THE MANAGEMENT OF NAUSEA AND VOMITING OF PREGNANCY AND HYPEREMESIS GRAVIDARUM- A 2013 UPDATE

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Summary

Nausea and vomiting of pregnancy (NVP) affects up to 85% of all pregnancies, yet many physicians are uncertain as to how to best treat their patients in the presence of controversial data on fetal risks. This review provides an update on the management of NVP, including pharmacological and non pharmacological approaches. Due to a high rate of recurrent symptoms, it is important for women to receive early treatment to reduce the severity of symptoms with the aim of preventing the need for hospitalization and improving quality of life.

Key Words: *Nausea, vomiting, pregnancy, hyperemesis gravidarum, antiemetics*

Nausea and vomiting of pregnancy (NVP) affects up to 85% of all pregnancies. The commonly used term "morning sickness" is misleading, as symptoms (nausea, retching and/or vomiting) can persist throughout the day and/or night, especially in severe cases.[1-5] Importantly, symptoms that begin after 10 weeks of gestation should be investigated for other causes. While typically symptoms subside between 12-16 weeks, up to 15% of women will experience symptoms beyond 16 weeks or for the duration of their pregnancy.[1-5]

NVP symptoms can have a negative impact on the overall well being of pregnant women, affecting family, work and social life. Women often describe feelings of isolation, fatigue, helplessness, depression, anxiety, frustration, difficulty in coping and irritability.[6-10]

In 2007, Piwko et al. reported that in Canada the weekly cost (including costs to society, the patients, and the health care system) of NVP in women with mild-severe symptoms. Total cost of NVP per woman-week with mild symptoms was $132, $355 for moderate and $653 for severe.[10]

Health care practitioners are often uncertain as to how to best treat their patients with NVP. The main issue in managing NVP is that both patients and physicians often fear the use of pharmacological therapies during pregnancy due to the concerns of potential fetal risks.

Hyperemesis Gravidarum

Between 0.5 - 2% of women are inflicted by the most severe form of NVP, known as hyperemesis gravidarum (HG).[3] HG is defined as severe and persistent nausea and vomiting, weight loss greater than 5% of pre-pregnancy weight, dehydration, electrolyte imbalances, and nutritional deficiencies, typically requiring hospitalization.[3,11,14] The recurrence risk for hospital admission is 29 times higher if the woman had also been hospitalized for HG in a previous pregnancy.[15]

In some cases, women choose to terminate otherwise wanted pregnancies.[16]

Negative maternal effects have been reported postpartum, such as longer recovery time from the pregnancy, muscle pain and food aversions, particularly with those women with extreme weight loss.[17-18] A 2005 study found that the average cost of HG admission to hospital is $5,900 per patient, with an average stay of 2.6 days.[19] A study investigating pre-emptive therapy demonstrated that initiating treatment prior to or on first day of symptoms effectively lessened the severity of symptoms and reduced the recurrence of HG.[20-24]

Management of NVP and HG

The symptoms and impact of NVP and/or HG can vary among women; therefore treatment must be tailored to the individual. While it is important to advise all women on dietary and lifestyle changes, for some women, non-pharmacological approaches may lack effectiveness, and therefore pharmacological approaches may be warranted.

Dietary and lifestyle approaches

Food and odour aversions in pregnancy and NVP may lead to weight loss and dehydration. To reduce symptoms, common dietary strategies include eating small, frequent meals or snacks of high-carbohydrate and low-fat types every 1-2 hours to avoid an empty stomach or feelings of hunger, preventing low blood sugar and gastric distension.[5,25-27] Nausea has been shown to be reduced significantly when ingesting protein-predominant meals, therefore protein (meat and/or alternatives) should be considered for all meals and snacks.[26] For women who are having difficulty eating solid foods, liquid nutritional products may be added. Colder fluids between meals and snacks may help keep favorable hydration.[5]

Treatment for acidity & indigestion

Given that symptoms of dyspepsia and/or gastroesophageal reflux disorders are common in pregnancy (affecting 40-85% of women) and that gastric dysrythmias are part of NVP, it is important to identify symptoms of acidity and/or digestive issues.[28]

A recent study demonstrated that adding acid-reducing medications (ex: antacids, H_2-receptor antagonists and proton pump inhibitors) resulted in a significant reduction of NVP symptoms, without making changes to the antiemetic regimen.[28] Acid and indigestion have been safely treated in pregnant women using antacids, H_2-blockersand proton pump inhibitors (PPIs).[28-31] PPI's have been studied in over 5000 pregnant women and have not been associated with increased risks of major malformations.[30-31]

