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Nutritional consequences and management of hyperemesis gravidarum: a narrative review

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Abstract

Hyperemesis gravidarum (HG) is a condition at the extreme end of the pregnancy sickness spectrum, estimated to affect 1–2 % of pregnant women. This narrative review provides an overview of the current literature concerning the nutritional implications and management of HG. HG can persist throughout pregnancy, causing malnutrition, dehydration, electrolyte imbalance and unintended weight loss, requiring hospital admission in most cases. In addition to its negative effect on maternal, physical and psychological wellbeing, HG can negatively impact fetal growth and may have adverse consequences on the health of the offspring. HG care and research have been hampered in the past due to stigma, inconsistent diagnostic criteria, mismanagement and lack of investment. Little is known about the nutritional intake of women with HG and whether poor intake at critical stages of pregnancy is associated with perinatal outcomes. Effective treatment requires a combination of medical interventions, lifestyle changes, dietary changes, supportive care and patient education. There is, however, limited evidence-based research on the effectiveness of dietary approaches. Enteral tube feeding and parenteral nutrition are generally reserved for the most intractable cases, where other treatment modalities have failed. Wernicke encephalopathy is a rare but very serious and avoidable consequence of unmanaged HG. A recent priority-setting exercise involving patients, clinicians and researchers highlighted the importance of nutrition research to all. Future research should focus on these priorities to better understand the nutritional implications of HG. Ultimately improved recognition and management of malnutrition in HG is required to prevent complications and optimise nutritional care.

Keywords: **Hyperemesis gravidarum: Pregnancy nutrition: Maternal malnutrition: Pregnancy sickness: Pregnancy nausea vomiting**

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Introduction

Nausea and vomiting of pregnancy (NVP) are normal, albeit unpleasant, symptoms of early pregnancy that appear on a spectrum of severity. At the extreme end of that spectrum is the complication hyperemesis gravidarum (HG) with symptoms so severe it can lead to weight loss, dehydration, poor quality of life and, without treatment, life-threatening complications[1]. Indeed, HG was a common cause of maternal mortality until the 1950s when intravenous (IV) hydration was introduced[2]. Despite affecting 1–2 % of pregnancies globally[3] the aetiology remains unclear and is likely to be multifactorial. Recent research has implicated appetite genes GDF15 and IGFBP7 as likely culprits[4] and builds on previous research suggesting a predominantly genetic aetiology[5]. A personal or family history of HG is thought to be the strongest risk factor, and recurrence in subsequent pregnancies is common[6]. Carrying a female foetus or having a multiple pregnancy may also increase risk of HG[7].

Although historical theories regarding psychosocial causes are still responsible for stigmas and mismanagement[8], they have now been widely debunked[9], and it is well established from a systematic review of fifty-nine studies that depression and/or anxiety, while strongly associated with HG, is a consequence rather than a cause[10]. The historical belief that HG is self-limiting and does not have long-term consequences was incorrect[11]. The wide-ranging physical and psychosocial adverse consequences of HG are summarised in Table 1. These include severe weight loss, which can be >15 % of pre-pregnancy weight[12], post-traumatic stress syndrome, relationship breakdown[13], long periods off work[14,15], elective termination of pregnancy[16] and reduced willingness to become pregnant again in the future[17].

Hyperemesis gravidarum has typically been a condition that has been under-researched. By way of example, although it has a similar prevalence to type 1 diabetes in pregnancy, it receives significantly less research funding, despite recognition that it causes maternal malnutrition with direct effects on the unborn child. In recent years, there has been growing momentum for the need to prioritise nutrition research in the management of HG. A James Lind Alliance Priority Setting Partnership exercise

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Table 1. Summary of potential adverse outcomes of hyperemesis gravidarum

Maternal		Fetal/child outcomes
Physical/metabolic	**Psychosocial/economic**	Fetal/neonatal death
Death	Anxiety, depression and social isolation	Preterm birth
Weight loss	Inability to work and loss of income	Small for gestational age
Electrolyte disturbances and hypotension	Memory loss and confusion	Low birth weight
Micronutrient deficiencies, including anaemia	Relationship breakdown	Termination of pregnancy
Oesophageal tear	Reluctance to become pregnant again	Autism spectrum disorder
Muscle weakness and fatigue	Consideration of termination pregnancy	Neurodevelopmental disorders
Wernicke encephalopathy	Lack of trust in health care professionals	Allergies, lactose intolerance
Constipation	Post-traumatic stress disorder	Chronic respiratory and ear infections
Liver and gallbladder dysfunction		
Renal failure		
Postpartum issues: postnatal depression, prolonged recovery from birth, difficulty breastfeeding, depression, migraine, gastroesophageal reflux, dental decay, chronic nausea		

published this year highlighted the importance of furthering our understanding of nutritional aspects of HG by clinicians, researchers and patients[18]. Additionally, an international consensus document[19] emphasised the importance of consistent outcome reporting in HG, specifying that food and fluid intake, weight, maternal wellbeing and perinatal outcomes are to be included in future studies. The present review aims to comprehensively summarise and critically appraise the current literature regarding nutritional implications and management of HG in developed countries. The review will not include the topics of mild-to-moderate nausea and vomiting in pregnancy (NVP) or herbal/alternative therapies for the management of HG, which are considered outside the remit.

