Arch Gynecol Obstet (2011) 283:1183–1192
DOI 10.1007/s00404-011-1877-y

MATERNO-FETAL MEDICINE

The clinical management of hyperemesis gravidarum

Shipra Sonkusare

Received: 22 September 2010 / Accepted: 7 March 2011 / Published online: 20 March 2011

Abstract Hyperemesis gravidarum is a severe and disabling condition with potentially life-threatening complications. It is likely to have a multifactorial etiology which contributes to the difficulty in treatment. Treatment is supportive with correction of dehydration and electrolyte disturbance, antiemetic therapy, prevention and treatment of complications like Wernicke's encephalopathy, osmotic demyelination syndrome, thromboembolism, and good psychological support. There are abundant data on the safety of antihistamines, phenothiazines, and metoclopromide in early pregnancy and treatment should therefore not be withheld on the basis of teratogenicity concerns. Thiamine replacement is indicated in hyperemesis gravidarum to prevent development of Wernicke's encephalopathy.

Keywords Nausea and vomiting of pregnancy · Hyperemesis gravidarum · Morning sickness · Wernicke's encephalopathy · Antiemetics

Introduction

Hyperemesis gravidarum (HG) is a disease of severe nausea, vomiting, and anorexia associated with early pregnancy leading to dehydration and weight loss. As the etiology remains obscure, the treatment remains supportive and symptomatic. HG occurs in approximately 0.3–2% of pregnancies [1]. The principal condition to diagnose HG is the presence of three or more vomiting episodes during the day, weight loss of over 5% (or 3 kg), and ketonuria [2, 3]. The problem is generally time-limited with onset about the fifth week after the last menstrual period, a peak at 8–12 weeks, and resolution by 16–18 weeks for most women; approximately 5% of women with hyperemesis will have symptoms throughout the pregnancy [4]. 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 birth weight, small for gestational age and a 5-min apgar score of less than 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.

Etiopathogenesis

The factors associated with hyperemesis are primarily medical and fetal factors that are not easily modifiable, but their identification may be useful in determining those women at high risk for developing hyperemesis. High risk for recurrence is observed in women with hyperemesis in the first pregnancy. The risk is reduced by a change in paternity [5]. 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 seen in hyperemesis [5]. A low prepregnancy weight: height ratio may predispose women to the development of hyperemesis [6]. Low maternal age and parity 1+ independently increases the risk for nausea and

S. Sonkusare
Department of Obstetrics and Gynaecology, Kasturba Medical College, Manipal University, Manipal, Karnataka 576104, India

S. Sonkusare (✉)
Kasturba Medical College, House No. 173, Near End-Point, KMC Quarters, Manipal, Karnataka 576104, India
e-mail: shipra_s18@rediffmail.com; shipra_s18@yahoo.co.in

vomiting in pregnancy [5]. Smoking before pregnancy and using vitamins in early pregnancy are associated with a decreased risk for nausea and vomiting (Level of Evidence—II-2 [7]). Women working outside the home have a lower rate of nausea and vomiting than do housewives and women out of work [8].

Hormonal factors are known to play an important role in the etiology. Chorionic gonadotropin, especially isoforms with relatively diminished amounts of sialic acid, act via the thyroid-stimulating hormone receptor to accelerate iodine uptake [9]. Also low levels of prolactin and high levels of estradiol can contribute to nausea in pregnancy [10].

Psychological and social factors may influence this disease, such as unwanted pregnancies as stated by a study [11]. However, psychological manifestations may be a result of HG rather than the cause [12]. Young unwed mothers 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.

Recently, association between *Helicobacter pylori* (*H. pylori*) and hyperemesis gravidarum has been found and serologically positive *H. pylori* infection has been demonstrated in the hyperemesis group [13]. The elevated human chorionic gonadotropin (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 socio-economic status may also be an important risk factor of infection with *H. Pylori* in pregnant women with hyperemesis gravidarum [14].

The recent reports also significantly correlate the severity of hyperemesis with increased concentrations of cell-free fetal deoxyribonucleic acid (DNA) [15]. The fetal DNA comes from the destruction of villous trophoblasts which border the intervillous space filled with maternal blood [16, 17]. 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 [18]. The clinical severity of hyperemesis is directly associated with the increase in fetal DNA. If the maternal immune system completely tolerates the fetus, the myometrium might be invaded by growing trophoblasts, but in the presence of anomalies of the immune interaction between the mother and the fetus, invasion of trophoblasts into the myometrium would lead to increased concentrations of fetal DNA in the maternal plasma. In hyperemesis, a similar situation can occur. Thus, hyperactivation of the maternal immune system may be responsible for the onset of hyperemesis, probably while maternal immune tolerance to the semiallograft is being established. This could explain why fetal DNA and hyperemesis are related and proportionally correlated.

Furthermore, levels of tumor necrosis factor-alpha are found to be significantly high in patients with hyperemesis and could be involved in the etiology [19]. Similarly, high levels of interleukin-6 are reported to enhance secretion of beta-hCG from trophoblastic cell line [20].

Diagnosis

Hyperemesis gravidarum is diagnosed when protracted vomiting is present along with the inability to tolerate solids or fluids and the presence of ketonuria. Certain scoring systems have been devised for quantification [21, 22] which include questions on the number of daily vomiting episodes, the length of nausea, and the number of retching episodes. However, these scores are not commonly used in regular clinical practice, as by the time the scoring is done, the symptoms are reduced by the end of the first trimester in most of these women.

