CLINICAL PRACTICE

Nausea and Vomiting in Pregnancy

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 25-year-old woman presents with persistent nausea and vomiting 8 weeks after her last menstrual period in her first pregnancy. Her primary care provider is reluctant to give her medications. She has lost 5 lb (2.3 kg) in 6 weeks. How should she be treated?

THE CLINICAL PROBLEM

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N Engl J Med 2010;363:1544-50.

An audio version of this article is available at NEJM.org

About 50% of women have nausea and vomiting in early pregnancy, and an additional 25% have nausea alone.[1,2] The popular term "morning sickness" is a misnomer, since this condition often persists throughout the day.[2] In about 35% of women who have this condition, nausea and vomiting are clinically significant, resulting in lost work time and negatively affecting family relationships.[3,4] In a small minority of patients, the symptoms lead to dehydration and weight loss requiring hospitalization.[5] The reported incidence of hyperemesis gravidarum is 0.3 to 1.0%; this condition is characterized by persistent vomiting, weight loss of more than 5%, ketonuria, electrolyte abnormalities (hypokalemia), and dehydration (high urine specific gravity).[5,6]

Although the cause of nausea and vomiting in pregnancy is unclear, the observation that pregnancies with a complete hydatidiform mole (no fetus) are associated with clinically significant nausea and vomiting indicates that the stimulus is produced by the placenta, not the fetus. The onset of the nausea is within 4 weeks after the last menstrual period in most patients. The problem typically peaks at approximately 9 weeks of gestation. Sixty percent of cases resolve by the end of the first trimester, and 91% resolve by 20 weeks of gestation.[1] Nausea and vomiting are less common in older women, multiparous women, and smokers; this observation has been attributed to the smaller placental volumes in these women. In one study, 63% of multiparous women who had nausea and vomiting also had symptoms in a previous pregnancy.[1] Nausea and vomiting are associated with a decreased risk of miscarriage.[7]

The clinical course of nausea and vomiting during pregnancy correlates closely with the level of human chorionic gonadotropin (hCG) (Fig. 1).[8] It is theorized that hCG may stimulate estrogen production from the ovary; estrogen is known to increase nausea and vomiting. Women with twins or hydatidiform moles, who have higher hCG levels than do other pregnant women, are at higher risk for these symptoms. Another theory is that vitamin B deficiency may contribute, since the use of multivitamins containing vitamin B reduces the incidence of nausea and vomiting. Although it has been suggested that nausea and vomiting may be caused by psychological factors, there are no good data to support this.

Preventable rare maternal complications of hyperemesis gravidarum include peripheral neuropathies due to vitamin B_6 and B_{12} deficiencies and, most serious, Wernicke's encephalopathy due to thiamine (vitamin B_1) deficiency.[9] Characterized by the triad of ophthalmoplegia, gait ataxia, and confusion, this condition may occur after at least 3 weeks of persistent vomiting. If patients are treated with intravenous dextrose without thiamine, metabolism of the dextrose rapidly consumes the available B_1, triggering acute encephalopathy. In one case series involving 19 patients in whom this complication developed, 74% had neurologic abnormalities on follow-up.[9] In some cases, the diagnosis is made only at autopsy.

Infants of mothers who have lost weight in early pregnancy, as compared with infants of women whose weight increased or stayed the same, have lower mean birth weights and lower percentile weights for gestational age, and they are more likely to be in less than the 10th percentile of birth weight at delivery.[10]

STRATEGIES AND EVIDENCE

EVALUATION

Hyperemesis gravidarum must be distinguished from other conditions that may cause persistent vomiting in pregnancy, including gastrointestinal conditions (e.g., appendicitis, hepatitis, pancreatitis, or biliary tract disease), pyelonephritis, and metabolic disorders such as diabetic ketoacidosis, porphyria, or Addison's disease. An onset of nausea and vomiting more than 8 weeks after the last menstrual period is rare in pregnancy.[1] The presence of fever, abdominal pain, or headache is atypical in women with hyperemesis and suggests another cause. Laboratory testing should generally include measurement of levels of urinary ketones, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, electrolytes, amylase, and thyrotropin (as well as free thyroxine [T_4] if thyrotropin is suppressed).

