

## Management of nausea and vomiting in pregnancy

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► Diagnosis and management of premenstrual disorders (*BMJ* 2011;342:d2994)

Nausea and vomiting are the most common symptoms of pregnancy. As a result many medical practitioners will encounter this problem and should be familiar with the appropriate investigations and current treatment options. Nausea and vomiting affect 50-90% of pregnant women, and in about 35% of these women symptoms are of clinical relevance, with both physical and psychosocial sequelae. Although colloquially referred to as “morning sickness,” for many women symptoms persist over the whole day, with a broad spectrum of severity ranging from occasional nausea to fulminant and intractable vomiting. Nausea and vomiting begin in the first trimester, at about six to eight weeks’ gestation, typically peaking at about nine weeks’ gestation and settling by about 12 weeks. Only a minority of women have symptoms after 20 weeks of gestation. Adequate oral hydration and avoidance of dietary triggers are often sufficient, but a proportion of women with severe and protracted nausea and vomiting will need antiemetic drugs.

A more severe form of nausea and vomiting in pregnancy affects less than 1% of women and is referred to as hyperemesis gravidarum.<sup>1</sup> Different definitions of hyperemesis gravidarum exist, but the important features are intractable vomiting associated with weight loss of more than 5% of pre-pregnancy weight, dehydration, electrolyte imbalances, ketosis, and the need for admission to hospital. Before reaching a diagnosis of hyperemesis gravidarum, exclude other causes of severe nausea and vomiting (box 1). Carefully assess and treat all women

### SOURCES AND SELECTION CRITERIA

We performed a PubMed search to identify peer reviewed original articles, meta-analyses, and reviews. Cochrane Collaboration and clinical evidence databases were reviewed as well. We considered only papers written in English and mainly included studies published during the past 15 years, where we deemed the scientific validity to be adequate.

who present with severe nausea and vomiting in pregnancy because this may obviate the need for admission. In hyperemesis gravidarum, many women will need to be admitted to hospital so that they can receive intravenous rehydration and parenteral antiemetic drugs to avoid serious maternal and fetal morbidity (box 2). Maternal complications of severe hyperemesis gravidarum include Wernicke’s encephalopathy as a result of thiamine (vitamin B-1) deficiency,<sup>2</sup> and fetal complications include fetal growth restriction.<sup>3 4</sup>

### Who gets hyperemesis gravidarum?

The results of epidemiological studies are conflicting. One large prospective study found that women who are primiparous, from lower socioeconomic background, younger, and non-smokers are more likely to have nausea and vomiting in pregnancy.<sup>5</sup> Studies have shown that hyperemesis gravidarum is more common in women with pre-existing diabetes, hyperthyroidism, gastrointestinal disorders, history of molar pregnancy, and psychiatric illness.

### SUMMARY POINTS

Nausea and vomiting occur in most pregnancies but hyperemesis gravidarum occurs in less than 1%; it requires exclusion of other causes and more aggressive management, usually in hospital

Perform a full investigation including blood tests, urinalysis, and a pelvic ultrasound to assess severity and to rule out other causes and molar pregnancy

Rehydration is first line treatment, but in cases with ongoing nausea and vomiting, antiemetics should be prescribed

Phenothiazine, antihistamines, dopamine agonists, and selective 5-hydroxytryptamine receptor antagonists are all safe in pregnancy

In cases of intractable vomiting, combinations of several parenteral antiemetics may be needed

Consider corticosteroids in women with severe hyperemesis gravidarum who are resistant to conventional management

### Box 1 | Differential diagnosis of nausea and vomiting in pregnancy

Gastrointestinal (for example, infection, gastritis, cholecystitis, peptic ulceration, hepatitis, appendicitis, and pancreatitis)

Neurological (for example, migraine, central nervous system diseases)

Urinary tract infection

Ear, nose, and throat disease (for example, labyrinthitis, Ménière’s disease, vestibular dysfunction)

Drugs (such as opioids and iron)

