

Best practice

Acute and chronic nausea – evaluation and treatment, what's new?

Nausea in pregnancy



Travellers' diarrhoea



Introduction

The nauseous patient consulting the primary care practitioner represents a clinical challenge, as they could be suffering from any one of a broad array of gastrointestinal and non-gastrointestinal disorders.

Acute nausea may be associated with a critical life event, such as early pregnancy, while seasonal or traveller's nausea can be caused by viral/bacterial gastroenteritis. Chemotherapy treatment can cause nausea in cancer patients, nausea may be a medication side-effect, or it may be associated with existing disease (e.g. diabetes, migraine, irritable bowel syndrome). The symptoms of acute nausea, which include a vague feeling of unease, the sensation that vomiting may occur, pallor, hypersalivation and tachycardia, provoke anxiety and distress in the affected patient.

Chronic nausea and vomiting are defined as being of four weeks' duration or longer, severely impacting the patient's overall quality of life and demanding different management and therapeutic approaches.

KEY MESSAGES

- The signs and symptoms of nausea can vary depending on the trigger and the way the neural pathway stimuli are interpreted
- Nausea or vomiting in pregnancy are common, possibly related to increased human chorionic gonadotropin (HCG) and oestradiol levels, with little apparent effect on pregnancy outcome if mild or moderate
- Chronic nausea and vomiting are defined as intermittent symptoms present for more than six months, with active symptoms within the last three months
- Evaluation of the chronic nausea and vomiting patient requires medical history, exclusion of common non-gastrointestinal causes and careful physical examination
- Dietary interventions and pharmacological therapies may relieve symptoms of nausea or vomiting during pregnancy and chronic nausea and vomiting, although treatment strategies differ.

This report was made possible by an unrestricted educational grant from Cipla. The content of the report is independent of the sponsor. The expert participated voluntarily.

What is nausea really?

Nausea is a term commonly used to describe an awareness that vomiting is imminent.¹ The signs and symptoms of nausea, preceding vomiting, can vary depending on the trigger and the way an individual interprets the neural pathway stimuli (Figure 1). Key neurotransmitters and hormones involved in this process include histamine, dopamine, serotonin, norepinephrine, acetylcholine, cortisol,

β -endorphins and vasopressin.

A working definition of nausea is ‘a condition that presents during or following exposure to a stimulus that can generate vomiting, such as toxins, motion and gastrointestinal disease, which produces stomach awareness, anxiety, or causes an individual to feel lethargic, drowsy and disinterested in routine daily activities.’

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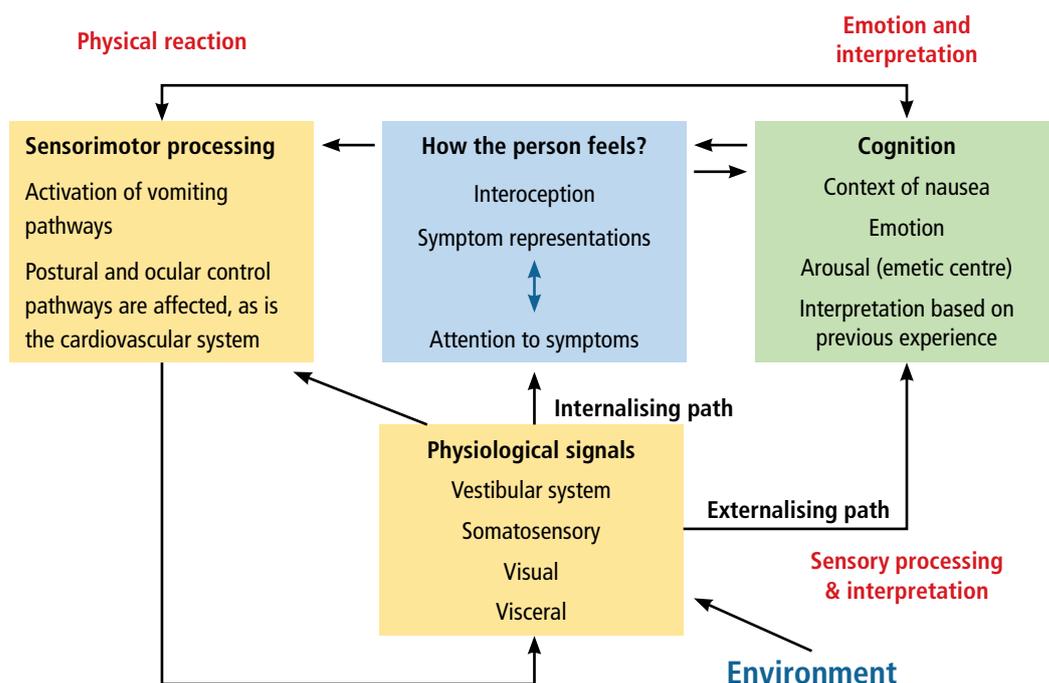


