Nausea and vomiting of pregnancy (NVP) is a common condition that affects almost 70% of women in the US and globally. Patients with NVP present with nausea and vomiting with or without retching, usually before 9 weeks of gestation. Secondary symptoms of NVP can include excessive salivation or a bitter/metallic taste in the mouth. Abdominal pain, fever, and headache are not usually seen. Patients who present to the emergency department (ED) will likely have more severe symptoms and may have already sought treatment as an outpatient from their primary care provider or obstetrician. The most severe form of NVP is hyperemesis gravidarum (HG), which affects approximately 1% of women and often leads to hospitalization. Those who have progressed to HG may additionally present with signs of acute starvation, weight loss, ketonuria, electrolyte imbalance, and liver, kidney, and thyroid abnormalities.
The total cost of treating NVP in the US was more than $1.7 billion in 2012, including the direct cost of healthcare and indirect costs associated with lost work or the need for additional caregivers in the home. The more than 240,000 ED visits for NVP and HG in 2012 were estimated to cost approximately $250 million. Total medical care costs increased with the severity of NVP symptoms and the use of second- and third-line medications such as metoclopramide and ondansetron. Effective treatment of NVP in the ED and at discharge is critical to reduce symptom progression and the number of repeat ED visits or hospitalization for severe NVP or HG, thereby reducing the cost of care.

**Treatment of NVP in the ED**

Overall, the goals of NVP treatment are to reduce the severity and impact of symptoms, and to reduce the risk of progression to more severe NVP or HG while minimizing any adverse effects of treatment on the fetus. The immediate priorities for a woman presenting to the ED with NVP are to replace fluids if the patient is dehydrated, using intravenous (IV) hydration, and to correct ketosis and vitamin deficiency. Thiamine may be needed to prevent Wernicke encephalopathy. It is also important to determine which therapies the patient has already tried to control her NVP symptoms, including dietary or lifestyle changes, herbal remedies, or over-the-counter treatments, as well as any prescription medications.

Intravenous (IV) or oral pharmacotherapy may be used to reduce nausea and vomiting in the ED. It is important to note that no studies have compared the efficacy of antiemetic medications used for treatment of acute symptoms of NVP in the ED, and there are no evidence-based guidelines for the emergency treatment of NVP. A recent retrospective study of 439 women with NVP who were treated in the ED over a period of two years evaluated the time from treatment administration to ED discharge as a proxy for treatment efficacy. Patients were given ondansetron (48%), metoclopramide (38%), prochlorperazine (1%), or promethazine (13%), and 9% of patients were given more than one medication. Each medication had a similar mean time from administration to discharge, suggesting no difference in efficacy for acute management of NVP in the ED. Another recent randomized controlled trial also found no difference between ondansetron and metoclopramide in reducing nausea or vomiting in hospitalized patients with HG. In the absence of evidence-based guidelines or evidence of superior efficacy, the choice of antiemetic medication in the ED for acute treatment of NVP should take into account the severity of symptoms, patient status, and the safety of each medication, carefully weighed against the potential benefits.

Hospital admission is reserved for the most severe forms of NVP. Hospitalization for treatment and observation is recommended for patients who cannot tolerate oral liquids without vomiting, do not respond to antiemetic medication, and continue to lose weight.

**Discharge Therapy for NVP**

Once a patient’s symptoms have been stabilized in the ED, a decision must be made about post-discharge instructions to control NVP symptoms at home. These instructions may include dietary and lifestyle recommendations, non-pharmacologic approaches, and pharmacologic therapies.

Patients may have already attempted to reduce NVP symptoms with dietary or lifestyle changes prior to their ED visit, and they should be encouraged to continue these practices to help keep symptoms under control. Non-pharmacologic options include pyridoxine (vitamin B6) and ginger, though these may not be suitable for women who initially presented to the ED with moderate to severe symptoms.