Metabolic and endocrine disorders (such as hypercalcaemia, Addison’s disease, uraemia, and thyrotoxicosis)

Psychological disorders (such as eating disorders)

Pregnancy associated conditions (such as pre-eclampsia and molar pregnancy)

**Box 2 | Complications of hyperemesis gravidarum**

**Maternal complications**

- Weight loss (10-20% of body weight)
- Dehydration
- Electrolyte abnormalities
  - Hyponatraemia, from persistent vomiting (leading to lethargy, headache, confusion, nausea, vomiting, and seizures), or overzealous correction of hyponatraemia, which can lead to central pontine myelinolysis
  - Hypokalaemia (skeletal muscle weakness, cardiac arrhythmias)
- Vitamin deficiencies
  - Vitamin B-1 deficiency can lead to Wernicke's encephalopathy.<sup>2</sup> This may also be precipitated by high concentrations of dextrose
  - Vitamin B-12 and vitamin B-6 deficiencies may also occur, leading to anaemia and peripheral neuropathies
- Mallory-Weiss tears of the oesophagus
- Postpartum complications: persistence of symptoms and food aversions, postpartum gallbladder dysfunction, and symptoms of post-traumatic stress disorder<sup>3</sup>

**Fetal complications**

- Fetal growth restriction and prematurity<sup>3 4</sup>

**What is the underlying pathophysiology of nausea and vomiting in pregnancy?**

The underlying pathophysiology is poorly understood but a combination of genetic, endocrine, gastrointestinal, environmental, and psychosocial factors are probably involved. Other theories offer evolutionary adaptation as an explanation, with the suggestion that it may be a defensive strategy to prevent the ingestion of noxious substances.<sup>6</sup> Indeed, pregnancies complicated by nausea and vomiting are less likely to result in miscarriage. In support of a role for genetics, a recent population based cohort study showed that women born to mothers who had hyperemesis gravidarum have a three times greater risk of experiencing this complication during pregnancy.<sup>7</sup>

Nausea and vomiting in pregnancy are mediated by placently derived human chorionic gonadotrophin (HCG)

and symptoms typically begin when concentrations are at their highest—at around nine weeks' gestation. Hyperemesis gravidarum is reported more often in women with high concentrations of HCG (for example, those with multiple and molar pregnancies). Thyroid function may be physiologically altered during pregnancy because the structural homology between HCG, thyroid stimulating hormone, and their receptors facilitates cross-reactivity between these two hormones. One prospective study found evidence of transient hyperthyroidism in 60% of women with hyperemesis gravidarum.<sup>8</sup> The degree of hyperthyroidism and HCG concentrations correlate with the severity of vomiting,<sup>9</sup> and in most women thyroid dysfunction is self limiting.

Higher concentrations of progesterone, adrenocorticotropic hormone, and leptin have also been associated with hyperemesis gravidarum.<sup>10</sup>

Many psychological and behavioural theories have been proposed to explain hyperemesis gravidarum. Nausea and vomiting in pregnancy have been correlated with poor communication between the woman and her partner, home life stressors, and insufficient information about the pregnancy, but it is difficult to prove causality. Nausea and vomiting in pregnancy itself may lead to considerable psychosocial stress through altered family, social, and occupational functioning.<sup>11 12</sup> The psychological impact on women may cause some women to decide to terminate the pregnancy.<sup>13</sup> Some studies have shown that women with a history of eating disorders, such as anorexia nervosa and bulimia nervosa, are more likely to develop nausea and vomiting in pregnancy. A recent large prospective study found that women with the purging subtype of bulimia nervosa had a significantly higher odds ratio of having nausea and vomiting in pregnancy than women without eating disorders.<sup>14</sup>

