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The Management of Nausea and Vomiting of Pregnancy

This Clinical Practice Guideline has been prepared and reviewed by the Clinical Practice Obstetrics Committee and approved by Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objectives: To review the evidence-based management of nausea and vomiting of pregnancy (NVP) and hyperemesis gravidarum.

Evidence: MEDLINE and Cochrane database searches were performed using the medical subject headings (MeSH) of treatment, nausea, vomiting, pregnancy, and hyperemesis gravidarum. The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.

Benefits: NVP has a profound effect on women's health and quality of life during pregnancy, as well as a financial impact on the health care system, and its early recognition and management are recommended. (III-B)

Cost: Costs, including hospitalizations, additional office visits, and time lost from work, may be reduced if NVP is treated early.

Recommendations:

1. Dietary and lifestyle changes should be liberally encouraged, and women should be counselled to eat whatever appeals to them. (III-C)
2. Alternative therapies, such as ginger supplementation, acupuncture, and acupressure, may be beneficial. (I-A)
3. A doxylamine/pyridoxine combination should be the standard of care, since it has the greatest evidence to support its efficacy and safety. (I-A)
4. H_1 receptor antagonists should be considered in the management of acute or breakthrough episodes of NVP. (I-A)
5. Pyridoxine monotherapy supplementation may be considered as an adjuvant measure. (I-A)
6. Phenothiazines are safe and effective for severe NVP. (I-A)
7. Metoclopramide is safe to be used for management of NVP, although evidence for efficacy is more limited. (II-2D)
8. Corticosteroids should be avoided during the first trimester because of possible increased risk of oral clefting and should be restricted to refractory cases. (I-B)
9. When NVP is refractory to initial pharmacotherapy, investigation of other potential causes should be undertaken. (III-A)

Sponsor: The Society of Obstetricians and Gynaecologists of Canada.

Key Words

Nausea, vomiting, pregnancy, treatment, hyperemesis gravidarum, pharmacology, teratogenicity

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INTRODUCTION

Nausea and vomiting of pregnancy (NVP) is the most common medical condition in pregnancy, affecting 50%–90% of women.[1] The most severe form of NVP is commonly referred to as hyperemesis gravidarum (HG). HG, defined as persistent vomiting that leads to weight loss greater than 5% of pre-pregnancy weight, with associated electrolyte imbalance and ketonuria,[1] occurs in about 1% of pregnancies.[1] Although NVP may be classified as mild, moderate, or severe, the severity of nausea or vomiting may not adequately reflect the distress it causes.

The physical and emotional impact of NVP often results in feelings of anxiety and worry about the effect of the symptoms on the fetus. It has a negative impact on family relationships and has major consequences on women's working abilities; 47% of working women with NVP feel job efficiency is reduced,[3] 35% lose work time (mean loss of 62 working hours per woman),[3] and 25% lose time from housework (mean loss of 32 hours per woman).[1-4] NVP is also cited as a reason for elective termination of pregnancy.[5] This is not surprising when it is recognized that nausea experienced by pregnant women with NVP (excluding HG patients) is comparable in severity to the nausea experienced by patients undergoing cancer chemotherapy.[6]

Each year, a significant number of women have one or more hospital admissions for NVP (as many as 14 hospitalizations/1000 births).[7] Therefore, early recognition and management of NVP could have a profound effect on women's health and quality of life during pregnancy, as well as a financial impact on the health care system.

The pathogenesis of NVP is poorly understood and the etiology is likely to be multifactorial. Other causes of nausea and vomiting must be ruled out, including gastrointestinal, genitourinary, central nervous system, and toxic/metabolic problems. Idiopathic NVP must be distinguished from NVP of known etiology, such as hydatidiform mole or multiple gestation.

