Sentara® Health Plans

SENTARA HEALTH PLANS CLINICAL PRACTICE GUIDELINE:

HYPEREMESIS GRAVIDARUM MANAGEMENT PROTOCOL

2025 Updates:

1. Added Partners in Pregnancy and Welcoming Baby Resources
2. Reviewed ACOG Bulletin to assure it is still the most up to date and suggested treatments are current and up to date.

Guideline History

Date Approved	6/01
Date Revised	07/03, 09/05, 3/07, 05/07, 7/09, 06/11, 7/13, 7/15, 7/17, 7/19, 7/21, 9/23
Date Reviewed	7/25
Next Review Date	7/27

Hyperemesis Gravidarum Management Protocol

Definition:

- Incidence is – 0.3-3% of pregnancies
- Fetal complications include IUGR (Intrauterine growth restriction) in about a third of fetuses
- Maternal complications include Wernicke's encephalopathy (ophthalmoplegia, gait ataxia and confusion),

Criteria:

- Persistent nausea and vomiting, weight loss greater than 5% of pre-pregnancy weight and large ketonuria
- Consider other etiologic causes if nausea and vomiting started after 9 weeks gestation
- TSH is almost always less than 2.5 mU/ml in hyperemesis, if not consider other etiologies

Exams and Laboratory Evaluation

- Physical exam.
- The following laboratory tests will be done to check for signs of dehydration:
    - Hematocrit
    - Urine ketones
- Tests to rule out liver and gastrointestinal problems
- Ultrasound to determine pregnancy with multiples and to check for a hydatidiform mole.

Management:

Step One: (Mild)

Dietary modification/Psychological support/OTC medications

- 6 Small, dry meals (try saltine crackers, potato chips, ginger ale and ginger snaps)
    - Avoid fried, spicy foods
    - Avoid cigarettes, caffeine
- Increase oral fluids as tolerated
- Psychological support with reassurance about well being of pregnancy, family counseling, brochure

OTC

- Start with 50mg of Vitamin B6 (pyridoxine) with ½ tablet Doxylamine (Unisom) at night.
- For Sentara Health Plan Members, refer to one of the two Sentara Health Plan OB programs which can assist with Case Management through pregnancy and 12 months postpartum:
    - **For Commercial Plans: "Partners in Pregnancy"**
        - Pregnancypartner@sentara.com
        - 866-239-0618 Option 2

For Medicaid Plans: "Welcoming Baby"

- Office visit once per week until resolution

Move to Step Two if no Improvement in 5-7 days

Step Two: (Moderate)

2A – Start with outpatient Anti-Emetic Therapy- First Line anti-emetic therapy

Table 1

Brand Name	Generic Name	Strength/Rate of Administration
Diclegis	Doxylamine succinate and pyridoxine	10mg/ po TID
Reglan	Metoclopromide	10mg/po QID
Phenergan	Promethazine	25mg/po or supp Q 4-6 hrs (prn)
Tigan	Trimethobenzamide	200mg/supp Q 4-6 hrs (prn)
Compazine	Prochlorperazine	25mg/supp Q 4-6 hrs (prn)
Zofran	Ondansetron	4mg/po Q 6 hrs (prn) up to 8mg/po TID * not recommended to be given prior to 12 weeks*

*** If not able to take PO – Compazine suppository, Phenergan suppository**

- More costly agents should only be used when the patient has failed a combination of less costly agents. For further information related to medications, please refer to www.SentaraHealthPlans.com under Provider/Pharmacy/Formularies/Drug Lists.

- Continue step one management

Please refer to this list when prescribing for your patient. Your patient will have lower drug costs if you prescribe generic drugs and allow brand substitution for dual-branded products.

2B – Start IV Hydration Intravenous hydration / Anti-emetic therapy

- Start at hospital outpatient IV center or Home Health with isotonic solution (NS or LR500 – 1000cc bolus then 100 – 125cc/hour). Replace Thiamine (100mg in 100cc NS over 30 minutes) before any dextrose containing solution. Supplement MVI-12 and 600 mcg folic acid (for a total of 1mg folic acid per day) in one bag IVF daily.

- Home Care resources:

    - **Sentara Home Care Services: (757) 553-3000 or Toll Free @ 1 (888) 461-5649**

- **Optum OB Homecare: 1 (800) 950-3963**

- Obtain Labs:
  - TSH
  - BMP
  - Magnesium
  - Phosphorus

- Replace electrolytes:
  - Potassium
  - Magnesium
  - Phosphorus as lab values indicate.

- Phenergan 25 mg IVPB.

Move to Step three if no improvement in 7 days

Step Three: (Inpatient) Failure of all other methods

Hospital admission / enteral – peripheral – Central alimentation

- Admit to hospital

- Full laboratory work up (CBC/BMP, magnesium, phosphorus, ionized calcium, pre-albumin, liver function, amylase, T4,TSH, urinalysis)

- Consider enteral nutrition.

- Consider peripheral or central parenteral nutrition

- Treat as inpatient for 2-3 days (or as indicated by clinical condition)

- Discharge to Home Health for continued enteral or parenteral nutrition

- SHP Partners in Pregnancy and Welcoming Baby can assist with Case Management through pregnancy and postpartum.

References

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The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician-Gynecologists

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Nausea and Vomiting of Pregnancy

Nausea and vomiting of pregnancy is a common condition that affects the health of a pregnant woman and her fetus. It can diminish a woman's quality of life and also significantly contributes to health care costs and time lost from work (1, 2). Because morning sickness is common in early pregnancy, the presence of nausea and vomiting of pregnancy may be minimized by obstetricians, other obstetric care providers, and pregnant women and, thus, undertreated (1). Furthermore, some women do not seek treatment because of concerns about the safety of medications (3). Once nausea and vomiting of pregnancy progresses, it can become more difficult to control symptoms. Treatment in the early stages may prevent more serious complications, including hospitalization (4). Safe and effective treatments are available for more severe cases, and mild cases of nausea and vomiting of pregnancy may be resolved with lifestyle and dietary changes. The woman's perception of the severity of her symptoms plays a critical role in the decision of whether, when, and how to treat nausea and vomiting of pregnancy. Nausea and vomiting of pregnancy should be distinguished from nausea and vomiting related to other causes. The purpose of this document is to review the best available evidence about the diagnosis and management of nausea and vomiting of pregnancy.

