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Day A, Hollamby S, Girling J. Early recognition of hyperemesis gravidarum can prevent complications.
Practitioner July/August 2021;265(1850):21-25

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Medical Publishing Ltd

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SPECIAL REPORT

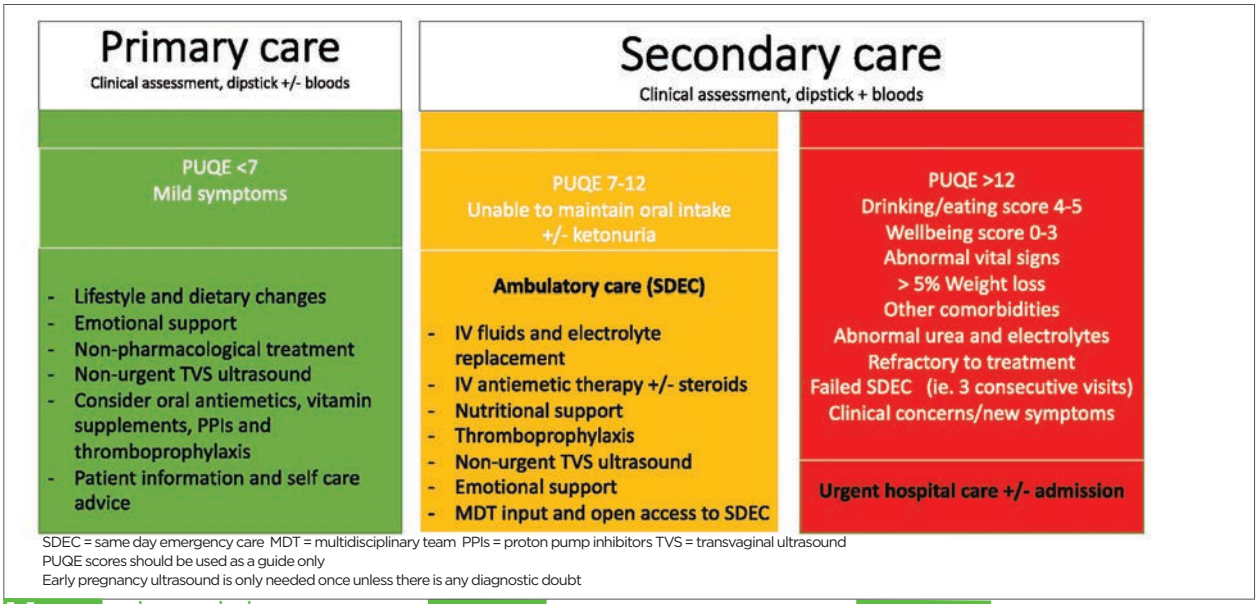
Early recognition of hyperemesis gravidarum can prevent complications

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SDEC = same day emergency care MDT = multidisciplinary team PPIs = proton pump inhibitors TVS = transvaginal ultrasound
PUQE scores should be used as a guide only
Early pregnancy ultrasound is only needed once unless there is any diagnostic doubt

FIGURE 1 Recommended place of care and action plan for women with nausea and vomiting in pregnancy and hyperemesis gravidarum

How should women be assessed?

NAUSEA AND VOMITING IN PREGNANCY IS VERY COMMON AND AFFECTS UP TO 80% OF WOMEN. It is usually mild and resolves during the first half of pregnancy. However, in a small proportion of women (0.3-3.6%) symptoms are so severe that they lead to dehydration, electrolyte imbalance and weight loss.[1] This condition is known as hyperemesis gravidarum. As well as affecting the woman's physical and mental health it can also cause fetal morbidity.

Traditionally, women with severe symptoms were referred to the emergency department and often required admission to hospital for parenteral treatment. As part of the Urgent and Emergency Care transformation programme within the NHS Long Term Plan, most women with hyperemesis gravidarum can now bypass the emergency department and receive immediate treatment in an ambulatory care setting without the need to stay in hospital overnight.

