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CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

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PDF Format

Nausea and Vomiting of Pregnancy

Nausea and vomiting of pregnancy is a common condition that affects the health of the pregnant woman and her fetus. It can diminish the 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 providers, and pregnant women and, thus, undertreated (1). Furthermore, some women do not seek treatment because of concerns about 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). Mild cases of nausea and vomiting of pregnancy may be resolved with lifestyle and dietary changes, and safe and effective treatments are available for more severe cases. 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. In addition, 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.

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). An estimated 50% of pregnant women have nausea and vomiting, 25% have nausea only, and 25% are unaffected (6, 7). Recurrence of nausea and vomiting of pregnancy with subsequent pregnancies ranges from 15.2% to 81% (8).

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, although these categories recognize nausea and vomiting of pregnancy as a continuum, they may not be clinically useful. The woman's perception of the severity of her symptoms, her desire for treatment, and the potential effect of treatment on her fetus are more likely to influence clinical decision making. Early treatment of nausea and vomiting of pregnancy is recommended to prevent progression to hyperemesis gravidarum.

From an epidemiologic perspective, hyperemesis gravidarum appears to represent the extreme end of the spectrum of nausea and vomiting of pregnancy (9). The incidence of hyperemesis gravidarum is approximately 0.3–3% of pregnancies (5). The reported incidence varies because of different diagnostic criteria and ethnic variation in study populations. There is no single accepted definition of hyperemesis gravidarum; it is a clinical diagnosis of exclusion based on a typical presentation in the absence of other diseases that could explain the findings (10). 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 (11). Electrolyte, thyroid, and liver abnormalities also may be present. 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.

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

A number of physical findings point to conditions other than nausea and vomiting of pregnancy as the cause of the nausea and vomiting. Abdominal pain is not a prominent characteristic of nausea and vomiting of pregnancy; abdominal pain or tenderness other than mild epigastric discomfort after retching is not seen with 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. In patients with hyperemesis gravidarum who also have suppressed thyroid-

stimulating hormone levels, treatment of hyperthyroidism should not be undertaken without evidence (such as goiter, thyroid autoantibodies, or both) of intrinsic thyroid disease.

Etiology and Risk Factors

Psychologic and Evolutionary

The etiology of nausea and vomiting of pregnancy is unknown. Various theories have been proposed, including a psychologic predisposition (16), evolutionary adaptation (17), and hormonal stimulus. 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. Two general hypotheses have been proposed to explain nausea and vomiting of pregnancy as a manifestation of psychopathology: 1) psychoanalytic theories describing hyperemesis gravidarum as a conversion or somatization disorder and 2) inability of the woman to respond to excessive life stress. There have been no controlled studies to support these hypotheses. 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 "questionable at best" (18). 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 (19).

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 (20). 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.

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 studies of thyroid hormones in pregnancy show an association between transient hyperthyroidism and nausea and vomiting of pregnancy. It has been conclusively shown that hCG is the thyroid stimulator of pregnancy (21); 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 hormone concentrations in women with and without vomiting, 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 levels of hCG 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).

Risk Factors

Women with increased placental mass (eg, advanced molar gestation or multiple gestation) are at risk of hyperemesis gravidarum. Other risk factors include family history (genetics) or a history of hyperemesis gravidarum in a previous pregnancy. 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; one half of women who described their symptoms as mild in one pregnancy found that the symptoms worsened in the next (6). Daughters and sisters of women who had hyperemesis gravidarum are more likely to have the same problem, as are women carrying a female fetus (27). Other risk factors include a history of motion sickness or migraines (26).

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 (28–36). Wernicke encephalopathy (caused by vitamin B_1 deficiency) related to hyperemesis gravidarum is associated with maternal death or permanent neurologic disability (29–31).

In addition to increased hospital admissions (37, 38), some women experience significant psychosocial morbidity caused by nausea and vomiting of pregnancy, resulting in a decision for pregnancy termination. A number of reversible responses to subacute disease states have been described in nausea and vomiting of pregnancy, including depression, somatization, and hypochondriasis (16). Poor support by their partners was reported by 85% of women who called a hotline for nausea and vomiting of pregnancy (39).