Background

Definition and Incidence

Nausea and vomiting of pregnancy is a common condition with prevalence rates for nausea of 50-80% and for vomiting and retching of 50% (5). Recurrence of nausea and vomiting of pregnancy with subsequent pregnancies ranges from 15-81% (6). One study has attempted to categorize nausea and vomiting of pregnancy into degrees of severity by assessing the duration of nausea and vomiting each day (from less than 1 hour in mild cases to more than 6 hours in severe cases) and the amount of vomiting and retching per day (up to two times for mild and moderate nausea and vomiting of pregnancy and more than five times in severe cases) (1). However, these categories were not compared against quality of life measures. A published, validated nausea and vomiting of pregnancy severity index known as the mother risk pregnancy-unique quantification of emesis and nausea (PUQE) assesses the severity of nausea and vomiting of pregnancy during the first trimester (7). Scores from the PUQE index are associated with quality of life measurements, which demonstrates the clinical utility of the index (Table 1) (8). The woman's perception of the severity of her symptoms, her desire for treatment, and the potential effect of treatment on her fetus all influence clinical decision making. Early treatment of nausea and vomiting of pregnancy may be beneficial to prevent progression to hyperemesis gravidarum.

No single accepted definition of hyperemesis gravidarum exists. It is a clinical diagnosis of exclusion based on a typical presentation in the absence of other diseases that could explain the findings (9). The most commonly cited criteria include persistent vomiting not related to other causes, a measure of acute starvation (usually large ketonuria), and some discrete measure of weight loss, most often at least 5% of prepregnancy weight (10). Electrolyte, thyroid, and liver abnormalities also may be present. From an epidemiologic perspective, hyperemesis gravidarum appears to represent the extreme end of the spectrum of nausea and vomiting of pregnancy (11). The incidence of hyperemesis gravidarum is

Table 1. Modified Pregnancy-Unique Quantification of Emesis and Nausea

Circle the answer that best suits your situation from the beginning of your pregnancy.				
1. On average in a day, for how long do you feel nauseated or sick to your stomach?				
Not at all	1 hr or less	2-3 hr	4-6 hr	More than 6 hr
(1)	(2)	(3)	(4)	(5)
2. On average in a day, how many times do you vomit or throw up?				
7 or more times	5-6 times	3-4 times	1-2 times	I did not throw up
(5)	(4)	(3)	(2)	(1)
3. On average in a day, how many times do you have retching or dry heaves without bringing anything up?				
None	1-2 times	3-4 times	5-6 times	7 or more times
(1)	(2)	(3)	(4)	(5)
Total score (sum of replies to 1, 2, and 3): mild NVP, 6 or less; moderate NVP, 7-12; severe NVP, 13 or more.				

Abbreviation: NVP, nausea or vomiting of pregnancy.

Reprinted from Lacasse A, Rey E, Ferreira E, Morin C, Berard A. Validity of a modified Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) scoring index to assess severity of nausea and vomiting of pregnancy. Am) Obstet Gynecol 2008;198:71.el-7.

approximately 0.3-3% of pregnancies (5). The reported incidence varies because of different diagnostic criteria and ethnic variation in study populations. Hyperemesis gravidarum is the most common indication for admission to the hospital during the first part of pregnancy and is second only to preterm labor as the most common reason for hospitalization during pregnancy (12, 13).

Differential Diagnosis

The timing of the onset of nausea and vomiting is important-symptoms of nausea and vomiting of pregnancy manifest before 9 weeks of gestation in virtually all affected women. When a patient experiences nausea and vomiting for the first time after 9 weeks of gestation, other conditions should be carefully considered in the differential diagnosis (see Box 1). A history of a chronic condition associated with nausea and vomiting that predates pregnancy should be sought (eg, cholelithiasis or diabetic gastroparesis). Rare cases of hyperemesis gravidarum related to a Mendelian disorder of hormone-receptor interaction (14) and mitochondrial disorders (15) suggest that at least some portion of hyperemesis is caused by discrete disease states that are unmasked or exacerbated in pregnancy.

A number of physical findings point to conditions other than nausea and vomiting of pregnancy as the cause of the nausea and vomiting. For example, abdominal pain or tenderness other than mild epigastric discomfort after retching is not a prominent characteristic of nausea and vomiting of pregnancy. Fever and headache are not present in nausea and vomiting of pregnancy. An abnormal neurologic examination suggests a primary neurologic disorder as the cause of the nausea and vomiting, although it rarely may be encountered as a consequence of severe nausea and vomiting of pregnancy (eg, thiamine-deficient encephalopathy or central pontine myelinolysis). Although biochemical hyperthyroidism may be seen with hyperemesis gravidarum, a palpable goiter is not due to nausea and vomiting of pregnancy. If a goiter is present, primary thyroid disease should be suspected. The findings of no prior history of thyroid disease, no evidence of Graves disease (such as goiter), and a self-limited disorder with symptoms of emesis, favor the diagnosis of gestational transient thyrotoxicosis and routine thyroid tests are not needed (16, 17). However, in patients with hyperemesis gravidarum in whom thyroid function tests are obtained, results may demonstrate a hyperthyroxinemia or gestational transient thyrotoxicosis. This is generally limited to the first half of pregnancy and may be characterized by elevated free T4 and suppressed serum thyroid stimulating hormone. The appropriate management of abnormal maternal thyroid tests attributable to gestational transient thyrotoxicosis, or hyperemesis gravidarum, or both, includes supportive therapy, and antithyroid drugs are not recommended (18).

Etiology and Risk Factors

The etiology of nausea and vomiting of pregnancy is unknown. Various theories have been proposed, including a hormonal stimulus, evolutionary adaptation, and psychologic predisposition (19, 20).

