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## Hyperemesis Gravidarum

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### INTRODUCTION

Nausea and vomiting of pregnancy has been a very common age-old phenomenon. Although not well understood, it occurs in almost 70% of pregnant women. While 'morning sickness' remains common, it is usually more troublesome when it is serious. The traditional practice of giving the symptomatic antiemetic treatment without much knowledge and confidence, has not changed over the years. The severe end of the continuum, hyperemesis gravidarum, may complicate up to 0.3–2% of pregnancies, causing pathological changes that may affect the mother and fetus. In most cases, affected individuals progress from mild or moderate nausea and vomiting to hyperemesis gravidarum which can be 'complicated' or 'uncomplicated', the former referring to acetonuria, fluid electrolyte imbalance and Wernicke's encephalopathy. Prematurity, low birthweight, small for gestational age and a 5-min Apgar score of <7, have been reported in fetuses of mothers affected with hyperemesis gravidarum (level of evidence II–2), more so in women with poor maternal weight gain associated with it.

### ETIOLOGY

The cause of hyperemesis is still not well understood. The associated risk factors and the significance of these associations are depicted in Table 1.

The factors associated with hyperemesis are primarily maternal and fetal factors that are not easily modifiable, but their identification may be useful in determining those women at high risk for developing hyperemesis and some might give clues on the choice of treatment as in hyperthyroidism and diabetes. High risk for recurrence is observed in women with hyperemesis in the first pregnancy. The risk is

reduced by a change in paternity. For women with no previous hyperemesis, a long interval between births slightly increases the risk of hyperemesis in the second pregnancy. So, relative impact of genetic and environmental factors and their possible interactions is also seen in hyperemesis<sup>1</sup>.

A low pre-pregnancy weight to height ratio may predispose women to the development of hyperemesis<sup>2</sup>. Low maternal age and multiparity independently increases the risk for nausea and vomiting in pregnancy. Smoking before pregnancy and using vitamins in early pregnancy are associated with a decreased risk for nausea and vomiting (level of evidence II–2<sup>3</sup>). Women working outside the home have a lower rate of nausea and vomiting than housewives and women out of work<sup>4</sup>. Hormonal factors are known to play an important role in the etiology. The cause seems to be associated with higher levels of selected forms of human chorionic gonadotropin (hCG) with the greatest thyroid-stimulating capacity. Few isoforms of chorionic gonadotropin act via the thyroid-stimulating hormone (TSH) receptor to accelerate iodine uptake. Also low prolactin levels and high estradiol levels are found to be associated with nausea in pregnancy<sup>5</sup>. Researchers theorized that during human evolution, sickness during pregnancy protected the fetus by making the mother too nauseous to eat foods that were most likely to be toxic in the early pregnancy. Support for this idea comes from the fact that many of the foods that tend to repulse pregnant women contain potentially harmful substances. Also, women who have virtually no nausea or vomiting appear to be more likely to miscarry than those who experience some sickness. Psychological and social factors influence this disease, such as unwanted pregnancies. Young unwed mothers

**Table 1** Risk factors for hyperemesis gravidarum

Risk factor	Significance	Study design	Numbers in the study
Prepregnancy underweight	Increased risk ( $p < 0.01$ )	Retrospective chart review <sup>1</sup>	38
Change in paternity	Decreased risk: 10.9% vs 16% OR = 0.60; 95% CI = 0.39–0.92	Cohort study <sup>2</sup> in logistic regression model	547,238
Second pregnancy	15.2% increased risk OR = 26.4; 95% CI = 24.2–28.7	Cohort study <sup>2</sup> in logistic regression model	547,238
Previous molar pregnancy	Increased risk (RR = 3.3) 95% CI = 1.6–6.8	Population-based cohort with logistic regression <sup>3</sup>	157,922
Maternal age > 30 years	Decreased risk	Population-based cohort <sup>3</sup>	157,922
Hyperthyroid disorders	Increased risk (RR = 4.5) 95% CI = 1.8–11.1; 38% increased incidence	Population-based cohort with logistic regression <sup>3</sup> (level of evidence II–2)	157,922
Pre-existing diabetes	Increased risk (RR = 2.6) 95% CI = 1.5–4.7	Population-based cohort <sup>3</sup> (level of evidence II–2)	157,922
Psychiatric illness	Increased risk (RR = 4.1) 95% CI = 3.0–5.7	Population-based cohort with logistic regression <sup>3</sup>	157,922
Gastrointestinal disorders	Increased risk (RR = 1.5) 95% CI = 1.8–3.6	Population-based cohort with logistic regression <sup>3</sup>	157,922
Asthma	Increased risk (RR = 1.5) 95% CI = 1.2–1.9	Population-based cohort with logistic regression <sup>3</sup>	157,922

are common sufferers of this syndrome. Remarkable improvement with hospitalization is often noted in such cases, with rapid relapse once released to the home environment. Women with personality disorders are predisposed to this condition.

