The Pharmacologic Management of Nausea and Vomiting of Pregnancy

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INTRODUCTION

Nausea and vomiting of pregnancy (NVP) is widely recognized as a common complication and occurs in 44% to 89% of pregnant women.[1] NVP usually begins between 4 and 6 weeks of gestation, peaks between 8 and 12 weeks, and resolves by 16 to 20 weeks in the majority of women.[1] Continuation beyond 20 weeks is generally thought to occur in 5% to 10% of women. However, recent evidence suggests that 29% to 45% of women experience NVP during late pregnancy, suggesting that inquiry about NVP should be made throughout a woman's pregnancy.[1,2]

Despite the high prevalence, undertreatment of NVP has been common in the United States, likely due to the beliefs that NVP is a natural part of pregnancy and that there is no need for concern unless there are signs or symptoms related to NVP in its most severe form, ie, hyperemesis gravidarum.[3] Hyperemesis gravidarum is typically characterized by persistent nausea and vomiting with or without retching, >5% weight loss, hypokalemia, high urine specific gravity due to dehydration, and ketonuria.[4] Other factors contributing to the undertreatment of NVP include fear of fetal harm caused by medications and, until recently, the lack of available prescription medications in the United States proven effective for NVP.[3]

Addressing these beliefs is important, since women who experience even mild or moderate NVP can suffer from depression and diminished functioning related to employment, household activities, parenting, and other physical and social activities. NVP can also lead to increased costs and utilization of health care resources.[5-10] While concerns about harm to the fetus due to medications are justified, many medications commonly used to treat NVP are not known to pose additional fetal risk.[11] Furthermore, initiating treatment at the recognition of pregnancy, before the occurrence of symptoms of NVP in women at high risk for recurrence of severe NVP, is superior to initiating treatment following the onset of symptoms.[12] Addressing these issues in the primary care management of the pregnant woman with nausea and vomiting is the focus of this article.

ASSESSMENT

Common symptoms associated with NVP include any combination of nausea, gagging, retching, dry heaving, vomiting, and odor and/or food aversion.[4] Since a focus of the assessment is to determine if the nausea and vomiting are due to the pregnancy or some other cause, the patient should be questioned about the onset, timing, severity, aggravating and alleviating factors, and appearance of the vomitus, as this can help to rule out causes other than pregnancy. Onset of nausea beyond 8 weeks after the last menstrual period is rare in pregnancy.[13]

NVP is often triggered by 1 or more factors, such as motion, heartburn, and food or other odors. The vomitus in NVP is usually nonbilious and nonbloody.[14] The patient history should include questions concerning fever, abdominal pain, and change in bowel habits; headache, neck stiffness, and changes in vision may suggest a neurological cause.[14]

Non–pregnancy-related causes of persistent vomiting include gastrointestinal disorders (eg, appendicitis, hepatitis, pancreatitis, biliary tract disease), pyelonephritis, metabolic disorders such as diabetic ketoacidosis, porphyria, or Addison disease, and central nervous system diseases such as migraine, infections, tumors, and seizures.[13,14] When a cause other than pregnancy is suspected, laboratory testing should

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generally assess urinary ketones, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, electrolytes, amylase, and thyrotropin.[13] Complications of NVP should be investigated as well, particularly in women who experience severe, persistent vomiting. Possible complications include dehydration or thiamine deficiency resulting in Wernicke encephalopathy, which can occur after 3 weeks of persistent vomiting.

The Pregnancy-Unique Quantification of Emesis (PUQE) score can be used to assess the severity of NVP, as well as to follow the response to treatment and improvement over time.[4] Both 12- and 24-hour scoring systems have been validated; the 24-hour system accounts for time sleeping and the severity of symptoms through the first trimester.[15]

Finally, the assessment should also include inquiry about treatments that have already been attempted by the patient to self-manage NVP. These include not only lifestyle and dietary changes, but also vitamins and complementary or alternative therapies.

TREATMENT

Variation in the symptoms of NVP and the impact they have on pregnant women and their families requires that treatment be individualized to achieve the following goals: 1) reduce the incidence, severity, and impact of symptoms; 2) reduce the risk of progression to more severe NVP; 3) correct the consequences or complications, including fluid/electrolyte imbalance and metabolic alkalosis; and 4) minimize the effects on the fetus, particularly the effects of treatment. To achieve these goals, nonpharmacologic therapies, followed by pharmacologic therapies if necessary, can be employed.

