Mechanistic and Phylogenetic Perspectives on Pregnancy Sickness

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Abstract

Evolutionary biologists have long been fascinated by the peculiar trait of pregnancy sickness, the syndrome experienced by two-thirds of pregnant individuals which includes nausea and vomiting of pregnancy and, in 2% of cases, progresses to a pathological extreme known as hyperemesis gravidarum. With the recent discovery of the placental hormone GDF15 as the main causal factor in pregnancy sickness, it is time for a comprehensive reassessment of the field. In this Review, I synthesize current knowledge and outstanding questions in the biology of pregnancy sickness at both mechanistic and evolutionary levels of analysis. Pregnancy sickness is a heritable, stereotyped complex of behavioral and physiological traits which likely represent a pregnancy-specific homolog of its closest counterpart in normal physiology, infection-induced sickness behavior. I review four leading adaptive hypotheses for pregnancy sickness (prophylactic, catabolic, autocrine, and anti-rejection) and argue that knowledge of adaptive origin and mechanism are intimately linked: whether GDF15 in pregnancy acts through the canonical brainstem receptor GFRAL or additionally by local non-canonical receptors will be the deciding factor between multiple classes of adaptive hypothesis. Phylogenetic analysis reveals that placental production of *GDF15* rose to prodigious amounts only in catarrhine primates and elephants, suggesting that GDF15-induced pregnancy sickness is of recent origin but is not human-specific, and may have evolved convergently. Finally, I review explanations for the persistence of pregnancy sickness in modern human populations, including mismatch, cliff edge selection, and parent-offspring conflict. With these advances, pregnancy sickness has become not just a curiosity of human evolution, but a compelling and low-hanging opportunity for the field to investigate the evolutionary mechanistic bases of complex adaptive behaviors.

Introduction

Nausea and vomiting of pregnancy (NVP), also known as “morning sickness”, is a constellation of physiological and behavioral changes experienced during the first trimester of pregnancy. Moderate NVP between weeks 6 and 18 of pregnancy is not beyond the norm: it affects some two-thirds of women (66% in a meta-analysis of 64,876 individuals in 56 studies) (Flaxman and Sherman, 2000). Symptoms include not just nausea and vomiting, but also affective changes such as increased sensitivity towards smells, lethargy or social withdrawal, and both positive and negative food preference changes. NVP causes considerable suffering, borne by both individuals with mild cases as well as those falling into the extreme tail of severity who are diagnosed with hyperemesis gravidarum, a disease involving fluid and electrolyte loss, pH imbalance, nutritional deficiency and weight loss (Fairweather, 1968). NVP exerts an estimated economic toll of more than $1.7 billion in the United States alone (Piwko et al., 2013).

Nausea and vomiting of pregnancy is widespread and highly heritable (see **Box 1**): why would evolution not eliminate such a seemingly costly trait? Competing theories exist for the evolutionary function of NVP, including that it is a direct adaptation to avoid the consumption of foods toxic to the embryo (Flaxman and Sherman, 2000; Hook, 1974; Profet, 1988), that it is a side-effect of maternal mechanisms to test embryo viability or quality (Forbes, 2017, 2002), and that it is a byproduct of fetal signaling to increase maternal nutrient allocation (Crespi, 2024; Flaxman and Sherman, 2008; Haig, 1993). For several decades, the cause of NVP was thought to be human chorionic gonadotropin (hCG) due to a tight temporal correlation of maternal serum hCG levels with symptom severity. However, in the last few years, this assumption has been shown to be incorrect, and understanding of the etiology of nausea and anorexia has greatly progressed due to the discovery that the peptide hormone GDF15 is the major factor underlying NVP (Fejzo et al., 2024, 2018). Any association between serum hCG and NVP symptoms is likely correlation, not causation, due to the fact that the same placental cell type (syncytiotrophoblast) produces both hCG and GDF15 (Vento-Tormo et al., 2018).

Ethologist Nikolaas Tinbergen (1963) proposed that explanations for a behavioral trait may be given at four levels of analysis: adaptive function, phylogenetic origin, physiological mechanism, and developmental origin. More succinctly, these can be grouped into ultimate “why” questions (“what for?”: adaptive function, and “how come?”: phylogenetic origin) and proximate “how” questions of physiological and developmental mechanism (Haig, 2013; Mayr, 1961). In this Review, I reassess the state of evolutionary medical investigation into NVP in light of recent discoveries. Does new knowledge of proximate cause justify a re-assessment of ultimate cause? Evolutionary biology often focuses on the former, whereas medicine addresses the latter; the interdisciplinary field of evolutionary medicine is an opportunity to bring these levels of analysis into productive interaction to provide a more complete understanding of human disease (Nesse and Williams, 1998).