## RECENT DEVELOPMENTS

### Role of *Helicobacter pylori*

Recently, an association between the bacterium *Helicobacter pylori* and hyperemesis gravidarum has been found as serologically positive *H. pylori* infection has been demonstrated in the hyperemesis group<sup>6</sup>. In this study, Karaca *et al.* compared 56 pregnant women with hyperemesis gravidarum to 90 pregnant women without hyperemesis and detected specific serum immunoglobulin G for *H. pylori* by the fluorescent enzyme immunoassay method in 82% of subjects of the hyperemesis gravidarum group, suggesting chronic infection, compared with 64% in the controls, the difference being statistically significant. Supporting this, agents active against *H. pylori* have been found to be very effective for the treatment of hyperemesis<sup>7,8</sup>. The

elevated hCG causing a shift in pH along with pregnancy-induced gastrointestinal dysmotility and altered humoral as well as cell-mediated immunity in pregnancy are believed to be the reasons for infection. Lower socioeconomic status may also be an important risk factor of infection with *H. pylori* in pregnant women with hyperemesis gravidarum<sup>6</sup>.

### Immunological factors

The recent reports also significantly correlate the severity of hyperemesis with increased concentrations of cell-free fetal deoxyribonucleic acid (DNA)<sup>9</sup>. Sugito *et al.* studied 202 pregnant women between 6 and 16 weeks bearing a single male fetus. The clinical severity of hyperemesis was directly associated with the increase in fetal DNA.

The fetal DNA comes from the destruction of villous trophoblasts which border the intervillous space filled with maternal blood<sup>10,11</sup>. These are destroyed by the hyperactivated maternal immune system while tolerating the fetus as a graft. The functional activation of natural killer and cytotoxic

T cells is found to be more prominent in hyperemesis than in women with an uncomplicated pregnancy<sup>12</sup>. Thus hyperactivation of the maternal immune system may be responsible for the onset of hyperemesis, probably while maternal immune tolerance to the semi-allograft is being established.

Various hormonal and immunological factors associated with hyperemesis are depicted in Table 2<sup>5,6,9,13-16</sup>.

## DIAGNOSIS

Hyperemesis gravidarum is diagnosed when protracted vomiting is present along with the inability to tolerate solid foods or fluids and the presence of ketonuria. Although nausea and vomiting are very common symptoms of pregnancy, hyperemesis gravidarum is considered when all other causes of persistent nausea and vomiting (as given in Table 3) such as pyelonephritis, pancreatitis, cholecystitis, hepatitis, appendicitis, gastroenteritis, peptic ulcer disease, thyrotoxicosis, malaria and hyperthyroidism are ruled out as the treatment differs. Epigastric pain and hematemesis should be specifically enquired about, which may be either an effect of prolonged vomiting (Mallory Weiss tear) or suggest other pathology which is causing the symptoms

such as peptic ulcer disease. The duration of vomiting is important in assessing the risk of complications, like Wernicke's encephalopathy as a result of thiamine deficiency, which has been reported from 3 weeks after the onset of symptoms<sup>17</sup>.

## Examination

Pulse rate and blood pressure along with assessment of hydration from mucous membranes and skin turgor and also abdominal examination for epigastric tenderness, organomegaly, renal angle tenderness and uterine size is required.

## Investigations

When available, electrolytes, liver function tests, thyroid function tests, creatinine, blood urea nitrogen, urinalysis mainly for ketonuria and a complete blood count including malaria are some of the investigations that need consideration in the work-up of severe hyperemesis gravidarum where starvation and fluid imbalance can be encountered. Initial assessment can be done with clinical findings and ketonuria (via dipstick method) whereas prolonged symptoms need investigations such as electrolytes, liver and renal function tests, as well as thyroid function tests. Investigations indicated for women

