CellPress

Trends in Molecular Medicine

Opinion

Hyperemesis gravidarum theories dispelled by recent research: a paradigm change for better care and outcomes

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Nausea and vomiting (NVP) affect most pregnant women. At the severe end of the clinical spectrum, hyperemesis gravidarum (HG) can be life-threatening. The condition is fraught with misconceptions that have slowed progress and left women undertreated. Herein, recent scientific advances are presented that dispel common myths associated with HG related to maternal/offspring outcomes, etiology, and evolution. There is now strong evidence that (i) HG is associated with poor outcomes, (ii) a common cause of NVP and HG has been identified, and (iii) NVP is likely a protective evolutionary mechanism that occurs throughout the animal kingdom but is no longer necessary for human survival. Therefore, it is encouraging that we are finally on the cusp of testing treatments that may put an end to unnecessary suffering.

Highlights

Recent large studies reveal that exposure to hyperemesis gravidarum (HG) *in utero* is associated with not only adverse maternal/fetal outcomes but also increased risk for adverse child outcomes, including abnormal brain growth, neurodevelopmental delay, autism spectrum disorder, childhood cancer, and respiratory disorders.

More attention to nutrient deficiencies and gestational weight gain is needed for HG patients.

Hypersensitivity to the rise of the hormone growth and differentiation factor 15 (GDF15) during pregnancy is the main cause of nausea and vomiting (NVP) and HG.

Gestational loss of appetite was likely a mechanism that provided an evolutionary advantage but is no longer necessary for humans.

We are on the cusp of testing prevention methods such as priming patients with metformin to increase GDF15 prior to pregnancy to desensitize patients to its rise during pregnancy.

Blocking GDF15 signaling during pregnancy may decrease symptoms, but questions remain.

Overview of HG

Most pregnancies are affected by **NVP** (see Glossary), and recently the main cause of NVP has been elucidated [1]. Although given the common misnomer 'morning sickness', it is generally not limited to the morning [2]. The condition affects approximately 70% of pregnancies, and over 24% of pregnant women in the USA are prescribed antiemetic medication [3,4]. When the condition is at the severe end of the clinical spectrum, patients are diagnosed with **HG**. HG affects 0.3–10.8% of pregnancies and is characterized by NVP symptoms that begin early in pregnancy and affect daily activity, with an inability to eat and drink normally usually leading to dehydration, electrolyte imbalances, and weight loss [3,5].

It is perplexing that the emphasis on appropriate nutrition in pregnancies for overall health of mother and baby has been historically overlooked in the case of HG. Patients are often released from hospital weighing less than when they were admitted [6]. The condition is associated with significant undernutrition, and patients generally cannot tolerate prenatal supplements. The **American College of Obstetricians and Gynecologists** guidelines recommend folic acid in lieu of prenatal supplements as first-line treatment [3,7], suggesting that folic acid is the only essential nutrient for maternal and fetal health. Although some progress has been made by the recent addition of referral to dietician in both UK and Australia/New Zealand guidelines, implementation worldwide likely remains an issue [8,9]. Therefore, the multitude of poor outcomes associated with HG seem evident (Figure 1) but remain largely unrecognized by providers [7].

There are many myths that contribute to undertreatment and lack of progress for HG and include historical misconceptions that (i) the baby is getting everything it needs from the mother, (ii) the cause is the pregnancy hormone **human chorionic gonadotropin**, and (iii) only humans have NVP. This article reviews new evidence that dispels these myths and introduces recent advances

