyme levels. The severity of hyperthyroidism appeared to be in direct connection to the intensity of hyperemesis.

Despite this evidence, liver function abnormalities are far from universal in hyperemesis gravidarum. Abnormal liver functions have been found in only 50% of patients hospitalized with the condition [41]. Because liver dysfunction does not occur universally with hyperemesis gravidarum and abnormalities resolve spontaneously upon its cessation, liver dysfunction may be secondary to hyperemesis gravidarum.

GASTRIC DYSFUNCTION

The role of gastric functioning in hyperemesis gravidarum has also been studied. During pregnancy, increased levels of progesterone cause relaxation of the esophageal sphincter, not only resulting in heartburn but in nausea and vomiting as well. Also as a result of progesterone, gastric emptying is delayed and small bowel motility is reduced.

The mechanical activity of the stomach is controlled by myoelectrical activity that propagates slow waves that move food from the proximal body of the stomach to the distal antrum at three cycles per minute. The electrogastragram (EGG) is a test that measures gastric myoelectrical activity. It was first used in 1922 and is mainly utilized as a research tool in gastroenterology. At this time, it is not commonly used as a clinical or diagnostic tool [42]. Changes in EGG activity have been associated with clinical syndromes such as dyspepsia, diabetes, anorexia nervosa, and nausea and vomiting in pregnancy [37].

Riezzo et al. used the EGG to study gastric activity in pregnant women and found abnormal EGG activity in nine women with severe nausea and vomiting in the first trimester when compared with their EGG activity after voluntary termination of the pregnancy [43]. The EGG activity of hyperemetic women was also abnormal when compared with a control group of pregnant women of similar gestational age but without nausea and vomiting. The study also found delayed gastric emptying in women with hyperemesis gravidarum.

HELICOBACTER PYLORI INFECTION

Infection with *Helicobacter pylori*, a gram-negative spiral bacterium strongly associated with peptic ulcers, has been investigated as a cause of hyperemesis gravidarum. In one study, the investigators found that 89% of pregnant patients with hyperemesis gravidarum were seropositive for *H. pylori*, compared to 30% of the control group [44]. A 2010 study reached a similar conclusion, finding that 87% of women with hyperemesis gravidarum were infected with *H. pylori*, compared to 32% without the condition [45]. A meta-analysis of 38 cross-sectional and case-

control studies, involving 10,289 patients, revealed a significant association between *H. pylori* infection and hyperemesis gravidarum [121]. As such, screening of *H. pylori* infection should be added to the investigation of hyperemesis gravidarum cases. IgG antibody testing may detect *H. pylori* infection in patients presenting with hyperemesis; post-eradication monitoring may be carried out by stool antigen testing. Eradication of *H. pylori* in pregnant patients can significantly improve symptoms. Treatment options include the utilization of triple therapy, consisting of a proton-pump inhibitor and two antibiotics (e.g., amoxicillin or erythromycin and metronidazole) for two weeks [121]. Several case reports have suggested that eliminating *H. pylori* infection may cure hyperemesis gravidarum or at least modify its course [44; 46; 47].

AUTONOMIC NERVOUS SYSTEM DYSFUNCTION

It is speculated that changes in gastric functioning may be related to changes in autonomic nervous system function, particularly sympathetic adrenergic function [4]. Other changes in autonomic function related to physiologic changes during pregnancy include increased basal metabolic rate, glomerular filtration rate, blood volume, body temperature, and heart rate. The positive response to acupuncture is considered by some as evidence of autonomic nervous dysfunction etiology [5].

NUTRITION

Very few studies on nutritional deficiencies as causal factors for hyperemesis gravidarum have been cited in the literature. The research related to nutrition that has been published has focused on trace elements, notably zinc and copper. However, an association between hyperemesis gravidarum and deficiency states of these elements has not been found [4]. Other deficiencies commonly found in patients with hyperemesis gravidarum are thiamine and pyridoxine [48]. When deficiencies are corrected with supplements, nausea and vomiting often decreases; however, vitamin deficiencies have not been conclusively proven as a causative factor.

Excessive calorie intake is another factor. A pre-pregnancy diet high in fat (specifically saturated fat) has been found to greatly increase the risk of developing hyperemesis gravidarum [37]. For every 25 g increase in intake of total fat per day, the odds multiply by a factor of 2.9, and for every 15 g increase of saturated fat per day, the odds multiply by a factor of 5.4.

In one large study, the prepregnancy intake of seafood, allium vegetables (e.g., onion, garlic), and water was significantly lower among women who developed hyperemesis than among women in the non-hyperemesis group [49]. However, it is unclear if this diet should be recommended. A Norwegian study involving more than 51,000 pregnancies found that women with hyperemesis gravidarum were more likely to have diets high in carbohydrates and added sugars, particularly soft drinks [50]. The researchers were unable to determine if the diets were the result of changes in appetite or the cause.

PSYCHOLOGICAL FACTORS

Most of the literature regarding a psychological causation for hyperemesis was published prior to and during the 1970s. One could conclude that this is not currently an active area of research. Psychological factors should not be entirely discounted, but the cause and effect relationship between hyperemesis and psychopathology, including social anxiety, anxiety, insomnia, or depression, is not clear. The trend of hyperemesis gravidarum being less prevalent during war and postwar periods is also considered evidence of psychogenesis [51]. Additionally, a meta-analysis showed that hypnosis may be somewhat successful in relieving symptoms of hyperemesis gravidarum, indicating its possible psychological relation [52]. However, additional well-designed studies are necessary to assess the efficacy of hypnosis and to establish a psychological cause [52; 53].

A psychological factor that may play a role in hyperemesis is the patient's perception of the patient-provider relationship. Some studies have shown that individuals with hyperemesis encounter physicians

and healthcare providers who may doubt, trivialize, or ignore their symptoms [54]. Patients were not satisfied with clinicians who implied that their symptoms were caused by psychological factors, stress, or poor coping. In helping a patient suffering from hyperemesis, it is important for healthcare providers and patients to explore their beliefs of causation and arrive at a mutually agreeable treatment plan [54].