**Table 2** Factors associated with hyperemesis gravidarum

<i>Association</i>	<i>Significance</i>	<i>Study design</i>	<i>Numbers in the study</i>
Low prolactin levels	$p < 0.01$	Prospective cohort study <sup>5</sup>	262
Higher levels of estradiol	$p = 0.06$	Prospective cohort study <sup>5</sup>	262
Estriol, progesterone, or sex hormone-binding globulin	No association	Prospective cohort study <sup>5</sup>	262
Increased plasma TNF-alpha concentration	$p < 0.05$	Case-control study <sup>13</sup>	90
Interleukin-2 receptor	No association	Case-control study <sup>13</sup>	90
Interleukin-8	No association	Case-control study <sup>13</sup>	90
High interleukin-6 levels	$p = 0.13$	Case-control study <sup>13,14</sup>	90
Lower socioeconomic status and association with <i>H. pylori</i>	$p = 0.013$	Case-control study <sup>6</sup>	146
Increased plasma fetal DNA concentration	$p < 0.001$	Double-blind case-control study <sup>9</sup>	202
Increased TSH level	$p < 0.05$	Case-control study <sup>15</sup>	84
High plasma adenosine level	$p < 0.05$		84
Serum anti- <i>H. pylori</i> IgG antibodies	No significant association	Prospective case-control study <sup>16</sup>	160

**Table 3** Differential diagnosis of hyperemesis gravidarum

- Acute appendicitis
- Cholecystitis
- Cholelithiasis
- Diabetic ketoacidosis
- Esophagitis
- Gastritis
- Gastroenteritis
- Gastroesophageal reflux disease
- Hepatitis
- Hydatidiform mole
- Hyperparathyroidism
- Hyperthyroidism
- Irritable bowel syndrome
- Ovarian torsion
- Pancreatitis
- Peptic ulcer disease
- Pre-eclampsia pregnancy
- Pseudotumor cerebri
- Pyelonephritis
- Malaria
- Small bowel obstruction
- Urinary tract infection
- Vestibular dysfunction

with hyperemesis are limited as the diagnosis is clinical, although the severity of disease may be indicated particularly by the electrolyte and liver function test results and consideration may be given to other tests which may exclude differential diagnoses in selected cases.

#### **Role of ultrasound**

Traditionally, twin and molar pregnancies have been associated with women having hyperemesis gravidarum<sup>3,18–20</sup>. However, a study found the same incidence of twin pregnancies in both groups with or without excessive vomiting<sup>21</sup>. This study also showed a lower miscarriage rate in women with hyperemesis gravidarum than controls consistent with previous reports of lower fetal loss rates in women with hyperemesis gravidarum than in the asymptomatic pregnant population<sup>22,23</sup>. Thus, a clear association between twin and molar pregnancies with hyperemesis gravidarum is questioned. However, ultrasound may be done to relieve maternal anxiety regarding her pregnancy viability status.

## **CLINICAL CONSEQUENCES OF HYPEREMESIS GRAVIDARUM**

### **Physical effects**

The vomiting, discomfort and reduced appetite that accompanies hyperemesis gravidarum interferes with caloric and fluid intake leading to weight loss, dehydration, deteriorating nutritional state and often acid base and electrolyte imbalance. Hyperemesis gravidarum symptoms that persist into the third trimester are associated with a higher incidence of low-birth-weight infants<sup>24</sup>.

A mild to moderate ketonuria may be seen which reflects metabolism of fatty acids due to inadequate caloric and protein intake. Ketones readily cross the placenta and may impair fetal neuro-psychological development<sup>25</sup>.

Thiamine (B<sub>1</sub>) deficiency has been reported in as many as 60% of hyperemesis gravidarum patients<sup>26</sup>. The woman with hyperemesis gravidarum is prone to thiamine deficiency due to the increased demand for glucose metabolism, added to the inability to tolerate adequate food and vitamin/mineral supplements. Glucose metabolism is very active in pregnant woman due to the hypermetabolic state of pregnancy and the developing fetus's energy needs and rapid tissue production. Thiamine deficiency can result in beri-beri symptoms that include fatigue, loss of appetite, emotional instability, sleep disturbances and abdominal discomfort. Advanced neuropathic manifestations of beri-beri include paresthesias, weakness, tenderness and cramps of the lower extremities. The cerebral progression of thiamine deficiency resulting in Wernicke's encephalopathy has been reported in 33 cases in the past 20 years<sup>27,28</sup>. The initiation of dextrose-containing intravenous fluids or aggressive nutrition support, without the provision of thiamine, can precipitate Wernicke's encephalopathy. Thiamine administration of 100mg intravenously (IV) or intramuscularly (IM) daily, or enterally if tolerated, has been suggested for any patient with more than 3–4 weeks of emesis<sup>29</sup>.

Hyperemesis gravidarum seems to be associated with higher levels of selected forms of hCG with the greatest thyroid-stimulating capacity by acting via the TSH receptor to accelerate iodine uptake. Biochemical thyrotoxicosis is common in hyperemesis gravidarum but the majority of women are clinically euthyroid. When thyroxine or TSH fall outside the normal range then this is termed

transient gestational thyrotoxicosis and resolves by the mid-second trimester<sup>30</sup>.