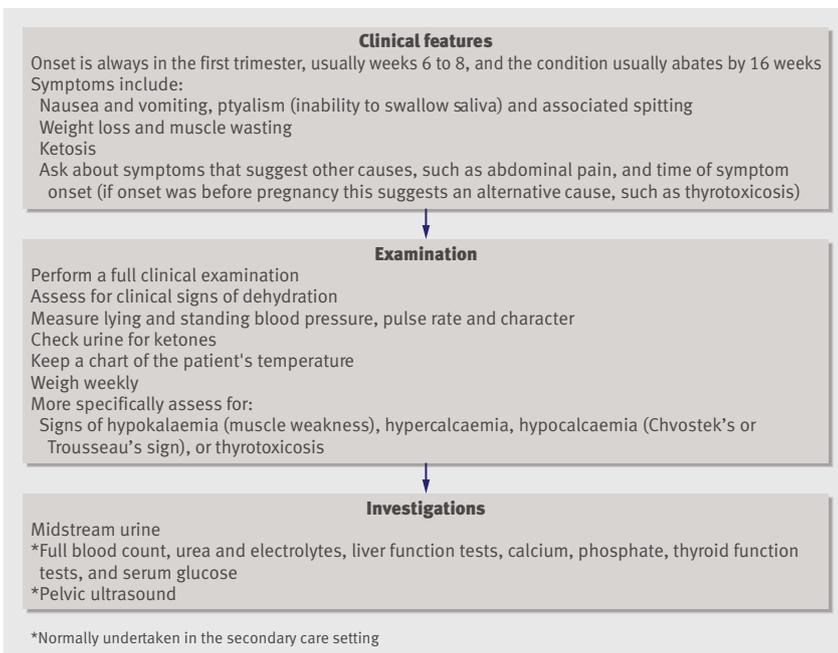
Physiological changes to the gastrointestinal system in pregnancy may have a role in the development of nausea and vomiting. Generalised relaxation of smooth muscle is mediated by progesterone and culminates in reduced oesophageal pressure and delayed gastric emptying. Several studies suggest that *Helicobacter pylori* seropositivity is associated with nausea and vomiting in pregnancy—a recent case-control study found that 71 of 80 women with hyperemesis gravidarum were seropositive.<sup>15</sup> Another study of 105 women exposed to *H pylori* found a dose dependent link between IgG and severity of hyperemesis gravidarum.<sup>16</sup>

**How is hyperemesis gravidarum diagnosed?**

Vomiting that begins after 12 weeks' gestation is unlikely to be caused by hyperemesis and other pathological causes should always be considered before attributing nausea and vomiting in pregnancy to hyperemesis gravidarum (box 1). Hyperemesis gravidarum is a diagnosis of exclusion that requires a thorough clinical assessment and systematic history taking (fig 1). Hyperemesis gravidarum tends to recur in subsequent pregnancies,<sup>5</sup> so absence of a history of nausea and vomiting in previous pregnancies makes the diagnosis less likely.

**What are the treatment options?**

Psychological, non-drug based, and drug based treatments are available for women with nausea and vomiting in pregnancy and hyperemesis gravidarum. Psychologi-



**Fig 1 | Clinical assessment of women with nausea and vomiting in pregnancy**

**TIPS FOR NON-SPECIALISTS**

Most standard antiemetics are safe in pregnancy; women will be prescribed these liberally if admitted to hospital so do not withhold them in primary care

Women require reassurance about the safety of antiemetics in pregnancy

Refer women with ketonuria or marked weight loss accompanied by protracted vomiting to hospital for further assessment

Nausea and vomiting that start at 12 weeks' gestation or later are unlikely to be caused by pregnancy so other causes should be sought

**QUESTIONS AND AREAS FOR FUTURE RESEARCH**

- What is the role of *Helicobacter pylori* eradication in the treatment of nausea and vomiting in pregnancy?
- What is the role of steroids in severe hyperemesis gravidarum?
- Can withholding food to "rest" the gastrointestinal tract help in women with severe hyperemesis gravidarum?
- Strategies for outpatient management of nausea and vomiting in pregnancy need formal evaluation, including cost effectiveness analysis