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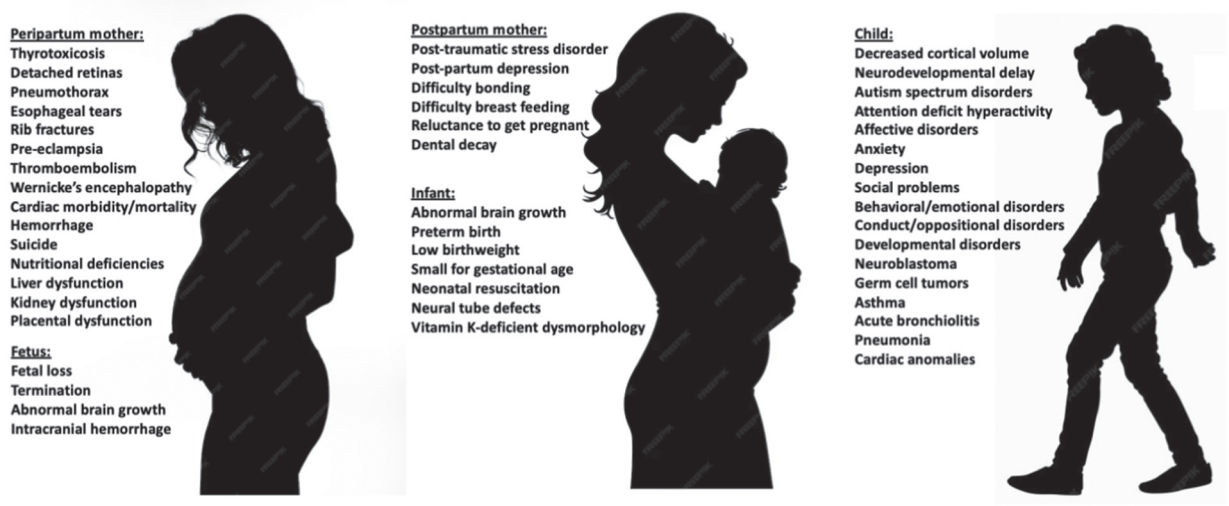
showing that HG has lasting effects on the mother and child, the most likely cause is the NVP hormone **growth and differentiation factor 15** (**GDF15**), and the condition likely gave an evolutionary advantage in the wild that is now superfluous for humans. These findings are driving development of new therapies that may make strides in eradicating one of the most common, distressing, and unnecessary pregnancy conditions.

Adverse outcomes

HG can be life-threatening and is associated with adverse maternal, fetal, and offspring outcomes (Figure 1). Due in part to electronic health records, it has become increasingly feasible to perform large studies on HG outcomes and, importantly, to identify children who have been exposed *in utero* to HG, resulting in new longitudinal data on the effects of HG.

(A)



(B)

Population	CASE*	CONTROL	Diagnosis (a) in Child	Ratio (b)
Military Health System database, US	2459	32,581	Autism spectrum disorders	1.4 OR(c)
Kaiser Permanente Hospital, US	14,526	455,263	Autism spectrum disorders	1.5 HR
Adolescent Brain Cognitive Development study, US	1,496	9,214	Total psychiatric score	1.3 HR
Danish National Cohort	14,189	1,095,181	Behavioral and emotional disorders	1.2 HR
Denmark Cancer Registry and Central Person Registry	6,420	160,500	Childhood cancer	1.4 OR
Soroka University Medical Center, Israel	3,227	229,249	Respiratory morbidity	1.4 OR

(a) Aggregate odds ratio was not included and multiple neurodevelopmental outcomes were reported, so the one with highest odds ratio was reported

(b) Odds Ratio (OR), Hazard Ratio (HR)

(c) OR reported for HG diagnosis and prescription

*HG, Severe NVP, Autism, Pediatric cancer

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Figure 1. Hyperemesis gravidarum (HG)-associated adverse outcomes. (A) List of adverse outcomes associated with HG during pregnancy (peripartum mother and fetus), postbirth (postpartum mother and infant), and in the child. (B) Size and scope of recent (2018–2023) large (>1000 cases) studies on HG associations with child outcomes [36–40]. Images were downloaded from https://www.Freepik.com and https://www.Shutterstock.com; Abbreviation: NVP, nausea and vomiting of pregnancy.

Maternal morbidity and mortality

Pregnant women are still dying from HG. It was the fourth leading cause of maternal death in Botswana in 2019[i], and deaths have been reported this century in the USA and UK due to thyrotoxicosis, thromboembolism, suicide, thiamin deficiency that led to brain damage/death from **Wernicke's encephalopathy**, and severe electrolyte disturbances that resulted in cardiac arrest [3][ii,iii]. Therapeutic terminations occur in 6% of pregnancies [10,11]. Maternal vitamin K deficiency has resulted in intracranial hemorrhage/fetal demise [12].

In our study, 26% of HG patients reported losing >15% of their prepregnancy weight, and 22% reported symptoms lasting until term, making HG a form of prolonged starvation in pregnancy with a serious psychological impact. Additionally, 26% reported suicidal ideation, 18% had full criteria for post-traumatic stress disorder, and 37% decided to never get pregnant again [13–15]. HG is a top predictor of postpartum depression [16]. Moreover, intense prolonged vomiting can result in retinal hemorrhage, pneumothorax, esophageal tears, and rib fractures [3]. HG is also associated with increased risk of placental dysfunction and liver and kidney disease [3].