In the aftermath of thalidomide and the voluntary withdrawal of Bendectin®, pharmacological antiemetic therapy is still used with great caution by some patients and health care providers to treat NVP, and is erroneously considered to be contraindicated in pregnancy.[2] Care providers play a major role in counselling and reassuring patients on safe and effective treatments available for NVP.[2]

This document aims to provide an evidence-based guideline to treat NVP. Early treatment with counselling is preferable, after appropriate history-taking and physical examinations have been done. Recognizing and treating NVP in a timely fashion will prevent the progression of NVP to HG and maternal complications, and reduce the risk of parenteral therapy and HG-related costs, including hospitalizations, additional office visits, and time lost from work. This should eventually result in improved maternal health and quality of life, as well as better family relationships.

The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam (Table).[8]

QUALITY OF EVIDENCE ASSESSMENT[8]

The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.

I: Evidence obtained from at least one properly randomized controlled trial.

II-1: Evidence from well-designed controlled trials without randomization.

II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.

II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.

III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

CLASSIFICATION OF RECOMMENDATIONS

Recommendations included in these guidelines have been adapted from the ranking method described in the Classification of Recommendations found in the Report of the Canadian Task Force on the Periodic Health Exam.

A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.

B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.

C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds.

D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.

E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

DIETARY AND LIFESTYLE CHANGES

There has been no evidence to prove the effectiveness of dietary changes on relieving NVP symptoms. Advice for women suffering from NVP has traditionally revolved around dietary changes. Recommendations have included separating solids and liquids; eating small, frequent meals consisting of bland foods; avoiding fatty foods such as potato chips; and avoiding drinking cold, tart, or sweet beverages. Other advice has been to avoid sensory stimuli, particularly strong odours. Women alter their dietary habits to eat small frequent meals, to tolerate the NVP. This makes a randomized controlled trial (RCT) of these habits very difficult to perform. There is no evidence that short-term dietary deficiencies during the early weeks of pregnancy will have long-term consequences on pregnancy outcome.

The use of vitamin supplements (including B-complex) is encouraged during pregnancy, and even if the woman is unable to tolerate her prenatal vitamin, it is important to maintain folic acid supplementation until the embryo's neural tube has closed. Caution is warranted with diets containing supra-pharmacological doses of individual vitamins, given the paucity of data regarding their safety for the fetus.

Sleep requirements increase in early pregnancy.[9] Because fatigue seems to exacerbate NVP, women should be encouraged to increase their rest, especially while they are symptomatic. It would seem appropriate for health care providers to adopt a liberal attitude toward providing leaves-of-absence from work. Such a policy should ultimately shorten the number of days lost from work.

Enlisting the support and understanding of close friends and family as well as supportive counselling may be of benefit to the woman suffering from NVP.

RECOMMENDATION

1. Dietary and lifestyle changes should be liberally encouraged, and women should be counselled to eat whatever appeals to them. (III-C)

NON-PHARMACOLOGICAL THERAPIES

GINGER

Ginger (*Zingiber officinale*) is present as a spice in foods and beverages. It can also be taken in the form of tea or tablet extracts. There is only one RCT examining the efficacy, but not the safety, of 1000 mg/day of ginger.[10] Ginger is a nonregulated food product and most preparations available are of uncertain purity and composition. No evidence-based studies have been published to exclude the possibility of teratogenicity, and at the present time, large quantities of ginger should not be recommended as a treatment for NVP.

ACUPUNCTURE AND ACUPRESSURE

Stimulation of the P6 (Neiguan) point, located three-fingers' breadth proximal to the wrist, has been used for thousands of years by acupuncturists to treat nausea and vomiting from a variety of causes. Though there are no theoretical concerns about the safety of acupressure in pregnancy, efficacy of P6 acupressure is difficult to prove because it is impossible to perform a true double-blind trial compared with no intervention. Nonetheless, non-blinded RCTs have demonstrated a decrease in "persisting nausea" by at least 50%.[11] Bands worn on the wrist to apply acupressure may also be helpful.[11]

RECOMMENDATION

2. Alternative therapies, such as ginger supplementation, acupuncture, and acupressure, may be beneficial. (I-A)

PHARMACOLOGICAL THERAPIES

When conservative measures have not been effective, pharmacological intervention is warranted. Treatment should start as soon as possible after the diagnosis of NVP.