Figure 1. The perception of nausea
Interoception represents the integration of physical and emotional components following physiological signals that are triggered by the environment, e.g. sea/air motion, chemotherapeutic agents, anxiety or endocrine changes during pregnancy. Adapted from Balaban and Yates.¹

Nausea in pregnancy

Nausea with the occurrence of vomiting is a common condition in pregnancy, with 50-80% of women experiencing nausea and approximately 50% experiencing vomiting and retching. The timing of the onset of nausea and vomiting is important; symptoms typically occur from the fourth week and stop around the end of the first trimester. The cause of nausea and vomiting in pregnancy is not known, but may be the result of several endocrine changes.

HCG is one of the hormones commonly thought to be associated with pregnancy-related nausea and vomiting because of the similar timing of peak HCG levels and peak symptoms of nausea and vomiting.² Another hormone

known to influence nausea and vomiting during pregnancy is oestrogen. Nausea is more common when oestradiol levels particularly are increased.

An interesting hypothesis is that nausea and vomiting might be related to evolutionary adaptations designed to protect the woman and her unborn infant from potentially dangerous foods. This evolutionary adaptation may also explain why pregnant women develop a sudden aversion to particular foods, tastes and smells.

Stress and psychological predisposition have not been shown to be factors influencing the occurrence of nausea and vomiting in pregnancy or its more serious complication of hyperemesis gravidarum.²

Risk factors that point to the more

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likely development of pregnancy-related nausea include a history of motion sickness, migraine headaches and a history

of hyperemesis gravidarum in a previous pregnancy (the latter occurs in 0.3-3% of pregnancies).

How serious is the nausea and vomiting? When should the clinician be concerned?

A severity score known as the pregnancy-unique quantification of emesis and nausea (PUQE) provides a useful question and rating scale (Table 1).³

When a patient experiences nausea and vomiting after ten weeks of pregnancy, other conditions should be carefully considered, such as gastroenteritis, urinary

tract infections, drug-induced disorders (iron preparations, antibiotics, etc.), vestibular syndromes, or a pre-pregnancy condition like diabetic gastroparesis. Fever and headache are not typically present in pregnancy-related nausea and vomiting.

Mint aroma, used in a prenatal care unit, has been shown to reduce severity of symptoms among pregnant women hospitalised with severe nausea, vomiting and anxiety

Table 1. Modified PUQE scoring				
Circle the answer that best suits your situation from the beginning of your pregnancy.				
1. On average in a day, for how long do you feel nauseated or sick to your stomach?				
Not at all (1)	1 hour or less (2)	2-3 hours (3)	4-6 hours (4)	More than 6 hours (5)
2. On average in a day, how many times do you vomit or throw up?				
I do not throw up (1)	1-2 times (2)	3-4 times (3)	5-6 times (4)	7 or more times (5)
3. On average in a day, how many times do you have retching or dry heaves without bringing anything up?				
None (1)	1-2 times (2)	3-4 times (3)	5-6 times (4)	7 or more times (5)
Total score (sum of replies 1, 2, 3): mild NVP ≤6; moderate NVP 7-12; severe NVP ≥13 NVP: nausea or vomiting of pregnancy				

What effects does nausea and vomiting during pregnancy have on the unborn child?

Mild and moderate symptoms have little apparent effect on pregnancy outcome. In fact, studies have shown a lower rate of miscarriage among women who

experience bouts of nausea and vomiting.⁴ This is likely to be related to healthy placental development and not to a protective effect from vomiting.

