Chapter 3
Approach to the Patient with Nausea and Vomiting in Pregnancy

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Introduction

Nausea and vomiting is a common problem during pregnancy estimated to impact 70–80% of pregnancies [1]. The exact incidence is difficult to determine because many women do not seek medical attention. The primary treatment for these patients is supportive, and symptoms typically resolve by 14–16 weeks of pregnancy. Although nausea and vomiting contributes to maternal stress and decreased quality of life, it is generally not associated with adverse maternal or fetal outcomes. Nausea and vomiting of pregnancy does, however, represent a significant cost burden to the healthcare system, estimated to cost nearly 2 billion dollars in 2012 alone [2]. Rarely, nausea and vomiting is severe, resulting in weight loss, dehydration, and electrolyte disturbances. When this occurs, it is known as hyperemesis gravidarum (HG). Estimates regarding the prevalence of HG vary, but it is thought to affect between 0.5 and 2% of pregnancies, with some literature suggesting it occurs in up to 3% of pregnancies [3]. According to a recent Cochrane review, HG is the leading cause of hospital admissions in early pregnancy [4]. HG typically occurs between the 4th and 10th week of gestation but may occur at any point during pregnancy. The exact etiology of HG is unknown and is thought to be multifactorial. Factors thought to contribute to the pathogenesis of HG include gestational-induced hormonal changes, genetics, preexisting upper GI dysmotility, and *H. pylori* infection [5, 6]. HG is associated with higher risk of pregnancy complications and negative outcomes such as preterm birth, small-for-gestational-age infants, and low birth weight [6].

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J. Borhart (ed.), *Emergency Department Management of Obstetric Complications*,
DOI 10.1007/978-3-319-54410-6_3

Emergency Department Management

Diagnosis

HG is a clinical diagnosis. Emergency department (ED) evaluation begins with a thorough history and physical exam in conjunction with basic laboratory work. The hallmark symptoms of HG are excessive or unrelenting nausea and severe vomiting associated with [7]:

1. Weight loss of greater than 5% prepregnancy weight.
2. Signs of dehydration including orthostatic hypotension, elevated BUN, elevated hematocrit, decreased urine output, and syncope.
3. Presence of ketones in the urine.
4. Electrolyte disturbance including hyponatremia, hypochloremia, and hypokalemia [8].

Relevant predisposing risk factors for HG include female fetus, multiple pregnancy, prior personal or family history of HG, and molar pregnancy [9, 10]. Additional elements in the history that may point toward HG include a report of hypersensitivity to smells, hypersalivation, and symptoms suggestive of dehydration such as feeling lightheaded, dizziness, or syncope. Suggested laboratory tests include urinalysis, basic metabolic panel, and liver function tests (Table 3.1).

If no prior prenatal care has been received, an ultrasound should also be obtained to ensure an intrauterine pregnancy is present and there is no evidence of trophoblastic disease. Transient depressed thyroid stimulating hormone occurs in up to 60% of patients with HG [11]. However, these patients are clinically euthyroid and do not require further treatment to correct thyroid levels [12]. Routine testing of thyroid function in the ED is not necessary in patients with HG.

Table 3.1 Recommended laboratory testing for evaluation of hyperemesis gravidarum

Test	Abnormalities seen in hyperemesis gravidarum
Urinalysis	Elevated urine specific gravity (>1.020) Presence of ketones
Basic metabolic panel	Electrolyte disturbances (hyponatremia, hypochloremia, hypokalemia) Acidosis Elevated BUN Evidence of acute kidney injury
Liver function tests	Elevated AST/ALT and total bilirubin may occur in up to 50% of HG patients

Treatment

A stepwise approach to the treatment of mild nausea and vomiting of pregnancy and HG in the emergency department is recommended (Table 3.2). Early recognition and treatment of nausea and vomiting in pregnancy is essential to minimize the impact of symptoms and prevent further disease progression. The first step is to restore normal volume status. Oral rehydration may be sufficient for more mild symptoms if tolerated by the patient. In cases of moderate to severe dehydration or inability to tolerate oral intake, intravenous fluids are required. Other therapies to consider for supportive care include vitamin repletion, specifically thiamine and folate, along with dextrose if prolonged symptoms. Lifestyle modifications and the use of alternative therapies can be suggested. Lifestyle changes commonly recommended include dietary changes and avoidance of triggers. Patients should be encouraged to take small continuous sips of neutral liquids (i.e., ginger ale) or electrolyte sports drinks. Eating small, frequent bland snacks (i.e., saltine crackers) to avoid an empty stomach may also decrease nausea [13]. A non-pharmacological alternative therapy that is considered safe in pregnancy is ginger supplements. Several small studies have shown benefit of ginger supplements in the reduction of nausea and vomiting in pregnancy when compared to placebo [14, 15]. Ginger supplements can be administered as 250 mg four times daily [16].