Because hCG cross-reacts with thyrotropin and stimulates the thyroid gland, thyrotropin is typically suppressed in these patients. This apparent hyperthyroidism usually resolves spontaneously, and treatment with propylthiouracil does not alleviate the nausea and vomiting.[11] Patients with primary hyperthyroidism rarely have vomiting.[12] The levels of T_4 and thyrotropin in patients with hyperemesis may be similar to those in patients with Graves' disease, but patients with hyperemesis do not have clinical findings of Graves' disease or thyroid antibodies.[13] If the level of free T_4 is elevated in the absence of other evidence of Graves' disease, this test should be repeated later in gestation, at around 20 weeks' gestation, since the level usually normalizes by then in the absence of hyperthyroidism.[13] Ultrasonographic testing should be performed to detect multiple gestation or hydatidiform mole.

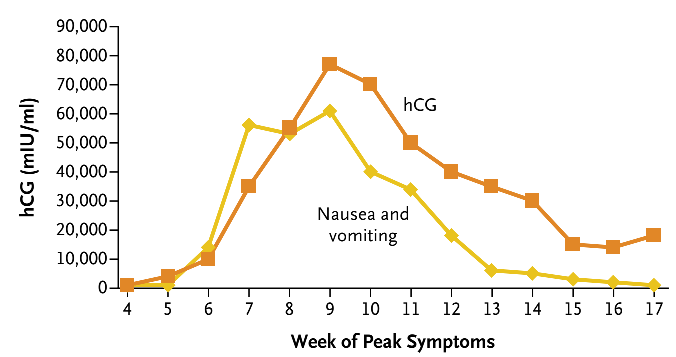

Figure 1. Relation between Peak Nausea and Vomiting Symptoms and Human Chorionic Gonadotropin (hCG) Levels.

MANAGEMENT

Women should be advised to avoid exposure to odors, foods, or supplements that appear to trigger nausea[14]; common triggers include fatty or spicy foods and iron tablets. Clinical experience suggests that eating small amounts of food several times a day and drinking fluids between meals may be helpful, as may bland, dry, and high-protein foods.[15] Traditionally, patients have been advised to manage nausea by keeping crackers at the bedside in the morning and avoiding an empty stomach. Data from randomized trials are lacking to compare different types of diets for the management of nausea and vomiting in pregnancy. In one crossover study involving 14 pregnant women with nausea, protein-predominant meals reduced nausea more than meals containing equal amounts of calories from carbohydrates and fat or noncaloric meals.[16]

Women who have persistent nausea and vomiting and high concentrations of ketones require intravenous hydration with multivitamins, including thiamine, with follow-up measurement of levels of urinary ketones and electrolytes. Antiemetic agents should be prescribed in these patients (Fig. 2).[17]

