Nausea and vomiting of pregnancy and hyperemesis gravidarum

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Abstract
Nausea and vomiting of pregnancy (NVP) is a common condition that affects as many as 70% of pregnant women. Although no consensus definition is available for hyperemesis gravidarum (HG), it is typically viewed as the severe form of NVP and has been reported to occur in 0.3–10.8% of pregnant women. HG can be associated with poor maternal, fetal and child outcomes. The majority of women with NVP can be managed with dietary and lifestyle changes, but more than one-third of patients experience clinically relevant symptoms that may require fluid, vitamin supplementation and/or antiemetic therapy; for example, combined doxylamine/pyridoxine is not teratogenic and may be effective in treating NVP. Ondansetron is commonly used to treat HG, but studies are urgently needed to determine whether it is safer and more effective than using first-line antiemetics. Thiamin (vitamin B1) should be introduced following protocols to prevent refeeding syndrome (the sudden shifts in fluids and electrolytes following a period of starvation) and Wernicke encephalopathy. Recent advances in the genetic study of NVP and HG suggest a placental component to the aetiology by implicating common variants in genes encoding placental proteins (namely *GDF15* and *IGFBP7*) and hormone receptors (namely *GFRAL* and *PGR*). New studies on aetiology, diagnosis, management, and treatment are under way. In the next decade, progress in these areas may improve maternal quality of life and limit adverse outcomes associated with HG.

[H1] Introduction

Nausea and vomiting of pregnancy (NVP) is common, usually begins during pregnancy weeks 6-8 and generally subsides by 16–20 weeks gestation[1]. Severe

NVP, or hyperemesis gravidarum (HG), is the leading cause of hospitalization in the first trimester and the second-most common indication for pregnancy hospitalization overall[2]. The term 'hyperemesis gravidarum' is likely to have first appeared in medical literature in 1898 (Ref[3]), although reports on NVP date back to ancient Egyptian times; the first death from vomiting in pregnancy was reported in 1706 (Ref[4]). Until intravenous fluids were introduced, HG incurred a high risk of maternal mortality[4]. In 1956, a panel appointed by the American Council on Pharmacy and Chemistry first defined HG as intractable vomiting and disturbed nutrition, with for example altered electrolyte balance, weight loss of ≥5%, ketosis and acetonuria, with ultimate neurological disturbances, liver damage, retinal haemorrhage and renal damage. In 1968, the distinction between mild or moderate NVP and HG was noted to be unclear and has remained challenging[4]. Even now, an international definition setting out the 'boundaries' of HG has yet to be established[5], but general guidelines can be applied to most cases (Table 1). A practical clinical use of these terms is that the most severe form of NVP with complications such as dehydration or metabolic deficiencies (weight loss, electrolyte deficiencies or malnutrition) will constitute HG.

The past belief that HG is self-limiting and does not have long-term consequences is incorrect. Although overall maternal and child outcomes are favourable, the past decade has produced a body of knowledge to support the assertion that HG can be associated with poor maternal and fetal sequelae and can be, in rare cases, a cause of maternal and fetal death[6]. Generally, the clinical presentation of HG includes severe intractable vomiting, often associated with >5% weight loss, dehydration, ketonuria, nutritional deficiencies and electrolyte imbalance[7]. With HG, symptoms can begin earlier in pregnancy than NVP, last the entire pregnancy and have effects postpartum[8,9]. The risk of extreme weight loss during pregnancy (>15% of pre-pregnancy weight) is increased in HG[10], as opposed to the recommended gain of 10-15 kg during pregnancy (given a normal BMI). In rare cases, nutritional and electrolyte imbalances secondary to HG can induce cardiac, neuromuscular and renal complications, thyrotoxicosis and have, even recently, led to maternal death[6,11,12]. Maternal undernutrition may cause vitamin K deficiency, which may induce coagulopathy[13]. Increased risk of

gestational anaemia has also been reported in HG pregnancies[14]. HG can also be associated with Wernicke encephalopathy (brain damage caused by vitamin B1 deficiency), acute liver and renal failure, splenic avulsion, oesophageal rupture, valsalva retinopathy (preretinal haemorrhage caused by a sudden increase in intrathoracic or intraabdominal pressure), pneumothorax, preeclampsia, and placental abruption[15-17].

NVP may have evolved as a mechanism of pathogen avoidance[18,19] and/or undernutrition resulting in increased placental growth to maintain early pregnancy[20]. Despite the prevalence of NVP and the severity of HG, there is a paucity of research on the pathophysiology, a lack of consensus on diagnosis and inconclusive evidence on the safety and effectiveness of common treatments. However, recent advances suggest progress is forthcoming. This Primer provides a comprehensive review of the current state of knowledge on NVP and HG. Directions to focus on for future study are also discussed.

[H1] Epidemiology

NVP is misleadingly referred to as 'morning sickness'. Only 1.8% of women report morning-only symptoms, whereas 80% report all-day nausea[21]. Researchers have also described an episodic pattern of NVP, with 95% of women having symptoms before and after midday[22]. A meta-analysis quantifying global rates found 70% of pregnant women experience NVP, with rates varying widely[23]. Almost 33% had nausea without vomiting; NVP was rated mild in 40%, moderate in 46% and severe in 14% of cases, with a 1.1% prevalence of HG[23]. Large epidemiological studies that provided the population characteristics of women with HG, its prevalence, risk factors, impact on perinatal outcome and recurrence rate have based their estimates entirely on registries[14,24-27], which use unvalidated definitions for HG[28]. For this reason, these studies are likely to be subject to considerable imprecision bias, rendering some of their estimates of limited use (Box 1). Nevertheless, symptoms of NVP are reported in 50–90% of pregnancies[29]. Age and gravidity may influence the level of symptoms. Women <20 years of age, and primigravidas (that is, women who are pregnant for the first time), are noted to have up to 40% higher rates of NVP[30].

The presence or absence of ethnic differences in NVP is less clear. Although some studies have shown lower rates of symptoms in Africa and Asia compared with Western countries, others indicate there is no difference[30-32]. Some of the inconsistencies have been attributed to the effects of confounding variables such as household income, parity and oral contraceptive use prior to pregnancy. In a multivariate analysis aimed at controlling for confounding factors, researchers noted lower rates of NVP in black and Asian women[33].

Estimated rates of HG vary between 0.3% reported by a Swedish registry to 10.8% noted in a study of pregnancies in China[34,35]. Ethnic variation in the incidence of HG is supported by large population studies. A study of 520,739 births in California linked to neonatal discharge data reported a 0.5% incidence of HG. Within this Californian population, non-white and non-Hispanic patients were found to have higher rates of HG compared with their white counterparts[36]. Using a perinatal database of deliveries in Nova Scotia, a Canadian study found an HG rate of 0.8%[37]. In Norway, a population-based study reported an overall incidence of HG of 0.9%[38], but higher rates of HG were noted in subsets of the Norwegian population (for example, women of Pakistani and Turkish descent). Women in Norway of Pakistani and sub-Saharan African origin (that is, other than North Africa) had rates of HG of 2.1% and 3.1%, respectively, whereas women born in India and Sri Lanka had a reported rate of HG of 3.2% [39]. A small study in northern Israel found a similar prevalence (1.2%) in Arabic and Jewish women[40]. In the UK, 2.1% of women were hospitalized for HG, with those of black and Asian origins more likely to be affected[41]. A New Zealand study reported a similar HG rate for people of European descent (2%), but a much higher rate for women of Pacific Island origin. Within the New Zealand population, Pacific Island women had an up to four-fold higher rate of HG[42]. High rates of HG have also been noted in some Asian populations. For example, a study of patients hospitalized for hyperemesis in Kuala Lumpur, Malaysia, reported an HG rate of 3.9% and pregnancies delivered in Osaka, Japan, were associated with an HG rate of 3.6%[43,44]. Some of the variation in the reported data may be due to socioeconomic, cultural and/or genetic differences, and inconsistent criteria used for diagnosing HG (Box 1).

The economic burden of NVP in the United States in 2012 was estimated at US$1.7 billion[45] whereas a recent report from the UK estimated the impact of NVP on the National Health System to be £62,373,961(Ref[46]). As many as 18% of women in the United States take medication for NVP[45] and emergency department visits for NVP are on the rise[47,48]. A Canadian study from 2007 showed the weekly direct and indirect costs to severe NVP totaled CAN$653 per patient[49]. It seems much of this economic burden is unevenly distributed, with higher rates of NVP reported in women of lower socioeconomic status[33,50].