Birth outcomes and offspring morbidity

Offspring morbidity is also significant, with a 2.8-fold increased risk of preterm birth prior to 34 weeks, 1.4-fold increased risk of low birth weight, and a 1.2-fold increased risk of neonatal intensive care unit admission [17]. The 2.1-fold increased risk for neural tube defects for patients unable to swallow folic acid and reports of vitamin K-deficient dysmorphology and intracranial hemorrhage are direct evidence that maternal nutrient deficiencies can have lasting effects on fetal outcome [12,17–19]. Importantly, the risk (4.8-fold) of **small for gestational age (SGA)** infants associated with HG was reportedly higher than for chronic hypertension, preeclampsia, cannabis, tobacco, cocaine, and amphetamine exposure [20]. In a study of women hospitalized for HG, inadequate pregnancy weight gain and not regaining prepregnancy weight by weeks 13–18 were both risk factors for delivering a baby that is SGA [21].

Child outcomes

Past studies significantly linking HG to adverse child outcomes were primarily based on sample sizes <1000 cases, but recently, several large studies have been published (Figure 1) [22–41]. Among them, two large US-based retrospective cohort studies showed that *in utero* exposure to HG is a significant risk factor for **autism spectrum disorder (ASD)** [36,37]. Another large study reported on results from both a US-based cohort of >10 000 children and a Danish cohort of >2 million children [38]. In the US cohort, HG-exposed offspring scored significantly higher for **attention deficit/hyperactivity disorder (ADHD)**, depression, and social problems, with an overall increased psychiatric problem score that was 25% higher than unexposed children. In the Danish cohort, exposed children were found to have significantly increased diagnoses of behavioral and emotional disorders, ADHD, conduct disorders/oppositional defiant disorders, pervasive developmental disorders, and ASD. The authors of the US/Danish study reported decreased cortical area/volume in children exposed *in utero* to HG and found that abnormal neurodevelopment was mediated by reduced brain size. Fetal head growth in HG patients is positively associated with maternal weight gain at midgestation, suggesting that HG-related undernutrition in the first half of pregnancy may affect fetal brain growth and development and explain the increased risk of neurodevelopmental delay in childhood [42].

Other adverse childhood outcomes reported recently include an increased risk of childhood cancer, including a 2.5-fold increased risk for neuroblastoma, a 1.4-fold increased risk of childhood respiratory morbidity, and an increased risk of cardiovascular disease in 3-year-olds [39–41]. Importantly, child outcome studies that included prescriptions found that associations

Glossary

American College of Obstetricians and Gynecologists: a leading professional membership organization for obstetricians/gynecologists representing various countries and regions in North and South America.
Attention deficit/hyperactivity disorder (ADHD): a common neurodevelopmental disorder characterized by difficulty paying attention and controlling impulsive behavior and overactivity.
Autism spectrum disorder (ASD): a developmental and neurological disorder characterized by differences in communication, behavior, learning, and interaction with others.
GDNF family receptor α-like (GFRAL): the GDF15 receptor located in the chemoreceptor trigger zone of the brainstem that, when activated, signals aversive responses, including appetite changes, nausea, and vomiting.
Genome-wide association study (GWAS): a method to study variations spanning the entire genome (DNA) in large groups of people to identify genes associated with diseases or traits.
Growth and differentiation factor 15 (GDF15): a stress response and pregnancy-associated hormone that can cause aversive responses, including appetite changes, nausea, and vomiting.
Human chorionic gonadotropin: a hormone produced by the trophoblast/placenta. Pregnancy tests often use human chorionic gonadotropin detection to confirm pregnancy.
HG: severe NVP of pregnancy associated with an inability to eat and/or drink normally, dehydration, and electrolyte imbalance.
Imaginal morphogenesis protein-late 2 (*IMPL2*): a nonmammalian homolog of IGFBP7 involved in insulin signaling and feeding behavior.
Insulin-like growth factor binding protein 7 (IGFBP7): belongs to a family of proteins that have low-affinity binding to insulin growth factor receptors 1 and 2. It is associated with feeding behavior, NVP of pregnancy, and HG.
NVP: common misnomer 'morning sickness'.
Small for gestational age (SGA): a term used to define infants born weighing less than the tenth percentile for gestational age.
Tyrosine-protein kinase receptor Ret: a receptor tyrosine kinase that serves as coreceptor with GFRAL and is

existed independent of medication exposures and hypothesized that nutritional deficiencies are a likely cause [25,36,37,39].

Thus, studies of adverse maternal, fetal, and child outcomes associated with HG have come to light. The new findings strongly suggest that HG can have lasting effects on the mother, can alter birth outcomes, and can be a detrimental pregnancy exposure akin to a teratogen. In the case of HG, the baby is not always getting everything it needs from the mother.

required to signal aversive responses, including appetite changes, nausea, and vomiting.

Wernicke's encephalopathy: a life-threatening neurological condition caused by a vitamin B1/thiamin deficiency.

