

HYPEREMESIS GRAVIDARUM

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Nausea and vomiting in pregnancy

- Nausea and vomiting in pregnancy (NVP) affects up to 80% of pregnant women and is one of the most common indications for hospital admission among pregnant women, with typical stays of between 3 and 4 days
- NVP is defined as the symptom of nausea and/or vomiting during early pregnancy where there are no other causes
- It typically starts between the 4-7th weeks of pregnancy, peaks around 9th week, and resolves by the 20th week in 90% of women.

Rule out other causes if first presentation is after 10 completed weeks of pregnancy

HYPEREMESIS GRAVIDARUM

hyperemesis gravidarum can be **defined** as intractable vomiting (severe) associated with loss of more than 5% of pre pregnancy weight, dehydration, electrolyte disturbances, or need for hospital admission.

ATEIOLOGY

- The aetiological theories for NVP and HG range from the **fetoprotective** and **genetic** to the **biochemical, immunological** and **biosocial**.

They are primarily thought to be associated with **rising** levels of **beta human chorionic gonadotrophin (hCG) hormone, progesterone, estrogen.**

Risk factors and associations

- First pregnancy
- Multiple pregnancy
- History of severe nausea and vomiting in previous pregnancies
- motion sickness, or nausea with oral contraceptive use
- Gestational Trophoblastic disease (GTD), including molar pregnancy
- History of migraines
- History of first degree relative with NVP
- Obesity
- Stress

The condition spontaneously resolves in the vast majority of patients and complications are rare.

Complications

- **Electrolyte imbalance:** NVP and HG are associated with hyponatraemia, hypokalaemia, low serum urea, raised haematocrit and ketonuria with a metabolic hypochloraemic alkalosis. If severe, a metabolic acidaemia may develop
- **Abnormal LFTs:** Liver function tests are abnormal in up to 40% of women with HG, with the most likely abnormality being a rise in transaminases. Bilirubin levels can be slightly raised but without jaundice, and amylase levels can be mildly raised too. *These abnormalities improve as the HG resolves*

The LFT abnormalities are mild and inconsequential with regard to the outcome. No specific intervention is required; however, atypical patterns may necessitate other investigations to rule out another underlying disease.

- **Abnormal thyroid function test** : In two-thirds of patients 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 inappropriate

- **Acute kidney injury (AKI)**:(Volume depletion) typically due to severe vomiting ,

(hyperemesis gravidarum), is a common cause of prerenal AKI early in pregnancy (<20 weeks).

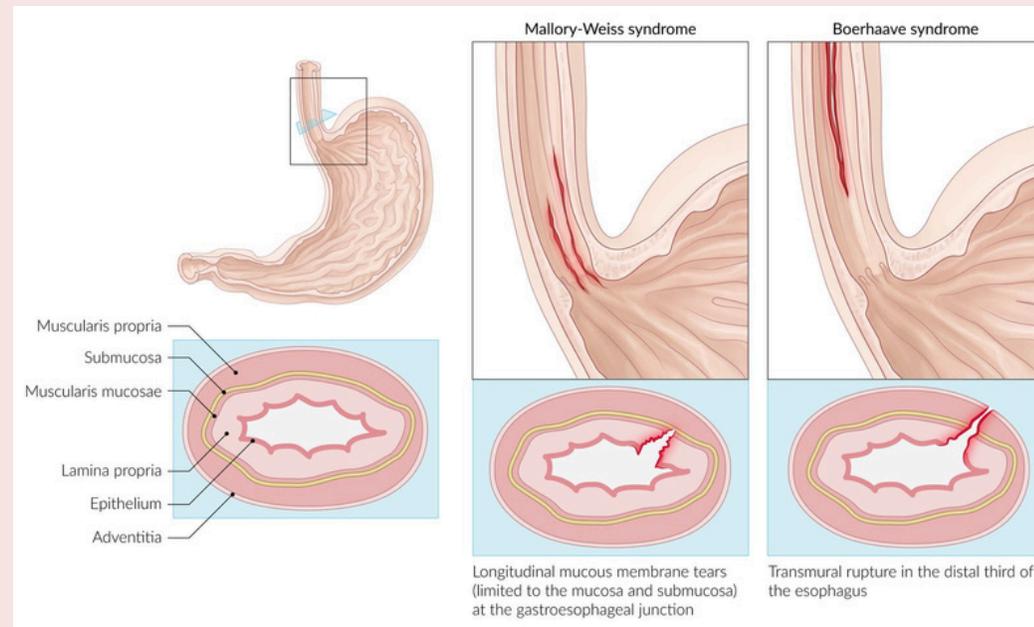
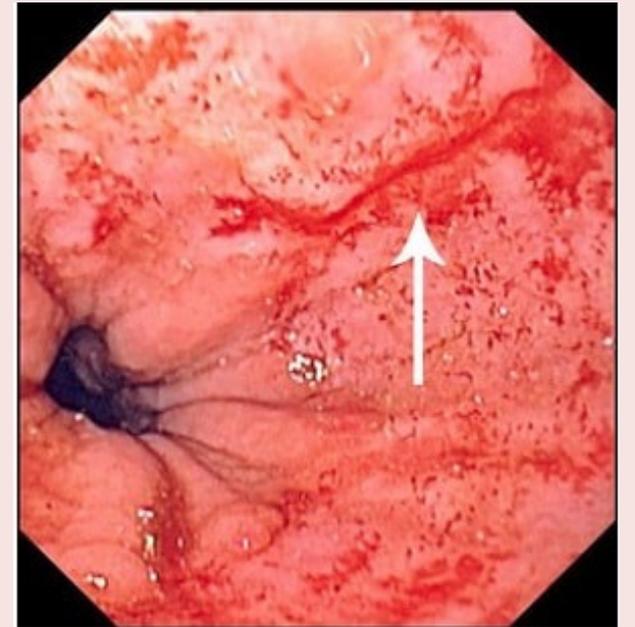
- **Wernicke's encephalopathy**