Diagnosis and screening

There is no distinct point at which NVP becomes HG. A lack of diagnostic criteria has led to challenges within research as well as in the management of HG and access to treatment[20]. Clinical guidance documents from the United Kingdom[21] and the United States[22] both include 'persistent vomiting in pregnancy in the absence of other causes' as required criteria, with additional criteria of '>5 % weight loss and electrolyte imbalance'. A systematic review of definitions of HG used in trials identified eleven different definition items[23], with vomiting, nausea and gestational age at onset of symptoms being the most common. Symptom severity, ketonuria and need for hospital treatment were also commonly used.

Patient history to rule out other potential causes, and assessment of clinical presentation to look for signs of dehydration and/or malnutrition, is required. Assessment of the impact symptoms are having on quality of life and mental health should be assessed[1]. The Pregnancy Unique Quantification of Emesis (PUQE) score is a validated tool for assessing the severity of NVP[24]. It includes questions on the duration of nausea, the number of vomiting episodes, occurrence of retching and overall quality of life. Symptoms during the past 24 h yield a summary score from 3 to 15; the higher the score the more severe the NVP symptoms. However, it has not been validated as a diagnostic tool for HG and does not consider aspects such as nutritional intake, medication or urination frequency. More recently, an HG-specific tool, the HyperEmesis Level Prediction score, was found to perform better than PUQE in identifying patients with severe symptoms requiring intervention[25].

Effects of HG on offspring

Direct short- and long-term effects of HG on the offspring have been widely reported in the literature and are summarised in Table 1. The largest cohort study to date, which analysed >8 million pregnancies over 15 years in England found that women with HG had a higher risk of preterm birth and babies born small for gestational age[26], with a systematic review of twenty-four studies finding similar results[27]. A population-based study of 2·2 million births in Norway, of which 20 004 women were reported to have HG, found babies exposed to HG had reduced birth weight and gestational length[28]. The study also found an association with perinatal death, when exploring data from 1967 to 2009; however, authors suggest interpreting this with caution, as the finding was not replicated when examining a subsample of infants born between 1999 and 2009, when different disease classification systems were used.

Recently published research reports that offspring born to women with HG are at increased risk of having developmental delay[29] and autism spectrum disorder[30,31]. Specifically, a retrospective longitudinal cohort study using medical records of pregnant women and their children ($n = 469\ 789$), found that children exposed to HG *in utero* had higher rates of physician-diagnosed autism spectrum disorder than unexposed children, which was not associated with medications and not explained by confounding variables[31]. Although causality cannot be proven based on this observational study, there is strong biological plausibility based on the effect of maternal malnutrition on the developing brain at critical time points[31,32]. A study of 312 children exposed *in utero* to HG found they have a 3·82-fold increase of being diagnosed with conditions including allergies, chronic constipation, growth restriction and chronic respiratory infections[33]. The authors postulate that failure to gain enough weight during pregnancy puts the child at risk for intra-uterine growth restriction, which in turn could incur greater risk for other neurodevelopmental and physical problems. The study was limited by sample size, retrospective recall of symptoms and self-report of conditions.

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Looking at the longer-term impact of HG on offspring into adolescence, there is less robust evidence, due to lack of long-term follow-up and prospective studies. There is emerging evidence of potential effects on the metabolic profile of offspring, similar to effects observed in those exposed to undernutrition in pregnancy famine studies[34,35]. However, evidence for this theory is equivocal, possibly due to heterogenous populations. A longitudinal analysis of a Finnish birth cohort of 8953 women with HG, did not find any evidence that prenatal exposure to HG has negative consequences on cardiometabolic health of the offspring at 16 years[36]; however, this study did not have data on duration, severity or onset of symptoms. It is important to recognise that none of these studies was designed to measure dietary intake or its effects, as the majority of research on HG to date has focused on medical management, with little attention paid to the outcomes of poor nutrition[32]. Additionally, most studies have employed a retrospective rather than a prospective study design, meaning they are potentially subject to recall bias. It is thought that retrospective evaluation of NVP/HG can distort the perception of the effectiveness of antiemetics and associations with long-term outcomes[37].

Nutritional implications of HG

Nutritional implications of HG are shown in Fig. 1 and detailed below.

