The Management of Nausea and Vomiting in Pregnancy and Hyperemesis Gravidarum (Green-top Guideline No. 69)

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PURPOSE AND SCOPE

- The aim of this guideline is to provide updated evidence-based or best clinical practice information regarding the diagnosis and subsequent management of nausea and vomiting of pregnancy (NVP) and hyperemesis gravidarum (HG) across community, ambulatory day care and inpatient settings.

INTRODUCTION AND BACKGROUND EPIDEMIOLOGY

- NVP affects up to 90% of pregnant women and is one of the most common indications for hospital admission among pregnant women, with typical stays of between three and four days.
- NVP is defined as the symptom of nausea and/or vomiting during pregnancy when onset is prior to 16 weeks of gestation and where there are no other causes.

INTRODUCTION AND BACKGROUND EPIDEMIOLOGY

- HG is a severe form of NVP, which affects between 0.3 and 3.6% of pregnant women, interfering with quality of life and the ability to eat and drink normally. Reported HG recurrence rates vary, from 15.2% in a Norwegian hospital registry study to 89% if using self-reported diagnosis.6–9 In a population based pregnancy cohort using general practice records prevalence of clinically recorded NVP/HG was 9.1%: 2.1% had hospital admissions, 3.4% were treated with antiemetics in primary care only, and 3.6% had only recorded diagnoses.

INTRODUCTION AND BACKGROUND EPIDEMIOLOGY

- The major mechanism of NVP and HG has recently been elucidated to be related to hypersensitivity to the (GDF15). GDF15 caused loss of appetite, taste aversion, nausea, vomiting and weight loss. Variation in the GDF15 gene both in families and in unrelated individuals is associated with HG.
- Both hCG and GDF15 are made when genes in the placenta are activated and circulating levels have a peak in the first half of pregnancy, but no genetic variants in hCG have been identified (even in very large studies) to be associated with HG. Higher circulating levels of GDF15 and not hCG were found in hospitalised HG patients, patients taking medication for NVP, and patients with 2nd trimester vomiting. hCG is therefore unlikely to be causative.
- Genetic variants associated with expression of GDF15 in families with HG have been identified as the greatest genetic risk factor for HG and are associated with recurrence in subsequent pregnancies.

HOW ARE NVP AND HG DEFINED AND DIAGNOSED?

- The Windsor definition describes HG as nausea and vomiting of which one is severe, beginning in early pregnancy (before 16 weeks of gestation), inability to eat and drink normally, and strongly limiting daily living activities.
- Signs of dehydration are considered contributory to diagnosis. This definition represents a shift from a historic reliance on objective measures such as weight loss and electrolyte imbalance, and towards subjective patient focused criteria which may lead to improved recognition and diagnosis of HG.

HOW ARE NVP AND HG DEFINED AND DIAGNOSED?

APPENDIX IIa: Pregnancy-Unique Quantification of Emesis (PUQE) index

Total score is sum of replies to each of the three questions. PUQE-24 Score: Mild 6; Moderate = 7–12; Severe = 13–15.

Motherisk PUQE-24 scoring system					
In the last 24 hours, for how long have you felt 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)
In the last 24 hours have you vomited or thrown up?	I did not throw up (1)	1–2 times (2)	3–4 times (3)	5–6 times (4)	7 or more times (5)
In the last 24 hours how many times have you had retching or dry heaves without bringing anything up?	No time (1)	1–2 times (2)	3–4 times (3)	5–6 times (4)	7 or more times (5)

PUQE-24 Score: Mild 6; Moderate = 7–12; Severe = 13–15.

How many hours have you slept out of 24 hours? Why?_____

On a scale of 0 to 10, how would you rate your wellbeing?_____
0 (worst possible) 10 (The best you felt before pregnancy)

Can you tell me what causes you to feel that way?_____

HOW ARE NVP AND HG DEFINED AND DIAGNOSED?