[H1] Mechanism/pathophysiology

In 1933, NVP was called a 'disease of theories'[51]. Although evidence-based science is still lacking and inconsistent findings have been reported, substantial progress has been made recently through genetic studies of NVP and HG that lends support to some of these hypotheses, opening promising new areas of research into causal factors. A recent review of NVP introduces the pathogenesis as multifactorial involving genetic, endocrine and gastrointestinal factors[52]. From the genetic studies, we now have evidence that supports that these factors are not mutually exclusive and also implicate placental-mediated mechanisms, reproductive hormones and gastrointestinal dysmotility, with serotonin and thyroid hormones potentially involved in rare cases.

Preliminary evidence that genes play a part in the aetiology of NVP and HG stems from studies of familial aggregation and twin studies. A threefold higher risk of HG is apparent in daughters of mothers who had HG[53]. Sisters of women who had HG have a 17-fold increased risk of having a pregnancy affected by HG[54]. Women with HG have also reported having maternal and paternal grandmothers affected at equal rates, providing evidence that HG might be inherited through maternal and/or the paternal lineages[54]. A twin study estimated heritability for the presence of NVP to be 73% and for variation in duration and severity to be >50% (Ref[55]).

[H2] GDF15 versus hCG

The prevailing hypothesis in the field has been that the pregnancy hormone human chorionic gonadotropin (hCG) is central to NVP and HG. This is primarily

based on the temporal relationship between hCG production and NVP symptoms, both of which generally peak between gestational weeks 9–12 (Ref[52]). A review published in 2014 found 18 studies showed increased hCG levels associated with NVP or HG, whereas 13 studies showed no such association[56]. The Generation R study analysed hCG levels in 8,195 women and found a significant correlation between hCG and daily NVP symptoms[57], but a retrospective cohort study of 4,372 pregnancies following in vitro fertilization found no evidence of an association between hCG concentrations and HG[58].

A genome-wide association study (GWAS) of >53,000 women of European descent did not find any evidence to support an association between HG and hCG. Instead, a region containing the gene *GDF15* (encoding growth/differentiation factor 15) was implicated as a genetic risk factor for both NVP and HG[59]. The GWAS also identified the gene encoding the GDF15 brainstem receptor, *GFRAL*, further implicating the GDF15–GFRAL pathway (Figure 1). GFRAL is localized to the area postrema (that is, the vomiting centre) of the brainstem (Box 2) and signals loss of appetite and taste aversion in animal models[60]. Interestingly, GDF15 has also been shown to delay gastric emptying[61], which can contribute to nausea in humans[62]. In a rodent model, GDF15 supplementation resulted in delayed gastric emptying that was abrogated by vagotomy, suggesting vagal efferents transmit the signal between the brain and the gut[61]. In addition, GDF15 is thought to play a part in suppression of maternal pro-inflammatory cytokines[63]. However, expression of GFRAL during pregnancy has not been thoroughly explored and more work must be done to resolve the issue of whether or not these proteins play a role in immunity during pregnancy.

Both GDF15 and hCG are hormones that are upregulated in early pregnancy when NVP and HG symptoms occur[64,65]. Both are believed to have roles in placentation and are present in significantly lower levels in women whose pregnancies end in miscarriage[66]. However, several additional studies further implicate GDF15 rather than hCG in NVP and HG. For example, GDF15 causes loss of appetite and weight loss in animal models via activation of neurons in the area postrema and hypothalamus through binding to GFRAL[60]. Abnormal overproduction of GDF15 is considered a key driver of cachexia, a condition with

similar symptoms to HG (such as nausea, weight loss and muscle wasting)[67,68]. Genetic variants associated with altered expression of GDF15 segregated with disease in families affected by HG, and were associated with recurrence of HG in subsequent pregnancies[69]. Increased maternal serum levels of GDF15 were associated with maternal antiemetic use and second-trimester vomiting, whereas hCG levels were not, despite being correlated with GDF15 levels[70]. Furthermore, in a separate study, at 12 weeks gestation, GDF15 was found to be significantly upregulated in the sera of women who were hospitalized for HG compared with women with NVP[71]. These conflicting data between hCG serum levels and HG could be explained by different hCG isoforms[52]. However, the GWAS study did not identify any associations between hCG variants and NVP or HG, providing evidence against this explanation[59].

[H2] IGFBP7

In addition to *GDF15*, the GWAS implicated additional loci, including a non-coding region neighboring *IGFBP7* (encoding insulin-like growth factor-binding protein 7). IGFBP7 regulates availability of insulin-like growth factors and can also bind directly to the insulin-like growth factor 1 receptor (IGF1R) to block its activation[72,73]. IGFBP7 is involved in implantation and decidualization of the pregnant uterus, and like GDF15, is significantly upregulated after implantation, is highly expressed in the developing placenta and is a biomarker for cachexia[74,75]. Inhibition of IGFBP7 causes pregnancy loss in a mouse model by shifting uterine cytokines from helper T type 2 (T_H2) to helper T type 1 (T_H1) cell dominance, which represses uterine decidualization and decreases uterine receptivity[74]. Additionally, the *Drosophila sp.* homologue of *IGFBP7* has been shown to play a part in neuronal coordination between metabolic status and feeding behaviour, potentially signalling food preferences or pregnancy cravings[76].

[H2] PGR

The GWAS implicated an additional region containing *PGR* (encoding the progesterone receptor), which has been replicated in an independent cohort[77]. PGR may be associated with the normal T_H1 to T_H2 switch to induce immune tolerance to fetal antigens and play a part in maintenance of early pregnancy, similar to the hypothesized role for GDF15 and the substantiated role for

IGFBP7[74,78-80]. Both PGR and GDF15 have roles in reduced gastrointestinal motility and gastric dysrhythmias during pregnancy[61,81].

A role for oestrogen and progesterone has been supported by the observation that women who have NVP or HG are more likely to also experience nausea while taking contraceptives containing a combination of the two hormones[52]. As with hCG, studies of total oestradiol or progesterone and NVP or HG are conflicting[56]. Progesterone alone or in combination with oestradiol in non-pregnant women can cause disruption in frequency and direction of gastric contractions, which may cause nausea[82]. The mechanism for this disruption is unknown, but likely involves hormonal signalling that causes a substantial disruption of slow-wave gastric rhythms. The anorectic and possibly nausea-inducing effects of oestrogen may be due in part to activation of oestrogen receptor-α in the brainstem, which increases the potency of cholecystokinin (CCK) by increasing the sensitivity of vagal CCK type A receptors in the gut. CCK slows gastric emptying and activates subdiaphragmatic vagal afferent neurons to decrease food intake[83].

[H2] Placenta

A role for the placenta rather than the fetus is supported in part due to the observation that complete hydatidiform mole (a growth typified by placental development with oedematously enlarged chorionic villi in the absence of an embryo) can be associated with severe nausea and vomiting[84]. A report of anorexia and weight loss in a Rhesus monkey with an ectopic (tubal) pregnancy consisting of a placenta but no embryo or amnion is also consistent with a placental role for NVP[85]. Additional support comes from the observation that NVP is less common in older women, women with singleton gestation and smokers, which are all associated with smaller placentas[84]. Women with HG carrying a female fetus also had a significantly higher risk of increased placental-weight to birth-weight ratio (>90th percentile), adding more support to the role of placental size in HG[86].

However, evidence against a fetal component is supported by the observation that gestational surrogates carrying fetuses with a maternal history of HG were

not affected with HG[87]. Additionally, partner change either does not, or minimally, affects the risk of recurrence, suggesting a minor role (if any) of paternal genes expressed in the fetus and/or fetal component of the placenta[25,88]. A study showing that consanguinity does not change HG risk also favors maternal genes over paternal-fetal genes in the aetiology[38]. Hypothetically, expression limited primarily to fetally-inherited maternal risk allele(s) could explain the evidence against a paternal-fetal role while permitting a fetal contribution, but it is currently unknown whether risk genes are imprinted in the placenta or fetus. Imprinting studies and studies of fetal inheritance of maternal risk loci may resolve this issue in the future. For now, the fact that all three risk genes (*GDF15*, *IGFBP7* and *PGR*) are expressed in the placenta suggest that the maternal decidual component of the placenta is likely to be involved in the pathogenesis of NVP and HG; theoretically, a larger placenta will give rise to more GDF15, IGFBP7 and PGR and these proteins may exacerbate NVP. A fetal and/or paternal GWAS may help to resolve this issue.