Wernicke's encephalopathy due to vitamin B1 deficiency classically presents with (thiamine) 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

- Depression and poor psychological health were found to be associated with NVP and HG in numerous studies,
.but resulted from the disease and were not the cause of HG or NVP

A prospective case-control study of 32 women compared with 41 matched controls found that compared with controls, women with HG had significantly higher levels of somatisation, depression anxiety and overall psychological distress even when HG had resolved to mild NVP

- Mechanical complications** including Mallory-Weiss tears, pneumothorax, pneumomediastinum, diaphragmatic rupture, and gastroesophageal rupture, which is **Boerhaave syndrome**



DIAGNOSIS

How is NVP diagnosed?

NVP should only be diagnosed when onset is in the first trimester of pregnancy and other causes of nausea and vomiting have been excluded.

Onset of NVP is in the first trimester and if the initial onset is after 10 weeks of gestation, other causes need to be considered. It 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.

How is HG diagnosed?

HG can be diagnosed when there is protracted NVP with the triad of more than 5% prepregnancy weight loss, dehydration and electrolyte imbalance.

history of NVP/HG:

nausea, vomiting, hypersalivation, spitting, loss of weight , inability to tolerate food and fluids, effect on quality of life

- **History to exclude**

other causes:- abdominal pain- urinary symptoms- infection- drug history- chronic Helicobacter pylori infection

physical exam:

- **Pulse • Blood pressure • Oxygen saturations •**
- **Respiratory rate • Abdominal examination**
- Weight • Signs of dehydration • Signs of muscle wasting • Other examination as guided by history**

INVESTIGATION

CBC, Serum Electrolyte and ketones	Urine dipstick (in particular ketones) and Urine culture	Liver enzymes and bilirubin
Blood glucose	Amylase/lipase	TSH, Free thyroxine
Calcium	hepatitis panel	ECG

Blood tests typically reveal the following finding:

Hyponatremia
Hypokalemia
Hypochloremic metabolic alkalosis
Low serum urea
Ketonuria
Raised hematocrit level and increased specific gravity of the urine
Liver function tests → abnormal in 50% of cases
Thyroid function tests → abnormal in ~66% of .cases
An ultrasound (US) scan of the uterus could be done to rule out multiple gestation or .hydatidiform mole

How can the severity of NVP be classified?

An objective and validated index of nausea and vomiting such as the Pregnancy-Unique Quantification of Emesis (PUQE) score can be used to classify the severity of NVP

They may ask you questions about how you have been feeling over the past 24 hours.

The “PUQE-24” scoring system below shows how they will rate your responses, to understand how severe your nausea and or vomiting has been.