Evolutionary theories for NVP have consequences for the design of interventions. The prevailing behavioral prophylactic theory, that NVP exists to induce behavioral avoidance of teratogenic substances during pregnancy, has influenced how physicians nutritionally advise patients during pregnancy and created a hesitancy to intervene in something “good” (Cardwell, 2012). Proposed interventions into GDF15 production to alleviate pregnancy sickness and hyperemesis gravidarum point towards its absence in rodent models such as the mouse as evidence that inhibition of GDF15 would be without consequence (Fejzo, 2024). However, an evolutionary perspective demands that we consider whether placental

GDF15 is not merely a vestigial trait, but continues to serve additional metabolic and immunological functions in primates which are novel and not present in model species such as rodents. If behavioral effects of placental GDF15 are a byproduct of local effects, rather than the selected function, then treatments targeting the GDF15 ligand rather than GFRAL directly may affect placental development in catarrhine primates which are absent in mouse models. Comparative investigation into the etiology of NVP may allow more targeted interventions may become evident. While such claims must be evaluated in the clinic, a more comprehensive view of NVP and its causes will aid in the design of better interventions.

Physiological mechanism

Nausea and vomiting of prengnancy is proximately caused by placental GDF15

Nausea and vomiting in pregnancy is elicited through activation of the brain stem's area postrema and gastrointestinal afferent nerves. The area postrema is a circumventricular organ located in the floor of the fourth ventricle, beyond the blood-brain and blood-cerebrispinal fluid barriers. Its function is to directly monitor circulating toxins, and modulates behavior in response by eliciting emesis, conditioned taste aversion, adipsia, or anorexia (specifically, reduced novelty-seeking and altered palatability) (Andrews and Whitehead, 1990), as well as reduced food intake and ambulatory activity (Macia et al., 2012). This suite of behavioral changes, known as sickness behavior, depends upon the activation of the area postrema-specific receptor complex of GFRAL and its coreceptor RET (Tsai et al., 2014) by the hormone GDF15.

GDF15 is a peptide in the transforming growth factor beta (TGFβ) superfamily, although it has markedly different amino acid sequence from signals TGFB1 and TGFB2. GDF15 is produced in adult liver in response to physiological stress (Patel et al., 2019) and by inflamed immune cells (Luan et al., 2019). It is associated with conditions such as anorexia, cancer cachexia and rheumatic disease. Although GDF15 modulates appetite, GDF15 levels do not change in response to food intake (Tsai et al., 2016), suggesting that it is not a homeostatic appetite regulator like leptin or ghrelin. GDF15 levels are not associated with direct bacterial or viral pathogen clearance (Luan et al., 2019). Instead, it functions to induce a different, indirect form of host defense: it acts allostatically (O'Rahilly, 2017) to increase tolerance of adverse physiological states, for instance by increased hepatic triglyceride production which protects the heart from inflammatory tissue damage (Luan et al., 2019).

GDF15 is produced in prodigious amounts by the placenta during pregnancy, and the vast majority of circulating GDF15 during pregnancy is of fetal origin (Fejzo et al., 2024). A 2018 genome-wide association study identified a NVP risk allele of *GDF15* (rs16982345), a non-coding variant leading to elevated expression, was associated with an 8-fold higher risk of recurrence of hyperemesis gravidarum, and the receptor *GFRAL* was also implicated to a lesser extent (Fejzo et al., 2018). A case-control study found that GDF15 levels in week 15 of pregnancy were associated with higher levels of nausea and vomiting (Petry et al., 2018). GDF15 production by the placenta rises rapidly during the first trimester, and its levels do not actually decrease in the second and third trimesters (Moore, 2000; Wertaschnigg et al., 2020). The concentration of symptoms in the first trimester can be explained by a desensitization effect, as animal models of GDF15-induced nausea shows a relationship not upon absolute GDF15 serum levels but rather the detection of rapid increases (Fejzo et al., 2024), a phenomenon known as fold-change sensing (Adler and Alon, 2018). Together, these findings have demonstrated strongly suggestive evidence for a causal role of placental GDF15 in pregnancy sickness. The remaining question is, how does placental GDF15 translate into the wide range of behaviors encompassed under the umbrella of pregnancy sickness? Furthermore, do the effects of GDF15 indicate a highly-adapted suite of behavioral changes promoting pregnancy success, or an incidental and sometimes pathological byproduct of placental production of the emetogenic hormone?