Nonpharmacologic and alternative therapies

A mainstay of treatment for NVP involves dietary and lifestyle approaches. Women should be advised to avoid factors that trigger nausea, including strong odors, fatty or spicy foods, and iron tablets.[13] Clinical experience indicates that avoiding an empty stomach by eating small meals consisting of bland, dry, high-protein food every 1 to 2 hours and drinking room-temperature fluids between meals (rather than with meals) may be helpful.[13,16,17] Dietary guidelines developed by the Motherisk NVP group at Toronto's Hospital for Sick Children are summarized in **TABLE 1**.[15] Beyond dietary factors, adequate sleep is also important.

Pyridoxine (vitamin B_6) and ginger are often used by patients prior to seeking medical care and have been shown to be safe and effective for NVP.[11] Pyridoxine is typically used in daily doses of 50 to 100 mg, although daily doses as high as 500 mg have been used.[18-21] Ginger is also effective in daily doses of 500 to 1000 mg, with reflux and heartburn the most common side effects.[13,22-25] A comparison of pyridoxine and ginger found ginger 1000 mg/day to be more effective than pyridoxine 40 mg/day for 4 days for reducing the severity of nausea. Both were similarly effective for decreasing the number of vomiting episodes in early pregnancy.[26]

Weak evidence indicates that acupressure may be effective for NVP.[27] Acupressure involves stimulation of the pericardium 6 (P6) acupoint, located 4.5 cm above the wrist on the inside of the forearm.[16,28-31] Stimulation is provided by wrist bands, with some emitting a weak electrical current. PrimaBella, formerly the ReliefBand, has been shown to be effective and is the only device approved by the US Food and Drug Administration (FDA) for NVP.[32,33]

TABLE 1 Dietary guidelines for nausea and vomiting of pregnancy[15]

• Maintain adequate hydration and electrolyte levels, drinking at least 2 liters of water a day
• Avoid an empty stomach at all times, with small frequent meals every 1-2 hours, consisting of bland foods throughout the day
• Prevent a full stomach (ie, not mixing solids with liquid, avoid large meals and very fatty food)
• Avoid strong-tasting, odorous foods (ie, spicy, metallic tastes)
• Snack on nuts and high-protein foods between meals
• Discontinue iron-containing prenatal multivitamins in early pregnancy and switch to children's chewable tablets and folic acid instead. Resume iron-containing prenatal vitamins after 12 weeks when iron is most needed by mother and baby. Pregnant women with past or current anemia should not discontinue prenatal vitamins, but may take them in divided doses
• Consume ice chips, ice pops, and very cold beverages to help reduce metallic taste
• Eat simple dry carbohydrates (ie, crackers, biscuits, etc) prior to getting out of bed in the morning

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Pharmacologic treatment

A wide variety of pharmacologic options have been utilized for the management of NVP **(TABLE 2)**.[11,34-39] Efficacy and safety are 2 key considerations in selecting treatment. A recent systematic, evidence-based review examined randomized controlled trials of any intervention for NVP.[27] Excluded were trials using a crossover design or those involving women with hyperemesis gravidarum. Twenty-seven trials of nonpharmacologic and pharmacologic treatment involving 4041 women were included. Due to the lack of high-quality evidence, the Cochrane investigators found limited evidence to support the use of pharmacologic antiemetic agents in early pregnancy. In contrast, the American

TABLE 2 Fetal safety of pharmacologic agents used to treat nausea and vomiting of pregnancy

Pharmacologic class/agent	Risk classification	
	FDA risk factor[a]	Briggs et al[11b]
Doxylamine succinate/pyridoxine hydrochloride	A[34]	Compatible
H_1-receptor blocker		
Dimenhydrinate	Not rated	Compatible
Diphenhydramine	Not rated	Compatible
Doxylamine	Not rated	Compatible
Hydroxyzine	Not rated	Human data suggest low risk
Meclizine	Not rated	Compatible
Metoclopramide	B[35]	Compatible
Phenothiazine		
Prochlorperazine	Not rated	Compatible
Promethazine	C[36]	Compatible
Ondansetron	B[37]	Human data suggest low risk
Pyridoxine hydrochloride	A[38]	Compatible
Corticosteroid	C[39]	Human data suggest risk; avoid during first 10 weeks of gestation
Prednisone		

Abbreviation: FDA, US Food and Drug Administration.

[a]FDA risk factor definitions:

A: adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)

B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester

C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

[b]Definitions from *Drugs in Pregnancy and Lactation, 9th ed.* by Briggs, Freeman, and Yaffe:

Compatible: Human pregnancy experience is adequate to demonstrate that the embryo-fetal risk is very low or nonexistent.