HELP (HyperEmesis Level Prediction Score)

My nausea level most of the time:	0	1 (Mild)	2	3 (Moderate)	4	5 (Severe)
I average __ vomiting episodes/day:	0	1-2	3-5	6-8	9-12	13 or more
I retch/dry heave __ episodes daily:	0	1-2	3-5	6-8	9-12	13 or more
I am urinating/voiding:	Same	More often due to IV fluids; or light color	Slightly less often, and normal color	Once every 8 hours; or slightly dark yellow	Less than every 8 hours or darker	Rarely; dark or bloody; or foul smell
Nausea/vomiting severity 1 hour *after* meds OR after food/drink if no meds:	0 or No Meds	1 (Mild)	2	3 (Moderate)	4	5 (Severe)
Average number of hours I'm unable to work adequately at my job and/or at home due to being sick has been:	0	1-2 (hours are slightly less)	3-4 (can work part time)	5-7 (can only do a little work)	8-10 (can't care for family)	11+ (can't care for myself)
I have been coping with the nausea, vomiting and retching:	Nor-mal	Tired but mood is ok	Slightly less than normal	It's tolerable but difficult	Struggling: moody, emotional	Poorly: irritable depressed
Total amount I have been able to eat/drink AND keep it down: *Medium water bottle/large cup = 2 cups/500mL.*	Same; no weight loss	Total of about 3 meals & 6+ cups fluid	Total of about 2 meals & some fluid	1 meal & few cups fluid; or only fluid or only food	Very little, <1 meal/minimal fluids; or frequent IV	Nothing goes or stays down, or daily IV/TPN/NG
My anti-nausea/vomiting meds stay down or are tolerated:	No meds	Always	Nearly always	Sometimes	Rarely	Never/IV/SQ (SubQ pump)
My symptoms compared to last week:	Great	Better	About Same	Worse	Much Worse	So Much Worse!!!
Weight loss over last 7 days: ___%	0%	1%	2%	3%	4%	5%
Number of Rx's for nausea/vomiting*	0	1	2	3	4	5+
	0 pts	1 pt/answer	2 pts/answer	3 pts/answer	4 pts/answer	5 pts/answer
TOTAL each column = (#answers in column) x (# points for each answer)	0	____	____	____	____	____
TOTAL for ALL columns: _____	None/Mild ≤ 19		Moderate 20-32		Severe 33-60	

HOW ARE NVP AND HG DEFINED AND DIAGNOSED?

- NVP and HG are associated with hyponatraemia, hypokalaemia, low serum urea, raised haematocrit and ketonuria with a metabolic hypochloraemic alkalosis. If severe, a metabolic acidosis may develop. In two-thirds of women with HG, there may be abnormal thyroid function tests (based on a structural similarity between thyroid-stimulating hormone [TSH] and hCG with a biochemical thyrotoxicosis, and raised free thyroxine levels with or without a suppressed thyroid stimulating hormone level. These patients rarely have thyroid antibodies and are euthyroid clinically. The biochemical thyrotoxicosis resolves as the HG improves and treatment with antithyroid drugs is unnecessary. A raised T4 and low TSH therefore do not need treatment in straightforward NVP/HG where the cause is clear and the patient is responding to treatment. Liver function tests are abnormal in up to **40%** of women with HG, with the most likely abnormality being a rise in transaminases. Levels of both bilirubin and amylase may be mildly elevated. These abnormalities improve as the HG resolves.

- **Clinicians should be aware of the features in history, examination and investigation that allow NVP and HG to be assessed and for their severity to be monitored**

Features in the history, examination, and investigations to aid diagnosis and exclude other causes of severe nausea and vomiting in pregnancy

History	• Previous history of NVP/HG
	• Quantify severity using PUQE/HELP score: nausea, vomiting, ptyalism (hypersalivation), spitting, weight loss, inability to tolerate food and fluids, effect on quality of life and ability to perform daily activities
	• Ask about self-reported nutritional status or rapid weight loss
	• Ask about co-morbidities which may be complicated by lack of oral intake of essential medications such as epilepsy, diabetes, HIV, psychiatric conditions and hypoadrenalism.
	• Relevant surgical history such as gastric bypass, band or sleeve
	• History to exclude other causes:
	  ◦ abdominal pain
	  ◦ urinary symptoms
	  ◦ infection
	  ◦ drug history (prescription and/or recreational)
	  ◦ chronic *Helicobacter pylori* infection