The 'Pregnancy Unique Quantification of Emesis (PUQE) Score' [21] questionnaire has been validated and shown to correlate with clinical outcomes such as rates of hospitalization and women's subjective feelings of well-being [22]. A modified PUQE score has also been developed to cover global nausea and vomiting for the whole first trimester of pregnancy [23]. The modified score shows good correlation with quality of life scores (the 12-item short-form health survey) and is useful in identifying the severity of symptoms over a longer time period [23].

Differential diagnosis

The diagnosis of uncontrollable vomiting is made by exclusion of other disease entities. It is necessary to exclude many chronic diseases involving other systems like diseases of digestive system such as hepatitis, pancreatitis, chronic peptic ulcer disease; urinary system and chronic endocrinological diseases like diabetic ketoacidsis or hyperthyroidism; neurological diseases like brain tumors, migraine; and other states connected with pregnancy such as fatty degeneration of the liver and pre-eclampsia [4, 24].

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 [25].

Examination

Pulse rate and blood pressure along with assessment of hydration from mucous membranes and skin turgor and abdominal examination for epigastric tenderness,

organomegaly, renal angle tenderness, and uterine size are required.

Investigations

Electrolytes, liver function tests, thyroid function tests, creatinine, blood urea nitrogen, urinalysis, and a complete blood count are some of the investigations that need consideration in the workup of severe hyperemesis gravidarum where starvation and fluid imbalance can be encountered. Investigations indicated for women with hyperemesis are limited as the diagnosis is clinical, though 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 HG [1, 7, 26, 27], However, a study has found the same incidence of twin pregnancies in both groups with or without excessive vomiting [28]. As the diagnosis of molar pregnancy is now made earlier due to the availability of ultrasound, hyperemesis may not be so strongly associated with molar pregnancy as the condition is rarely allowed to progress beyond the first few weeks of pregnancy. This study also showed a lower miscarriage rate in women with HG than in controls, consistent with previous reports of lower fetal loss rates in women with HG than in the asymptomatic pregnant population [29, 30]. Thus, a clear association between twin and molar pregnancies with HG is questioned. However, ultrasound may be performed to relieve maternal anxiety regarding her pregnancy viability status.

Physiologic effects of hyperemesis gravidarum

The vomiting, discomfort, and reduced appetite that accompany HG interfere with caloric and fluid intake leading to weight loss, dehydration, deteriorating nutritional state and often acid base, and electrolyte imbalance. HG symptoms that persist into the third trimester are associated with a higher incidence of low-birth-weight infants [31].

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 neuropsychological development [32].

Thiamine (B1) deficiency has been reported in as many as 60% of HG patients[33]. The woman with HG 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. The cerebral progression of thiamine deficiency resulting in Wernicke's encephalopathy has been reported in 33 cases in the past 20 years [2, 34]. The initiation of dextrose containing intravenous fluids or aggressive nutrition support, without the provision of thiamine, can precipitate Wernicke's encephalopathy. Thiamine administration of 100 mg IV or IM daily, or enterally if tolerated, has been suggested for any patient with more than 3–4 weeks of emesis [35].

Temporary suppression of TSH is common in HG but the majority of women are clinically euthyroid. When thyroxine or TSH falls outside the normal range, then this is termed transient gestational thyrotoxicosis and resolves by the mid second trimester [36]. Women who are clinically hyperthyroid may have Graves' disease and should have autoantibodies measured. Treatment with antithyroid drugs or beta-adrenergic blockers is only indicated if clinical and biochemical features of hyperthyroidism are apparent. Hyperthyroidism is often over-diagnosed and inappropriately treated in women with hyperemesis gravidarum [37].

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 HG is successfully treated [38]. Serum amylase may rise up to five times greater than normal, but this is usually salivary and not pancreatic amylase [39].

Psychosocial effects of hyperemesis gravidarum

There has long been a presumption that women with HG develop their physical symptoms as a result of psychological or social factors [40, 41]. A review of the literature regarding this found no evidence to support the theory. A study suggests that the psychological manifestations may be a result of HG rather than the cause [12]. 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 (HG) on individuals [42].

Management

Hyperemesis gravidarum is 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 remains the mainstay. Dehydrated and

Table 1 Fluid replacement in hyperemesis gravidarum [47]

Fluid	Usage
In first 24 h	1 l 0.9% saline over 2 h with 20 mmol potassium chloride
	1 l 0.9% saline over 4 h with 20 mmol potassium chloride
	1 l 0.9% saline over 6 h
	1 l 0.9% saline over 8 h
Followed by	1 l 0.9% saline every 8 h as maintenance regime
	Potassium replacement according to serum potassium level
	Avoid dextrose containing solutions
	Avoid high concentration sodium chloride

ketotic women require admission. Outpatient management has been mentioned with daily attendance to hospital for intravenous fluids and antiemetics [43]. Few studies done in the USA report home care management (with home intravenous fluids or continuous subcutaneous metoclopromide) thus avoiding hospitalization, but is not practical in most healthcare settings [44–46]. Response to therapy is monitored daily by reduction in the vomiting episodes, 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 (Table 1).

