

SURVIVING MORNING SICKNESS SUCCESSFULLY: FROM PATIENT'S PERCEPTION TO RATIONAL MANAGEMENT

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ABSTRACT

Nausea and vomiting of pregnancy (NVP) affects up to 85% of pregnant women, with varying degrees of severity. The most severe form of NVP, known as hyperemesis gravidarum (HG), affects up to 2% of pregnancies. Women who have suffered with severe NVP/HG in a previous pregnancy have a 75-85% recurrence rate. Both patients and physicians often fear the use of pharmacological therapies during pregnancy due to the concerns of potential risks to the fetus. The symptoms and impact of NVP and HG can vary greatly among women, therefore treatment must be tailored to the individual. Updated Motherisk guidelines are presented.

Key Words: *Pregnancy, nausea and vomiting, hyperemesis gravidarum, pharmacological and non-pharmacological management*

INTRODUCTION

Up to 85% of pregnant women will experience nausea and vomiting of pregnancy (NVP).^{1,2} NVP symptoms (nausea, retching and/or vomiting) range from mild to severe and usually begin between 4 to 9 weeks of gestation and peak between 7 and 12 weeks. Typically, symptoms subside between 12 and 16 weeks of gestation; however, up to 15% of women will experience symptoms beyond 16 weeks or for the duration of their pregnancy. Symptoms beginning after 10 weeks of gestation should be investigated for other possible causes (see differential diagnosis).¹⁻⁵

The most severe form of NVP is hyperemesis gravidarum (HG), which affects up to 2% of pregnant women.^{1,2} Once a woman has experienced HG, there is a high recurrence rate (75-85%) of experiencing severe NVP or HG in future pregnancy/ies.^{6,7}

NVP can have negative physical and psychological effects on the pregnant woman. Support and treatment are important, and may include a number of modalities.

Impact of NVP

The impact of NVP can negatively affect a woman's quality of life. In a 1992 study, 82% of women reported that their usual activities were disrupted.⁸ About 72% of women reported that their parenting abilities were affected by NVP and many women reported losing time from work. These disruptions in daily routine can lead to frustration, isolation, anxiety, and even depression.^{7,8}

In 2007, Piwko and colleagues showed that the estimated cost (both direct and indirect) of NVP per woman per week was \$132 for mild NVP, \$355 for moderate NVP and \$653 for severe NVP.⁹ In a recently published study by the same author, the 2012 estimated total economic burden from NVP in the United States was shown to be \$ 1,778,473,782 (60% in direct costs and 40% in indirect costs), with the average cost of managing one woman's NVP symptoms to be \$1,827.¹⁰ However, the estimated costs for medical care alone, depending on the severity of NVP symptoms, were \$40 (mild NVP), \$57 (moderate NVP), \$267 (severe NVP), and \$7,089 (HG).¹⁰

Physical effects of NVP and HG can be very debilitating. Women suffering from HG have severe and persistent nausea and vomiting, weight loss greater than 5% of their pre-pregnancy weight, dehydration, electrolyte imbalances, and malnutrition, typically requiring hospitalization.^{7,11,12} Consequently, both maternal and fetal complications, such as longer recovery time from pregnancy, postpartum gallbladder dysfunction, as well as muscle pain, have been shown to occur.^{7,11,12} Additionally, higher incidence of premature babies, lower birth weight and small for gestational age, have been reported.^{7,11,12} Due to the tremendous impact of NVP/HG, some women may choose to terminate an otherwise wanted pregnancy.¹³

Etiology of NVP

The etiology of NVP remains unknown, but is most likely multi-factorial. The following are some of the most common factors that may be implicated:^{4,7,14-16}

- Hormonal stimuli - Elevated levels of hCG and estradiol
- Thyroid disorders
- Vitamin deficiency/ies - B6, B1 and K
- Psychological factors
- Evolutionary adaptation - Maternal and embryonic protection from toxins
- Gastric dysrhythmia - Slow gastric emptying
- *Helicobacter pylori* infection - Significant association with occurrence of HG¹⁴
- Genetic influences - Familial recurrence and carrying a female fetus
- Larger placenta

Differential Diagnosis

A differential diagnosis needs to include consideration of a number of conditions that can mimic the symptoms of NVP, but may or may not be related to NVP. Some of these include gastrointestinal disorders, hypo/hyperthyroidism, migraines/headaches, psychological disorders, gestational diabetes, viral or bacterial infections, molar and multiple pregnancies, untreated or poorly managed medical conditions, lack of sleep

and insomnia.^{1,4,7,15,16} Moreover, a thorough medical and symptom history must be taken, as patients may not disclose all relevant information. The presence of signs or symptoms, such as abdominal tenderness or pain, fever, headache, diarrhea, constipation, or goiter, can point to other disorders. Importantly, laboratory abnormalities (such as elevations of liver enzymes, bilirubin, amylase and lipase) may be present with severe NVP/HG and could influence differential diagnosis.^{1,7,15,16}