For patients with symptoms refractory to lifestyle and dietary modifications who require pharmacological antiemetic therapy, pyridoxine (vitamin B6) alone or pyridoxine with doxylamine is considered first-line therapy and recommended by the American College of Obstetricians and Gynecologists (ACOG) [17].

Historically, pyridoxine and doxylamine was sold in the USA as Bendectin from 1956 to 1983. Despite claims in the 1970s and 1980s of possible teratogenic effects of Bendectin, the Food and Drug Administration (FDA) found no link between Bendectin and human birth defects [18, 19]. Subsequently, the voluntary removal of Bendectin from the US market did not correlate with a reduction in birth defect reports, and the hospitalization rate for women with hyperemesis gravidarum doubled [20–22].

The use of pyridoxine with doxylamine has been shown to be safe and effective in the treatment of nausea and vomiting in pregnancy in the meta-analysis of multiple cohort and case-control studies [23]. A 2015 matched, controlled cohort study found improved nausea control with pyridoxine with doxylamine therapy in comparison to pyridoxine therapy alone. This difference was most evident in patients with moderate to severe symptoms [24]. Pyridoxine with doxylamine has been available commercially in the USA as a delayed-release combination 10 mg/10 mg tablet under the brand name Diclegis® since 2013 and remains the only FDA-approved medication for the treatment of nausea and vomiting in pregnancy with an FDA pregnancy category A rating [25] (Table 3.3). For patients discharged from the

Table 3.2 Recommended treatment algorithm for nausea and vomiting in pregnancy

Step in therapy	Treatment option	Clinical considerations
1. Supportive care	• Restoration of normal volume status with oral (if tolerated) or IV fluids (D5 ½ normal saline) • Add 20 mEq KCL if hypokalemic • Vitamin repletion • A multivitamin containing folate	Avoid rapid correction of hyponatremia Consider thiamine repletion, especially prior to dextrose administration if prolonged symptoms or concern for Wernicke's encephalopathy
2. Antiemetic therapy: first line	• Diclegis®, pyridoxine 10 mg + doxylamine 10 mg (two pills taken at bedtime) • Pyridoxine 25 mg every 6 h + doxylamine 12.5 mg every 6 h	Diclegis®: pregnancy category A Onset of action 5–7 h, oral dose only, ideal for home use
3. Antiemetic therapy: second line, for moderate to severe vomiting	• H1 antagonists Diphenhydramine 25 mg every 6 h or dimenhydrinate 50 mg every 6 h	Diphenhydramine: pregnancy category B Side effects: sedation, dry mouth, urinary retention
	• Dopamine antagonists: Metoclopramide 10 mg	Metoclopramide: pregnancy category B Side effects: sedation, tardive dyskinesia, acute dystonic reaction
4. Antiemetic therapy: alternate second line, for refractory symptoms	• Selective serotonin antagonists Ondansetron 4 mg every 8 h, maximum 16 mg IV	Ondansetron: pregnancy category B, high efficacy in studies Recommend EKG and electrolyte monitoring with IV use Side effects: maternal QT prolongation in IV formulation, may cause fetal cardiac septum malformation
	• Phenothiazines Prochlorperazine 10 mg every 6 h or promethazine 25 mg every 4 h	Promethazine: pregnancy category C, may be administered rectally Prochlorperazine: less well studied
	• Steroids Methylprednisolone 40 mg daily, after 10 weeks' gestation, limit 3-day therapy	Steroids: may cause fetal oral clefts, low birth weight, last resort therapy, routine use not recommended
5. Adjunctive treatments	• Dietary changes Eat bland foods, small frequent meals, avoid having an empty stomach	No reported adverse effects
	• Avoidance of triggers Especially olfactory triggers	No reported adverse effects
	• Supplements Ginger 250 mg supplements four times daily	Avoid supplements with multiple active ingredients with unknown safety profiles

ED with nausea and vomiting in pregnancy, Diclegis® remains the recommended prescription therapy due to its delayed-release formulation. Diclegis® should be used daily rather than on an as-needed basis. Diclegis® is prescribed with the initial dose of two tablets at bedtime to address morning symptoms. If symptoms persist in the afternoon, an additional tablet may be taken in the morning, up to four tablets per