Early recognition in primary care and appropriate escalation to secondary care can prevent complications and improve quality of life.

What are the potential complications?

The aetiology and pathogenesis of hyperemesis gravidarum remain unknown. However, it is well recognised that the following factors and medical disorders are associated with the condition:

- A history of hyperemesis gravidarum in a previous pregnancy. This is the strongest independent risk factor with a recurrence rate of 26%[2]
- Increased pregnancy hormone levels present in a multiple pregnancy or molar pregnancy[3]
- Preexisting medical conditions such as diabetes, hyperthyroidism, gastrointestinal disorders (specifically being seropositive for *Helicobacter pylori*) and psychiatric illness[3,6]

Young maternal age, Asian or Black ethnicity, nulliparity and carrying a female fetus may also be associated with an increased likelihood of hyperemesis gravidarum.[2,4,5]

ASSESSMENT

Most women usually complain of nausea, inability to swallow saliva, gagging, retching, dry heaving, vomiting, and odour and/or food aversion. These symptoms typically start between the fourth and seventh weeks of gestation, peak around the ninth week and resolve by the 20th week in 90% of women.

Which women should be referred?

Hyperemesis gravidarum is a diagnosis of exclusion. If the onset of symptoms occurs after ten weeks' gestation, the symptoms are unremitting or the presentation is atypical with or without other symptoms, a different clinical condition needs to be considered. Table 1, below, outlines the most common differential diagnoses. »

Table 1

Differential diagnoses to consider when assessing women with nausea and/or vomiting in pregnancy

- Peptic ulcers
- Cholecystitis
- Gastroenteritis
- Hepatitis
- Pancreatitis
- Appendicitis
- Genitourinary conditions
- Metabolic conditions
- Neurological or ENT conditions
- Hyperthyroidism
- Drug-induced

A full history, examination and targeted investigations are essential to exclude other diagnoses and also to establish severity of hyperemesis gravidarum. It is always important to:

- **Enquire** about the onset, duration and frequency of symptoms, dehydration symptoms (urine volume and colour) as well as response to any antiemetic treatment if used.
- **Exclude** other causes, especially if women present with vaginal bleeding, symptoms of systemic infection, severe abdominal pain, haematemesis, urinary or bowel symptoms, late onset of vomiting or significant headache or confusion.
- **Assess** the woman for any coexisting conditions in which the efficacy of oral medications can be reduced (i.e. epilepsy) or where dehydration could cause complications (i.e. sickle cell disease, diabetes).
- **Measure** vital signs (consider using maternity specific warning scores) including lying and standing blood pressure.
- **Look** for signs of significant dehydration and/or muscle wasting, sepsis, hypokalaemia (muscle weakness), hypocalcaemia, thyrotoxicosis or abdominal pathology. Perform a symptom guided examination if required (i.e. neurological examination if headache is present).
- **Classify** the severity and quantify the ability to tolerate food/fluids using objective and validated measures (see table 2 and table 3, below).
- **Evaluate** mental health status and the effects on quality of life. This can be done using the Edinburgh Postnatal Depression Scale.[7]
- **Monitor** weight at initial presentation and then weekly and escalate care if weight loss > 5% when compared with prepregnancy weight.
- **Test** the urine, for evidence of infection (± MSU) and ketonuria. The presence of ketones does not always correlate with severity of symptoms and more commonly reflects a state of starvation rather than dehydration, and therefore should not be used as a sole marker of severity of symptoms.[8,9]
- **Calculate** venous thromboembolism (VTE) risk using the maternity VTE assessment tool (note hyperemesis already scores 3 points) and prescribe antiembolism stockings or low molecular weight heparin as indicated.[10]
- **Organise** an ultrasound in the early pregnancy unit to exclude multiple pregnancy and trophoblastic disease and confirm viability.
- **Prescribe** antiemetics (see details on page 23).
- **Consider** the need for outpatient parenteral treatment and/or hospitalisation (see figure 1, p21).
- **Signpost** to self-help resources and support groups (see Useful information box, p25)
- **Monitor** progress and arrange follow-up to prevent hospital admission and complications.