Developmental origin: What is the underlying trait?

Marjorie Profet, who made famous the prophylactic theory of NVP, described her analytical style as adaptationist (Profet, 1993), citing George Williams's *Adaptation and Natural Selection* (1966). Adaptationism means to interpret a biological system first using functional or engineering principles: asking, what is this trait good for? Evolutionary medicine has often utilized this framework (Williams and Nesse, 1991). A lacuna in adaptationist analysis is that it considers elements of the organism's phenotype independently when inferring function. Incorrect or overzealous atomization can lead one to propose adaptive functions for parts of an organism which are simply strung along by linked traits undergoing evolution by natural selection, or are necessary byproducts of developmental or physiological processes (Gould and Lewontin, 1979). The classical example is the human chin: early theories for a the chin as a sexual signal were made obsolete by a more parsimonious developmental explanation that the chin is a byproduct of the coming together of alveolar and mandibular growth fields. Might proposed functions for individualized components of pregnancy sickness, such as food aversion, be making the same mistake?

Pregnancy sickness is a syndrome – i.e. a collection of correlated symptoms – beyond just nausea and vomiting alone (Goodwin, 2002). As "syndrome" connotes pathology, I will instead use the term "behavioral character complex" (after "character complex" of Wagner, 1996) to refer to the underlying behavioral modules activated in pregnancy sickness.

Just as the vertebrate skeleton is divided into elements which are co-adapted to function as modular complexes (Schwenk and Wagner, 2001), so the functional modules within the brain and patterns of behavior can be identified by analyzing how changes to one part affect another (Lorenz, 1937). Evolutionary hypotheses for behavioral traits must make operational assumptions about this behavioral "anatomy".

The underlying behavioral character complex associated with the symptoms of NVP has been variously called sickness behavior (Hart, 1988) or sickness syndrome (Saper et al., 2012) in medical literature, and the behavioral immune system in psychological literature (Schaller and Park, 2011). Just as the physiological immune system stretches organism-wide including lymphatics, spleen, thymus, and a battery of hematopoietic cells, the behavioral immune system consists of a number of both proactive and reactive behaviors. Reactive sickness behaviors are elicited after an individual becomes infected by a pathogen, such as nausea, anorexia, and malaise (Hart, 1988). Anticipatory avoidance behaviors include innate visual, olfactory, and gustatory avoidance of dangers such as toxins, phytochemicals, and waste products (Harmon et al., 2021). Sickness-associated increases in social behaviors such as in-group bias and out-group aversion (Schaller and Neuberg, 2012) and social withdrawal and depressive symptoms (reduced energy expenditure and altruistic self-quarantine to avoid infecting others), have also been interpreted as anticipatory behavioral defenses (Shakhar, 2019).

Identification of molecular and cellular pathways is essential, but not a necessary prerequisite for developmental insight into sickness behavior and its relation to pregnancy sickness. By analogy, fundamental genetics principles were first identified by empirical discovery of regularities (genetic linkage mapping and crosses) long before knowledge of the molecular structure of DNA. Likewise, a crucial step in NVP research will be identifying which behavioral patterns show strong co-occurring patterns versus independently activated behavioral modules (**Figure 1a**), by methods such as co-occurrence network analysis (Changizi and He, 2005). Furthermore, to understand whether pregnancy sickness behavior itself is an adaptation and what its function may be, it will be essential to know more about the induction of generic sickness behavior in normal physiology, and whether it represents activation of the same, or a different, behavioral mechanism as NVP.

Does sickness behavior have a pregnancy-specific program?

Like all defenses (Okin and Medzhitov, 2012), sickness behavior is subject to cost-benefit tradeoffs. A cost to the organism of sickness behaviors is incurred due to decreased food intake and decreased social opportunities. One of the ways to overcome functional trade-offs is by the duplication and sub-functionalization of phenotypic modules (Stearns, 2011). This can happen at higher-level units, but is best understood for genes. If a gene locus duplicates in one lineage, one copy can maintain the original function while the second is free to acquire novel functions (neo-functionalization). This process of duplication and divergence is thought to underpin the evolution of novelty more broadly, including genes, cell types, and behaviors (Wagner, 1996). With this framework, it is worth asking whether mammals may have escaped some of the costs of generic sickness behavior in the reproductive context by evolving pregnancy sickness as a behavioral program of its own.