NVP hormone GDF15 and NVP/HG discovery

Discovery of GDF15 in pregnancy

In 1997, the *GDF15* gene was cloned by three groups, including one searching for highly expressed genes in the placenta that reported higher placental expression of *GDF15* than any other healthy human fetal or adult tissue tested, which was higher at 8–9 weeks than at term [43–45]. Then in 2000, detection of high levels of GDF15 in the sera of pregnant women was reported [46]. GDF15 was subsequently measured at 12 timepoints during pregnancy and labor. The study did not find an association with labor (or preeclampsia) but revealed the pattern of GDF15 levels in healthy pregnancies. Specifically, GDF15 rises rapidly in the first trimester, steadies in the second trimester, and rises again at 24–26 weeks, with a second peak at 33–35 weeks [47].

GDF15 and appetite loss

In 2007 a discovery linking GDF15 to appetite control was published [48]. The landmark study showed that GDF15 was overexpressed by many tumors, and circulating levels were directly proportional to cachexia-associated weight loss. In mouse models, GDF15 induced appetite and weight loss that was reversed by blocking GDF15. The study suggested lowering GDF15 as a novel treatment for cachexia (a condition with similar symptoms to HG characterized by hypophagia and weight loss) and conversely increasing GDF15 to treat obesity.

In 2014, the team showed that the site of action of GDF15 was the hindbrain, with complete loss of anorectic effects following ablation [49]. Meanwhile, pharmaceutical companies pounced on the molecule in a race to find the hindbrain-restricted receptor, and in 2017, four separate groups published the discovery of **GDNF family receptor α-like** (**GFRAL**) and the coreceptor proto-oncogene **tyrosine-protein kinase receptor Ret** [50–53]. Programs to develop weight loss and weight gain drugs based on these findings followed [54][iv,v].

Genetic link between GDF15 and NVP/HG

Earlier in 2017 our group presented the first evidence linking GDF15 to HG using a **genome-wide association study (GWAS)** of >50 000 23andMe, Inc., research participants [55]. In addition, we found significant associations with the **insulin-like binding factor protein 7 (IGFBP7)**, the progesterone receptor, and the GDF15 receptor GFRAL [56]. We also showed that circulating levels of GDF15 and IGFBP7 are significantly elevated in patients hospitalized at 12 weeks gestation with HG compared with patients with normal and no NVP, but levels are similar at 24 weeks gestation [57][vi]. A study posted online in late 2017 (published in 2018) further supported the finding that significantly higher levels of GDF15 are detected in pregnancies affected by more severe NVP [58]. In addition, another study revealed that circulating GDF15 levels are significantly higher in people carrying female fetuses, and nausea was reported in 72% of women carrying a female and 42% carrying a male, providing a biological explanation for the observation of worse NVP in pregnancies with female offspring [59].

In 2022 we published the results of our second genetic study using a separate population (>1,500 recruited through hyperemesis.org) and using a whole-exome sequencing approach [60]. The only significant locus was again a variant in *GDF15*. In addition, there was only one damaging variant that occurred in greater than or equal to ten cases and no controls, a mutation in *GDF15*. Every participant with the mutation had at least one pregnancy with HG, strongly implicating a causal etiology for GDF15. Admittedly, the genetic studies included primarily white participants of European ancestry, and, therefore, more work must be done to determine generalizability of the results to other populations. To that end, it is important to note that recently, the lead association with the *GDF15* locus was replicated in GWASs that included Asian populations [61].

Maternal–fetal genetic interplay: a mechanism affecting recurrence

Perhaps the most common question patients have following a pregnancy affected by HG is 'will I have this again?', and ~37% of HG patients limit family size due to fear of recurrence [15]. Assuming a strong maternal genetic component to the condition, understanding why some patients do not have HG in every pregnancy was critical to unraveling the genetic mechanism (the exception proves the rule). Among patients carrying a rare *GDF15* mutation, 18% of pregnancies were not affected by HG [1]. It was reasoned that since GDF15 causes nausea/vomiting, the mutation must cause overexpression/activity. Therefore, it was hypothesized that patients whose fetus inherited the mutation from their mothers had greater risk for HG, while patients who inherited the wild-type variant could be protected. Surprisingly, the reverse was observed.