Medical therapies

There are good safety data to support the use of antihistamines, phenothiazines, and metoclopromide in hyperemesis gravidarum. Other causes of nausea and vomiting should be excluded before proceeding with medicinal therapies.

Though the commercially available combination, Benedectin, was taken off the market in the United States in the 1980s because of liability issues, the ACOG Guidelines 2004 recommend 10 mg of pyridoxine plus one-half of 25 mg of doxylamine (antihistamine) administered orally every 8 h as first line pharmacotherapy. If it is not available over the counter, then sleep medications that contain doxylamine are recommended [48].

Various cohort and case–control studies with over 170,000 exposures demonstrated the pyridoxine and doxylamine combination to be safe, in particular relating to effects on the fetus [49].

Antihistamines act by inhibition of histamine at the histamine$_1$-receptor and also via the vestibular system, with a combined effect of decreasing stimulation of the vomiting center [50]. A meta-analysis of over 200,000 women treated with antihistamines for nausea and vomiting in pregnancy showed no evidence of teratogenicity [51]. A recent report suggests a protocol consisting of the combination of metoclopramide and diphenhydramine as a good option for management of hyperemesis gravidarum [52]. The use of antihistamines seems to have increased by 100% between 2000 and 2004 due to the increased evidence of safety as shown by a survey, wherein 765 women described treatment options received in 1,193 pregnancies on hyperemesis gravidarum website [53]. A recent report has shown that exposure to metoclopramide in the first trimester was not associated with increased risk of any adverse outcomes [54]. Out of 81,703 infants, 3,458 were exposed to metoclopramide during the first trimester of pregnancy. The rate of major congenital malformations identified in the group that was exposed to metoclopramide during the first trimester was 5.3% (182 of 3,458 infants) as compared with a rate of 4.9% (3,834 of 78,245 infants) in the unexposed group with odds ratio of 1.04, and no significant association was found when pregnancy terminations were included in the analysis. Similarly, exposure to metoclopramide during the first trimester of pregnancy was not significantly associated with an increased risk of minor congenital malformations or of multiple malformations, increased risks of preterm birth, low Apgar scores or perinatal death. No differences between the exposed and unexposed groups were found in the rates of low birth weight or very low birth weight. In unadjusted analyses, the frequency of major congenital malformations in the group exposed to daily doses of 30 mg per day for 22 or more days (6.1%) appeared to be greater than the frequency in the groups with less exposure (5.5, 4.3, and 4.2% in the groups that were exposed to 30 mg per day for 1 to 7, 8 to 14, and 15 to 21 days defined daily doses, respectively) and greater than the frequency in the unexposed group (4.9%), but there was no significant trend according to the defined daily doses either in the univariate analysis ($P = 0.55$ for trend) or in the analysis adjusted for maternal age, ethnic group, presence or absence of maternal diabetes, maternal smoking status, and parity ($P = 0.82$ for trend in multivariate analysis).

Similarly, a recent report showed good tolerance with desloratadine with no adverse drug reactions [55]. A prospective recent observational cohort study on cetrizine in pregnancy suggests that the use of drug is safe during the first trimester [56]. Rarely, extrapyramidal side effects of antiemetic drugs are seen as acute dystonic reactions in

facial muscle spasms or as oculogyric crises which are usually self-limiting. Avoiding further administration of the anti-emetic responsible often suffice. Procyclidine 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_2 receptors. There have been case reports of cleft palate, skeletal, limb, and cardiac abnormalities with its use [50]. 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 [50]. Thus, their use in pregnancy should be avoided as other better drugs are available.

The 5HT3 antagonist ondansetron also has a central chemoreceptor inhibition as well as a peripheral action on the small bowel and vagus nerve which inhibits vomiting. There is no reported increase in birth defects in humans with its use [57].

Vitamin B6 (pyridoxine) is shown to be effective in reducing nausea and vomiting during pregnancy [58, 59], though not studied for the management of acute hyperemesis.

Antipsychotic drugs such as levomeprazine [60] and haloperidol [61] 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

Corticosteroid use during pregnancy for hyperemesis shows conflicting results. One group found similar efficacy but lower readmission rates in the steroid group when compared with oral promethazine [62]. Another trial showed oral prednisolone to be less effective than promethazine at 48 h, though similar efficacy was noted after the first 7 days of treatment [63]. Nelson-Piercy found non-significant improvement in nausea and vomiting and reduced dependence on intravenous fluids with steroids as compared with placebo though a significant increase in appetite and improvement in sense of well-being was seen [64]. In those with hyperemesis gravidarum admitted to intensive care unit given hydrocortisone or metoclopromide, significantly less vomiting and no readmissions with steroids than metoclopromide was found [65].

Regarding safety with corticosteroids in the first trimester of pregnancy, some studies have suggested possible malformations, particularly an association with cleft lip and palate. 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 [66]. Also, the cleft is already formed by the 10th week of pregnancy after which steroids can be considered in resistant cases. As steroid treatment for hyperemesis remains controversial, the drug should be reserved for women with prolonged or severe symptoms which are unresponsive to other treatments.