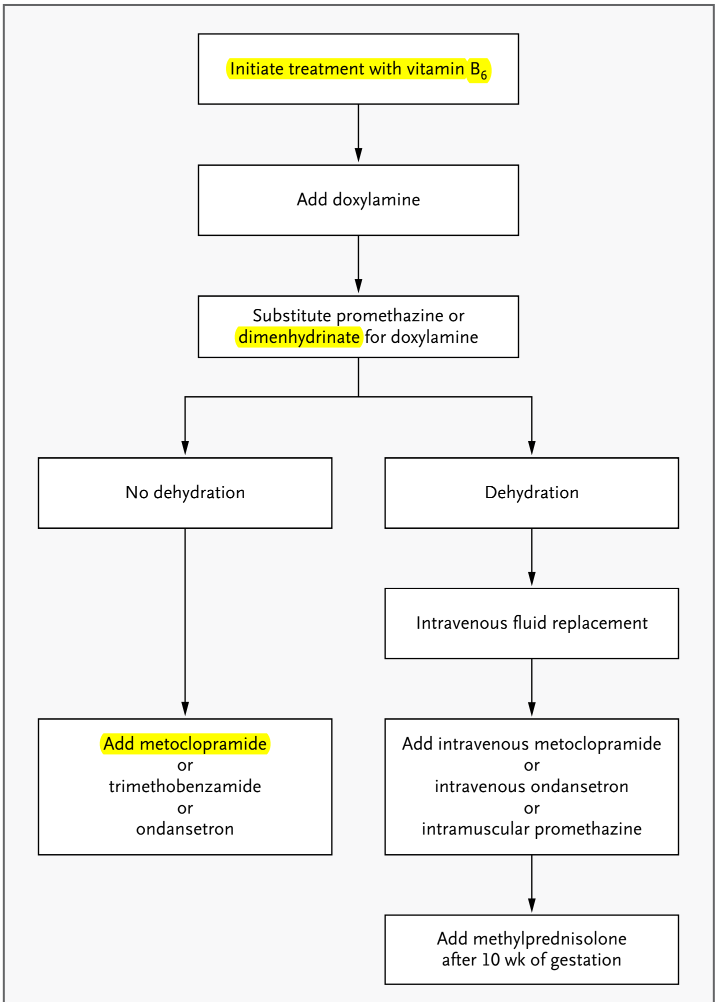

Figure 2. Pharmacologic Therapy for Nausea and Vomiting in Pregnancy.

Ginger may be added to pharmacologic therapy at any time. At any step, enteral or parenteral nutrition may be considered if dehydration or persistent weight loss is noted; it should be limited to patients with persistent nausea and weight loss who do not tolerate enteral nutrition.

PHARMACOLOGIC THERAPIES

Approximately 10% of women with nausea and vomiting in pregnancy require medication. Pharmacologic therapies include vitamin B_6, antihistamines, prokinetic agents, and other medications.

Randomized, placebo-controlled trials have shown the effectiveness of vitamin B_6 (10 to 25 mg every 8 hours) in the treatment of nausea and vomiting in pregnancy.[18,19] In one trial, the "difference in nausea" score after treatment, as measured on a visual analogue scale ranging from 1 to 10 (with higher scores indicating more severe symptoms) was 4.3 for women receiving active treatment versus 1.8 for controls. Also, in the Hungarian Family Planning Program, a periconceptional multivitamin trial,[20] women randomly assigned before conception to a daily multivitamin (containing vitamin B_6, 2.6 mg) were significantly less likely than those randomly assigned to placebo to report nausea, vomiting, and vertigo (3.4% vs. 7.4%) or to require a physician visit for nausea and vomiting (3.0% vs. 6.6%).[20] However, in another prospective study, there was no correlation between serum vitamin B_6 levels and the occurrence of morning sickness.[21]

A combination of vitamin B_6 and the antihistamine doxylamine (Bendectin) was removed from the U.S. market by the manufacturer in 1983 because of allegations of teratogenicity; these allegations were subsequently shown to be unjustified.[22] This drug combination still remains available in Canada in a sustained-released formulation (Diclectin), and its use has been associated with a decreased incidence of hospitalization for nausea and vomiting in pregnancy in observational studies.[23,24] Oral vitamin B_6 and doxylamine (Unisom SleepTabs) are available over the counter in the United States. This combination has been studied in more than 6000 patients and controls, with no evidence of teratogenicity,[25] and, in randomized trials, it has been associated with a 70% reduction in nausea and vomiting.[26] It is recommended by the American College of Obstetricians and Gynecologists (ACOG) as first-line therapy for nausea and vomiting in pregnancy.[26]

Other antihistamines used for nausea and vomiting in pregnancy are listed in Table 1. None of these agents have been shown to be teratogenic.[23,27]