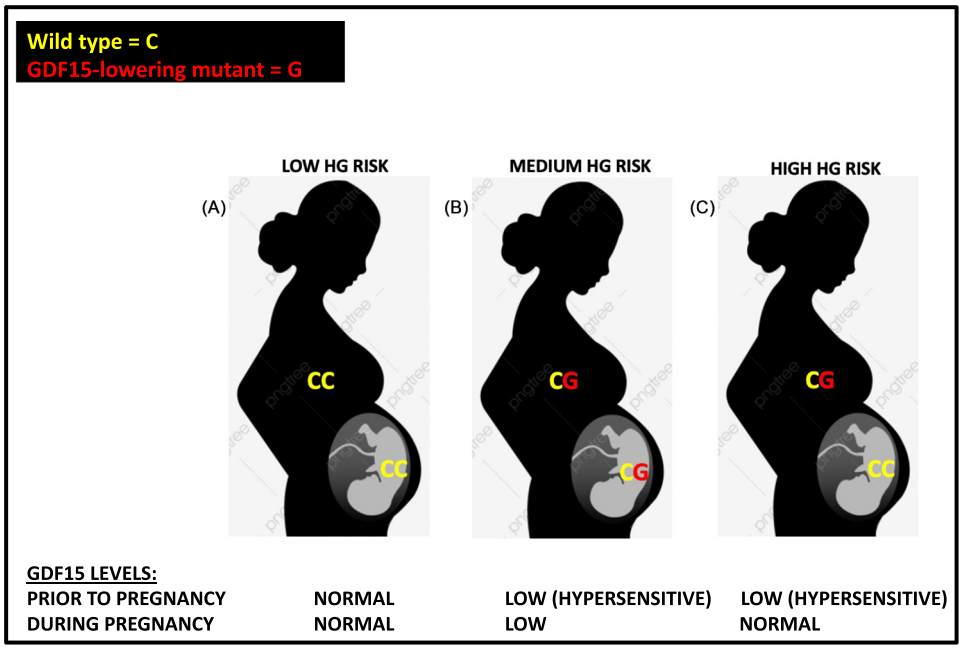

Figure 2. Different genetic combinations of *GDF15* in the mother and fetus alter the risk of nausea and vomiting of pregnancy. Nausea and vomiting of pregnancy severity depends on a combination of (i) the mother's prepregnancy GDF15 levels (determined by genetics but also environmental factors like smoking tobacco or taking metformin and/or certain conditions/diseases like β-thalassemia) and (ii) the levels produced during pregnancy by the fetus/placenta (i.e., determined by fetal genes, fetal sex, and multiples). (A–C) A GDF15-lowering mutation (G) in the mother increases sensitivity to GDF15 rise in pregnancy due to lower levels prior to pregnancy, but the same mutation decreases symptoms during pregnancy if inherited by the fetus due to lower levels of GDF15 during pregnancy. In addition to factors prior to pregnancy, other factors associated with circulating levels of GDF15 during pregnancy may also alter risk. Images were downloaded from https://www.Freepik.com and https://www.Shutterstock.com.

In all pregnancies where the fetus inherited wild-type (normal) *GDF15*, the mother had HG, and by contrast, when the fetus inherited the mutation, the mother was less likely to be affected by the condition [1]. Although a small sample size, this provided the first evidence for interplay between maternal and fetal genes in HG risk and the first biological explanation for why HG can occur in one pregnancy but not the next (Figure 2). However, the results provided a paradox as they suggested that the same mutation that increased HG risk in the mother reduced that risk when inherited by the fetus. The solution began to unfold in an experiment showing that the mutation did not result in an increase in GDF15 levels/activity but, by contrast, was a knockout, resulting in approximately half of the normal levels of GDF15 circulating in nonpregnant healthy people who were heterozygous carriers of the mutation [1]. Furthermore, two additional variants in GDF15 associated with HG followed the same pattern of association with lower circulating levels in nonpregnant individuals [1].

A role for desensitization

To understand how lower levels of a nausea/vomiting hormone can cause HG, it was then hypothesized that patients with HG, genetically predisposed to lower circulating levels of GDF15 prior to pregnancy, are hypersensitive to the rapid rise in GDF15 levels during pregnancy. Both a murine model and observation in humans supported a role for desensitization [1]. Mice were desensitized to the aversive effects of GDF15 by administration of low-dose GDF15 prior to a high dose [1]. In humans, conditions and substances associated with high levels of circulating GDF15 prior to pregnancy had reduced HG risk during pregnancy [1][vii]. The discovery of a role for desensitization suggests that there may be a way to prevent HG.