Sensory issues relating to taste and olfaction

Although it is generally accepted that taste changes occur during pregnancy, specific scientific evidence is lacking[38]. Similarly, although there is abundant anecdotal evidence for a heightened sense of smell during pregnancy, there is a lack of conclusive studies[39]. It is hypothesised that an evolutionary mechanism exists, whereby increased olfactory sensitivity protects the developing embryo by reducing the likelihood that the mother will ingest toxins[39,40]. It is not known whether this applies to pregnancies affected by HG, as limited studies on this topic have had mixed results. Yasar *et al.*[41] reported that odour and taste identification scores were different between pregnant women and non-pregnant women; however, there was no difference between women with HG and controls. A more recent study found the opposite. Tan *et al.*[42] reported a deficiency in taste and smell identification in women hospitalised for HG. Specifically, those with HG were hypersensitive to taste, with the exception of sweet taste, compared with gestation-matched controls. Sweet, crunchy and uncooked (fresh) food characteristics were preferred by women experiencing HG. Limitations exist with these sensory studies, namely small sample sizes and applicability to nutritional intake not having been demonstrated.

Nutritional intake

Although poor intake is a key feature of HG, there is a distinct lack of research about this topic[32,43,44]. A systematic literature search conducted in April 2020[45] has identified only four previous research studies which assess nutritional intake in women with HG[46–49]. Studies by van Stuijvenberg[46] and Birkeland[47], which both assessed women admitted to hospital, reported that many with HG had energy intakes <50 % of recommended levels and were significantly deficient compared with control participants. Median energy intakes of 443[46] and 990 kcal[47] (1854 and 4141 kj), respectively, over a 24-h period were recorded, compared with recommendations of 2500 and 2285 kcal (10460 and 9560 kj), respectively. Actual intake is likely to have been even lower, due to amounts lost through vomiting. With such low energy intakes, the intake of the majority of macro- and micronutrients were also significantly lacking. Of note, increasing frequency and severity of symptoms was inversely related to nutritional intake. A Turkish study[48] examined antioxidant intake, finding that vitamin E, E equivalent, vitamin C, carotene and vitamin A levels were significantly lower in women with HG, compared with control participants. Each of these

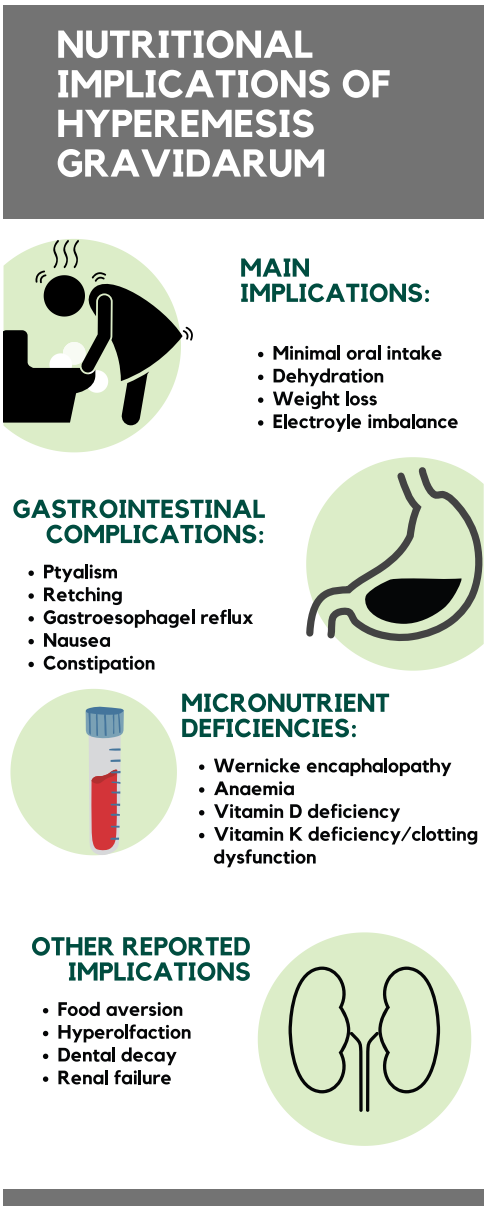

Fig. 1. Nutritional implications of hyperemesis gravidarum (see separate pdf)

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studies examined nutritional intake at one time point only, with relatively small sample sizes. None of the studies assessed fluid intake.