In primary care, laboratory investigations are generally not required and are usually reserved for cases where

Table 2

The 24-hour Pregnancy-Unique Quantification of Emesis (PUQE-24) score that can be used to classify severity[19]

Question	Points (in brackets)				
PUQE score Q1: In the past 24 hours for how long have you felt nauseated?	Not at all (1)	1 hour or less (2)	2-3 hours (3)	4-6 hours (4)	More than 6 hours (5)
PUQE score Q2: In the past 24 hours how many times have you vomited?	None (1)	1-2 (2)	3-4 (3)	5-6 (4)	7 or more times (5)
PUQE score Q3: In the past 24 hours, how many times have you had retching or dry heaves without bringing anything up?	None (1)	1-2 (2)	3-4 (3)	5-6 (4)	7 or more (5)
Severity according to PUQE-24 score	**Mild <7**	**Moderate 7-12**	**Severe 13-15**		

Table 3

Drinking, eating and wellbeing scores that can be used in conjunction with PUQE-24

Question	Points (in brackets)				
Drinking score: In the past 24 hours have you been drinking?	Normally (1)	Nearly normally (2)	Less than normal (3)	Virtually nothing (4)	Nothing (5)
Eating score: In the past 24 hours have you been eating?	Normally (1)	Nearly normally (2)	Less than normal (3)	Virtually nothing (4)	Nothing (5)
Wellbeing score: How would you rate your overall sense of wellbeing over the past 24 hours on a scale of 0-10?	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 (0 = awful 10 = wonderful)				

intravenous hydration is needed. However, if an alternative diagnosis is considered these may be indicated.

POTENTIAL COMPLICATIONS

Persistent vomiting can cause serious complications, both for the woman and the baby,[11] see table 4, right.

REFERRAL

Figure 1, p21, outlines the recommended criteria and place of treatment for women with nausea and vomiting in pregnancy and hyperemesis gravidarum. Urgent referral to secondary care should be considered for those women with:

- Persistent severe symptoms despite oral antiemetic treatment (with or without ketonuria), PUQE score > 7
- Weight loss > 5% of prepregnancy weight
- Medical comorbidities needing oral treatment (such as disease modifying drugs in rheumatic or inflammatory bowel disorders, blood pressure control, antibiotics, antiepilepsy drugs) and/or any clinical concerns needing specialist input.

Hospital assessment and treatment is currently provided in two settings: ambulatory care, i.e. at an ambulatory emergency care unit, where women receive prompt intravenous replacement treatment and usually can be discharged after 2-4 hours with open access to reattend as needed, or the emergency department (usually out of hours), where women may need brief admission to an observation unit to receive similar treatment. Both settings have provision for multidisciplinary team (MDT) care (pharmacists, endocrinologists, dietitians, medical and surgical specialists and mental health professionals) with the option of relocation for inpatient care if indicated, a typical length of stay is 2-3 days.

Nausea and vomiting in pregnancy or hyperemesis gravidarum has a substantial emotional impact and can significantly affect a woman's ability to carry out daily tasks. Signposting to support groups, self-help resources or a referral to the mental health team should be considered.

A non-urgent early pregnancy unit referral should be made for all women with hyperemesis gravidarum to rule out a molar or multiple pregnancy and confirm viability.

MANAGEMENT

Most women with mild nausea and vomiting in pregnancy should be advised to avoid foods, odours and activities that exacerbate symptoms, discontinue iron supplements, drink adequate amounts of fluids, eat small meals frequently and snack on carbohydrate-rich foods.[12,13]

Pharmacological treatment and psychological support (psychotherapy and possible involvement of the mental health team) may need to be considered in certain patients.