Human data suggest low risk: The limited human pregnancy experience suggests that the drug does not represent a significant risk of developmental toxicity (growth restriction, structural anomalies, functional/neurobehavioral deficits, or death) at any time in pregnancy.

Human data suggest risk: The human data suggest there may be a risk for developmental toxicity throughout pregnancy. Usually, pregnancy exposure should be avoided, but the risk may be acceptable if the maternal condition requires the drug.

Congress of Obstetricians and Gynecologists (ACOG) concluded that pyridoxine alone or in combination with doxylamine is safe and effective for NVP and should be considered first-line pharmacotherapy.[40]

In considering the safety of these agents, 2 points need to be kept in mind. First, there is the inherent problem of ethically conducting trials in pregnant women to assess medication safety in humans. Thus, safety is often inferred from animal studies. For older medications, such as antihistamines and some phenothiazines, there is no FDA pregnancy rating (**TABLE 2**).[34-39] Second, the risk of having a baby with a birth defect by chance alone is 1% to 3%.[41] Meta-analyses and epidemiologic studies have not found a higher incidence of birth defects with antihistamines (H_1-receptor blockers), phenothiazines, and metoclopramide.[42-46] A marginally increased risk of major malformations following first-trimester exposure to corticosteroids has been observed.[47] In addition, the same study found an increased risk (odds ratio, 3.35) of oral cleft. An increased risk of hypospadias (odds ratio, 2.87) with corticosteroid use during the first trimester has also been identified from an analysis of data from the National Birth Defects Prevention Study.[48] These findings indicate that corticosteroids should be reserved for NVP refractory to other treatments until after the first trimester of pregnancy.

Doxylamine/pyridoxine

Bendectin, the combination of doxylamine and pyridoxine (also in combination with dicyclomine until 1978), was used as an antiemetic by more than 33 million pregnant women in the United States and throughout the world for nearly

3 decades. In the late 1970s, published studies began to appear that raised the possibility of an association of doxylamine/pyridoxine with birth defects. In-depth review by the FDA and regulatory agencies throughout the world found no association between doxylamine/pyridoxine and birth defects. Nonetheless, allegations continued and litigation mounted, causing the principal manufacturer to remove doxylamine/pyridoxine worldwide in 1983.[49] A generic form of doxylamine/pyridoxine, Diclectin, remained on the market in Canada, where it continues to be first-line therapy for NVP.[50]

Following the withdrawal of Bendectin, 2 meta-analyses involving data from more than 200,000 pregnancies found no increased risk for major malformations with exposure to doxylamine/pyridoxine.[51,52] Subsequent studies have provided further support regarding the safety of doxylamine/pyridoxine, finding no association with birth defects.[16,53] Doxylamine/pyridoxine has remained classified as risk level A in the standard reference *Drugs in Pregnancy and Lactation* by Briggs, Freeman, and Yaffe.[11] This rating was based on the authors' independent ongoing review of the evidence that found doxylamine/pyridoxine safe in human pregnancy, including in the first trimester. In 2004 and again in 2009, ACOG concluded that "treatment of nausea and vomiting of pregnancy with pyridoxine or pyridoxine plus doxylamine is safe and effective and should be considered first-line pharmacotherapy."[40]

In 2005, the manufacturer of doxylamine/pyridoxine in Canada submitted a new drug application to the FDA. As part of its review, the FDA required a new phase III placebo-controlled study to be conducted in the United States.[54] The study involved 241 women 7 to 14 weeks pregnant experiencing NVP. Results showed doxylamine/pyridoxine to be superior to placebo in improving NVP symptoms (change from baseline in the PUQE score: –4.8 vs –3.9, respectively; $P = .006$). Nineteen percent of women took 2 tablets daily, 21% took 3 tablets daily, and 60% took 4 tablets daily. Quality of life after 2 weeks was also improved and women treated with doxylamine/pyridoxine required less rescue therapy and reported fewer days missed from work. In April 2013, the FDA approved Diclegis, the combination of doxylamine succinate 10 mg plus pyridoxine hydrochloride 10 mg delayed-release tablets, for the treatment of NVP in women who do not respond to conservative management.[34] The FDA also classified the product as pregnancy category A, which is the strongest evidence of fetal safety possible.

