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The Management of Nausea and Vomiting in Pregnancy and Hyperemesis Gravidarum

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Guideline

This is the second edition of this guideline which was previously published in 2016 under the same name.

1. Key recommendations

Recommendation	Evidence Quality	Strength
An objective and validated index of nausea and vomiting such as the Pregnancy-Unique Quantification of Emesis (PUQE) and HyperEmesis Level Prediction (HELP) tools can be used to classify the severity of NVP and HG.	**2–**	**C**
Ketonuria is not an indicator of dehydration and should not be used to assess severity.	**1++**	**A**
There are safety and efficacy data for first line antiemetics such as anti (H1) histamines, phenothiazines and Xonvea and they should be prescribed initially when required for NVP and HG (Appendix III).	**2++**	**A**
There is evidence that ondansetron is safe and effective. Its use as a second line antiemetic 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.	**2++**	**B**
Metoclopramide is safe and effective and can be use 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.** **Women should be asked about previous adverse reactions to antiemetic therapies. If adverse reactions occur, there should be prompt cessation of the medications.**	**2++** **2+** **4**	**B** **C** **GPP**
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.	**3**	**C**
Combinations of different drugs should be used in women who do not	**4**	**GPP**

respond to a single antiemetic. Suggested antiemetics for UK use are given in Appendix III.		
A woman's quality of life can be adversely affected by NVP and HG and practitioners should address the severity of a woman's symptoms in relation to her quality of life and social situation.	**2–**	**C**
All therapeutic measures should have been tried before considering termination of pregnancy.	**2–**	**C**

2. Purpose and scope

There is variation in the management of women who have nausea and vomiting of pregnancy (NVP) or hyperemesis gravidarum (HG) with the potential for lack of understanding of its severity and options for treatment and support.

The aim of this guideline is to provide updated evidence-based or best clinical practice information regarding the diagnosis and subsequent management of NVP and HG across community, ambulatory day care and inpatient settings. It gives advice for multidisciplinary professionals involved in the care of women with these conditions, including how to counsel and support women before, during and after their pregnancies.

Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

3. Introduction and background epidemiology

NVP affects up to 90% of pregnant women[1] and is one of the commonest indications for hospital admission among pregnant women, with typical stays of between three and four days. The annual cost to the NHS of NVP has been estimated to be up to £62 million due to hospital admissions, general practice (GP) visits and ambulance call-outs.[1-4] 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. The term often used in the lay media for NVP is "morning sickness" which is not only inaccurate (as symptoms occur both before and after noon), but is felt by sufferers to trivialise the condition.[5]

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]

The precise cause of NVP and HG is as yet uncertain but aetiological theories range from the feto-protective and genetic to the biochemical, immunological and biosocial.[10,11] Increased serum levels of beta-human chorionic gonadotropin (hCG) have historically been favoured as an aetiological theory on account of the association between severe NVP/HG and elevated-hCG states such as multiple pregnancy or trophoblastic disease, however this likely represents an over-simplification and incomplete account of the true pathogenesis.[11,12] More recently, genetic variants associated with expression of growth differentiation factor-15 (GDF15) in families with HG have been identified as the greatest genetic risk factor for HG[13] and are associated with recurrence in subsequent pregnancies.[14]

4. Identification and assessment of evidence

The Cochrane Library and electronic databases (DARE, EMBASE, Trip, MEDLINE and PubMed) were searched using the relevant Medical Subject Headings (MeSH) terms, including all subheadings and synonyms, and this was combined with a keyword search and was limited to humans and English language; search terms included 'hyperemesis', 'nausea and vomiting' 'pregnan*', 'morning sickness' and 'hyperemesis gravidarum'. The search was restricted to articles published between 2015 and February 2020. The full search strategy is available to view online as supporting information (Appendix S1 and S2).

This guideline was developed using the standard methodology for Green-top Guidelines.[15] Where possible, recommendations are based on available evidence. In the absence of published evidence, these have been annotated as 'good practice points'. Further information about the assessment of evidence and the grading of recommendations may be found in Appendix I.

5. How are NVP and HG defined and diagnosed?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
NVP is diagnosed when onset is prior to 16 weeks of gestation and other causes of nausea and vomiting have been excluded.	**2–**	**D**	Onset of NVP is in the first trimester and if the initial onset is after 16 weeks this should be investigated for other causes.
HG can be diagnosed when symptoms start in early pregnancy, nausea and/or vomiting are severe enough to cause an inability to eat and drink normally and strongly limits daily activities of living. Signs of dehydration are contributory to diagnosis.	**2–**	**D**	Definition of HG has been agreed by international consensus in published literature.
An objective and validated index of nausea and vomiting such as the Pregnancy-Unique Quantification of Emesis (PUQE) and HyperEmesis Level Prediction (HELP) tools can be used to classify the severity of NVP and HG.	**2–**	**C**	The PUQE score is a validated score to objectively assess severity of mild to moderate NVP. The HELP score is a validated score to determine severity of all NVP including HG.
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.	**4**	**D**	Thorough history, examination and investigation ensure accurate assessment of severity and exclusion of other causes
Ketonuria is not an indicator of dehydration in pregnancy and should not be used to assess severity.	**1++**	**A**	Ketonuria is not associated with HG or its severity.

NVP typically starts between the fourth and seventh weeks of gestation, peaks in approximately the ninth week and resolves by the 20th week in 90% of women.[16] *[Evidence level 2–]*

A multi-stakeholder international consensus process developed a definition for HG to aid clinical diagnosis. The Windsor definition[17] 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.[17] *[Evidence level 2–]*

The Rhodes Index[18,19] was originally validated to measure nausea and vomiting in chemotherapy patients, including assessment of physical symptoms and the resulting stress, but has subsequently been used for NVP. A shorter disease-specific questionnaire (PUQE) was developed by the Motherisk Program,[20] an NVP helpline in Canada, which highly correlated with the Rhodes Index and assessed symptoms over the previous 12 hours.[21] The PUQE was modified to include symptom profile over the previous 24 hours including a wellbeing score that correlated with hydration status and, more recently, over the duration of the first trimester.[22,23] The PUQE score can be used to determine whether the NVP is mild, moderate or severe (Appendix II). *[Evidence level 2+]* The PUQE score can also be used to assess the response to treatment for mild to moderate NVP but is not valid for severe NVP and HG.

The HELP score was developed and validated by the Hyperemesis Education and Research Foundation in the USA[24] to quantify HG symptoms into a score that can be trended over time to monitor progress and response to treatment. It is available as an online calculator (https://www.hyperemesis.org/tools/help-score/) and in app form. The HELP score (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7815331/figure/FI13091997-1/?report=objectonly) can be used to track progress with treatment in women with severe NVP and HG. *[Evidence level 2+]*

Table 1. 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
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 muscle circumference • Neurological signs such as confusion, nystagmus or ataxia which could indicate Wernicke's encephalopathy

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 – ABG: exclude metabolic disturbances to monitor severity

ABG arterial blood gas; **LFTs** liver function tests; **MSU** midstream urine; **TFTs** thyroid function tests.

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.[25] 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. *[Evidence level 2–]*

Liver function tests are abnormal in up to 40% of women with HG,[26] 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. *[Evidence level 3]*

Ketonuria is not an indicator of dehydration and is not associated with severity of NVP or HG.[27,28] *[Evidence level 1++]*

Clinical assessment as outlined in table 1 or with the HELP or PUQE scores are better indicators of severity. Assessment of urinary ketosis may mislead clinical judgement of hydration and nutrition status and should be avoided in the assessment or monitoring of NVP and HG.

Severe malnutrition can be assessed with anthropometric measures such as mid-upper arm circumference and validated nutrition screening tools such as the Malnutrition Universal Screening Tool (MUST) which can be adapted for pregnancy.[29-34]

6. How should women with NVP and HG be cared for?

6.1 What initial clinical assessment and baseline investigations should be performed?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Women with mild NVP should be cared for in the community with antiemetics.	**D**	**4**	Since most women with NVP require only oral or intramuscular antiemetics, management in the community/primary care is appropriate to avoid unnecessary hospital admissions and disruption to the woman's life.[35]
Ambulatory day care should be used when community/primary care measures have failed.	**C**	**2+**	If women are unable to tolerate oral antiemetics or oral fluids then ambulatory day care management is appropriate.
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 or HIV, where symptoms and inability to tolerate oral intake and medication could present further complications.**	**GPP**	**4**	Women who have recurrent/on-going NVP/HG despite adequate ambulatory day care treatment should be cared for as inpatients because of the associated complications, in particular electrolyte imbalance and nutritional deficiencies.
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. Unless there are other medical reasons for an urgent scan, this can be scheduled for the next available appointment.	**GPP**	**4**	Trophoblastic disease and multiple pregnancy are associated with an increased risk of HG but do not affect the initial care**.**

Women who have nausea and vomiting but are not dehydrated can be cared for in the community with antiemetics, reassurance, oral hydration and dietary advice. In areas where 'acute care at home' or 'hospital at home' services are operating to provide IV treatment in the community, these services

can be utilised for IV rehydration at home for women who are unable to maintain hydration orally but who do not have co-morbidities or complications. Women may be reluctant to take, and non-specialist clinicians may be reluctant to prescribe, pharmacological treatments owing to concerns about teratogenic risk.[36,37] Women should be counselled that the benefits of antiemetics outweigh the risks, and that the absolute risk is low.[38] *[Evidence level 4]*

If women are unable to tolerate oral antiemetics or oral fluids then ambulatory day care management, which provides intravenous fluids, vitamins (especially B1- thiamine)[39,40] and parenteral antiemetics, is appropriate. Thiamine stores in a previously healthy individual can deplete rapidly and cause symptoms of tachycardia, weakness and decreased deep tendon reflexes within one week without intake.[40] Various rehydration regimens have been shown to be effective.[41,42] A randomised controlled trial (RCT) of 98 women showed that ambulatory day care management involving intravenous fluids and stepwise increments in antiemetic therapy versus inpatient care was acceptable to women and resulted in fewer days as an inpatient.[43] In a study of 428 women who had ambulatory day care subcutaneous metoclopramide therapy (SMT), improvement in symptoms occurred in 89.3%.[42] Those women who failed the SMT regimen (10.7%) had higher mean PUQE scores at the start of ambulatory day care treatment than those for whom it was successful (10.0 ± 3.0 versus 7.6 ± 2.8 respectively, $P < 0.001$). Moreover, they were more likely to have a PUQE score of 13 or higher, SMT was started earlier in pregnancy (9.7 ± 2.9 weeks versus 11.4 ± 3.2 weeks, $P = 0.005$) and they were more likely to need intravenous hydration (91.3% versus 65.2%, $P < 0.001$). In addition to the SMT regimen, women received adjuvant therapies at home such as intravenous hydration, subcutaneous ondansetron, histamine type-2 receptor blockers, and received total parenteral nutrition. Ambulatory day care management has been successfully and safely set up in units and is associated with high patient satisfaction.[44] *[Evidence level 2+]*

6.2 How should women with NVP and HG be cared for?

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

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Combinations of different drugs should be used in women who do not respond to a single antiemetic. Suggested antiemetics for UK use are given in Appendix III.	**4**	**GPP**	Various drug classes have different mechanisms of action and work synergistically, therefore, combination antiemetics should be used in women who do not respond to a single agent. Some women may require combinations of two or more medications from first- and second- line options (see appendix III)
A delayed-release combination of doxylamine and pyridoxine (vitamin B6) is the only licensed treatment of NVP in the UK so can be used first-line for mild-moderate NVP requiring treatment.	**2++**	**B**	A larger improvement in PUQE score from baseline to day 15 and increased wellbeing has been reported as compared with placebo.[45]

For women with persistent or severe HG, the parenteral, transdermal, or rectal route may be necessary and more effective than an oral regimen.	**2-**	**D**	
Corticosteroids should be reserved for cases where standard therapies have been ineffective and used in combination with antiemetics.	**1+**	A	Systematic review suggests a beneficial effect for steroids.[46]

Clinicians should use antiemetics with which they are familiar and should use drugs from different classes if the first drug is not effective or only partially effective. Many women will require a combination of two or more antiemetics[47].

A slow-release combination of doxylamine and pyridoxine (vitamin B_6) called Xonvea™ is the only licensed treatment of NVP in the UK.[45] A delayed-release formulation containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride has been available in Canada since 1979 and since 2013 in the USA. The combination of doxylamine and pyridoxine resulted in a larger improvement in PUQE score from baseline to day 15 compared with placebo (mean difference −0.90, 95% CI −1.55– −0.25; *P* = 0.006) in a randomised double-blind multicentre trial of 256 women. There was also a significantly larger increase in wellbeing score with active treatment (+1.0, *P* = 0.005). Although no high quality evidence exists to suggest that delayed release formulations are more effective than other antiemetics in treating NVP, evidence from other fields, such as chemotherapy nausea and vomiting management supports their use to create stable blood levels of the drug.[45] *[Evidence level 2++]*

A study of 1037 admissions[47] for HG demonstrated that antihistamines were more commonly prescribed in combination with other antiemetics at hospital discharge after a first admission and that combinations of dopamine antagonists and serotonin antagonists are common after second and subsequent admissions. Furthermore, persistent vomiting may mean that oral doses of antiemetics are not absorbed and therefore the sublingual, intravenous, rectal, transcutaneous, subcutaneous or intramuscular routes may be necessary and more effective. *[Evidence level 2++]*

Three small randomised studies[48-50] have shown ondansetron to be superior to doxylamine and pyridoxine in reducing nausea and vomiting,[48] equally effective as metoclopramide, but with fewer adverse effects,[49] and more effective than metoclopramide at reducing severe vomiting.[50] *[Evidence level 2++]* Because there are large amounts of safety data for doxylamine / pyridoxine and the antihistamines in general have fewer adverse effects than ondansetron (which may cause constipation) the antihistamines remain first line over ondansetron which is second line (see appendix III).