Choosing the best antiemetic drug presents challenges as there is a lack of evidence from controlled trials and a concern about potential teratogenesis in the first trimester.[14] Regimens recommended are usually guided by the approach for treatment of nausea and vomiting secondary to chemotherapy or postoperative care with consideration of safety data in pregnancy and the side effect profile.

Women should be given the necessary information to make an informed decision, weighing the potential harm from pharmacological interventions against the harm of the complications resulting from dehydration, weight loss, nutritional deficiencies, metabolic imbalance, and the potential impact on mental health.

Figure 2, p24, reflects the Royal College of Obstetricians and Gynaecologists' (RCOG) advice illustrated in a stepwise approach. Previous efficacy, adverse reactions and route of administration should be considered in the decision making. If a woman does not respond to a single antiemetic, an incremental approach adding a second agent that has a different mode of action is advocated. Prescribing 'as needed' may be required together with appropriate counselling.

The RCOG recommends using antihistamines (cyclizine, promethazine) and phenothiazines (prochlorperazine and chlorpromazine) as first-line treatment. These agents are thought to be effective, have few and mild side effects, and are not known to be associated with any fetal malformations. A delayed release tablet containing doxylamine succinate (an antihistamine) and pyridoxine hydrochloride (vitamin B6) was licensed in the UK in 2018 for use in pregnancy and has been recommended in a NICE evidence summary document published in 2019.[15] It is recommended only after conservative measures have failed.

Second-line medications include the dopamine antagonists (metoclopramide and domperidone) and a serotonin 5-HT3 antagonist (ondansetron). The safety profile of metoclopramide is well established[16] but the risk of short-term extrapyramidal disorders and tardive dyskinesia limits its use to a maximum dose of 30 mg in 24 hours and a maximum recommended duration of treatment of five days.

Ondansetron is very commonly used and usually well tolerated. However, an American observational study[17] »

Table 4

Maternal and fetal complications secondary to hyperemesis gravidarum

Maternal complications

Electrolyte imbalance

- Hyponatraemia: (lethargy, headache, confusion and seizures). Quick and exaggerated correction of hyponatraemia can lead to central pontine myelinolysis[6]
- Hypokalaemia (muscle weakness and cardiac arrhythmias). Measure potassium and do an ECG (inverted T wave, ST segment depression and prominent U wave). Measure magnesium levels to rule out deficiency as a contributing factor for hypokalaemia
- Hypochloraemia
- Hypercalcaemia or hypocalcaemia (Chvostek's or Trousseau's sign)

Nutritional deficiencies

- Vitamin B1 (thiamine) deficiency can lead to Wernicke's encephalopathy. It is important to note that dextrose-containing solutions can precipitate Wernicke's encephalopathy in thiamine-deficient states
- Vitamin B12 (cobalamin) and vitamin B6 (pyridoxine) deficiency can cause anaemia and peripheral neuropathies
- Folic acid

Metabolic disturbances

- Metabolic hypochloraemic alkalosis
- Transient biochemical thyrotoxicosis. Resolves as the hyperemesis gravidarum improves and treatment with antithyroid drugs is not usually indicated.[1,3] Present in up to 60% of women with hyperemesis gravidarum[20]
- Acute kidney injury
- Liver function tests may be abnormal in up to 40% of women with hyperemesis gravidarum, mostly transaminitis

Gastrointestinal complications

Oesophageal reflux disease, oesophagitis or gastritis, Mallory-Weiss tear of the oesophagus

Other

Depression,[21,22] anxiety and thromboembolism

Fetal complications[23]

It is suggested that the increased risk of fetal complications is probably due to the low pregnancy weight gain (< 7 kg during the pregnancy) and nutritional deficiencies. Complications include:

- Fetal growth restriction
- Prematurity
- Low birthweight
- Low 5 min Apgar scores
- Anomalies of the central nervous system and skeletal malformations

key points

SELECTED BY

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Nausea and vomiting in pregnancy is very common and affects up to 80% of women. It is usually mild and resolves during the first half of pregnancy. However, in a small proportion of women (0.3–3.6%), symptoms are so severe that they lead to dehydration, electrolyte imbalance and weight loss. This is known as hyperemesis gravidarum. A history of hyperemesis gravidarum in a previous pregnancy is the strongest independent risk factor with a recurrence rate of 26%. Increased pregnancy hormone levels caused by a multiple or molar pregnancy and preexisting medical conditions such as diabetes, hyperthyroidism, gastrointestinal disorders (specifically being seropositive for *H. pylori*) and psychiatric illness also increase risk.