Box 1. Differential Diagnosis of Nausea and Vomiting of Pregnancy

Gastrointestinal conditions
- Gastroenteritis
- Gastroparesis
- Achalasia
- Biliary tract disease
- Hepatitis
- Intestinal obstruction
- Peptic ulcer disease
- Pancreatitis
- Appendicitis

Conditions of the genitourinary tract
- Pyelonephritis
- Uremia
- Ovarian torsion
- Kidney stones
- Degenerating uterine leiomyoma

Metabolic conditions
- Diabetic ketoacidosis
- Porphyria
- Addison's disease
- Hyperthyroidism
- Hyperparathyroidism

Neurologic disorders
- Pseudotumor cerebri
- Vestibular lesions
- Migraine headaches
- Tumors of the central nervous system
- Lymphocytic hypophysitis

Miscellaneous conditions
- Drug toxicity or intolerance
- Psychologic conditions

Pregnancy-related conditions
- Acute fatty liver of pregnancy
- Preeclampsia

Reprinted from Goodwin TM. Hyperemesis gravidarum. Obstet Gynecol Clin North Am 2008;35:401-17, viii, with permission from Elsevier.

Hormones

Human Chorionic Gonadotropin

Because of the close temporal relationship between peak human chorionic gonadotropin (hCG) concentrations and peak symptoms of nausea and vomiting of pregnancy, hCG arising from the placenta has been considered a likely candidate for the emetogenic stimulus. The role of hCG also is suggested by the fact that almost all stud- ies of thyroid hormones in pregnancy show an associa- tion between transient hyperthyroidism and nausea and vomiting of pregnancy. It has been conclusively shown that hCG is a thyroid stimulator of pregnancy (21), but because hyperthyroidism itself rarely causes vomiting, this finding has focused attention back on hCG and its relationship to nausea and vomiting of pregnancy. Among the many studies comparing nonthyroidal hor- mone concentrations in women with and without vomit- ing, only hCG and estradiol have been found to have an association. The failure of some studies to show an association of nausea and vomiting of pregnancy with hCG may be related to the varying biologic activity of different hCG isoforms as well as variation in the susceptibility of the individual woman to any emetogenic stimulus. The extent of the hCG stimulus may be modified by placental conditions that increase its concentration (eg, multiple gestation or molar gestation) and by hormone-receptor interactions modifying the effect of the hormone.

Estrogen

Another hormone known to influence nausea and vomiting of pregnancy is estrogen. Nausea and vomiting of pregnancy is more common when estradiol levels are increased and less common when estradiol levels are decreased (22, 23). Cigarette smoking is associated with lower lev- els ofhCG and estradiol (24), and numerous studies have shown that smokers are less likely to have hyperemesis gravidarum. Estrogen in the combined oral contraceptive pill was shown to induce nausea and vomiting in a dose-related fashion (25). Women with nausea and vomiting after estrogen exposure were more likely to have nausea and vomiting of pregnancy than women who did not demonstrate such sensitivity to estrogen (26).

Evolutionary Adaptation

It also has been posited that nausea and vomiting of pregnancy is an evolutionary adaptation that developed to protect the woman and her fetus from foods that might be potentially dangerous (27). This theory may explain the temporary aversions to tastes and smells that pregnant women experience. Proponents of the adaptation theory suggest nausea and vomiting of pregnancy is a healthy,

protective response to pregnancy. Clinical application of this theory, however, may lead to undertreatment of women whose quality of life is diminished by nausea and vomiting of pregnancy.

Psychologic Predisposition

It is likely that the concept that nausea and vomiting of pregnancy reflects a psychologic disorder has impeded progress toward a greater understanding of the condition (28). Experts continue to debate whether psychologic illness is a predisposing factor for or a complication of hyperemesis gravidarum. The question of whether certain personality types or specific psychologic disorders predispose someone to hyperemesis gravidarum has been raised in the literature for many years. Small case-control trials have noted that neither de novo nor recurrent hyperemesis gravidarum is associated with any underlying psychiatric condition when compared with pregnant women without nausea and vomiting of pregnancy (29, 30). A review of psychologic theories proposed to explain the etiology of nausea and vomiting of pregnancy concluded that the evidence that nausea and vomiting of pregnancy is caused by a conversion disorder or an abnormal response to stress is "question- able at best" (31).

Risk Factors

Women with increased placental mass (eg, advanced molar gestation or multiple gestation) are at increased risk of hyperemesis gravidarum. Other risk factors include a history of motion sickness, migraine headaches, a family history (genetics), or a history of hyperemesis gravidarum in a previous pregnancy (26). One study found that approximately two thirds of women who described their vomiting as severe in one pregnancy had similar symptoms in the next pregnancy, and one half of women who described their symptoms as mild in one pregnancy found that the symptoms worsened in the next (32). Daughters and sisters of women who had hyperemesis gravidarum are more likely to have the same problem, as are women carrying female fetuses (33).

Maternal Effects of Nausea and Vomiting of Pregnancy

Although death from nausea and vomiting of pregnancy is reported rarely today, significant morbidity, such as Wernicke encephalopathy, splenic avulsion, esophageal rupture, pneumothorax, and acute tubular necrosis, have been reported (34-42). Wernicke encephalopathy (caused by vitamin B deficiency) related to hyperemesis gravidarum has been associated with maternal death or permanent neurologic disability (35-37).

In addition to increased hospital admissions (43, 44), some women experience significant psychosocial morbidity caused by nausea and vomiting of pregnancy, resulting in a decision for pregnancy termination. A systematic review of psychological morbidity in relation to hyperemesis gravidarum did demonstrate significantly higher depression and anxiety scale scores in women with the condition. However, these findings are limited by the high level of heterogeneity between studies (45).

Fetal Effects of Nausea and Vomiting of Pregnancy

The severity of nausea and vomiting dictates its effect on the embryo and fetus. With mild or moderate vomit- ing, there is little apparent effect on pregnancy outcome. Studies have documented a lower rate of miscarriage among women with nausea and vomiting of pregnancy and hyperemesis gravidarum when compared with controls (46). This result is thought to be related to robust placental synthesis in a healthy pregnancy rather than a protective effect of vomiting. No significant association of hyperemesis gravidarum with congenital anomalies has been demonstrated (47). The outcome most frequently examined is the incidence of low birth weight (LBW). However, some studies have identified no increase in LBW with nausea and vomiting of pregnancy (11, 48-50). Conversely, a systematic review and meta-analysis of women with hyperemesis gravidarum showed a higher incidence of LBW and small-for-gestational-age infants and premature infants (47). However, no association of hyperemesis gravidarum and perinatal or neonatal mortality has been demonstrated in large retrospective cohorts (51). Although little may be known about the long-term health of children or women after pregnancies complicated by hyperemesis gravidarum, it is appropriate to reassure patients that the presence of nausea and vomiting of pregnancy and even hyperemesis gravidarum most often portends well for pregnancy outcome.