Women who are clinically hyperthyroid may have Graves' disease and should have autoantibodies measured if available. Treatment with anti-thyroid drugs or beta-adrenergic blockers is only indicated if clinical and biochemical features of hyperthyroidism are apparent. Hyperthyroidism is often overdiagnosed and inappropriately treated in women with hyperemesis gravidarum<sup>31</sup>.

Hyperemesis gravidarum can cause a mild increase in liver enzymes (up to four times the upper limit of normal) that return to normal when the hyperemesis gravidarum is successfully treated<sup>32</sup>.

Serum amylase may rise up to five times greater than normal, but this is usually salivary and not pancreatic amylase<sup>33</sup>. Excessive retching during hyperemesis gravidarum may lead to esophageal rupture, Mallory Weiss tears, pneumothorax and pneumomediastinum.

### Psychosocial effects

There has long been a presumption that women with hyperemesis gravidarum develop their physical symptoms as a result of psychological or social factors<sup>34</sup>; a review of the literature regarding this found no evidence to support this theory, although it is reported that psychological responses to hyperemesis may contribute to disease severity<sup>35</sup>. A study suggests that the psychological manifestations may be a result of hyperemesis gravidarum rather than the cause<sup>36</sup>. It is likely that hyperemesis involves an interaction of biological, psychological and socio-cultural factors.

A recent study has devised 'The Hyperemesis Impact of Symptoms Questionnaire' as a clinical tool to assess holistically the impact of the physical and psychosocial symptoms of hyperemesis gravidarum on individuals<sup>37</sup>.

### MANAGEMENT

Hyperemesis gravidarum is in general a self-limiting condition and the management remains supportive. Symptomatic treatment of nausea and vomiting, correction of dehydration and electrolyte imbalance and prevention of complications of the disease remain the mainstay. Dehydrated and ketotic women require admission. Out-patient management has been mentioned with daily attendance at hospital for intravenous fluids and antiemetics<sup>38</sup>. A

few studies done in the USA report home care management (with home intravenous fluids or continuous subcutaneous metoclopramide) thus avoiding hospitalization but it is not practical in most healthcare settings<sup>39-41</sup>. Response to therapy is monitored daily by reduction in vomiting episodes, by the amount of fluid and food tolerated, increased maternal weight, reduction in ketonuria and balanced serum electrolytes.

Therapy with intravenous fluids for correction of dehydration is the mainstay of management. The volume of fluid should replenish the deficit along with the loss through vomiting as well as meet normal fluid and electrolyte requirements.

Fluid replacement is tailored to ketonuria or electrolytes and stopped once these are equalized and a normal diet is resumed.

### Fluid usage

#### *In first 24 hours*

- 11 Lactated Ringer's solution over 2 h
- 11 Lactated Ringer's solution over 4 h
- 11 0.9% saline over 6 h
- 11 0.9% saline over 8 h

#### *Followed by*

- 11 0.9% saline every 8 h as maintenance regimen

Avoid dextrose-containing solutions.<sup>17</sup>

Avoid high concentration sodium chloride.

### MEDICAL THERAPIES

There are good safety data to support the use of antihistamines, phenothiazines and metoclopramide in hyperemesis gravidarum. For an overview, see Table 4.

Pharmacological treatment is usually required in hyperemesis as it causes severe vomiting leading to ketosis. However, other causes of nausea and vomiting should be excluded before proceeding with medicinal therapies.

A few cohort and case-control studies with over 170,000 exposures demonstrated pyridoxine and doxylamine combination to be safe, in particular relating to effects on the fetus<sup>42</sup>.

Corticosteroids are considered only as a last resort if vomiting does not respond to antihistamines<sup>27,43</sup>. Antihistamines act by inhibition of histamine at the H<sub>1</sub> receptor and also via the vestibular