**ADDITIONAL EDUCATIONAL RESOURCES****Resources for healthcare professionals**

Matthews A, Dowswell T, Haas DM, Doyle M, O'Mathúna DP. Interventions for nausea and vomiting in early pregnancy. *Cochrane Database Syst Rev* 2010;9:CD007575

**Resources for patients**

NHS Choices ([www.nhs.uk/conditions/morning-sickness/Pages/Introduction.aspx](http://www.nhs.uk/conditions/morning-sickness/Pages/Introduction.aspx))—Information for women on morning sickness and how to deal with it, including links to other useful websites

cal support—reassuring women that nausea can be part of normal pregnancy, that nausea is likely to settle as the pregnancy progresses, and that it is unlikely to harm their baby—will be helpful in itself, and women respond well to this knowledge and support. Non-drug treatments include dietary modifications and alternative treatments, such as ginger (and other herbal remedies—for example, chamomile and peppermint), acupuncture and B6 acupressure, psychosocial interventions, and behavioural interventions. Drug treatments go hand in hand with adequate hydration. If hyperemesis gravidarum develops, intravenous rehydration and vitamin supplementation need to be instituted to avoid potential complications (box 2).<sup>2</sup>

**Diet and supplements**

Advise women to avoid exposure to triggers such as specific odours and particular foods. Symptoms may be reduced by eating dry bland foods, little and often, and ensuring adequate hydration. Data suggest that women with a high intake of fatty foods have a higher risk of hyperemesis gravidarum and that low energy high protein diets are associated with a reduction of nausea and vomiting in pregnancy compared with a diet high in carbohydrates.<sup>17</sup> After admission to hospital with hyperemesis gravidarum, some advocate withholding food to "rest" the gastrointestinal tract, but this has never been formally evaluated.

All women at less than 12 weeks' gestation should be taking folic acid 0.4 mg daily. Pyridoxine (vitamin B-6) supplements reduce symptoms, and in many countries pyridoxine is used first line in combination with an antiemetic such as doxylamine. Individual responses vary greatly, however, probably because of large differences in the onset and action of pyridoxine.<sup>18</sup> Ginger has also

been used as an antiemetic in several small randomised controlled trials (RCTs), both alone and combined with pyridoxine, but with no significant difference in nausea scores between the two groups. The conflicting data on the efficacy of ginger may result from different preparations and potencies of ginger used in various studies.<sup>19</sup> The benefits of ginger are likely to be in early nausea and vomiting in pregnancy, with no convincing evidence of benefit in severe hyperemesis gravidarum.

**Intravenous fluids, vitamin supplements, and thromboprophylaxis**

Women who are severely dehydrated and ketotic need to be assessed in secondary care, with timely fluid and electrolyte replacement intravenously. Normal saline (0.9%; 150 mmol/L sodium) or Hartmann's solution are appropriate fluid replacement choices. Although it is often thought that infusions of dextrose containing fluids (5% dextrose, 10% dextrose, or dextrose saline) are useful to provide the patient with energy, this assumption is erroneous and dangerous. Firstly, Wernicke's encephalopathy may be precipitated by intravenous dextrose. Secondly, hyponatraemia requires the infusion of sodium containing fluids, with a close eye on fluid status and sodium concentrations, to ensure that changes are not corrected too rapidly because this can lead to central pontine myelinolysis. Fluid and electrolyte balance must be reassessed frequently and management titrated according to clinical assessment and fluid balance. Specifically, potassium must be replaced appropriately, with 40 mmol in each litre of fluid until hypokalaemia is corrected. Replacement must be titrated to serial measurements of urea and electrolytes. Thiamine supplements should be given routinely to all women admitted to hospital for prolonged vomiting, and the requirements increase in pregnancy to 1.5 mg daily. If tolerated this may be given orally (thiamine 25-50 mg three times daily) or intravenously (weekly infusions of 100 mg thiamine in 100 ml 0.9% saline infused over 30-60 minutes or as Pabrinex). Pyridoxine supplements may also be considered. Risk assessment for venous thrombosis and consideration of prophylactic low molecular weight heparin while dehydrated, unwell, or immobile is important.<sup>20</sup>