Ginger (zingiber officinale)

Ginger root is reported to have chemoprotective activity in animal models. The gingerols are a group of structurally related polyphenolic compounds isolated from ginger and are known to be the active constituents. The methanol extract of ginger rhizome has been seen to inhibit the growth of 19 strains of *H. pylori* by Mahady et al. [67]. The fraction containing the gingerols is found to be active and inhibits the growth of all *H. pylori* strains with significant activity against the cytotoxin-associated gene (Cag) A+ strains, one of the important strains causing infection. Ginger has shown superior efficacy compared with placebo without any adverse outcomes or side effects in cases of nausea and vomiting during pregnancy [68–72], but not for hyperemesis gravidarum. Trials for HG are lacking and only one trial has suggested a possible benefit [61]. It has not been approved by the United States Food and Drug Administration (US FDA) with concerns of potential effect on testosterone binding and thromboxane synthetase activity, though no evidence exists to support the concern. However, these are remedies believed to improve symptoms and are strongly recommended by ACOG 2004 [2]. Powdered ginger root has to be administered orally at a dosage of 250 mg every 6 h. 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 demonstrate no adverse effects [73].

Non-pharmacological antiemetic therapies

Non-pharmacological therapies like acupressure bands and acupuncture have been tried for treating nausea and vomiting during pregnancy, but not for hyperemesis gravidarum. The systematic Cochrane Review supports the use of P6 acupoint stimulation which seems to reduce the risk of nausea [74]. National Evidence-based Clinical (NICE) Guidelines October 2003 on antenatal care recommend ginger, P6 acupressure, and antihistamines for the treatment of nausea and vomiting during pregnancy showing level I evidence. Low-level nerve stimulation therapy over the volar aspect of the wrist has shown to reduce nausea and vomiting and promote weight gain during pregnancy [74].

Table 2 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 1 h 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, or foods 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, 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 best 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

Dietary guidelines for hyperemesis gravidarum

Once the nausea and vomiting are under control and a liquid diet is tolerated, a dietitian 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 2.

Vitamin supplementation

According to American College of Obstetricians and Gynecologists (ACOG) [2], taking multivitamins at the time of conception decreases the severity of symptoms.

Women with HG symptoms need to be prescribed thiamine if their symptoms are prolonged, especially for 3 weeks or more [25]. Oral thiamine 50 mg daily, or 100 mg intravenous are the suitable regimens, or the compound multivitamin preparation as an infusion once weekly can be given until normal oral intake has resumed.

Supply of pyridoxine (vitamin B6) three times a day 10–25 mg, up to maximal dose 100 mg/24 h is recommended. The treatment is considered to be safe and its efficiency has been confirmed in three randomized clinical trials [60, 75, 76].

Folic acid requirements increase in pregnancy and supplementation is recommended in all pregnancies until the end of the first trimester to reduce neural tube defects. Empirically, women with hyperemesis can be prescribed folic acid 5 mg daily once oral intake has resumed to make up for the deficiency induced by vomiting.

Supplementary feeding in HG

Enteral nutrition allows the infusion of nutrients and fluid without the associated cephalic phase (visual cues, food aromas and flavors) that stimulates salivary and gastric secretions, which may play a role in inducing nausea and vomiting in HG. If a woman with HG has not responded to dietary manipulation and oral antiemetics, enteral nutrition should be considered. Enteral nutrition, ideally via the gastric route, is an approach that has been shown to offer significant relief from nausea and vomiting, prevent hospitalization, and lead to positive fetal outcomes [77–79]. The health care provider should explain to the patient how nutrition via a nasogastrically placed small bore feeding tube could offer rapid HG symptom relief while providing needed nutrition and fluids for both patient and infant. The possibility of symptom relief usually outweighs the esthetic concerns of having a feeding tube. In 1990, Barclay reported a retrospective review of eight HG patients with persistent emesis and weight loss that was unresponsive to dietary manipulation, IV fluids, and antiemetic medications. A continuous infusion via a nasoduodenal feeding tube placed fluoroscopically was well tolerated. During enteral nutrition, lasting a mean of 21 days, overall weight gain was reported in six women; vomiting varied from sporadic to daily, five patients had ptyalism (an excessive flow of saliva) and all eventually had successful pregnancy outcomes [80]. In addition, Barclay noted that ptyalism was common in the HG patients fed via the small bowel. Thus, gastric enteral nutrition appears to offer more rapid

relief of nausea and emesis when compared with small bowel feedings in the HG population. One more factor to consider is that endoscopic, radiographic or special bedside techniques are required to guide the feeding tube tip through the pylorus and advance it well into the small bowel.

For women who do not to respond to enteral nutrition, parental nutrition is used. As pregnancy suppresses the immune system, pregnant women are at greater risk for central venous catheter-related bacterial and fungal sepsis [81, 82]. Pregnant women also have elevated coagulation factors that make them more prone to catheter-related thromboembolism [83]. Safe initiation of parenteral nutrition requires hospitalization to stabilize the patient's hydration, fluid and electrolytes, establish good glucose control, and provide adequate home parenteral nutrition training which is expensive. There is no evidence to support the use of parenteral nutrition and it should only be used as a last resort when all other treatments have failed. Some authors have described the use of either a percutaneous endoscopic gastrostomy or percutaneous endoscopic gastro-jejunostomy tube in a few HG patients and have reported successful outcomes [84, 85]. The authors stated that drawbacks to feeding tubes were tube dislodgment and blockage.