A phenothiazine or metoclopramide is usually prescribed if antihistamines fail. Prochlorperazine (Compazine) is also available as a buccal tablet (Bukatel), which is usually associated with less drowsiness and sedation than oral tablets.[28]

Metoclopramide (Reglan) is a prokinetic agent, a dopamine antagonist. It has been associated in rare cases with tardive dyskinesia, and the Food and Drug Administration (FDA) has issued a black-box warning concerning the use of this drug in general. The risk of the development of this complication increases with the duration of treatment and the total cumulative dose; treatment for

Table 1. Pharmacologic Treatment of Nausea and Vomiting in Pregnancy.*

Agent	Oral Dose	Side Effects	FDA Category†	Comments
Vitamin B_6 (pyridoxine)	10–25 mg every 8 hr		A	Vitamin B_6 or vitamin B_6–antihistamine combination recommended as first-line treatment
Vitamin B_6–doxylamine combination	Pyridoxine, 10–25 mg every 8 hr; doxylamine, 25 mg at bedtime, 12.5 mg in the morning as needed plus 12.5 mg in the afternoon as needed	Sedation	A	
Vitamin B_6–doxylamine combination, delayed-release formulation (Diclectin, Canada)	10 mg pyridoxine and 10 mg doxylamine, extended release; 2 tablets at bedtime, 1 tablet in the morning as needed plus 1 tablet in the afternoon as needed			
Antihistamines		Sedation		
Doxylamine (Unisom SleepTabs)	12.5–25 mg every 8 hr		A	
Diphenhydramine (Benadryl)	25–50 mg every 8 hr		B	
Meclizine (Bonine)	25 mg every 6 hr		B	
Hydroxyzine (Atarax, Vistaril)	50 mg every 4–6 hr		C	
Dimenhydrinate (Dramamine)	50–100 mg every 4–6 hr		B	
Phenothiazines		Extrapyramidal symptoms, sedation		
Promethazine (Phenergan)	25 mg every 4–6 hr		C	Severe tissue injuries with intravenous use (black-box warning); oral, rectal, or intramuscular administration preferred
Prochlorperazine (Compazine)	5–10 mg every 6 hr		C	Also available as buccal tablet
Dopamine antagonists		Sedation, anticholinergic effects		
Trimethobenzamide (Tigan)	300 mg every 6–8 hr		C	
Metoclopramide (Reglan)	10 mg every 6 hr	Tardive dyskinesia (black-box warning)	B	Treatment for more than 12 wk increases risk of tardive dyskinesia
Droperidol (Inapsine)	1.25 mg to 2.5 mg intramuscularly or intravenously only		C	Black-box warning regarding torsades de pointes
5-hydroxytryptamine$_3$–receptor antagonist		Constipation, diarrhea, headache, fatigue		
Ondansetron (Zofran)	4–8 mg every 6 hr		B	Also available as oral disintegrating tablet; more costly than oral ondansetron tablets
Glucocorticoid				
Methylprednisolone (Medrol)	16 mg every 8 hr for 3 days, then taper over 2 wk	Small increased risk of cleft lip if used before 10 wk of gestation	C	Avoid use before 10 wk of gestation; maximum duration of therapy 6 wk to limit serious maternal side effects
Ginger extract	125–250 mg every 6 hr	Reflux, heartburn	C	Available over the counter as food supplement

* This list of agents is not exhaustive. FDA denotes Food and Drug Administration.