Dehydration, ketonuria and electrolyte disturbances

Dehydration is a widespread consequence of HG that can lead to severe electrolyte imbalances, the most frequently reported being hypokalaemia[11]. Dehydration can be assessed using a combination of patient-reported fluid intake and output, reduced or concentrated urine output, skin turgor, dry mucous membranes, reduced blood pressure and/or tachycardia[50]. IV hydration should be used for those who cannot tolerate oral liquids for a prolonged period or if clinical signs of dehydration are present[22]. Normal saline with additional potassium chloride is recommended and should be guided by daily electrolyte monitoring[21]. Thiamine (IV or orally) should also be given to those admitted with prolonged vomiting who require rehydration[21,22] (see late paragraph on thiamine deficiency). Overall, IV hydration has been found to be highly effective in symptom relief, compared with other treatment modalities. In a survey of 765 women from twenty-six countries, IV hydration and antihistamines were the most commonly used treatment modalities, with 83 % reporting IV hydration as 'effective or maybe effective'[51].

Ketonuria is a condition in which ketone bodies are present in the urine. It is often listed as a diagnostic criterion with dehydration[23] and can be an indication that the body is using fat as an alternative source of energy to glucose, as occurs in starvation. It is commonly used in the assessment of HG and often as a decision-making criterion for treatment, particularly IV hydration[23]. However, ketones do not indicate dehydration and may in fact provide misleading information about the severity of the condition, either underestimating how unwell a patient is or indeed preventing discharge from hospital where they are still present[52]. The risks associated with misleading results outweigh the potential benefit of identifying malnutrition, which could be more accurately assessed in other ways[1,53]. It is therefore now recommended that ketonuria is not used to identify or assess HG[52].

Malnutrition and weight loss

'Malnutrition', a term often used interchangeably with the term 'undernutrition', is widely described as a state of nutritional imbalance in calories, macronutrients, vitamins and/or minerals. However, specific definitions for malnutrition during pregnancy or 'gestational malnutrition' are lacking from current international guidelines[54,55]. Nutritional screening is a rapid, simple and general procedure used by nursing, medical or other staff, often at first contact with the patient, to detect those with significant risk of nutritional problems, so that clear guidelines for action can be implemented[56]. It is not known to what extent formal nutritional screening takes place in patients with HG admitted to hospital, and variation in practice may exist[57]. The combination of physiological changes in lean mass, fat mass, weight and blood volume during pregnancy means that standard nutrition screening tools and biochemical reference ranges used in the adult non-pregnant population are not appropriate. As such, an evidence review conducted in 2018 concluded that more research is needed to examine the validity and reliability of screening/assessment tools in identifying malnutrition in pregnancy, which would help to standardise care pathways and treatment goals[58].

The gastrointestinal symptoms of HG (including nausea, vomiting and retching, but hyperolfaction, ptyalism, abdominal pain, gastroesophageal reflux) profoundly affect the ability to eat, digest and absorb nutrients and maintain caloric balance. These symptoms have the potential to persist throughout the entire pregnancy[59], causing malnutrition, dehydration and extreme weight loss[12]. As such, HG has been likened to a form of prolonged starvation[46,47], and unintended weight loss or inability to achieve gestational weight gain guidance is common. It is difficult to quantify average weight loss/gain in those with HG for a number of reasons. Studies on gestational weight gain/loss often rely on recall of self-reported preconception weight, which may be subject to error. Weight change during pregnancy may be expressed in a number of different ways, using a number of different timeframes (e.g. percentage weight loss, absolute weight loss, change in BMI, or categories of sub-optimal/expected/excessive gestational weight gain). Two small cross-sectional hospital-based studies reported a measured mean weight loss of ~3 kg from preconception to admission[46,47], whereas a longitudinal study of hospital admissions for HG reported a mean weight loss of 4·4 kg at 9 weeks gestation ($n = 892$)[60]. A recent international survey study of 445 people with HG reported a self-reported average weight loss of 12·5 % of pre-pregnancy weight[25]. However, it has been suggested that, due to women's tendency generally to underreport their weight, there is potential for an underestimation of initial weight loss in HG[58]. Although a threshold of >5 % weight loss is commonly used as a clinical diagnostic criterium for HG, 'extreme weight loss', being defined as >15 % of preconception weight has been estimated to affect 25 %[11]. However, it has been suggested that, due to women's tendency generally to underreport their weight, there is potential for an underestimation of initial weight loss in HG[60]. Although a threshold of >5 % weight loss is commonly used, a clinical diagnostic criterium for HG, 'extreme weight loss', being defined as >15 % of preconception weight has been estimated to affect 25 %[12]. Those that experience this extreme weight loss were more likely to be hospitalised and have prolonged symptoms, gallbladder dysfunction, liver dysfunction and renal failure[12].