It is important to note that most research indicates that those with hyperemesis gravidarum have no psychiatric diagnoses prior to pregnancy [55]. It is hypothesized that hyperemesis could cause or exacerbate psychopathology.

GENETIC FACTORS

A more recent finding is the association of hyperemesis gravidarum with genetic factors, which has given some insights into possible etiology and also targets for therapeutic development [131]. Studies have shown that hyperemesis gravidarum can be passed down through generations; having a mother who experienced hyperemesis gravidarum increases one's risk by 3-fold and having a sister with hyperemesis gravidarum increases the risk by 17-fold. Twins studies suggest a heritability of around 73% for nausea and vomiting of pregnancy, with variations in duration and severity [131].

A genome-wide association study identified two factors, growth/differentiation factor 15 (GDF15) and insulin-like growth factor-binding protein 7 (IGFBP7), associated with hyperemesis gravidarum. GDF15, a hormone secreted by placenta and other cells under stress, is linked to nausea-associated behaviors through its neuroreceptor glial-derived neurotrophic factor family receptor alpha-like (GFRAL). Elevated GDF15 levels are found in nutritional stress and conditions like cancer-associated cachexia, mirroring hyperemesis gravidarum symptoms. Research indicates that GDF15 is increased in women with hyperemesis gravidarum and associated with familial cases. A 2024 study found that fetal production of GDF15 and maternal sensitivity to it both contribute substantially to the risk of hyper-

emesis gravidarum [133]. The GDF15-GFRAL axis is considered a potential mechanism for nausea and vomiting of pregnancy and hyperemesis gravidarum, warranting further study to develop targeted interventions and improve maternal and fetal outcomes [131].

POPULATIONS AT RISK

Using the criteria of weight loss greater than 5% during the first 16 weeks of pregnancy, the incidence of hyperemesis gravidarum is estimated to be 0.1% to 0.2% of all pregnancies [56]. This rate is lower than that found by Abell and Riely, who estimated the incidence to be 0.3% to 1% [4]. Currently, the incidence is considered to be between 0.2% and 3.6% of all pregnancies [10; 57; 115].

Little research has been done on the rate of hospitalization attributable to hyperemesis during pregnancy. Older studies indicate that approximately 5% of hospital admissions during pregnancy were due to hyperemesis [5; 35; 58; 59; 60]. A 2016 study found that 0.65% of hospital admissions during pregnancies across the United States were for hyperemesis [132]. There is evidence that hospital admission rates may be declining, though emergency department visits are increasing [128].

A 2012 study using data from the California State Inpatient Database also showed that hyperemesis gravidarum was the second most common reason for obstetric antepartum hospitalizations, comprising 7% of total antepartum hospitalizations [116]. Other studies estimate admission rates of 0.8% for hyperemesis gravidarum and an average of 1.3 hospital admission per patient with hyperemesis, with an average hospital stay of 2.6 to 4 days [59].

High prepregnancy body weight and nulliparity (having not given birth to a child) have been cited as risk factors for hyperemesis, and as discussed, a

high-fat diet has been found to greatly increase the odds [4; 63]. Maternal age younger than 20 years and twin gestation are also noted as risk factors [4]. The condition can repeat itself in subsequent pregnancies and is more common in patients with a history of spontaneous abortions [13]. Trostad et al. found that if an individual experienced hyperemesis in her first pregnancy, there was a 15.2% risk that she would experience it in subsequent pregnancies [64]. Those never having suffered from the condition have a 0.7% risk in later pregnancies.

There is a high risk of recurrence in second pregnancies, which may be reduced by a change in paternity, although research on this point is conflicting [65]. For those with no history of hyperemesis, a long interval between births slightly increased the risk of hyperemesis in the second pregnancy [64]. Conversely, pregnant patients older than 35 years of age and those who smoke cigarettes seem to be less at risk [4]. A generational study showed a 3% risk of experiencing hyperemesis among women whose own gestation was complicated by hyperemesis [66]. This is compared to a risk of 1.1% in women born after typical gestation.

There are limited demographic data relating to hyperemesis gravidarum, but some (also limited) evidence suggests a higher rate among certain racial/ethnic minority groups [67]. One study did note an increased risk among Pacific Islander patients [68]. Inuit and Native American populations tend to have a lower incidence of hyperemesis gravidarum [10]. In a study of 67 women with hyperemesis presenting at Los Angeles Women's Hospital, 94% were Hispanic [23]. However, the authors did not evaluate the racial mix of the general population served by this facility. Several studies have shown no clear racial predominance for hyperemesis gravidarum [10]. A large study of 417,028 pregnancies in England showed a statistical predominance in Asian and Black patients [118; 119].

INTERVENTION STRATEGIES

Generally, treatment of hyperemesis gravidarum is dependent on the severity of symptoms. Mild nausea and vomiting without dehydration may be treated on an outpatient basis with a conservative approach. Treatment begins with a modification of the diet and alternative treatments before utilizing pharmacologic treatment.

If nausea and vomiting are accompanied by dehydration, inpatient care may be indicated for rehydration and vitamin and mineral replacement as well as antiemetic therapy. After ketonuria and nausea and vomiting are resolved, home care might include antiemetic treatment, either orally or by home infusion via subcutaneous pump.

Intractable cases may require total parenteral nutrition (TPN) via a central venous catheter or parenteral nutrition via a percutaneous endoscopic gastrostomy (PEG) tube. This may be continued as long as oral feeding is not tolerated.

While treatment strategies to this point have focused on symptomatic management of patients already experiencing hyperemesis gravidarum, one study shows promise for pre-emptive treatment for those who experienced hyperemesis in a previous pregnancy [69]. In this study, women who had hyperemesis in a previous pregnancy were assigned to either the treatment group or the control group. Women in the treatment group received a standard form of antiemetic pharmacologic therapy prior to the onset of symptoms, while those in the control group received treatment only after the onset of symptoms. The authors found that there was a substantial decrease in the symptoms of hyperemesis in the treatment group versus the control group [69]. In a subsequent randomized controlled trial, the authors again found pre-emptive treatment to be superior in decreasing the risk of hyperemesis when compared with treatment that begins after the onset of symptoms [70].