Women may be cautious about taking medication for NVP out of concern for the potential effects on the fetus. As with acute treatment in the ED, the choice of antiemetic to prescribe at discharge should take into account all available data on maternal and fetal safety, weighed against the benefits of treatment. Decisions about antiemetic medications for NVP prescribed at discharge can be guided by evidence-based recommendations from the American College of Obstetricians and Gynecologists (ACOG). The use of ACOG guidelines for treatment decision-making at ED discharge will facilitate continuity of care with the patient’s obstetrician or primary care provider, and may produce better outcomes for women with NVP and reduce the risk of repeat ED visits or hospitalization. Similarly, the Association of Professors of Gynecology and Obstetrics (APGO) dedicated an educational series on women’s health issues to NVP (https://www.apgo.org/), as well as, their first app called APGO WellMom “Managing Nausea and Vomiting of Pregnancy (NVP)” (http://www.wellmomapp.com/). This app was designed for raising awareness for NVP, educating all parties affected by the condition, and managing and treating the symptoms.

2 JUNE 2016
Delayed-Release Doxylamine/Pyridoxine as First-Line Pharmacotherapy at Discharge

ACOG recommends that pyridoxine alone or in combination with doxylamine (an histamine 1 [H1] receptor blocker) be considered as first-line pharmacotherapy for the treatment of NVP (Figure). A recent matched cohort study of 160 women with NVP found a greater effect of the combination of doxylamine and pyridoxine compared with pyridoxine alone for reducing the symptoms of NVP, particularly in women with moderate to severe symptoms. In the US, a delayed-release formulation of doxylamine 10 mg and pyridoxine 10 mg (marketed as Diclegis®) is currently the only medication approved for use for the treatment of NVP in patients who have not responded to conservative treatment, including dietary and lifestyle changes.

The combination of doxylamine 10 mg/pyridoxine 10 mg was available in the US from 1958 to 1983, marketed as Bendectin®. During that time period, up to 30% of all pregnant women (an estimated 33 million women) received Bendectin for NVP. Case reports of teratogenic effects of Bendectin eventually led to its voluntary removal from the US market in 1983, despite evidence from several large cohort studies and meta-analyses demonstrating the maternal and fetal safety of doxylamine/pyridoxine. While the removal of Bendectin from the market did not result in a change in the overall number of reported birth defects in the US, as would be expected for a teratogen, the number of severe NVP cases resulting in hospitalization doubled. In Canada, a delayed-release combination of doxylamine 10 mg/pyridoxine 10 mg (Diclectin®) remained on the market and no increases in birth defects have been noted. These epidemiological and ecological data provided strong support for the safety and efficacy of delayed-release doxylamine/pyridoxine for treatment of NVP, and its return to the US market as Diclegis in 2013.

A phase 3 placebo-controlled study was conducted in the US as part of the Diclegis New Drug Application to the FDA. The study included 131 women randomized to Diclegis and 125 randomized to placebo who were in weeks 7-14 of pregnancy and were experiencing symptoms of NVP that were not responsive to dietary or lifestyle changes. Delayed-release doxylamine/pyridoxine was found to be superior to placebo in reducing NVP symptoms, with improvement in quality of life after two weeks, less need for concomitant therapies, and fewer days of work missed. Somnolence was the only adverse reaction seen with greater than 5% frequency in both the treatment and placebo groups, likely due to the anticholinergic effects of doxylamine. A secondary analysis

Figure. Pharmacotherapeutic Approach to NVP after Discharge from the Emergency Department: Application of American College of Obstetricians and Gynecologists (ACOG) Guidelines