[H2] Serotonin receptor

The serotonin receptor has been suggested as a potential aetiological factor because, like PGR and GDF15, it plays a part in gastrointestinal motility in humans[89]. Located in the vagal afferent neurons of the gastrointestinal tract and vomiting centre (Box 2), the serotonin receptor can activate nausea and vomiting through serotonin signalling from the gut. Stimulation of the 5-HT_3 subtype of serotonin receptor (encoded by *HTR3C*) induces vomiting and 5-HT_3 antagonists are often prescribed to treat NVP and HG[90,91]. However, 5-HT_3 receptor antagonists have a beneficial effect in treating NVP and HG in some, but not all studies[52]. These drugs possibly block the excitatory receptors located on sensory, ascending and descending neuronal pathways involved in peristalsis[89]. The association between NVP and a rare variant in *HTR3C*, lends further support that this receptor may be involved at least in a subset of HG cases[92].

[H2] Thyroid hormones

The association between HG symptoms and thyroid dysfunction in as many as 60% of patients with HG led to speculation that thyroid-stimulating hormone

receptor (TSHR) may have a role in the condition[93,94]. Identification of mutations in *TSHR* in two patients with HG and gestational thyrotoxicosis (excessive thyroid hormone) support this hypothesis[95,96]. However, transient hyperthyroidism is generally not associated with severity of HG[97], primary hyperthyroidism is rarely associated with vomiting[98] and treatment with propylthiouracil, an antithyroid medication that decreases thyroid hormone by blocking conversion of thyroxine (T4) to triidiothyronine (T3), does not resolve HG symptoms[99]. Interestingly, thyroid hormone has been shown to induce overexpression of *RYR2*, which encodes ryanodine receptor 2, a stress-induced calcium channel that has been associated with cyclic-vomiting syndrome[100]. The ryanodine receptor family is expressed in the vomiting centre (Box 2) and has been linked to vomiting as well as thyroid function[90,100]. Propranolol, a non-selective beta-blocker used to treat hyperthyroidism, blocks RYR2 phosphorylation and lowers its expression, and was used to successfully treat a patient who was hospitalized with HG and severe thyrotoxicosis[100]. More work is needed to determine whether thyroid dysfunction may exhibit an effect on NVP through the RYR2-receptor mediated vomiting pathway, specifically in those who harbour genetic variants that result in a 'leaky' RYR2 receptor. Along these lines, a whole-exome sequencing study of five HG-affected families identified new and low-frequency variants in *RYR2* that segregate with disease in two families [100].

Additionally, patients with hyperthyroidism have significantly increased GDF15 levels, and thyroid hormone treatment upregulates GDF15 expression in mice[101]. Thus, thyroid dysfunction may have a role in NVP and HG by contributing to elevated GDF15 levels. Long-term fasting and nutrient deprivation also contribute to elevated GDF15 (Refs[60,102]). Thus, it may be that a combination of genetic susceptibility, abnormal thyroid hormone levels and low nutrient levels in pregnancies affected by HG can exacerbate NVP symptoms by increasing GDF15 (Figure 1).

[H2] *H. pylori* and other factors

Several other factors have been implicated in NVP and HG, but their association may be due to secondary effects. For example, in epidemiological studies, *Helicobacter pylori* has consistently been shown to be associated with increased

occurrence of NVP and HG[56,103], and may be associated with severity and persistence of HG symptoms into the second and third trimester[104]. However, some studies find no correlation, and the majority of pregnant women seropositive for *H. pylori* do not have HG[103]. Infection with *H. pylori* possibly exacerbate symptoms, but studies are lacking that demonstrate eradication of infection prior to pregnancy significantly lowers HG risk. It has been suggested that maternal immunological changes that prevent allogenic rejection of the fetus may reactivate the bacterium[105]. Although it remains to be proven, GDF15 and IGFBP7 may have primary roles in these immunological changes; the same may be true for other markers showing conflicting results, such as leptin[56] and inflammatory markers, such as CRP[106,107].

In another study, two women affected by HG who had children with riboflavin deficiency were found to be carriers of *SL52A1* mutations[108]. *SLC52A1* encodes riboflavin transporter-1, which is expressed at high levels in the placenta. The role it has in the placenta is unknown, but riboflavin (vitamin B2) has a critical role in energy metabolism. As GDF15 levels are increased in response to nutritional stress[60] and vitamin B2 deficiency has been associated with nausea and vomiting[109], theoretically, vitamin B2 deficiency can signal nausea and vomiting through upregulation of GDF15.

[H2] Effects on the mother

In addition to extreme loss of quality of life (QOL), HG can be associated with substantial maternal risks and outcomes. These outcomes may be related to prolonged nutritional deficiencies (for example, Wernicke encephalopathy), electrolyte imbalance (for example hypokalaemia and hyponatremia, which can contribute to abnormal electrocardiography parameters) and prolonged stress (for example, post-traumatic stress disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-R)). The most-documented nutritional deficiency secondary to HG is vitamin B1 (thiamine) deficiency, which leads to Wernicke encephalopathy and is associated with ataxia, ocular disturbances and mental status change. Despite the fact that it is preventable with appropriate thiamine supplementation, reports of Wernicke encephalopathy are on the rise[110]. Thiamine has a role in carbohydrate

metabolism in the brain that is critical to neurological functioning and demands of thiamine are estimated to increase by >45% during pregnancy. Accordingly, the inability to eat thiamine-rich foods (such as beef, pork and eggs) or prenatal vitamins containing thiamine can result in permanent neurological damage to the mother if left untreated.

Dehydration can lead to severe electrolyte imbalances, the most frequently reported, being hypokalaemia. Potassium is required for normal heart and skeletal muscle contraction. Hypokalaemia can result in a prolonged QT interval and arrhythmias such as Torsade de pointes, which if left untreated can degenerate to ventricular fibrillation and cardiac arrest[11]. In addition to maternal cardiac arrest, refeeding syndrome and respiratory distress have also been attributed to severe hypokalaemia in pregnancies affected by HG[11].

There is conflicting evidence regarding other long-term associations including increased risk of autoimmune disease, breast cancer, and thyroid cancer, but no association has been found between HG and subsequent cardiovascular risk [111-114]. One exploratory study found an increased maternal risk of 7 common conditions (for example, anxiety and dental cavities) and 50 rare conditions (for example, blood clots and debilitating muscle weakness) following HG pregnancies[15].

[H2] Effects on the fetus

Although some evidence suggests that NVP may be associated with favourable pregnancy outcomes such as lower rates of miscarriage, malformations and preterm birth[115], pregnancies complicated with HG might have poorer perinatal outcomes, such as low birth weight, small size for gestational age and preterm birth[28]. Poorer perinatal outcomes occur in particular in women with little weight gain during pregnancy or in whom symptoms persist into the second trimester, suggesting that severe undernutrition retards fetal growth and increases the risk of perinatal problems[37,116]. Evidence that severe nutritional deficiency in HG-affected pregnancies can result in adverse fetal outcomes is based on reports of fetal death secondary to thiamine deficiency in 50% of HG pregnancies affected by Wernicke encephalopathy[110]. In addition, reports of vitamin K-deficient

embryopathy secondary to HG suggest a direct effect of maternal vitamin deficiency on the developing fetus[117,118]. A recent cohort study, which is by far the largest to date with >8 million pregnancies, showed that women who had been admitted to hospital for HG were more likely to be induced, have a caesarean section and deliver preterm[14]. Their babies were more likely to be small for gestational age and have low birthweight, and also were more likely to need neonatal care and/or resuscitation. Long-term effects have also been noted (Box 3).

[H1] Diagnosis, screening and prevention

Despite the aforementioned challenges in defining HG and difficulties delineating HG from NVP, current clinical practice is that HG can be diagnosed in a pregnant woman with severe vomiting and/or severe nausea after other causes have been ruled out. Other potential causes include gastrointestinal tract conditions (such as peptic ulcers, appendicitis, obstructions, cholecystitis, pancreatitis and gastroenteritis), endocrine or metabolic conditions (such as hyperparathyroidism, hyperthyroidism or diabetic ketoacidosis), neurological conditions (such as hydrocephalus, tumour in the central nervous system or migraine), drug-induced or drug-withdrawal nausea, complete hydatidiform molar pregnancy or urinary tract infection. Definitions of HG are available in practice guidelines but differ in terms of their symptom requirements and additional criteria (Table 2). For example, ketonuria, weight loss and gestational age at first presentation of symptoms are not consistently included in HG definitions[5].

[H2] Diagnosis

A thorough history is the cornerstone in diagnosing HG; laboratory tests are used to determine the extent of metabolic consequences and to exclude other diseases.

[H3]Severity.