DIET AND BEHAVIOR MODIFICATION

Nausea and vomiting of pregnancy is usually initially treated conservatively with diet in the hopes that the problem will not progress to hyperemesis gravidarum. General recommendations include choosing a bland diet, increasing carbohydrate intake, decreasing fat intake, avoiding offensive food odors, and avoiding iron supplementation, if possible. Omitting prenatal vitamins containing iron until the nausea resolves may also be helpful.

Specific suggestions are to eat bread or crackers before getting out of bed in the morning, when nauseated, and before retiring for the night. Experts also recommend eating small meals every two to three hours; drinking liquids between meals rather than with meals to avoid gastric distention; eating low-fat, high-protein foods; avoiding fried foods; and salting food to taste.

One controversial approach involves feeding patients with hyperemesis potato chips and lemonade [71]. The study found that potato chips were superior to the commonly prescribed saltine crackers in that they supplied more folic acid, vitamin C, and potassium. Potato chips also drive thirst, particularly for cold, tart, or sweet liquids. Researchers found that lemonade was better tolerated by patients than either ginger ale or plain water.

Because of the electrolytes lost in vomiting, consuming foods high in potassium and magnesium is recommended, as well as salting food, as tolerated, to replace chloride. Chewing one milk of magnesia tablet two to three times per day may help to settle the stomach and replace magnesium stores. Other frequently recommended foods are legumes, dairy products, nuts, oral nutrition supplements, and electrolyte-replacement drinks to preserve the body's electrolyte balance [46].

Behavioral changes recommended for patients with hyperemesis gravidarum are to take frequent rests, get plenty of fresh air, avoid sudden movements, avoid brushing teeth immediately after eating, and

sit upright for some time after meals to reduce the frequency of gastric reflux. Acupressure wristbands, which are sometimes used by passengers on boats to prevent seasickness, have been found to be helpful for some patients with nausea in pregnancy [72].

Avoiding offensive odors is of special importance. An overly sensitive sense of smell is common in pregnancy, possibly due to increased estrogen levels. Offensive odors commonly are food odors but can also be perfumes or chemicals. Minimizing odors and increasing fresh air are key ways to avoid nausea.

Patients with hyperemesis should also have psychological support, including reassurance, perhaps family and individual counseling, and a reduction in demands of daily living and environmental stimulation. Because the smell of hot or cooking food often induces nausea, it may be helpful for a partner, spouse, friend, or other person to prepare meals [32]. If eating hot foods cause patients to feel ill, it is recommended they stick with cold foods, such as sandwiches [73].

It is important that healthcare professionals accept patients' complaints of nausea and vomiting as a real physical problem and not necessarily psychological in origin. Patients who think their providers do not believe their complaints of nausea and vomiting may feel anger, diminished self-esteem, and confusion [54]. Acceptance of the patient's complaint and the assurance that it is not all in her head are paramount to establishing a therapeutic relationship.

A nursing assessment should first evaluate the frequency of vomiting episodes. Next, the nurse should determine any patterns to the nausea and vomiting episodes, such as what time of day or night they occur. It should also be determined which conditions lead to vomiting, such as an empty stomach or certain smells. Assessment must also include which, if any, foods seem to make the situation worse or better. Finally, the nurse must determine which measures the patient has already tried to alleviate the symptoms.

A dietary plan may be created using most of the discussed strategies (e.g., eating small meals every two to three hours, avoiding an empty stomach, avoiding fried or highly seasoned foods, and maintaining adequate hydration). The nurse can suggest that the patient keep a log of the type and amount of food consumed, as well as any episodes of nausea and vomiting. This may help both the patient and the nurse find patterns and dietary solutions to the problem.

Evaluation of a dietary plan should be ongoing at every prenatal visit. The goal is normal weight gain, fewer episodes of nausea and vomiting, normal vital signs, and no ketonuria. The dietary plan is also an important adjunct to pharmacologic therapy for hyperemesis.

PHARMACOLOGIC MANAGEMENT

If diet and lifestyle changes do not resolve the problem of nausea and vomiting, drug therapy may be indicated (**Table 1**). Approximately 10% of patients with hyperemesis require pharmacologic treatment [74].

The dilemma in treating hyperemesis gravidarum pharmacologically is the fear of possible teratogenic effects; both providers and pregnant patients are reluctant to use pharmacologic agents with possible fetal effects, especially in the first trimester of pregnancy. This is complicated by the fact that only one drug (Diclegis) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of nausea and vomiting of pregnancy [83].

The antiemetic medications used to treat nausea and vomiting in pregnancy fall into two broad classes: antihistamines and phenothiazines. Despite evidence of safety to the fetus, most antiemetics are contraindicated in pregnancy.