Included in this guideline is an evidence-based algorithm for nausea and vomiting of pregnancy, developed from evidence-based material on the safety and efficacy of available medications.[12] Therapies will be discussed in the same order as they appear in the algorithm.

ANTIHISTAMINES

Doxylamine

Doxylamine is an H_1 receptor antagonist that has been shown to be effective in the treatment of NVP. It is currently marketed in Canada as a fixed combination of 10 mg doxylamine with 10 mg of pyridoxine (vitamin B_6), in a delayed-release formulation (Diclectin®). The standard recommended dose is up to four tablets a day, but recent data suggest that additional daily tablets (between 5 to 8 or up to 2.0 mg/kg) may be beneficial to address larger body size or suboptimally controlled symptoms.[13] A recent update of the Briggs' *Drugs in Pregnancy and Lactation*[14] revised the monograph of the product, and based on numerous studies on the safety and effectiveness of the doxylamine/pyridoxine-dicyclomine combination (previously marketed as Bendectin®) has changed the risk factor rating to "A," indicating that there is no risk to the fetus.

RECOMMENDATION

3. A doxylamine/pyridoxine combination should be the standard of care, since it has the greatest evidence to support its efficacy and safety. (I-A)

Other Antihistamines

Other H_1 receptor antagonists (e.g., dimenhydrinate [Gravol®], diphenhydramine [Ergocryl®], and hydroxyzine [Atarax®]) are

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(If no improvement, go to next step)

Give 10 mg of doxylamine combined with 10 mg of pyridoxine, up to four tablets a day (i.e., two at bedtime, one in the morning, and one in the afternoon). Adjust schedule and dose according to severity of symptoms.

↓

Add dimenhydrinate, 50 to 100 mg q4–6h po or suppository (pr) (up to 200 mg/d when taking four doxylamine/pyridoxine tablets/d)

or promethazine, 5 to 10 mg q6–8h po or pr

↓

No dehydration

Add any of the following (in order of proven fetal safety):
- chlorpromazine, 10 to 25 mg q4–6h po or intramuscular injection (IM), 50 to 100 mg q4–6h pr
- prochlorperazine, 5 to10 mg q6–8h IM or po or pr
- promethazine, 12.5 to 25 mg q4–6h IM or po
- metoclopramide, 5 to 10 mg q8h IM or po
- ondansetron,* 8 mg q12h po

Notes:
- The use of this algorithm assumes that other causes of nausea and vomiting of pregnancy (NVP) have been ruled out.
- **At any time you may add any or all:**
  pyridoxine 25 mg q8h
  ginger§ 250 mg q6h
  P6 acupressure/acupuncture
- **At any step, when indicated, consider parenteral nutrition.**

*Safety, particularly in the first trimester of pregnancy, not yet determined.
†No study has compared different fluid replacements for NVP.
‡Steroids may increase risk for oral clefts in first 10 weeks of gestation.
§Safety of doses higher than 1000 mg/day not yet determined in pregnancy.

Dehydration

Start rehydration treatment:
- intravenous (IV) fluid replacement† (per local protocol)
- multivitamin IV supplementation
- dimenhydrinate, 50 mg (in 50 mL of saline, over 20 min) q4–6h IV

Add any of the following (in order of proven fetal safety):
- chlorpromazine, 25 to 50 mg q4–6h IV
- prochlorperazine, 5 to 10 mg q6–8h IV
- promethazine, 12.5 to 25 mg q4–6h IV
- metoclopramide, 5 to 10 mg q8h IV

Add methylprednisolone,‡ 15 to 20 mg q8h IV
or ondansetron* 8 mg, over 15 min q12h IV or
1 mg/h continuously up to 24 hours

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considered safe in pregnancy, with no human teratogenic potential. This conclusion is supported by a wide body of evidence and meta-analysis.[14] Data have actually shown a slightly reduced incidence of major and minor malformations with first trimester exposure to various antihistamines.[15]

Pooled data from seven controlled trials looking at the effectiveness of various antihistamines for NVP indicate that these drugs are effective.[16] Availability in parenteral and suppository formulations makes these agents a good choice for treatment of acute or breakthrough episodes of NVP. Caution should be taken to avoid excessive dosing of H_1 receptor antagonists by combining different antihistamines in therapy.