The severity of NVP can be assessed using the three-tier Pregnancy-Unique Quantification of Emesis/nausea (PUQE-24) questionnaire, which includes questions on the duration of nausea, the number of vomiting episodes, the occurrence of retching and overall QOL (supplementary Table 1). Symptoms

during the past 24 hours yield a summary score from 3 to 15; the higher score the more severe the NVP symptoms. A PUQE score of ≤6 signifies mild NVP, 7–12 signifies moderate NVP and ≥13 equals severe NVP[119,120]. After antiemetic treatment and/or hospital treatment for hyperemesis, PUQE scores have been shown to decrease to levels comparable to those of healthy pregnant women[120]. The HyperEmesis Level Prediction (HELP) score[121] (supplementary Table 2) more accurately define the severe symptoms of HG that may be underestimated using PUQE by adding additional questions such as ability to eat and drink and weight loss[122].

[H3] Screening.

Screening and early recognition of NVP and HG in primary (general practice) antenatal care is not routine practice, resulting in lack or delayed onset of treatment[41]. At present, ketonuria screening in HG is often used as an aid to decide on the diagnosis, eligibility for rehydration and eligibility for hospital admission and discharge. HG is the only example of nausea and vomiting syndromes in which screening for ketonuria is so widespread and recommended in guidelines[123-125]. Ketones in the urine are measured on dipstick. Their presence indicates lipolysis, which is 'a measure of starvation'[125]. However, the increased metabolic demands of pregnancy, even in the absence of vomiting or poor oral intake, is a predisposing factor for ketonuria, which Prentice et al.[126] coined as 'accelerated fasting'. A systematic review, including 81 studies of 9 biomarkers as diagnostic tests for HG[56] found no evidence for utility of most biomarkers in diagnosing HG. Interestingly, this study was also unable to find evidence for the use of ketonuria in establishing the presence or severity of HG. We, therefore, cannot recommend the use of ketonuria to diagnose HG[127].

A promising new area of study is based on recent research linking GDF15 and IGFBP7 to HG[59,69]. A small study showed the combination of elevated serum levels of both of these proteins at 12 weeks significantly increased the risk of HG (P=0.0002)[71]. Larger studies are needed to determine whether combined measures of GDF15 and IGFBP7 may be useful as a diagnostic tool for HG.

[H3] Other abnormalities.

At present, women with potential HG are usually screened for the complications of prolonged vomiting and poor nutritional intake such as electrolyte abnormalities, dehydration and weight loss, and sometimes also specific vitamin deficiencies[123,127]. In women with HG and neurological symptoms including eye movement disorders, confusion and/or gait abnormalities, Wernicke encephalopathy should be considered and neurological assessment and treatment should be urgently sought[128]. Wernicke encephalopathy is a clinical diagnosis, for which defining symptoms are dietary deficiencies, eye movement disorders, cerebellar dysfunction and an altered mental state (reported as delirium, confusion and problems in alertness or cognition) and can be supported by MRI neuroimaging[129].

[H3] Psychological factors.

A pregnancy affected by HG can leave 18% of women affected by postpartum PTSD (DSM-IV-R), and is more common in women who experience symptoms for the entire pregnancy[9]. Screening for symptoms associated with PTSD among women who have experienced HG may help identify those who may benefit from psychotherapy[130]. Specific questions about avoidance, hyperarousal, re-experiencing, dissociation, mood changes and associated functional impairment can alert clinicians to the possibility of PTSD in postnatal settings[131].

[H3] The fetus.

Especially when women experience severe weight loss or prolonged symptoms, third trimester ultrasonography screening for fetal growth restriction may be indicated, as HG increases the risk for this obstetric complication[17,132].

[H2] Prevention

The evidence base for HG preventive measures is, at present, limited but prevention is the most prudent first step and can begin before conception. A preconception multivitamin B complex, initiated at the time of fertilization, has been noted to decrease symptoms and the amount of treatment needed for NVP

but not for HG[133,134]. The mechanism is unknown, but may relate to the role B vitamins play in increasing appetite[135] and/or as a rate-limiting co-factor for synthesis of neurotransmitters including dopamine and serotonin[136].

Having had a previous pregnancy affected by HG is the single largest risk factor for HG[24,26,137]. Reports on recurrence of HG in subsequent pregnancies are widely divergent, ranging from 81% in a small self-selected cohort[137] to as low as 15–27% in studies that made used of the International Classification of Disease (ICD) code-based diagnosis (Box 1)[24,26]. The clinical implication of unreliable recurrence rate estimates is that women base their decision to attempt another pregnancy on their chance of HG recurrence, and may, therefore, be misinformed about this statistic, possibly misguiding their reproductive choices, with emotional, economic and medical consequences.

Nevertheless, prevention of HG in women who experienced HG in their previous pregnancies might be plausible. For example, a small (*n*=60) open-label randomized controlled trial (RCT) in women with a history of severe NVP or HG showed that pre-emptive combination of doxylamine (an antihistamine) and pyridoxine (vitamin B6) taken from the time of a positive pregnancy test led to fewer instances of substantial nausea or vomiting in early pregnancy compared with treatment after manifest nausea symptoms commenced (15% versus 39%); the pre-emptive treatment also was associated with a smaller likelihood of recurrent HG in subsequent pregnancies (32% versus 55%)[138]. Due to its small size, lack of extensive baseline characteristics reported, open-label nature and lack of pre-published protocol, the findings of this study should be interpreted with caution. On the other hand, the study provides an incentive for further investigation of preemptive strategies.

[H1] Management

In general, aspects regarding treatment of NVP and HG are profoundly understudied, partly hampered by a lack of a distinct definition to compare studies. Studies regarding lifestyle modifications and complementary therapy are often small and of poor methodological quality. Even for medical (antiemetic) treatments and fluid or nutritional therapies, well designed, powered RCTs are

sparse. Indeed, the Cochrane reviews[139,140] conclude that evidence is lacking to properly determine one treatment as superior to another. The guidelines issued by the American College of Obstetricians and Gynecologists (ACOG)[141] and Royal College of Obstetricians and Gynaecologists (RCOG)[142], as well as this Primer, are mostly based on lower quality evidence rather than level I evidence.

Many women will experience a level of NVP that requires some form of intervention, either non-pharmacological or pharmacological (Figure 2)[45]. Interventions can be adjusted according to the frequency and severity of symptoms. Mild NVP (PUQE ≤6) can be self-managed in the community with support of primary health care professionals. Moderate NVP (PUQE 7−13) may respond to complementary therapy but, if no improvement, antiemetics should be provided. Severe NVP and HG (PUQE ≥13) will generally need hospital care, either ambulatory or inpatient to provide fluid and nutritional treatment. As discussed below, using the PUQE score alone to guide treatment cannot be recommended, as evaluation of treatment response within the severe category (which includes HG) has not been specifically evaluated. The HELP score potentially provides more granular descriptions to guide management, but this requires further evaluation.

[H2] Lifestyle modifications

Mild NVP can be addressed with dietary and lifestyle modifications. Small, frequent meals, higher proportions of proteins and carbohydrates and avoidance of spicy foods have been reported to provide some symptom relief[143,144]. An empty stomach has been noted to increase nausea, so fluids containing electrolytes are also recommended between meals[81,145,146]. Adequate rest is advised in addition to dietary changes to combat the exacerbation of nausea caused by fatigue[147]. As there is a general lack of RCTs evaluating lifestyle and dietary changes and the majority of reviews involve cohort studies of patients reporting personal preferences, these interventions are only appropriate for patients with mild NVP. For women with severe NVP or HG, lifestyle and dietary changes alone are insufficient.

[H2] Complementary treatment

When mild symptoms of nausea and vomiting are not relieved by diet and lifestyle changes alone, other non-pharmacological treatment options are considered. Ginger has been the most researched and found to be effective for nausea in pregnancy in some studies[140]. Gingerols have gastrointestinal motility-enhancing action by acting as dopamine and serotonin antagonists[148]. ACOG recommends ginger as first-line non-pharmacological treatment for NVP and RCOG suggests ginger for women with mild to moderate NVP who wish to avoid antiemetic therapies[141,149]. Ginger has been reported as safe to use in the first trimester and is superior to placebo and pyridoxine[139]. However, safety studies for doses >1,000mg/day are lacking and due to potential inhibitory action on platelet function, ginger is not recommended in patients receiving anticoagulant therapy[150]. As with all therapies using herbs or plant extracts, scientific evaluation and/or comparison of effect is hampered by lack of standardization of actual active doses.

Additional non-pharmacological options including acupressure, acupuncture and electrical nerve stimulation of the P6 point (Neiguan point, located near the wrist on the inner forearm) have shown varying results[140]. Acupressure was found to have similar effects in those with NVP when compared with vitamin B6, but contrasting results when compared with placebo[140]. Acupuncture showed minimal symptom relief in comparison with sham acupuncture whereas electrical nerve stimulation provided some benefit to patients when compared with placebo[140]. However, many of the studies were limited by flawed designs. Systematic reviews showed no benefit from acupuncture and limited symptom improvement associated with acupressure[105,140]. Again, the same difficulty arises regarding comparison of different types of acupressure or acupuncture; the pressure or stimulation given to the different parts of the body varies widely.