**Antiemetics**

Drug treatment is based on the use of antiemetics, which include anticholinergics, antihistamines (H<sub>1</sub> receptor antagonists), dopamine agonists, selective 5-hydroxytryptamine receptor antagonists (5-HT<sub>3</sub>), or combinations of these agents. Proton pump inhibitors (such as omeprazole) and H<sub>2</sub> blockers (such as ranitidine) may be used in women who also have dyspepsia and may be a useful adjunctive treatment that is safe for use in pregnancy.

A meta-analysis of 28 RCTs showed that antiemetics reduced nausea of early pregnancy compared with placebo.<sup>21</sup> Despite worries about teratogenicity, extensive data show that most of these agents have no teratogenic effects. A meta-analysis of 24 studies of 200 000 women with varying degrees of nausea and vomiting in pregnancy concluded that antiemetics such as doxylamine-pyridoxine combinations, antihistamines, and phenothiazines were safe and efficacious.<sup>22</sup> The authors infer that they may also protect against fetal defects as a result of metabolic improvements.<sup>22</sup>

**Box 3 | Suggested antiemetics**

- Cyclizine 50 mg orally, intramuscularly, or intravenously, three times daily
- Metoclopramide 10 mg orally, intramuscularly, or intravenously, three times daily
- Prochlorperazine 5 mg orally, 12.5 mg intramuscularly or intravenously, three times daily; 25 mg rectally, followed if necessary six hours later by an oral dose
- Promethazine 25 mg orally, at night
- Chlorpromazine 10-25 mg orally up to three times daily; 25 mg intramuscularly, three times daily
- Domperidone 10 mg orally, four times daily; 30-60 mg rectally, three times daily
- Ondansetron 4-8 mg orally, intramuscularly, or by slow intravenous infusion, two to three times daily

The selective 5HT<sub>3</sub> receptor antagonist, ondansetron, has shown benefits in patients with intractable hyperemesis gravidarum, with few side effects and no reports of teratogenicity.<sup>23</sup> There are no large trials of its effectiveness in nausea and vomiting in pregnancy, although one small RCT of 30 women with severe disease found that ondansetron was no more effective than promethazine.<sup>24</sup>

There is no evidence that any one antiemetic is superior to another. In terms of side effects, most antiemetics can lead to drowsiness, but this is most common with the phenothiazines. Extrapyramidal effects and oculogyric crises are reported with metoclopramide and phenothiazines. Headache, tremors, and myalgia have been reported with prednisolone, prochlorperazine, promethazine, dimenhydrinate, doxylamine, and metoclopramide.<sup>25</sup>

**Box 4 | Criteria for referral to secondary care**

- Continued nausea and vomiting associated with ketonuria or weight loss (>5% body weight), despite oral antiemetics
- Continued nausea and vomiting and inability to keep down oral antiemetics
- Confirmed or suspected comorbidity (such as confirmed urinary tract infection and unable to tolerate oral antibiotics)