Table 3.3 FDA drug risk classification in pregnancy[a]

Category	Description
A	Controlled studies in humans show no risk to the fetus
B	Animal studies show no risk to the fetus, no controlled studies in humans
C	No controlled studies in animals or humans
D	Evidence of human risk to the fetus exists; however, benefits may outweigh risks
X	Controlled studies demonstrate fetal abnormalities. Risk outweighs any possible benefit

[a]As of 2014 the FDA is changing drug labeling regarding use during pregnancy or lactation and phasing out the letter categories [42]

day [26]. Diclegis® is expensive for some patients and not covered by all insurances. As an alternative, clinicians may prescribe doxylamine 12.5 mg by mouth every 6 h and pyridoxine 25 mg by mouth every 6 h. However, over-the-counter immediate-release doxylamine has not been shown to have similar therapeutic efficacy, exhibits higher sedative effects than the delayed-release formulation, and may contain other active ingredients that have not been studied for safety in pregnancy [25].

Pyridoxine with doxylamine is not approved for IV administration or for the treatment of HG. Other antiemetic therapies should be considered in patients with persistent nausea and vomiting or HG. These medications include H1 antagonists, selective serotonin inhibitors, and dopamine antagonists (Table 3.2). These medications have limited fetal safety data and are used off-label in the treatment of nausea and vomiting in pregnancy. Maternal benefit versus fetal safety should be weighed when considering these options.

H1 antagonists used in pregnancy include diphenhydramine, dimenhydrinate, and meclizine. These medications hold an FDA pregnancy category B rating; however, there are no well-controlled studies of fetal safety with these medications [28]. These medications may cause maternal drowsiness.

Metoclopramide is a dopamine receptor antagonist classified as FDA pregnancy category B and is used off-label for HG. A large retrospective cohort study evaluating for congenital malformations, perinatal death, low birth weight, and low Apgar scores found no adverse pregnancy or fetal outcomes associated with metoclopramide use in first trimester of pregnancy [27]. Metoclopramide may cause drowsiness and dizziness and comes with risk of acute dystonic reactions and tardive dyskinesia. Risk of serotonin syndrome with concomitant use of antidepressants should be considered. Promethazine and prochlorperazine are additional dopamine receptor antagonists to be considered as third-line agents, as promethazine is a category C medication and limited safety data exists for prochlorperazine [28]. Promethazine may be administered rectally if the patient is unable to tolerate any oral medications.

Ondansetron is a 5-HT3 receptor antagonist that is designated by the FDA as pregnancy category B. Several studies have shown it to be as effective and perhaps more effective compared to other commonly used antiemetics including pyridoxine in the treatment of nausea and vomiting in pregnancy [29, 30]. One study comparing ondansetron to metoclopramide showed not only similar efficacy but also less adverse effects including decreased drowsiness with use of ondansetron [31].

Several small studies as well as two large retrospective cohort studies have reported conflicting results as to the safety of ondansetron in pregnancy. A large retrospective cohort study by Pasternak et al. included 608,385 pregnant patients in Denmark. This study compared the risk of several adverse fetal outcomes including spontaneous abortion, stillbirth, any major birth defect, preterm delivery, and low birth weight between pregnant women exposed to ondansetron and women not exposed. They found that exposure to ondansetron was not associated with a significantly increased risk of any of the adverse fetal outcomes studied [32]. Another large cohort study by Danielsson et al. was performed using data from the Swedish Medical Birth Register. The authors found no statistically significant increased risk for major fetal malformation. This study did, however, show a statistically significant increased risk of cardiovascular defects, specifically cardiac septum defects among neonates exposed to maternal ondansetron use (OR = 1.62, 95% CI 1.04–2.14, and RR 2.05, 95% CI 1.19–3.28, respectively) [33]. The analysis by Danielsson et al., however, was less rigorous (adjusted for fewer confounders, importantly maternal medical history), as compared to the study by Pasternak et al.

Two systematic reviews of current literature on ondansetron use in pregnancy were conducted in the past year. One review performed by Siminerio et al. concluded that current data does not support avoiding ondansetron in the treatment of pregnant women based on "the principle of absence of harm to date and presence of efficacy." The authors concluded that maternal benefit outweighs potential risk [34]. A separate systematic review recommends reserving ondansetron for women whose symptoms are not adequately controlled by other treatments given reports of a small increase in the incidence of neonate cardiac abnormalities with maternal ondansetron use [35]. Maternal risks with intravenous ondansetron use include QT prolongation and risk of torsades de pointes. Intravenous doses should be limited to 16 mg and require EKG and electrolyte monitoring per FDA recommendations [36].