Management of NVP

In helping a patient to manage her NVP, the practitioner needs to acknowledge the patient's concerns, to recognize the disruption and negative effects on her daily routine and her quality of life. As noted above, it is essential to identify and treat other possible influences or concurrent conditions that may be causing or aggravating NVP symptoms. All women experiencing NVP, be it mild or severe, should be counselled on strategies to help manage their symptoms, such as lifestyle and dietary changes, and non-pharmacological and pharmacological approaches.⁷ If possible, it would be beneficial to have support and assistance from family and friends, such as help with daily activities, cooking, housework/chores, and shopping, as well as child care.⁷

The Motherisk Program at the Hospital for Sick Children in Toronto has the only specialized Nausea and Vomiting of Pregnancy (NVP) Helpline that has been dedicated to counselling women for over 19 years. The helpline provides evidence-based information, including the safety of medications used for NVP. This program offers unique help by providing support and counselling to pregnant women experiencing NVP/HG and information to their healthcare providers. The Motherisk NVP counsellors advise women on the best way to deal with their symptoms, including dietary and lifestyle strategies (see Table 1), non-pharmacological and pharmacological approaches, according to the Motherisk NVP protocol.^{2,5,17-19} Callers are also counselled to refer back to their healthcare practitioner to ensure a continuum of care.

TABLE 1 Some dietary and lifestyle strategies advised by Motherisk NVP Helpline^{1,2,5,7,17-19}

<p><i>Dietary strategies</i></p> <ul style="list-style-type: none">• Eat smaller portions every 1 to 2 hours and ensuring to add any source of protein (such as nuts, seeds and/or dairy) to each snack and meal. This not only helps to balance blood sugar levels, but also calms down stomach acid.• Keep solids and liquids separate. Try to drink 20 to 30 minutes before or after meals and snacks.• Try not to wait to be too hungry or too thirsty, as this may increase of NVP symptoms.• Try not to skip meals.• Gradually increase fluid intake to 8 cups daily.• For tolerability and maintaining hydration, colder fluids, such as ice chips, slushies, popsicles or smoothies are helpful. Oral rehydration products, such as coconut water, sport drinks, jello made with an unflavoured electrolyte solution may also be added.• If unable to keep food down or to get extra nutrients, consider adding liquid (nutritional or protein) supplements, bars, or puddings.• For constipation, increase dietary fibre intake (from cereals, psyllium or inulin products, fruits) along with fluids; and if needed, docusate sodium.• Symptoms of gas, bloating or lactose-intolerance can be aided by switching to lactose-free products, taking probiotics or digestive enzymes; and if needed, simethicone.
<p><i>Lifestyle strategies</i></p> <ul style="list-style-type: none">• Food and odour aversions may aggravate the symptoms of NVP, which may lead to weight loss and dehydration. To reduce heightened sense of smell, try ventilating living or working area, sniffing lemons or oranges, and consuming meals lukewarm or cold.• To minimize metallic, bitter, sour or odd taste in the mouth, having candies or chewing gum, and drinking cold/icy fluids may be helpful.• Avoid brushing teeth after eating meals and snacks.• Try not to lie down after meals.• Get plenty of sleep and rest.• Try not to get overly tired.• Have a snack before getting up from bed in the morning and get up slowly• For excess saliva, spit it out and consider frequent use of a mouthwash.

Symptoms of heartburn, dyspepsia or gastroesophageal reflux are common complaints in pregnancy, affecting 40-85% of women.²⁰ Gastric dysrhythmias are associated with the etiology of NVP; hence, it is important for practitioners to investigate any symptoms of acidity or digestive issues. Gill and colleagues demonstrated that there was an increased severity of NVP in women who were experiencing reflux or heartburn during their pregnancy.²⁰ In another study by the same authors, adding acid-reducing pharmacotherapy to the existing antiemetic regimen(s) resulted in a reduction of NVP severity.²¹ For women experiencing symptoms such as burping, belching, nausea at night, burning, indigestion, or a lump at the back of the throat during their pregnancy, some helpful suggestions include the dietary recommendations in Table 1, avoiding high fat or fried foods, and being propped up in bed with more pillows or sleeping in an elevated position.¹⁸ If dietary and lifestyle modifications are not enough to decrease acid symptoms, then safe antacid therapy may be needed, such as calcium carbonate, H₂ blockers, and proton pump inhibitors.^{17,18,22} Probiotics and digestive enzymes may also be helpful.¹⁸