Due to expanding legalization of cannabis in the United States, its use in pregnancy to self-treat NVP, albeit controversial, is on the rise and warrants discussion[151]. For example, in Northern California, 7.1% of patients use marijuana (inhaled and/or edible) in pregnancy (based on self-report and/or toxicology screens)[152]. The mechanism of action is unknown, but may act through its effect on serotonin and dopamine signalling, which can activate the

vomiting centre[153,154]. Alongside a growing perception of safety, despite insufficient evidence[152], the self-reported effectiveness of cannabis in treating NVP is high[155]. Studies of cannabis use in the context of HG need to establish efficacy and safety, in consideration of other confounding factors, before any recommendations can be made in support of its use. Therefore, currently ACOG recommends against its use[141].

[H2] Pharmacological treatment

Nausea and vomiting are mediated by different mechanisms of activation (Box 2), but which of these are involved in NVP in general or in individual patients is unknown[156]. Theoretically, combining antiemetics with different mechanisms of action could work synergistically to give the antiemetic effect compared with changing from one antiemetic to another; this strategy is recommended for chemotherapy-induced emesis[157]. Although empirical clinical practice use of multiple antiemetics to patients with refractory NVP or HG, this strategy has not been systematically tested in HG and it remains uncertain whether this practice reduces nausea and/or increases adverse effects for the woman and her fetus.

The effect of treatment may be monitored using the PUQE score (supplementary Table 1), or the HELP score (supplementary Table 2) for more severe cases[121, 122]. However, how well the PUQE score evaluates treatment response in women in the severe category (likely the dominant part of HG spectrum) is unclear as this has not been specifically evaluated. Given that the 'severe' score is limited to 13–15 points, the PUQE may well be of limited use in these patients, in particular those with HG. The HELP score was designed in part to address this limitation, and gives scores from 0-50, with the 'severe' group scoring 31–40 and 'extreme' scoring 41–50. Accordingly, the HELP score might provide a robust tool to evaluate treatment in those with HG. However, this tool is still under initial evaluation.

[H3] Antihistamines.

The evidence for antiemetic effectiveness includes a recent study showing women who were hospitalized for HG were significantly less likely to have been treated with antiemetics prior to admission than women with HG who were not

hospitalized[41]. Additionally, hospitalization rates increased significantly after removal of combined doxylamine and pyridoxine from the US market due to unfounded safety concerns. Antihistamines such as doxylamine, dimenhydrinate, meclizine and promethazine have been used for decades and are the first-line antiemetics used globally to treat NVP. Antihistamines mainly act on the vestibular nausea pathway by blocking histamine H1 receptors in the vomiting centre from communicating with the chemoreceptor trigger zone (Box 2)[156]. No harmful fetal effects have been described[158]. Combined doxylamine and pyridoxine has been prescribed to treat NVP in Canada for decades, was approved by the FDA in the United States in 2013 to treat NVP and is gaining approval elsewhere, expanding to Israel in 2015 and to the United Kingdom in 2018. Approximately 70–80% of women with NVP reported symptom improvement with the combination, although effectiveness remains controversial[159]. Pyridoxine alone was found effective and recommended as one of the first-line options by ACOG[141] but not by RCOG[149]. ACOG recommends diphenhydramine as a second-line agent. The combination of diclectin and pyridoxine combination has been extensively studied, with several reports and meta-analyses finding no increased risk for fetal malformations[160]. With increasing severity of NVP and with HG, other medications are warranted.

[H3] Neurotransmitter blockade.

Metoclopramide (a dopamine receptor antagonist), dopamine antagonists and serotonin antagonists have shown variable benefits in clinical trials on NVP. The dopamine antagonists block dopamine stimulation in the gastrointestinal tract and the chemoreceptor trigger zone, reducing stimulation of the vomiting centre[156]. A Cochrane meta-analysis reviewing 41 clinical trials of NVP treatment (excluding HG) concluded that none of these antiemetics had documented superior clinical efficacy compared with each other[140]. In line with this finding, a Cochrane analysis of 25 studies for treatment of HG that compared antiemetics pairwise showed no preferable antiemetic regarding effect but their adverse effect profiles were different[139]. Metoclopramide, although not teratogenic, can cause extra-pyramidal reactions (such as dystonia) but this event was mainly reported with long-term use and primarily in older patients (above traditional reproductive age) who had other nausea conditions or in those on anticholinergic medication[161].

Hence, without considering the specific indication for use in NVP and/or HG, the European Medicines Agency (EMA) advises total daily doses as no more than 30mg and use that does not exceed 5 days. Metoclopramide has been recommended by ACOG as a second-line or third-line option in patients with persistent symptoms. Other dopamine D2 antagonists such as phenothiazine derivates (prochlorperazine, promethazine and chlorpromazine) may cause profound sedation. Newer cohort studies regarding dopamine antagonists have found no or very low risk for fetal malformations[162, 163]. Preliminary results (*n*=355) are promising for continuous subcutaneous micro-infusions of metoclopramide; initiated in the hospital, doses are titrated based on the therapeutic response, after which patients can continue at home[164].

Ondansetron, a selective serotonin 5-HT_3 receptor antagonist inhibits serotonin receptors in the small bowel, vagus nerve and the chemoreceptor trigger zone[156]. This antiemetic is used off-label by ~20% of pregnant women in the United States[91,165]. In Europe, ondansetron is generally considered a third-line option. A meta-analysis and review of recent large studies (>76,000 exposures) concluded ondansetron is not associated with an increased overall risk of any major congenital malformation, but continued surveillance is warranted particularly for cleft palate and genitourinary malformations such as hypospadias; future studies should include gestational age, dose and duration of exposure in the evaluation[166]. The studies were unable to comment on the inability of women with HG to meet nutritional folic acid demands and, therefore, could not assess whether confounding by indication may have had a role in their findings; folic acid deficiency is associated with an increased likelihood of oral clefting[167]. Both ACOG and RCOG recommend the use of ondansetron as a second-line drug and the risks of birth defects, although likely to be minimal or due to chance, need to be discussed with the patients. Prolonged QT interval and serotonin syndrome may be rare adverse effects[153]. A US retrospective cohort study found ondansetron use is linked to fewer miscarriages and terminations and higher live birth rates compared with women not using ondansetron[168].

[H3] Corticosteroids.

Corticosteroids are reserved for patients with severe and/or refractory HG, to achieve anabolism and to act as an adjunct to traditional antiemetics. However, studies regarding the antiemetic effect of corticosteroids are contradictory. A network meta-analysis supported the therapeutic benefits of methylprednisolone in women with refractory HG[169]. However, a recent Cochrane review showed corticosteroids provided no difference in hospital duration but did reduce readmission rates compared with placebo; however, similar readmission rates were observed when comparing corticosteroids and metoclopramide[139]. Some studies show an increased risk of oral clefts with corticosteroid administration during the first trimester[170], but the aforementioned Cochrane review could not exclude confounding factors such as reduced nutritional intake. Accordingly, administration of parenteral corticosteroids should preferably be limited to short durations of treatment and if patients do not respond in 3 days, the medication should be discontinued. If an adequate response is observed, the dose should be tapered according to proposed guidelines[149].

[H2] Fluid and nutritional therapy

Severe (PUQE $\geq$13) or protracted (>14 days) moderate NVP requires assessment of the patient's general condition, extent of weight loss, ketonuria or dehydration (that is, signs that she has developed HG) and, therefore, consideration for hospital treatment. Rehydration and/or parenteral nutrition or tube feeding may be implemented as an outpatient treatment, depending on the woman's medical and psychosocial condition, her personal preferences and local hospital practices[105,171]. However, the efficacy and safety of nutritional strategies needs further investigation.

Fluid volume should be given according to reversal of signs of dehydration and any electrolyte deficiencies corrected before further parenteral nutritional interventions. Severe hyponatraemia (<120 mmol/l) should be corrected slowly to avoid the rare, but potentially severe, complication of central pontine myelinoysis[172]. Similarly, hypokalaemia should be corrected slowly to avoid cardiac arrhythmias. Thiamine should be given when parenteral nutrition is instituted to reduce the risk of refeeding syndrome and Wernicke encephalopathy[173]. For women with continuous vomiting and/or very low food

intake for >2 weeks, parenteral infusion of thiamine (100mg in 100ml 0.9% NaCl, a formulation that differs from most over the counter thiamine supplements) is recommended before commencing of parenteral treatment, including before infusing dextrose 10% (the 5% solution is not considered as nutritional supplementation).