Emotional support

Women with HG need to be encouraged to express their feelings. She requires a caring and supportive attitude from health care providers. The woman with HG tends to isolate herself and is unable to resort to usual methods of coping. Phone contact from the health care 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 [86]. A patient requires reassurance that this is a self-limiting condition. The health care provider should look for factors causing emotional and family stress that may aggravate the woman's HG symptoms. These stressors need to be minimized to optimize tolerance to the nutritional plan.

Hyponatraemia

Hyponatraemia can occur in hyperemesis gravidarum 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 [87, 88].

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 protracted 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 the bleeding occurs without protracted vomiting, is profuse, or if the hemoglobin level falls.

Venous thromboembolism

Ten of the 33 women who were reported to have died from pulmonary embolism in the latest Confidential Enquiry into Maternal and Child Health report (2003–2005) were in the first trimester of pregnancy; one of them had hyperemesis gravidarum [89]. The combination of pregnancy, immobility and dehydration is 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. The Royal College of Obstetricians and Gynaecologists guideline on thromboprophylaxis suggests the use of LMWH heparin in any woman with three recognized risk factors and as these include hyperemesis, immobility and dehydration, such prophylaxis should be considered in women admitted for HG management [90], especially if these factors last for a longer duration.

Termination of pregnancy

Women suffering HG have an increased likelihood of considering termination of pregnancy (TOP). In a questionnaire survey of 3,201 callers to a helpline for NVP, 413 had considered TOP and 108 underwent TOP [91]. 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 [92]. However, interventions against depression have not been studied. Whether early psychological input would decrease complications related to depression is not known.

Prognosis

Fetal prognosis

Some studies have reported increased rate of prematurity, small for gestational age babies and APGAR scores less than 7 at 5 min in women with HG [93, 94]. However, no increase in adverse fetal outcomes has been found in one recent study of 166 women [95]. The risk of small for gestational age fetuses was found to be increased only in cases with inadequate maternal weight gain due to chronic hyperemesis gravidarum. Ninety percent of hyperemesis resolved by 16 weeks and most maternal weight is gained in the latter half of pregnancy.

Exposure to maternal nausea and vomiting during pregnancy and treatment with Dilectin (delayed release combination of doxylamine succinate and pyridoxine hydrochloride) has shown no adverse effects on fetal brain development [96].

Maternal prognosis

Other than Wernicke 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 HG being 15.2% in a woman who has had a previous episode of HG, compared with 0.7% in a woman who did not have HG in her previous pregnancy [5]. Koren studied women with previous HG and commenced antiemetic medication before conception or within the 7 weeks of gestation and found 40% of the women developing HG compared with 80% of the women in the group of controls not given antiemetics [97].

Conclusion

With all these proven effective medications available, the severity of hyperemesis gravidarum will definitely be decreased over the next few years. Outpatient management of hyperemesis will be further explored to minimize the social and financial cost of admission to hospital for hyperemesis gravidarum. Mental health gaining importance now, studies of psychological interventions for hyperemesis are likely to be conducted to determine whether cognitive or behavioral interventions may reduce disease severity or duration, though many women may resist such therapy denying the suggestion of a psychological element to their illness.

Conflict of interest The author declares that she has no conflict of interest.

References

1. Kallen B (1987) Hyperemesis during pregnancy and delivery outcome: a registry study. Eur J Obstet Reprod Bio 26:292–302
2. Goodwin TM (2004) Nausea and vomiting of pregnancy. ACOG Practice Bulletin 52. American College of Obstetricians and Gynecologists. Obstet Gynecol 103:803–815
3. King TL, Murphy PA (2009) Evidence-based approaches to managing nausea and vomiting in early pregnancy. J Midwifery Women Health 54(6):430–444
4. Sherman PW, Flaxman SM (2002) Nausea and vomiting of pregnancy in evolutionary perspective. Am J Obstet Gynecol 186:S190–S197
5. Trogstad LI, Stoltenberg C, Magnus P et al (2005) Recurrence risk in hyperemesis gravidarum. BJOG 112:1641–1645
6. Rochelson B, Vohra N, Darvishzadeh J et al (2003) Low prepregnancy ideal weight: height ratio in women with hyperemesis gravidarum. J Reprod Med 48:422–424
7. Fell DB, Dodds L, Joseph KS et al (2006) Risk factors for hyperemesis gravidarum requiring hospital admission during pregnancy. Obstet Gynecol 107:277–284
8. Kallen B, Lundberg G, Aberg A (2003) Relationship between vitamin use, smoking, and nausea and vomiting of pregnancy. Acta Obstet Gynecol Scand 82:916–920
9. Tsuruta E, Tada H, Tamaki H et al (1995) Pathogenic role of asialo human chorionic gonadotropin in gestational thyrotoxicosis. J Clin Endocrinol Metab 80(2):350–355
10. Lagiou P, Tamini R, Mucci LA et al (2003) Nausea and vomiting in pregnancy in relation to prolactin, estrogens, and progesterone: a prospective study. Obstet Gynecol 101:639–644
11. Munch S (2002) Chicken or the egg? The biological-psychological controversy surrounding hyperemesis gravidarum. Soc Sci Med 55(7):1267–1278
12. Swallow B, Lindow S, Masson E et al (2004) Psychological health in early pregnancy: relationship with nausea and vomiting. J Obstet Gynaecol 24(1):28–32
13. Sandven I, Abdelnoor M, Nesheim B et al (2009) *Helicobacter pylori* infection and hyperemesis gravidarum: a systematic review and meta-analysis of case-control studies. Acta Obstet Gynecol Scand 88(11):1190–1200
14. Karaca C, Guler N, Yazar A et al (2004) Is lower socio-economic status a risk factor for *Helicobacter pylori* infection in pregnant women with hyperemesis gravidarum? Turk J Gastroenterol 15:86–89
15. Yumi S, Akihiko S, Antonio F et al (2003) Relationship between severity of hyperemesis gravidarum and fetal DNA concentration in maternal plasma. Clin Chem 49:1667–1669
16. Sekizawa A, Jimbo M, Saito H et al (2003) Cell-free fetal DNA in the plasma of pregnant women with severe fetal growth restriction. Am J Obstet Gynecol 188:480–484
17. Sekizawa A, Yokokawa K, Sugito Y et al (2003) Evaluation of bi-directional transfer of plasma DNA through placenta. Hum Genet 113:307–310
18. Minagawa M, Narita J, Tada T et al (1999) Mechanisms underlying immunologic states during pregnancy: possible association of the sympathetic nervous system. Cell Immune 196:1–13
19. Kaplan PB, Gucer F, Sayin NC et al (2003) Maternal serum cytokine levels in women with hyperemesis gravidarum in the first trimester of pregnancy. Fertil Steril 79:498–502