Features in the history, examination, and investigations to aid diagnosis and exclude other causes of severe nausea and vomiting in pregnancy

Examination	• Temperature • Heart rate (tachycardia in dehydration) • Blood pressure (hypotension in dehydration) • Oxygen saturations • Respiratory rate (tachypnoea in dehydration) • Abdominal examination • Weight • Signs of dehydration such as sunken eyes, dry lips and mouth, oliguria or anuria, tachycardia and hypotension • Signs of malnutrition or rapid weight loss (≥5% pre pregnancy weight), and muscle wasting as measured by mid-arm circumference[1] • Neurological signs such as confusion, nystagmus or ataxia which could indicate Wernicke's encephalopathy

Features in the history, examination, and investigations to aid diagnosis and exclude other causes of severe nausea and vomiting in pregnancy

Investigation	• Urinalysis: Nitrites may indicate infection. The presence or absence of ketonuria in pregnancy is not an indicator of dehydration. Assessing urinary ketones does not have a use in the management of NVP or HG and may be misleading.
	• MSU (if dipstick indicates signs of UTI)
	• Urea and electrolytes: (to guide intravenous fluid and electrolyte replacement)
	• hypokalaemia/hyperkalaemia
	  ◦ hyponatraemia
	  ◦ chronic kidney disease
	  ◦ high creatinine / urea (acute kidney injury) due to dehydration
	• Full blood count:
	  ◦ infection
	  ◦ anaemia
	  ◦ raised haemoglobin and haematocrit
	• Blood glucose level:
	  ◦ diagnose diabetes
	  ◦ exclude diabetic ketoacidosis in patients with diabetes
	• Ultrasound scan:
	  ◦ assess if viable intrauterine pregnancy, multiple pregnancy or trophoblastic disease
	• In refractory cases or history of previous admissions, check:
	  ◦ TFTs: hypothyroid/hyperthyroid
	  ◦ LFTs: exclude other liver disease such as hepatitis or gallstones, monitor malnutrition
	  ◦ calcium and phosphate
	  ◦ amylase: exclude pancreatitis
	  ◦ VBG: exclude metabolic disturbances to monitor severity

HOW SHOULD WOMEN WITH NVP AND HG BE CARED FOR?

Women with mild NVP should be cared for in the community with antiemetics.

Ambulatory day care should be used when community/primary care measures have failed.

HOW SHOULD WOMEN WITH NVP AND HG BE CARED FOR?

Inpatient care should be considered if there is at least one of the following:

- Continued nausea and vomiting and inability to keep down oral antiemetics
- Continued nausea and vomiting associated with clinical dehydration or weight loss (greater than 5% of body weight), despite oral antiemetics
- Confirmed or suspected comorbidity (such as urinary tract infection and inability to tolerate oral antibiotics).
- Comorbidities such as epilepsy, diabetes, HIV, hypoadrenalism or psychiatric disease where symptoms and inability to tolerate oral intake and medication could present further complications.

HOW SHOULD WOMEN WITH NVP AND HG BE CARED FOR?

Where inpatient care is required an ultrasound scan should be scheduled to confirm **viability** and **gestational age**, and to assess for **multiple pregnancy** or **trophoblastic** disease.

HOW SHOULD WOMEN WITH NVP AND HG BE CARED FOR?

- What pharmacological therapeutic options are available and effective for women with NVP and HG?