RECOMMENDATION

4. H_1 receptor antagonists should be considered in the management of acute or breakthrough episodes of NVP. (I-A)

VITAMINS

PYRIDOXINE

Pyridoxine, vitamin B_6, has been proven to be non-teratogenic in combination with doxylamine.[17] A retrospective cohort study also concluded that pyridoxine monotherapy had no increased risk for major malformations.[16] The effectiveness of vitamin B_6 monotherapy versus placebo has been shown in two RCTs (75 mg/day and 30 mg/day orally).[14]

RECOMMENDATION

5. Pyridoxine monotherapy supplementation may be considered as an adjuvant measure. (I-A)

DOPAMINE ANTAGONISTS

PHENOTHIAZINES

Like antihistamines, phenothiazines (i.e., chlorpromazine, perphenazine, prochlorperazine, promethazine, trifluoperazine) have also been proven safe for use in pregnancy. Prospective and retrospective cohort, case-control, and record-linkage studies of patients with exposure to various and multiple phenothiazines have failed to demonstrate an increased risk for major malformations.[16]

Significant therapeutic effect was demonstrated by three RCTs of various phenothiazines versus placebo for the treatment of severe NVP.[16,18]

RECOMMENDATION

6. Phenothiazines are safe and effective for severe NVP. (I-A)

METOCLOPRAMIDE

Metoclopramide is an upper gastrointestinal motility stimulant. Since NVP is associated with gastric dysrhythmia, the use of metoclopramide is common in clinical practice in many countries. There are limited studies of its potential to cause teratogenesis, but information to date is reassuring; two recently published studies have confirmed that there is no association between the drug exposure during the first trimester and congenital malformations.[19,20]

No RCTs have been published to support the effectiveness of metoclopramide in the treatment of NVP. An observational study using home subcutaneous therapy for HG suggested that metoclopramide is effective, safe, and economical.[21]

RECOMMENDATION

7. Metoclopramide is safe to be used for management of NVP, although evidence for efficacy is more limited. (II-2D)

SEROTONIN 5-HT_3 ANTAGONISTS

Limited data are available on 5-HT_3 antagonist safety. No malformations were reported in three case reports of exposure in pregnancy.[16] One RCT of 15 first trimester exposures demonstrated no increased risk of malformation.[16]

ONDANSETRON

Limited evidence is available on the effectiveness of ondansetron for NVP. Intravenous ondansetron did not demonstrate a therapeutic benefit over promethazine in one trial for the treatment of HG.[16] Ondansetron is also significantly more expensive per dose than promethazine.

In general, 5-HT_3 antagonists may be safe to use during the first trimester, but the data are scant. Because of their limited effectiveness, they should not be advocated for first-line use until agents with established safety and effectiveness have been tried and have failed.

CORTICOSTEROIDS

Recent case-control studies revealed a small but significantly increased risk of oral clefting associated with first trimester exposure to corticosteroids.[16] However, the data on effectiveness are weak. Although a few controlled studies showed some effectiveness,[22] pooled results of those studies comparing corticotropin to placebo and methylprednisolone to promethazine in HG women failed to show a reduction in the number of subsequent re-admissions to hospital compared with controls.[16] In addition, corticotropin was not found to be superior to placebo based on "severity" or "relief" scores.[16,22]

Until more data are available, corticosteroids should be kept as the last line of therapy under ten weeks' gestation, and only when maternal benefits outweigh fetal risk.