A Cochrane systematic review including two RCTs demonstrated that treatment with ondansetron was associated with improvement in symptoms of all severities.[51] *[Evidence level 2++]*

There are small studies of the use of Granisetron with limited evidence as yet of its use.[52,53] *[Evidence level 3]*

There is no association between the degree of NVP at 12 weeks and vitamin B6 levels measured at 15 weeks.[54] A Cochrane review concluded that there is a lack of consistent evidence that pyridoxine is an effective therapy for NVP.[55] Furthermore, a placebo-controlled trial of its use in HG did not

demonstrate any improvement in nausea, vomiting or rehospitalisation in 46 women given 20 mg orally three times a day in addition to intravenous fluids, intravenous metoclopramide three times a day and oral thiamine, compared with the control group given placebo in addition to standard therapy.[56] A matched non-randomised study demonstrated that the combination of doxylamine and pyridoxine was significantly more effective than pyridoxine alone.[57] *[Evidence level 2++]*

Corticosteroids have resulted in dramatic and rapid improvement in case series of women with refractory HG.[58] The results of randomised studies are conflicting[59] and the largest study failed to show improvement in the primary outcome of rehospitalisation (however, both groups also received metoclopramide and promethazine).[60,61] 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.[46] *[Evidence level 1+]*

Corticosteroids should not be used until conventional treatment with intravenous fluid replacement and regular antiemetics has failed. 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.[35]

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. Women with severe NVP and HG found it demeaning and demoralising to be offered ginger by a HCP. Because prior awareness and self-administration of ginger as a home remedy prior to seeking medical help was extremely high HCPs should not suggest it and doing so may delay access to effective treatment.[62]

6.2.2 What is the safety of the pharmacological agents used to treat NVP and HG? (*See appendix III)*

Recommendation	Evidence quality	Strength	Rationale for the recommendation
First line - There are safety data for antiemetics such as anti (H1) histamines, phenothiazines and Xonvea and they should be prescribed initially when required for NVP and HG (Appendix III).	**2++**	**A**	Cochrane review reports no increased risk of congenital malformation or other adverse pregnancy outcomes.[63]
Second line - There is evidence that ondansetron is 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.	**2++**	**B**	Absolute risk of orofacial clefting increases from a background risk of 11 cases per 10 000 births to 14 cases per 10 000 births with ondansetron.

Additional second line – Metoclopramide is safe and can be used alone or in combination with other antiemetics.	**2++**	**B**	Drug-induced extrapyramidal symptoms and oculogyric crises can occur with the use of phenothiazines and metoclopramide.
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.	**2+**	**C**	Dystonic reactions have been shown to be significantly less common in non-pregnant patients receiving a slow infusion as opposed to a bolus injection of 10 mg of metoclopramide
Women should be asked about previous adverse reactions to antiemetic therapies. If adverse reactions occur, there should be prompt cessation of the medications.	**4**	**GPP**	

A Cochrane review[64] , other systematic reviews and meta-analyses[38,65-67] and birth registry data[38] 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)[68] and dimenhydrinate; phenothiazines including prochlorperazine, chlorpromazine and perphenazine; and dopamine antagonists including metoclopramide[69] 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 data[6]. *[Evidence level 2++]*

Use of ondansetron for NVP/HG is increasing[70] as is the body of literature to support no overall increased risk of congenital malformations.[71-74] However, conflicting findings from large epidemiological studies (some of which have shown a small increased risk of either cardiac defects[75] or orofacial clefting[71]) have, controversially, led to warnings from the European Medicines Authority to avoid ondansetron in the first trimester. The Medicines and Healthcare products Regulatory Agency (MHRA) did not issue a warning. 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.'[74] They summarised the data for congenital malformations 'Twelve studies, including one meta-analysis of data from seven studies, collectively including more than 97 000 unique first trimester-exposed pregnancies have assessed the overall malformation rate following maternal ondansetron use in pregnancy.[71,76-86] The majority of these studies,[71,76,81-85] including the largest and most statistically robust (>88 000 first trimester exposures)[71] and the meta-analysis,[86] did not identify increased risks in comparison with disease-matched and/or healthy or population unexposed controls.' *[Evidence level 2++]*

Two large cohort studies form the majority of the data in the meta-analysis.[86 75 71] Although one study[75] found a significant risk of cardiac defects (adjusted OR 1.43, 95% CI 1.28–1.61), the larger (1.8 million pregnancy cohort of which almost 5% [88 467 women] were exposed to ondansetron during the first trimester) study[71] did not find a significant association for cardiac defects after adjusting for pre-defined confounding factors (aRR 0.99, 95% CI 0.93–1.06). However, a small increased risk of orofacial clefting was noted [71] (adjusted relative risk [aRR] 1.24, 95% CI 1.03–1.48). It is important to put this into context as the background risk of orofacial clefting is low, and therefore the increase in absolute risk is small. If the increase in risk is real, then ondansetron represents an additional three oral clefts

per 10 000 births (14 cases per 10 000 births with ondansetron exposure versus 11 cases per 10 000 births in the unexposed population). *[Evidence level 2++]*

A limitation of these two cohort studies is that they compare women with severe NVP and HG taking ondansetron to women who do not have severe NVP and HG. This leaves open the possibility that any effects are confounded by indication, nor do they consider the competing risks to women with severe NVP and HG of leaving their illness poorly controlled. A study comparing women with HG taking ondansetron with women with HG taking other antiemetics found no increased risk of major malformations in the ondansetron group.[87] A study [85] comparing women with HG taking ondansetron vs those with HG not taking ondansetron found a higher rate of terminations of pregnancy in those not taking ondansetron and higher rate of live birth in those taking ondansetron.

Due to the risk of extrapyramidal effects with metoclopramide it should be used as second-line therapy. A review of metoclopramide,[88] conducted by the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use, has confirmed the risks of short-term extrapyramidal disorders and tardive dyskinesia, particularly in young people. The review recommends metoclopramide should only be prescribed for short-term use (maximum dose of 30 mg in 24 hours or 0.5 mg/kg body weight in 24 hours [whichever is lowest] and maximum duration of 5 days) and that intravenous doses should be administered by slow bolus injection over at least 3 minutes to help minimise these risks. Dystonic reactions have been shown to be significantly less common in non-pregnant patients receiving a slow infusion as opposed to a bolus injection of 10 mg of metoclopramide.[89] Notwithstanding the EMA's recommendation the authors of this guideline recommend that it can be prescribed for more than five days in those women who gain symptomatic relief from it. *[Evidence level 2++]*

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.[90] Data on corticosteroids use in the first trimester is limited to a maximum of approximately 3500 exposures, and therefore is less well studied in comparison to other anti-emetic medication. *[Evidence level 2++]*

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

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Urea and serum electrolyte levels should be checked daily in women requiring intravenous fluids.	**4**	**GPP**	NVP can be associated with electrolyte imbalances.
Histamine type-2 receptor blockers or proton pump inhibitors may be used for women developing gastro-oesophageal reflux disease, oesophagitis or gastritis.	**4**	**D**	Recurrent intractable vomiting may lead to gastro-oesophageal reflux disease, oesophagitis or gastritis.
Thiamine supplementation (either oral or intravenous) should be given to all women admitted with vomiting, or severely reduced dietary intake, especially before	**4**	**D**	NVP/HG can lead to Wernicke encephalopathy due to vitamin B1 (thiamine) deficiency.

administration of dextrose or parenteral nutrition.			
Women admitted with HG should be offered thromboprophylaxis with low-molecular-weight heparin. Graduated compression stockings should be used when low-molecular-weight heparin is contra-indicated (as per GTG 37a). Thromboprophylaxis can be discontinued upon discharge providing no other indications exist for continuation of thromboprophylaxis.	**3**	**C**	Women with HG have increased risk of venous thromboembolism with odds ratio 2.5 (95% CI 2–3.2).[91]
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	**4**	**D**	Oral iron can cause nausea and vomiting.
Consider prophylactic vitamin K supplementation, particularly where weight loss and malnutrition is severe and rapid.	**3**	**D**	A systematic review has shown that vitamin K deficiency may affect up to 26% of HG patients and can lead to severe adverse maternal and neonatal outcomes. Vitamin K supplementation does not increase the risk of thromboembolism.

Inability to tolerate oral fluids and excessive vomiting due to NVP and HG can affect other medical conditions requiring oral medication, such as epilepsy (where oral medication is not tolerated seizures may result), psychiatric medications (which may have problematic withdrawal effects) and HIV (where even mild sporadic nausea and vomiting may make antiretroviral drugs difficult to take at precise times). It is vital that there is early recourse to prescribe antiemetics for women in these situations. Medication times may need to be adjusted so women can take them when symptoms are better controlled.

HG increases risks in some conditions such as those with diabetes, or a history of gastric band, gastric bypass and gastric sleeve surgery. Specialist advice is required for these women. A previous history of gastric reduction surgery may cause malabsorption of oral medication and increase the risk of nutrient and vitamin deficiency, particularly thiamine and vitamin K.

In women requiring intravenous fluids, daily monitoring of fluid and serum electrolyte levels is important to recognise and treat hyponatraemia and hypokalaemia.[35,92]

Oesophago-gastroduodenoscopy is safe in pregnancy and indicated in cases of haematemesis or severe epigastric pain. A therapeutic trial with a proton pump inhibitor is appropriate for treatment and prevention and is safe in pregnancy.[93,94]

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.[95] 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.[95] Therefore thiamine supplementation is recommended for all women admitted with HG. *[Evidence level 2]*

A Canadian study[96] using hospital discharge data found an adjusted odds ratio for deep vein thrombosis of 4.4 (95% CI 2.4–8.4) in women with HG. However, since women with HG are only at markedly increased risk while persistently vomiting, thromboprophylaxis can be discontinued at discharge or when the HG resolves.[97]

In a Canadian prospective cohort study, two-thirds of 97 women who discontinued iron supplements reported improvement in their severity of NVP.[98]

7. How should women with NVP and HG be offered ongoing antenatal care?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
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.	**4**	**GPP**	Continued treatment may reduce the need for hospital readmission.
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.	**2+**	**B**	Women with low pregnancy weight gain are at increased risk of preterm delivery and low birthcoweight.

Almost one third of women will be readmitted within the same pregnancy,[99] 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 if their symptoms and/or signs recur (e.g. persistent vomiting, dehydration). Rehydration and a review of antiemetic treatment should ideally be undertaken in an ambulatory day care setting.[100] Better communication and advice about the safety of antiemetics may enable general practitioners to adequately support women with HG.[100,101] *[Evidence level 2–]*

Level of ketones should not be used to inform clinical decision making about treatments or hydration status.[28] *[Evidence level 2+]*

An observational study has shown that women with HG and low pregnancy weight gain (less than 7 kg during pregnancy) are at an increased risk of preterm delivery (adjusted relative risk 3.0, 95% CI 1.9–4.3) and low birthweight (less than 2500g; adjusted relative risk 2.8, 95% CI 1.7–4.3).[102] *[Evidence level 2+]*

A population-based cohort study using secondary healthcare records demonstrated that HG was significantly associated with low birthweight (OR 1.12, 99% CI 1.08–1.17) and small-for-gestational-age (OR 1.06, 99% CI 1.01–1.11) babies and the offspring was more likely to undergo resuscitation or intensive care treatment, albeit with small absolute risk.[103] The Cambridge Baby Growth Study also found that vomiting during the first and second trimesters of pregnancy was associated with a higher

risk of low birthweight (OR 3.5 95% CI 1.2–10.8 *P* = 0.03) even when vomiting was not perceived to be severe enough to warrant treatment.[104] *[Evidence level 2+]*

7.1 What are optimal rehydration regimens for ambulatory and inpatient care?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
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.	**3**	**C**	There is no evidence to determine which fluid regimen is most appropriate but given that most women admitted to hospital with HG are hyponatraemic, hypochloraemic and hypokalaemic, it seems appropriate to use normal saline (0.9% NaCl) and potassium chloride.
The use of dextrose infusions for fluid replacement in NVP and HG is not recommended	**4**	**D**	Intravenous fluid and electrolyte replacement is likely to be the most important intervention in the treatment of those requiring ambulatory or inpatient care for NVP. General guidance on fluid management in adults can be found in NICE clinical guideline 174 [Ref 11]. Dextrose-containing solutions may precipitate Wernicke encephalopathy in thiamine deficient states.

The most important intervention is likely to be appropriate intravenous fluid and electrolyte replacement. General adult fluid management guidance can be found in NICE clinical guideline 174.[105] Dextrose-containing solutions can precipitate Wernicke encephalopathy in thiamine-deficient states (see section 7.1); hence, they should be avoided, and high (e.g. 100 mg) doses of parenteral thiamine should be given to prevent Wernicke encephalopathy. *[Evidence level 3]*

7.2 What is the effect of NVP and HG on the quality of life of the woman and family?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
A woman's quality of life can be adversely affected by NVP and HG and practitioners should address the severity of a woman's symptoms in relation to her quality of life and social situation.	**2–**	**C**	NVP has been reported to reduce quality of life, impairing a woman's ability to function on a day-to-day basis, and negatively affects relationships with her partner and family.
Practitioners should carry out a full assessment of both physical and mental health status during the pregnancy and	**2+**	**C**	Depressive symptoms and poor mental health are associated with severity of NVP.

refer for psychological support if necessary.			Acknowledgement by healthcare professionals of the effect of these physical symptoms on patients' mental health is likely to lead to an improved patient experience.
Pre-existing mental health conditions may be exacerbated by HG particularly where prescribed oral medications are not being taken or kept down because of vomiting, therefore consideration to alternative routes of administration, proactive use of anti-emetics and appropriate referrals should be considered.	**4**	**GPP**	
Advice about patient support groups should be provided to all women admitted with nausea and vomiting in pregnancy	**4**	**GPP**	Many women and their partners find support groups (e.g. Pregnancy Sickness Support) online or in person extremely helpful.