Recommended therapies for acute nausea and vomiting

Non-pharmacological therapies

Dietary changes that may be helpful include eating small meals more frequently, avoiding spicy or fatty foods, eating bland or dry foods, and eating crackers in bed before getting up. There is very little published evidence that these approaches are efficacious, however.

Ginger may reduce nausea and vomiting

in pregnancy, although evidence is mainly from small randomised clinical trials. In these trials, ginger was taken as either a capsule or as an essence.⁵ Mint aroma, used in a prenatal care unit, has been shown to reduce severity of symptoms among pregnant women hospitalised with severe nausea, vomiting and anxiety.⁶

Pharmacological interventions

Iron-containing multivitamins, a potential cause of nausea, should be replaced with a folic acid supplement. Vitamin B₆ (pyridoxine) 25mg once/twice daily is safe and effective and should be considered as first-line pharmacotherapy. Peppermint-flavoured syrup (glucose and fructose) can also be helpful, particularly if nausea and bouts of vomiting occur frequently.

Antacids that *do not contain* salicylates are useful when there are nausea and gastro-oesophageal reflux symptoms.⁷ Antihistamines, such as dimenhydrinate and diphenhydramine, have been shown to be helpful and not associated with birth defects; side-effects such as sedation, dry mouth, light-headedness and constipation do, however, reduce their overall use. A very recent Canadian study of more than 45 000 pregnancies has associated

medications such as doxylamine-pyridoxine and metoclopramide with an increased risk of spina bifida, and nervous system and musculoskeletal system defects in the exposed infant.⁸ These agents should not be used in the first trimester.

The anti-emetic serotonin 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonist, ondansetron, has also been shown to increase the risk of malformations with early first trimester use and ideally should not be used in the first 10 weeks of gestation.⁵

Intravenous hydration should be used in the patient who cannot tolerate oral liquids for a prolonged period and in the event of clinical dehydration. In milder cases of nausea and vomiting, replacement of electrolytes and fluid loss is restorative. Correct usage is important.

Antacids that do not contain salicylates are useful when there is nausea and gastro-oesophageal reflux symptoms

Chronic nausea and vomiting

Chronic nausea, according to the most recent ROME IV guidelines, is when symptoms are intermittently present for more than six months and have been active within the last three months. Quality of life is severely affected in patients with chronic nausea.

The first and most important step in the evaluation of a patient with chronic

nausea is to exclude common non-gastro-intestinal causes such as medication, vestibular disorders, renal insufficiency, and neurological and mechanical processes. Categories of chronic nausea and vomiting are provided in Table 2, together with more common specific causes, as a useful diagnostic guide.^{9,10}

Table 2. Categories of chronic nausea and vomiting with some specific causes^{9,10}

Gastrointestinal disorders	<ul style="list-style-type: none"> • Mucosal inflammation (peptic ulcer disease, functional dyspepsia) • Mechanical obstruction (gastric outlet obstruction, small intestinal obstruction) • Motility disorders (gastroparesis, Foregut dysmotility syndrome, chronic intestinal pseudo-obstruction) 	
Medications and toxins	<ul style="list-style-type: none"> • Marijuana (cannabinoid hyperemesis) • Opiate analgesia • NSAIDs • Anticholinergic agents • Oestrogen/progesterone 	<ul style="list-style-type: none"> • Lubiprostone • Amylin analogues • Chemotherapy • Digitalis
Metabolic/ endocrine causes	<ul style="list-style-type: none"> • Pregnancy • Diabetes (gastroparesis, diabetic ketoacidosis) 	<ul style="list-style-type: none"> • Uraemia • Adrenal insufficiency • Thyroid disorders
Central nervous system disorders	<ul style="list-style-type: none"> • Migraine headache • Cyclic vomiting syndrome 	<ul style="list-style-type: none"> • Mass lesion, brain tumours • Pseudotumour cerebri
Psychiatric disease	<ul style="list-style-type: none"> • Anorexia, bulimia • Conditioned vomiting 	

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Evaluation of the patient

Patient history forms the essential framework for diagnosis; in particular, the use of opiates and cannabis needs to be excluded as these drugs are associated with nausea and vomiting.