† FDA categories are as follows: A, controlled studies show no risk; B, no evidence of risk in humans; C, risk cannot be ruled out; D, positive evidence of risk; and X, contraindicated in pregnancy.

more than 12 weeks should be avoided. There have not been other safety concerns specific to pregnancy. In a recent randomized trial, intravenous metoclopramide and intravenous promethazine (Phenergan) had similar efficacy in the treatment of hyperemesis, but metoclopramide caused less drowsiness and dizziness.[29] An Israeli cohort study involving 3458 women who were exposed to metoclopramide in the first trimester (in most cases for 1 to 2 weeks) showed no significant association between exposure and the risk of congenital malformations, low birth weight, preterm delivery, or perinatal death.[30]

The 5-hydroxytryptamine$_3$-receptor antagonists, such as ondansetron (Zofran), are increasingly used for hyperemesis in pregnancy, but information is limited to inform their use in pregnant women.[31] A randomized trial comparing ondansetron and promethazine in pregnancy showed similar efficacy, but ondansetron was less sedating.[32] In a case series involving 169 infants exposed to ondansetron in the first trimester, 3.6% had major malformations; this rate was not significantly different from the rates in two control groups.[31]

Droperidol (Inapsine) has been used effectively for nausea and vomiting in pregnancy, but it is now used infrequently because of its risks. Droperidol can cause a prolonged QT interval on electrocardiographic (ECG) testing and even torsades de pointes, a potentially fatal arrhythmia; deaths have been reported in patients who received doses that were lower than the standard doses of this agent. As a result, there is a black-box warning associated with its use in all patients, and it is recommended that all patients undergo 12-lead ECG testing before, during, and 3 hours after administration.[33]

Methylprednisolone is an option in refractory cases. In a randomized trial involving 40 women,[34] methylprednisolone was superior to promethazine for treating nausea and vomiting in pregnancy. However, a larger trial, involving 110 women, showed no difference in the rate of rehospitalization for women who received methylprednisolone as compared with those who received placebo.[35] In the latter trial, all patients received promethazine at a dose of 25 mg and metoclopramide (Reglan) at a dose of 10 mg intravenously, as well as the glucocorticoid regimen.

In a meta-analysis of four studies, use of glucocorticoids before 10 weeks of gestation was associated with a risk of cleft lip with or without cleft palate that was increased by a factor of 3 to 4; higher doses were associated with greater risks. Thus, it is recommended that glucocorticoids be used only after 10 weeks of gestation.[36]

ALTERNATIVE AND COMPLEMENTARY THERAPIES

Alternative therapies such as acupuncture and ginger have also been studied for nausea and vomiting in pregnancy, with inconsistent results. In one randomized trial involving 33 patients with hyperemesis gravidarum, acupuncture reduced symptoms, as compared with sham acupuncture,[37] whereas a trial comparing traditional versus sham acupuncture in 55 patients with hyperemesis gravidarum showed no differences in outcomes between the two study groups.[38]

Randomized trials of acupressure on the Neiguan P6 point on the wrist with the use of the Sea-Band or BioBand[39,40] have yielded inconsistent results and have been limited by a lack of blinded testing. In the largest study,[39] no beneficial effect of acupressure was noted. In a randomized trial of the ReliefBand, which emits an electrical current to stimulate the P6 acupuncture point,[41] patients who were randomly assigned to the active device, as compared with those assigned to a sham device, were reported to have significantly less nausea and vomiting and were more likely to gain weight (77% vs. 54%, with an average weight gain of 5.5 lb vs. 2.9 lb [2.5 kg vs. 1.3 kg]); however, this study also was limited by a lack of blinded assessment of the outcomes.

Randomized, double-blind trials have provided support for a benefit of ginger in the management of nausea and vomiting in pregnancy.[42] In four randomized trials with a total of 675 participants, ginger in capsules (tasteless) was superior to placebo,[43-45] and in two trials, the efficacy of ginger was similar to that of vitamin B_6.[42] Adverse effects of ginger (reflux and heartburn) were not serious. In one observational cohort study involving 187 patients, ginger, as compared with other nonteratogenic agents, was not associated with clinically significant side effects or with increased risks of an adverse pregnancy outcome.[45] Ginger is considered to be not a drug but rather a food supplement, and therefore, it is not regulated by the FDA. It may not be available in hospital pharmacies.