NVP has been reported to reduce quality of life, impairing a woman's ability to function on a day-to-day basis, and negatively affects relationships with her partner and family.[106-126] Women with HG are three to six times more likely than women with NVP to have low quality of life.[25] Constant nausea is the symptom that most adversely affects quality of life.[114,127] Furthermore, causes of stress as a consequence of NVP include lack of understanding and support, inability to eat healthily, regret for the loss of a positive pregnancy experience, financial pressures, absence from work, isolation, inability to care for family, others' belief that it is psychosomatic and perception that doctors are reluctant to provide treatment.[108,128,129] Perceived stress positively correlated with NVP and negatively correlated with social support in a cross-sectional study of 243 women.[130] It has been recommended that social support is necessary as an adjunct to treatment and the circle of support should be expanded to include family, friends and healthcare professionals.[131] A cohort study of 648 women found that having support from at least three other persons was protective in women with NVP.[108] *[Evidence level 2–]*

Depressive symptoms and poor mental health are associated with severity of NVP.[132,133] Poor psychological health of women with HG is considered as the demoralisation of suffering from a prolonged, severe chronic illness and in this regard it is similar to mental health problems suffered in other chronic illnesses.[134] *[Evidence level 2+]*

Advice about patient support groups (e.g. Pregnancy Sickness Support) should be provided as many women and their partners find this form of support helpful.[135-137]

A follow-up appointment for antenatal care is important in women with HG. Psychological and social support should be organised depending upon the clinical and social circumstances.

The erroneous belief in the psychogenic aetiology of HG is still prevalent among healthcare professionals[134,136,138-141] and such attitudes towards women contribute to a worse experience for NVP and HG sufferers.[134,136,141-143] Women often struggle to obtain treatment for NVP and HG, are dissatisfied with communication during their appointments and found healthcare professionals dismissive and unsympathetic.[141,144-147] A cohort study of 808 women demonstrated that women who feel that their healthcare professional is unsympathetic report more depression and anxiety.[134] A

review paper recommends an integrated approach which addresses both physical and psychological suffering in HG.[148]

Pre-existing mental health conditions may be exacerbated by HG particularly where prescribed oral medications are not being taken or kept down due to vomiting, therefore consideration to alternative routes of administration, aggressive use of antiemetics and appropriate referrals should be considered. *[Evidence level 4]*

Clinical assessment should be considered for depression and postnatal depression with appropriate referral. Depression and poor psychological health have been found to be associated with NVP and HG in numerous studies,[108,109,126,132,133,142,149-157] including a systematic review and meta-analysis, but resulted from the disease and were not the cause of HG or NVP.[122] A UK wide survey of 5071 participants found a quarter of those suffering HG occasionally reported suicidal ideation and 6.6% regularly considered suicide due to the severity of the condition, 4.9% had a termination of pregnancy (TOP) due to HG and 52.1% considered TOP due to HG. Both suicidal ideation and TOP of a wanted pregnancy were associated with perceived poor care from their healthcare providers. Those reporting extremely poor perception of both primary and secondary care were less likely to have been offered medication compared with those reporting excellent care.[158] *[Evidence level 2++]*

A cohort study of 648 women found that symptoms of major depression are associated with moderate and severe NVP but prior history of depression is not a determinant.[108,159] *[Evidence level 2–]*

Poor mental health can persist post-partum and HG is a risk factor for postpartum PTSD.[157,160,161] *[Evidence level 2+]*

Pregnancy sickness specific counselling may be helpful either during or after pregnancy.[162] Measures that address NVP, poor social support and depression are warranted throughout pregnancy.[108] A prospective cohort study of 367 women suggests that practitioners could improve their management of NVP by addressing symptoms and life situation.[111] *[Evidence level 3]*

The theory of psychogenic aetiology proposed by Fairweather has been severely criticised for poor methodology and bias.[96,163-165] Studies have failed to find a convincing association between a prior history of psychological poor health and having HG.[150,152,154,156,166-168] Similarly, these suggest that poor mental health can be exacerbated by HG rather than being caused by it.[110,138,142,148,149,156,159,168,169] *[Evidence level 2+]*

8. How should women with NVP and HG be cared for when standard treatment measures fail to control symptoms of nausea and vomiting?

8.1 What is the role of the multidisciplinary team?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
In women with severe NVP or HG, input should be sought from other allied professionals.	**4**	**D**	There are many facets to severe NVP and HG and a holistic approach to assessment and treatment should be adopted.

Involvement of the mental health team in the woman's care may improve quality of life and the ability to cope with the impact of a complicated pregnancy.[106] Emotional support and psychological or

psychiatric care may be required[122,170] with targeted interventions specifically designed to treat mental health issues occurring as a result of HG.[149,150,171,172] *[Evidence level 2–]*

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

Recommendation	Evidence quality	Strength	Rationale for the recommendation
When all other medical therapies have failed to sufficiently manage symptoms, enteral or parenteral treatment should be considered with a referral to gastroenterology and a multidisciplinary approach in parallel to ongoing medical therapies.	**3**	**D**	Total parenteral nutrition is a high-risk intervention; however, it may be useful in refractory cases to ensure sufficient nutritional intake.

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.[173,174] 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.[175] *[Evidence level 2+]*

There are no defined criteria for starting parenteral or enteral feeding. Their effectiveness is not well established. Anecdotally, they can be successful and are often employed as a last resort when all other medical therapy has failed and the only other practical option is TOP.[176,177] Close monitoring of metabolic and electrolyte balance, related complications and nutritional requirements are needed with a multidisciplinary approach. *[Evidence level 2–]*

Enteral 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.[178] *[Evidence level 2+]*

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.[179] A recent randomised controlled trial recruited 116 women hospitalised for HG between 5 and 20 weeks and allocated them to either enteral (nasogastric) tube feeding (n=59) or standard care (n=57). Outcomes did not differ between the groups and adherence to protocol was low due to adverse effects in the enteral feeding arm. Many women could not tolerate tube feeding due to discomfort suggesting it is poorly tolerated as an early routine treatment. *[Evidence level 2+]*

In nasojejunal feeding, the tube is inserted endoscopically or under radiological guidance to the jejunum and feeding can be administered by a continuous infusion. One study showed that although the majority of women improved greatly within 48 hours, ongoing vomiting and retching can dislodge gastric and postpyloric feeding tubes.[179] *[Evidence level 3]*

Feeding via a percutaneous endoscopic gastrojejunostomy (PEG-J), placed under general anaesthetic in the second trimester, [180,181] has been shown to be an effective, safe and well-tolerated treatment of HG. In the majority of women, the tube is removed after birth. The risk of early dislodgement is

minimised compared with nasoenteric placement. Potential complications of percutaneous endoscopic gastrojejunostomy include tube dislodgement, obstruction or migration, cutaneous or intra-abdominal abscesses, fistula formation, pneumatosis, occlusion and intestinal ischaemia. *[Evidence level 2+]*

8.3 When should termination of pregnancy be discussed?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
All therapeutic measures should have been tried before considering termination of pregnancy.	**2–**	**C**	HG is associated with a higher risk of termination of pregnancy. As many as 10% of women with HG undergo termination of pregnancy due to the severity of symptoms, who would not otherwise have chosen to[182].

Around 10% of women with HG will terminate a wanted pregnancy, due to the condition.[136,158] 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.[182] *[Evidence level 2–]*

Treatment options of antiemetics, corticosteroids, enteral and parenteral feeding, and correction of electrolyte or metabolic disturbances should be considered before deciding that the only option is TOP.[183,184] 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. *[Evidence level 2–]*

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.[184] 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%). In one study, women who underwent a pregnancy termination were more likely to report a negative attitude from their caregiver. Initiation of a prompt and responsive treatment plan may reduce this.[176] Rarely, HG or its treatment may lead to life-threatening illness and TOP is seen as the only option.[95,185] *[Evidence level 4]*

9. What are the long-term effects of NVP and HG?

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

Recommendation	Evidence quality	Strength	Rationale for the recommendation
There is no evidence of significant impact on long-term all-cause mortality.	**2++**	**B**	In a large population cohort study from Norway, HG was not associated with an increased risk of long-term all-cause mortality.[186]
Women who experience HG in pregnancy are at increased risk of PND and PTSD post-partum.	**2++**	**B**	Systematic review has shown a significantly increased risk of depression and anxiety in women with HG which extended into the

			postnatal period.[122] A subsequent two-point case control study demonstrated long-lasting psychological morbidity associated with HG.[157]
Women with previous HG should be advised that there is a risk of recurrence in future pregnancies.	**2++**	**B**	The reported rates of recurrence varied from 15% to 81%.

Women who experience HG in pregnancy are at increased risk of postnatal depression (PND) and post-traumatic stress disorder (PTSD) post-partum.[122]

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 post-natally.[187]

A systematic review published in 2019 found five eligible papers reporting on 40 350 women with HG which investigated the chance of recurrence of HG in subsequent pregnancies.[7] The quality of the five papers was low and meta-analysis was not possible due to clinical and statistical heterogeneity. The reported rates of recurrence varied from 15% to 81%. The paper concluded that a prospective longitudinal cohort study using an agreed definition of HG and outcomes meaningful to patients is required to establish the true recurrence rate of HG.[9] *[Evidence level 2++]*

9.2 What are the long-term effects of NVP and HG on the infant and child?

Mild-moderate NVP does not appear to have a negative long-term effect on the developing fetus and may have a protective effect for the pregnancy.[188]

In contrast a recent systematic review and meta-analysis of nineteen studies with 619 cases showed an association with a small increase in adverse health outcomes of children born to women who had suffered with HG.[189] A recent meta-analysis suggested a small increase in the risk of certain adverse health outcomes in infants born to women who suffered with HG including anxiety disorder, testicular cancer (aged up to 40 years), attention deficit hyperactivity disorder and autism, however there was considerable heterogeneity between individual studies. *[Evidence level 2-]*

9.3 What advice should be given about future pregnancies?

Recommendation	Evidence quality	Strength	Rationale for the recommendation
Early use of lifestyle/dietary modifications and antiemetics that were useful in the index pregnancy is advisable to reduce the risk of NVP and HG in the current pregnancy.	**2+**	**B**	There is a lower recurrence risk with pre-emptive anti-emetics before symptoms begin.

A Canadian study comparing women with NVP (PUQE score of 13 and above) who took pre-emptive antiemetics before pregnancy or before the onset of symptoms with those who did not, reported a lower recurrence rate of HG in the group that took pre-emptive antiemetics.[107] There was also a

significant improvement in the PUQE score of NVP severity compared with the previous pregnancy in the pre-emptive group. Women who have experienced severe NVP in a previous pregnancy may benefit from initiating dietary and lifestyle changes, such as arranging childcare to facilitate rest and adjusting to a "little and often" diet, and commencing antiemetics before or immediately at the start of symptoms in a subsequent pregnancy.[107] *[Evidence level 2++]*

A small randomised study in women with previous NVP demonstrated that pre-emptive treatment with antiemetics resulted in fewer women with moderate to severe NVP.[190] *[Evidence level 2++]*

Women who have experienced HG in two or more pregnancies reported that earlier use of antiemetics was a factor in reducing the number of hospital admissions they had in the second pregnancy.[147] *[Evidence level 3]*

10. Recommendations for future research

A James Lind Alliance Priority Setting Partnership has reported 26 priorities for research.[191] Recommendations based on this guideline are:

- To establish optimum dose and route of administration for ondansetron to maximise efficacy with the least adverse effects
- To evaluate the feasibility, cost efficiency and patient satisfaction of community/home based rehydration treatment
- To establish the most effective combinations of therapies to maximise efficacy with the least adverse effects
- To develop and assess interventions to reduce the risk of negative psychological outcomes
- To evaluate the effect of pre-emptive intervention on the severity and duration of symptoms in subsequent pregnancies

All future research should use the Core Outcome Set for Hyperemesis Gravidarum research.[191]

11. Auditable topics

- Percentage of women with access to recommended first and second line antiemetic HG treatment (100%)
- Percentage of women prescribed appropriate rehydration regimes (100%)
- Incidence of termination of wanted pregnancy due to NVP/HG (0%)

12. Useful links and support groups

- Pregnancy Sickness Support [https://www.pregnancysicknesssupport.org.uk/] Provides information and peer support to people affected by NVP and HG across the UK
- Hyperemesis Education and Research (HER) Foundation [https://www.hyperemesis.org/]
- UK Teratology Information Service (UKTIS): www.uktis.org
- bumps (best use of medicines in pregnancy). *Treating nausea and vomiting in pregnancy* [http://www.medicinesinpregnancy.org/Medicine--pregnancy/NV/].
- For professionals: UKTIS. *Treatment of nausea and vomiting in pregnancy* [https://uktis.org/monographs/treatment-of-nausea-and-vomiting-in-pregnancy/].