Clinical Considerations and Recommendations

In many studies, patients with hyperemesis gravidarum are grouped with those with other degrees of nausea and vomiting of pregnancy. Because it is likely that hyperemesis gravidarum is part of the continuum of nausea and vomiting of pregnancy, the following discussion focuses on treatment for all stages of this condition.

Are nonpharmacologic therapies effective for the treatment of nausea and vomiting of pregnancy?

Treatment of nausea and vomiting of pregnancy begins with prevention. Two studies found that women who were taking a multivitamin at the time of fertilization were less likely to need medical attention for vomiting (52, 53). Although the biological basis of this observation is unclear, the authors speculate that this may have been because of a generalized optimization of nutritional status or because increasing levels of vitamin B_6 (pyridoxine) may reduce vomiting in some women (52, 53). Therefore, the standard recommendation to take prenatal vitamins for 1 month before pregnancy may reduce the incidence and severity of nausea and vomiting of pregnancy (54).

There is little published evidence regarding the efficacy of dietary changes for prevention or treatment of nausea and vomiting of pregnancy. Frequent, small meals every 1-2 hours to avoid a full stomach often are recommended (55). Other dietary modifications that may be helpful include avoiding spicy or fatty foods; eliminating supplemental iron and substituting folic acid for iron-containing prenatal vitamins; and eating bland or dry foods, high-protein snacks, and crackers in the morning before arising (56). A small study showed that protein meals were more likely to alleviate nausea and vomiting of pregnancy than carbohydrate or fatty meals (57). The woman's perception of the severity of her symptoms and her desire for treatment are influential in clinical decision making. Common recommendations to alleviate initial signs of nausea and vomiting of pregnancy include rest and avoidance of sensory stimuli such as odors, heat, humidity, noise, and flickering lights that may provoke symptoms.

Treatment of nausea and vomiting of pregnancy with ginger has shown some beneficial effects in reducing nausea symptoms and can be considered as a nonpharmacologic option. Systematic reviews of randomized controlled and nonrandomized controlled trials have found that ginger was associated with improvement in nausea; however, none of the trials showed benefit in reducing vomiting (5, 58, 59).

Acupressure, acupuncture, or electrical nerve stimulation (acustimulation) at the P6 or Neiguan point (located three finger breadths below the wrist on the inside of the wrist in between the two tendons) has been studied for nausea and vomiting of pregnancy with conflicting results. Most studies report a benefit, but many have significant methodologic flaws, and the two largest, best-designed studies showed no benefit compared with sham stimulation (60). Two systematic reviews found limited benefit with P6 acupressure but no benefit in P6 acupuncture or nerve stimulation in the treatment of nausea and vomiting of pregnancy (5, 59).

Are pharmacologic therapies effective for treatment of nausea and vomiting of pregnancy?

Effective pharmacologic therapy is available, but agreement on the appropriate timing of antiemetic therapy has changed in recent years. Early treatment of nausea and vomiting of pregnancy is recommended to prevent progression to hyperemesis gravidarum. In a randomized controlled trial (RCT) of women with a history of severe nausea and vomiting of pregnancy in their previous gestation, the initiation of antiemetic therapy before the onset of nausea and vomiting symptoms was associated with a reduction in the severity of nausea and vomiting of pregnancy compared with initiation of a combination of doxylamine and vitamin B_6 (pyridoxine) after the onset of symptoms (61).

When women with nausea and vomiting of pregnancy are unable to tolerate oral medications, other administration modalities may be beneficial. Besides oral and intravenous routes, there are other options of delivery for several medications used to treat nausea and vomiting of pregnancy. Some of the phenothiazine prod- ucts (promethazine and prochlorperazine) are available as rectal suppositories. The serotonin 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists are available as an oral dissolvable tablet (ondansetron) or a transder- mal patch (granisetron) formulation.

There is limited evidence regarding the clinical efficacy of the use of continuous subcutaneous microinfusion pumps to administer metoclopramide or ondansetron for the treatment of nausea and vomiting of pregnancy (62, 63). Moreover, adverse effects with the use of continuous subcutaneous pumps were seen in 11-31% of selected patients (62). At present, subcutaneous microinfusion pumps of these antiemetic therapies do not appear to be cost effective when compared with conventional treatment alternatives, including periodic hospitalization (64).

Although no single approach has been proved to be more effective than the other, Figure 1 depicts a hierarchy of therapeutic interventions that balances safety and efficacy. As with all medications, the potential risks, benefits, adverse effects and costs should be weighed in each case. Care should be exercised if multiple antiemetic medications are used simultaneously. Parallel use of a dopamine antagonist (such as metoclopramide) and various phenothiazine medications (eg, promethazine, prochlorperazine, or chlorpromazine) may result in an