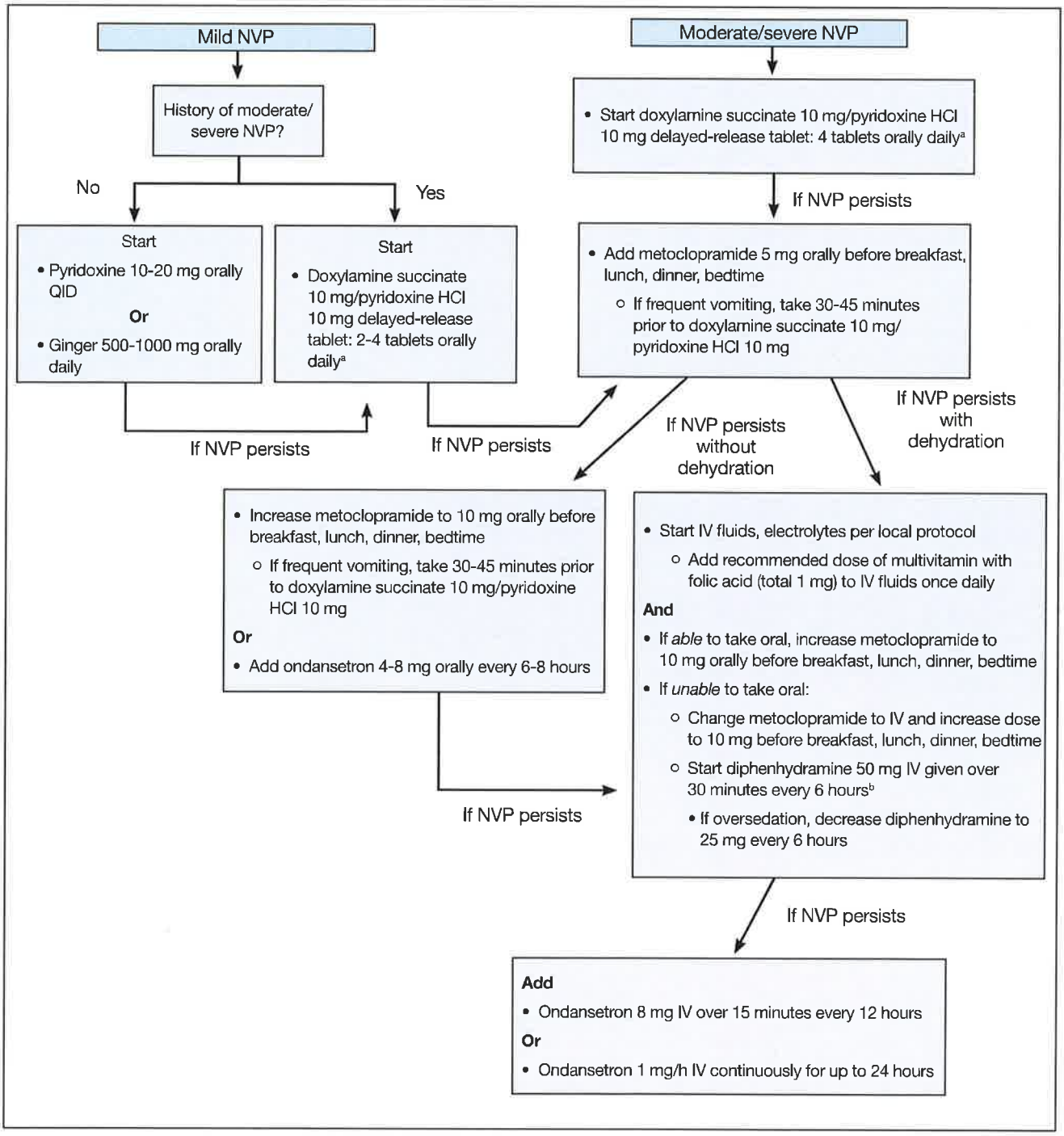
Beyond safety, clinical studies as well as clinical experience over more than 4 decades demonstrate the combination of doxylamine and pyridoxine to be effective in reducing the incidence and severity of NVP.[54] The product now available in the United States is recommended to be given as 2 tablets at bedtime. If symptoms are not adequately controlled within 24 to 48 hours, the dose can be increased to 4 tablets daily (1 tablet in the morning, 1 midafternoon, and 2 at bedtime).[34] The morning dose can be added after 1 day and the afternoon dose after another day. Somnolence is the most common adverse event observed (14.3% vs 11.7% for placebo), likely due to the anticholinergic effects of doxylamine, an H_1-receptor antagonist.[34]

Although the Cochrane systematic review cited above found only limited evidence to support the use of pharmacological antiemetic agents for NVP, clinical experience indicates that some treatment options are effective. The **FIGURE** shows a suggested approach for the pharmacologic treatment of women with NVP during early pregnancy. As the only medication approved by the FDA for NVP and as recommended by ACOG, doxylamine succinate/pyridoxine hydrochloride delayed-release tablets are first-line pharmacologic therapy.[40] For those who have an inadequate response to doxylamine succinate/pyridoxine hydrochloride delayed-release tablets, a drug from a different pharmacologic class, such as metoclopramide, should be added. This has the benefits of utilizing drugs with different mechanisms of action while reducing the likelihood of additive adverse events such as sedation. The same options are also appropriate as monotherapy for women who are intolerant of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets.