20. Kuscu NK, Yildirim Y, Koyuncu F et al (2003) Interleukin–6 levels in hyperemesis gravidarum. Arch Gynecol Obstet 269:13–15
21. Koren G, Boskovic R, Hard M et al (2002) Motherisk-PUQE (pregnancy-unique quantification of emesis and nausea) scoring system for nausea and vomiting of pregnancy. Am J Obstet Gynecol 186(5 Suppl Understanding):S228–S231
22. Koren G, Piwko C, Ahn E et al (2005) Validation studies of the Pregnancy Unique-Quantification of Emesis (PUQE) scores. J Obstet Gynaecol 25(3):241–244
23. Lacasse A, Rey E, Ferreira E et al (2008) Validity of a modified Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) scoring index to assess severity of nausea and vomiting of pregnancy. Am J Obstet Gynecol 198(1):71 e1–e7
24. Leylek OA, Toyaksi M, Erselcan T et al (1999) Immunologic and biochemical factors in hyperemesis gravidarum with or without hyperthyroxinemia. Gynecol Obstet Invest 47:229–234
25. Chiossi G, Neri I, Cavazzuti M et al (2006) Hyperemesis gravidarum complicated by Wernicke encephalopathy: background, case report, and review of the literature. Obstet Gynecol Surv 61(4):255–268
26. Basso O, Olsen J (2001) Sex ratio and twinning in women with hyperemesis or pre-Eclampsia. Epidemiology 12(6):747–749
27. Felemban A, Bakri Y, Alkharif H et al (1998) Complete molar pregnancy: clinical trends at King Fahad Hospital, Riyadh, Kingdom of Saudi Arabia. J Reprod Med 43:11–13
28. Kirk E, Papageorghiou A, Condous G et al (2006) Hyperemesis gravidarum: is an ultrasound scan necessary? Hum Reprod 21(9):2440–2442
29. Bashiri A, Neumann L, Maymon E et al (1995) Hyperemesis gravidarum: epidemiologic features, complications and outcome. Eur J Obstet Gynecol Reprod Biol 63(2):135–138
30. Depue R, Bernstein L, Ross R et al (1987) Hyperemesis gravidarum in relation to estradiol levels, pregnancy outcome, and other maternal factors: a seroepidemiologic study. Am J Obstet Gynecol 156:1137–1141
31. Gross S, Librach C, Cocutti A (1989) Maternal nutritional effects and severe hyperemesis gravidarum: a predictor of fetal outcome. Am J Obstet Gynecol 160(4):906–909
32. Moore R (1999) Diabetes in pregnancy. In: Creasy RK, Resnik R (eds) Maternal-fetal medicine, 4th edn. W.B. Saunders, Philadelphia, p 964
33. Van Stuijevenberg E, Schabort I, Labadarios D et al (1995) The nutritional status and treatment of patients with hyperemesis gravidarum. Am J Obstet Gynecol 172:1585–1591
34. Selitsky T, Chandra P, Shiavello HJ (2006) Wernicke's encephalopathy with hyperemesis and ketoacidosis. Obstet Gynecol 107(2 Pt 2):486–490
35. Spruill C, Kuller A (2002) Hyperemesis gravidarum complicated by Wernicke's encephalopathy. Obstet Gynecol 99(5):875–877
36. Albaar M, Adam J (2004) Gestational transient thyrotoxicosis. Acta Med Indones 41(2):99–104
37. Hershman J (2004) Physiological and pathological aspects of the effect of human chorionic gonadotropin on the thyroid. Best Pract Res Clin Endocrinol Metab 18(2):249–265
38. Fagan A (1999) Diseases of the liver, biliary system, and pancreas. In: Creasy R (ed) Maternal-fetal medicine, 4th edn. W.B. Saunders, Philadelphia, p 1056
39. Robertson C, Millar H (1999) Hyperamylasemia in bulimia nervosa and hyperemesis gravidarum. Int J Eat Disord 26(2):223–227
40. Deuchar N (1995) Nausea and vomiting in pregnancy: a review of the problem with particular regard to psychological and social aspects. BrJ Obstet Gynaecol 102:6–8