If antiemetics and fluids are not sufficient to reduce the nausea/vomiting, ketonuria persists, and the patient is unable to improve nutritional intake, additional nutritional therapy should be considered. Tube feeding is preferred when prolonged nutritional therapy is needed as it has none of the serious risks of total parenteral feeding by central venous catheter such as thrombosis, pneumothorax, phlebitis and sepsis[174]. Enteral tube feeding may be given by a gastric tube[175] or a jejunal tube positioned by gastroscopy [176,177]; a jejunal tube potentially has less risk of regurgitation of the nutritional solution. The commercial enteral solutions are 'complete' regarding vitamins and trace elements if a daily dose of 2L is achieved. A Dutch RCT with tube feeding starting on day 1 of hospital admission for HG did not find significant differences in short or long-term outcome compared with intravenous rehydration alone[175]. However, a Norwegian hospital cohort study of women whose primary interventions failed and who were given jejunal tube feeding (*n*=108) started to regain weight and achieve similar total maternal weight gain and fetal birth weight as those women not needing enteral treatment[177]. Patients may experience tubes as discomforting, demanding their removal. Otherwise, there are no risks related to enteral tube feeding in noncomatose patients.

Parenteral nutritional supplementation (in which the standard manufactured solutions provide 1,000kcal per litre) may be given by peripheral venous line, but vitamins and trace elements need to be specifically added before infusion is started to avoid severe vitamin deficiencies. If total parenteral nutrition is needed, the patient must be fitted with a central line. This regimen will need prolonged hospitalization or specialized home care by infusion nurses.

[H2] Additional support

The HG Care Application for iPhone[178] was designed for pregnant women taking medication to treat NVP and to improve patient–provider communication and care[122]. It potentially helps with tracking weight loss, symptoms and treatments, provides reminders to complete the app daily and alerts the patient and/or provider when symptoms progress, requiring intervention. A beta-testing study[122] suggested the app is accurate in defining symptoms and improving communication and care; a trial is being planned to assess its influence on outcomes such as emergency room visits (M.S.F.). A similar application, Symptom Tracking and Reporting (STAR), for measuring symptoms during chemotherapy, showed patients who used it were significantly less likely to visit the emergency department or be hospitalized[179]. Patients can choose to share their data to alter treatment or for research.

In addition to these tools, various organizations provide patient support and management recommendations for patients with HG in several countries (Table 3). These organizations are primarily not-for-profit and patient-run and provide online and, in some cases, telephone support and information to women with HG, their providers and families. These organizations also play key parts in research through participation, conference organization, setting priorities, networking opportunities, designing treatment protocols, providing content and algorithms (for example, for the HG Care App), and fundraising.

[H2] Global variation

Although the majority of published treatment studies are from United States and Europe and very little from less-resourced settings such as African and Asian countries, the medical treatment of HG follow the same principles across continents: antiemetics and intravenous rehydration/electrolyte substitution[180,181]. Settings with general lack of access to specialist or hospital care will affect the availability of infusion therapy and use of relevant antiemetics may be hampered by lack of medications in stock or being too costly (for example, ondansetron[182]). In line with cultural differences in food habits, different herbal remedies are promoted to alleviate NVP in different countries[183,184]. In Asia, non-pharmacological management such as acupuncture and acupressure is widely used for many conditions, including HG[185,186]. One study describing trends in

treatment of HG between 1985-2004 in the US, UK, Australia/New Zealand, and Canada, showed vitamin supplementation ranged from as low as 10% in the UK to 33% in the US, suggesting two-thirds to as many as 90% of women with HG may have prolonged vitamin deficiencies[187].

[H2] Quality of life

The PUQE is the best-validated, disease-specific questionnaire for NVP[120], which includes a rating for effects on QOL and for which high scores correlate with reduced nutritional intake and reduced QOL. Nonspecific QOL scales have revealed that women with NVP have QOL levels similar to those with breast cancer or myocardial infarction[188]. Standardized tools for measuring the distribution, duration and intensity of nausea showed that severity was comparable to that induced by moderately nausea-producing chemotherapy, which is deemed an important adverse effect of treatment that often warrants intervention, demonstrating that NVP has been widely underestimated[21]. Accordingly, the Health-Related Quality of Life for Nausea and Vomiting during Pregnancy (NVPQOL) was developed as a disease-specific scale[189,190].

A large body of research shows that NVP reduces QOL by negatively affecting work and family life, physical and mental health and economic well-being[191,192]. However, inconsistencies between studies may reflect differences in design, mode of measurement and sample size; furthermore, when interpreting QOL results, consideration of environmental, cultural and socio-political aspects is needed, as well as an understanding that results may not apply to all populations. Between 37% and 55% of women with NVP lose time at work, and 15.2% of women with HG terminated at least one pregnancy due to NVP — with inability to care for self and family as major reasons[193,194]. Only 1.2% of women have a history of depression prior to their HG pregnancy[195], but HG is associated with depression and anxiety during pregnancy, and post-traumatic stress following pregnancy[196]. The prolonged physical and emotional distress of HG results in an increased risk of postpartum PTSD (DSM-IV-R), especially when symptoms persist until term. Indeed, women with HG were more likely to report emotional distress during pregnancy and up to 6 months post-delivery. However, this difference disappeared 18 months post-delivery[195]. Women may limit their family

size or turn to other methods (such as adoption and/or surrogacy) to avoid a subsequent HG-affected pregnancy[9,87,137].

Despite strong evidence of reduced NVP-related QOL, women experience a lack of empathy and care, reporting isolation and lack of understanding and support from healthcare providers[197]. Clearly, patient satisfaction for these women is associated with being believed by doctors and health care providers[198], highlighting the need for increased awareness of the NVP burden. Additionally, 24% of patients report never mentioning NVP symptoms to health care professionals, and two-thirds of general practitioners (GPs) do not address QOL in pregnancy care[199]. Moreover, GPs seem to trivialize its symptoms[200,201], and women who have a therapeutic termination of their pregnancy are threefold more likely to state their medical provider is uncaring or does not understand how sick they are[193]. In the United States, most providers taking care of pregnant women are obstetricians or in family medicine. By contrast, in many European countries, Australia, New Zealand, and others, GPs are also responsible for family medicine, providing care to healthy pregnant women in collaboration with other practitioners, such as midwives. In many of these jurisdictions, pregnant women are referred to specialist obstetricians only if complications occur. A Norwegian study identified that attitudes of GPs toward pregnant women hindered appropriate care for those with NVP; the GP added to the woman's reluctance to use antiemetics[200]. This may reflect past fears of thalidomide use during pregnancy, which caused infants to be born with limb deformities after women took the drug for NVP. The majority of women have reported not using anything to alleviate symptoms, or practices based on previous experience, more than evidence-based guidelines aiming to improve QOL by treating NVP[202].

[H1] Outlook

Although NVP is a common problem in pregnancy, historically, research into the condition is lacking. The thalidomide tragedy is responsible, in part, for this research deficit; the events that took place led to fear of researching, developing, prescribing and taking medication for use during pregnancy. Another issue is that NVP is often considered normal and self-limiting, and the burden is largely

underestimated. However, recent developments suggest a shift in this attitude is forthcoming. For example, the contribution of patients and patient-led organizations and charities to research has and will continue to play a key part moving forward in guiding research priorities, helping with recruitment to clinical trials and other studies, developing patient–provider partnerships through organization and support of international conferences, raising funds for research and providing education and support to the community. One such organization, the James Lind Alliance, has established Priority Setting Partnerships to prioritize evidence uncertainties in HG that could be answered by research[203]. Additionally, it was women with and those without a history of HG who voluntarily participated in consumer-driven research by 23andMe that led to the discovery of the first genes associated with NVP and HG [59].

The identification of these genes and their abnormal expression levels that confer risk in affected women opens a new and promising area of research into understanding the aetiology of NVP and HG. Efforts should focus on understanding why common variants in genes *GDF15*, *GFRAL*, *PGR* and *IGFBP7* are all confirmed susceptibility loci for NVP and HG. We need to know whether the proteins encoded by these genes are causal and if so, whether they can be used for prediction, diagnosis and new treatments for the condition. Indeed, a GDF15 inhibitor has already proven to successfully restore appetite in animal models[67,61]. Drugs targeting the GDF15–GFRAL pathway are under development to treat cancer-associated cachexia, which is also associated with abnormally high levels of GDF15 (Refs[204,205]); this strategy, if proven safe in pregnancy, may be effective in treating HG. In addition, if drugs can be developed to target progesterone signalling without effecting pregnancy outcomes, they may help to treat women with HG. The recent development of an organoid model for placental development provides a novel reagent for elucidating the role these factors may have in placental biology[206].