If your PUQE-24 score is:

- between 4 – 6, you have mild NVP
- between 7 – 12, you have moderate NVP
- ≥ 13 , you have severe NVP (also known as HG).

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?	7 or more times (5)	5–6 times (4)	3–4 times (3)	1–2 times (2)	I did not throw up (1)
In the last 24 hours how many times have you had retching or dry heaves without bringing anything up?	No time (1)	1–2 times (2)	3–4 times (3)	5–6 times (4)	7 or more times (5)

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

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

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

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

MANAGEMENT

History

Quantify severity

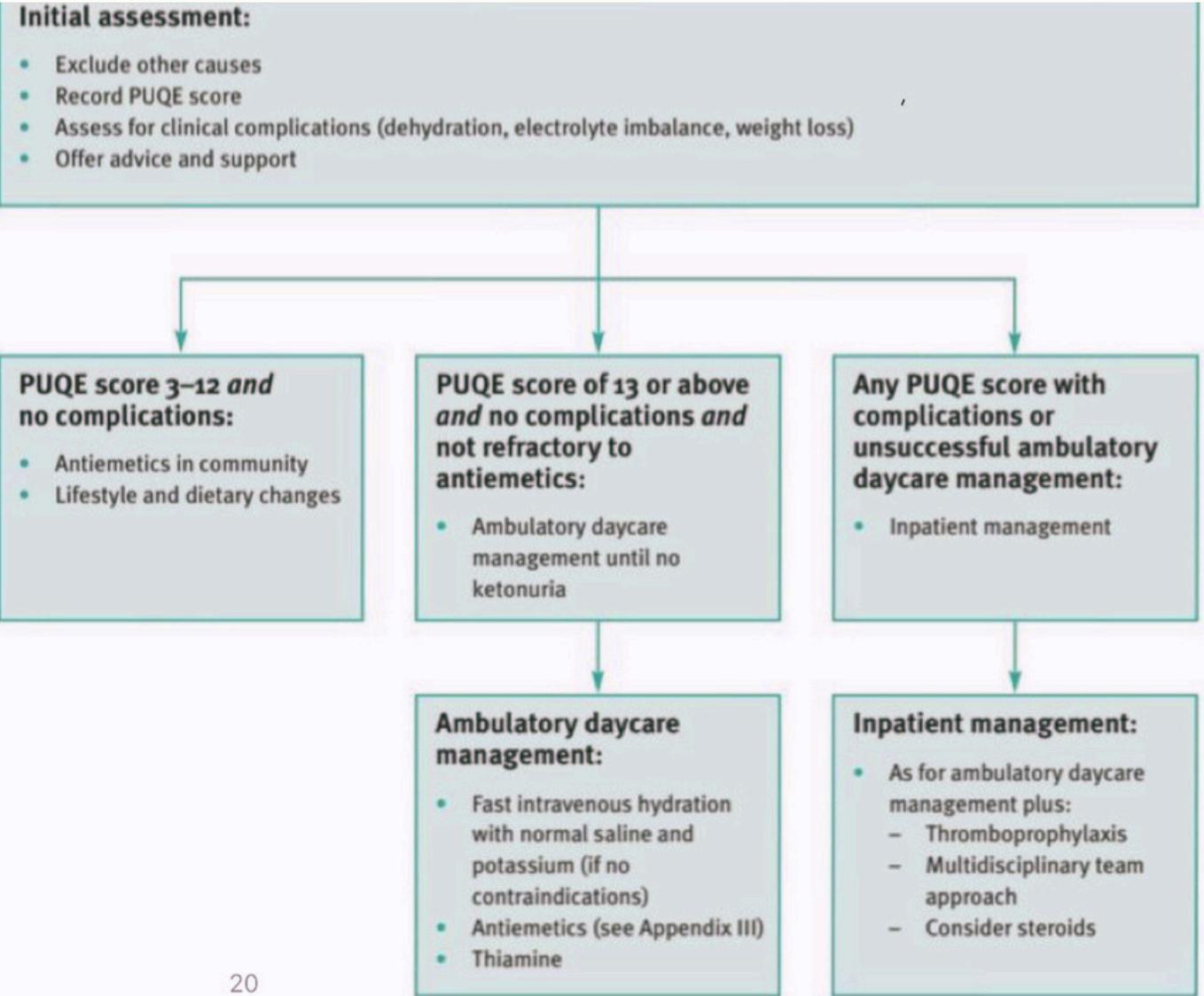
To exclude other causes: abdominal pain, urinary symptoms, infection, drug history