41. Buckwalter G, Simpson S (2002) Psychological factors in the etiology and treatment of severe nausea and vomiting in pregnancy. Am J Obstet Gynecol 186(5 Suppl. Understanding):S210–S214
42. Power Z, Campbell M, Kilcoyne P et al (2010) The Hyperemesis Impact of Symptoms Questionnaire: development and validation of a clinical tool. Int J Nurs Stud 47(1):67–77
43. Alalade O, Khan R, Dawlatly B (2007) Day-case management of hyperemesis gravidarum: feasibility and clinical efficacy. J Obstet Gynaecol 27(4):363–364
44. Naef R, Chauhan S, Roach H et al (1995) Treatment for hyperemesis gravidarum in the home: an alternative to hospitalization. J Perinatol 15(4):289–292
45. Jennings-Sanders A (2009) A case study approach to Hyperemesis Gravidarum: home care implications. Home Healthc Nurse 27(6):347–351
46. Buttino L Jr, Coleman S, Bergauer N et al (2000) Home subcutaneous metoclopramide therapy for hyperemesis gravidarum. J Perinatol 20(6):359–362
47. Bottomley C, Bourne T (2009) Management strategies for hyperemesis. Best Prac Res Clin Obstet Gynaecol 23:549–564
48. McKeigue M, Lamm H, Linn S et al (1994) Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. Teratology 50:27–37
49. Quinlan D, Hill A (2003) Nausea and vomiting of pregnancy. Am Fam Physician 8(1):121–128
50. Gill S, Einarson A (2007) The safety of drugs for the treatment of nausea and vomiting of pregnancy. Expert Opin Drug Saf 6(6):685–694
51. Seto A, Einarson T, Koren G (1997) Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis. Am J Perinatol 14(3):119–124
52. Lacasse A, Lagoutte A, Ferreira E et al (2009) Metoclopramide and diphenhydramine in the treatment of hyperemesis gravidarum: effectiveness and predictors of rehospitalisation. Eur J Obstet Gynecol Reprod Biol 143(1):43–49
53. Goodwin T, Poursharif B, Korst L et al (2008) Secular trends in the treatment of hyperemesis gravidarum. Am J Perinatol 25(3):141–147
54. Ilan M, Rafael G, Gideon K et al (2009) The safety of metoclopramide use in the first trimester of pregnancy. N Engl J Med 360:2528–2535
55. Layton D, Wilton L, Shakir S (2009) Examining the tolerability of the non-sedating antihistamine desloratadine: a prescription-event monitoring study in England. Drug Saf 32(2):169–179
56. Weber-Schoendorfer C, Schaefer C (2008) The safety of cetrizine during pregnancy: A prospective observational cohort study. Reprod Toxicol 26(1):19–23
57. Asker C, Norstedt Wikner B, Källén B (2005) Use of antiemetic drugs during pregnancy in Sweden. Eur J Clin Pharmacol 61(12):899–906
58. Sahakian V, Rouse D, Sipes S et al (1991) Vitamin B6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double-blind placebo-controlled study. Obstet Gynecol 78(1):33–36
59. Vutyavanich T, Wongtra-ngan S, Ruangsri R (1995) Pyridoxine for nausea and vomiting of pregnancy: a randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol 173(3):881–884
60. Heazell A, Langford N, Judge J et al (2005) The use of levomepromazine in hyperemesis gravidarum resistant to drug therapy—a case series. Reprod Toxicol 20(4):569–572
61. Einarson A, Boskovic R (2009) Use and safety of antipsychotic drugs during pregnancy. J Psychiatr Pract 15(3):183–192
62. Safari H, Fassett M, Souter I et al (1998) The efficacy of methylprednisolone in the treatment of hyperemesis gravidarum: a randomized, double-blind, controlled study. Am J Obstet Gynecol 179(4):921–924