MEDICATIONS USED IN THE TREATMENT OF HYPEREMESIS GRAVIDARUM			
Drug	Dosage	Pregnancy Category	Notes
Antihistamines			
Meclizine (Antivert, Dramamine Less Drowsy)	25–50 mg/day PO	B	Antihistamine that decreases excitability of middle ear. Associated with relief of nausea and vomiting.
Dimenhydrinate (Dramamine, Driminate)	Oral: 50–100 mg every 4 to 6 hours Max: 400 mg/day IV/IM: 50 mg every 4 hours Max: 100 mg every 4 hours	B	Antihistamine that has anticholinergic and antiemetic properties. Decreases vestibular stimulation.
Diphenhydramine (Benadryl)	Oral: 25 mg every 4 to 6 hours or 50 mg every 6 to 8 hours Max: 300 mg/day IV/IM: 10–50 mg every 6 hours Max: 400 mg/day	B	Antihistamine with anticholinergic and sedative properties. Can be used for vestibular disorders that may cause nausea and vomiting.
Antiemetics			
Prochlorperazine (Compazine)	Oral/IM: 5–10 mg every 6 to 8 hours Max: 40 mg/day Rectal: 25 mg twice daily IV: 2.5–10 mg every 3 to 4 hours Max: 10 mg/dose or 40 mg/day	C	Antidopaminergic drug that blocks dopamine receptors. Has an anticholinergic effect.
Promethazine (Phenergan)	Oral/IV/IM/Rectal: 12.5–25 mg every 4 to 6 hours	C	An H ₁ receptor-blocking antihistamine that provides sedative and antiemetic effects. Black box warning: Risk of severe tissue injury regardless of the route of administration.
Metoclopramide (Reglan)	Oral/IV/IM: 5–10 mg every 6 to 8 hours	B	Blocks the dopamine receptor agents in the chemoreceptor zone of the central nervous system and stimulates intestinal motility. Negative synergistic CNS effects when combined with phenothiazines. Black box warning: May cause tardive dyskinesia.
Hydroxyzine (Vistaril)	IM: 25–100 mg/dose	C	An H ₁ receptor-blocking antihistamine agent that provides sedative and antiemetic effects.
Trimethobenzamide (Tigan)	Oral: 300 mg 3 or 4 times daily IM: 200 mg every 3 or 4 times daily IV/IM: 0.25–1.25 mg every 3 to 4 hours Loading dose: 1.0–2.5 mg	C	Acts centrally to inhibit the medullary chemoreceptor trigger zone by blocking emetic impulses to the vomiting center.
Droperidol (Inapsine)	IV/IM: 0.25–1.25 mg every 3 to 4 hours Loading dose: 1.0–2.5 mg	C	Neuroleptic agent that blocks dopamine stimulation of the chemoreceptor zone to reduce nausea and vomiting. Black box warning: Associated with fatal cardiac arrhythmias.
Ondansetron (Zofran)	Oral/IV/IM: 4 mg as a single dose	B	Selective 5-HT ₃ receptor antagonist that blocks serotonin.
Doxylamine/pyridoxine (Diclegis)	Oral: 20 mg on days 1 and 2 (at bedtime); if needed, 30 mg on day 3 (1 morning, 2 bedtime); if needed, 40 mg per day (1 morning, 1 afternoon, 2 bedtime) Max: 40 mg/day	B	—
Antipsychotics			
Chlorpromazine (Thorazine)	IV/IM: 25–50 mg every 4 to 6 hours Max: 300 mg/day Oral: 10–25 mg every 4 to 6 hours Max: 150 mg/day	C	Generally used short-term in a monitored setting, in conjunction with other agents and supportive measures, as an alternative to corticosteroids in patients in whom steroid side effects may be more serious

Table 1 continues on next page.

MEDICATIONS USED IN THE TREATMENT OF HYPEREMESIS GRAVIDARUM			
Drug	Dosage	Pregnancy Category	Notes
Antidepressants			
Mirtazapine (Remeron)	15–45 mg/day	C	Acts on nonadrenergic, serotonergic, histaminergic, and muscarinic receptors. This gives it antiemetic, sedative, anxiolytic, and appetite-stimulating effects. Common side effects include sedation, weight gain, dry mouth, and constipation. Monitor for suicidal ideation, especially in women younger than 24 years of age.
Corticosteroids			
Methylprednisolone (Medrol)	PO/IV: 16 mg every 8 hours for 3 days, then taper over 2 weeks to lowest effective dose	C	—
Supplements and Herbal Medications			
Pyridoxine (Vitamin B ₆ , Nestrex)	Oral: 10–25 mg 3 to 4 times per day	A	—
Ginger	Oral: 250 mg every 6 hours	A	—
Source: [2; 10; 32; 46; 73; 75; 76; 77; 78; 79; 80; 81; 82; 125]			Table 1

Antihistamines

Antihistamines block the effects of histamine at the H₁ receptor and do not block histamine release. Most antihistamines have anticholinergic effects, such as constipation, dry eyes, dry mouth, blurred vision, and sedation. They are used to treat motion sickness and insomnia as well as allergic conditions [84]. Antihistamines dry the mucous membranes, thus decreasing the excessive salivation associated with hyperemesis gravidarum. A meta-analysis of studies published in the last 30 years shows that antihistamines are not teratogenic in the first trimester of pregnancy and are effective in reducing vomiting [85].



EVIDENCE-BASED
PRACTICE
RECOMMENDATION

The Royal College of Obstetricians and Gynaecologists recommends antihistamines (i.e., H₁ receptor antagonists) and phenothiazines are considered the first-line choices when pharmacotherapy is indicated for hyperemesis gravidarum.

(<https://www.rcog.org.uk/media/y3fen1x1/gtg69-hyperemesis.pdf>. Last accessed August 21, 2023.)

Grade of Recommendation: C (A body of evidence including well-conducted case-control or cohort studies directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from high-quality systematic reviews of case-control or cohort studies)

Among the antihistamines used by patients for nausea and vomiting during pregnancy is doxylamine in combination with pyridoxine hydrochloride (vitamin B₆). It carries an FDA pregnancy Category B, which indicates that human fetal risk is relatively unlikely [76]. The FDA approved the combination of 10 mg doxylamine and 10 mg pyridoxine (marketed as Diclegis) in 2013 for the treatment of hyperemesis gravidarum. It is the only drug specifically approved

for this indication and has become a first-line therapy [83; 92]. A version of this combination that also included dicyclomine hydrochloride (marketed as Bendectin) was originally introduced in 1956 and was taken off the market in 1983 [86]. Despite the fact that controlled studies found no increased risk of birth defects, highly publicized lawsuits in the 1970s, involving neonates with severe malformations whose mothers had taken Bendectin, were judged unfavorably against the manufacturer. It is interesting to note that after Bendectin was removed from the market, the incidence of the type of limb deformities and congenital heart disease attributed to the medication did not decrease [86].