The use of steroids for the treatment of HG remains controversial. Studies have yielded conflicting results regarding fetal outcomes of prenatal maternal systemic steroid use. Steroids have been linked to low birth weight and low head circumference as well as mixed reports of an increase in cleft lip and cleft palate [37–39]. A systematic review and meta-analysis on the utility of steroid use in the treatment of HG concluded that there was insufficient evidence to support its use [18]. ACOG states that methylprednisolone may be of benefit in refractory cases of HG; however, given its risk profile, it should be a last resort after 10 weeks' gestation [20]. The authors do not recommend the routine use of steroids in HG in the emergency department. The decision to use steroids as a last resort should be made in consultation with an obstetrician.

Disposition

The majority of patients presenting to the emergency department with nausea and vomiting in pregnancy can be safely discharged at home. Admission to the hospital is reserved for persistent/severe nausea and vomiting, severe dehydration, or lab

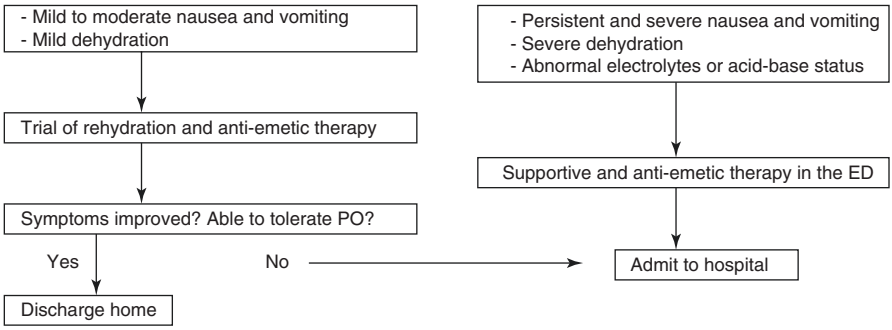

Fig. 3.1 Disposition algorithm for nausea and vomiting in pregnancy

abnormalities including electrolyte or acid-base derangements that require intravenous correction (Fig. 3.1). For patients discharged from the emergency department, close obstetrics follow-up, dietary counseling, and prescription of pyridoxine with doxylamine as first-line preventive therapy are indicated.

Complications

Although rare, there are several important potential maternal complications associated with HG. These include, but are not limited to, Wernicke's encephalopathy (WE), osmotic demyelination syndrome from overly rapid correction of hyponatremia, esophageal rupture, Mallory-Weiss tears, pneumomediastinum from forceful vomiting, and acute tubular necrosis [23]. As of 2010 there were only 49 cases reported in the literature of WE in pregnancy [40]. Despite the rarity of this complication, WE can lead to devastating and persistent neurologic sequelae with complete remission observed in only 14 of the reported cases [41]. Thiamine repletion before dextrose infusion is therefore a critical intervention in patients that have had prolonged vomiting and concern for nutritional compromise.

Summary

Nausea and vomiting affects up to 80% of pregnancies and can have significant negative impact on the patient's quality of life. Prompt treatment is essential to preventing further progression of symptoms. Initial evaluation of the pregnant patient with nausea and vomiting in the ED should focus on detecting more severe disease including dehydration, electrolyte imbalances, and hyperemesis gravidarum. In addition to supportive care with fluid and volume repletion, first-line pharmacologic therapy should consist of pyridoxine with doxylamine. Patients with persistent symptoms can be managed with additional antiemetic agents

including diphenhydramine, metoclopramide, and ondansetron. Hospital admission is necessary for cases of refractory vomiting requiring continued IV fluids and antiemetics, failed outpatient management of symptoms, and severe fluid or electrolyte imbalance.

Key Points

- Early prevention of nausea and vomiting in pregnancy consists of dietary and lifestyle modifications: bland diet, small frequent meals, and consideration of ginger supplements.
- Pyridoxine with doxylamine remains the first-line pharmacotherapy for outpatient treatment of nausea and vomiting in pregnancy and may prevent repeat ED visits and the development of severe symptoms.
- Diphenhydramine, metoclopramide, and ondansetron used off-label use are second-line agents to consider in refractory cases.
- Recommended ED laboratory evaluation includes urinalysis, basic metabolic panel, and liver function tests to assess for electrolyte abnormalities and severity of dehydration.
- Consider thiamine, folate, and dextrose in cases of severe or prolonged symptoms.

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