Recently published research from a Norwegian cohort has identified that not regaining pre-pregnancy weight specifically by week 13–18 is an independent risk factor for delivering a baby born small for gestational age, even when adjusted for total pregnancy weight gain, pre-pregnancy body mass index (BMI), parity, age and smoking status. The results from 892 women hospitalised for HG between 2002 and 2016 demonstrated on odds ratio of 2·66 for infants born small for gestational age, underlining the importance of medical and nutritional treatment for HG during early pregnancy, in order to reverse any first-trimester weight loss[60]. The data also showed that weight gain patterns within pregnancy time intervals are different among different BMI categories. Recognition of weight loss (or poor weight gain) is particularly important in light of the fact that

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HG may be more common in women who are either under- or overweight[61]. Indeed, with an increasing population of pregnant women entering pregnancy already living with overweight or obesity[62,63], there is a risk that weight loss due to persistent nausea and vomiting may be overlooked.

Thiamine deficiency

One of the most commonly occurring micronutrient deficiencies in HG is thiamine deficiency[11], a condition that can rapidly deteriorate into a medical emergency if not managed correctly[64]. Thiamine is an essential nutrient for carbohydrate metabolism[65]. In pregnancy, thiamine requirements are estimated to increase by 45·5 %, based on an additional calorie needs[66]. Although thiamine is widespread in many foods and food groups, it is not included in sufficient levels in all preconception vitamin preparations. Levels therefore can rapidly deplete during pregnancy, especially in women with HG, who experience frequent vomiting, poor oral intake, and intolerance of oral vitamin preparations. To complicate matters, symptoms of thiamine deficiency include nausea, vomiting, anorexia and fatigue[65], meaning it can mimic HG, making it difficult at times to determine when thiamine deficiency is present[2].

When thiamine levels are rapidly depleted, Wernicke's encephalopathy (WE) can occur. WE is an acute neuropsychiatric syndrome characterised by the classic triad of ataxia, eye movement disorders and mental status change[65]. It is most commonly observed in individuals with chronic alcoholism and accompanying malnutrition; however, numerous cases in women with HG have been reported. A systematic review published in 2019 examining cases of WE in HG identified 146 case studies reporting on 177 cases[64]. Pregnant WE patients became thiamine depleted between 10 and 15 weeks of gestation, had been vomiting for a median of 7 weeks before WE was diagnosed and had lost an average of 12·1 kg. Commonly reported signs of WE across all cases were nausea and vomiting (100 %), double vision (37·4 %) and blurred vision (27·4 %). In half of the cases, spontaneous miscarriage occurred, and 5 % of the cases resulted in maternal fatality. In cases in which the offspring survived, patients had a shorter duration of excessive vomiting before the onset of WE, than in cases where the offspring did not survive (6·2 compared with 9 weeks)[64]. This underlines the critical importance of obtaining medical help sooner rather than later when intractable vomiting of pregnancy occurs.

The systematic review found that thiamine supplementation was insufficient or absent from treatment plans, and in 14 % of cases it was explicitly reported that HG patients received intravenous glucose supplementation without thiamine, which exacerbates WE[64]. This highlights the lack of awareness of the potential severity of the condition, which could have been prevented by giving prophylactic thiamine injections[64]. Thiamine supplementation, either oral or intravenous, should be given to all women admitted with prolonged vomiting, especially before administration of dextrose or parenteral nutrition[21]. The American College of Obstetricians and Gynecologists advise that 100 mg should be given, intravenously with the initial rehydration fluid and 100 mg daily for the next 2–3 d (followed by intravenous multivitamins), for women who require IV hydration and have vomited for more than 3 weeks[22]. For those at home, it has been suggested that those with prolonged symptoms and/or weight loss who are unable to tolerate prenatal vitamins that include thiamine should have thiamine levels monitored regularly[66]. It is also recommended that basic screening for signs of WE should be shared with the patient and her family/caretakers, including signs of confusion, unsteady gait and oculomotor symptoms[66].

Iron deficiency anaemia

Hospital admission data from >8 million pregnancies in the United Kingdom suggests that those with HG have higher rates of anaemia; however, the timing of onset relative to HG was difficult to confirm, and it is unclear whether it is related to iron intake[7]. Data from small-scale studies of hospitalised patients with HG suggest iron intake is <50 % that of control participants[46,47] and that intakes are significantly lower in those with the most vomiting episodes per day[46]. Anecdotally, supplements containing iron can worsen nausea[67], and those with HG may be advised to omit them, replacing with a separate folic acid supplement instead[21,22,68]. In the pregnant population generally, a review of eleven European studies showed that the prevalence of iron deficiency and iron deficiency anaemia was 28–85 % and 21–35 % at 32 and 39 weeks gestation, respectively, in those who did not take iron supplements[69]. It is therefore highly likely that those with HG are at risk of iron deficiency anaemia, and therefore, their offspring may be more susceptible to the potential negative consequences it can cause, including cognitive and neurodevelopmental disorders[70,71].