Many studies have shown an association between *Helicobacter pylori* (*H. pylori*) infection and HG or severe NVP.^{7,14,15} Screening for *H. pylori* should be recommended to women who have experienced HG in a previous pregnancy and are planning to become pregnant or are in early pregnancy, as a history of HG is associated with severe NVP. If screening is positive for *H. Pylori*, it may be beneficial to treat the infection.^{4,7,17,18}

Some women complain that their prenatal vitamins make them feel sick. The iron content of these supplements may increase or cause symptoms of nausea or vomiting, in addition to other gastrointestinal effects, such as constipation or upset stomach.²³ Management recommendations depend on whether the woman has an iron deficiency or not. If iron deficiency is not present, then the prenatal vitamin may be stopped and switched to a folic acid supplement plus a children's chewable or gummy vitamin. Iron is very important for both mother and baby after 12 weeks of pregnancy, so a prenatal vitamin

can be reintroduced at that stage. If there is a previous history or a current iron deficiency, then splitting the prenatal vitamin and taking it in divided doses may be helpful.^{5,17,18, 23}

Non-pharmacological Approaches

Non-pharmacological approaches are commonly used to treat NVP symptoms and offer good alternatives to pregnant women. A number of treatment modalities have been studied, found to be useful in managing symptoms of NVP, and their use recommended in review publications.^{5,7,17,18} These include ginger, vitamin B6 (pyridoxine), acupressure, and acupuncture. Vitamin B6 has been well studied and maximum doses of up to 200 mg per day (from all sources, whether prescription or multivitamins) may be taken in pregnancy. The effectiveness of ginger has been shown in randomized trials and may be taken at maximum doses of up to 1000 mg per day (equivalent to dried ginger root powder). In addition, acupuncture or acupressure of the P6 point may also be used. Of note, medical hypnosis has reportedly been used for NVP, and counselling and supportive therapy have been recommended for women with more severe NVP symptoms.

Pharmacological Approaches

There are a number of antiemetics that are given to help alleviate NVP symptoms, as monotherapy or polytherapy, with varying levels of safety and effectiveness. Healthcare practitioners should assess the best course of treatment, based not only on the severity of symptoms, but also on the patient's reported impact of NVP on her daily life. Practitioners should reiterate the importance of compliance with therapy, i.e., taking medications daily and consistently to sustain symptom management, and upon improvement (NVP symptoms have lessened), to gradually taper down the medication(s).¹⁸

The Motherisk NVP Helpline has developed an NVP treatment algorithm, and updates it as new research gets published (see Figure 1).^{2,5,7,17-19,24,33} The algorithm begins with Diclectin® a delayed release formulation of 10 mg doxylamine succinate/10 mg vitamin B6

(pyridoxine) as first line treatment for NVP. In Canada, it is labelled and approved for use in pregnancy by Health Canada, due to its safety profile. The standard dose is up to 4 tablets per day, with dose and schedule adjusted according to severity of NVP symptoms.²⁴ A 2001 study on Diclectin[®] has shown maternal and fetal safety for doses of up to 12 tablets daily.²⁵ Furthermore, a 2009 study showed no association with any long-term effects on fetal neurodevelopment.²⁶ In regards to its efficacy, a randomized, placebo controlled trial published in 2010 showed Diclectin[®] was more effective than placebo in treating NVP in 280 American women.²⁷

Antihistamines (such as dimenhydrinate or meclizine) are H1 blockers and have been widely used for the treatment of NVP as breakthrough relief. They may be taken daily or as needed until NVP symptoms improve. Numerous studies have documented their effectiveness, and a meta-analysis, including over 24 studies, found no increased risk of birth defects.²⁸ For uncontrolled vomiting, the algorithm (Figure 1) suggests taking dimenhydrinate 30-45 minutes before Diclectin[®] scheduled dose.^{2,5,17} Of note, H1 blockers may cause sedation, tiredness, or dizziness.^{5,17}

Phenothiazines (such as promethazine or prochlorperazine) have been commonly used as antiemetics and antipsychotics. When taken during pregnancy, many studies have not shown an increased risk of major malformations.²⁹ Moreover, if used continuously into the third trimester, neonatal withdrawal and extrapyramidal effects have been reported.²⁹

Metoclopramide is commonly used to treat NVP. Several studies, including a 2009 paper by Matok and colleagues, showed no increased risk of birth defects when used in the first