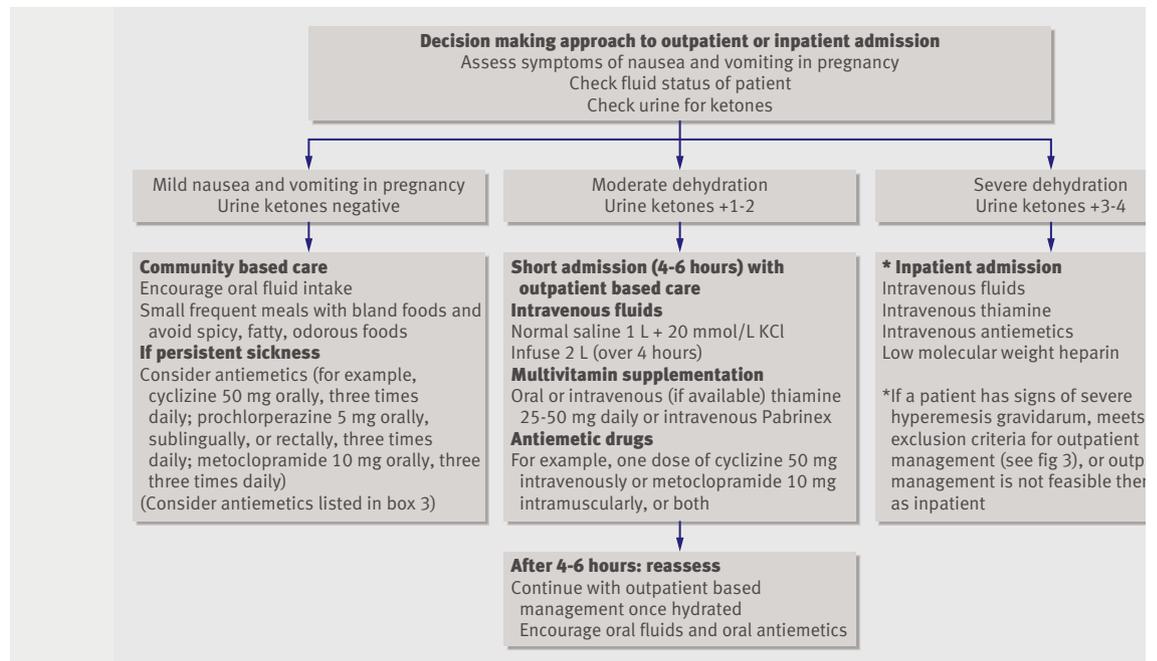
**Corticosteroids**

Limit the use of corticosteroids to intractable cases of severe hyperemesis gravidarum in secondary care. One small RCT showed that, compared with placebo, corticosteroids improved symptoms, with reduced dependence on intravenous fluids.<sup>26</sup> Although promising, the results were not statistically significant because of the small numbers; however, cohort studies have shown dramatic and complete responses in women with severe hyperemesis gravidarum who were taking corticosteroids, with no deleterious effects on birth weight.<sup>27, 28</sup> A small RCT of women with severe hyperemesis gravidarum in intensive care randomised to 300 mg hydrocortisone a day or metoclopramide showed a 41% versus 17% reduction in symptoms by 48 hours, respectively.<sup>29</sup> Methylprednisolone has been used successfully in severe refractory hyperemesis gravidarum. It seems to be more effective than standard antiemetics, such as promethazine, at reducing hospital admissions, but it may be associated with adverse effects.<sup>30</sup>

If steroids are needed because of failure to respond to conventional treatment, the usual protocol is 100 mg intravenous hydrocortisone, twice daily. If clinical improvement occurs, this is followed by oral prednisolone 40-50 mg daily; the dose should be gradually tapered until the lowest maintenance dose that continues to control symptoms is reached.

**Summary of antiemetic use**

Offer antiemetics to women in primary care in whom nausea and vomiting in pregnancy interferes with normal functioning. In hyperemesis gravidarum, offer antiemetics to women who fail to respond to intravenous hydration and electrolyte replacement. Clinicians should use drugs with confirmed safety profiles in a regimen that they feel comfortable prescribing. Box 3 shows possible antiemetic regimens in order of suggested use. In severe cases, combinations of antiemetics and parenteral treatment are necessary.