References

1. Gadsby R, Rawson V, Dziadulewicz E, Rousseau B, Collings H. Nausea and vomiting of pregnancy and resource implications: the NVP Impact Study. *Br J Gen Pract*. Mar 2019;69(680):e217-e223. doi:10.3399/bjgp18X700745
2. Lacasse A, Lagoutte A, Ferreira E, Bérard A. Metoclopramide and diphenhydramine in the treatment of hyperemesis gravidarum: effectiveness and predictors of rehospitalisation. *Eur J Obstet Gynecol Reprod Biol*. Mar 2009;143(1):43-9. doi:10.1016/j.ejogrb.2008.11.007
3. Gazmararian JA, Petersen R, Jamieson DJ, et al. Hospitalizations during pregnancy among managed care enrollees. *Obstet Gynecol*. Jul 2002;100(1):94-100. doi:10.1016/s0029-7844(02)02024-0
4. Atanackovic G, Wolpin J, Koren G. Determinants of the need for hospital care among women with nausea and vomiting of pregnancy. *Clin Invest Med*. Apr 2001;24(2):90-3.
5. Gadsby R, Ivanova D, Trevelyan E, Hutton JL, Johnson S. Nausea and vomiting in pregnancy is not just 'morning sickness': data from a prospective cohort study in the UK. *Br J Gen Pract*. 08 2020;70(697):e534-e539. doi:10.3399/bjgp20X710885
6. Trogstad LI, Stoltenberg C, Magnus P, Skjaerven R, Irgens LM. Recurrence risk in hyperemesis gravidarum. *BJOG*. Dec 2005;112(12):1641-5. doi:10.1111/j.1471-0528.2005.00765.x
7. Dean CR, Bruin CM, O'Hara ME, et al. The chance of recurrence of hyperemesis gravidarum: A systematic review. *Eur J Obstet Gynecol Reprod Biol X*. Jan 2020;5:100105. doi:10.1016/j.eurox.2019.100105
8. Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. *J Popul Ther Clin Pharmacol*. 2013;20(2):e171-83.
9. Nijsten K, Dean C, van der Minnen LM, et al. Recurrence, postponing pregnancy, and termination rates after hyperemesis gravidarum: Follow up of the MOTHER study. *Acta Obstet Gynecol Scand*. Sep 2021;100(9):1636-1643. doi:10.1111/aogs.14197
10. Buckwalter JG, Simpson SW. Psychological factors in the etiology and treatment of severe nausea and vomiting in pregnancy. *Am J Obstet Gynecol*. May 2002;186(5 Suppl Understanding):S210-4. doi:10.1067/mob.2002.122600
11. O'Brien B, Relyea MJ. Use of indigenous explanations and remedies to further understand nausea and vomiting during pregnancy. *Health Care Women Int*. 1999 Jan-Feb 1999;20(1):49-61. doi:10.1080/073993399245953
12. Fejzo MS, Sazonova OV, Sathirapongsasuti JF, et al. Placenta and appetite genes GDF15 and IGFBP7 are associated with hyperemesis gravidarum. *Nat Commun*. 03 2018;9(1):1178. doi:10.1038/s41467-018-03258-0
13. Marlena S. Fejzo KWM, Olivia First, Courtney Quan, Patrick M. Mullin. Whole-exome sequencing uncovers new variants in GDF15 associated with hyperemesis gravidarum. Review. *BJOG*. 2022;doi:https://doi.org/10.1111/1471-0528.17129
14. Fejzo MS, Arzy D, Tian R, MacGibbon KW, Mullin PM. Evidence GDF15 Plays a Role in Familial and Recurrent Hyperemesis Gravidarum. *Geburtshilfe Frauenheilkd*. Sep 2018;78(9):866-870. doi:10.1055/a-0661-0287
15. Gynaecologists RCoOa. Developing a Green-top Guideline: guidance for developers. London: RCOG; 2020.
16. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. *Br J Gen Pract*. Jun 1993;43(371):245-8.
17. Jansen LAW, Koot MH, Van't Hooft J, et al. The windsor definition for hyperemesis gravidarum: A multistakeholder international consensus definition. *Eur J Obstet Gynecol Reprod Biol*. Nov 2021;266:15-22. doi:10.1016/j.ejogrb.2021.09.004
18. Rhodes VA, Watson PM, Johnson MH. Development of reliable and valid measures of nausea and vomiting. *Cancer Nurs*. Feb 1984;7(1):33-41.
19. Rhodes VA, McDaniel RW. The Index of Nausea, Vomiting, and Retching: a new format of the Index of Nausea and Vomiting. *Oncol Nurs Forum*. Jun 1999;26(5):889-94.

679 20. Koren G, Boskovic R, Hard M, Maltepe C, Navioz Y, Einarson A. Motherisk-PUQE (pregnancy-
680 unique quantification of emesis and nausea) scoring system for nausea and vomiting of pregnancy.
681 *Am J Obstet Gynecol*. May 2002;186(5 Suppl Understanding):S228-31. doi:10.1067/mob.2002.123054
682 21. Koren G, Piwko C, Ahn E, et al. Validation studies of the Pregnancy Unique-Quantification of
683 Emesis (PUQE) scores. *J Obstet Gynaecol*. Apr 2005;25(3):241-4. doi:10.1080/01443610500060651
684 22. Lacasse A, Rey E, Ferreira E, Morin C, Bérard A. Validity of a modified Pregnancy-Unique
685 Quantification of Emesis and Nausea (PUQE) scoring index to assess severity of nausea and vomiting
686 of pregnancy. *Am J Obstet Gynecol*. Jan 2008;198(1):71.e1-7. doi:10.1016/j.ajog.2007.05.051
687 23. Ebrahimi N, Maltepe C, Bournissen FG, Koren G. Nausea and vomiting of pregnancy: using the
688 24-hour Pregnancy-Unique Quantification of Emesis (PUQE-24) scale. *J Obstet Gynaecol Can*. Sep
689 2009;31(9):803-807. doi:10.1016/S1701-2163(16)34298-0
690 24. MacGibbon KW, Kim S, Mullin PM, Fejzo MS. HyperEmesis Level Prediction (HELP Score)
691 Identifies Patients with Indicators of Severe Disease: a Validation Study. *Geburtshilfe Frauenheilkd*. Jan
692 2021;81(1):90-98. doi:10.1055/a-1309-1997
693 25. Goodwin TM, Montoro M, Mestman JH. Transient hyperthyroidism and hyperemesis
694 gravidarum: clinical aspects. *Am J Obstet Gynecol*. Sep 1992;167(3):648-52. doi:10.1016/s0002-
695 9378(11)91565-8
696 26. Rotman P, Hassin D, Mouallem M, Barkai G, Farfel Z. Wernicke's encephalopathy in
697 hyperemesis gravidarum: association with abnormal liver function. *Isr J Med Sci*. Mar 1994;30(3):225-
698 8.
699 27. Koot MH, Grooten IJ, Post JAMV, et al. Ketonuria is not associated with hyperemesis
700 gravidarum disease severity. *Eur J Obstet Gynecol Reprod Biol*. Nov 2020;254:315-320.
701 doi:10.1016/j.ejogrb.2020.08.014
702 28. Niemeijer MN, Grooten IJ, Vos N, et al. Diagnostic markers for hyperemesis gravidarum: a
703 systematic review and metaanalysis. *Am J Obstet Gynecol*. Aug 2014;211(2):150.e1-15.
704 doi:10.1016/j.ajog.2014.02.012
705 29. Miele MJ, Souza RT, Calderon I, et al. Proposal of MUAC as a fast tool to monitor pregnancy
706 nutritional status: results from a cohort study in Brazil. *BMJ Open*. May 24 2021;11(5):e047463.
707 doi:10.1136/bmjopen-2020-047463
708 30. Mayimbo S HC, Kwaleyela C, Phoebe B, Chirwa E, Kaonga P, Ngoma C. Assessing Malnutrition
709 in Pregnant Women Using the Dietary Diversity Score and the Mid-Upper Arm Circumference: A Cross-
710 Sectional Study, Zambia. *Food and Nutrition Sciences*. 2021;11:712-725.
711 31. Mareschal J, Achamrah N, Norman K, Genton L. Clinical Value of Muscle Mass Assessment in
712 Clinical Conditions Associated with Malnutrition. *J Clin Med*. Jul 17 2019;8(7)doi:10.3390/jcm8071040
713 32. Bharadwaj S, Ginoya S, Tandon P, et al. Malnutrition: laboratory markers vs nutritional
714 assessment. *Gastroenterol Rep (Oxf)*. Nov 2016;4(4):272-280. doi:10.1093/gastro/gow013
715 33. BAPEN. Malnutrition Universal Screening Tool. Worcestershire: BAPEN; 2003.
716 34. BAPEN. The 'MUST' Explanatory Booklet. Worcestershire: BAPEN; 2011.
717 35. Jarvis S, Nelson-Piercy C. Management of nausea and vomiting in pregnancy. *BMJ*. Jun
718 2011;342:d3606. doi:10.1136/bmj.d3606
719 36. Figueroa Gray M, Hsu C, Kiel L, Dublin S. Getting through the day: a pilot qualitative study of
720 U.S. women's experiences making decisions about anti-nausea medication during pregnancy. *BMC*
721 *Pregnancy Childbirth*. Dec 2018;18(1):475. doi:10.1186/s12884-018-2093-6
722 37. Widnes SF, Schjøtt J. Risk perception regarding drug use in pregnancy. *Am J Obstet Gynecol*.
723 04 2017;216(4):375-378. doi:10.1016/j.ajog.2016.12.007
724 38. Gill SK, Einarson A. The safety of drugs for the treatment of nausea and vomiting of pregnancy.
725 *Expert Opin Drug Saf*. Nov 2007;6(6):685-94. doi:10.1517/14740338.6.6.685
726 39. Erick M. Hyperemesis gravidarum: a case of starvation and altered sensorium gestosis (ASG).
727 *Med Hypotheses*. May 2014;82(5):572-80. doi:10.1016/j.mehy.2014.02.014
728 40. Pacei F, Tesone A, Laudi N, et al. The Relevance of Thiamine Evaluation in a Practical Setting.
729 *Nutrients*. Sep 13 2020;12(9)doi:10.3390/nu12092810

41. McParlin C, Carrick-Sen D, Steen IN, Robson SC. Hyperemesis in Pregnancy Study: a pilot randomised controlled trial of midwife-led outpatient care. *Eur J Obstet Gynecol Reprod Biol*. May 2016;200:6-10. doi:10.1016/j.ejogrb.2016.02.016
42. Lombardi DG, Istwan NB, Rhea DJ, O'Brien JM, Barton JR. Measuring outpatient outcomes of emesis and nausea management in pregnant women. *Manag Care*. Nov 2004;13(11):48-52.
43. McCarthy FP, Murphy A, Khashan AS, et al. Day care compared with inpatient management of nausea and vomiting of pregnancy: a randomized controlled trial. *Obstet Gynecol*. Oct 2014;124(4):743-748. doi:10.1097/AOG.0000000000000449
44. TN K, S K, M S. Hyperemesis day centre audit [E-poster EP13.25]. *BJOG*. 2013;120(Suppl 1)
45. Doxylamine/pyridoxine for nausea and vomiting in pregnancy. *Drug Ther Bull*. Mar 2019;57(3):38-41. doi:10.1136/dtb.2018.000053
46. Grooten IJ, Vinke ME, Roseboom TJ, Painter RC. A Systematic Review and Meta-Analysis of the Utility of Corticosteroids in the Treatment of Hyperemesis Gravidarum. *Nutr Metab Insights*. 2015;8(Suppl 1):23-32. doi:10.4137/NMI.S29532
47. Fiaschi L, Housley G, Nelson-Piercy C, et al. Assessment of discharge treatment prescribed to women admitted to hospital for hyperemesis gravidarum. *Int J Clin Pract*. Jan 2019;73(1):e13261. doi:10.1111/ijcp.13261
48. Oliveira LG, Capp SM, You WB, Riffenburgh RH, Carstairs SD. Ondansetron compared with doxylamine and pyridoxine for treatment of nausea in pregnancy: a randomized controlled trial. *Obstet Gynecol*. Oct 2014;124(4):735-742. doi:10.1097/AOG.0000000000000479
49. Abas MN, Tan PC, Azmi N, Omar SZ. Ondansetron compared with metoclopramide for hyperemesis gravidarum: a randomized controlled trial. *Obstet Gynecol*. Jun 2014;123(6):1272-1279. doi:10.1097/AOG.0000000000000242
50. Kashifard M, Basirat Z, Golsorkhtabar-Amiri M, Moghaddamnia A. Ondansetrone or metoclopromide? Which is more effective in severe nausea and vomiting of pregnancy? A randomized trial double-blind study. *Clin Exp Obstet Gynecol*. 2013;40(1):127-30.
51. Boelig RC, Barton SJ, Saccone G, Kelly AJ, Edwards SJ, Berghella V. Interventions for treating hyperemesis gravidarum: a Cochrane systematic review and meta-analysis. *J Matern Fetal Neonatal Med*. Sep 2018;31(18):2492-2505. doi:10.1080/14767058.2017.1342805
52. Le TN, Adler MT, Ouillette H, Berens P, Smith JA. Observational Case Series Evaluation of the Granisetron Transdermal Patch System (Sancuso) for the Management of Nausea/Vomiting of Pregnancy. *Am J Perinatol*. 07 2017;34(9):851-855. doi:10.1055/s-0037-1598652
53. Aleyasin A, Saffarieh E, Torkamandi H, et al. Comparison of Efficacy of Granisetron and Promethazine in Control of Hyperemesis Gravidarum. *J Obstet Gynaecol India*. 12 2016;66(6):409-414. doi:10.1007/s13224-015-0709-6
54. Schuster K, Bailey LB, Dimperio D, Mahan CS. Morning sickness and vitamin B6 status of pregnant women. *Hum Nutr Clin Nutr*. Jan 1985;39(1):75-9.
55. Boelig RC, Barton SJ, Saccone G, Kelly AJ, Edwards SJ, Berghella V. Interventions for treating hyperemesis gravidarum. *Cochrane Database Syst Rev*. May 11 2016;(5):CD010607. doi:10.1002/14651858.CD010607.pub2
56. Tan PC, Yow CM, Omar SZ. A placebo-controlled trial of oral pyridoxine in hyperemesis gravidarum. *Gynecol Obstet Invest*. 2009;67(3):151-7. doi:10.1159/000181182
57. Pope E, Maltepe C, Koren G. Comparing pyridoxine and doxylamine succinate-pyridoxine HCl for nausea and vomiting of pregnancy: A matched, controlled cohort study. *J Clin Pharmacol*. Jul 2015;55(7):809-14. doi:10.1002/jcph.480
58. Taylor R. Successful management of hyperemesis gravidarum using steroid therapy. *QJM*. Feb 1996;89(2):103-7. doi:10.1093/qjmed/89.2.103
59. Nelson-Piercy C, Fayers P, de Swiet M. Randomised, double-blind, placebo-controlled trial of corticosteroids for the treatment of hyperemesis gravidarum. *BJOG*. Jan 2001;108(1):9-15. doi:10.1111/j.1471-0528.2001.00017.x