• Examination

Undertake an examination as per the ICP pathway. Includes basic observations, weight, abdominal examination, signs of dehydration, urine output, and other examination as guided by history

• Investigations:

On admission all patients require:
Urine dipstick to quantify ketonuria
MSU to exclude UTI if any positive findings on urine dip
U&Es to identify electrolyte imbalance
FBC and CRP to exclude infection
Random blood glucose
For diabetic patients, checking capillary blood glucose regularly is mandatory



- **The potential maternal and fetal complications of HG argue for early and aggressive treatment.**

- **All patients with HG require emotional support with frequent reassurance and encouragement from nursing and medical staff.**

Drugs that may cause nausea and vomiting should be temporarily discontinued. The commonest example is **iron supplements.**

- **Any woman who is ketotic and unable to maintain adequate hydration requires i.v.fluids and parenteral anti-emetics.**

- **For less severe cases, outpatient management with administration of i.v.fluid therapy and anti-emetics as required should be first line.**

- **The natural history of HG is gradual improvement with increasing gestation, although in a minority of women symptoms may persist beyond 20 weeks' gestation. The only definitive cure is termination of the pregnancy**

1-Intravenous fluid therapy

- Adequate and appropriate fluid and electrolyte replacement is the most important component of management.
- Normal saline (sodium chloride 0.9%; 150 mmol/L Na⁺) and Hartmann's solution (sodium chloride 0.6%; 131 mmol/L Na⁺) are appropriate solutions.

Administering **dextrose** to a patient with hyperemesis without giving thiamine first is a **serious therapeutic error**. Thiamine must always be given before any glucose-containing solution to prevent Wernicke's encephalopathy."

- Correction of the hypokalaemia is essential and it is usually necessary to use infusion bags containing 40 mmol/L of potassium chloride.
- There is no place for the use of double-strength saline (2n saline), even in cases of severe hyponatraemia, as this results in too rapid a correction of serum sodium with the risk of **central pontine myelinolysis**.

2- Thiamine Therapy

Thiamine supplementation should be given to anyone suffering from prolonged vomiting. Requirements for thiamine increase during pregnancy to 1.5 mg/day, and women admitted with a diagnosis of hyperemesis have usually been vomiting for at least 1-2 weeks prior to admission.

- If the woman is able to tolerate tablets, thiamine can be given as thiamine hydrochloride tablets 25-50 mg thrice daily.

If i.v.treatment is required for those unable to tolerate tablets, this is given as thiamine 100 mg diluted in 100 ml of normal saline and infused over 30-60 minutes. Alternatively, this may be given as Pabrinex® which contains 250 mg of thiamine hydrochloride per pair of ampoules

In Wernicke's encephalopathy requires much higher doses of thiamine

3- Thromboprophylaxis

- HG is a risk factor for venous thrombosis probably because of dehydration and immobilization .Therefore, all women admitted with hyperemesis should receive appropriate doses of low-molecular-weight heparin (LMWH

4-PHARMACOLOGICAL THERAPY

- **Anti-emetics**

- Women presenting to secondary care who do not respond to i.v.fluids and electrolytes alone should be offered anti-emetic therapy.
- Extensive data exist to show a lack of teratogenesis or other adverse pregnancy outcomes with:

- *Antihistamines (H1-receptor antagonists, e.g., promethazine, cyclizine, cinnarizine, doxylamine, dimenhydrinate)

- **Phenothiazines (chlorpromazine, prochlorperazine)

- *Dopamine antagonists (metoclopramide, domperidone)

- **Serotonin (5HT3) inhibitors (ondansetron)

If symptoms do not improve, the anti-emetic should be prescribed and given regularly.

4-Histamine2 (H2)-receptor blockers and proton pump inhibitors (PPIs):

- H2-receptor blockers (e.g., ranitidine) and the PPIs (e.g., omeprazole) are used in cases where oesophagitis or gastritis accompanies the nausea and vomiting of HG. They are safe for use in pregnancy.