Other micronutrient deficiencies

A range of different micronutrient deficiencies have been reported; however, it is impossible to compare rates because of the varying study designs used. In a South African study of women hospitalised with HG ($n = 20$)[46], more than 60 % had suboptimal biochemical status of thiamine, riboflavin, vitamin B6 and vitamin A. Results need to be interpreted with caution owing to the dilutional affect that occurs with expansion of blood volume during pregnancy. A study examining factors associated with bone resorption indices found that serum 25OHD3 levels were significantly lower in women with HG compared with the control group[72]. It was not clear, however, whether this was attributable to poor sun exposure or dietary intake, or a combination of factors. The authors hypothesised that women with HG may have an increased risk for lower bone mass in offspring due to maternal dietary deficiency and increased maternal bone mobilisation. Finally, a number of cases of maternal and neonatal vitamin K deficiency secondary to HG have also been reported in the literature[73], as has biotin deficiency[74].

Clinical and nutritional management of HG, evidence for effectiveness and current guidelines

Overview of the clinical management of HG

In the absence of a definitive cause, the management of HG focuses on symptom relief and prevention of serious

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morbidity[75]. First line advice is that women who have vomiting, but are not dehydrated, can be managed in the community with antiemetics, support, reassurance, oral hydration and dietary advice. Screening for thyroid dysfunction is recommended[21,22]. Medical management consists of anti-emetic medication applied in a stepwise approach[76]; however, treatment can be challenging as some women simply do not respond to any anti-emetic treatment sufficiently[75,77]. Medications with the most evidence of safety are generally used first. In addition to anti-emetic medications, anti-reflux medications may offer benefit. The proton pump inhibitor omeprazole is licensed for use in pregnancy as an antacid and may offer some benefit to women with HG where acid is painful or exacerbating symptoms[1]. Laxatives also play a role in HG management, particularly for those prescribed ondansetron for which constipation is a significant side effect.

Hospital admission

In the United Kingdom, the Royal College of Obstetricians and Gynaecologists recommends that inpatient management should be considered if there is at least one of the following:

- continued nausea and vomiting and inability to keep down oral antiemetics,
- continued nausea and vomiting associated with ketonuria and/or weight loss (greater than 5 %) despite oral antiemetics
- and/or confirmed or suspected comorbidity[21]. Additionally, the National Institute for Health and Care Excellence[78] recommends there should be:
- a lower threshold for admitting to hospital or seeking specialist advice if the woman has a co-existing condition (e.g. diabetes) which may be adversely affected by nausea and vomiting. Similar recommendations are in place internationally[22,68,79].

Typically, secondary care involves admission to either an antenatal or a gynaecology ward for treatment with IV fluids, antiemetics and vitamin supplements. It is anticipated that oral intake would gradually be resumed followed by discharge back into the community. Resumption of symptoms would result in readmission and a repeat of previous care, possibly trying different antiemetics or a combination thereof[75]. An analysis of HG hospital statistics from England between 1998 and 2011[26] found the readmission rate to be 28 %, with 11 % having three or more admissions. Only 10 % of pregnancies with admissions for HG were managed as day cases, whereas 33 % had more than 4 d of inpatient hospital stay during the pregnancy. Developments in clinical practice research suggest, however, that ambulatory day case management is an effective direct alternative to inpatient management of severe NVP, proving more cost-effective[80–82].

Dietary and lifestyle management

As there is little high-quality and consistent evidence supporting any one intervention in the management of HG[83], effective treatment requires a combination of medical interventions, lifestyle changes, dietary changes, supportive care and patient education[66]. Women with HG can experience severe food aversions and poor appetite, meaning a dietetic consultation may be helpful in expanding food choices, prescribing oral nutritional support[57] and monitoring nutritional deficiencies[66]. Assessment by a dietitian is recommended on admission to hospital in some countries[68,79], although there is a lack of consensus on referral criteria and management[57]. A Cochrane review was published in 2016, which focused solely on interventions for HG (rather than mild or moderate NVP)[83]. It identified only one nutrition-related study, whereby women taking vitamin B6 had a slightly longer hospital stay compared with placebo. There was no clear evidence of differences in other outcomes, including vomiting episodes, readmission rate or side effects[84]. The mechanism of action of vitamin B6 is unknown, and the review did not identify any lifestyle or dietary interventions.

Anecdotally, advice concerning avoidance of fatty and odorous foods, eating small amounts of liquid or food at frequent intervals, avoiding an empty stomach, eating dry crackers and/or eating a high-protein snack before bed has been recommended[67,85]. However, there has been no evidence-based research on the effectiveness of these approaches. Although they may provide some symptomatic relief in women with mild or moderate NVP[86], an international survey of 765 women from twenty-six countries found only 22 % reported dietary interventions to be either 'maybe effective' or 'effective'[51]. Overall research suggests that, for the severe symptoms of HG, lifestyle and dietary changes alone are insufficient[11]. This does not necessarily reflect health care professional practices. An Australasian study of doctors[87] investigating prescription practices in HG found the first choice of treatment was dietary advice, followed by metoclopramide and ondansetron. Of note, dietary advice was rated the most effective for HG by clinicians; however, there were no patient-reported data collected to support this finding.