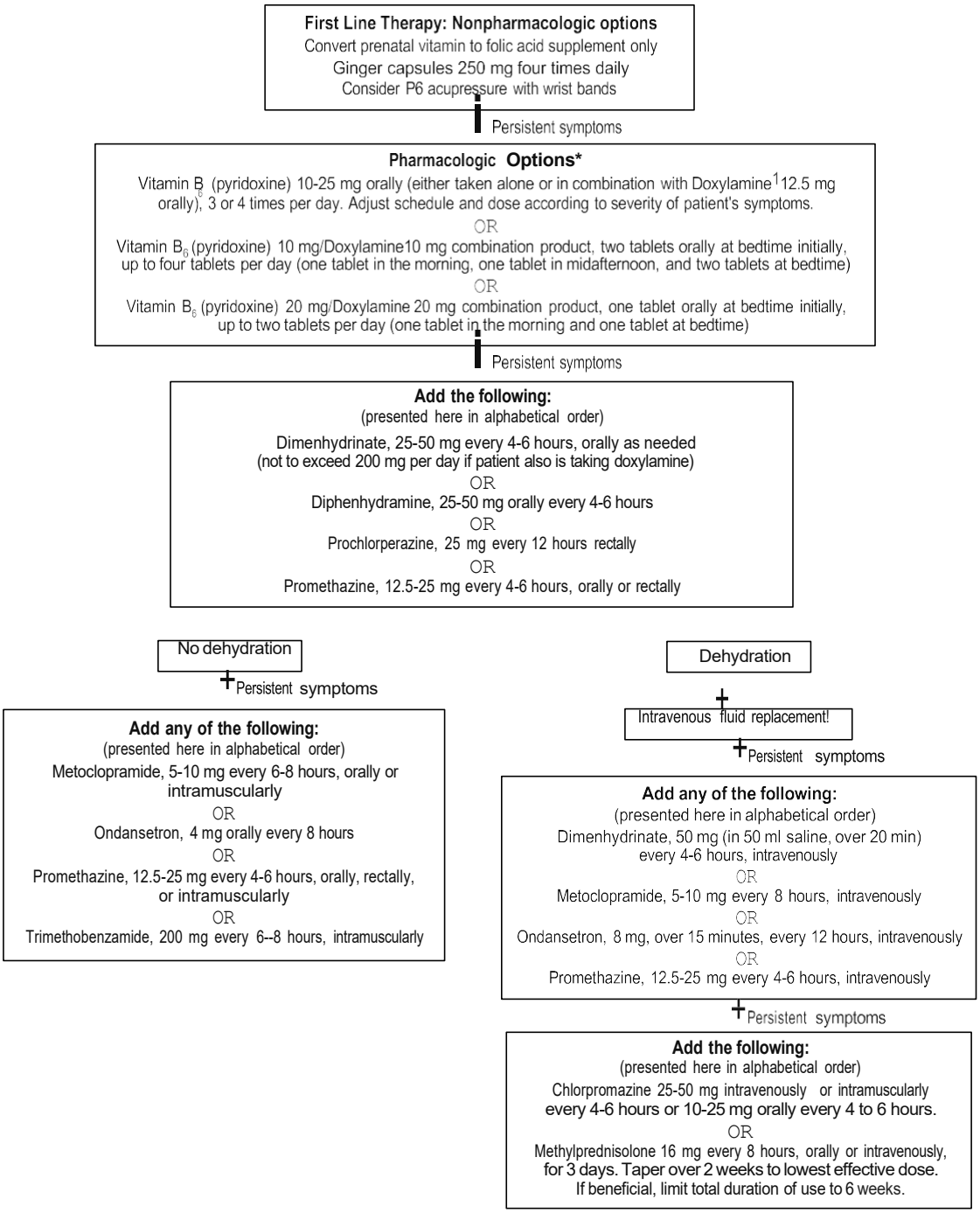

Figure 1. Algorithm of therapeutic treatment of nausea and vomiting of pregnancy (if no improvement, proceed to next step in algorithm). This algorithm assumes other causes of nausea and vomiting have been ruled out. At any step, consider enteral nutrition if dehydration or persistent weight loss is noted. *Some antiemetic medications have only been approved by the U.S. Food and Drug Administration for use in nonpregnant patients; however, off-label use is common. Obstetricians and other obstetric care providers should counsel patients and document such discussions accordingly. Care should be exercised if multiple antiemetic medications are used simultaneously. Parallel use of some medications (see text) may result in an increased risk of adverse effects. [1]In the United States, doxylamine is available as the active ingredient in some over-the-counter sleep aids; one half of a scored 25-mg tablet can be used to provide a 12.5-mg dose of doxylamine. †Thiamine, intravenously, 100 mg with the initial rehydration fluid and 100 mg daily for the next 2-3 days (followed by intravenous multivitamins), is recommended for women who require intravenous hydration and have vomited for more than 3 weeks to prevent a rare but serious maternal complication, Wernicke encephalopathy. (Modified from Levichek Z, Atanackovic G, Oepkes D, Maltepe C, Einarson A, Magee L, et al. Nausea and vomiting of pregnancy. Evidence-based treatment algorithm. Can Fam Physician 2002;48:267-8, 277.) ¢,

increased risk of extrapyramidal effects (eg, tardive dyskinesia) or rarely neuroleptic malignant syndrome (a life-threatening reaction, including high fever, confusion, rigid muscles, and symptoms of autonomic nervous system instability). The serotonin 5-HT3 inhibitor (eg, ondansetron) when used with phenothiazine medications (such as chlorpromazine) may result in a potential cardiac risk of QT interval prolongation.

Vitamin B_6 (Pyridoxine) With or Without Doxylamine

Treatment of nausea and vomiting of pregnancy with vitamin B_6 (pyridoxine) alone or vitamin B_6 (pyridoxine) plus doxylamine in combination is safe and effective and should be considered first-line pharmacotherapy. Randomized controlled trials have evaluated vitamin B_6 (pyridoxine) alone for treatment of varying degrees of severity of nausea and vomiting of pregnancy (65, 66). One study compared a vitamin B_6 (pyridoxine) dosage of 25 mg every 8 hours with placebo and found a significant reduction in severe vomiting but minimal effect on mild vomiting (65). A larger study (N=342) used a vitamin B_6 (pyridoxine) dosage of 10 mg every 8 hours and found a reduction in nausea and vomiting compared with placebo (66). A systematic review of RCTs found that it was difficult to determine the effectiveness of vitamin B_6 (pyridoxine) in relieving nausea and vomiting symptoms, given the paucity of high-quality evidence (5). In contrast, a recent systematic review of RCTs and non-RCTs found that vitamin B_6 (pyridoxine) was associated with improvement in mild nausea and vomiting symptoms (59).