Clinical implications

The new findings that nausea/vomiting is most severe when patients have lower levels of GDF15 prior to pregnancy and higher levels during pregnancy suggests a road to prevention and treatment (Figure 3). Patients at risk for HG may be primed by raising GDF15 levels prior to pregnancy

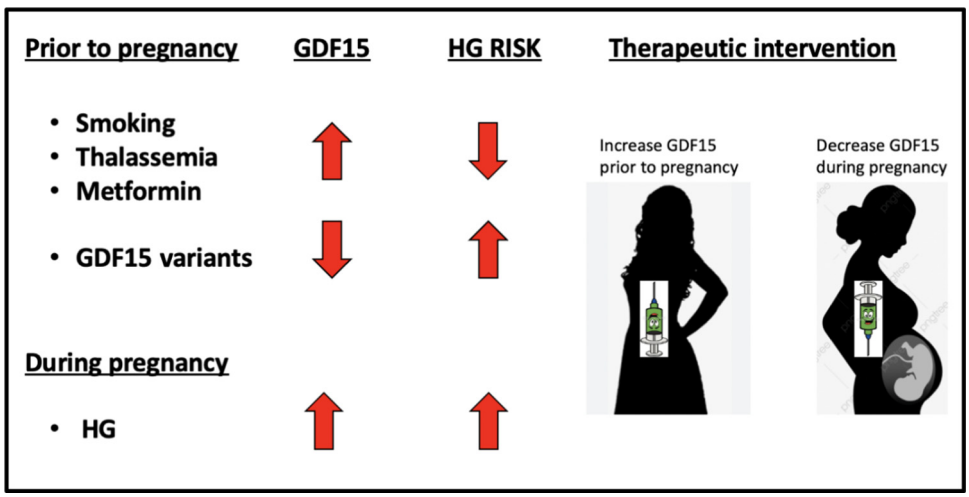

Figure 3. From mechanism to potential therapies. Factors associated with increased circulating levels of the nausea and vomiting hormone GDF15 when not pregnant are associated with lower hyperemesis gravidarum (HG) risk. Conversely, *GDF15* genetic variants associated with lower circulating GDF15 when not pregnant are associated with increased HG risk. During pregnancy, HG patients have increased levels of GDF15. Therapeutic interventions can be to increase GDF15 levels or signaling prior to pregnancy to desensitize people to GDF15 and decrease HG risk. During pregnancy, lowering GDF15 levels or signaling may decrease HG risk. Images were downloaded from https://www.Freepik.com and https://www.Shutterstock.com.

to decrease their sensitivity to GDF15 during pregnancy. One approach would be to use metformin, a drug known to increase circulating GDF15 levels that has been used to improve fertility in patients with polycystic ovarian syndrome [1]. In addition, during pregnancy, lowering GDF15 levels, such as was presumably the result in patients whose fetuses inherited the GDF15-lowering mutation, may significantly reduce HG symptoms [1]. The patients carrying the *GDF15*-knockout mutation were fertile and had healthy pregnancies/babies when the fetus inherited the mutation, presumably reducing GDF15 by half [1]. These lived human examples suggest that reduction of GDF15 may be safe. This observation is further supported by the recent identification and characterization of human homozygous *GDF15* knockouts, revealing that humans completely lacking GDF15 can exceed average life expectancy and are fertile, with no evidence of increased disease prevalence or metabolic dysfunction [62]. Additionally, a heterozygous *GDF15* knockout in the study who had three children (two who were homozygous knockouts) reported no nausea/vomiting in any pregnancy, providing support that blocking GDF15 may prevent HG (and NVP).

However, there is evidence for pause. In a study of miscarriage, GDF15 levels at weeks 7–13 predicted fetal loss, with one-third of levels in the miscarriage cohort (although this observation is likely the consequence of abnormal placentation) [63]. Additionally, GDF15 peaks at 33–35 weeks gestation, a time when most pregnancies are not affected by NVP [27]. So, what is its role at this time? Some evidence suggests that in addition to NVP, GDF15 may be a T cell inhibitor, protecting the rapidly growing fetal/placental unit from maternal immune attack (although it is hard to reconcile this with the lack of a local receptor and lack of altered GDF15 levels in preeclampsia) [3,47,63–68]. Therefore, until we have a better understanding, moderate GDF15 reduction or blocking the brainstem-restricted receptor GFRAL may present less risk. Indeed, the company NGM Bio announced its plans to initiate a Phase 2 proof-of-concept study of its GFRAL inhibitor NGM120 for the treatment of HG by the end of 2024[viii].

GDF15 outside of pregnancy

In addition to its role in pregnancy, GDF15 may be a hormone that evolved to alert nonpregnant animals/people that they are more likely to survive in a weakened state if they rest and recover rather than search for food. Support for this theory comes from studies of circulating levels of GDF15, showing that it is upregulated in numerous disease states and in response to multiple environmental stressors, including cancer; cardiovascular, kidney, mitochondrial, liver, and lung disease; thalassemia; infection; undernutrition; overnutrition; overexercise; hypoxia; and environmental toxins including cytotoxic chemotherapy, smoking, potassium depletion, and hyperthyroidism [69–71]. Of note, undernutrition; potassium deficiency; heart, kidney, and liver stress; *Helicobacter pylori* infection; and hyperthyroidism are all associated with HG pregnancies and may explain, in part, the higher levels of GDF15 observed in HG patients [3].