Symptoms typically start between the 4th and 7th weeks of gestation, peak around the 9th week and resolve by the 20th week. If the onset of symptoms occurs after 10 weeks' gestation, the symptoms are unremitting or the presentation is atypical, the possibility of a different clinical condition needs to be considered. An alternative diagnosis may also be suggested by vaginal bleeding, symptoms of systemic infection, severe abdominal pain, haematemesis, urinary or bowel symptoms, significant headache or confusion.

It is important to enquire about the onset, duration and frequency of nausea and vomiting, symptoms of dehydration (e.g. oliguria, dark urine), and the response to antiemetic treatment if used. Check for signs of significant dehydration and/or muscle wasting, sepsis, hypokalaemia (muscle weakness), hypocalcaemia, thyrotoxicosis and abdominal pathology. Monitor weight weekly, test the urine for evidence of infection, calculate VTE risk and organise an ultrasound in the early pregnancy unit.

Urgent referral to secondary care, for intravenous fluids, electrolyte and vitamin replacement, should be considered for those women with: persistent severe symptoms despite oral antiemetic treatment; a PUQE score >7; weight loss > 5% of the prepregnancy weight; medical comorbidities requiring oral treatment and/or any clinical concerns needing specialist input. Hyperemesis scores 3 points on the maternity VTE assessment tool, so any further risk factor is an indication to consider thromboprophylaxis.

Most women with mild nausea and vomiting should be managed with lifestyle and dietary modifications. If these are ineffective and symptoms are persistent, antiemetic treatment should be considered. The RCOG recommends using antihistamines (cyclizine, promethazine) or phenothiazines (prochlorperazine, chlorpromazine) first line. Second-line medications include dopamine antagonists (metoclopramide and domperidone) and ondansetron. If polytherapy with second-line agents is ineffective and symptoms are severe, steroids can be considered. Women who have persistent symptoms into the second trimester of pregnancy should have consultant-led antenatal care and serial fetal growth ultrasound.

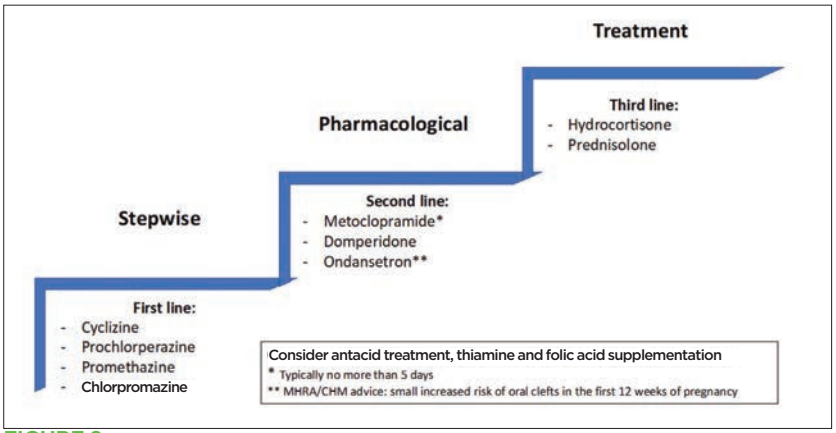


FIGURE 2
Stepwise pharmacological treatment of women with nausea and vomiting in pregnancy and hyperemesis gravidarum (adapted from the RCOG guideline)[1]

reported in 2018 that its use was associated with an additional 3 cases of oral clefts per 10,000 births (14 cases vs 11 per 10,000 births in the unexposed population). The European Medicines Agency Pharmacovigilance Risk Assessment Committee then responded by banning ondansetron in the first trimester of pregnancy. However, the UK Teratology Information Service in collaboration with the European Network of Teratology Information Service reviewed all available evidence and issued a joint statement in September 2019 advocating that ondansetron can be used (with adequate counselling) as a second-line agent for the treatment of nausea and vomiting in pregnancy (as currently recommended by the RCOG Green-top Guideline).[1]