**Table 4** Medicinal therapies commonly used in hyperemesis gravidarum<sup>27,43</sup>

<i>Agents</i>	<i>Dosage</i>	<i>Classification*</i>	<i>Comments</i>
<i>Antinausea agents</i>			
Promethazine (Phenergan <sup>®</sup> )	12.5–25 mg orally, rectally, or IM q. 4–6 h	C	No teratogenicity
Prochlorperazine (Compazine <sup>®</sup> )	5–10 mg orally q. 6–8 h; 5–10 mg IM q. 3–4 h; 2.5–10 mg IV q. 3–5 h; 25 mg rectally q. 12 h	C	Clinically effective, conflicting reports on safety
<i>Motility agents</i>			
Metoclopramide	5–10 mg q. 6–8 h orally, IM or IV	B	Safe and effective
<i>Vitamin/mineral supplements</i>			
Pyridoxine (vitamin B <sub>6</sub> )	10–25 mg t.i.d.–q.i.d. orally	A	Safe and effective, component of Bendectin <sup>®</sup>
Doxylamine	12.5 mg t.i.d.–q.i.d. orally	B	Component of Bendectin <sup>®</sup>
<i>Antihistamine medications</i>			
Droperidol	0.625–1.25 mg IM/IV q. 3–4 h	C	Limited data, use with caution
Meclizine	25–50 mg orally q. 12–24 h	B	Conflicting reports on safety, not used very often
Dimenhydrinate	50–100 mg orally q. 4–6 h. Do not exceed 400 mg per day. If used with doxylamine, do not exceed 200 mg per day	B	
Diphenhydramine (Benadryl <sup>®</sup> )	25–50 mg orally/IM/IV q. 4–8 h	B	
<i>Corticosteroid</i>			
Methylprednisolone	16 mg q. 8 h orally or IV × 3 days. Then taper over 2 weeks to lowest effective dose. Limit usage to 6 weeks if found beneficial. If no symptoms do not improve in 3 days – discontinue	C	Avoid before 10 weeks, use with caution
<i>Ginger</i>	1–4 g/day in divided doses orally		

\*Category A, well-controlled studies in humans show no fetal risk; category B, animal studies show no risk, but human studies inadequate or animal studies show some risk not supported by human studies; category C, animal studies show risk, but human studies are inadequate or lacking.

system, with a combined effect of decreasing stimulation of the vomiting center<sup>44</sup>. A meta-analysis of over 200,000 women treated with antihistamines for nausea and vomiting in pregnancy showed no evidence of teratogenicity<sup>45</sup>. A recent report suggests a protocol consisting of the combination of metoclopramide and diphenhydramine as a good option for management of hyperemesis gravidarum<sup>46</sup>.

The use of antihistamines increased by 100% between 2000 and 2004 due to the increased evidence of safety as shown by a survey<sup>47</sup>. A recent report has shown that exposure to metoclopramide in the first trimester was not associated with increased risk of any adverse outcomes<sup>48</sup>. Similarly, a recent report showed good tolerance with desloratadine with no adverse drug reactions<sup>49</sup>. A prospective recent observational cohort study on cetirizine

in pregnancy suggests that use of the drug is relatively safe during the first trimester<sup>50</sup>.

Rarely, extrapyramidal side-effects of antiemetic drugs are seen as acute dystonic reactions in facial muscles spasms or as oculogyric crises which are usually self-limiting. Avoiding further administration of the antiemetic responsible often suffices. Prochlorperazine is rarely needed.

Phenothiazines such as prochlorperazine and chlorpromazine are dopamine antagonists and inhibit vomiting by inhibiting the chemoreceptor trigger zone along with a direct action on the gastrointestinal tract D<sub>2</sub> receptors. There have been case reports of cleft palate, skeletal, limb and cardiac abnormalities with its use<sup>44</sup>. The higher doses used for antipsychotic effect have been associated with temporary extrapyramidal effects postnatally but the doses used for antiemetic treatment are much lower<sup>44</sup> and hence for short-term emergency treatment of hyperemesis gravidarum, they should be used.

Vitamin B<sub>6</sub> (pyridoxine) is effective in reducing nausea and vomiting in pregnancy, although not hyperemesis<sup>51,52</sup>. A placebo-controlled trial of oral pyridoxine in conjunction with metoclopramide did not show reduced rehospitalization rate, vomiting score or the nausea score compared with placebo in conjunction with metoclopramide<sup>53</sup>.

Other antipsychotic drugs such as levomepromazine<sup>54</sup> and haloperidol<sup>55</sup> do not have enough data to assess the safety of their use. Similarly, domperidone inhibits the central chemoreceptor trigger zone, but there are no reported data on its safety in pregnancy.

### Role of corticosteroids

Corticosteroids use in pregnancy for hyperemesis shows conflicting results. One group found similar efficacy but lower readmission rates in the steroid group when compared with oral promethazine<sup>56</sup>. Another trial showed oral prednisolone to be less effective than promethazine at 48 h, although similar efficacy was noted after the first 7 days of treatment<sup>57</sup>. Nelson-Piercy *et al.* found non-significant improvement in nausea and vomiting and reduced dependence on intravenous fluids with steroids compared with placebo although a significant increase in appetite and improvement in sense of well-being was seen<sup>58</sup>. In those with intractable hyperemesis gravidarum admitted to an intensive care unit given hydrocortisone or metoclopramide, there was significantly less vomiting and no

readmissions with steroids compared with metoclopramide<sup>59</sup> (level of evidence 1a).