NVP in the animal kingdom: genetic link between placental and nonplacental animals alters evolutionary theory

NVP is hypothesized to be an evolutionary adaptation to protect the fetus from teratogens during organogenesis [72–75]. This is supported by overlooked evidence of gestational nausea in the animal kingdom (Figure 4). Studies in the 1970s showed that monkeys can experience NVP and appetite disturbances in early pregnancy [76,77]. In addition, dogs can have early anorexia and vomiting that can be severe enough to require pregnancy termination[ix]. Veterinary advice for pregnant cats warns that an early lack of appetite is common, and if the cat stops eating for >1–2 days, consult the vet[x].

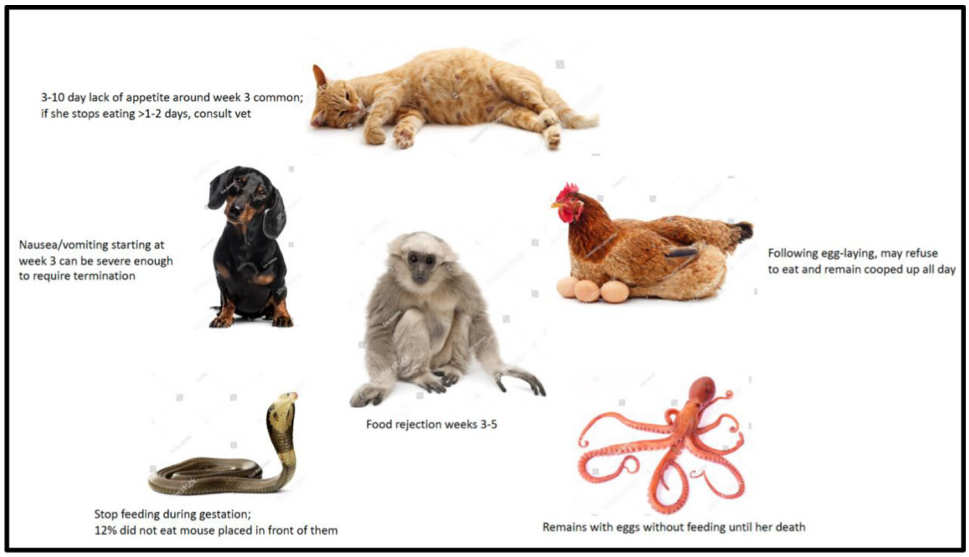

Figure 4. Gestational appetite loss, nausea, and vomiting in the animal kingdom. Reports in nonplacental animals suggest that teratogen avoidance is not the only evolutionary driver of the condition. Nausea and vomiting of pregnancy is a biological behavior coded by our genes that gave an evolutionary advantage probably even prior to our divergence from octopi for reasons that are likely no longer relevant to human survival. Images were downloaded from https://www.Freepik.com and https://www.Shutterstock.com.

However, maternally ingested teratogens cannot fully explain the condition as there are also reports of lack of appetite in nonplacental animals, including birds and reptiles. Following egg laying, hens may refuse to eat and remain in their coop[xi]. A snake study revealed that aspic vipers stop hunting during gestation, and 12% refused a mouse placed directly in front of them [78]. The most extreme maternal behavior is observed in the octopus, where the mother cares for her eggs without feeding until death [79]. These examples suggest that gestational loss of appetite is a biological behavior that has evolved and is coded for by genes, whereby in some species, the benefit of complete starvation until death outweighs the risk of a hostile environment.

Until modern times, finding food was no quick trip to the market but was fraught with risks, not only from ingesting teratogenic foods but also from predators, pathogens, and other environmental risks, such as extreme weather. Genes that encode a behavior that results in avoiding those risks in lieu of nutritional needs likely provide some survival advantage, which may no longer exist for modern human pregnancy. Support for this comes from the observations that approximately 30% of pregnancies are unaffected by NVP, and recently, human knockouts of *GDF15* have been identified that are viable and fertile [56,62].

Fascinatingly, *IGFBP7*, the second greatest genetic risk factor associated with HG in the GWAS study, is the human homolog of the wasting factor gene **imaginal morphogenesis protein-late 2 (*IMPL2*)**, which has been implicated in both diapause (dormancy) in response to environmental stress (i.e., cold temperatures) in *Drosophila* and in the maternal death spiral of the octopus. This finding biologically linking the behavior between placental and nonplacental species suggests that modification of evolutionary theories is required [56,79–82]. Obviously, what the mother consumes after laying eggs cannot have a teratogenic effect on offspring, so the condition cannot have evolved solely to avoid teratogens during organogenesis, debunking the most commonly accepted explanation as the sole rationale for NVP.