60. Safari HR, Fassett MJ, Souter IC, Alsulyman OM, Goodwin TM. The efficacy of methylprednisolone in the treatment of hyperemesis gravidarum: a randomized, double-blind, controlled study. *Am J Obstet Gynecol*. Oct 1998;179(4):921-4. doi:10.1016/s0002-9378(98)70189-9
61. Yost NP, McIntire DD, Wians FH, Ramin SM, Balko JA, Leveno KJ. A randomized, placebo-controlled trial of corticosteroids for hyperemesis due to pregnancy. *Obstet Gynecol*. Dec 2003;102(6):1250-4. doi:10.1016/j.obstetgynecol.2003.08.013
62. CR D, ME OH. Ginger is ineffective for hyperemesis gravidarum, and causes harm: an internet based survey of sufferers. *MIDRIS Midwifery Digest*. 2015;25(4):449-55.
63. Pereira N, Hutchinson AP, Irani M, et al. 5-millimeter Trocar-site Hernias After Laparoscopy Requiring Surgical Repair. *J Minim Invasive Gynecol*. 2016 May-Jun 2016;23(4):505-11. doi:10.1016/j.jmig.2016.03.001
64. Matthews A, Dowswell T, Haas DM, Doyle M, O'Mathúna DP. Interventions for nausea and vomiting in early pregnancy. *Cochrane Database Syst Rev*. Sep 2010;(9):CD007575. doi:10.1002/14651858.CD007575.pub2
65. Mazzotta P, Magee LA. A risk-benefit assessment of pharmacological and nonpharmacological treatments for nausea and vomiting of pregnancy. *Drugs*. Apr 2000;59(4):781-800. doi:10.2165/00003495-200059040-00005
66. Magee LA, Mazzotta P, Koren G. Evidence-based view of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). *Am J Obstet Gynecol*. May 2002;186(5 Suppl Understanding):S256-61. doi:10.1067/mob.2002.122596
67. McParlin C, O'Donnell A, Robson SC, et al. Treatments for Hyperemesis Gravidarum and Nausea and Vomiting in Pregnancy: A Systematic Review. *JAMA*. 10 2016;316(13):1392-1401. doi:10.1001/jama.2016.14337
68. Koren G, Clark S, Hankins GD, et al. Maternal safety of the delayed-release doxylamine and pyridoxine combination for nausea and vomiting of pregnancy; a randomized placebo controlled trial. *BMC Pregnancy Childbirth*. Mar 2015;15:59. doi:10.1186/s12884-015-0488-1
69. Pasternak B, Svanström H, Mølgaard-Nielsen D, Melbye M, Hviid A. Metoclopramide in pregnancy and risk of major congenital malformations and fetal death. *JAMA*. Oct 2013;310(15):1601-11. doi:10.1001/jama.2013.278343
70. Parker SE, Van Bennekom C, Anderka M, Mitchell AA, Study NBDP. Ondansetron for Treatment of Nausea and Vomiting of Pregnancy and the Risk of Specific Birth Defects. *Obstet Gynecol*. 08 2018;132(2):385-394. doi:10.1097/AOG.0000000000002679
71. Huybrechts KF, Hernández-Díaz S, Straub L, et al. Association of Maternal First-Trimester Ondansetron Use With Cardiac Malformations and Oral Clefts in Offspring. *JAMA*. 12 2018;320(23):2429-2437. doi:10.1001/jama.2018.18307
72. Lavecchia M, Chari R, Campbell S, Ross S. Ondansetron in Pregnancy and the Risk of Congenital Malformations: A Systematic Review. *J Obstet Gynaecol Can*. 07 2018;40(7):910-918. doi:10.1016/j.jogc.2017.10.024
73. Kaplan YC, Richardson JL, Keskin-Arslan E, Erol-Coskun H, Kennedy D. Use of ondansetron during pregnancy and the risk of major congenital malformations: A systematic review and meta-analysis. *Reprod Toxicol*. 06 2019;86:1-13. doi:10.1016/j.reprotox.2019.03.001
74. Monograph U. Use of ondansetron in pregnancy. 2019.
75. Zambelli-Weiner A, Via C, Yuen M, Weiner DJ, Kirby RS. First trimester ondansetron exposure and risk of structural birth defects. *Reprod Toxicol*. 01 2019;83:14-20. doi:10.1016/j.reprotox.2018.10.010
76. Einarson A, Maltepe C, Navioz Y, Kennedy D, Tan MP, Koren G. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. *BJOG*. Sep 2004;111(9):940-3. doi:10.1111/j.1471-0528.2004.00236.x
77. Bérard A, Sheehy O, Gorgui J, Zhao JP, Soares de Moura C, Bernatsky S. New evidence for concern over the risk of birth defects from medications for nausea and vomitting of pregnancy. *J Clin Epidemiol*. 12 2019;116:39-48. doi:10.1016/j.jclinepi.2019.07.014

78. Huybrechts KF, Hernandez-Diaz S, Straub L, et al. Intravenous Ondansetron in Pregnancy and Risk of Congenital Malformations. *JAMA*. 01 2020;323(4):372-374. doi:10.1001/jama.2019.18587
79. Lemon LS, Bodnar LM, Garrard W, et al. Ondansetron use in the first trimester of pregnancy and the risk of neonatal ventricular septal defect. *Int J Epidemiol*. 04 2020;49(2):648-656. doi:10.1093/ije/dyz255
80. J A, E J-S, N A, H P. Ondansetron Use in Early Pregnancy and the Risk of Congenital Malformations – A Register Based Nationwide Cohort Study [ABSTRACT]. *Pharmacoepidemiology and Drug Safety*. 2003;12(Supple 1):13-14.
81. Pasternak B, Svanström H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. *N Engl J Med*. Feb 2013;368(9):814-23. doi:10.1056/NEJMoa1211035
82. Colvin L, Gill AW, Slack-Smith L, Stanley FJ, Bower C. Off-label use of ondansetron in pregnancy in Western Australia. *Biomed Res Int*. 2013;2013:909860. doi:10.1155/2013/909860
83. Danielsson B, Wikner BN, Källén B. Use of ondansetron during pregnancy and congenital malformations in the infant. *Reprod Toxicol*. Dec 2014;50:134-7. doi:10.1016/j.reprotox.2014.10.017
84. Özdemirci SA, F Bilge, M Özdemirci, F Yılmaz, S Esinler, D Kahyaoğlu, I. The safety of ondansetron and chlorpromazine for hyperemesis gravidarum in first trimester pregnancy. *Gynecology Obstetrics & Reproductive Medicine*. 2014;20:81-4.
85. Fejzo MS, MacGibbon KW, Mullin PM. Ondansetron in pregnancy and risk of adverse fetal outcomes in the United States. *Reprod Toxicol*. 07 2016;62:87-91. doi:10.1016/j.reprotox.2016.04.027
86. Picot C, Berard A, Grenet G, Ripoche E, Cucherat M, Cottin J. Risk of malformation after ondansetron in pregnancy: An updated systematic review and meta-analysis. *Birth Defects Res*. 08 2020;112(13):996-1013. doi:10.1002/bdr2.1705
87. Dormuth CR WB, Fisher A, et al. Comparison of Pregnancy Outcomes of Patient Treated With Ondansetron vx Alternative Antiemetic Medications in a Multinational, Population-Based Cohort *JAMA Network Open*. 2021;4(4)e215329. doi:10.1001/jamanetworkopen.2021.5329
88. Agency EM. *European Medicines Agency recommends changes to the use of metoclopramide*. EMA/13239/2014 Corr. 1 ed. London: EMA; 2013.
89. Regan LA, Hoffman RS, Nelson LS. Slower infusion of metoclopramide decreases the rate of akathisia. *Am J Emerg Med*. May 2009;27(4):475-80. doi:10.1016/j.ajem.2008.03.044
90. Monograph U. Use of Corticosteroids in Pregnancy. Version 1 ed2016.
91. Sanghvi U, Thankappan KR, Sarma PS, Sali N. Assessing potential risk factors for child malnutrition in rural Kerala, India. *J Trop Pediatr*. 12 2001;47(6):350-5. doi:10.1093/tropej/47.6.350
92. Bergin PS, Harvey P. Wernicke's encephalopathy and central pontine myelinolysis associated with hyperemesis gravidarum. *BMJ*. Aug 1992;305(6852):517-8. doi:10.1136/bmj.305.6852.517
93. Debby A, Golan A, Sadan O, Glezerman M, Shirin H. Clinical utility of esophagogastroduodenoscopy in the management of recurrent and intractable vomiting in pregnancy. *J Reprod Med*. May 2008;53(5):347-51.
94. Gill SK, O'Brien L, Einarson TR, Koren G. The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis. *Am J Gastroenterol*. Jun 2009;104(6):1541-5; quiz 1540, 1546. doi:10.1038/ajg.2009.122
95. Oudman E, Wijnia JW, Oey M, van Dam M, Painter RC, Postma A. Wernicke's encephalopathy in hyperemesis gravidarum: A systematic review. *Eur J Obstet Gynecol Reprod Biol*. May 2019;236:84-93. doi:10.1016/j.ejogrb.2019.03.006
96. Liu S, Rouleau J, Joseph KS, et al. Epidemiology of pregnancy-associated venous thromboembolism: a population-based study in Canada. *J Obstet Gynaecol Can*. Jul 2009;31(7):611-620. doi:10.1016/S1701-2163(16)34240-2
97. Gynaecologists RCoOa. Reducing the Risk of

Venous Thromboembolism during

Pregnancy and the Puerperium. Green-top Guideline No. 37a. . London: RCOG; 2015.

98. Gill SK, Maltepe C, Koren G. The effectiveness of discontinuing iron-containing prenatal multivitamins on reducing the severity of nausea and vomiting of pregnancy. *J Obstet Gynaecol*. Jan 2009;29(1):13-6. doi:10.1080/01443610802628528

99. Fiaschi L, Nelson-Piercy C, Tata LJ. Hospital admission for hyperemesis gravidarum: a nationwide study of occurrence, reoccurrence and risk factors among 8.2 million pregnancies. *Hum Reprod*. Aug 2016;31(8):1675-84. doi:10.1093/humrep/dew128

100. Power Z, Thomson AM, Waterman H. Understanding the stigma of hyperemesis gravidarum: qualitative findings from an action research study. *Birth*. Sep 2010;37(3):237-44. doi:10.1111/j.1523-536X.2010.00411.x

101. Pregnancy Sickness Support BPAS. I could not survive another day. Improving treatment and tackling stigma: lessons from women's experience of abortion for severe pregnancy sickness. . [Par]: PSS; 2015.

102. Dodds L, Fell DB, Joseph KS, Allen VM, Butler B. Outcomes of pregnancies complicated by hyperemesis gravidarum. *Obstet Gynecol*. Feb 2006;107(2 Pt 1):285-92. doi:10.1097/01.AOG.0000195060.22832.cd

103. Fiaschi L, Nelson-Piercy C, Gibson J, Szatkowski L, Tata LJ. Adverse Maternal and Birth Outcomes in Women Admitted to Hospital for Hyperemesis Gravidarum: a Population-Based Cohort Study. *Paediatr Perinat Epidemiol*. Jan 2018;32(1):40-51. doi:10.1111/ppe.12416

104. Petry CJ, Ong KK, Beardsall K, Hughes IA, Acerini CL, Dunger DB. Vomiting in pregnancy is associated with a higher risk of low birth weight: a cohort study. *BMC Pregnancy Childbirth*. May 4 2018;18(1):133. doi:10.1186/s12884-018-1786-1

105. Excellence NIoHaC. Intravenous fluid therapy in adults in hospital. NICE clinical guideline 174. [Manchester]: NICE; 2013.

106. Mazzotta P, Stewart DE, Koren G, Magee LA. Factors associated with elective termination of pregnancy among Canadian and American women with nausea and vomiting of pregnancy. *J Psychosom Obstet Gynaecol*. Mar 2001;22(1):7-12. doi:10.3109/01674820109049946

107. Koren G, Maltepe C. Pre-emptive therapy for severe nausea and vomiting of pregnancy and hyperemesis gravidarum. *J Obstet Gynaecol*. Aug 2004;24(5):530-3. doi:10.1080/01443610410001722581

108. Kramer J, Bowen A, Stewart N, Muhajarine N. Nausea and vomiting of pregnancy: prevalence, severity and relation to psychosocial health. *MCN Am J Matern Child Nurs*. 2013 Jan-Feb 2013;38(1):21-7. doi:10.1097/NMC.0b013e3182748489

109. O'Brien B, Evans M, White-McDonald E. Isolation from "being alive": coping with severe nausea and vomiting of pregnancy. *Nurs Res*. 2002 Sep-Oct 2002;51(5):302-8. doi:10.1097/00006199-200209000-00006

110. Ezberci İ, Güven ES, Ustüner I, Sahin FK, Hocaoğlu C. Disability and psychiatric symptoms in hyperemesis gravidarum patients. *Arch Gynecol Obstet*. Jan 2014;289(1):55-60. doi:10.1007/s00404-013-2934-5

111. Lacasse A, Rey E, Ferreira E, Morin C, Bérard A. Nausea and vomiting of pregnancy: what about quality of life? *BJOG*. Nov 2008;115(12):1484-93. doi:10.1111/j.1471-0528.2008.01891.x

112. Attard CL, Kohli MA, Coleman S, et al. The burden of illness of severe nausea and vomiting of pregnancy in the United States. *Am J Obstet Gynecol*. May 2002;186(5 Suppl Understanding):S220-7. doi:10.1067/mob.2002.122605

113. Munch S. Women's experiences with a pregnancy complication: causal explanations of hyperemesis gravidarum. *Soc Work Health Care*. 2002;36(1):59-76. doi:10.1300/J010v36n01_05

114. Magee LA, Chandra K, Mazzotta P, Stewart D, Koren G, Guyatt GH. Development of a health-related quality of life instrument for nausea and vomiting of pregnancy. *Am J Obstet Gynecol*. May 2002;186(5 Suppl Understanding):S232-8. doi:10.1067/mob.2002.122604

115. Munch S, Korst LM, Hernandez GD, Romero R, Goodwin TM. Health-related quality of life in women with nausea and vomiting of pregnancy: the importance of psychosocial context. *J Perinatol*. Jan 2011;31(1):10-20. doi:10.1038/jp.2010.54

116. Smith C, Crowther C, Beilby J, Dandeaux J. The impact of nausea and vomiting on women: a burden of early pregnancy. *Aust N Z J Obstet Gynaecol*. Nov 2000;40(4):397-401. doi:10.1111/j.1479-828x.2000.tb01167.x

117. O'Brien B, Naber S. Nausea and vomiting during pregnancy: effects on the quality of women's lives. *Birth*. Sep 1992;19(3):138-43. doi:10.1111/j.1523-536x.1992.tb00671.x

118. Wood H, McKellar LV, Lightbody M. Nausea and vomiting in pregnancy: blooming or bloomin' awful? A review of the literature. *Women Birth*. Jun 2013;26(2):100-4. doi:10.1016/j.wombi.2012.10.001

119. Clark S, Hughes B, McDonald SS. The Impact of Nausea and Vomiting of Pregnancy on Quality of Life: Report of a National Consumer Survey and Recommendations for Improving Care. *Obstetrical and Gynecological Survey*. 2013;68(Suppl 1):S1-S10.