Behavioral changes in early pregnancy shows substantial, but incomplete, overlap of symptoms with infection-associated sickness behavior (**Figure 1**). Overlap includes not just nausea and vomiting, but also affective components of sickness behavior. Women with NVP symptoms score higher on the Edinburgh Depression Scale during the first trimester relative to the rest of pregnancy (Dekkers et al., 2020) and show reduced risk-taking (Mielcarska et al., 2017). Geophagy cravings, or consumption of non-edible substances such as dirt, is another GDF15-associated sickness behavior (Borner et al., 2020) elevated in the first trimester of human pregnancy (Young et al., 2011).

Other pregnancy sickness behaviors diverge from generic sickness behavior (**Figure 1a**). Fever, adipsia (reduced fluid intake), and hyperalgesia, although induced by infection, are not commonly reported in pregnancy. Pregnancy-associated avoidance of meats, alcohol, coffee, and other potential teratogens or pathogen vectors go above and beyond the blanket anorexia repoted in sickness behavior (Duffy et al., 1998; Pepper and Craig Roberts, 2006; Rodin and Radke-Sharpe, 1991). Pregnant women also experience positive food cravings in addition to negative aversions: meta-analysis of 21 studies found consistent reports of cravings for dairy, sweets, starches, and fruits (Flaxman and Sherman, 2000). Furthermore, the first trimester of pregnancy is colloquially associated with heightened taste (hypergeusia) and smell (hyperosmia), which have not been identified in the context of infection-induced sickness behavior. One of the only longitudinal studies to follow individuals across time points found increased sensitivity to sour and bitter taste during the first trimester (Duffy et al., 1998). Sensitivity of pregnant women to the scent of the synthetic musk exaltolide used in perfumes is also increased during pregnancy (Clarós et al., 2021). Care must be taken to avoid confirmation bias, i.e. that studies on pregnancy or infection preferentially test for or report behaviors which are expected. Nevertheless, these differences and their apparent functional fittedness push in favor of pregnancy sickness being an at least partially independent module of behaviors adapted to pregnancy, rather than merely a byproduct of incidental activation of the same sickness-induced behaviors as infection by pregnancy hormones or early gestational inflammation. In developmental terms, pregnancy sickness evolved by duplication and modification of generic sickness behavior.

Aversive behaviors are mediated by the disgust response. The disgust response has been classified into three modules (Rozin et al., 2008; Rozin and Fallon, 1987; Rozin and Haidt, 2013): core disgust, which facilitates avoidance of

foods, animals, and bodily fluids, animal-reminder disgust, which encompasses reminders of death, body envelope violations, and non-normative sexual behavior, and sociomoral disgust, which targets transgressive behavior such as crime, politics, or tribal affiliations. Animal reminder and sociomoral disgust have been found to be unaffected by pregnancy status, whereas core disgust is significantly elevated in the first trimester (Żelaźniewicz and Pawłowski, 2015). The hypothesis that pregnancy sickness specifically targets foods rather than pathogen vectors is supported by a study which found that disgust towards foods and bodily fluids was significantly elevated by ~10% in the 1st trimester, whereas disgust towards cues of contagion, sexual stimuli, death, and poor hygiene showed no effect (Fessler et al., 2005). These findings somewhat contradict a study finding that nationality-based xenophobia is increased in the first trimester of pregnancy (Navarrete et al., 2007). Together, these studies suggest that food-related aversive behaviors are uniquely activated during pregnancy, whereas aversions towards non-orally transmitted pathogens is less pronounced.