Recommended antiemetic therapies and dosages

First line

Doxylamine and Pyridoxine (vitamin B6) 20/20mg PO at night, increase to additional 10/10 mg in morning and 10/10mg at lunchtime if required.
Cyclizine 50 mg PO, IM or IV 8 hourly
Prochlorperazine 5–10 mg 6–8 hourly PO (or 3 mg buccal); 12.5 mg 8 hourly IM/IV; 25 mg PR daily
Promethazine 12.5–25 mg 4–8 hourly PO, IM or IV
Chlorpromazine 10–25 mg 4–6 hourly PO, IM or IV

Second line

Metoclopramide 5–10 mg 8 hourly PO, IV/IM/SC
Domperidone 10 mg 8 hourly PO; 30 mg 12 hourly PR
Ondansetron 4 mg 8 hourly or 8 mg 12 hourly PO; 8 mg over 15 minutes 12 hourly IV; 16 mg daily PR
(Women taking ondansetron may require laxatives if constipation develops)

Third line

Hydrocortisone 100 mg twice daily IV and once clinical improvement occurs, convert to prednisolone 40–50 mg daily PO, with the dose gradually tapered (by 5-10 mg per week) until the lowest maintenance dose that controls the symptoms is reached
(Corticosteroids should be reserved for cases where standard therapies have failed; when initiated they should be prescribed in addition to previously started effective antiemetics. Women taking corticosteroids should have their blood pressure monitored and a screen for diabetes mellitus)

IM intramuscular; **IV** intravenous; **PO** by mouth; **PR** by rectum.

HOW SHOULD WOMEN WITH NVP AND HG BE CARED FOR?

- Combinations of different drugs should be used in women who do not respond to a single antiemetic.
- A delayed-release combination of doxylamine and pyridoxine (vitamin B6) is the only licensed treatment of NVP in the UK so can be used firstline for mild-moderate NVP requiring treatment.
- For women with persistent or severe HG, the parenteral, transdermal, or rectal route may be necessary and more effective than an oral regimen.
- Corticosteroids should be reserved for cases where standard therapies have been ineffective and used in combination with antiemetics.

HOW SHOULD WOMEN WITH NVP AND HG BE CARED FOR?

- Corticosteroids have resulted in dramatic and rapid improvement in case series of women with **refractory** HG. The results of randomised studies are conflicting and the largest study failed to show improvement in the primary outcome of rehospitalisation (however, both groups also received metoclopramide and promethazine). Case selection and route and dose of corticosteroid administration may explain the different results, with beneficial results being described in more severe cases. A systematic review and meta-analysis identified five trials of 310 women and showed no effect on readmission rates, with one study showing reduced vomiting and one showing improved wellbeing.

HOW SHOULD WOMEN WITH NVP AND HG BE CARED FOR?

- Corticosteroids should not be used until conventional treatment with intravenous fluid replacement and regular antiemetics has been proven to be ineffective. The suggested dose is IV hydrocortisone 100 mg twice daily, and once clinical improvement occurs conversion to oral prednisolone 40–50 mg daily, with the dose gradually tapered until the lowest maintenance dose that controls the symptoms is reached. In most cases prednisolone needs to be continued until the gestational age at which HG would have resolved and in some extreme cases, prednisolone is continued until birth. Women receiving corticosteroids should be screened for gestational diabetes.

- There are no trials of community use of **ginger** for severe NVP and HG. A large cross-sectional survey of 512 women with HG found that ginger foodstuffs or over the counter tablets have little or no efficacy but caused unpleasant adverse effects and worsening of symptoms in over half (54%) of participants. Recommendations by a healthcare professional (HCP) to try ginger was found to cause a loss of trust in the HCP and damaged clinician-patient relationships.

What is the safety of the pharmacological agents used to treat NVP and HG?

- First line - There are safety data for antiemetics such as anti (H1) histamines, phenothiazines and pyridoxine-doxylamine (Xonvea®) and they should be prescribed initially when required for NVP and HG
- Second line - There is evidence that **ondansetron i**s safe. Its use should not be discouraged if first line antiemetics are ineffective. Women can be reassured regarding a very small increase in the absolute risk of orofacial clefting with ondansetron use in the first trimester, which should be balanced with the risks of poorly managed HG

What is the safety of the pharmacological agents used to treat NVP and HG?

- The UK Teratology Information Service (UKTIS) have published a systematic review of the literature that concludes ‘currently available data do not provide evidence that ondansetron use in the first trimester of pregnancy is associated with an increase in the overall malformation rate.

What is the safety of the pharmacological agents used to treat NVP and HG?