120. Bai G, Korfage IJ, Groen EH, Jaddoe VW, Mautner E, Raat H. Associations between Nausea, Vomiting, Fatigue and Health-Related Quality of Life of Women in Early Pregnancy: The Generation R Study. *PLoS One*. 2016;11(11):e0166133. doi:10.1371/journal.pone.0166133

121. Heitmann K, Nordeng H, Havnen GC, Solheimsnes A, Holst L. The burden of nausea and vomiting during pregnancy: severe impacts on quality of life, daily life functioning and willingness to become pregnant again - results from a cross-sectional study. *BMC Pregnancy Childbirth*. 02 2017;17(1):75. doi:10.1186/s12884-017-1249-0

122. Mitchell-Jones N, Gallos I, Farren J, Tobias A, Bottomley C, Bourne T. Psychological morbidity associated with hyperemesis gravidarum: a systematic review and meta-analysis. *BJOG*. Jan 2017;124(1):20-30. doi:10.1111/1471-0528.14180

123. Kjeldgaard HK, Eberhard-Gran M, Benth J, Vikanes Å. Hyperemesis gravidarum and the risk of emotional distress during and after pregnancy. *Arch Womens Ment Health*. 12 2017;20(6):747-756. doi:10.1007/s00737-017-0770-5

124. Tan A, Lowe S, Henry A. Nausea and vomiting of pregnancy: Effects on quality of life and day-to-day function. *Aust N Z J Obstet Gynaecol*. Jun 2018;58(3):278-290. doi:10.1111/ajo.12714

125. Beyazit F, Sahin B. Effect of Nausea and Vomiting on Anxiety and Depression Levels in Early Pregnancy. *Eurasian J Med*. Jun 2018;50(2):111-115. doi:10.5152/eurasianjmed.2018.170320

126. Dean C, Bannigan K, Marsden J. Reviewing the effect of hyperemesis gravidarum on women's lives and mental health. *British Journal of Midwifery*. 2018;26(2):109-19.

127. Chandra K, Magee L, Einarson A, Koren G. Nausea and vomiting in pregnancy: results of a survey that identified interventions used by women to alleviate their symptoms. *Journal of Psychosomatic Obstetrics & Gynecology*. 2003;24(2):71-75.

128. Davis M. Nausea and vomiting of pregnancy: an evidence-based review. *J Perinat Neonatal Nurs*. 2004 Oct-Dec 2004;18(4):312-28. doi:10.1097/00005237-200410000-00002

129. Dørheim SK, Bjorvatn B, Eberhard-Gran M. Sick leave during pregnancy: a longitudinal study of rates and risk factors in a Norwegian population. *BJOG*. Apr 2013;120(5):521-30. doi:10.1111/1471-0528.12035

130. Chou FH, Kuo SH, Wang RH. A longitudinal study of nausea and vomiting, fatigue and perceived stress in, and social support for, pregnant women through the three trimesters. *Kaohsiung J Med Sci*. Jun 2008;24(6):306-14. doi:10.1016/S1607-551X(08)70157-8

131. Soltani H, Taylor GM. Changing attitudes and perceptions to hyperemesis gravidarum. *RCM Midwives*. Dec 2003;6(12):520-4.

132. Yilmaz E, Yilmaz Z, Cakmak B, et al. Nausea and Vomiting in Early Pregnancy of Adolescents: Relationship with Depressive Symptoms. *J Pediatr Adolesc Gynecol*. Feb 2016;29(1):65-8. doi:10.1016/j.jpag.2015.06.010

133. Sahin S, Ozdemir K, Unsal A, Cevrioglu AS, Beydag KD. Evaluation of frequency of nausea and vomiting as well as depression level in pregnant women. *Clin Exp Obstet Gynecol*. 2016 2016;43(5):691-697.

134. Poursharif B, Korst LM, Fejzo MS, MacGibbon KW, Romero R, Goodwin TM. The psychosocial burden of hyperemesis gravidarum. *J Perinatol*. Mar 2008;28(3):176-81. doi:10.1038/sj.jp.7211906

135. Support PS. Accessed 1 March 2016, https://www.pregnancysicknesssupport.org.uk
136. Foundation HEar. Hyperemesis Education and research Foundation. Accessed 1 March 2016, 2016. https://www.hyperemesis.org
137. A S, C S. The impact of online information on health related quality of life amongst women with nausea and vomiting in pregnancy and hyperemesis gravidarum. *MIDRIS Midwifery Digest*. 2014;24:179-85.
138. Tan PC, Zaidi SN, Azmi N, Omar SZ, Khong SY. Depression, anxiety, stress and hyperemesis gravidarum: temporal and case controlled correlates. *PLoS One*. 2014;9(3):e92036. doi:10.1371/journal.pone.0092036
139. Nana M TF, Bevan G, Boulding H, Kavanagh K, Dean C, Williamson C. Termination of wanted pregnancy and suicidal ideation in hyperemesis gravidarum: A mixed methods study. *Obstetric Medicine*. 2021;
140. Locock L, Alexander J, Rozmovits L. Women's responses to nausea and vomiting in pregnancy. *Midwifery*. Jun 2008;24(2):143-52. doi:10.1016/j.midw.2006.12.001
141. Sykes C, Swallow B, Gadsby R, et al. Seeking medical help for Nausea and Vomiting in Pregnancy and Hyperemesis Gravidarum in primary careeeking medical help for nausea andvomiting in pregnancy and hyperemesis. *MIDRIS Midwifery Digest*. 2013;23:321-6.
142. McCarthy FP, Khashan AS, North RA, et al. A prospective cohort study investigating associations between hyperemesis gravidarum and cognitive, behavioural and emotional well-being in pregnancy. *PLoS One*. 2011;6(11):e27678. doi:10.1371/journal.pone.0027678
143. Dean C. Does the historical stigma of hyperemesis gravidarum impact healthcare professional's attitudes and treatment towards women with the condition today? A review of recent literature. *MIDRIS Midwifery Digest*. 2016;26:186–193.
144. O'Hara M. Survey of HCP attitudes responses: form responses.
145. O'Hara M. Women's experience of hyperemesis gravidarum: results of self reported online surveys.
146. Havnen GC, Truong MB, Do MH, Heitmann K, Holst L, Nordeng H. Women's perspectives on the management and consequences of hyperemesis gravidarum - a descriptive interview study. *Scand J Prim Health Care*. Mar 2019;37(1):30-40. doi:10.1080/02813432.2019.1569424
147. O'Hara M. Experience of hyperemesis gravid arum in a subsequent pregnancy. *MIDRIS*. 2017;27:309–318.
148. Kim DR, Connolly KR, Cristancho P, Zappone M, Weinrieb RM. Psychiatric consultation of patients with hyperemesis gravidarum. *Arch Womens Ment Health*. Apr 2009;12(2):61-7. doi:10.1007/s00737-009-0064-7
149. Magtira A, Schoenberg FP, MacGibbon K, Tabsh K, Fejzo MS. Psychiatric factors do not affect recurrence risk of hyperemesis gravidarum. *J Obstet Gynaecol Res*. Apr 2015;41(4):512-6. doi:10.1111/jog.12592
150. McCormack D, Scott-Heyes G, McCusker CG. The impact of hyperemesis gravidarum on maternal mental health and maternal-fetal attachment. *J Psychosom Obstet Gynaecol*. Jun 2011;32(2):79-87. doi:10.3109/0167482X.2011.560691
151. Swallow BL, Lindow SW, Masson EA, Hay DM. Psychological health in early pregnancy: relationship with nausea and vomiting. *J Obstet Gynaecol*. Jan 2004;24(1):28-32. doi:10.1080/01443610310001620251
152. Chou FH, Lin LL, Cooney AT, Walker LO, Riggs MW. Psychosocial factors related to nausea, vomiting, and fatigue in early pregnancy. *J Nurs Scholarsh*. 2003;35(2):119-25. doi:10.1111/j.1547-5069.2003.00119.x
153. Tan PC, Vani S, Lim BK, Omar SZ. Anxiety and depression in hyperemesis gravidarum: prevalence, risk factors and correlation with clinical severity. *Eur J Obstet Gynecol Reprod Biol*. Apr 2010;149(2):153-8. doi:10.1016/j.ejogrb.2009.12.031
154. Bozzo P, Einarson TR, Koren G, Einarson A. Nausea and vomiting of pregnancy (NVP) and depression: cause or effect? *Clin Invest Med*. Aug 2011;34(4):E245. doi:10.25011/cim.v34i4.15367

155. Chou FH, Avant KC, Kuo SH, Fetzer SJ. Relationships between nausea and vomiting, perceived stress, social support, pregnancy planning, and psychosocial adaptation in a sample of mothers: a questionnaire survey. *Int J Nurs Stud*. Aug 2008;45(8):1185-91. doi:10.1016/j.ijnurstu.2007.08.004
156. Fejzo MS, Macgibbon K. Hyperemesis gravidarum: it is time to put an end to the misguided theory of a psychiatric etiology. *Gen Hosp Psychiatry*. 2012 Nov-Dec 2012;34(6):699-700; author reply 700-1. doi:10.1016/j.genhosppsych.2012.06.019
157. Mitchell-Jones N, Lawson K, Bobdiwala S, et al. Association between hyperemesis gravidarum and psychological symptoms, psychosocial outcomes and infant bonding: a two-point prospective case-control multicentre survey study in an inner city setting. *BMJ Open*. 10 2020;10(10):e039715. doi:10.1136/bmjopen-2020-039715
158. Nana M, Tydeman F, Bevan G, et al. Hyperemesis gravidarum is associated with increased rates of termination of pregnancy and suicidal ideation: results from a survey completed by >5000 participants. *Am J Obstet Gynecol*. Mar 2021;doi:10.1016/j.ajog.2021.03.006
159. Aksoy H, Aksoy Ü, Karadağ Ö, et al. Depression levels in patients with hyperemesis gravidarum: a prospective case-control study. *Springerplus*. 2015;4:34. doi:10.1186/s40064-015-0820-2
160. Seng JS, Oakley DJ, Sampselle CM, Killion C, Graham-Bermann S, Liberzon I. Posttraumatic stress disorder and pregnancy complications. *Obstet Gynecol*. Jan 2001;97(1):17-22. doi:10.1016/s0029-7844(00)01097-8
161. Kjeldgaard HK, Vikanes Å, Benth J, Junge C, Garthus-Niegel S, Eberhard-Gran M. The association between the degree of nausea in pregnancy and subsequent posttraumatic stress. *Arch Womens Ment Health*. 08 2019;22(4):493-501. doi:10.1007/s00737-018-0909-z
162. Nicholson M. Women's experiences of the therapeutic value of writing about pregnancy sickness. *Counselling & Psychotherapy Research*. 2017;18(1):26–34.
163. Fairweather DV. Nausea and vomiting in pregnancy. *Am J Obstet Gynecol*. Sep 1968;102(1):135-75. doi:10.1016/0002-9378(68)90445-6
164. Munch S. Chicken or the egg? The biological-psychological controversy surrounding hyperemesis gravidarum. *Soc Sci Med*. Oct 2002;55(7):1267-78. doi:10.1016/s0277-9536(01)00239-8
165. Swallow B. Nausea and vomiting in pregnancy: psychological and social aspects [PhD dissertation]. Lincoln: University of Lincoln; 2009.
166. D'Orazio LM, Meyerowitz BE, Korst LM, Romero R, Goodwin TM. Evidence against a link between hyperemesis gravidarum and personality characteristics from an ethnically diverse sample of pregnant women: a pilot study. *J Womens Health (Larchmt)*. Jan 2011;20(1):137-44. doi:10.1089/jwh.2009.1851
167. Bozzo P, Koren G, Nava-Ocampo AA, Einarson A. The incidence of nausea and vomiting of pregnancy (NVP): a comparison between depressed women treated with antidepressants and non-depressed women. *Clin Invest Med*. Dec 2006;29(6):347-50.
168. Simpson SW, Goodwin TM, Robins SB, et al. Psychological factors and hyperemesis gravidarum. *J Womens Health Gend Based Med*. Jun 2001;10(5):471-7. doi:10.1089/152460901300233948
169. Kara N, Kalem M, Balci H, Kalem Z. Psychiatric Symptoms, Perceived Social Support, Coping Styles, and Dyadic Adjustment in Pregnant Women with Hyperemesis Gravidarum. *Dusunen Adam*. 2016;29(4):307–316.
170. Li L, Zhou X, Xiao S, Gu H, Zhang G. Helicobacter pylori Infection Is Associated with an Increased Risk of Hyperemesis Gravidarum: A Meta-Analysis. *Gastroenterol Res Pract*. 2015;2015:278905. doi:10.1155/2015/278905
171. Loveland Cook CA, Flick LH, Homan SM, Campbell C, McSweeney M, Gallagher ME. Posttraumatic stress disorder in pregnancy: prevalence, risk factors, and treatment. *Obstet Gynecol*. Apr 2004;103(4):710-7. doi:10.1097/01.AOG.0000119222.40241.fb

172. Christodoulou-Smith J, Gold JI, Romero R, et al. Posttraumatic stress symptoms following pregnancy complicated by hyperemesis gravidarum. *J Matern Fetal Neonatal Med*. Nov 2011;24(11):1307-11. doi:10.3109/14767058.2011.582904

173. Jueckstock JK, Kaestner R, Mylonas I. Managing hyperemesis gravidarum: a multimodal challenge. *BMC Med*. Jul 2010;8:46. doi:10.1186/1741-7015-8-46

174. Holmgren C, Aagaard-Tillery KM, Silver RM, Porter TF, Varner M. Hyperemesis in pregnancy: an evaluation of treatment strategies with maternal and neonatal outcomes. *Am J Obstet Gynecol*. Jan 2008;198(1):56.e1-4. doi:10.1016/j.ajog.2007.06.004

175. Peled Y, Melamed N, Hiersch L, Pardo J, Wiznitzer A, Yogev Y. The impact of total parenteral nutrition support on pregnancy outcome in women with hyperemesis gravidarum. *J Matern Fetal Neonatal Med*. Jul 2014;27(11):1146-50. doi:10.3109/14767058.2013.851187

176. Tan PC, Omar SZ. Contemporary approaches to hyperemesis during pregnancy. *Curr Opin Obstet Gynecol*. Apr 2011;23(2):87-93. doi:10.1097/GCO.0b013e328342d208

177. Stokke G, Gjelsvik BL, Flaatten KT, Birkeland E, Flaatten H, Trovik J. Hyperemesis gravidarum, nutritional treatment by nasogastric tube feeding: a 10-year retrospective cohort study. *Acta Obstet Gynecol Scand*. Apr 2015;94(4):359-67. doi:10.1111/aogs.12578

178. Goodwin TM. Hyperemesis gravidarum. *Obstet Gynecol Clin North Am*. Sep 2008;35(3):401-17, viii. doi:10.1016/j.ogc.2008.04.002

179. Vaisman N, Kaidar R, Levin I, Lessing JB. Nasojejunal feeding in hyperemesis gravidarum--a preliminary study. *Clin Nutr*. Feb 2004;23(1):53-7. doi:10.1016/s0261-5614(03)00088-8

180. Serrano P VA, Garcia-Luna PP, et al. Enteral nutrition by percutaneous endoscopic gastrojejunostomy in severe hyperemesis gravidarum: a report of two cases. *Clinical Nutrition*. 1998;(17):135-139.