The individual components of Bendectin have been available in both over-the-counter and prescription forms and have not demonstrated to be teratogenic [87]. Moreover, a form of Bendectin has remained available in the United Kingdom and in Canada. This, along with the fact that Bendectin has not been conclusively shown to be teratogenic, initiated the move to reintroduce combination doxylamine/pyridoxine [86].

The delayed-release tablet is intended for patients who do not respond to other approaches to the management of nausea and vomiting in pregnancy. The recommended initial daily dose is two tablets (a total of doxylamine 20 mg and pyridoxine 20 mg) at bedtime on an empty stomach [76; 83]. In severe cases or in cases with nausea/vomiting during the day, the dosage may be increased to up to four tablets by adding a morning and/or afternoon dose. Studies have indicated that doxylamine/pyridoxine does not pose an increased threat to the fetus [83].

Dimenhydrinate is also Category B, but it has an oxytocic effect near term, which could induce labor if used in the last trimester. However, it has been used in the first trimester with no reports of congenital malformations [76]. Meclizine has been used for nausea and vomiting in pregnancy since the 1960s, with recommended dosages of 25–50 mg per day [76]. Diphenhydramine is another Category B

antihistamine that has shown some effectiveness in treating nausea and vomiting in pregnancy. Prior to the introduction of Diclegis, promethazine was used as a first-line pharmacologic treatment for hyperemesis gravidarum, particularly in rectal suppository form [32].

Nursing considerations for these medications include informing the patient that the medications may cause drowsiness and to avoid driving or operating machinery while taking them. These medications may also cause oral dryness, so frequent mouth rinses and good oral hygiene may be indicated to alleviate these symptoms, provided they do not trigger vomiting episodes.

Phenothiazines

Phenothiazines are dopamine antagonists that act on the chemoreceptor trigger zone to inhibit nausea and vomiting. Commonly used phenothiazines are chlorpromazine, prochlorperazine, promethazine, and trifluoperazine. As a class, the phenothiazines have been found to be non-teratogenic in clinical studies, although some anecdotal case reports have shown major malformations associated with first trimester use [85]. Aside from prochlorperazine, the phenothiazines are not commonly prescribed for treatment of hyperemesis gravidarum [84].

Nursing management of patients receiving phenothiazines should include monitoring for urinary retention; dizziness; hypotension; symptoms of akathisia, a restlessness or desire to keep moving; and tardive dyskinesia, an uncontrolled rhythmic movement of muscles including the face and mouth. Assessment for neuroleptic malignant syndrome is important. It is manifested by fever, respiratory distress, tachycardia, convulsions, diaphoresis, pallor, fatigue, and loss of bladder control. The patient should be taught to expect drowsiness, to change position slowly to avoid orthostatic hypotension, and to avoid sun exposure and extremes in temperature because the medication causes both photosensitivity and impairment of body temperature regulation.

Other Medications

Metoclopramide is a dopamine-receptor blocker in the chemoreceptor trigger zone of the central nervous system. It has an anticholinergic effect and stimulates mobility of the upper gastrointestinal (GI) tract and accelerates gastric emptying. While it is commonly available for injection or in oral form, pharmacists may make rectal suppositories [84]. Nursing management must include monitoring for extrapyramidal side effects, tardive dyskinesia, and drowsiness. This treatment is usually used as a last resort [2].

Hydroxyzine is an antianxiety agent that works as a central nervous system depressant and has anticholinergic, antihistamine, and antiemetic properties. It is available orally or for intramuscular injection. Because of these properties, nursing implications include teaching the patient about the common side effects of drowsiness, dizziness, and dry mouth. If administered intramuscularly, hydroxyzine must not be given in the deltoid muscle, but should be injected by Z-track because it is both painful and caustic to tissue [84]. The recommended injection site of IM hydroxyzine is the upper outer quadrant of the buttock or mid-lateral thigh [78].

Trimethobenzamide is an anticholinergic that has been used with some success in hyperemesis gravidarum. It is available by intramuscular injection or oral form.

Droperidol is often used as a tranquilizer prior to the administration of anesthesia, but it has also been used to treat hyperemesis gravidarum as it suppresses nausea and vomiting. It is used in inpatient settings only and is given parenterally. Droperidol may cause cardiac arrhythmias, particularly a prolonged QT interval, so nurses should obtain a 12-lead electrocardiogram (ECG) in all patients prior to, during, and three hours after administration [76]. Monitoring must also include signs of extrapyramidal reactions, hallucinations, hypotension, and tachycardia [84]. This drug is classified as a pregnancy Category C medication.

Ondansetron is a selective 5-HT₃ receptor antagonist that has been widely used in treatment of chemotherapy-induced nausea and vomiting. It acts by blocking the effects of serotonin at the receptors in the vagal nerve terminals and the chemoreceptor trigger zone in the central nervous system. In the past several years, it has become the most widely used drug of its class in the treatment of hyperemesis, although it should not be a first-line choice. Animal studies have shown no teratogenicity, and human studies have shown the same result [85]. It is classified as a pregnancy Category B medication, and there is some evidence of a slightly increased risk of cardiac abnormalities in neonates exposed to ondansetron [113].

In a double-blind clinical trial that compared ondansetron to promethazine, there was no statistical difference in the relief of nausea, weight gain, or days of hospitalization [88]. A separate randomized, placebo-controlled, double-blind superiority trial focusing on hyperemesis (though not during gestation) also found that ondansetron and promethazine produce statistically similar effects [89]. This is particularly relevant because ondansetron is considerably more expensive than promethazine.

In a small, double-blind, randomized controlled trial comparing ondansetron to promethazine and doxylamine for the treatment of nausea and vomiting in pregnancy, patients using ondansetron experienced significantly less nausea and vomiting [114].

Nursing implications for ondansetron include monitoring for headache, constipation, or diarrhea. Less commonly, side effects may include dizziness, drowsiness, and dry mouth. While it has been available in oral or intravenous form for some time, it has also been used in subcutaneous pumps, which deliver a basal rate of medication with occasional boluses as needed.