**Fig 2 | Treatment options (community, outpatient, or inpatient based management)**

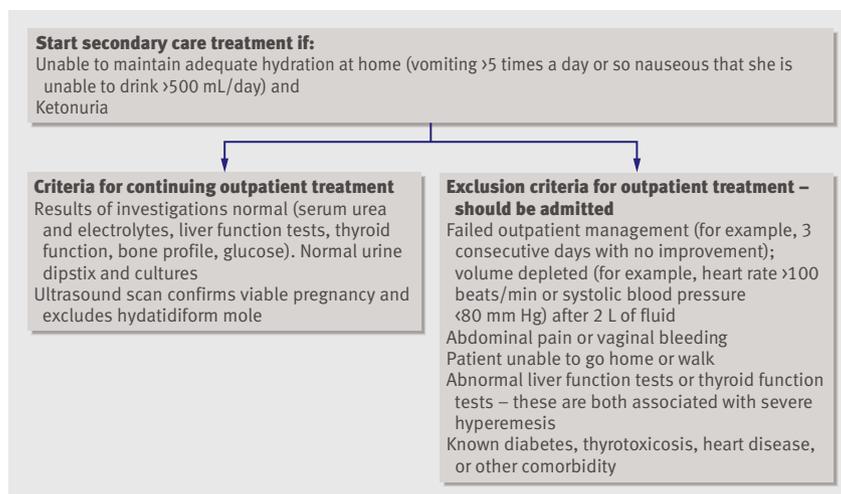


Fig 3 | Criteria for outpatient and inpatient management in secondary care

### Clinical model of care in nausea and vomiting in pregnancy

Most women with nausea and vomiting in pregnancy can be successfully managed in primary care. Judicious assessment enables recognition of women whose symptoms are severe and intractable despite treatment with oral antiemetics, who are unable to maintain oral hydration and have ketonuria, and who therefore require referral to hospital (box 4). Many women improve rapidly after the administration of intravenous fluids and electrolytes alone. “Outpatient” management of milder cases of hyperemesis gravidarum has been adopted in some trusts to manage women who improve rapidly after intravenous rehydration with or without parenteral antiemetics, who otherwise would be in and out of hospital for one to two day stays. This form of management may be cost effective, but it requires an emergency gynaecology or early pregnancy unit with adequate staffing to supervise outpatient intravenous treatment and has yet to be formally evaluated.

### Box 5 | Inpatient management of hyperemesis gravidarum in patients with dehydration who are unable to tolerate tablets

#### Intravenous infusion

Normal saline 1 L+40 mmol/L of KCl. Infuse 3 L over 24 hours

Continue intravenous fluids; continually reassess fluid status and ketonuria; repeat urea and electrolytes daily

#### Thiamine supplements

Intravenous thiamine: 100 mg diluted in 100 ml of normal saline and infused over 30-60 minutes (once a week)

Alternatively this may be given as Pabrinex, which contains 250 mg of thiamine hydrochloride in each pair of ampoules

#### Antiemetic drugs

Intravenous cyclizine 50 mg three times daily

Intravenous metoclopramide 10 mg three times daily

Other antiemetics to consider in refractory nausea and vomiting:

- Prochlorperazine 5 mg orally three times daily; 12.5 mg intramuscularly or intravenously, three times daily; 25 mg rectally, followed if necessary six hours later by an oral dose
- Chlorpromazine 10-25 mg orally or 25 mg intramuscularly, three times daily
- Domperidone 10 mg orally four times daily; 30-60 mg rectally, three times daily
- Ondansetron 4-8 mg intramuscularly or by slow intravenous infusion, two to three times daily
- Hydrocortisone 100 mg twice daily, or prednisolone 40-50 mg orally each day in divided doses

#### Thromboprophylaxis

Low molecular weight heparin and thromboembolic stockings

Figure 2 shows an algorithm to support the clinical decision making approach to community based, outpatient, or inpatient care. Women who can maintain hydration, do not have ketonuria, and are vomiting fewer than five times a day can usually be managed in primary care. Those who respond to intravenous rehydration and in whom both normal blood tests and pelvic ultrasound have been obtained can be considered for outpatient management, with the proviso of continual reassessment to ensure symptoms are improving (fig 3).

If women fail to respond to the suggested outpatient approach, or if they have pre-existing illnesses, comorbidities, or abnormal test results, they should be managed as inpatients. Women who need to be admitted to hospital should be managed as suggested by the inpatient management approach (box 5). Most will require antiemetics, which can be continued on discharge until symptoms abate.