- Additional second line – **Metoclopramide** is safe and can be used alone or in combination with other antiemetics
- Because of the risk of extrapyramidal effects **metoclopramide** should be used as second-line therapy. Intravenous doses should be administered by slow bolus injection over at least 3 minutes to help minimise these
- Data confirm that corticosteroid use in the first trimester is not associated with an increase in risk of congenital malformations overall and specifically no increase in orofacial clefting, cardiac defects or hypospadias following first trimester use of corticosteroids.

What is the safety of the pharmacological agents used to treat NVP and HG?

- A Cochrane review, other systematic reviews and meta-analyses and birth registry data have reported on the **safety and efficacy** of many antiemetics for use in NVP and HG, with **no increased risk of teratogenesis** or other adverse pregnancy outcomes. These drugs include: antihistamines (H1 receptor antagonists) such as promethazine, cyclizine, cinnarizine, pyridoxine-doxylamine (Xonvea®) and dimenhydrinate; phenothiazines including prochlorperazine, chlorpromazine and perphenazine; and dopamine antagonists including metoclopramide and domperidone. Because there are no clear data supporting increased efficacy of one class of antiemetic over others the suggested step wise approach (Appendix III) is based predominantly on safety data6.

What adverse effects can occur from NVP and HG and how can they be prevented?

- Urea and serum electrolyte levels should be checked daily in women requiring intravenous fluids
- Histamine type-2 receptor blockers or proton pump inhibitors may be used for women developing gastro-oesophageal reflux disease, oesophagitis or gastritis
- Thiamine supplementation (either oral 100 mg tds or intravenous as part of vitamin B complex (Pabrinex®)) should be given to all women admitted with vomiting, or severely reduced dietary intake, especially before administration of dextrose or parenteral nutrition.
- Women admitted with HG should be offered thromboprophylaxis with low-molecularweight heparin and those being managed in the community should be assessed for VTE

What adverse effects can occur from NVP and HG and how can they be prevented?

- Women with previous or current NVP or HG should consider avoiding iron-containing preparations if these exacerbate symptoms or consider alternative route of administering iron.
- Women should be questioned about their bowel habits and offered laxatives if constipated, and particularly if ondansetron is used

What adverse effects can occur from NVP and HG and how can they be prevented?

- Wernicke encephalopathy due to vitamin B1 (thiamine) deficiency classically presents with **blurred vision, unsteadiness and confusion/memory problems/drowsiness and on examination there is usually nystagmus, ophthalmoplegia, hyporeflexia or areflexia, gait and/or finger–nose ataxia.** In HG, the presentation tends to be episodic and of slow onset. Wernicke encephalopathy is a potentially fatal medical emergency. In the context of HG, it is preventable and studies have stressed the association between Wernicke encephalopathy and administration of **intravenous dextrose** and **parenteral nutrition**. A systematic review of 177 cases found that chronic cognitive disorders occurred in 65.4%, pregnancy loss in 50%, and maternal death in 5% of cases.96 Therefore thiamine supplementation is recommended for all women admitted with HG.

HOW SHOULD WOMEN WITH NVP AND HG BE OFFERED ONGOING ANTENATAL CARE?

- Women should only be discharged once
- • appropriate antiemetic therapy has been tolerated
- • adequate oral nutrition and hydration has been tolerated
- • management of concurrent conditions is completed

HOW SHOULD WOMEN WITH NVP AND HG BE OFFERED ONGOING ANTENATAL CARE?

- Almost one third of women will be readmitted within the same pregnancy. Therefore at the time of discharge, it is essential that women are advised to continue with their antiemetics where appropriate and that they know how to access further care.
- Women with severe NVP or HG who have continued symptoms into the late second or the third trimester should be offered serial scans to monitor fetal growth

What are optimal rehydration regimens for ambulatory and inpatient care?

- Normal saline (0.9% NaCl) with additional potassium chloride in each bag, with administration guided by daily monitoring of electrolytes, is the most appropriate intravenous hydration.

What are optimal rehydration regimens for ambulatory and inpatient care?