On the subject of genetic testing, although having a family history of HG is suggestive of a genetic predisposition, it is important to recognize that even if there is no family history, a genetic predisposition to the disease may still be present. That is, genetic variant(s) can be inherited down the paternal line or a

combination of predisposing gene variants and other unknown factors may be required to predispose to NVP and/or HG. More research is needed to unravel the genetic and non-genetic components leading to NVP and HG, and understand how these factors work independently or together to increase symptoms. Until then, genetic testing will not be very informative.

In the majority of countries, very few antiemetics are formally approved for NVP and HG, although combined doxylamine and pyridoxine is increasingly gaining approvals. As many as 20% of pregnant women in the United States are taking the off-label drug ondansetron and increasingly using medical marijuana[91,165], which suggests that although fear of medications in pregnancy is subsiding, the burden of NVP is substantial, and there is a large market for antiemetics to treat it. And yet, low rates of antiemetic prescriptions are still reported in some settings, both prior to and upon discharge from the hospital for HG [41,177]. Providers and the patients themselves clearly do not always follow national recommendations. Thus, more research into the safety and efficacy of the current treatments for NVP and HG must follow.

An international consensus on definition is needed for the research to be robust, for the external validity of study findings and for the possibility of aggregation of research findings. For example, in the most recent Cochrane review on treatment of HG[139], the authors point out that the variations in definition contributed to heterogeneity, which hampered their ability to perform meta-analyses, a lament echoed in other systematic reviews in HG[105,207,208]. In turn, this lack has slowed the progress of research in HG treatment. Importantly, the variation in definitions, or variation in additional criteria, can lead to patients being denied care in some situations. Unclear definitions can have an impact on patient care, exemplified by the use of ketonuria as a criterion for treatment. A patient presenting with severe nausea, frequent vomiting and inability to hold down food and drink, but without ketonuria, could be unrightfully considered ineligible for treatment with anti-emetics or rehydration.

It is becoming increasing clear that mother and child are at more risk from leaving HG untreated than from treatment with most antiemetic therapies. For

antiemetics with inconsistent safety data, inclusion of gestational age at exposure in outcome studies will help determine windows of exposure that may be unsafe. Alternative routes of administration for antiemetics (such as patches or suppositories) that cannot be affected by vomiting but still enables patient self-administration are needed. Optimal nutritional regimens should be determined to identify which patients benefit from nutritional supplementation and which patients only require fluids. More studies must be initiated to determine whether early intervention can stop progression of NVP to HG.

Although most providers now recognize HG is a serious condition with a biological basis, some providers may need to be better educated to understand that patient QOL can improve dramatically with adequate treatment, care and understanding. Ignoring the patient can result in serious and long-term maternal, fetal and child consequences. The ongoing efforts toward establishing an international consensus on the definition of HG and a universal application for data collection (for example, with the HG Care App) will improve standardization of future studies aimed at properly resolving some of the important issues. They will provide a critical first step to move forward.

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Box 1. Definitions for NVP and HG used in epidemiology and registry studies.

Over the past several decades, the International Classification of Disease (ICD) coding for nausea and vomiting of pregnancy (NVP) and hyperemesis gravidarum (HG) has increased in its degree of elaboration of the requirements for diagnosis to its current (ICD11) definition:

- Mild HG (JA60.0): vomiting occurring during pregnancy responsive to dietary modification and antiemetic treatment
- HG with metabolic disturbance (JA60.1): vomiting in pregnancy, not responsive to dietary modification and antiemetic treatment and associated with electrolyte disturbances and acid-base imbalance
- Excessive vomiting in pregnancy, unspecified (JA60.Z)

Although ICD codes accurately reflect the occurrence of life-threatening conditions including cardiac arrest and cancer [209,210], the codes have much lower diagnostic accuracy for less well-defined conditions, including some obstetric diagnoses[211]. For example, one study looking at the application of ICD8 to ICD10 codes in Norway showed only 9 out of 14 women (64%) with severe HG (defined as hospital admission for HG with weight loss, dehydration and/or ketonuria) according to the hospital records could be identified by ICD code. The study also showed that codes were incorrectly applied in 5 of 503 (1%) of cases that did not have severe HG according to hospital chart[212]. Other studies have used unvalidated registry definitions for HG[28]. As with other early pregnancy conditions, there is an increased likelihood of underreporting due to the design of many perinatal registries, which make use of records that are retrospectively completed at the point of delivery, and often only include pregnancies >20 weeks in gestational age. Any complications that only affected early pregnancy will not be registered if the pregnancy ended in miscarriage or termination before 20 weeks, or if these complications were no longer evident at the time of delivery[213]. Besides being imprecisely reported, HG and termination due to HG[214] are therefore likely to be underreported in registries.

Box 2. The area postrema (vomiting centre)

Vomiting is a reflex. Firstly, the gastrointestinal contents are forced back toward the oesophagus via retrograde peristalsis. Secondly, there is a deep breath followed by closing of the epiglottis to protect the airway. Finally, ejection of gastric contents occurs via contraction of the abdomen, diaphragm and oesophagus[153]. The vomiting reflex is controlled by the vomiting centre (the area postrema) and the chemoreceptor trigger zone in the medulla oblongata. At least five known receptors are involved in feedback to the brainstem: 5-hydroxytriptamine or 5-HT_3 (serotonin), neurokinin NK_1 (substance P), dopaminergic (D_2), histaminergic (H_1) and muscarinic M_1. These receptors are associated with one or more stimulus, including dysmotility and irritation in the gastrointestinal tract and lumen; visceral pathology; vestibular disturbance; and toxins in the blood or cerebrospinal fluid. Multiple receptors may be affected. For example, 5-HT_3, NK_1, H_1, and M_1 receptors all play a part in stimulation of the vagus nerve of the gut in response to gastrointestinal disturbances, which in turn activates the chemoreceptor trigger zone and vomiting centre. Visceral pain, anxiety and stress can activate the receptors and signal the vomiting centre by providing sensory input through the cerebral cortex. Vestibular disturbances that cause, for example, motion sickness, are mediated primarily through H_1 and M_1 receptors in the vomiting center. Toxins such as certain drugs or drug metabolites can travel through the blood stream to activate 5-HT_3, NK_1, and D_2 receptors in the chemoreceptor trigger zone. In the vomiting center, at the cellular level, vomiting can be achieved via crosstalk between extracellular and intracellular receptors. For example, activated 5-HT_3 receptors, ryanodine receptors, and L-type Ca^{2+} receptors all release intracellular Ca^{2+} that cause activation of the Ca^{2+}/CamKII-dependent ERK molecular signalling cascade, which activates vomiting[90]. In addition, pathways may interact to exacerbate nausea and vomiting. For example, motion sickness can cause anxiety, and vagal afferents in the gut also mediate anxiety, which can in turn worsen nausea and vomiting[215]. Finally, the newly discovered receptor GFRAL is localized to the vomiting center of the brain where it reduces appetite and causes taste aversion when activated by GDF15, but its potential role in vomiting requires further investigation[60,216].

Box 3. Long-term effects for the fetus

The conditions in which the fetus develops have lasting consequences for later growth, development and health. Organs and tissues are most sensitive to environmental insults such as limited nutrient supply and stress during critical periods of development. As HG usually presents during the critical period of organ formation and can last the entire pregnancy, it might affect fetal development and thereby its later health and wellbeing[132]. Indications suggest that severe NVP and HG negatively affects neurodevelopment of the offspring[217] with potential risks that include development of autism spectrum disorder[218], attention deficit disorders[217], learning difficulties or delays[217], psychological disorders[219], sensory integration or processing disorders[217] and social anxiety[217]. However, HG may not have effects on cognitive development[217,220]. The consequences of HG for cardiometabolic health of the offspring may include reduced insulin sensitivity and higher blood pressure[218], although not all studies have demonstrated such an effect[221]. Baseline cortisol levels may be increased in children born from pregnancies with severe HG[218]. Also, small studies have shown a slight increased risk of leukaemia or testicular cancer in offspring of affected pregnancies[218,222]. By contrast, a large Scandinavian registry-based study concluded that HG was not associated with increased cancer risk in offspring (including leukaemia and testicular cancer), but did find an association with lymphoma, which they suggest could be due to chance and needs further exploration[113]. Disease severity and heterogeneous patient populations might explain inconsistencies between studies.

Figure 1. Possible model for the role of GDF15 in HG pregnancies.