Careful physical examination may help to determine the underlying disease. Some useful associations are:

- Postural decrease in blood pressure without any change in pulse rate – indicative of neuropathy
- Auscultation may demonstrate increased bowel sounds – indicative of an obstruction
- A succession ‘splash’ on listening over the epigastrium when shifting the

When to refer?

Referral for specialist evaluation should be considered when diagnosis is in doubt or requires further investigations and specialised tests such as endoscopy, manometry, electrogastrography and gastric imaging. Where there is suspicion of an

abdomen from side to side – suggestive of gastroparesis or gastric outlet obstruction

- Tenderness in the epigastrium – peptic ulcer disease
- Fingernails may show findings of self-induced vomiting, together with loss of dental enamel – suggestive of bulimia, gastroparesis or reflux disease
- Cranial nerve abnormalities suggest a central nervous system cause or a brainstem tumour
- The patient’s gait may be suggestive of chronic vestibular dysfunction. Observe carefully.

intracranial lesion, based on the presence of headaches or other neurological signs, referral to a neurologist for computerised tomography (CT) or magnetic resonance imaging (MRI) is essential.

Commonly prescribed agents for nausea and vomiting include antihistamines (e.g. cyclizine, promethazine), phenothiazines (e.g. prochlorperazine) or 5-HT₃ receptor antagonists (e.g. ondansetron)

Treatment of chronic nausea and vomiting

General measures

- Medications that reduce gastrointestinal motility should be discontinued – including opiates, tramadol, dopamine agonists, calcium channel blockers (CCBs) and glucagon-like peptide-1 (GLP-1) receptor agonists
- Glycaemic control should be improved as acute hyperglycaemia can slow gastric emptying
- Diet and oral nutrition – poor food intake may result in calorie, vitamin

or mineral deficiencies. Dietary advice should include recommending frequent intake of small meals that are low in fat and fibre, as non-digestible fibre may delay gastric emptying and is not recommended for nausea related to constipation. Blended solids can be taken in severe cases of gastroparesis

- Smoking and alcohol should be avoided.

Medication

Gastritis, oesophagitis or peptic ulcer disease requiring proton pump inhibitors, and conditions such as achalasia and other oesophageal motility disorders, require individualised therapy.

Medications that can be helpful for chronic nausea and vomiting caused by gastroparesis or functional dyspepsia include anti-emetic agents, macrolide antibiotics, dopamine receptor antagonists, prokinetics and corticosteroids.

Commonly prescribed anti-emetic agents for nausea and vomiting include antihistamines (e.g. cyclizine, promethazine), phenothiazines (e.g. prochlorperazine) and 5-HT₃ receptor antagonists (e.g.

ondansetron).

Macrolide antibiotics such as erythromycin and azithromycin stimulate gastric emptying by their action on the motilin receptor, which stimulates smooth muscle directly.

Dopamine receptor antagonists stimulate gastric emptying. Metoclopramide is the only Food and Drug Administration approved medication for gastroparesis and should be started at the lowest possible dose (5mg, 15 minutes before meals and at bedtime), and up-titrated to a maximum of 40mg/day. There are side-effects such as restlessness, insomnia and agitation, which can be managed with diphenhydramine.

Low-dose gabapentin may improve both visceral pain and symptoms of nausea

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Major side-effects include tardive dyskinesia, depression and prolongation of the QT complex.

Domperidone, a galactagogue prokinetic, is generally safe but should be used with caution in patients with cardiac conduction problems. The recommended dose is 10–20mg three times a day.

Corticosteroids such as dexamethasone

are commonly used in oncology practice as an adjunct to other anti-emetics for chemotherapy-related symptoms.

Mirtazapine helps to alleviate associated abdominal pain and to ameliorate nausea symptoms. Low-dose gabapentin may improve both visceral pain and symptoms of nausea.

Conclusion

The presentation of nausea and vomiting requires the clinician to tease out key characteristics, so that unnecessary testing and inappropriate medications are eliminated.

In pregnancy, care must be taken to differentiate normal early nausea (and to treat this condition conservatively) from the more severe hyperemesis gravidarum

and other potential causes of symptoms in later pregnancy.

If chronic nausea and vomiting are not responsive to broad therapeutic approaches using dietary modification, anti-emetics and selective 5-HT₃ receptor antagonists, referral to specialist level is recommended.

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Published by

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Reg: 2012/216456/07

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