Repeated studies and a meta-analysis have shown an association between *Helicobacter pylori* infection and HG and/or severe NVP.[32-33] Screening for *H. pylori* should be performed in all women who had a previous pregnancy with HG, or who are currently experiencing moderate to severe NVP. Subsequent treatment of *H. pylori* with antibiotics and PPIs may improve NVP symptoms.[1,5,32,33]

Non-pharmacological approaches

With increased fear of taking medications in the pregnancy, non-pharmacological treatments may offer a good alternative in some cases. Vitamin B6 and ginger are both anti emetics, and are most commonly used for NVP. The effectiveness of Vitamin B6 has been well studied and can be taken safely in pregnancy with doses up to 200 mg/day.[1,5,34] The effectiveness of ginger has been shown in randomized trials and can be taken safely with doses of up to 1000 mg/day.[1,3,5,35] In addition, traditional acupuncture or acupressure of the P6 (Neiguan point) can be safely tried to treat NVP although data on efficacy efficacy are limited.[1,3,5,36] Small studies and case reports have been published using psychotherapy and medical hypnosis for the treatment of NVP.[1,37-38] For women experiencing more severe symptoms counseling and supportive therapy have been recommended.[38,39]

Pharmacological approaches

There are numerous antiemetics that have been used to help alleviate NVP with varying levels of proven safety and effectiveness.[1,3,5] Before considering fetal safety, it is important to note that

all pregnancies have a 1-3% baseline risk of having a baby with a birth defect by chance alone.[25] Health care providers should assess the best course of treatment, based on the severity of symptoms, as well as impact on daily life. Importantly, many of the available antiemetics have anti-cholinergic properties and therefore, if the patient reports anticholinergic drug reactions, modifications in treatment regimen, dose schedule may be needed.[11-13] Physicians should reiterate to their patients the importance of adherence in order to sustain effective symptom management.

The combination therapy of doxylamine succinate (10mg) and vitamin B6(10mg) is recommended as first line therapy for the treatment of NVP by the Canadian and American Colleges of Obstetricians and Gynecologists[3,40] and the Association of Professors of Gynecology and Obstetrics.[1] This formulation was originally known as Bendectin, which was voluntarily removed in 1983 due to concerns of teratogenicity; however, since this time many studies including two meta-analyses have confirmed its fetal safety.[41,42] In Canada, this medication, known as Diclectin®, is the only drug labelled for pregnancy by Health Canada due to its large safety profile. Furthermore, the use of Diclectin® during pregnancy was not associated with any long term effects on neurodevelopment in a 2009 study.[43] In regards to its efficacy, a randomized placebo controlled trial published in 2010 showed Diclectin® was effective over placebo in 280 American women.[44] In April 2013, this combination has been approved in the USA by the FDA under the name Diclegis®.

Metoclopramide use in pregnancy has not been associated with increased risk of birth defects in several prospective studies.[45-47] A recent study did not show an increased risk of birth defects following first trimester use in over 3400 women.[47] As a stomach motility agent, it may be helpful for women also suffering with heartburn and indigestion. Yet, the effectiveness of metoclopramide in NVP has been only sparsely documented.

In 2009, a preliminary study by Choi et al. investigated 146 women unintentionally exposed to domperidone in early pregnancy for gastrointestinal tract symptoms and found no apparent increased risk of major malformations.[48]

Phenothiazines, such as prochlorperazine, promethazine and chlorpromazine, are commonly used antiemetics and antipsychotics. With regards to NVP/HG, repeated studies have not shown an increased risk for major malformations.[1,13,15] When used continuously in the third trimester of pregnancy, neonatal withdrawal, and extra-pyramidal effects have been reported in newborns.[13]

Ondansetron is a selective 5-HT3 serotonin receptor antagonist designed for the treatment of chemotherapy-induced nausea and vomiting. Studies are available on several thousands of women exposed to ondansetron in pregnancy, which have not reported any increased risk of birth defects. In contrast, a large case control study reported on an increased risk of oral cleft.[1,45,49] Of note, recent warning by the FDA have highlights risks for cardiac dysrhythmias by ondansetron.

Droperidol is a butyrophenone tranquilizer that has been used in the treatment of hyperemesis gravidarum.[45,50,51] In 2001, Turcotte et al. found no differences in any pregnancy outcome between their treatment group receiving droperidol and diphenhydramine (n=28) and the control group (n=54).[50] In a 2003 study, Ferreira et al. looked at two different doses of droperidol combined with diphenhydramine (total n=101) and found an increase in major malformations; however, the differences were not significant when compared to controls (n=54).[51] These two non-randomized, prospective studies found a reduction of nausea and vomiting symptoms following treatment.