Fetal Effects of Nausea and Vomiting of Pregnancy

The effect of maternal vomiting on the embryo and fetus depends on the severity of the condition. With mild or moderate vomiting, there is little apparent effect on pregnancy outcome. 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 (9, 40–42). 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 (43). In another study, 6.4% of 81,486 nulliparous women with singleton pregnancies who experienced nausea and vomiting had LBW, preterm birth, and pregnancy-related hypertension (44).

Numerous studies have documented a lower rate of miscarriage among women with nausea and vomiting of pregnancy and hyperemesis gravidarum when compared with controls. This result is thought to be related to robust placental synthesis in a healthy pregnancy rather than a protective effect of vomiting. It is unlikely that hyperemesis gravidarum is associated with a significantly increased risk of malformations in offspring (43). Little is known about the long-term health of children or women after pregnancies complicated by hyperemesis gravidarum. Although some cases of fetal death are still reported with hyperemesis gravidarum, they are very rare. 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

Many studies mix patients with hyperemesis gravidarum and 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 and because evidence indicates that failure to treat early manifestations of nausea and vomiting of pregnancy increases the likelihood of hospital admission for hyperemesis gravidarum (37, 38), the following discussion focuses on treatment for all stages of nausea and vomiting of pregnancy.

- *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 conception were less likely to need medical attention for vomiting (45, 46). The standard recommendation to take prenatal vitamins for 3 months before conception may reduce the incidence and severity of nausea and vomiting of pregnancy.

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. Frequent, small meals every 1–2 hours to avoid a full stomach often are recommended (47). Other dietary modifications that may be helpful include avoiding spicy or fatty foods; eliminating pills with iron; and eating bland or dry foods, high-protein snacks, and crackers in the morning before arising (48). However, there is little published evidence regarding the efficacy of dietary changes for prevention or treatment of nausea and vomiting of pregnancy. A small study showed that protein meals were more likely to alleviate nausea and vomiting of pregnancy than carbohydrate or fatty meals (49).

A randomized double-masked placebo controlled trial of ginger capsules in 70 women with nausea and vomiting of pregnancy of varying severity found significant improvement in nausea and vomiting (50). Similarly, a recent systematic review and meta-analysis of randomized clinical trials showed improvement in nausea symptoms in pregnant women treated with ginger compared with placebo. However, ginger did not significantly reduce the episodes of vomiting (51). Treatment of nausea and vomiting of pregnancy with ginger has shown beneficial effects in reducing nausea symptoms and can be considered as a nonpharmacologic option.

Acupressure, acupuncture, or electrical nerve stimulation (acustimulation) at the P6 (or Neiguan) point on the inside of the wrist 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 (52). A recent systematic review of randomized controlled trials (RCTs) found no difference in P6 acupuncture and acupressure wristbands compared with placebo in the treatment of nausea and vomiting of pregnancy (5).

- *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. Randomized controlled trials have evaluated pyridoxine (vitamin B_6) for treatment of varying degrees of severity of nausea and vomiting of pregnancy (53, 54). One study compared pyridoxine, 25 mg every 8 hours, with placebo and found a signif-icant reduction in severe vomiting but minimal effect on mild vomiting (53). A larger study (N=342) used pyridoxine, 10 mg every 8 hours, and found a reduction in nausea and vomiting compared with placebo (54). A recent systematic review of RCTs found that nausea was improved with vitamin B_6, but emesis was not (5).

When the combination of vitamin B_6 (10 mg) plus doxylamine (10 mg) was available in the United States from 1958 to 1983, it is estimated that 25–30% of all pregnant women received this agent. Analysis of hospital admissions during this period suggests that the ready availability of vitamin B_6 and doxylamine for the treatment of the spectrum of nausea and vomiting of pregnancy was associated with fewer hospital admissions for hyperemesis gravidarum (38). After the combination was removed from the U.S. market in 1983, use of antiemetics to treat nausea and vomiting of pregnancy diminished considerably, and hospitalization rates for nausea and vomiting of pregnancy increased (38).