The degree to which sickness behavior is divided into context-specific sub-programs, such as viral sickness behavior, bacterial sickness behavior, and allergen sickness behavior, is currently unknown. If they *are* distinct behavioral programs, they likely are triggered by unique combinations of inductive signals downstream of host sensing of infection (Wang and Medzhitov, 2019). If pregnancy sickness is a distinct behavioral program, it must have a unique triggering mechanism beyond just GDF15. A logical candidate for this pregnancy-specific signal would be ovarian hormones such as progesterone, or other pregnancy-specific hormones which, together with GDF15, inform the organism that it is undergoing pregnancy rather than infection-induced sickness (**Figure 1c**). Nausea, anorexia, and avoidance behaviors have been shown to act through GDF15 (Borner et al., 2020; Florsheim et al., 2023). Cytokines such as IL-6, IL-1β, and the inflammatory mediator prostaglandin E_2 induce sickness behaviors including anorexia, fever, and increased sensitivity to pain (hyperalgesia) (Lima et al., 2017; Pecchi et al., 2009; Saper et al., 2012). Cytokines may in fact be upstream of GDF15 induction during infection, as *GDF15* has an enhancer which has been shown to bind the inflammatory second messenger NF-KB (Ratnam et al., 2017). Some symptoms of cytokine sickness, such as fever and pain, may be better characterized as inflammatory sequelae rather than sickness behaviors, but the mechanistic overlap is not without counterpart in pregnancy. Beyond fever, prostaglandins also regulate behaviors associated with female reproduction in a wide range of vertebrates, including nest-building in pigs (Walton et al., 2002), female sexual behavior in fish and rats (Kidd et al., 2013; Rodriguez-Sierra and Komisaruk, 1977), and parturition-related huddling posture in marsupials (Rose and Fadem, 2000). Due to the rapid degradation of these small molecules, it has yet to be demonstrated that prostaglandins produced in the uterus make their way to sensors in the brain (Pecchi et al., 2009). In all, the biological basis of sickness behaviors is still poorly understood, with a major outstanding question being the degree to which different pathogens elicit distinct behavioral responses. It remains to be seen whether pregnancy sickness behavior yet another distinct program, and if so, how it is developmentally specified.

Adaptive function: What for?

NVP has properties indicative of it being an adaptation (**Box 1**). However, questions of its function encompass both the question of what was the cause of NVP when it first arose – a byproduct or a functional trait in and of itself – and what selective forces drive the persistence or continued evolution of NVP risk today. Below, I address both questions in order.

Box 1: Does NVP meet the criteria for continued evolution under natural selection?

For a trait to be subject to continued natural selection, it must be 1) heritable 2) vary across individuals and 3) have a non-zero correlation with reproductive success (Lewontin, 1978; Stearns and Medzhitov, 2016). With respect to (1), NVP is highly heritable. A consortium study of 1723 women from Australia, Finland, Spain, the UK and Denmark found heritability values for presence/absence of NVP of 73% (95% CI 57-84%), for duration 51% (95% CI 36-63%) and for severity 53% (95% CI 38-65%) (Colodro-Conde et al., 2017, 2016). With respect to (2), NVP severity varies considerably between individuals, as well as between global populations. At any given month of pregnancy, the severity of NVP among individuals follows a right-skewed distribution, with a larger tail of individuals with severe NVP and a mean and median at the more moderate end severity, but substantially above zero (Fiurašková et al., 2021). As for the correlation between the trait and reproductive success (3), a study of 873 pregnancies found that mothers who experienced vomiting during the first 20 weeks had an adjusted odds ratio of 0.18 (95% CI 0.06-0.53) of miscarriage (Weigel and Weigel, 1989). In a different study of 414 women (but notably not in the previous one), individuals with vomiting during pregnancy experienced a reduced rate of fetal death (4.7%) compared to those with no nausea or vomiting (20.0%) and those who experienced nausea alone (10.3%) (Tierson et al., 1986). While not always replicated exactly, these findings are suggestive of an adaptive benefit to NVP via increased pregnancy success (Flaxman and Sherman, 2000).

Functional theories for the origin of pregnancy sickness

Several theories have been advanced for the original selective advantage of NVP. These can be classified into those in which nausea and vomiting induced by GFRAL-dependent brain stem sensing of GDF15 is the selected trait, and those where it is a byproduct of selection on other physiological features (**Figure 2**).

The oldest and most persistent is the prophylactic hypothesis, which holds that NVP functions to induce behavioral avoidance of noxious foods, such as meats and toxic plants (Flaxman and Sherman, 2000; Hook, 1974; Profet, 1988). In this model, behavioral changes due to NVP are directly selected for (**Figure 2a**). Apparent functional fittedness of NVP to behavioral teratogen avoidance is supported by a temporal correlation between mean symptom severity and events in embryonic organogenesis, when the fetus is most vulnerable to teratogens (Flaxman and Sherman, 2000). Mediation of food aversion behaviors by GDF15, and the fact that GDF15 is produced by the placenta rather than the mother, do not substantially affect this hypothesis.