RECOMMENDATION

8. Corticosteroids should be avoided during the first trimester because of possible increased risk of oral clefting and should be restricted to refractory cases. (I-B)

ADJUVANT THERAPIES

ESOPHAGEAL REFLUX THERAPIES

The following adjuvant therapies are used primarily to reduce esophageal acid reflux associated with NVP. They have all been shown to bring symptomatic relief in the non-pregnant population and are presumed to be effective in pregnancy as well.

Antacids usually contain salts of magnesium, calcium, or aluminum. A wide proportion of pregnant women already use this kind of medication. These are not considered human teratogens when used in recommended doses.

H_2 receptor antagonists include cimetidine, ranitidine, and famotidine. Use of these medications has not been associated with an increased risk for major malformations following first trimester exposure.[16,23]

Proton pump inhibitors such as omeprazole have been used in limited numbers during pregnancy. A recent study did not show an increased risk of congenital malformations.[16,23]

REHYDRATION

When dehydration is demonstrated at any time in the course of evaluation and treatment of NVP, intravenous rehydration may be warranted. Careful attention is paid to electrolyte imbalances present, and appropriate crystalloid therapy is instituted. Intravenous vitamin supplementation may be provided at the same time. In centres that have the ability to offer home parenteral therapy, NVP may be an appropriate condition to treat in this manner.

OTHER CAUSES OF NVP

When NVP is refractory to initial pharmacotherapy, it may be appropriate to investigate other potential causes or exacerbating factors associated with NVP. Electrolytes, TSH, renal function, liver function, drug levels, ultrasound, and *Helicobacter pylori* testing may be considered.

RECOMMENDATION

9. When NVP is refractory to initial pharmacotherapy, investigation of other potential causes should be undertaken. (III-A)

MOOD DISORDERS

It is common for mood disorders to accompany NVP. Some of those disorders may require treatment with safe therapeutic agents, such as antidepressants.

Selective serotonin re-uptake inhibitors (fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) are effective, not cardiotoxic, and are safe even if used in excess (with the exception of citalopram). They are not associated with an increased risk for major malformations when used in the first trimester.[24]

Tricyclic antidepressants (TCAs) (amitriptyline, nortriptyline, and imipramine) have now been used for many years for several conditions. Although studies involving more than 1000 patients have shown TCAs are not teratogenic when used in the first trimester,[25] their narrow therapeutic index, life-threatening cardiotoxicity in overdose, and severe anticholinergic effects make them less appealing.

HELICOBACTER PYLORI

An increased rate of seroposivity to *Helicobacter pylori* among patients with HG compared to asymptomatic, healthy pregnant controls has been recently reported.[18,26,27] Several case reports have suggested a beneficial effect of *Helicobacter pylori* eradication.[26] Gastric dysmotility has also been demonstrated among patients with HG. Several serendipitous cases have been reported in which erythromycin, administered for other indications, was effective in the resolution of otherwise intractable HG.[26] It is possible that the benefit resulted from the motilin-like action of erythromycin. This new field of evidence appears to be of significance in severe cases of NVP only and warrants further investigations before recommendations can be made.

CONCLUSION

NVP can and should be managed safely and effectively. A doxylamine/pyridoxine combination should be the standard of care since it has the greatest evidence to support its efficacy and safety (I-A). Other drugs may also be used, primarily dimenhydrinate, in conjunction with the doxylamine/pyridoxine combination. When these are not optimal in relieving NVP symptoms, consideration should be given to dopamine antagonists (phenothiazines and metoclopramide). If possible, corticosteroid use should be avoided in the first 10 weeks of pregnancy, a critical period for oral cleft formation. *Helicobacter pylori* colonization diagnosis and treatment warrants further investigation.

The choice of pharmacological treatment for NVP is as important as the choice of when to start using it. Because newer evidence suggests that the quality of life may be impaired before severe physical symptoms occur,[3] even women with mild or moderate physical symptoms should be counselled early in their pregnancy on safe and effective treatments.

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