MANAGEMENT OF REFRACTORY CASES

Patients with nausea and vomiting that are not controlled with outpatient regimens require intravenous hydration and nutritional supplementation. Enteral tube feeding may be effective, although some patients continue to have persistent emesis.[46] Total parenteral nutrition is associated with a substantial risk of line sepsis (25%)[47]; steatohepatitis may also occur with the use of lipid emulsion during pregnancy. Given these risks, total parenteral nutrition should be reserved for patients with clinically significant weight loss (>5% of body weight) who have had no response to antiemetic regimens and whose condition cannot be managed with enteral feedings.[12,26]

AREAS OF UNCERTAINTY

The cause or causes of nausea and vomiting in pregnancy remain unclear. The mechanism of action of vitamin B_6 is unknown. Few large trials have identified the optimal therapy for nausea and vomiting in pregnancy, and data are lacking to identify factors predicting the response to therapies. Vitamin B_6 levels do not predict the response to therapy with vitamin B_6.[21]

GUIDELINES FROM PROFESSIONAL SOCIETIES

The ACOG has published an algorithm for the management of nausea and vomiting in pregnancy (Fig. 2),[26] and the recommendations in this article are concordant with these guidelines. The Society of Obstetricians and Gynaecologists of Canada has published similar guidelines.[48,49]

CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette has nausea and vomiting in the first trimester of pregnancy, and she is losing weight, so pharmacologic therapy is warranted. It is also important to consider other causes of nausea and vomiting in early pregnancy such as migraine headaches or gastrointestinal disorders. Levels of blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, electrolytes, and amylase should be assessed. Dietary advice (e.g., frequent small meals) may be helpful. Given data from randomized trials suggesting that vitamin B_6 and doxylamine are beneficial, I would recommend this combination (vitamin B_6 [pyridoxine], 10 to 25 mg every 8 hours, and doxylamine, 25 mg at bedtime and 12.5 mg each in the morning and afternoon). If this regimen is not effective, a phenothiazine, metoclopramide, or ondansetron can be tried in succession. Methylprednisolone should be reserved for refractory cases after 10 weeks of gestation. Alternative remedies such as ginger and acupuncture may be tried at any time.

Pregnant women with dehydration should receive intravenous fluid replacement with multivitamins, especially thiamine. If, after 12 hours of intravenous therapy, the vomiting continues, hospitalization may be required. Enteral[48] or parenteral nutrition should be reserved for patients in whom weight loss continues despite pharmacologic therapies.[26]

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

I thank Dr. Barbara Stegmann for her expertise in epidemiology and help in characterizing the cited studies and Dr. T. Murphy Goodwin for providing data for Figure 1.

REFERENCES

1. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. Br J Gen Pract 1993;43:245-8.
2. Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: a prospective study of its frequency, intensity, and patterns of change. Am J Obstet Gynecol 2000;182:931-7.
3. Attard CL, Kohli MA, Coleman S, et al. The burden of illness of severe nausea and vomiting of pregnancy in the United States. Am J Obstet Gynecol 2002;186: Suppl:S220-S227.
4. Mazzotta P, Stewart D, Atanackovic G, Koren G, Magee LA. Psychosocial morbidity among women with nausea and vomiting of pregnancy: prevalence and association with anti-emetic therapy. J Psychosom Obstet Gynaecol 2000;21: 129-36.
5. Goodwin TM. Hyperemesis gravidarum. Clin Obstet Gynecol 1998;41:597-605.
6. Bashiri A, Neumann L, Maymon E, Katz M. Hyperemesis gravidarum: epidemiologic features, complications and outcome. Eur J Obstet Gynecol Reprod Biol 1995;63:135-8.
7. Weigel MM, Weigel RM. Nausea and vomiting of early pregnancy and pregnancy outcomes: an epidemiological study. Br J Obstet Gynaecol 1989;96:1304-11.