<table>
<thead>
<tr>
<th>Emergency Department</th>
<th>Acute Management of NVP</th>
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<tbody>
<tr>
<td><strong>Discharge</strong></td>
<td></td>
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<tr>
<td>Doxylamine 10 mg/pyridoxine 10 mg delayed-release tablets* (Pregnancy Category A)</td>
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</tr>
<tr>
<td><strong>ADD</strong></td>
<td></td>
</tr>
<tr>
<td>Dimenhydrinate (Pregnancy Category B) 50-100 mg every 4-6 hours*</td>
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<tr>
<td><strong>OR</strong></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide (Pregnancy Category B) 5-10 mg every 8 hours before breakfast, lunch, dinner, bedtimeę</td>
<td></td>
</tr>
<tr>
<td><strong>ADD</strong></td>
<td></td>
</tr>
<tr>
<td>Promethazine (Pregnancy Category C) 12.5-25 mg every 4 hours, orally or rectally</td>
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</tr>
<tr>
<td><strong>OR</strong></td>
<td></td>
</tr>
<tr>
<td>Ondansetron (Pregnancy Category B) 4-8 mg orally, every 6-8 hours</td>
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</tr>
<tr>
<td><strong>ADD</strong></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone (Pregnancy Category C)* 16 mg every 8 hours for 3 days</td>
<td></td>
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</tbody>
</table>

*If 2 tablets/day, take 2 at bedtime; if 3 tablets/day, take 1 in the morning and 2 at bedtime; if 4 tablets/day, take 1 in the morning, 1 mid-afternoon, and 2 at bedtime. Not to exceed 400 mg per day. Not to exceed 200 mg per day if patient also is taking doxylamine to reduce sedation effect. If frequent vomiting, take 30-45 minutes prior to doxylamine/pyridoxine. Corticosteroids are associated with an increased risk of oral clefts when used during the first 10 weeks of gestation, and should be used as a last resort in patients with severe NVP or HG that is not responsive to other medications. After 3 days, taper over 2 weeks to lowest effective dose. If beneficial, limit total duration of use to 6 weeks.
focused on maternal safety using data from the phase 3 study found that the adverse event rate with delayed-release doxylamine/pyridoxine was no different from that of placebo.23

Delayed-release doxylamine/pyridoxine (Diclegis) is the only pharmacologic option for NVP that has an FDA Pregnancy Category A rating (Table). This rating is based on numerous epidemiological studies, including the findings of two separate meta-analyses of cohort and case-control studies performed between 1963 and 1991, that found no increased risk of fetal abnormalities with the combined use of doxylamine and pyridoxine during the first trimester of pregnancy.20,21 A more recent study examined the effects of maternal exposure to delayed-release doxylamine/pyridoxine on the long-term neurodevelopment of children exposed in utero.23 The study compared three groups of mother-child pairs: mothers who had NVP and took delayed-release doxylamine/pyridoxine (n=45), those who had NVP but did not take delayed-release doxylamine/pyridoxine (n=47), and those who did not have NVP (n=29). Children were assessed at 3 to 7 years of age. The study found no evidence of an adverse effect of delayed-release doxylamine/pyridoxine exposure on the children’s IQ, verbal fluency, phonological processing, or numerical memory.

Based on efficacy and fetal safety data, Diclegis should be prescribed when women are discharged from the ED. Women should be informed that Diclegis is a delayed-release formulation designed to release the active ingredients approximately 5-7 hours after ingestion, and hence, should be taken daily as prescribed and not on an as-needed basis.16 Over-the-counter (OTC) immediate-release doxylamine is not therapeutically equivalent to the delayed-release combination, and due to safety concerns with the sedating effects of OTC doxylamine, which is indicated as a sleep aid, the use of this immediate-release therapy should not be recommended.15 To match the peak serum concentration with onset of symptoms, delayed-release doxylamine/pyridoxine is prescribed as a starting dose of two tablets at bedtime each day to control morning symptoms of NVP. If symptoms persist into the afternoon, patients can add one tablet in the morning. A fourth tablet can be taken mid-afternoon to control evening symptoms.16 Due to the severity of their NVP symptoms, patients discharged from the ED may require the maximum of four tablets per day.

**Other Antiemetic Medications as Second-Line or Third-Line Pharmacotherapy at Discharge**

According to the ACOG treatment guidelines, additional antiemetics can be added to the doxylamine/pyridoxine combination, if required. Although the use of these medications would be off-label and fetal safety data may be limited, maternal benefits may warrant use.