Clinician's corner

For nausea and vomiting of pregnancy (NVP), American College of Obstetricians and Gynecologists guidelines recommend replacing prenatal vitamins with folic acid, but the most severe form of NVP, hyperemesis gravidarum (HG), is associated with increased risk for adverse maternal, fetal, and child outcomes, some known to be associated with severe nutritional deficiencies. Folic acid supplementation is likely inadequate. Thiamin supplementation may prevent Wernicke's encephalopathy.

Genes that encode proteins upregulated during the maternal death spiral in the octopus [*IGFBP7* (*IMPL2*)] and a hormone involved in appetite loss in cachexia and chemotherapy nausea (GDF15) are associated with NVP and HG risk. The condition likely resulted in an evolutionary advantage in some species that is no longer necessary in humans.

The hormone GDF15 produced by the fetus/placenta is the primary cause of NVP and HG. It is circulating at higher levels in people with HG, but there is some overlap, and sensitivity to GDF15 also plays a role.

The severity of NVP is determined by the woman's sensitivity to GDF15, which can be determined by her genes. Women who have lower levels of GDF15 prior to pregnancy are more sensitive to the rise of GDF15 during pregnancy.

Methods to raise circulating GDF15 levels prior to pregnancy (such as with metformin) may decrease risk of HG during pregnancy.

Blocking GDF15 signaling during pregnancy, if safe, may lead to more effective treatments to alleviate symptoms.

Concluding remarks

HG increases the risk of multiple adverse outcomes for mother and offspring, and, therefore, there is a benefit to effectively preventing and/or treating HG safely to improve symptoms and nutritional intake. We now have strong biological evidence to support a causal role for GDF15 and a path for development of novel prevention and treatment methods. Even before these treatments come into clinical practice, it is important for patients to know that there has been progress in understanding their condition (see Clinician's corner). Finally, NVP and HG, probably still advantageous in the wild, are likely antiquated evolutionary mechanisms for humans. Future research should focus on (i) improving nutritional intake of HG patients and understanding nutrient roles in adverse outcomes, (ii) developing and testing therapeutics for prevention and treatment based on the new findings, (iii) understanding the mechanism of GDF15 desensitization and whether the hormone has a secondary role in pregnancy, (iv) determining the generalizability of the genetic findings in additional populations, and (v) identifying and elucidating the role of additional risk genes. While outstanding questions remain (see Outstanding questions), it is time to pave the road for clinical trials and hopefully, if safe and effective, limit or maybe even eradicate HG.

Outstanding questions

What nutrient deficiencies (including folic acid, vitamin B1, and vitamin K) contribute to the increased risk of adverse maternal, fetal, and child outcomes associated with HG, and how can we create and/or implement guidelines to improve intake?

Why are there such high levels of circulating GDF15 during pregnancy, particularly in the third trimester when NVP of pregnancy is generally limited to the first trimester, and how does desensitization work?

Will increasing GDF15 prior to pregnancy lower HG risk during pregnancy? If so, how much do we need to increase it and for how long, and will it be safe for mother and baby?

Will lowering GDF15 signaling during pregnancy lessen NVP symptoms during pregnancy, and if so, how low does it need to be to have a meaningful clinical significance, and will it be safe for mother and baby?

What other genes/mechanisms are associated with HG etiology across distinct populations (i.e., what is the role of IGFBP7, which is also genetically associated with HG)?

Declaration of interests

M.S.F. is Chief Scientific Officer, shareholder, and a paid consultant of Harmonia Healthcare and is a paid consultant for NGM Biosciences. M.S.F. is also a Board Member and Research Director for the Hyperemesis Education and Research Foundation and a Board Member for the Foundation for Women's Health.

Resources

[i] www.statsbots.org.bw

[ii] www.primescholars.com/articles/why-are-women-still-dying-from-nausea-and-vomiting-of-pregnancy-95146.html

[iii] https://uk.news.yahoo.com/young-mum-died-while-28-050000406.html?guccounter=1&guce_referrer=aHR0cHM6Ly93d3cuZ29vZ2xlLmNvbS8&guce_referrer_sig=AQAAAGGoR_0e3totsMiYlzD25FMa0aNJJllvz4HH3gaCFG4K-Av_A3Y86q2wV_zAVZcpCkR1dpFW44lG4UoUXrXQkJ7wyjEXPlZCw9i4Rq5pp-FBje2h0lxafd9Fsf4BDdiKNatp5mZEQkaeu10GD-xSuAGKER9HslXT6NJxO2jLs8L1

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[xi] www.gardenbetty.com/how-to-break-a-broody-hen/

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