8. Braunstein GD, Hershman JM. Comparison of serum pituitary thyrotropin and chorionic gonadotropin concentrations throughout pregnancy. J Clin Endocrinol Metab 1976;42:1123-6.
9. Gárdián G, Vörös E, Járdánházy T, Ungureán A, Vécsei L. Wernicke's encephalopathy induced by hyperemesis gravidarum. Acta Neurol Scand 1999;99:196-8.
10. Gross S, Librach C, Cecutti A. Maternal weight loss associated with hyperemesis gravidarum: a predictor of fetal outcome. Am J Obstet Gynecol 1989;160:906-9.
11. Kirshon B, Lee W, Cotton DB. Prompt resolution of hyperthyroidism and hyperemesis gravidarum after delivery. Obstet Gynecol 1988;71:1032-4.
12. Eliakim R, Abulafia O, Sherer DM. Hyperemesis gravidarum: a current review. Am J Perinatol 2000;17:207-18.
13. Goodwin TM, Montoro M, Mestman JH, Pekary AE, Hershman JM. The role of chorionic gonadotropin in transient hyperthyroidism of hyperemesis gravidarum. J Clin Endocrinol Metab 1992;75:1333-7.
14. Broussard CN, Richter JE. Nausea and vomiting of pregnancy. Gastroenterol Clin North Am 1998;27:123-51.
15. Newman V, Fullerton JT, Anderson PO. Clinical advances in the management of severe nausea and vomiting during pregnancy. J Obstet Gynecol Neonatal Nurs 1993;22:483-90.
16. Jednak MA, Shadigian EM, Kim MS, et al. Protein meals reduce nausea and gastric slow wave dysrhythmic activity in first trimester pregnancy. Am J Physiol 1999;277:G855-G861.
17. Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev 2003;4:CD000145.
18. Sahakian V, Rouse D, Sipes S, Rose N, Niebyl J. Vitamin B6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double-blind placebo-controlled study. Obstet Gynecol 1991;78:33-6.
19. Vutyavanich T, Wongtra-ngan S, Ruangsri R-A. Pyridoxine for nausea and vomiting of pregnancy: a randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol 1995;173:881-4.
20. Czeizel AE, Dudás I, Fritz G, Técsöi A, Hanck A, Kunovits G. The effect of periconceptional multivitamin-mineral supplementation on vertigo, nausea and vomiting in the first trimester of pregnancy. Arch Gynecol Obstet 1992;251:181-5.
21. Schuster K, Bailey LB, Dimperio D, Mahan CS. Morning sickness and vitamin B6 status of pregnant women. Hum Nutr Clin Nutr 1985;39:75-9.
22. McKeigue PM, Lamm SH, Linn S, Kutcher JS. Bendectin and birth defects. I. A meta-analysis of the epidemiologic studies. Teratology 1994;50:27-37.
23. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998;338:1128-37.
24. Neutel CI, Johansen HL. Measuring drug effectiveness by default: the case of Bendectin. Can J Public Health 1995;86:66-70.
25. Holmes LB. Teratogen update: Bendectin. Teratology 1983;27:277-81.
26. ACOG (American College of Obstetrics and Gynecology) practice bulletin: nausea and vomiting of pregnancy. Obstet Gynecol 2004;103:803-14.
27. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2008.
28. Singh S, Sharma D, Chaudhary A. Evaluation of prochlorperazine buccal tablets (Bukatel) and metoclopramide oral tablets in the treatment of acute emesis. J Indian Med Assoc 1999;97:346-7.
29. Tan PC, Khine PP, Vallikkannu N, Omar SZ. Promethazine compared with metoclopramide for hyperemesis gravidarum: a randomized controlled trial. Obstet Gynecol 2010;115:975-81.