When the combination of vitamin B_6 (pyridox- ine) (10 mg) plus doxylamine (10 mg) was available in the United States (from 1958 to 1983), an estimated 25-30% of all pregnant women received this agent. Analysis of hospital admissions during this period sug- gests that the ready availability of vitamin B_6 (pyridox- ine) plus doxylamine for the treatment of the spectrum of nausea and vomiting of pregnancy was associated with fewer hospital admissions for hyperemesis gravidarum (44). Although some initial studies suggested an association of the combination of vitamin B_6 (pyridoxine) plus doxylamine with birth defects, large epidemiologic studies demonstrated no measurable teratogenic effects (67). However, despite continued U.S. Food and Drug Administration (FDA) approval of this medication, the manufacturer ceased worldwide production of the combination vitamin B_6 (pyridoxine) plus doxylamine product because of liability costs. After the combination was removed from the U.S. market in 1983, use of all antiemetics to treat nausea and vomiting of pregnancy diminished considerably, and hospitalization rates for nausea and vomiting of pregnancy increased (44, 68).

First in 2013, and then an extended-release ver- sion in 2016, the combination vitamin B_6 (pyridoxine) plus doxylamine medications were approved by the FDA in the United States for treatment of nausea and vomiting of pregnancy in women who do not respond to dietary and lifestyle changes (69). A multicenter RCT of a combination medication of vitamin B_6 (pyridoxine) plus doxylamine for nausea and vomiting of pregnancy found a significant improvement in nausea and vomiting symptoms compared with placebo (70). A secondary analysis of this RCT found that the vitamin B_6 (pyridoxine) plus doxylamine medication was well tolerated in women with nausea and vomiting of pregnancy and was not associated with increased adverse maternal effects (71). Central nervous system adverse effects (sleepiness, tiredness, or drowsiness, or all three) occurred in 28% of women who took the combined medication. The fetal safety of the combination vitamin B_6 (pyridoxine) plus doxylamine medication has been demonstrated in numerous epidemiologic studies (72).

Dopamine Antagonists

Several dopamine antagonists have been described in the medical literature for treatment of nausea and vomit- ing of pregnancy, such as metoclopramide and various phenothiazine medications (promethazine, prochlorperazine, or chlorpromazine). These medications may be given orally, rectally, intramuscularly, or intravenously. Relief of nausea and vomiting has been demonstrated in large groups of patients (73). A double-blind RCT of intravenous promethazine versus metoclopramide in women with hyperemesis gravidarum found that both medications had similar efficacy in reducing nausea and vomiting symptoms at 24 hours but the rates of drowsiness, dizziness, and dystonia were less with metoclopramide use (74). Adverse effects of these medications include dry mouth, drowsiness, dystonia, and sedation. Although phenothiazines were identified as a possible cause of congenital malformations in one study (75), the aggregate of studies attests to their safety (73). Metoclopramide use during pregnancy has not been shown to increase risk of congenital malformations.

Antihistamines

Antihistamines (such as dimenhydrinate and diphenhydramine) have been shown to be effective in controlling nausea and vomiting symptoms of pregnancy and

are frequently used. The efficacy of these medications in reducing nausea and vomiting of pregnancy was demonstrated in a meta-analysis of various antihistamines (73). Further, the majority of studies have shown no association of prenatal antihistamine exposure and birth defects (76). Common adverse effects include sedation, dry mouth, lightheadedness, and constipation.

Serotonin 5-hydroxytryptamine type 3 receptor antagonists

Evidence is limited on the safety or efficacy of the serotonin 5-HT3 inhibitors (eg, ondansetron) for nausea and vomiting of pregnancy; however, use appears to be increasing (77). A double-blind RCT of intravenous ondansetron versus metoclopramide in women with hyperemesis gravidarum found that both medications had similar efficacy in reducing nausea and vomiting symptoms but the rates of drowsiness, xerostomia, and persistent ketonuria at 24 hours were less with ondansetron use (78). In another randomized trial of oral ondansetron versus metoclopramide in women with severe vomiting, ondansetron was better at controlling vomiting but had a similar effect to metoclopramide in managing nausea (79). Ondansetron also was found to be more effective than the combination of doxylamine and vitamin B_6 (pyridoxine) in controlling nausea and vomiting symptoms in a small double-blind RCT of 36 women (80).

Common adverse effects of ondansetron include headache, drowsiness, fatigue, and constipation. Ondansetron can prolong the QT interval, especially **in** patients with underlying heart problems, hypokalemia, or hypomagnesemia (63, 81). In December 2012, the FDA announced the removal of the 32-mg single intra- venous dose of ondansetron from the market because of the potential cardiac risk of QT interval prolongation leading to torsade de pointes, a potentially fatal heart rhythm. The FDA recommends that ondansetron not be given intravenously in doses greater than 16 mg. Electrolyte and electrocardiogram monitoring are rec- ommended in patients being treated with ondansetron who have risk factors for arrhythmia, including family or personal history of prolonged QT interval, heart failure, hypokalemia, hypomagnesemia, or use of concomitant medications that lead to prolongation of the QT interval (Box 2) (82).

There are insufficient data on fetal safety with ondansetron use and further studies are warranted. A possible association of ondansetron use in the first trimester and cleft palate has been reported, but the data were limited by a small sample size and potential recall-reporting bias (83). Individual studies of the association between ondansetron and congenital malformations are inconsistent, with some showing an increase in birth defects and others showing no difference (81, 84, 85). A recent systematic review of ondansetron use in early pregnancy found eight studies that were adequate for inclusion (86). Although there was a small increase in the risk of cardiac defects in two of the studies (odds ratio [OR], 2.0; 95% Cl; 1.3-3.1 and OR, 1.62; 95% CI; 1.04-2.14), there was no increase in the overall rate of malformations in the ondansetron-exposed patients. Thus, although some studies have shown an increased risk of birth defects with early ondansetron use, other studies have not and the absolute risk to any fetus is low. However, women should be counseled regarding the available data, and the use of ondansetron before 10 weeks of gestation should be individualized weighing the risks and benefits.