63. Ziaei S, Hosseiney F, Faghihzadeh S (2004) The efficacy low dose of prednisolone in the treatment of hyperemesis gravidarum. Acta Obstet Gynecol Scand 83(3):272–275
64. Nelson-Piercy C, Fayers P, De Swiet M (2001) Randomised, double-blind, placebo-controlled trial of corticosteroids for the treatment of hyperemesis gravidarum. BJOG 108(1):9–15
65. Bondok R, El Sharnouby N, Eid H et al (2006) Pulsed steroid therapy is an effective treatment for intractable hyperemesis gravidarum. Crit Care Med 34(11):2781–2783
66. Fraser F, Sajoo A (1995) Teratogenic potential of corticosteroids in humans. Teratology 51:45–46
67. Mahady B, Pendland L, Yun S et al (2003) Ginger (Zingiber officinale Roscoe) and the gingerols inhibit the growth of Cag A+ strains of *Helicobacter pylori*. Anticancer Res 23:3699–3702
68. Borrelli F, Capasso R, Aviello G et al (2005) Effectiveness and safety of ginger in the treatment of pregnancy-induced nausea and vomiting. Obstet Gynecol 105(4):849–856
69. Fischer-Rasmussen W, Kjaer S, Dahl C et al (1991) Ginger treatment of hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol 38(1):19–24
70. Vutyavanich T, Kraisarin T, Ruangsri R (2001) Ginger for nausea and vomiting in pregnancy: randomized, double-masked, placebo-controlled trial. Obstet Gynecol 97(4):577–582
71. Willetts K, Ekangaki A, Eden J (2003) Effect of a ginger extract on pregnancy-induced nausea: a randomised controlled trial. Aust N Z J Obstet Gynaecol 43(2):139–144
72. Smith C, Crowther C, Willson K et al (2004) A randomized controlled trial of ginger to treat nausea and vomiting in pregnancy. Obstet Gynecol 103(4):639–645
73. Portnoi G, Chng LA, Karimi-Tabesh L et al (2003) Prospective comparative study of the safety and effectiveness of ginger for the treatment of nausea and vomiting in pregnancy. Am J Obstet Gynecol 189:1374–1377
74. Jewell D, Young G (2003) Interventions for nausea and vomiting in early pregnancy. The Cochrane Database of Systematic Reviews Issue 4 Art No CD000145. doi:10.1002/14651858.CD000145
75. Levicheck Z, Atanackovitc G, Oepkes D et al (2002) Nausea and vomiting of pregnancy. Evidence-based treatment algorithm. Can Fam Physician 48:267–277
76. Sahakian V, Rouse D, Siepes S et al (1991) Vitamin B6 is effective therapy for nausea and vomiting in pregnancy a randomized, double-blind placebo control study. Obstet Ginecol 78:33–36
77. Hsu J, Clark-Glena R, Nelson D et al (1991) Nasogastric enteral feeding in the management of hyperemesis gravidarum. Obstet Gynecol 88(3):343–346
78. Boyce RA (1992) Enteral nutrition in hyperemesis gravidarum: a new development. J Am Diet Assoc 92(6):733–736
79. Gulley RM, Pleog NV (1993) Gulley J (1993) Treatment of hyperemesis gravidarum with nasogastric feeding. Nutr Clin Pract 8:33–35
80. Barclay BA (1990) Experience with enteral nutrition in the treatment of hyperemesis gravidarum. Nutr Clin Pract 5:153–155
81. Ogura JM, Francois KG, Perlow JH et al (2003) Complications associated with peripherally inserted central catheter use during pregnancy. Am J Obstet Gynecol 188:1223–1225
82. Paranyuk Y, Levine G, Figueroa R (2006) Candida septicemia in a pregnant woman with hyperemesis receiving parenteral nutrition. Obstet Gynecol 107(2 Part 2):535–537
83. Holmes VA, Wallace JMW (2005) Haemostasis in normal pregnancy: a balancing act? Biochem Soc Trans 33(part 2):428–432
84. Godil A, Chen YK (1998) Percutaneous endoscopic gastrostomy for nutrition support in pregnancy associated with hyperemesis gravidarum and anorexia nervosa. J Parenter Enteral Nutr 22:238–241
85. Serrano P, Velloso A, Garcia-Luna PP et al (1998) Enteral nutrition by percutaneous endoscopic gastrojejunostomy in severe hyper emesis gravidarum: a report of two cases. Clin Nutr 17:135–139
86. Mazzotta P, Stewart D, Atanackovic G et al (2000) Psychosocial morbidity among women with nausea and vomiting of pregnancy: prevalence and association with anti-emetic therapy. J Psychosom Obstet Gynaecol 21:129–136
87. Castillo R, Ray R, Yaghmai F (1989) Central pontine myelinolysis and pregnancy. Obstet Gynecol 73:459–461
88. Bergin P, Harvey P (1992) Wernicke's encephalopathy and central pontine myelinolysis associated with hyperemesis gravidarum. BMJ 305(6852):517–518
89. Lewis G (2007) The confidential enquiry into maternal and child health (CEMACH). Saving mothers' lives: reviewing maternal deaths to make motherhood safer—2003–2005. The seventh report on confidential enquiries into maternal deaths in the United Kingdom. London: CEMACH
90. RCOG guideline number 37 (2004) Thromboprophylaxis during pregnancy, labour and after vaginal delivery. RCOG Press, London
91. Mazzotta P, Stewart D, Koren G et al (2001) Factors associated with elective termination of pregnancy among Canadian and American women with nausea and vomiting of pregnancy. J Psychosom Obstet Gynaecol 22(1):7–12
92. Andersson L, Sundström-Poromaa I, Wulff M et al (2004) Implications of antenatal depression and anxiety for obstetric outcome. Obstet Gynecol 104(3):467–476
93. Bailit J (2005) Hyperemesis gravidarum: epidemiologic findings from a large cohort. Am J Obstet Gynecol 193(3 Pt 1):811–814
94. Dodds L, Fell D, Joseph K et al (2006) Outcomes of pregnancies complicated by hyperemesis gravidarum. Obstet Gynecol 107(2 Pt 1):285–292
95. Tan P, Jacob R, Quek R et al (2007) Pregnancy outcome in hyperemesis gravidarum and the effect of laboratory clinical indicators of hyperemesis severity. J Obstet Gynaecol Res 33(4):457–464
96. Nulman I, Rovet J, Barrera M et al. (2009) Long-term neurodevelopment of children exposed to maternal nausea and vomiting of pregnancy and dilectin. J Pediatr Jul 155(1):45–50, 50 e1–2
97. Koren G, Maltepe C (2004) Pre-emptive therapy for severe nausea and vomiting of pregnancy and hyperemesis gravidarum. J Obstet Gynaecol 24(5):530–533