181. Kruchko D SN, Broy C, Silas D. Percutaneous Endoscopic Jejunostomy Tube Placement for Treatment of Severe Hyperemesis Gravidarum in Pregnancy. *Journal of investigative Medicine High Impact Case Reports*. 2020;(8)2324709620975954. doi:10.1177/2324709620975954

182. Pregnancy Sickness Support BPAS. I could not survive another day. Improving treatment and tackling stigma: lessons from women's experience of abortion for severe pregnancy sickness. . PSS. https://www.pregnancysicknesssupport.org.uk/documents/HGbpasPSSreport_docx.pdf

183. Al-Ozairi E, Waugh JJ, Taylor R. Termination is not the treatment of choice for severe hyperemesis gravidarum: Successful management using prednisolone. *Obstet Med*. Mar 2009;2(1):34-7. doi:10.1258/om.2008.080046

184. Poursharif B, Korst LM, Macgibbon KW, Fejzo MS, Romero R, Goodwin TM. Elective pregnancy termination in a large cohort of women with hyperemesis gravidarum. *Contraception*. Dec 2007;76(6):451-5. doi:10.1016/j.contraception.2007.08.009

185. MacGibbon K FM, Mullin P. Mortality Secondary to Hyperemesis Gravidarum: A Case Report. *Women's Health & Gynecology*. 2015;1

186. Fossum SV, A. V.; Naess, O.; Vos, L.; Grotmol, T.; Halvorsen, S. Hyperemesis gravidarum and long-term mortality: a population-based cohort study. *BJOG : an international journal of obstetrics and gynaecology*. 2017;124(7):1080-1087. doi:https://dx.doi.org/10.1111/1471-0528.14454

187. Tsa iW, Lee C, Cheng S, Zeng Y. Hyperparathyroidism presenting as hyperemesis and acute pancreatitis in pregnancy: A case report. *Medicine (Baltimore)*. Apr 9 2021;100(14)e25451. doi:10.1097/MD.0000000000025451

188. Koren G, Madjunkova S, Maltepe C. The protective effects of nausea and vomiting of pregnancy against adverse fetal outcome—A systematic review. . *Reproductive Toxicology* 2014;47:77-80.

189. Nijsten K, Jansen LAW, Limpens J, et al. Long-term health outcomes of children born to mothers with hyperemesis gravidarum: a systematic review and meta-analysis. *Am J Obstet Gynecol*. Sep 2022;227(3):414-429 e17. doi:10.1016/j.ajog.2022.03.052

190. Maltepe C, Koren G. Preemptive treatment of nausea and vomiting of pregnancy: results of a randomized controlled trial. *Obstet Gynecol Int*. 2013;2013:809787. doi:10.1155/2013/809787

1133 191. Dean CR, Bierma H, Clarke R, et al. A patient-clinician James Lind Alliance partnership to
1134 identify research priorities for hyperemesis gravidarum. *BMJ Open*. 01 2021;11(1):e041254.
1135 doi:10.1136/bmjopen-2020-041254

1136

Appendix I: Explanation of guidelines and evidence levels

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of Recommendation

A At least one meta-analysis, systematic reviews or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

Good Practice Points

✓ Recommended best practice based on the clinical experience of the guideline development group.*

*on the occasion when the guideline development group find there is an important practical point that they wish to emphasise but for which there is not, nor is there likely to be any research evidence. This will typically be where some aspect of treatment is regarded as such sound clinical practice that nobody is likely to question it. These are marked in the guideline, and are indicated by ✓. It must be emphasised that these are NOT an alternative to evidence-based recommendations, and should only be used where there is no alternative means of highlighting the issue.

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)

[footnote]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?_____

[centre text under question]*0 (worst possible) 10 (The best you felt before pregnancy)*

Can you tell me what causes you to feel that

way?_____

Appendix IIb:
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**

Appendix III: Recommended antiemetic therapies and dosages

Recommended antiemetic therapies and dosages

First line

Doxylamine and Pyridoxine (vitamin B6) 20/20mg PO at night, increase to additional 10/10mg 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, IV or PR
Chlorpromazine 10–25 mg 4–6 hourly PO, IV or IM; or 50–100 mg 6–8 hourly PR

Second line

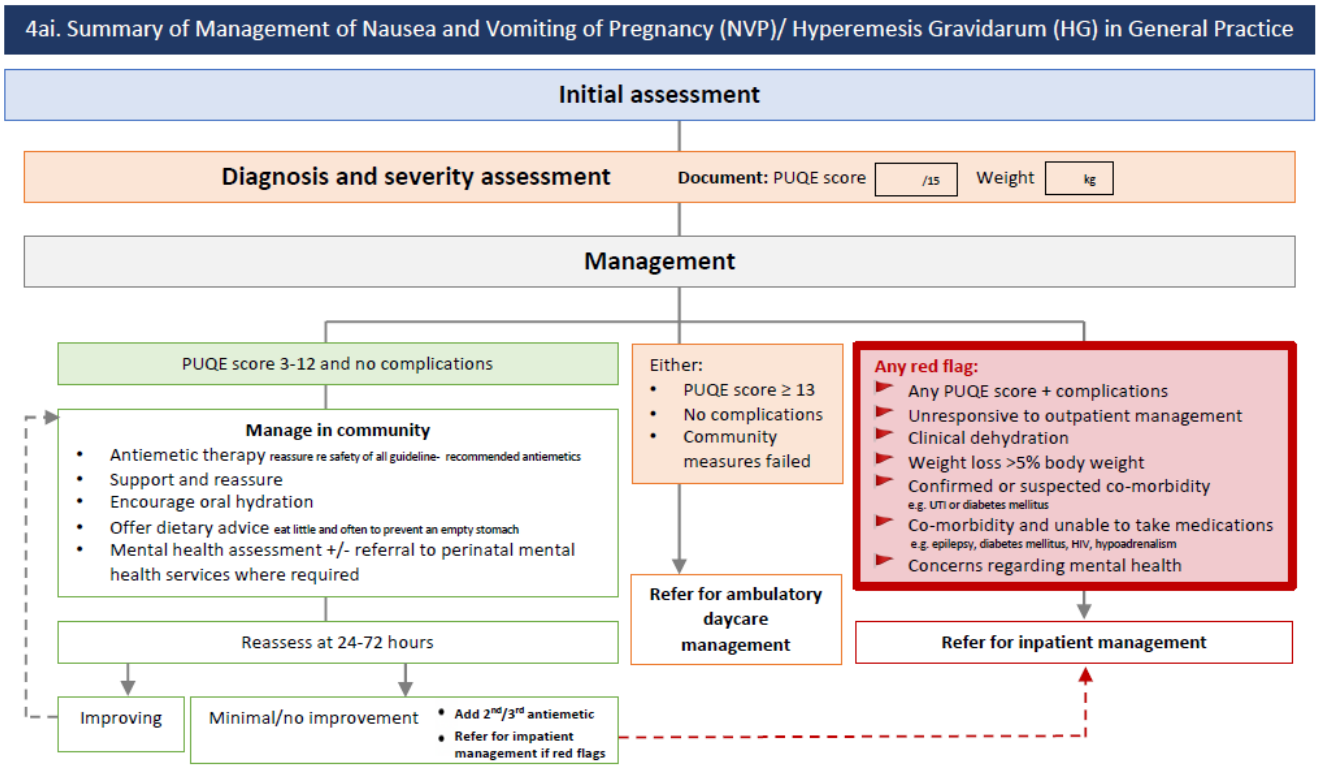
Metoclopramide 5–10 mg 8 hourly PO, IV/IM/SC
Domperidone 10 mg 8 hourly PO; 30–60 mg 8 hourly PR
Ondansetron 4–8 mg 6–8 hourly PO; 8 mg over 15 minutes 12 hourly IV

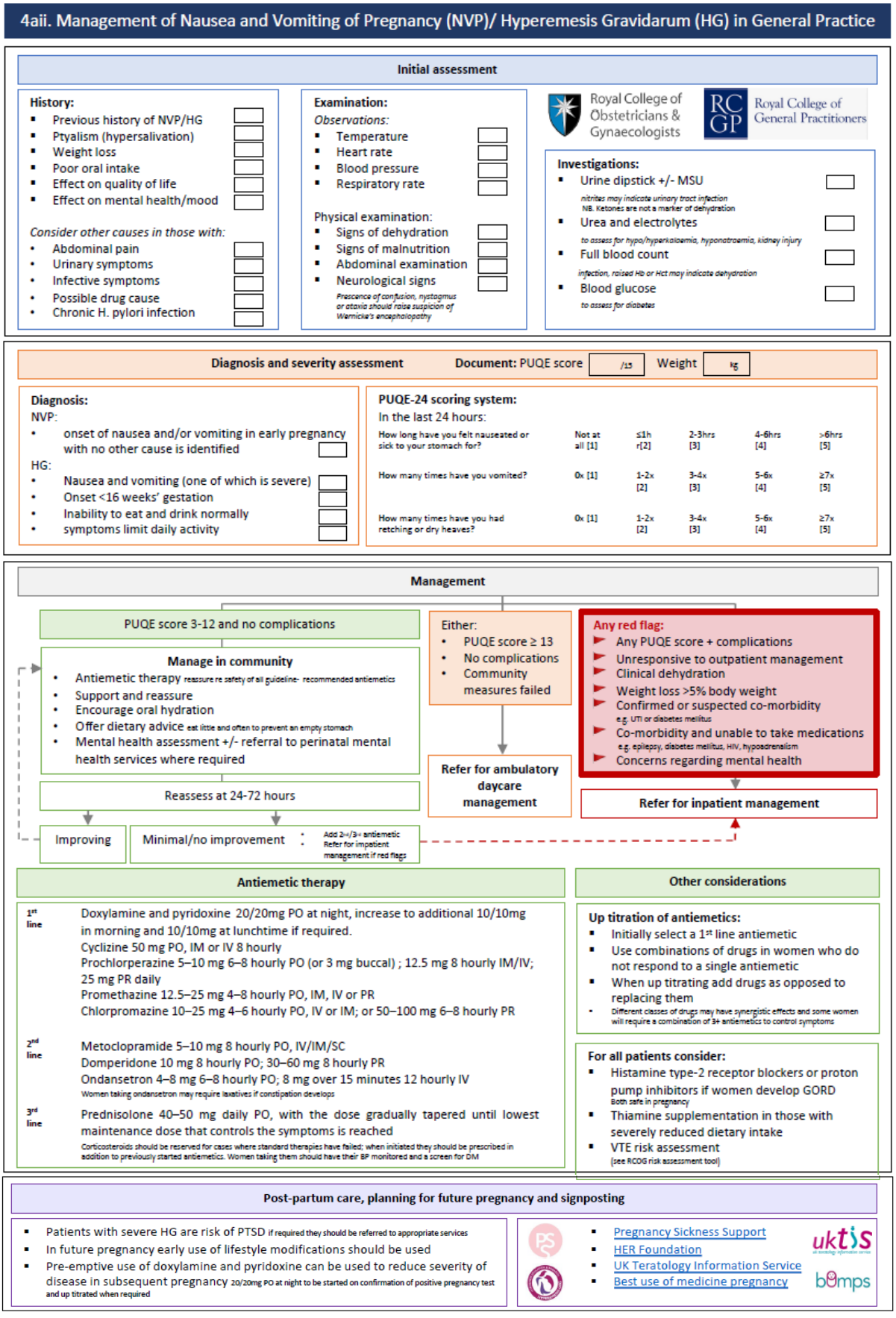
Third line

Hydrocortisone 100 mg twice daily IV and once clinical improvement occurs, convert to prednisolone 40–50 mg daily PO, with the dose gradually tapered until the lowest maintenance dose that controls the symptoms is reached

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

Appendix IV: Treatment algorithms for NVP and HG in primary care (4ai and ii), ambulatory care (4b), emergency department (4c) and inpatient care (4d)





4b. Management of Nausea and Vomiting of Pregnancy (NVP)/ Hyperemesis Gravidarum (HG) in the ambulatory care

Initial assessment

Confirm diagnosis:

NVP:
- onset of nausea and/or vomiting in early pregnancy with no other cause is identified ☐

HG:
- Nausea and vomiting (one of which is severe) ☐
- Onset <16 weeks' gestation ☐
- Inability to eat and drink normally ☐
- symptoms limit daily activity ☐

Consider other causes in those with:
- Abdominal pain ☐
- Urinary symptoms ☐
- Infective symptoms ☐
- Possible drug cause ☐
- Chronic H. pylori infection ☐

Examination:

Observations:
- Temperature ☐
- Heart rate ☐
- Blood pressure ☐
- Respiratory rate ☐