Similarly, although ginger may be more effective than placebo in alleviating symptoms in some women with *mild* NVP, there is no evidence of its effect in women with severe symptoms. A survey conducted by the Pregnancy Sickness Support charity of >500 women with HG found that, although 88 % of respondents had tried ginger, 87·6 % of them found it not at all helpful, with more than half experiencing negative side effects including acid reflux[88]. Some 60 % of respondents had been recommended to try ginger more than twenty times, by multiple different healthcare professionals, family members and strangers. Of note, 79 % of women who had ginger suggested by a healthcare professional reported that it eroded their trust and confidence in the healthcare professional. Separately, other qualitative research suggests that women with HG find some health care professionals to be unsympathetic, not fully appreciating the extent of their symptoms and the impact on their quality of life[89].

Enteral nutrition support (tube feeding)

Optimising medical therapy to relieve symptoms and enable sufficient oral intake is the goal in HG; however, that may not be achievable in all patients[66]. In situations where antiemetic medication and IV fluids are not sufficient to reduce the nausea and/or vomiting, ketonuria persists and the patient is unable to

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improve oral nutritional intake, additional nutritional therapy should be considered. A threshold of 8–10 % weight loss has been suggested[66]; however, this needs to be assessed on an individual basis, considering pre-pregnancy weight, co-morbidities and clinical status. Modes for enteral nutrition delivery in HG include nasogastric tubes (NGT), nasojejunal tube (NJT), endoscopic gastrostomy and gastrojejunostomy. However, percutaneously inserted tubes in pregnancy are very rare and carry additional risks attributable to changing anatomy[90]. Due to their recent absence of nutritional intake, weight loss and electrolyte imbalance, women with HG are at high risk of refeeding syndrome[63]. Clinical consensus guidelines recommend that those at risk of refeeding syndrome should be managed by starting with minimal nutritional support (i.e. 10–20 kcal/kg/d) and advancing feeding slowly to meet full needs by 4–7 d or by 33 % of goal every 1–2 d[91,92]. Oral or IV thiamine, plus potassium, phosphate and magnesium, may also be recommended, with close monitoring of fluid and electrolyte balance required. Dietetic advice can be very helpful to treat or avoid potentially serious complications of HG[44], and a dietitian should be consulted when tube feeding is being considered[21,79].

A case series of data collected over 10 years of women hospitalised with HG in Norway ($n = 558$) found that, compared with IV fluid or peripheral parenteral nutrition regimens, NJT feeding ($n = 107$) was associated with adequate maternal weight gain and favourable pregnancy outcomes[93]. Although inadvertent tube expulsions occurred in 54 % of patients, the majority (79 %) accepted a new tube placement. Those who were tube fed had significantly longer hospital stay, receiving tube feeding for a median of 5 d. Overall, the study concluded that enteral nutrition for HG might be both feasible and beneficial in reversing hyperemesis-induced weight loss, although patient acceptability was not assessed due to the retrospective study design. It also recommended that prospective studies are needed to investigate the optimal time point for initiating enteral nutrition and to evaluate the best tube placement (NGT/NJT). In a smaller case series of eleven women hospitalised with HG in Israel, Vaisman *et al.*[94] concluded that NJT feeding could be an effective option in those with persisting symptoms despite IV fluids and antiemetic drugs. A clear reduction in vomiting was apparent within the first 48 h after tube insertion, with vomiting ceasing completely after a mean of 5 ± 4 d. The patients were encouraged to drink and eat along with tube feeding from day 3 onwards and were discharged 1–3 d after tube removal when no symptoms recurred. They noted that that post-pyloric feeding might be advantageous due to its effect on intestinal dysmotility, however acknowledged the aesthetic and discomfort issues that patients may feel with tube feeding.

In contrast, a trial investigating early NGT feeding in addition to standard care with intravenous rehydration and antiemetic treatment did not find an improvement in birth weight or secondary outcomes[95]. The MOTHER (Maternal and Offspring outcomes after Treatment of HyperEmesis by Refeeding) trial ($n = 116$), based in hospitalised women in the Netherlands, also did not find beneficial effects of NGT on maternal weight gain, duration of stay, readmission rate, symptoms or quality of life. However, the study had a number of limitations. Firstly, more than half of the women who were eligible declined participation, and secondly, protocol completion was poor in the tube feeding group, both of which suggest low levels of acceptability of NGT feeding. A sensitivity analysis found that those with more marked weight loss were more likely to tolerate tube feeding, enabling them to complete the study protocol. The authors recommended that future trials are needed to study whether tube feeding is beneficial in women with severe HG that is complicated by marked weight loss and/or prolonged symptoms.