**Antihistamines**

Other H1-antihistamines have been used for the treatment of NVP, including dimenhydrinate (Dramamine),25 and diphenhydramine (Benadryl).26 These medications are considered second-line therapies that can be taken after or in addition to doxylamine/pyridoxine (Figure). Both dimenhydrinate and diphenhydramine are FDA

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**Table. FDA Pregnancy Categories**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Adequate and well-controlled 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).</td>
</tr>
<tr>
<td>B</td>
<td>Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.</td>
</tr>
<tr>
<td>C</td>
<td>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.</td>
</tr>
<tr>
<td>D</td>
<td>There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.</td>
</tr>
<tr>
<td>X</td>
<td>Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.</td>
</tr>
<tr>
<td>N</td>
<td>FDA has not classified the drug.</td>
</tr>
</tbody>
</table>

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classified as Pregnancy Category B, with no well-controlled studies of fetal safety.\textsuperscript{25,26}

**Antidopaminergic Medications**

Metoclopramide is a dopamine receptor antagonist\textsuperscript{27} that is commonly used off-label to treat intraoperative and postoperative nausea in women undergoing Cesarean section\textsuperscript{26} and in hospitalized women with HG.\textsuperscript{7,29} Metoclopramide is FDA classified as Pregnancy Category B based on several large cohort studies that found no adverse pregnancy or fetal outcomes with metoclopramide use in early pregnancy.\textsuperscript{30-32} Metoclopramide has a black box warning on the association between tardive dyskinesia, a severe movement disorder, and extended use of metoclopramide for more than 12 weeks. At higher doses, metoclopramide blocks serotonin receptors.\textsuperscript{27} Women who take metoclopramide with other medications that increase serotonin levels, such as certain antidepressant medications, may be at increased risk of developing serotonin syndrome.\textsuperscript{33} ACOG recommends that metoclopramide be considered as a third-line treatment for NVP (Figure).\textsuperscript{13}

Other antidopaminergic medications used for NVP include the phenothiazines, such as promethazine\textsuperscript{34} and prochlorperazine.\textsuperscript{35} Promethazine is also an H\textsubscript{1} histamine, and is listed by ACOG as a second-line agent for NVP after doxylamine/pyridoxine (Figure);\textsuperscript{13} however, promethazine is classified as Pregnancy Category C,\textsuperscript{34} and therefore should only be considered in cases where the maternal benefits outweigh the fetal risks. The fetal safety of prochlorperazine has been less studied. There have been some reports of adverse fetal effects with phenothiazines, though the effect differs across medications in the class.\textsuperscript{36}

**Antiserotonergic Medications**

The selective serotonin inhibitor ondansetron is not approved for use for NVP\textsuperscript{37} but is commonly prescribed off-label\textsuperscript{38} based on evidence of its efficacy in non-pregnant patients, particularly in the treatment of chemotherapy-induced and postoperative nausea and vomiting. Two studies have demonstrated the efficacy of IV or oral ondansetron compared with metoclopramide in treating severe NVP or HG.\textsuperscript{7,39} A recent small, single-center randomized study (n=30) showed that daily oral ondansetron 4 mg controlled nausea and vomiting better than daily immediate-release doxylamine 12.5 mg/pyridoxine 25 mg during a 5-day treatment period as reported by patients using a visual analog scale.\textsuperscript{40} Note that this study did not compare ondansetron with delayed-release doxylamine 10 mg/pyridoxine 10 mg, which would be taken up to 4 times per day.