Physical examination:
- Signs of dehydration ☐
- Signs of malnutrition ☐
- Abdominal examination ☐
- Neurological signs ☐
  Prescence of confusion, nystagmus or ataxia should raise suspicion of Wernicke's encephalopathy

Royal College of Obstetricians & Gynaecologists

The Association of Early Pregnancy Units

Investigations:
- Urine dipstick +/- MSU ☐
  nitrites may indicate urinary tract infection
  NB. Ketones are not a marker of dehydration ☐
- Urea and electrolytes
  to assess for hypo/hyperkalaemia, hyponatraemia, kidney injury ☐
- Full blood count
  infection, raised Hb or Hct may indicate dehydration ☐
- Blood glucose *to assess for diabetes* ☐
- Amylase *to assess for pancreatitis* ☐
- ABG *in severe cases to exclude metabolic disturbance*

Assess mental health status: ☐ **if concerns refer to mental health services**

Severity assessment using PUQE-24 scoring system and management

Document: PUQE score ☐ /15

In the last 24 hours:

How long have you felt nauseated or sick to your stomach for?	Not at all [1]	≤1hr[2]	2-3hrs [3]	4-6hrs [4]	>6hrs [5]
How many times have you vomited?	0x [1]	1-2x [2]	3-4x [3]	5-6x [4]	≥7x [5]

Management

Both:
- PUQE score 3-12 and
- No red flags

Discharge to community
- Up titrate antiemetic therapy and reassure regarding safety ☐
- Encourage oral hydration ☐
- Offer dietary advice eat little and often to prevent an empty stomach ☐
- Referral to perinatal mental health services where required ☐

Either:
- PUQE score ≥ 13 and no red flags
- Community measures failed

Send to ambulatory unit if available or treat in emergency department
- Insert venflon and send relevant blood tests ☐
- Prescribe antiemetics IM or IV ☐
- Prescribe IV fluids either: ☐
  - Hartmann's solution 1L over 1 hour
  - 0.9% saline +20mmol Kcl over 1-2 hours
- Thiamine supplementation either: ☐
  - Thiamine 50mg TDS PO
  - Pabrinex I+II (vial of each) IV

Reassess

Any red flags:
- Any PUQE + complications
- Unresponsive to outpatient management
- Clinical dehydration
- Weight loss >5% body weight
- Confirmed or suspected co-morbidity
  e.g. UTI or diabetes mellitus
- Co-morbidity and unable to take medications
  e.g. epilepsy, diabetes mellitus, HIV, hypoadrenalism

Refer for inpatient management

Pregnancy Sickness Support

HER Foundation

UK Teratology Information Service

Best use of medicine pregnancy

For all patients consider:
- Histamine type-2 receptor blockers or proton pump inhibitors if women develop GORD ☐
- Thiamine supplementation in those with severely reduced dietary intake ☐
- VTE risk assessment (see RCOG risk assessment tool) ☐

Antiemetic therapy

1st line	Doxylamine and pyridoxine 20/20mg PO at night, increase to additional 10/10mg 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, IV or PR Chlorpromazine 10–25 mg 4–6 hourly PO, IV or IM; or 50–100 mg 6–8 hourly PR
2nd line	Metoclopramide 5–10 mg 8 hourly PO, IV/IM/SC Domperidone 10 mg 8 hourly PO; 30–60 mg 8 hourly PR Ondansetron 4–8 mg 6–8 hourly PO; 8 mg over 15 minutes 12 hourly IV Women taking ondansetron may require laxatives if constipation develops
3rd line	Prednisolone 40–50 mg daily PO, with the dose gradually tapered until 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 antiemetics. Women taking them should have their BP monitored and a screen for DM

Up titration of antiemetics:
- Initially select a 1st line antiemetic
- Use combinations of drugs in women who do not respond to a single antiemetic
- When up titrating add drugs as opposed to replacing them different classes of drugs may have synergistic effects and some women will require a combination of 3+ antiemetics to control symptoms

4c. Management of Nausea and Vomiting of Pregnancy (NVP)/ Hyperemesis Gravidarum (HG) in the Emergency Department

Initial assessment

Confirm diagnosis:

NVP:
- Onset of nausea and/or vomiting in early pregnancy with no other cause is identified ☐

HG:
- Nausea and vomiting (one of which is severe) ☐
- Onset <16 weeks' gestation ☐
- Inability to eat and drink normally ☐
- symptoms limit daily activity ☐

Consider other causes in those with:
- Abdominal pain ☐
- Urinary symptoms ☐
- Infective symptoms ☐
- Possible drug cause ☐
- Chronic H. pylori infection ☐

Examination:

Observations:
- Temperature ☐
- Heart rate ☐
- Blood pressure ☐
- Respiratory rate ☐

Physical examination:
- Signs of dehydration ☐
- Signs of malnutrition ☐
- Abdominal examination ☐
- Neurological signs ☐
  Prescence of confusion, nystagmus or ataxia should raise suspicion of Wernicke's encephalopathy

Royal College of Obstetricians & Gynaecologists

Royal College of Emergency Medicine

Investigations:
- Urine dipstick +/- MSU ☐
  nitrites may indicate urinary tract infection
  NB. Ketones are not a marker of dehydration ☐
- Urea and electrolytes ☐
  to assess for hypo/hyperkalaemia, hyponatraemia, kidney injury
- Full blood count ☐
  infection, raised Hb or Hct may indicate dehydration ☐
- Blood glucose *to assess for diabetes* ☐
- Amylase *to assess for pancreatitis* ☐
- ABG/VBG *in severe cases to exclude metabolic disturbance*

Assess mental health status: ☐ **if concerns refer to mental health services**

Severity assessment using PUQE-24 scoring system and management

Document: PUQE score /15

In the last 24 hours:

How long have you felt nauseated or sick to your stomach for?	Not at all [1]	≤1hr[2]	2-3hrs [3]	4-6hrs [4]	>6hrs [5]
How many times have you vomited?	0x [1]	1-2x [2]	3-4x [3]	5-6x [4]	≥7x [5]
How many times have you had retching or dry heaves?	0x [1]	1-2x [2]	3-4x [3]	5-6x [4]	≥7x [5]

Management

Both:
- PUQE score 3-12 and
- No red flags

Discharge to community
- Start or up titrate antiemetic therapy *and reassure regarding safety* ☐
- Encourage oral hydration ☐
- Offer dietary advice *eat little and often to prevent an empty stomach* ☐
- Provide contact number for early pregnancy unit ☐
- Referral to perinatal mental health services where required ☐

Either:
- PUQE score ≥ 13 and no red flags
- Community measures failed

Send to ambulatory unit if available or treat in emergency department
- Prescribe antiemetics IM or IV ☐
- Prescribe IV fluids either: ☐
  - Hartmann's solution 1L over 1 hour
  - 0.9% saline +20mmol Kcl over 2 hours
- Thiamine supplementation either: ☐
  - Thiamine 50mg TDS PO
  - Pabrinex I+II (vial of each) IV

Reassess

Any red flag:
- Any PUQE + complications
- Unresponsive to outpatient management
- Clinical dehydration
- Weight loss >5% body weight
  Pre-pregnancy body weight
- Confirmed or suspected co-morbidity
  e.g. UTI or diabetes mellitus
- Co-morbidity and unable to take essential medication
  e.g. epilepsy, diabetes mellitus, HIV, hypoadrenalism

Refer for inpatient management

Pregnancy Sickness Support

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UK Teratology Information Service

Best use of medicine pregnancy

For all patients consider:
- Histamine type-2 receptor blockers or proton pump inhibitors if women develop GORD *(safe in pregnancy)* ☐
- Thiamine supplementation in those with severely reduced dietary intake *to prevent Wernicke's encephalopathy* ☐
- VTE risk assessment *(see RCOG risk assessment tool)* ☐

Antiemetic therapy

1st line	Doxylamine and pyridoxine 20/20mg PO at night, increase to additional 10/10mg 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, IV or PR Chlorpromazine 10–25 mg 4–6 hourly PO, IV or IM; or 50–100 mg 6–8 hourly PR
2nd line	Metoclopramide 5–10 mg 8 hourly PO, IV/IM/SC Domperidone 10 mg 8 hourly PO; 30–60 mg 8 hourly PR Ondansetron 4–8 mg 6–8 hourly PO; 8 mg over 15 minutes 12 hourly IV *Women taking ondansetron may require laxatives if constipation develops*
3rd line	Prednisolone 40–50 mg daily PO, with the dose gradually tapered until 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 antiemetics. Women taking them should have their BP monitored and a screen for DM*

Up titration of antiemetics:
- Initially select a 1st line antiemetic
- Use combinations of drugs in women who do not respond to a single antiemetic
- When up titrating add drugs as opposed to replacing them different classes of drugs may have synergistic effects and some women will require a combination of 3+ antiemetics to control symptoms

4d. Management of Nausea and Vomiting of Pregnancy (NVP)/ Hyperemesis Gravidarum (HG) as an In-patient

Royal College of Obstetricians & Gynaecologists

Initial assessment

History:
- Previous history of NVP/HG ☐
- Ptyalism (hypersalivation) ☐
- Weight loss ☐
- Poor oral intake ☐
- Effect on quality of life ☐
- Effect on mental health/mood ☐

Consider other causes in those with:
- Abdominal pain ☐
- Urinary symptoms ☐
- Infective symptoms ☐
- Possible drug cause ☐
- Chronic H. pylori infection ☐

Examination:

Observations:
- Temperature ☐
- Heart rate ☐
- Blood pressure ☐
- Respiratory rate ☐

Physical examination:
- Signs of dehydration ☐
- Signs of malnutrition ☐
- Abdominal examination ☐
- Neurological signs ☐

Prescence of confusion, nystagmus or ataxia should raise suspicion of Wernicke's encephalopathy

Investigations:
- Urine dipstick +/- MSU *nitrites may indicate urinary tract infection* ☐
  NB. Ketones are not a marker of dehydration ☐
- Urea and electrolytes *to assess for hypo/hyperkalaemia, hyponatraemia, kidney injury* ☐
- Full blood count *infection, raised Hb or Hct may indicate dehydration* ☐
- Blood glucose *to assess for diabetes* ☐

In refractory cases:
- Thyroid function tests ☐
- Liver function tests to exclude liver disease ☐
- Bone profile to monitor calcium and phosphate ☐
- Amylase to exclude pancreatitis ☐
- ABG/VBG to exclude metabolic disturbance ☐

Diagnosis and severity assessment

Document: PUQE score /15 Weight kg

Diagnosis:

NVP:
- onset of nausea and/or vomiting in early pregnancy with no other cause is identified ☐

HG:
- Nausea and vomiting (one of which is severe) ☐
- Onset <16 weeks' gestation ☐
- Inability to eat and drink normally ☐
- symptoms limit daily activity ☐

PUQE-24 scoring system:

In the last 24 hours:

How long have you felt nauseated or sick to your stomach for?	Not at all [1]	≤1h r[2]	2-3hrs [3]	4-6hrs [4]	>6hrs [5]
How many times have you vomited?	0x [1]	1-2x [2]	3-4x [3]	5-6x [4]	≥7x [5]
How many times have you had retching or dry heaves?	0x [1]	1-2x [2]	3-4x [3]	5-6x [4]	≥7x [5]

Admission criteria and management

Admit if any of the following:
- Any PUQE score plus:
- Unresponsive to outpatient management
- Clinical dehydration
- Weight loss >5% body weight
- Confirmed or suspected co-morbidity e.g. UTI or diabetes mellitus
- Co-morbidity and unable to take medications e.g. epilepsy, diabetes mellitus, HIV, hypoadrenalism

Inpatient management:
- Prescribe antiemetics IM or IV ☐
- Prescribe IV fluids: ☐
  - 0.9% saline with potassium chlorine guided by **daily monitoring of electrolytes** ☐
- Prescribe thiamine supplementation either: ☐
  - Thiamine 50mg TDS PO or Pabrinex I+II (vial of each) IV
- Prescribe venous thromboprophylaxis ☐
- Prescribe histamine type-2 receptor blockers or proton pump inhibitors in women with GORD ☐
- Undertake a mental health assessment +/- refer to mental health services ☐
- Schedule ultrasound scan to confirm viability, gestational age and to assess for trophoblastic disease or multiple pregnancy ☐
- Consider enteral or parenteral nutrition in cases where all other medical therapies have failed to sufficiently manage symptoms ☐

Antiemetic therapy

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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
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2nd line Metoclopramide 5–10 mg 8 hourly PO, IV/IM/SC
Domperidone 10 mg 8 hourly PO; 30–60 mg 8 hourly PR
Ondansetron 4–8 mg 6–8 hourly PO; 8 mg over 15 minutes 12 hourly IV
Women taking ondansetron may require laxatives if constipation develops

3rd line Prednisolone 40–50 mg daily PO, with the dose gradually tapered until 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 antiemetics. Women taking them should have their BP monitored and a screen for DM

On discharge

- Up titrate antiemetic therapy and reassure regarding safety ☐
- Encourage oral hydration ☐
- Offer dietary advice eat little and often to prevent an empty stomach ☐
- Provide contact number for early pregnancy unit ☐

Up titration of antiemetics

- Initially select a 1st line antiemetic
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Post-partum care, planning for future pregnancy and signposting

- Patients with severe HG are risk of PTSD if required they should be referred to appropriate services
- In future pregnancy early use of lifestyle modifications should be used
- Pre-emptive use of doxylamine and pyridoxine can be used to reduce severity of disease in subsequent pregnancy 20/20mg PO at night to be started on confirmation of positive pregnancy test and up titrated when required

- Pregnancy Sickness Support
- HER Foundation
- UK Teratology Information Service
- Best use of medicine pregnancy

This guideline was produced on behalf of the Royal College of Obstetricians and Gynaecologists by: **Professor C Nelson-Piercy FRCP FRCOG, London; Dr C Dean PhD, Patient Representative (Pregnancy Sickness Support); Dr M Shehmar FRCOG, Birmingham; Dr R Gadsby, Coventry; Ms M O'Hara; Dr G Holder MRCP, Birmingham; Dr K Hodson Newcastle Upon Tyne.**

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The final version is the responsibility of the Guidelines Committee of the RCOG.

The guideline will be considered for update 3 years after publication, with an intermediate assessment of the need to update 2 years after publication.

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