Growth/differentiation factor 15 (GDF15) is a hormone produced at the highest levels by the placenta (decidual stromal cells and trophoblasts) and is expressed as early as the 8–10 cell blastocyst stage[223,206,224]. Factors including genetic variants contribute to altered GDF15 levels[59], nutrient deprivation[60], long-term fasting[102] and hyperthyroidism[101] may result in a rapid rise and/or abnormally high levels in the maternal bloodstream. When GDF15 travels to the area postrema and nucleus of the solitary tract (of the medulla oblongata) via the circulatory system, it binds to its receptor, GFRAL, where it signals appetite

loss[216] and taste aversion[60]. Normally, GDF15 activates GFRAL when the body is under physical stress, but when the pathway is overactivated it might also lead to nausea and vomiting. Genetic variants of *GFRAL* are also associated with hyperemesis gravidarum (HG)[77]. Theoretically, in pregnancies affected by HG, abnormally high levels of GDF15–GFRAL pathway signalling in the vomiting centre (area postrema) of the brainstem may cause appetite loss, taste aversion, nausea and vomiting, although this has not been definitively proven. RET is the RET Receptor Tyrosine-Protein Kinase that interacts with its co-receptor GFRAL, and is required for downstream signalling of appetite loss by GDF15 (Ref[216]).

Figure 2. Flowchart for the management of NVP and HG

If the patient presents with mild nausea and vomiting of pregnancy (NVP), dietary and lifestyle changes are recommended. If symptoms persist and/or the patient presents initially with moderate NVP, complementary treatment is advised beginning with non-pharmacological treatment, followed by pharmacological intervention if symptoms do not resolve. Patients who present with severe NVP or whose symptoms do not improve after second line pharmacological treatment will require more aggressive treatment and interventions that may require hospitalization. [a]The Pregnancy Unique Quantification of Emesis/nausea (PUQE) score (supplementary Table 1) is used as a general guideline to roughly assess rate of nausea and vomiting, but categories may not apply to all cases, especially at the severe end of the clinical spectrum. In particular, the PUQE score may be less robust for assessing symptoms in patients with hyperemesis gravidarum (HG). Quality of life should also be taken into consideration when determining a treatment plan.

Table 1. NVP versus HG.

Normal NVP	HG
Minimal weight loss	Weight loss >5%
Adequate intake most days	Inadequate intake for weeks or months
Nausea and vomiting are unpleasant but do not limit most essential activities	Nausea and vomiting cause misery and often limit daily activities including self-care
Dietary and lifestyle changes make symptoms mostly manageable	Medical treatments, such as medications and intravenous therapy, are needed
Symptoms generally ease considerably by 14 weeks gestation	Symptoms may ease or persist until delivery
Family responsibilities can be completed most days, especially after 14 weeks gestation	Family responsibilities are very difficult or impossible to complete for weeks to months

NVP, nausea and vomiting of pregnancy; HG, hyperemesis gravidarum. Used with permission from K. MacGibbon, Hyperemesis Education and Research Foundation. [CE: please update permission line, iLTP received]

Table 2. Clinical definitions of hyperemesis gravidarum in practice guidelines

Guideline	Required criteria	Additional criteria	Ref
RCOG Green Top Guideline	• Protracted nausea and/or vomiting • Onset in the first trimester • No other causes identified	• >5% weight loss • Dehydration • Electrolyte imbalance	• [123]
ACOG Practice Guideline	Persistent vomiting in the absence of other diseases that could explain findings	• Ketonuria • Weight loss >5% • Electrolyte abnormalities • Thyroid and liver abnormalities	• [125]
SOGC Clinical Practice Guidelines	Persistent vomiting in pregnancy	• Weight loss >5% • Electrolyte imbalance • Ketonuria	• [124]

ACOG, American College of Obstetricians and Gynecologists; RCOG, Royal College of Obstetricians and Gynaecologists; SOGC, Society of Obstetricians and Gynecologists of Canada.

Table 3. Organizations that are sources of education, support, research, fundraising, and other resources related to NVP and HG.

Country	Name	URL
Australia	Hyperemesis Australia	hyperemesisaustralia.org.au
Finland	Hyperemesis Finland	hyperemeesi.fi
France	Hyperemesis France	associationhg.fr
Germany	Hyperemesis DE	hyperemesis.de
Ireland	Hyperemesis Ireland	hyperemesis.ie
Netherlands	ZEHG	zehg.nl/wordpress
Norway	Hyperemesis Norway	hyperemesis-norge.com
United Kingdom	Pregnancy Sickness Support	pregnancysicknesssupport.org.uk
United States	Hyperemesis Education and Research Foundation	hyperemesis.org;helpher.org

Supplementary Table 1. Modified Pregnancy-Unique Quantification of Emesis[a]

Circle the answer that best suits your situation for the last 24 hours				
1. On average in a day, how long do you feel nauseated or sick to your stomach?				
>6 hours	4-6 hours	2-3 hours	≤1 hour	Not at all
5 points	4 points	3 points	2 points	1 point
2. On average in a day, how many times do you vomit or throw up?				
≥ 7 times	5-6 times	3-4 point	1-2 points	Not at all
5 points	4 points	3 points	2 points	1 point
3. On average in a day, how many times do you have retching or dry heaves without bringing anything up?				
≥ 7 times	5-6 times	3-4 point	1-2 points	Not at all
5 points	4 points	3 points	2 points	1 point
Total score (sum of replies to 1, 2 and 3)	≤6 Mild NVP	7-12 Moderate NVP	≥13 Severe NVP	
Quality of life question				
On a scale of 1 to 10, how would you rate your well being?	0 = worst possible 10 = as good as you felt before pregnancy			

Adapted from Refs[1,2].[a] **The original PUQE was a 12-hour assessment and this is modified to cover a 24-hour period]**

1. Koren, x et al. J. Obstet. Gyn. xx

2. Lacasse, x et al. AJOG xx

To the editor:I attached separately the document Jone sent related to this-she said: I have attached a dokument displaying the different PUQE-figures and appropriate references, to use for how to properly use and cite for «our» PUQE-figure. Perhaps best to discuss with Mina as she is the professional in what is the correct way regarding copyright/citations?**]**

Supplementary Table 2. The HyperEmesis Level Prediction (HELP) Score to assess HG

My nausea level most of the time:	0	1 (Mild)	2	3 (Moderate)	4	5 (Severe)
I average __ vomiting episodes/day:	0	1-2	3-5	6-8	9-12	13 or more
I retch/dry heave __ episodes daily:	0	1-2	3-5	6-8	9-12	13 or more
I am urinating/voiding:	Same	More often, IV fluids; light or dark color	Slightly less often, and normal color	Once every 8 hours; slightly dark yellow	Less than every 8 hours or darker	Rarely; dark, blood; foul smell
Nausea/vomiting severity 1 hour *after* meds OR after food/drink if no meds:	0 or No Meds	1 (Mild)	2	3 (Moderate)	4	5 (Severe)
Average number of hours I'm unable to work adequately at my job and/or at home due to being sick has been:	0	1-2 (hours are slightly less)	3-4 (can work part time)	5-7 (can only do a little work)	8-10 (can't care for family)	11+ (can't care for myself)
I have been coping with the nausea, vomiting and retching:	Nor-mal	Tired but mood is ok	Slightly less than normal	It's tolerable but difficult	Struggling: moody, emotional	Poorly: irritable depressed
Total amount I have been able to eat/drink AND keep it down: *Medium water bottle/large cup = 2 cups/500mL.*	Same; no weight loss	Total of about 3 meals & 6+ cups fluid	Total of about 2 meals & some fluid	1 meal & few cups fluid; only fluid or only food	Very little, <1 meal & minimal fluids; daily IV	Nothing goes or stays down, or daily **IV/TPN**
My anti-nausea/vomiting meds stay down/are tolerated:	No meds	Always	Nearly always	Sometimes	Rarely	Never/**IV/SQ** (subQ pump)
My symptoms compared to last week:	Great	Better	About Same	Worse	Much Worse	Much Worse!!!
Weight loss over last 7 days: ___%	0%	1%	2%	3%	4%	5%
Number of Rx's for nausea/vomiting	0	1	2	3	4	5+
	0 pts	**1 pt/answer**	**2 pts/answer**	**3 pts/answer**	**4 pts/answer**	**5 pts/answer**
TOTAL each column = (#answers in column) x (# points for each answer)	0	____	____	____	____	____
TOTAL for ALL columns: _____	**None/Mild ≤ 19**			**Moderate 20-32**		**Severe 33-60**

Weight Loss % = (Amount lost ÷ Pre-pregnancy weight) x 100

HG, hyperemesis gravidarum; NVP, nausea and vomiting of pregnancy. Used with permission from Kimber MacGibbon, RN, Director, Hyperemesis Education and Research Foundation. [CE: please update permission line, iLTP received]