Trimethobenzamide is an older antiemetic that is structurally similar to antihistamines and has been reported to reduce NVP symptoms. In over 1000 women exposed in pregnancy, many in the first trimester, trimethobenzamide was not associated with increased risk of major malformations.[46,52-54]

For breakthrough relief, antihistamines such dimenhydrinate or meclizine have been

widely used in the treatment of NVP and may be taken daily or as needed until symptoms improve.[1,3,5,45,55] A meta-analysis including over 24 different studies have shown no increased risk of birth defects.[46,55]

As a last resort, corticosteroids, specifically methylprednisolone, have been used in the treatment of NVP/HG, though reports of efficacy are conflicting.[56,58] Corticosteroids are recommended to be used *after* the first trimester because they are associated with a slight increased risk of oral clefts.[56,57] The use of corticosteroids throughout pregnancy have been associated with a higher rate of preterm births and reduced birth weight.[58]

Management of HG

When a pregnant patient presents with persistent nausea, dehydration, uncontrolled vomiting and/or excessive weight loss, hospitalization may be required. For most patients, symptoms will improve with IV hydration and antiemetics. For some women who fail to respond to treatment enteral or parenteral nutrition should be considered.[1,59-61]

Enteral feedings via nasogastric, gastric or jejunostomy feeding tubes can be used to either complement or replace oral feeding in women with HG.[1,59-61] Total parenteral nutrition (TPN) may be associated with serious complications, but it has been successfully used for over 30 years.[61] Of importance, while the woman is improving under IV hydration, it is critical to start effective oral antiemetic therapy, to avoid cyclic readmission due to similar presentation.[1,59-61]

Although NVP is the most common medical condition in pregnancy, many health care practitioners are uncertain as to how to best treat their patients. Optimal management of NVP/HG is multi-dimensional and often complex. Treatment regimens should be tailored on an individual basis and all women should be counseled on dietary management, non-pharmacological and pharmacological treatment options. Importantly, as studies have shown a high rate of recurrent symptoms, it is beneficial to consider early, or even pre-emptive treatment to help reduce the severity of symptoms in future pregnancies, hopefully preventing hospitalization and improving quality of life.

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TABLE 1 Other Contributors to Nausea and Vomiting*[1,3,11,21,24]

Central nervous system disorders
- Migraine, headache
- Tumors
- Balance disorders (eg. meniere's disease, labyrinthitis, motion sickness)
- Psychologic and psychiatric disorders (eg. depression, anxiety)
- Increased intracranial pressure (eg. pseudotumor cerebri, hemorrhage, hydrocephalus)

Gastrointestinal disorders
- Pancreatitis
- Gastroesophageal reflux disease
- Gastroenteritis
- Hepatitis
- Appendicitis
- Intestinal obstruction
- *Helicobacter Pylori* infection
- Irritable bowel syndrome
- Peptic ulcer disesase
- Biliary tract disease
- Achalasia
- Gastroparesis
- Cholecystitis

Metabolic and endocrine disorders
- Hyperthyroidism /Hypothyroidism
- Hypercalcemia
- Addison's disease
- Diabetes mellitus
- Diabetic ketoacidosis

Genitourinary Tract disorders
- Uremia
- Kidney stones
- Ovarian torsion
- Porphyria
- Pyelonephritis

Pregnancy-related conditions
- Preeclampsia
- Acute fatty liver of pregnancy
- Gestational trophoblast disease
- HELLP syndrome
- Multiple pregnancies

Other
- Viral and/or bacterial infections
- Drug toxicity, intolerance or dependence

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TABLE 2 Symptom Management for NVP[1,5,25-31]

Dietary

- Eating every 1-2 hrs smaller portions
- Dry, salty, bland, and soft foods may help
- Add protein or its alternates to all meals and snacks (ex: nuts, seeds, beans, dairy, nut butters)
- Drink 20-30 min prior to and after solid foods
- Liquid intake should be 2 liters per day; colder fluids, such as slushies, popsicles, ice chips, will help maintain hydration
- Electrolytes can be added to prevent dehydration (ex: sport drinks, vitamin waters)
- To minimize bitter or metallic taste, add candies, gums and colder fluids
- For constipation, increase dietary fiber, such as psyllium, fruits; and if needed, add docusate sodium daily
- For gas and/or bloating, switch to lactose-free and if needed, add simethicone daily or prn
- For symptoms of acidity, such as burping, burning, indigestion, reflux, modify diet and if needed antacids, H2-blockers or PPI's daily or prn.