Transdermal scopolamine is an anticholinergic that has been suggested as a treatment for hyperemesis gravidarum; however, there have been no clinical trials of its effectiveness. Like many other medications used to treat hyperemesis gravidarum, it carries a Category C designation because of its possible teratogenic effects, based on animal studies [76]. However, no teratogenic effects were noted in an epidemiologic study inclusive of 309 patients [85].

Mirtazapine is being investigated as a promising option for treating hyperemesis when other treatments have failed. It is an antidepressant drug often used to treat patients undergoing chemotherapy because it acts on nonadrenergic, serotonergic, histaminergic, and muscarinic receptors. This gives it antiemetic, sedative, anxiolytic, and appetite-stimulating effects. Common side effects include sedation, weight gain, dry mouth, and constipation. It is unlikely to cause many clinically relevant drug interactions. In one small study, 15 patients began treatment with mirtazapine between 6 and 25 weeks' gestation and continued for up to 22 weeks [125]. All patients responded favorably to treatment within one week. It is important to screen patients for bipolar disorder prior to treatment as agitation, anxiety, and suicidal ideation may occur.

Pyridoxine, or vitamin B₆, is recommended for patients with hyperemesis gravidarum because a deficiency in the vitamin can lead to nausea and vomiting; it is also essential in protein synthesis. Reviews of vitamin B₆ supplementation indicate that it is effective in significantly decreasing mild-to-moderate nausea, but not vomiting [90]. A combination of doxylamine and vitamin B₆ has proven effective in several studies, along with a decrease in nausea and vomiting of 70% [87; 91; 92]. The recommended dosage for vitamin B₆ is 10–25 mg three to four times per day [76; 93].

A 1953 report indicated that cortisone relieved chemotherapy-related nausea and vomiting and hyperemesis gravidarum. However, only in 2000 did randomized clinical trials support the use of steroids as treatment. Corticosteroids are thought to affect a chemoreceptor trigger zone in the brain to reduce nausea and vomiting. An alternative explanation is that corticosteroids correct an adrenal insufficiency that is caused by increased adrenal demands during pregnancy [94]. A controlled study compared treatment of hyperemesis gravidarum with oral methylprednisolone to treatment with oral promethazine. The methylprednisolone was given for three days and then tapered for two weeks, while the dosage of promethazine remained the same. The study showed that methylprednisolone was more effective at three days than treatment with promethazine [95]. However, the regimen should be discontinued if the condition does not improve within three days [82]. Prednisolone has been shown to improve symptoms after the first two days, with few side effects [96].

It is recommended that steroid therapy, either oral or intravenous, be used as a last resort for patients whose hyperemesis does not respond to conventional antiemetics and intravenous hydration. Nurses who are monitoring patients receiving steroid therapy must pay particular attention to glucose control, as the use of glucocorticoids increases blood glucose levels [96].

It is once again important to note that none of the discussed medications, with the exception of Diclegis, have been approved by the FDA to treat morning sickness or hyperemesis gravidarum. The drugs have been used with some success as described, but these are off-label uses and are not FDA approved. Also, the authors of a comprehensive review of the safety and efficacy of the available interventions for hyperemesis gravidarum concluded that there is little high-quality and consistent evidence supporting any one intervention [97].

INTRAVENOUS THERAPY

Intravenous therapy is designed to replace fluid and electrolyte levels while resting the GI tract. An infusion of Ringer's solution with 5% dextrose (D5RL) is recommended over 5% dextrose in normal saline (D5NS), because D5RL supplies some potassium and calcium, whereas D5NS does not [98; 99]. Blood levels of sodium, potassium, magnesium, and calcium should be obtained before initiating IV therapy so any missing minerals can be added to the standard formulation. Vitamins, particularly those that are water-soluble, should also be added to the formulation. In cases of hyponatremia, rapid replacement of sodium levels may result in confusion, spastic quadriplegia, horizontal gaze paralysis, delirium, brain damage, or death. This is known as central pontine myelinolysis [16].

Thiamine stores must be restored before intravenous therapy begins, as the dextrose in the solution causes the body to metabolize thiamine. As previously mentioned, thiamine deficiency can lead to Wernicke encephalopathy. Signs and symptoms of Wernicke encephalopathy include visual disturbances, such as diplopia or nystagmus, as well as disorientation, delusion, and gait ataxia. While there is no specific treatment regimen, some experts recommend parenteral thiamine 100–500 mg daily for three days and 2–3 mg per day thereafter [100].

Nursing assessments should include starting and maintaining the patency of the intravenous infusion, maintaining the infusion rate, and assessing the IV site for infection or infiltration. Venipuncture can be difficult in dehydrated patients, but placing the site in a dependent position and warming the area with warm compresses may cause enough vasodilation to enable an easy insertion. Warming the first liter of fluid may prevent the feeling of coldness that dehydrated patients experience.

Assessments might also include intake and output, as well as assessing for episodes of vomiting. Vital signs are one marker of hydration status and should be monitored per protocol. Antiemetic therapy is often initiated as well as IV hydration; therefore, ongoing assessments for side effects should be included.

Shortly after IV therapy is initiated, oral feeding may be resumed. The diet is usually initiated with clear liquids and proceeds to small, frequent meals. Nurses should monitor dietary intake and advance the diet as tolerated. If the diet is not tolerated, enteral feeding may be an option [99].

Discharge planning should be initiated on admission. The goal is to discharge the patient to home as soon as dehydration is treated, vomiting has subsided, and the patient is able to keep food down. Discharge planning should include counseling regarding diet, as well as educating the patient regarding her medications, side effects, and warning signs.

Enteral nutrition works in conjunction with antiemetics and is useful if the patient's vomiting is not acute. A standard or small-bore nasogastric feeding tube is used to introduce 25 mL/hour of an iso-osmolar formula, increasing volume for 24 to 48 hours until the desired outcome is achieved (100 mL/hour) [101]. The risk of enteral therapy is that aspiration pneumonia can develop if vomiting leads to displacement of the feeding tube [99]. A small study found that nasogastric tube feedings led to fewer complications, such as infection, deep vein thrombosis, and intrauterine growth restriction, than the use of a peripherally inserted central catheter (PICC) [102].