### Conclusion

Nausea and vomiting in pregnancy are common, but they are mostly self limiting and resolve by 16-20 weeks' gestation. Women need reassurance and support. In a subset of women, symptoms can be severe and hyperemesis gravidarum can ensue. Clinicians must therefore be aware of the need for timely community based treatment if appropriate, and when they should refer to secondary care. Persistent and intractable vomiting requires aggressive inpatient treatment to prevent complications, and intravenous fluids are needed. Although good safety data exist for a large number of widely used antiemetics in pregnancy, few large RCTs exist. In addition, studies vary in their definitions of hyperemesis gravidarum and nausea and vomiting in pregnancy, are of heterogeneous methodological quality, and are often prone to bias.

Early drug treatment may be necessary to avoid maternal metabolic disarray from uncontrolled nausea and vomiting, which may affect the fetus. All healthcare providers who care for pregnant women must be aware of the range of symptoms and be able to assess severity while providing effective treatment in a timely manner.

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**Competing interests:** All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/doi\\_disclosure.pdf](http://www.icmje.org/doi_disclosure.pdf) (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Provenance and peer review:** Commissioned; externally peer reviewed.

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**ANSWERS TO ENDGAMES, p 1427.** For long answers go to the Education channel on [bmj.com](http://bmj.com)

**STATISTICAL QUESTION**

**Screening tests: indices of performance**

Answer b is the correct calculation.

**ON EXAMINATION QUIZ**

**Palpitations**

Answer D is correct.

**PICTURE QUIZ A limping child**

- 1 A limp caused by a shortened stance phase in the gait cycle is known as an antalgic gait.
- 2 Limping and knee pain in children must alert the investigator to the possibility of hip pathology. The main diagnoses to consider are fracture or soft tissue injury, transient synovitis, Legg-Calvé-Perthes disease, infective processes (septic arthritis or osteomyelitis), and developmental hip dysplasia. Rarer diagnoses include rheumatological, neoplastic, haematological, and neuromuscular diseases.
- 3 The plain radiographs show subtle flattening and sclerosis of the left femoral epiphysis (fig 1). The T2 weighted MRI images show altered marrow signal in the left femoral epiphysis, which is indicative of necrosis (fig 2). This is consistent with avascular necrosis of the left femoral epiphysis. In childhood, idiopathic avascular necrosis of the femoral epiphysis is known as Legg-Calvé-Perthes disease.
- 4 In a child with an acute limp of unclear aetiology, haematological investigations may help differentiate between septic arthritis and transient synovitis. In this case, septic arthritis and transient synovitis were unlikely because the limp had lasted for two weeks. Because the radiographs were deemed inconclusive, blood investigations were performed to look for an inflammatory arthropathy or neoplastic disease (such as acute lymphoblastic leukaemia).
- 5 The child should be referred promptly to a paediatric orthopaedic surgeon. Broadly speaking, the clinician will try to contain the femoral epiphysis within the acetabulum to maintain sphericity. An aspherical hip is prone to early onset of osteoarthritis.



Fig 1 | Plain anteroposterior radiograph of the pelvis showing subtle flattening and sclerosis of the left femoral epiphysis (arrow)

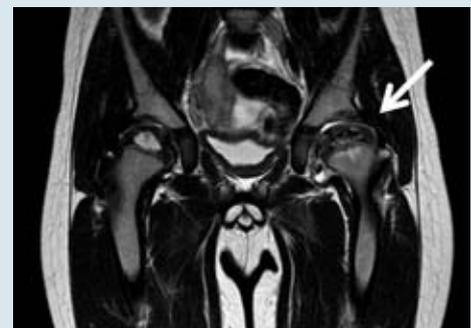


Fig 2 | T2 weighted coronal magnetic resonance imaging section of the pelvis showing altered marrow signal in the left femoral epiphysis, which is indicative of necrosis (arrow)