Ondansetron continues to be prescribed for NVP, despite the emergence of concerning maternal and fetal safety data associated with ondansetron use.\textsuperscript{37,38} Several studies have examined the possible fetal effects of ondansetron exposure in early pregnancy. A population-based case-control study reported a higher risk of cleft palate with exposure to ondansetron in the first trimester of pregnancy (n=55; adjusted OR=2.37, 95\% CI 1.18-4.76).\textsuperscript{41} Another study of 1349 women identified in the Swedish Medical Birth Register who took ondansetron in early pregnancy were found to have a higher risk of cardiovascular defects (OR=1.62, 95\% CI 1.04-2.14) and cardiac septum defects (RR=2.05, 95\% CI 1.19-3.28) among their infants.\textsuperscript{42} The results of a similar registry study in Denmark also showed an increased risk of congenital heart defects among children whose mothers filled a prescription for ondansetron during the first trimester of pregnancy (n=1248; adjusted OR=2.0, 95\% CI 1.3-3.1).\textsuperscript{43} Other studies have reported no adverse pregnancy outcomes or fetal abnormalities with ondansetron use in early pregnancy for NVP.\textsuperscript{44,45}

There may also be maternal risks associated with IV ondansetron use. In June 2012, the FDA issued a warning of possible serious QT prolongation and increased risk of torsades de pointes with intravenous (IV) ondansetron.\textsuperscript{46} The FDA subsequently recommended that IV ondansetron doses be limited to 16 mg\textsuperscript{47} and that patients should undergo electrolyte or ECG monitoring if they have a history of arrhythmias, heart failure, hypokalemia, or hypomagnesemia, or are taking other medications that cause QT prolongation prior to starting IV ondansetron.\textsuperscript{3,48} A recent analysis concluded that a single oral dose of ondansetron is not associated with a significant risk of arrhythmia.\textsuperscript{48}

Because ondansetron is a serotonin inhibitor, the FDA has called for additional warnings and precautions to be included in the labeling regarding the risk of serotonin syndrome when taking ondansetron with other medications that promote serotonin activity.\textsuperscript{37,49} Given the limited and contradictory data on ondansetron maternal and fetal safety, ACOG does not recommend the use of ondansetron as a first-line treatment for NVP; its use is restricted to patients who fail on first- and second-line therapies (Figure).\textsuperscript{3} As such,
patients discharged from the ED should not receive oral ondansetron unless they have not responded to other medications.13

Corticosteroids
Corticosteroids such as methylprednisolone have been shown to improve symptoms in patients hospitalized for HG, though the findings have been mixed.50,51 Several studies have reported an increased risk in oral clefts with methylprednisolone exposure,41,52 leading several studies have reported an increased risk in oral clefts with methylprednisolone exposure,41,52 leading to increased risk in the treatment of NVP. These side effects have been widely reported in the literature, and as such, should be prescribed first-line for women discharged from the ED. Several other antiemetic medications have been used off-label for NVP, and although none are indicated for the treatment of NVP or considered safe for use in pregnant women, their use may be warranted as second- or third-line therapy.

Conclusion
NVP is a common medical condition with symptoms of nausea and vomiting that can range from mild to severe. Women with NVP who present to the ED have more severe symptoms, and may be dehydrated. Treatment of NVP not only alleviates symptoms and improves quality of life, but also reduces the risk of progression to more severe NVP or HG, which is associated with serious complications that may lead to repeat ED visits and hospitalization. Acute treatment of NVP in the ED involves replacement of fluids and reduction of symptoms with pharmacologic therapies. In the absence of evidence-based guidelines for acute treatment of NVP in the ED, treatment decisions should take into account the safety of each treatment weighed against the severity of the symptoms and the potential benefits of treatment. ACOG recommends the use of pyridoxine alone or in combination with doxylamine as first-line pharmacotherapy for outpatient treatment of NVP. A delayed-release formulation of doxylamine/pyridoxine (Diclegis®) is the only NVP treatment option that is indicated for NVP and classified as Pregnancy Category A by the FDA based on evidence from large, well-controlled studies in pregnant women, and as such, should be prescribed first-line for women discharged from the ED. Several other antiemetic medications have been used off-label for NVP, and although none are indicated for the treatment of NVP or considered safe for use in pregnant women, their use may be warranted as second- or third-line therapy.

References
15. Madjunkova S, Maltepe C, Koren G. The delayed-release combination of doxylamine and pyridoxine (Diclegis®)