Percutaneous endoscopic gastrostomy (PEG) tubes have been used for feedings in patients with intractable hyperemesis gravidarum. Studies comparing the safety and efficacy of this method as compared to TPN are lacking, however.

As a last resort, TPN may be indicated for long-term therapy in hyperemesis gravidarum. A central catheter (Hickman type) is inserted into the subclavian vein, and after verification of placement and instructions on care, the therapy can be continued at home or as an outpatient. A PICC permits long-term administration of hyperosmolar solutions without the insertion risks associated with central venous access. A study of 122 women receiving parenteral nutrition support during pregnancy demonstrated it provided a safe means of maintaining maternal nutrition and supported good fetal growth during the first trimester [103].

With TPN, nurses must assess the insertion site for signs of infection and change dressings per protocol. Sepsis is a considerable concern [104]. Due to the dehydration associated with hyperemesis as well as the elevated coagulation factors associated with pregnancy, these patients are at higher risk for catheter-related thromboembolism. Because TPN is a hyperosmolar solution, it may damage the walls of blood vessels, further leading to a risk of thrombosis. During initial administration, the nurse should check for signs of hyperglycemia. Home health nurses provide important care of outpatient hyperemesis patients, monitoring the infusions, assessing the insertion site, monitoring weight gain and response to treatment, teaching self-care techniques, and planning for removal of TPN and return to eating normally.

NONPHARMACOLOGIC MANAGEMENT

Before beginning a discussion of alternative treatments for hyperemesis gravidarum, it should be mentioned that while they may be adequate for the normal nausea and vomiting of early pregnancy, they may be inadequate for treatment of hyperemesis gravidarum. Generally, because of their low risks and few side effects, they may be appropriate as adjunctive therapy.

Massage therapy has been shown to increase serotonin and dopamine and decrease cortisol levels, all helpful in relaxation and in decreasing stress. Tactile massage is a form of soft, slow massage that can be given on the hands and feet or on the entire body. One small study found that tactile massage was helpful in promoting relaxation, diverting thoughts of nausea and vomiting, and giving the patient a feeling that her body is functioning again. The authors suggest that tactile massage is a good alternative and complementary therapy for hyperemesis [105].

Acupressure has been used for the treatment of morning sickness, as well as motion sickness and post-chemotherapy nausea and vomiting. As such, it is the best-studied alternative therapy. Treatment includes wearing wristbands that apply pressure to the inner forearm approximately three finger breadths proximal to the wrist (e.g., Sea-Bands). A 2014 Cochrane review did not find P6 acupuncture or acupressure wristbands significantly more effective than placebo for the treatment of nausea and vomiting in early pregnancy, but it is unclear if the approach would be more effective for patients with hyperemesis gravidarum [106]. While many clinical trials show statistically significant improvement in nausea, fewer studies show improvement in vomiting [90]. However, many of the studies are flawed, having small sample sizes, inadequate control groups, and little if any blinding [90].

A similar method is an acustimulation device, commonly worn around the wrist, that transmits an electrical stimulus to the acupressure point. Studies have shown some benefit in using this device to treat nausea of early pregnancy [90].

Ginger ale has been recommended for many years to alleviate the nausea and vomiting in early pregnancy. In fact, ginger is the only herbal remedy formally studied for the treatment of morning sickness. However, ginger is not without risks; it has adverse effects on clotting factors and may potentiate anti-

coagulants. In some cases, it may actually exacerbate nausea and vomiting and associated symptoms, such as heartburn and reflux [74]. A meta-analysis of studies of ginger for the treatment of nausea and vomiting during pregnancy concluded that the use of ginger (<1,500 mg daily) may provide relief from nausea but not vomiting [107]. Because study participants experienced few side effects or adverse effects, the authors concluded that ginger could be considered a safe alternative option for patients with nausea and vomiting of pregnancy.

Most herbal medications touted for amelioration of nausea and/or vomiting have not been rigorously tested, particularly in pregnant patients, and should be avoided. The FDA issued a warning to avoid the traditional African remedy of Nzu, also known as Calabash clay, Calabar stone, Mabele, Argile, and La Craie, as it can contain arsenic and lead and may result in a number of harmful effects [108; 117].

As noted, hypnosis has been shown to be effective in treating morning sickness [5; 52]. Nausea and vomiting may have a psychological as well as a physiologic component in that expectations, beliefs, and conditioning may trigger episodes. Hypnosis may prove to be of use as adjunctive therapy in treating hyperemesis gravidarum, particularly because of the lack of side effects or complications from the technique.

NURSING IMPLICATIONS

NURSING ASSESSMENT

Patients with hyperemesis gravidarum are typically between the 4th and the 10th week of gestation and may complain that they are unable to keep anything down or are vomiting constantly. It is important to ascertain how frequent the vomiting episodes are, when they are worse, what the triggers are, and what remedies the patient has already tried.

On physical examination, the patient may appear weak, pale, and with dry mucous membranes. A ketotic breath smell may be noted. Infrequently, jaundice might be noted. A weight check may reveal weight loss, as much as 5 pounds in a week. Blood pressure may manifest orthostatic changes, and pulse may be elevated secondary to dehydration.

A urine dipstick analysis should be performed, with particular attention to the presence of ketones. Specific gravity will be increased [109].

RELATED NURSING DIAGNOSES, PLANS, INTERVENTIONS, AND EVALUATIONS

Applicable nursing diagnoses are listed below, with suggested interventions and rationales. These are based on the North American Nursing Diagnosis Association (NANDA) diagnoses.

Nausea

Nausea is defined as “a subjective unpleasant, wave-like sensation in the back of the throat, epigastrium, or abdomen that may lead to the urge or need to vomit” [111]. Olfactory stimulation can sometimes trigger nausea. Interventions include avoiding unpleasant odors and food smells, particularly those that trigger the nausea. The patient should avoid fried or greasy meals because these also promote nausea. The patient should attempt small, frequent meals and drink fluids in between meals to help reduce the amount of food in the stomach and avoid the feeling of fullness that can aggravate nausea. The patient should avoid lying supine for at least 30 minutes after eating, because this position applies pressure on the diaphragm and digestion is improved by gravity.