Box 2. Contraindicated Medications for Patients Receiving Ondansetron ¢i

Examples of medications to be avoided by patients receiving ondansetron include but are not limited to the following:

- Antihistamines (hydroxyzine)
- Analgesics and sedatives (methadone, oxycodone, and chloral hydrate)
- Diuretics
- Anticholinergics
- Antiarrhythmics (amiodarone, sotalol, quinidine, procainamide, and flecainide)
- Antipsychotics (thioridazine, haloperidol, chlorpromazine, and clozapine)
- Tricyclic and tetracyclic antidepressants (amitriptyline, imipramine, and clomipramine)
- Macrolide antibiotics (erythromycin and azithromycin)
- Trazodone
- Fluoxetine
- Antimalarials (chloroquine, mefloquine, and quinine)
- Metronidazole
- Human immunodeficiency virus (HIV) protease inhibitors

Steroids

Several case series have suggested a benefit of corticosteroids in the treatment of hyperemesis gravidarum.

A randomized trial that compared methylprednisolone (16 mg, three times per day for 3 days, followed by a 2-week taper) with oral promethazine (25 mg, three times a day for two weeks) showed equal rates of improvement among hospitalized patients; however, readmission to the hospital within 2 weeks of discharge occurred significantly less frequently in those taking steroids (87). In contrast, a later RCT of intravenous methylprednisolone followed by a tapered dose of an oral prednisone among women hospitalized for hyperemesis gravidarum found that the use of corticosteroids did not reduce the need for rehospitalization (88). A recent systematic review of RCTs on corticosteroids for the treatment of hyperemesis gravidarum found a reduction in the rehospitalization rate but no difference in hospital admission days (89).

Three studies have confirmed an association between oral clefts and methylprednisolone use in the first trimester (90--92). The teratogenic effect is weak, probably accounting for no more than one or two cases per 1,000 treated women (93). Nevertheless, in view of this probable association, corticosteroid use for hyperemesis gravidarum should be used with caution and avoided as a first-line agent before 10 weeks of gestation. The most commonly described regimen is methylprednisolone, 48 mg daily for 3 days, given orally or intravenously (87). Patients who do not respond within 3 days are not likely to respond, and treatment should be stopped. For those who do respond, the dose may be tapered over a period of2 weeks. For recurrent vomiting, the tapered dose may be stopped and the patient continued on the effective dose for up to 6 weeks. To limit serious maternal adverse effects, corticosteroids should not be continued beyond this period for the treatment of hyperemesis gravidarum. Treatment of severe nausea and vomiting of pregnancy or hyperemesis gravidarum with methylprednisolone may be efficacious in refractory cases; however, the risk profile of methylprednisolone suggests it should be a last-resort treatment.

▶ *Is there a role for laboratory or radiologic assessment in the diagnosis of hyperemesis gravidarum?*

An ultrasound examination may be useful in cases of severe presumed nausea and vomiting of pregnancy. It may identify a predisposing factor such as multiple gestation or molar gestation. Most patients with nausea and vomiting of pregnancy do not require laboratory evaluation, but in those with nausea and vomiting of pregnancy that is severe or persistent, laboratory assessment may help establish the differential diagnosis of hyperemesis gravidarum and assess the severity of the condition. Common laboratory abnormalities in hyperemesis gravidarum include increased liver enzymes (usually less than 300 units/L), serum bilirubin (less than 4 mg/dL), and serum amylase or lipase concentrations (up to five times greater than normal levels). Primary hepatitis as a cause of nausea and vomiting of pregnancy results in increased liver enzyme levels, often in the thousands; bilirubin concentrations usually are greatly increased as well. Acute pancreatitis may cause vomiting and elevated amylase concentrations, but serum amylase concentrations usually are 5-10 times greater than the elevations associated with nausea and vomit- ing of pregnancy. A hypochloremic metabolic alkalosis can be seen as a result of severe vomiting of any cause. Studies do show an association between higher hCG levels and the presence of hyperemesis gravidarum but the fact that hCG levels have not been standardized for the duration of pregnancy (eg, reporting them as multiple of medians) makes levels incomparable (94). Urinalysis may show elevated specific gravity, or ketonuria, or both. However, a systematic review and meta-analysis of biomarkers for the diagnosis of hyperemesis gravi- darum found no association between ketonuria and the presence or severity of hyperemesis gravidarum (94). Gastric ulcer should be considered in patients with per- sistent hyperemesis gravidarum who are unresponsive to standard therapy and consideration should be given to test for *Helicobacter pylori* infection. Treatment with antibiotics and H2-receptor antagonists is safe in pregnancy (95, 96) and has been reported to be beneficial in case reports (97).

Hyperthyroidism itself rarely may present with significant vomiting, but in the patient who has no goiter, thyroid tests are not routinely needed to clarify the differential diagnosis unless the individual exhibits clinical signs or symptoms of hyperthyroidism (16, 17). Depending upon the definition used for hyperthyroidism in pregnancy, between 5% and 66% of patients with hyperemesis gravidarum will have suppressed thyroid-stimulating hormone levels or elevated free thyroxine concentrations (16, 98). For the patient who has no history of hyperthyroidism before pregnancy and no goiter, the hyperthyroidism of hyperemesis gravidarum can be expected to resolve by 20 weeks of gestation without specific antithyroid therapy.

▶ *When is enteral or parenteral nutrition recommended?*

Intravenous hydration should be used for the patient who cannot tolerate oral liquids for a prolonged period or if clinical signs of dehydration are present. Correction of ketosis and vitamin deficiency should be strongly considered. Dextrose and vitamins should be included

in the therapy when prolonged vomiting is present, and thiamine should be administered before dextrose infusion to prevent Wernicke encephalopathy (99). Enteral tube feeding (nasogastric or nasoduodenal) should be initiated as the first-line treatment to provide nutritional support to the woman with hyperemesis gravidarum who is not responsive to medical therapy and cannot maintain her weight.