Treatment of nausea and vomiting of pregnancy with vitamin B_6 or vitamin B_6 plus doxylamine is safe and effective and should be considered first-line pharmacotherapy. Available over the counter as separate medications, the two medications are commonly taken together for nausea and vomiting of pregnancy. The doxylamine-vitamin B_6 medication was approved by the Food and Drug Administration in 2013 in the United States for treatment of nausea and vomiting of pregnancy in women who do not respond to dietary and lifestyle changes (55). A multicenter RCT of doxylamine and pyridoxine for nausea and vomiting of pregnancy found that a delayed-release formulation of doxylamine and pyridoxine significantly improved nausea and vomiting of pregnancy compared with placebo (56). Other randomized, placebo controlled trials have shown a 70% reduction in nausea and vomiting (57–59). Several case-control and cohort studies involving more than 170,000 exposures have found the combination to be safe with regard to fetal effects (60). In an RCT, 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 Diclectin, a combination of doxylamine and pyridoxine (available in Canada), initiated after the onset of symptoms (61). Other conventional antiemetics have been described in the literature for treatment of nausea and vomiting of pregnancy. The safety of antihistamine H1-receptor blockers (eg, doxylamine) is supported by a review of more than 200,000 first-trimester exposures (62). Phenothiazines were identified as a possible cause of malformations in one study (63), but the aggregate of studies attest to their safety (64). Two studies attest to the safety of trimethobenzamide (65, 66).

Medications for which there are some safety data but no conclusive evidence of efficacy include anticholinergics and metoclopramide. Additionally, evidence is limited on the safety or efficacy of the 5-

hydroxytryptamine 3 inhibitors (eg, ondansetron) for nausea and vomiting of pregnancy; however, because of their effectiveness in reducing chemotherapy-induced emesis, their use appears to be increasing.

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 (67). 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 (68). Ondansetron also was found to be more effective than the combination of doxylamine and pyridoxine in controlling the nausea and vomiting symptoms in a double-blind RCT of 36 women (69).

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 (70, 71). Moreover, complications with the use of continuous subcutaneous pumps were seen in 25–31% of selected patients (70).

The 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 (71, 72). In December 2012, the U.S. Food and Drug Administration (FDA) announced the removal of the 32-mg single intravenous dose of ondansetron from the market because of the potential cardiac risk of QT interval prolongation leading to torsades de pointes, a potentially fatal heart rhythm. The FDA recommends that ondansetron not be given intravenously in doses greater than 16 mg (see Box 2) (73). Electrolyte and electrocardiogram monitoring are recommended 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, and use of concomitant medications that lead to prolongation of QT interval (74). Another drug that may affect the QT interval is droperidol. Although rare, a specific type of prolonged QT interval, torsades de pointes, is possible with droperidol, and the FDA has issued a warning about its use (75, 76).

Box 2. Contraindicated Medications for Patients Receiving Ondansetron

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

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 was reported, but the data are limited (77). Another study of 1,349 pregnant women with presumed first-trimester exposure found an association between ondansetron use in early pregnancy and cardiac anomalies (odds ratio, 1.62; 95% confidence interval, 1.04–2.14), especially septum defects (risk ratio, 2.05; 95% confidence interval, 1.19–3.28) (78). Conversely, a prospective cohort study of 176 pregnant women found no increase in major fetal anomalies associated with ondansetron use and a retrospective study of 1,233 pregnant women with presumed first-trimester ondansetron exposure found no increase in congenital abnormalities (72, 79). 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. As with all medications, the potential risks and benefits should be weighed in each case.

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 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 (80). 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 (81).

Three studies have confirmed an association between oral clefts and methylprednisolone use in the first trimester (82–84). The teratogenic effect is weak, probably accounting for no more than one or two cases per 1,000 treated women (85). 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. 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 of 2 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 ultrasonographic evaluation 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 in the differential diagnosis of hyperemesis gravidarum and to 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 vomiting of pregnancy. A hypochloremic metabolic alkalosis can be seen as a result of severe vomiting of any cause. Serum concentrations of hCG are not helpful in determining whether vomiting is caused by hyperemesis gravidarum. Urinalysis may show elevated specific gravity, ketonuria, or both. However, a systematic review and meta-analysis of biomarkers for the diagnosis of hyperemesis gravidarum found no association between ketonuria and the presence or severity of hyperemesis gravidarum (86). Gastric ulcer should be considered in patients with persistent hyperemesis gravidarum that is 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 (87, 88) and has been reported to be beneficial in case reports (89).