The nurse can teach the patient diversion techniques, such as taking a whiff of isopropyl alcohol. This intervention diverts attention from the nausea. The nurse can also teach the patient guided imagery and relaxation techniques or recommend acupuncture bands.

The expected outcome would be a decrease in nausea within a given time frame, perhaps 24 to 72 hours. However, because nausea is often accompanied by vomiting, time is of the essence; dehydration can easily occur in 72 hours [112].

Imbalanced Nutrition, Less than Body Requirements

Simply defined, imbalanced nutrition is the inability to meet metabolic needs by nutritional intake. The recommended daily amount (RDA) for caloric intake in early pregnancy is similar to the RDA for nonpregnant women: 1,500–2,200 calories per day, depending on activity level. Later in the pregnancy, the recommended caloric intake increases by 300 calories per day.

Nursing interventions are similar to those for nausea. Nurses may counsel the patient to eat low-fat foods and carbohydrates, such as fruit, breads, cereals, rice, and pasta. These foods provide calories and help prevent hypoglycemia, which can cause nausea. Salting foods can help to replace chloride, which is lost in vomiting.

Evaluation of the nursing interventions should include monitoring for weight gain and monitoring urine for ketonuria. The patient should be asked about the number and severity of nausea and vomiting episodes or complaints of fatigue [112].

Dehydration

Dehydration is a state in which an individual is at risk for or experiencing fluid depletion. The nursing assessment may reveal dry mucous membranes, decreased skin turgor, tachycardia, hypotension, increased body temperature, and ketonuria. The hemoglobin and hematocrit may be elevated, but sodium, potassium, and chloride may be reduced due to vomiting.

Because patients with hyperemesis gravidarum are unable to maintain oral hydration, inpatient treatment is initially required to intravenously hydrate the patient. Therefore, nursing interventions are

collaborative and supportive to medical management. The intravenous site is monitored for signs of infection and infiltration, and site care is provided per institutional policies. Intravenous intake is monitored, as well as output, including bowel, urine, and vomitus. Normal urinary output is about 1 mL/kg/hour. A record of bowel elimination may yield information as to the effectiveness of dietary interventions.

The nurse may be responsible for administering parenteral antiemetics and vitamins as well as monitoring for any adverse reactions to medications. Daily weight gain may also be monitored, and the patient is assessed for readiness to tolerate oral feedings, with the diet being advanced as tolerated.

Patient education should focus on teaching about taking medications and maximizing caloric intake. Arranging for home health services for intravenous infusions or subcutaneous antiemetic therapy may be indicated [112].

Impaired Tissue Integrity

This nursing diagnosis includes impaired oral mucous membrane integrity, due to both dehydration and vomiting. Nursing assessments might reveal a complaint of dry mouth, bad taste, or even excessive salivation. Inspection may reveal dry or cracked mucous membranes, pallor, ulcerations, edema, coated tongue, or hemangiomas (a network of small blood-filled capillaries near the surface of the skin).

Interventions should include teaching oral hygiene, such as brushing at least three times per day, after each meal, or after each episode of vomiting. The use of a soft-bristle brush is indicated, as bleeding gums are common in pregnancy and a hard-bristle brush could further injure soft oral tissue. An alcohol-free mouthwash should be used, as alcohol-based products can be drying. However, these interventions must be evaluated on an individual basis as they may exacerbate the nausea and vomiting. Treatment of dehydration will generally improve oral mucous membrane integrity [112].

RESOURCES

Several support groups for those with hyperemesis gravidarum have emerged on the Internet.

The Hyperemesis Education and Research (HER) Foundation

<https://www.hyperemesis.org>

Pregnancy Sickness Support

<https://www.pregnancysicknesssupport.org.uk>

CONCLUSION

Hyperemesis gravidarum is a serious complication of pregnancy in the first trimester. If untreated, it can lead to intrauterine growth restriction, low-birth-weight infants, and possibly neonatal abnormalities. The effects on the mother include weight loss, fluid and electrolyte disturbances, dehydration, starvation, Wernicke encephalopathy, esophageal fistulas, and in rare cases, death.

There is probably no single etiology for hyperemesis gravidarum. This disorder has been referred to as a multifactorial syndrome and may involve psychological factors as well as physiologic and metabolic disorders. The possible roles of hyperthyroidism/thyrotoxicosis, gestational hormones, hepatic dysfunction, gastric dysfunction, infection, autonomic nervous system dysfunction, nutritional deficiencies, and psychological factors as causes for hyperemesis gravidarum have been explored. A review of the literature has shown that there are deficiencies of sample sizes, lack of control groups, and variations in how the disorder is diagnosed, and for every study that suggests a connection between hyperemesis and a metabolic disorder, another study refutes it.

Risk factors are defined, but ethnic and demographic data are lacking. Resources for affected individuals are scarce. The litigious nature of American society has made it unlikely that research will be done on other possible pharmacologic treatments for the disorder, although other, potentially more dangerous pharmaceuticals are commonly bought over-the-counter and used for treatment. Conversely, intrave-

nous, enteral, and parenteral feeding of hyperemesis patients have been quite effective in treatment.

Nurses play a key role in all aspects of the management of hyperemesis gravidarum. Often, they are the first to hear of the patient's complaints of nausea and vomiting. Nursing assessment may lead to an initial diagnosis, and nurses are responsible, in inpatient and home visitation settings, for the administration and monitoring of pharmacologic therapy and fluid replacement therapy. Nurses teach all aspects of the disease process, from dietary and alternative methods of management to side effects of pharmacologic therapy. Ongoing nursing evaluations should monitor treatment and screen for exacerbations of the condition. Nurses provide psychological support for patients and facilitate the mobilization of community resources necessary to treat this disorder.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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