If polytherapy with second-line agents is not effective and symptoms are severe, steroids can be considered, usually prednisolone or hydrocortisone which do not cross the placenta. However, yet again, evidence for efficacy is weak. The side effects include hyperglycaemia and hypertension, and steroids are only recommended when other treatment combinations have been exhausted.[18]

Hyperemesis gravidarum is a recognised risk factor for VTE as dehydration and reduced mobility aggravate the prothrombotic risk already imposed by pregnancy.[10] Any further risk factor increases the threat considerably which in early pregnancy includes any of the following: age ≥ 35 years, BMI ≥ 30, smoking, parity ≥ 3, gross varicose veins, personal or family history of VTE, thrombophilia or medical comorbidity, multiple pregnancy, conception by assisted reproductive technology, ovarian hyperstimulation syndrome, infection, hospitalisation and reduced mobility.

All women with hyperemesis gravidarum should have a documented risk assessment which should be repeated in any change of circumstances, such as an admission. Once hyperemesis resolves the risk should be reassessed and thromboprophylaxis stopped if appropriate.

FOLLOW-UP

Priority appointments should be given to women suffering from nausea and vomiting in pregnancy and hyperemesis gravidarum as they can deteriorate quickly if treatment is not started promptly. This should include patient information leaflets, advice on tracking food, fluid and medication intake at home, the option of providing a fit note and clear guidance on how to stop medication using a pragmatic approach is vital.

Women who have persistent symptoms into the second trimester of pregnancy should have consultant-led antenatal care and serial fetal growth ultrasound.

CONCLUSION

Assessment of women with nausea and vomiting in pregnancy and hyperemesis gravidarum should be holistic, recognising that no one measure can reliably indicate severity or guide management.

Early intervention with a stepwise approach allowing patients to make an informed decision is essential to avoid maternal and fetal complications.

Women with severe symptoms should have a prompt and appropriate referral (ideally before 5pm) for same day emergency care which

expedites treatment and allows patients to self-refer for ongoing treatment. Primary care has a vital role including supporting emotional wellbeing.

Competing interests: None

Acknowledgements
We would like to thank our colleagues in ambulatory emergency care, obstetrics and gynaecology, and the early pregnancy unit at Chelsea and Westminster Hospital NHS Foundation Trust for their hard work in developing the hyperemesis gravidarum ambulatory emergency care pathway.

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Useful information

For healthcare professionals
Advice on medicines in pregnancy
UK Teratology Information Service (UKTIS)
UKTIS helpline: 0344 892 0909
Mon-Fri 9am to 5pm
https://www.medicinesinpregnancy.org/Medicine--pregnancy/NV/

MHRA drug safety advice
www.gov.uk/drug-safety-update/ondansetron-small-increased-risk-of-oral-clefts-following-use-in-the-first-12-weeks-of-pregnancy

NICE Clinical knowledge summaries
Nausea and vomiting in pregnancy
https://cks.nice.org.uk/topics/nausea-vomiting-in-pregnancy/

For patients
Pregnancy Sickness Support
www.pregnancysicknesssupport.org.uk

RCOG patient information leaflets
www.rcog.org.uk/en/patients/patient-leaflets/pregnancy-sickness

Chelsea and Westminster NHS Foundation Trust
Hyperemesis treatment in AEC: patient information video
www.chelwest.nhs.uk/services/medicine/ambulatory-care

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