30. Matok I, Gorodischer R, Koren G, Sheiner E, Wiznitzer A, Levy A. The safety of metoclopramide use in the first trimester of pregnancy. N Engl J Med 2009;360:2528-35.
31. Einarson A, Maltepe C, Navioz Y, Kennedy D, Tan MP, Koren G. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. BJOG 2004;111:940-3.
32. Sullivan CA, Johnson CA, Roach H, Martin RW, Stewart DK, Morrison JC. A pilot study of intravenous ondansetron for hyperemesis gravidarum. Am J Obstet Gynecol 1996;174:1565-8.
33. Kovac AL. Prevention and treatment of postoperative nausea and vomiting. Drugs 2000;59:213-43.
34. Safari HR, Fassett MJ, Souter IC, Alsulyman OM, Goodwin TM. The efficacy of methylprednisolone in the treatment of hyperemesis gravidarum: a randomized, double blind, controlled study. Am J Obstet Gynecol 1998;179:921-4.
35. Yost NP, McIntire DD, Wians FH Jr, Ramin SM, Balko JA, Leveno KJ. A randomized, placebo-controlled trial of corticosteroids for hyperemesis due to pregnancy. Obstet Gynecol 2003;102:1250-4.
36. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000;62:385-92.
37. Carlsson CPO, Axemo P, Bodin A. Manual acupuncture reduces hyperemesis gravidarum: a placebo-controlled, randomized, single-blind, crossover study. J Pain Symptom Manage 2000;20:273-9.
38. Knight B, Mudge C, Openshaw S, White A, Hart A. Effect of acupuncture on nausea of pregnancy: a randomized, controlled trial. Obstet Gynecol 2001;97:184-8.
39. O'Brien B, Relyea MJ, Taerum T. Efficacy of P6 acupressure in the treatment of nausea and vomiting during pregnancy. Am J Obstet Gynecol 1996;174:708-15.
40. Dundee JW, Sourial FB, Ghaly RG, Bell PF. P6 acupressure reduces morning sickness. J R Soc Med 1988;81:456-7.
41. Rosen T, de Veciana M, Miller HS, Stewart L, Rebarber A, Slotnick RN. A randomized controlled trial of nerve stimulation for relief of nausea and vomiting in pregnancy. Obstet Gynecol 2003;102:129-35.
42. Borrelli F, Capasso R, Aviello G, Pittler MH, Izzo AA. Effectiveness and safety of ginger in the treatment of pregnancy-induced nausea and vomiting. Obstet Gynecol 2005;105:849-56.
43. Vutyavanich T, Kraisarin T, Ruangsri RA. Ginger for nausea and vomiting in pregnancy: randomized, double-masked, placebo-controlled trial. Obstet Gynecol 2001;97:577-82.
44. Fischer-Rasmussen W, Kjaer SK, Dahl C, Asping U. Ginger treatment of hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol 1991;38:19-24.
45. Portnoi G, Chng LA, Karimi-Tabesh L, Koren G, Tan MP, Einarson A. Prospective comparative study of the safety and effectiveness of ginger for the treatment of nausea and vomiting in pregnancy. Am J Obstet Gynecol 2003;189:1374-7. [Erratum, Am J Obstet Gynecol 2004;190:1140.]
46. Hsu JJ, Clark-Glena R, Nelson DK, Kim CH. Nasogastric enteral feeding in the management of hyperemesis gravidarum. Obstet Gynecol 1996;88:343-6.
47. Folk JJ, Leslie-Brown HF, Nosovitch JT, Silverman RK, Aubry RH. Hyperemesis gravidarum: outcomes and complications with and without total parenteral nutrition. J Reprod Med 2004;49:497-502.
48. Levichek Z, Atanackovic G, Oepkes D, et al. Nausea and vomiting of pregnancy: evidence-based treatment algorithm. Can Fam Physician 2002;48:267-8, 277.
49. Arsenault MY, Lane CA, MacKinnon CJ, et al. The management of nausea and vomiting of pregnancy. J Obstet Gynaecol Can 2002;24:817-31.