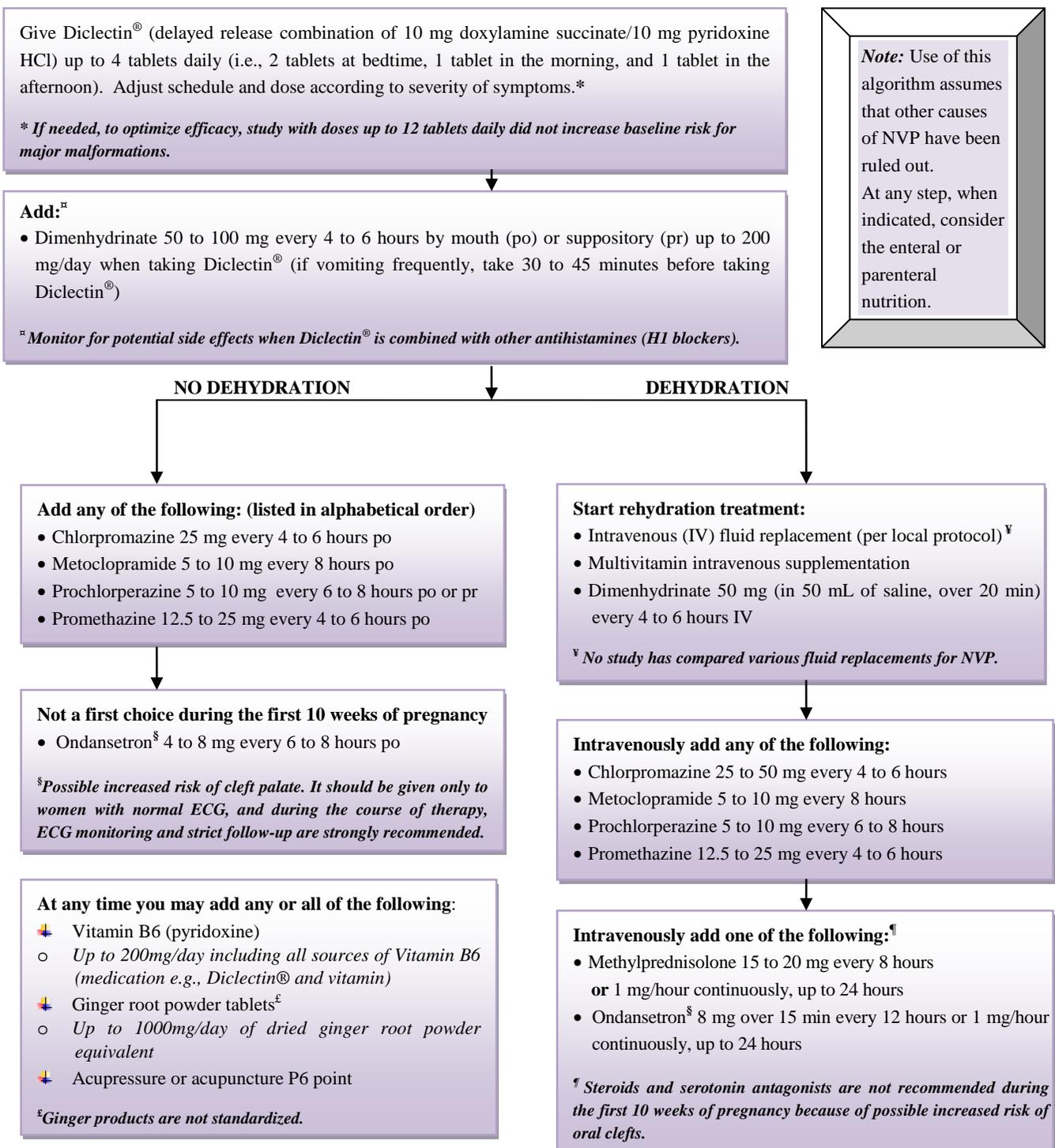
trimester.^{5,29,30} In 2013, Pasternak and colleagues reported on a register-based cohort study in Denmark, where they found no increased risk of major congenital malformations, spontaneous abortion, or stillbirth in over 28,486 women exposed in the first trimester.³¹ Additionally, metoclopramide is a stomach motility agent, and it may be helpful for women who have indigestion or vomit undigested food many hours after eating.² It is important to advise women to take their dose no more than 30 minutes before eating.