No randomized trials compare enteral with parenteral nutrition in women with nausea and vomiting of pregnancy who continue to lose weight despite antiemetic therapy. Several case reports and small series (100, 101) suggest that enteral tube feeding is well tolerated in pregnancy. In a retrospective study on nutritional treatment in pregnant women with hyperemesis, enteral tube feeding in 107 women was associated with sufficient maternal weight gain and good pregnancy outcomes (102). However, in a RCT of women with hyperemesis gravidarum allocated to enteral tube feeding for 7 days plus standard therapy versus standard therapy only (intravenous hydration, antiemetic medication and vitamin supplements), no differences were noted in infant birth weight or maternal weight gain (103). Yet the findings were limited because one half of women assigned to early enteral tube feeding either refused placement, failed insertion, or discontinued the intervention in fewer than 7 days. Total parenteral nutrition is a potentially life-threatening intervention because of associated sepsis and thromboembolic events. Adverse neonatal outcomes associated with the use of total parenteral nutrition in women with hyperemesis have been reported (104). Because life-threatening complications of parenteral nutrition have been described (41, 42, 105), enteral tube feeding initially should be used to provide nutritional support to a pregnant woman with hyperemesis who cannot maintain her weight.

Despite potential complications, total parenteral nutrition has been described for hyperemesis gravidarum for women who cannot tolerate enteral tube feedings. (41, 106). Peripherally inserted central catheters (PICCs) can be used to avoid some of the complications of central access (105), but they are still associated with significant morbidity (101, 107-109) and should be used only when enteral feeding is not possible. A 50% complication rate was found in a retrospective study of 52 pregnant women who received PICCs, including culture-proven and presumed line infection, cellulitis, mechanical line failure, pain necessitating discontinua- tion of PICCs, and superficial thrombophlebitis (107). A significant maternal complication rate (66.4%) associ- ated with the use of PICCs also was noted in a retrospec- tive study of 33 women with hyperemesis gravidarum and included infection, thromboembolism, bacteremia, and sepsis (101). Similarly, another retrospective study of 66 pregnant women with hyperemesis who received PICCs for intravenous fluid, parenteral nutrition, and antibiotic administration also found complications in 55.9% of PICCs (109). The overall complication rate was 18.5 per 1,000 PICC days. Bacteremia was the most frequent major complication occurring in 20.2% of major complications. Thus, PICCs should not be used routinely in women with hyperemesis gravidarum given the significant complications associated with this intervention. Peripherally inserted central catheters should be used only as a last resort in the management of a woman with hyperemesis gravidarum because of the potential of severe maternal morbidity.

▶ *When is hospitalization indicated?*

When a woman cannot tolerate liquids without vomiting and has not responded to outpatient management, hospitalization for evaluation and treatment of dehydration and electrolyte imbalance is recommended. A RCT of 98 pregnant women assigned either to daily hydration obtained as an outpatient (day care) treatment or inpatient management of nausea and vomiting found that outpatient treatment resulted in fewer overnight hos- pital stays (110). Whereas a subsequent RCT of 53 preg- nant women reported no differences in symptoms over 7 days between groups who received outpatient rehydra- tion and antiemetic therapy versus inpatient care (111). After the patient has been hospitalized and a workup for other causes of severe vomiting has been undertaken, intravenous hydration, nutritional support, and modification of antiemetic therapy often can be accomplished at home. Nevertheless, the option of hospitalization for observation and further assessment should be preserved for patients who experience a change in vital signs or a change in mental status, continue to lose weight, and are refractory to treatment.

▶ *Is there a role for behavioral interventions in treatment?*

There is little evidence for a therapeutic effect of traditional behavioral intervention in hyperemesis gravidarum. There are case examples of effective medical hypnosis therapy used in women with hyperemesis gravidarum (112, 113). Hypnosis was found to be effective by the induced deep relaxation leading to decreased sympathetic nervous system arousal and by the response to hypnotic suggestion of symptom removal (113). A recent **RCT** of vitamin B_6 (pyridoxine) and mindfulness-based cognitive therapy versus vitamin **B_6** (pyridoxine) alone in 86 women with moderate nausea and vomiting found that the vitamin B_6

(pyridoxine)-mindfulness-based cognitive therapy group had significant improvement in symptoms (114). The behavioral intervention was mindfulness-based cogni- tive therapy in eight sessions over a 3-week period. It is unclear if the improvement in symptoms was because of the mindfulness-based cognitive therapy alone or because of the additional contact received by the patients in the vitamin B_6 (pyridoxine)-mindfulness-based cognitive therapy group.

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- Treatment of nausea and vomiting of pregnancy with vitamin B_6 (pyridoxine) alone or vitamin B_6 (pyridoxine) plus doxylamine in combination is safe and effective and should be considered first-line pharmacotherapy.
- The standard recommendation to take prenatal vitamins for 1 month before fertilization may reduce the incidence and severity of nausea and vomiting of pregnancy.
- The appropriate management of abnormal maternal thyroid tests attributable to gestational transient thyrotoxicosis, or hyperemesis gravidarum, or both, includes supportive therapy, and antithyroid drugs are not recommended.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Treatment of nausea and vomiting of pregnancy with ginger has shown some beneficial effects in reducing nausea symptoms and can be considered as a nonpharmacologic option.
- Treatment of severe nausea and vomiting of pregnancy or hyperemesis gravidarum with methylprednisolone may be efficacious in refractory cases; however, the risk profile of methylprednisolone suggests it should be a last-resort treatment.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Early treatment of nausea and vomiting of pregnancy may be beneficial to prevent progression to hyperemesis gravidarum.
- Intravenous hydration should be used for the patient who cannot tolerate oral liquids for a prolonged period or if clinical signs of dehydration are present. Correction of ketosis and vitamin deficiency should be strongly considered. Dextrose and vitamins should be included in the therapy when prolonged vomiting is present, and thiamine should be administered before dextrose infusion to prevent Wernicke encephalopathy.
- Enteral tube feeding (nasogastric or nasoduodenal) should be initiated as the first-line treatment to provide nutritional support to the woman with hyperemesis gravidarum who is not responsive to medical therapy and cannot maintain her weight.
- Peripherally inserted central catheters should not be used routinely in women with hyperemesis gravidarum given the significant complications associated with this intervention. Peripherally inserted central catheters should be utilized only as a last resort in the management of a woman with hyperemesis gravidarum because of the potential of severe maternal morbidity.

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000 and September 2017. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician-gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A-Recommendations are based on good and consistent scientific evidence.

Level B-Recommendations are based on limited or inconsistent scientific evidence.

Level C-Recommendations are based primarily on consensus and expert opinion.

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