Regarding safety with corticosteroids in the first trimester of pregnancy, some studies have suggested possible malformations, particularly an association with cleft defects. However, a review concluded that reporting bias may have contributed to these findings and that the teratogenic potential of corticosteroids is so low as to be undetectable from the data available<sup>60</sup>. Also, the cleft is already formed by the 10th week of pregnancy after which steroids can be considered in resistant cases. Steroid treatment for hyperemesis remains controversial reserving the drug for women with severe prolonged symptoms unresponsive to other treatments.

### Ginger (*Zingiber officinale*)

Ginger root is reported to have chemoprotective activity in animal models. The methanol extract of ginger rhizome has been seen to inhibit the growth of 19 strains of *H. pylori* by Mahady *et al.*<sup>7</sup>.

Ginger has shown superior efficacy compared to placebo without any adverse outcomes or side-effects in cases of nausea and vomiting in pregnancy<sup>61-65</sup>, but not for hyperemesis gravidarum. Trials for hyperemesis gravidarum are lacking and only one trial has suggested a possible benefit<sup>54</sup>. Ginger-containing drugs are not approved by the United States Food and Drug Administration (US FDA) with concerns of potential effect on testosterone binding and thromboxane synthetase activity, but are remedies believed to improve symptoms and strongly recommended by the American College of Obstetrics and Gynecology (ACOG) 2004<sup>27</sup>. The dose to be given is 250 mg of powdered ginger root administered orally every 6h. Ginger is available in a number of forms such as tea, biscuits, confectionary, and crystals or sugared ginger, and although none has been subject to randomized controlled trials, there is some evidence that these forms of ginger may be beneficial and without adverse effects<sup>66</sup>. Fresh ginger can also be used as it is available at most grocery stores and health food stores. To prepare it for eating, the brown skin is peeled off and ginger is washed under running water. It is cut into small, thin slices to be eaten plain or added to salad, stew or soup. Women can put a slice of fresh ginger between their cheek and gum and chew on it throughout the day or they can nibble on small pieces of crystallized ginger.

They can also go to a Chinese food store and get a container of pickled ginger, which is moist and has a very stomach-soothing effect. Tea can also be prepared with fresh ginger by boiling about five of the small slices and letting them steep in the boiled water for up to 20 min. Ginger is then removed from the tea and tea is prepared as normal by adding honey, milk or sugar.

Commonly used medical therapies with their dosage are depicted in Table 4.

### Non-pharmacological antiemetic therapies

Non-pharmacological therapies like acupressure bands and acupuncture have been tried in the treatment for nausea and vomiting in pregnancy, but not hyperemesis gravidarum. A systematic Cochrane review supports the use of P6 acupoint stimulation which seems to reduce the risk of nausea<sup>67</sup>. National evidence-based clinical guidelines (National Institute for Health and Clinical Excellence, NICE) October 2003 on antenatal care recommend ginger, P6 acupressure and antihistamines for the treatment of nausea and vomiting in pregnancy showing level I evidence. Acupuncture requires a trained practitioner and acupressure may be a cheaper and more readily available option. Acupressure involves the stimulation of the P6 Neiguan point either manually or with elasticized bands. The P6 point is on the inside of the wrist, about 2–3 finger breadths proximal to the wrist crease between the tendons about 1 cm deep. Manual pressure is applied to this point for 5 min every 4h. Alternatively pressure can be applied by wearing an elasticized band with a 1 cm round plastic protruding button centered over the acupressure point<sup>68</sup>.

Low-level nerve stimulation therapy over the volar aspect of the wrist has been shown to reduce nausea and vomiting and promote weight gain in pregnancy<sup>67</sup>.

### DIETARY GUIDELINES FOR HYPEREMESIS GRAVIDARUM

Once the nausea and vomiting are under control and a liquid diet is tolerated, a healthcare provider can begin counseling the patient on initiation of an oral diet. Although there is very little scientific evidence to support these dietary interventions, practitioners have relied on these guidelines with reported success. Dietary management consists of small, frequent meals of bland, low odor, high-

complex carbohydrate and low-fat foods. Oral dietary guidelines can be found in Table 5.

### Vitamin supplementation

According to ACOG<sup>27</sup>, taking multivitamins at the time of conception decreases the severity of symptoms. Women with hyperemesis gravidarum symptoms need to be prescribed thiamine (vitamin B<sub>1</sub>) if their symptoms are prolonged, especially for 3 weeks or more<sup>17</sup>. Oral thiamine 50 mg daily, or 100 mg IV are suitable regimens, or the compound multivitamin preparation as an infusion once weekly can be given until normal oral intake has resumed.