Lifestyle and Other

- For heightened sense of smell, try to sniff lemons, limes, or oranges, ventilate the area, consume room temperature/cold meals or snacks
- Women experiencing ptyalism, advise to spit out excessive saliva and use mouthwash more frequently
- Avoid brushing teeth after eating meals or snacks
- Get plenty of sleep and rest, try not to get overly tired
- When rising snack beforehand and try to get up slowly
- Try not to lie down after meals
- If possible, ask for help from family members or friends
- If iron deficient, to continue with prenatal vitamins, break in half and take in divided doses for tolerability. If not, avoid for 1st trimester and switch to children's chewable along with folic acid; resume with prenatal vitamin after 12 weeks.

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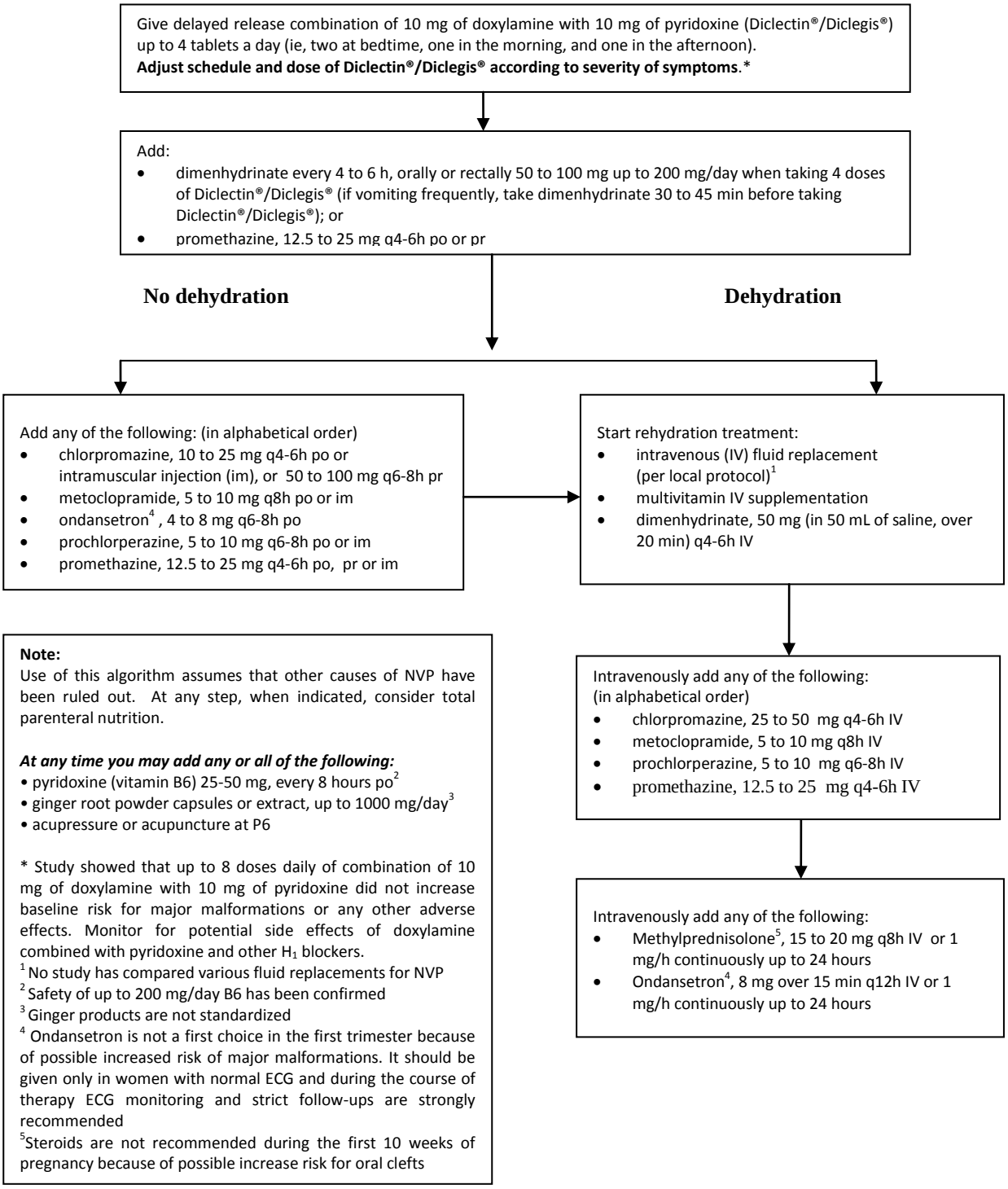
FIG.1 Algorithm for Treatment of NVP* (If no improvement, proceed to next step)



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