- The most important intervention is likely to be appropriate intravenous fluid and electrolyte replacement.
- IV fluids have been shown to reduce vomiting and are therefore valuable for both outpatient and inpatient management of the symptoms of HG and severe NVP as well as associated dehydration and electrolyte disorders.
- Dextrose-containing solutions can precipitate Wernicke encephalopathy in thiamine-deficient states; hence, they should be avoided, and high (e.g. 100 mg) doses of parenteral thiamine should be given to prevent Wernicke encephalopathy. Dextrose containing fluids are appropriate for nausea and vomiting in the third trimester to prevent and treat starvation ketosis.

When should enteral and parenteral nutrition be considered and what are the risks to the woman and fetus?

- When all other medical therapies have failed to sufficiently manage symptoms, enteral tube feeding or parenteral treatment should be considered with a referral to gastroenterology and a multidisciplinary approach in parallel to ongoing medical therapies.

When should enteral and parenteral nutrition be considered and what are the risks to the woman and fetus?

- Parenteral nutrition should only be considered as a multidisciplinary approach when all other treatments have failed to sufficiently control symptoms as it is inconvenient, expensive and can be associated with serious complications such as thrombosis, metabolic disturbances and infection. A single nonrandomised study has shown that total parenteral nutrition (TPN) was associated with a decreased risk of perinatal morbidity compared with those with HG who did not receive TPN.

When should enteral and parenteral nutrition be considered and what are the risks to the woman and fetus?

- There are no defined criteria for starting parenteral or enteral tube feeding. Their effectiveness is not well established. Anecdotally, they can be effective and are often employed as a last resort when all other medical therapy has failed and the **only other practical option is TOP**. Close monitoring of metabolic and electrolyte balance, related complications (including refeeding syndrome) and nutritional requirements are needed with a multidisciplinary approach.

When should enteral and parenteral nutrition be considered and what are the risks to the woman and fetus?

- Enteral tube feeding options to consider include nasogastric, nasoduodenal or nasojejunal tubes, or percutaneous endoscopic gastrostomy or gastrojejunostomy feeding, all of which should only be considered in consultation with gastroenterology and with a multidisciplinary approach. Parenteral feeding with a peripherally inserted central catheter (PICC line) is often **better tolerated** than enteral feeding; however, it carries a higher risk of infection and vascular complications.

When should enteral and parenteral nutrition be considered and what are the risks to the woman and fetus?

- In some women, feeding by nasogastric or percutaneous endoscopic gastrostomy tube increases the risk of nausea and vomiting. It may be tolerated in the short term but not in protracted HG.

When should termination of pregnancy be discussed?

- Around **10%** of women with HG will terminate a wanted pregnancy, due to the condition.137,170 **Pregnancy Sickness Support in the UK** found that many of these women **have not been** offered the full range of treatments available and fewer than 10% had been offered steroids. Treatment options of antiemetics, corticosteroids, enteral tube and parenteral feeding, and correction of electrolyte or metabolic disturbances should be considered before deciding that the only option is TOP. Consider seeking psychiatric opinion if there are concerns regarding mental health, and the decision for TOP needs to be multidisciplinary, with documentation of therapeutic failure if this is the reason for the termination. Women should be offered counselling before and after a decision of pregnancy termination is made. **In a survey of 808 women who had TOP secondary to HG, 123 (15.2%) had at least one termination due to HG, and 49 (6.1%) had multiple terminations.190 Common reasons given for the terminations were inability to care for the family and self (66.7%), fear that they and their baby could die (51.2%), or that the baby would be abnormal (22%).**

What are the long-term effects of NVP and HG on women?

- Women who experience HG in pregnancy are at increased risk of PND, anxiety and PTSD postpartum.
- Women with previous HG should be advised that there is a risk of recurrence in future pregnancies

What are the long-term effects of NVP and HG on women?

- Symptoms of NVP and HG should resolve rapidly after the birth. Where symptoms do not resolve further investigation should occur with referrals to endocrinology and gastroenterology as appropriate. Case reports have highlighted hyperparathyroidism as a potential differential diagnosis for HG which does not resolve postnatally.