Ondansetron, a selective serotonin, 5-HT₃-receptor antagonist, seems to have a conflicting safety profile. A case control study detected a two-fold increased risk of cleft palate when ondansetron was taken for NVP in the first trimester of pregnancy.³² Two studies using data from the Danish birth registry resulted in mixed findings. In 2013, Pasternak and colleagues collected data for 1,233 births between 2004-2011, and showed no increased risk of birth defects when mothers had taken ondansetron.³³

However, Andersen and colleagues collected data from the same registry for 1,248 births between 1997-2010 and findings suggested an increased risk of heart defects.³⁴ Furthermore, the US Food and Drug Administration issued a warning about possible serious QT prolongation and *Torsade de Pointes* among people receiving ondansetron.³⁴ Strict ECG monitoring and follow-up of patients at risk were recommended, such as in cases of electrolyte imbalance (hypokalemia/hypomagnesemia), which can occur in women with severe NVP or HG, and in cases of patients with severe congestive heart failure, or patients receiving other medications that can prolong the QT interval.^{35,36}

FIG. 1 *NVP TREATMENT ALGORITHM - MOTHERISK UPDATE 2014^{2,5,7,17-19,25,34-36}

If no improvement, move to the next step.



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Further down the treatment algorithm is methylprednisolone. This drug is suggested to be used after the first trimester, due to the possible increased risk of oral clefts, although this finding has not been consistent.³⁷⁻³⁹ If methylprednisolone is used throughout the pregnancy, it may be associated with a higher rate of preterm birth and reduced birth weight.³⁹ It is therefore recommended to monitor fetal growth, as well as maternal blood pressure and blood sugar.

Management of Hyperemesis Gravidarum

The most severe form of NVP is hyperemesis gravidarum (HG). Women require hospitalization due to persistent nausea and vomiting, weight loss and dehydration. Treatment is then intravenous (IV) fluid replacement and antiemetics; intravenous acid suppression is also suggested.⁴⁰ For most women, symptoms will improve after receiving IV hydration therapy and antiemetics, however, some women will continue to have symptoms of NVP, weight loss and lack of response to antiemetic therapy, which may require enteral or parenteral nutrition.^{7,15,16,40} The latter may be used to supplement or replace oral feeding. As each woman is different, nutritional needs must be assessed on an individual basis. When symptoms stabilize, gradually introduce fluids and solid foods in addition to the continued use of antiemetic therapy.^{7,15,16,40}

The concept of using prophylactic (pre-emptive) antiemetic treatment for severe NVP/HG stems from the proven effectiveness of similar approaches in chemotherapy-induced nausea and vomiting, cyclic vomiting and motion sickness.⁴¹⁻⁴³ A prospective non-randomized study investigating pre-emptive use of any antiemetic treatment of anticipated severe NVP and HG, in women who had suffered symptoms in their previous pregnancy was published in 2004.⁶ The study demonstrated that initiating treatment prior to or on first day of symptoms effectively lessened the severity of symptoms, reduced the recurrence of HG, and that continuous individualized counselling was very beneficial.

In 2013, a prospective, randomized, open-label, pre-emptive Diclectin[®] study was published.¹⁹ This study included only women with

history of severe NVP or HG in their previous pregnancy/ies, randomized to start taking Diclectin[®] upon recognition of their pregnancy and before NVP symptoms were experienced (pre-emptive group) or only at first sign of NVP symptoms (control group). The results showed that there were 70% fewer cases of moderate to severe NVP in the pre-emptive group compared to the control group. There was also a significant reduction of HG with pre-emptive Diclectin[®] use. The Diclectin[®] dose ranged from 2 to 9 tablets in both groups. Both pre-emptive and control groups, received intensive protocol-based counselling and a mean of 8 follow-up calls. Overall, there was an earlier resolution of symptoms in the pre-emptive group (26 weeks) vs. the control group (33 weeks).

Many women are afraid and anxious of again having severe NVP or HG in a future pregnancy. When planning a pregnancy or in early pregnancy, they should be encouraged to follow dietary and lifestyle suggestions (as outlined in *How to Survive Morning Sickness Successfully*¹⁸), be screened for *Helicobacter pylori* infection, and be encouraged to find a support network. Early symptom management, and using counselling and evidence-based guidelines tailored to the individual, can help improve maternal quality of life.

SUMMARY

NVP is the most common medical condition in pregnancy. All women calling the Motherisk NVP Helpline are counselled on dietary and lifestyle strategies, in addition to non-pharmacological and pharmacological approaches. Optimal symptom management of NVP or HG is multi-dimensional and often complex and should be designed on an individual basis. Importantly, as studies have shown a high rate of recurrence of NVP symptoms in predisposed women, it is beneficial for them to receive pre-emptive or early treatment, as it may help decrease the severity of symptoms in subsequent pregnancies, reduce maternal and fetal complications, and prevent hospitalization, while improving quality of life.

Disclosure

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