In a qualitative study of thirteen women from the Netherlands that investigated patient perspectives of HG management[89], eight had received NGT feeding and underlined the benefits of it. Women who did not have NGT said they wished they had, in order to prevent severe weight loss, dehydration and need for multiple hospital admissions. Other reasons cited for wanting to be fed via NGT were to provide sufficient nutritional intake for the baby and to reduce vomiting by preventing an empty stomach. The authors, however, acknowledged the limitations and lack of external generalisability of the study findings, highlighting differences in management strategies internationally. In some countries, enteral feeding is viewed as an effective but extreme method of supporting women suffering from very severe symptoms as a last resort[68,95]. The American College of Obstetricians and Gynecologists[22] recommends enteral tube feeding be initiated as the first-line treatment to provide nutritional support to those with HG who are not responsive to medical therapy and cannot maintain their weight. Other researchers note that the risks of enteral feeding may be less than those of chronic malnutrition and dehydration, especially in women with severe or prolonged symptoms[66].

Total parenteral nutrition

In situations where conventional drug therapy has failed, total parenteral nutrition (TPN) may be an alternative to enteral feeding in women with a long course of HG accompanied by a significant weight loss[94]. TPN may be used in refractory cases to ensure sufficient calorie intake, but should be used only as a last resort in those where enteral feeding is not possible[21,22], due to the associated risks and complications, including infection and thrombosis, as well as the high cost. Peripherally inserted central catheters (PICCs) are a popular alternative to other types of central venous access because of ease of insertion and perceived lower risk of complications[96]; however, because use of PICCs may not meet the daily caloric needs of the pregnant woman, a prolonged period of IV administration will require central vein insertion[11].

A retrospective cohort study of women who had received TPN ($n = 122$) found that TPN support during early pregnancy is associated with a decreased risk for perinatal morbidity[97]. Specifically, compared with women with HG who did not receive TPN, administration of TPN during early pregnancy was associated with a lower rate of labour induction and preterm delivery. In addition, neonates in the subgroup of mothers who received TPN had a higher birth weight percentile, as well as a lower rate of composite morbidity and NICU admission. The

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authors highlighted that women who required TPN likely had a more severe presentation of HG, thereby further underlining the potential beneficial effect of TPN in the most critical cases.

In contrast, a retrospective study that compared TPN delivered via PICC line, compared with NGT/NJT or medication alone, reported serious complications of bacteraemia, sepsis and thrombosis observed in the majority (66·4 %) of the patients in the PICC line group[98]. Indeed, in several cases, the researcher noted the complications were severe enough to require admission to an intensive care unit. The authors recommended that, to avoid PICC, a more aggressive attempt at enteral feeding and hydration via insertion of NGT/NJT should be made. A recent systematic review on this topic yielded five eligible studies, concluding there are limited data regarding complication rates due to PICC use in pregnancy, with a high level of heterogeneity among existing studies stating a pooled rate of combined infectious and thromboembolic complications of 26 %[99].

Research gaps, priorities and recommendations for future research

As previously mentioned, results from a James Lind Alliance Priority Setting Partnership exercise were published this year, which underlined that clinicians, researchers and patients see nutrition as a priority in HG research[18]. Three of the ten research priorities were specific to nutrition, namely:

- What are the immediate and long-term effects of HG (including malnutrition and dehydration) on the developing foetus?

- What are the immediate and long-term physical, mental and social consequences and complications of HG (including malnutrition and dehydration) on the pregnant person's body?

- What are the nutritional requirements of the first, second and third trimesters, and how can people with HG achieve these goals?

In addition to these research questions, understanding the training needs of healthcare professionals in relation to nutrition to ensure consistent messaging is important. Dissemination and implementation of any new nutritional evidence into pragmatic clinical practice guidelines is also paramount. We acknowledge that this review has been narrative rather than systematic and has focused on research and healthcare in developed countries. Information on prevalence and management of HG in developing countries is limited, and future research should take a broader view, considering cultural, geographical and social issues known to impact maternal health[18].

Conclusion

Although poor nutritional intake and weight loss are both a characteristic and consequence of HG, very few studies have assessed the nutritional intake and extent of malnutrition in women with HG. The evidence base for dietary management of HG is poor, and it is not known what (if any) clinical nutrition advice is routinely provided, if it is acceptable and if it is effective. Although hospital admission and administration of IV fluids and vitamins is very common, enteral and parenteral nutrition are usually only used in exceptional circumstances, with a particularly limited evidence base around the use of NGT/NJT feeding. Better recognition and management of malnutrition in HG is required to prevent complications and optimise nutritional care. Future research should investigate the role and outcomes of targeted nutritional strategies in the management of HG, using agreed diagnostic criteria, guidelines and core outcomes.

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