### Supplementary feeding in hyperemesis gravidarum

If women do not respond to medical treatment, feeding by nasogastric tube or parenteral nutrition has been used. However, the latter is associated with complications of venous thromboembolism and sepsis<sup>69–73</sup>.

### EMOTIONAL SUPPORT

The woman with hyperemesis gravidarum needs to be encouraged to express her feelings. She requires a caring and supportive attitude from healthcare providers. The woman with hyperemesis gravidarum tends to isolate herself and is unable to resort to the usual methods of coping. Phone contact from the healthcare provider can be comforting for the patient. One survey reported 85% of pregnant women with nausea and vomiting who phoned a helpline received inadequate support from their close family members<sup>74</sup>. The patient and her family require reassurance that this is a self-limiting condition with no harm to the fetus. The healthcare provider should look for factors causing emotional and family stress that may aggravate the woman's hyperemesis gravidarum symptoms. These stressors need to be minimized to optimize tolerance to the nutritional plan through sensitization of the family.

### CLINICAL CONSEQUENCES OF HYPEREMESIS GRAVIDARUM

#### Wernicke's encephalopathy

Wernicke's encephalopathy occurs due to vitamin B<sub>1</sub> (thiamine) deficiency and is potentially fatal. The earliest reported onset of encephalopathy was



**Table 5** Suggested dietary guidelines to improve oral tolerance

*When fixing meals*

Avoid cooking if possible. Ask for help from friends or family  
 Prepare foods that do not require cooking, like sandwiches  
 Avoid smell of hot food – try having cold food instead  
 Drink chilled beverages – flat lemonade, diluted fruit juice, weak tea or clear soup as they are tolerated better than water  
 Avoid eating in a place that is stuffy, too warm, or has cooking odors  
 Have someone else to remove covers from cooked foods

*When eating*

Eat small frequent meals – nibble on light snacks between meals  
 Drink fewer liquids with meals. Drink liquids half to one hour after meals  
 Drinking liquids can cause a full, bloated feeling  
 Avoid food that is fatty, fried, spicy, very sweet, such as candy, cake or cookies, with strong odors, like cooked broccoli, cabbage, fish, etc.  
 Choose bland foods. Try toast, crackers, pretzels, rice, oatmeal, skinned chicken (baked or broiled, not fried), and fruits and vegetables that are soft or bland  
 Eat easily digested starches, like rice, millet, potatoes, noodles, cereal and bread  
 Choose low-fat protein foods like skinless chicken and boiled beans  
 Try eating salty, sweet food combinations, like potato chips or pretzels before meals

*Other tips*

Eat when you feel best or hungry  
 Rest after meals. Sit up in a chair for about an hour after meals  
 Avoid sudden movements. Rise slowly from the bed  
 Eat crackers, toast, pretzels, or rice cakes before getting out of bed  
 When feeling nauseated, slowly sip on carbonated beverages  
 Wear loose clothes  
 Taking a multivitamin at the time of conception may decrease the severity of nausea and vomiting during pregnancy  
 Avoid stress – constant threat of nausea or vomiting is itself a stressor

3 weeks after the onset of vomiting and mean duration of vomiting was  $7.7 \pm 2.8$  weeks before the onset of symptoms<sup>17</sup>.

The classical presentation is the triad of confusion, ocular abnormalities and ataxia, which has been reported in 47% of cases<sup>17</sup>. For many women, the presentation may be subtle with memory loss, apathy and decreased level of consciousness. It is reversible with treatment although some residual impairment may remain. The fetal loss rate with Wernicke's encephalopathy is reported to be 37%<sup>17</sup>.

Any woman presenting with a neurological abnormality in association with hyperemesis gravidarum should be treated with intravenous thiamine 100mg daily, and observation of rapid improvement helps confirm the diagnosis. Treatment should be continued initially intravenously and subsequently with oral thiamine 50mg per day until a balanced diet resumes. In those receiving intravenous fluids, this should be preceded by administration of thiamine as the dextrose load

increases vitamin B<sub>1</sub> requirements and thus may precipitate encephalopathy.

**Hyponatremia**

Hyponatremia can occur in hyperemesis gravidarum. Symptoms of hyponatremia include nausea and vomiting, headache, confusion, lethargy, fatigue, appetite loss, restlessness and irritability, muscle weakness, spasms, or cramps, seizures and decreased consciousness or coma, which should be treated with intravenous infusion of sodium chloride 0.9% as described above. Rapid correction results in osmotic demyelination syndrome characterized by the loss of myelin in the pontine neurons resulting in confusion, dysarthria, dysphagia, paralysis and muscle spasm which may be irreversible<sup>75,76</sup>.