5- Corticosteroids:

Corticosteroids have resulted in dramatic and rapid improvement in case series of women with severe refractory HG. Randomized studies also support a beneficial effect for those with very severe disease.

- They should not be used until conventional treatment with i.v.fluid replacement and regular parenteral anti-emetics has failed
- › Suggested doses are **prednisolone** 40-50 mg orally daily in divided doses or **hydrocortisone** 100 mg i.v.twice daily.
- › In cases who do respond to steroid therapy, the dose must be reduced slowly and prednisolone cannot usually be discontinued until the gestation at which the HG would have resolved spontaneously (in some extreme cases this occurs at delivery).

6- Enteral feeding:

- If women fail to respond to i.v.fluid and anti-emetic treatment and corticosteroid treatment, then nutritional support may be required in the form of enteral or parenteral feeding.
 - When the gastrointestinal tract is intact it is preferable to use enteral rather than parenteral hyperalimentation to treat malnutrition.
- › Enteral feeding options include nasogastric (NG), nasoduodenal or nasojejunal (NJ) tubes, or percutaneous endoscopic gastrostomy or jejunostomy feeding.

7- Total parenteral nutrition:

- TPN with peripherally inserted central catheters (PICC line) is often better tolerated than enteral, but it carries more risk.
- TPN has also been shown to have a rapid therapeutic effect in some case
- Metabolic and infectious complications are a risk and strict protocols and careful monitoring are obligatory
- The central line site must be inspected regularly for signs of infection.
- Phlebitis and thrombosis are other recognized complications of TPN.
- Because TPN involves the use of high concentrations of glucose, thiamine supplementation is mandatory.
- Parenteral feeding is usually reserved for extremely severe life-threatening cases.

Pre-pregnancy counselling/recurrence

- **Hyperemesis almost invariably recurs in subsequent pregnancies.**
- **In very severe cases, especially those necessitating TPN or termination of the pregnancy, women may be advised that studies suggest a beneficial effect of steroids and anti emetic therapy which may provide a therapeutic option in subsequent pregnancies**

- HG is a diagnosis of exclusion.
- HG may be associated with both abnormal liver and thyroid function tests.
- Adequate and appropriate (normal saline and potassium chloride) fluid and electrolyte replacement is the most important component of management.

Thiamine supplementation to prevent Wernicke's encephalopathy and thromboprophylaxis should be given to all women admitted with hyperemesis

. . .

.Corticosteroids may have a role to play in severe resistant cases

• **points to remember** •

Drug	Dose	Major side-effects	Class
First Line			
Cyclizine	50mg PO/IM/IV TDS	Drowsiness, dizziness	H1 receptor antagonist
Prochlorperazine	5-10mg 6-8 hourly PO (also available as oral solution), 12.5mg 8 hourly IM, 3-6mg 12 hourly buccal	Hypotension, extrapyramidal symptoms (tardive dyskinesia, dystonia)	Antipsychotic phenothiazines
Promethazine (Phenergen)	12.5-25mg 4-8 hourly PO /Deep IM	Drowsiness, sedation	H1 receptor antagonist
Chlorpromazine	10-25mg 4-6 hourly PO/ Deep IM	Sedation, hypotension, extrapyramidal symptoms	Antipsychotic phenothiazines
Second Line			
Metoclopramide	5-10mg 8 hourly PO/IV/IM (also available as oral solution)	Extrapyramidal symptoms (torticollis, oculogyric crisis)	D2 receptor antagonist
Domperidone	10mg 8 hourly PO, 30-60mg 8 hourly PR	Minimal	D2 receptor antagonist
Second line if >13 weeks			
Ondansetron	4-8mg 8 hourly PO/IV	Headache, GI upset, Should be given >13 weeks only due to fetal risk of cleft palate and renal abnormalities	5-HT3 receptor antagonist
Third Line			
Corticosteroids	Hydrocortisone 100mg BD IV, convert to prednisolone 40-50mg OD PO and taper dose to lowest level which still controls symptoms	Patients should be given clear advice about self-management of tapering, and a steroid alert card	30

- Because different drug classes may have different mechanisms of action and therefore synergistic effects, combinations of drugs from different classes should be used in women who do not respond to a single antiemetic. Furthermore, persistent vomiting may mean that oral doses of antiemetics are not absorbed and therefore the intravenous, rectal, subcutaneous or intramuscular routes may be necessary and more effective.