  Up to 70% of patients with hyperemesis gravidarum will have suppressed thyroid-stimulating hormone levels or elevated free thyroxine concentrations (90). 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. Hyperthyroidism itself

rarely may present with significant vomiting (91), but in the patient who has no goiter, thyroid tests are not routinely needed to clarify the differential diagnosis. To confirm the diagnosis of hyperthyroidism in the setting of nausea and vomiting of pregnancy, measurement of free thyroxine and free triiodothyronine concentrations should be obtained.

- *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 (92). Enteral tube feeding (nasogastric or nasoduodenal) should be initiated as 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 (93, 94) 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 (95). 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 (96). Because life-threatening complications of parenteral nutrition have been described (35, 36, 97), enteral tube feeding initially should be used to provide nutritional support to the pregnant woman with hyperemesis who cannot maintain her weight.

  For women who cannot tolerate enteral tube feedings, the use of total parenteral nutrition has been described for hyperemesis gravidarum (35, 98). Peripherally inserted central catheters (PICCs) can be used to avoid some of the complications of central access (99), but they are still associated with significant morbidity (94, 100–102) and should only be used in the circumstance 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 discontinuation of PICCs, and superficial thrombophlebitis (100). A significant maternal complication rate (66.4%) associated with the use of PICCs also was noted in a retrospective study of 33 women with hyperemesis gravidarum and included infection, thromboembolism, bacteremia, and sepsis (94). 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 (102). The overall complication rate was 18.5 per 1,000 PICC days; bacteremia was the most frequent major complication occurring at a rate of 20.2% of major complications. Thus, PICCs should not be routinely used in women with hyperemesis gravidarum given the significant complications associated with this intervention. Peripherally inserted central catheters should only be utilized 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?*

An RCT of 98 pregnant women to either outpatient (day care) treatment or inpatient management of nausea and vomiting found that outpatient treatment decreases hospital inpatient stays (103). When a woman cannot tolerate liquids without vomiting and has not responded to outpatient management, hospitalization for evaluation and treatment is recommended. 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 psychotherapy in treatment?*

  There is little evidence for a therapeutic effect of traditional psychotherapy in hyperemesis gravidarum. No controlled trials have evaluated behavioral therapy in nausea and vomiting of pregnancy (104), but there are case examples of effective medical hypnosis therapy (105, 106). 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 (106).

Summary of Recommendations

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

- The standard recommendation to take prenatal vitamins for 3 months before conception may reduce the incidence and severity of nausea and vomiting of pregnancy.
- Treatment of nausea and vomiting of pregnancy with vitamin B_6 or vitamin B_6 plus doxylamine is safe and effective and should be considered first-line pharmacotherapy.
- In patients with hyperemesis gravidarum who also have suppressed thyroid-stimulating hormone levels, treatment of hyperthyroidism should not be undertaken without evidence (such as goiter, thyroid autoantibodies, or both) of intrinsic thyroid disease.

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

- Treatment of nausea and vomiting of pregnancy with ginger has shown beneficial effects in reducing nausea symptoms and can be considered as a nonpharmacologic option.
- Early treatment of nausea and vomiting of pregnancy is recommended to prevent progression to 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.

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

- 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 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 routinely used in women with hyperemesis gravidarum given the significant complications associated with this intervention. Peripherally inserted central catheters should only be utilized as a last resort in the management of a woman with hyperemesis gravidarum because of the potential of severe maternal morbidity.

Performance Measure

The proportion of women suffering with nausea and vomiting of pregnancy that are treated with vitamin B_6 or vitamin B_6 plus doxylamine as first-line pharmacotherapy

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985–April 2015. 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.