**Mallory Weiss tears**

Disruption of the esophageal mucosa due to the effects of vomiting may result in a Mallory Weiss

tear and hematemesis. This must be differentiated from hematemesis from other more serious causes such as peptic ulceration. Most women with a Mallory Weiss tear will have relatively small amounts of hematemesis, occurring after retracted vomiting. A pragmatic approach is to administer intravenous ranitidine to women with epigastric pain or history suggestive of Mallory Weiss tear, but to consider upper gastrointestinal tract endoscopy if available or referral to a higher level unit if the bleeding occurs without protracted vomiting, is profuse or if the hemoglobin level falls.

#### **Acute renal failure**

Renal failure has been reported as a result of dehydration, requiring haemodialysis<sup>77</sup>.

#### **Venous thromboembolism**

Of the six women who had a pulmonary embolism in their antenatal period in the latest Confidential Enquiry into Maternal and Child Health report (2006–2008), three died in the first trimester; three women had excessive vomiting in pregnancy, and two died after prolonged immobility<sup>78</sup>. The combination of pregnancy, immobility and dehydration are likely to confer significant risk of thrombosis and therefore prophylaxis is deemed pragmatic in the form of good hydration, mobilization when possible, thromboembolic stockings and low-molecular-weight heparin where available. The updated Royal College of Obstetrics and Gynaecology (RCOG) guideline lists hyperemesis as a risk factor for thrombosis<sup>79</sup>.

#### **Termination of pregnancy**

Women with hyperemesis gravidarum have an increased likelihood of considering termination of pregnancy (TOP). In a questionnaire survey of 3201 callers to a helpline for nausea and vomiting in pregnancy, 413 had considered TOP and 108 underwent TOP<sup>80</sup>. Unplanned pregnancy, multiparity and depression were significant risk factors for undergoing TOP. Consideration of termination in these women is associated with psychosocial circumstances, which should be taken into consideration when managing such women.

#### **Depression**

Hyperemesis is strongly associated with depression<sup>81</sup>. However, interventions against depression have not been studied. Whether early psychological input would decrease complications related to depression is not known.

#### **PROGNOSIS**

##### **Fetal**

Some studies have reported increased rate of prematurity, small-for-gestational-age babies and Apgar scores <7 at 5 min in women with hyperemesis gravidarum<sup>82,83</sup>. However, no increase in adverse fetal outcomes has been found in one recent study of 166 women<sup>84</sup>. The risk of small-for-gestational-age fetuses is found to be increased only in cases with inadequate maternal weight gain due to chronic hyperemesis gravidarum. Ninety per cent of hyperemesis resolves by 16 weeks and most maternal weight is gained in the latter half of pregnancy.

Long-term neurodevelopment of children exposed to maternal nausea and vomiting during pregnancy and treatment with Diclectin® (delayed release combination of doxylamine succinate and pyridoxine hydrochloride) has shown no adverse effects on fetal brain development<sup>85</sup>.

##### **Maternal**

Other than Wernicke's encephalopathy, long-term effects on the mother are not reported. Whether there are long-term psychological effects, poor bonding with the baby, or fear of future pregnancies is not clear.

There is an increased risk of recurrence for hyperemesis, with the risk of being 15.2% in a woman who has had a previous episode of hyperemesis gravidarum, compared with 0.7% in a woman who did not have hyperemesis gravidarum in her previous pregnancy<sup>1</sup>. Koren and Maltepe studied women with previous hyperemesis gravidarum and commenced antiemetic medication before conception or within the 7 weeks of gestation and found 40% of the women developing hyperemesis gravidarum compared with 80% of the women in the group of controls not given antiemetics<sup>86</sup>.

## KEY ISSUES

- Intravenous rehydration should be with 0.9% sodium chloride to prevent iatrogenic complications of Wernicke's encephalopathy from dextrose infusion or of osmotic demyelination syndrome from too rapid correction of serum sodium concentration.
- There is good evidence of safety from antihistamine antiemetics and little evidence of adverse outcomes. 5HT<sub>3</sub> antagonists have a less clear safety record and thus should not be used unless other treatments fail, and after consultation with the woman.
- The benefit of intravenous corticosteroid treatment remains equivocal.
- Ginger (*Zingiber officinale*) 500–1500 mg orally in divided doses has been shown to be effective in reducing nausea and vomiting in four randomized controlled trials.
- There is equivocal evidence of benefit from acupressure at the P6 point (wrist).
- Thiamine replacement is indicated in hyperemesis gravidarum, particularly once vomiting has been occurring for at least 3 weeks (the minimum time shown for thiamine stores to be depleted), to prevent development of Wernicke's encephalopathy.

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