Adverse events are also a consideration when selecting treatment. The use of an antihistamine (H_1-receptor antagonist) or a phenothiazine may be limited by sedation, particularly with increasing doses. Although tardive dyskinesia may occur with a phenothiazine or metoclopramide, the risk is low with the doses and duration of therapy used for NVP. Another potential complication with metoclopramide is serotonin syndrome, a potentially life-threatening set of symptoms caused by serotonin toxicity. The risk of serotonin syndrome is increased when a patient taking metoclopramide is also taking another medication that promotes serotonin activity, such as an antidepressant (selective serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, tricyclic monoamine oxidase inhibitor, or bupropion), a triptan, lithium, or ondansetron. [Note: many of these medications are categorized as pregnancy class C or D by the FDA.] Serotonin syndrome may also be possible with ondansetron and is under investigation by the FDA.[55] Ondansetron is also associated with the potential for QT prolongation; investigation to identify patients at high risk is ongoing.[56]

The fetal safety of ondansetron, a 5-hydroxytryptamine$_3$-receptor antagonist, has been investigated in a retrospective review of data from the National Birth Defects Prevention Study involving women with NVP. Compared with controls

FIGURE **Pharmacologic treatment of nausea and vomiting of pregnancy**[34,35,37,40]



Abbreviations: HCl, hydrochloride; IV, intravenous; NVP, nausea and vomiting of pregnancy; QID, 4 times daily.

[a]If 2 tablets/day, take 2 at bedtime; if 3 tablets/day, take 1 in the morning, afternoon, and bedtime; if 4 tablets/day, take 1 in the morning and afternoon and 2 at bedtime.

[b]Doxylamine and diphenhydramine are ethanolamines, a subclass of the H_1 antihistamine group. They have marked sedative properties, as well as anticholinergic and antiemetic actions. The anticholinergic action will prevent metoclopramide-related tardive dyskinesia.

Notes

Phenothiazines also cause tardive dyskinesia and would potentiate that adverse reaction if used with metoclopramide.

If NVP persists after the above therapy, hyperemesis gravidarum should be considered and, if suspected, the patient should be hospitalized.

without birth defects, children born of mothers treated with ondansetron during the first trimester showed an increased risk of cleft palate (odds ratio, 2.37).[48] The risks of nonsyndromic cleft lip with or without cleft palate, neural tube defects, and hypospadias were similar between controls and those treated with ondansetron. Recently, the results of 2 Danish studies investigating the fetal safety of ondansetron have been reported, but with opposite findings. Both were retrospective analyses based on birth defect and prescription medication information from similar registries and from overlapping time periods. One study involving 897,018 women found a doubling in the prevalence of major congenital heart defects in children whose mothers were treated with ondansetron during the first trimester of pregnancy.[57] In the other study, involving 608,385 pregnancies, there was no increased risk of stillbirth, no major birth defect, and no infants born at low birth weight or at small size for gestational age associated with ondansetron exposure.[58] However, the risk of preterm delivery was significantly increased with ondansetron (odds ratio, 1.28; 95% confidence interval, 1.05-1.55). The reason for these discrepant findings is unclear. In women with hyperemesis gravidarum refractory to standard treatment (N = 16), no teratogenic effects were observed; however, 1 minor birth defect, 2 premature births, and 6 pregnancy or neonatal adverse outcomes were observed.[59]

Referral

Pregnant women with severe symptoms of NVP, particularly those with an inadequate response to combination therapy and those who experience significant morbidity or complications, should be considered for referral to an obstetrician or treatment in the hospital.

SUMMARY

Nausea and vomiting are common in early pregnancy. Forty percent or more of pregnant women may continue to suffer beyond the first trimester and 10% beyond the second trimester. A focus of the assessment is to confirm that the nausea and vomiting is due to the pregnancy and not some other cause. Nonpharmacologic options, particularly dietary modification, are a mainstay of treatment. For those who continue to experience symptoms, pharmacologic management can be employed. The combination of doxylamine succinate/pyridoxine hydrochloride was reintroduced in the United States following FDA approval in early 2013. The product was given a pregnancy safety rating of A and is recommended as first-line pharmacologic treatment for NVP. Other options include antihistamines, metoclopramide, ondansetron, phenothiazines, and after the first trimester, corticosteroids. ●

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