Alternatively, Crespi (2024) has proposed that GDF15's anorectic effects on the brain via GFRAL induce catabolism in maternal tissues which increase blood glucose, in turn facilitating nutrient transfer to the placenta or fetus by starving the mother (**Figure 2b**). Reduced energy intake in the 1st trimester is associated with lower maternal levels of anabolic growth factors insulin and insulin-like growth factor 1 (Huxley, 2000). Although apparently paradoxical, reduced maternal nutrient intake is associated with greater placental growth. In the 1944-1945 Dutch famine, women who either conceived or were in the 1st trimester during the onset of the famine gave birth to offspring with larger placental weights, whereas those who were later in pregnancy at the onset of the famine did not (Lunney, 1998). The weight of the baby, however, was unchanged between the two groups. Thus, even if maternal anorexia does not truly benefit the embryo's birth weight or post-natal survival, placental GDF15 production could be the consequence of a positive-feedback loop in placental cells which the embryo and the mother have not evolved to counteract.

A third possibility, deriving from the placental source of GDF15, is that GDF15 has local effects on placental invasion and growth, and that maternal effects, including NVP, are a byproduct of its passage into the bloodstream (**Figure 2c**). Human extravillous trophoblast has reduced invasion capacity after *GDF15* knockdown (Lyu et al., 2023). Furthermore, patients with preeclampsia, a hypertensive disease caused by insufficient trophoblast invasion, have lower levels of circulating GDF15 (Chen et al., 2016). In normal gestation, the placental cell types which produce GDF15 are the syncytiotrophoblast and extravillous trophoblast (Vento-Tormo et al., 2018). GDF15 has been shown to enhance the development and invasiveness of trophoblast cells in *in vitro* monoculture, requiring a non-neuronal explanation (Lyu et al., 2023; Zeng et al., 2023). The existence of non-GFRAL receptors for GDF15 has long been supposed due to demonstrated local effects of GDF15 in the kidneys, liver, and tumor microenvironment which are not readily attributable to behavioral or dietary change (Sjøberg et al., 2023). However, the lack of a rigorously verified receptor by which these effects may be mediated has made these results controversial. Early posited effects of GDF15 through the TGF-β receptors TGFBR1 and TGFBR2 have been contradicted by a comprehensive ligand-binding panel of TGF-β receptor gene family members in which only GFRAL showed binding (Yang et al., 2017). However, one potential receptor not included in this panel but shown to mediate an autocrine growth effect of GDF15 in ovarian cancer cells is the EGF receptor family member ERBB2 (HER2) (Joshi et al., 2011). Although ERBB2 lacks a ligand-binding domain, it acts as a co-receptor and binds GDF15 as part of a protein complex whose other members have not yet been identified (Li et al., 2018). ERBB2 is highly expressed in GDF15-producing placental cells, including invasive extravillous trophoblast and syncytiotrophoblast (Tseng et al., 2004). If trophoblast expression of GDF15 evolved to establish an autocrine positive feedback loop promoting placental invasion, an EGF family member receptor complex containing ERBB2 is an attractive potential mechanism (**Figure 2c**).

Finally, the anti-rejection or embryo quality hypothesis (Forbes, 2017, 2002) predicts that the hormone causing NVP exerts local effects on the endometrium which determine whether pregnancy continues or is terminated (**Figure 2d**). This argument can be broken into two points, beginning with the purely mechanistic assertion that the observed relationship between nausea and reduced miscarriage is not causal from (emetogenic hormone production → maternal teratogen avoidance → embryo survival), but rather the reverse (high embryo survival potential → emetogenic hormone production → suppression of spontaneous abortion and maternal nausea as a byproduct). Human blastocysts begin to express *GDF15* at an early stage before most decisions of implantation success or failure have been made (Petropoulos et al., 2016), and GDF15 administration was demonstrated to prevent embryo resorption in mouse infection models of bacterial lipopolysaccharide-induced spontaneous abortion (Lyu et al., 2023). It is not apparent how a GFRAL-dependent behavioral mechanism would have an anti-abortive function, so this functional theory would likely require non-GFRAL-mediated effects of GDF15 on the local uterine environment (**Figure 2d**). A plausible pathway for GDF15 to have anti-abortive effects is via its demonstrated immunoregulatory effects. When paired with IL-4 and IL-15, GDF15 has been shown to enhance the polarization of M2 (anti-inflammatory) macrophages (Takenouchi et al., 2020). GDF15 has also been shown to bind CD48 on regulatory T cells (Wang et al., 2021), acting via a post-translational modification of FOXP3 to promote $CD4^+$ $CD25^{hi}$ $FOXP3^+$ regulatory T cell (iTreg) fate. $FOXP3^+$ iTreg cells function during pregnancy to suppress allorecognition-based immune rejection of offspring (Samstein et al., 2012), and therefore GDF15 at the fetal-maternal interface may function to avoid uterine rejection.

The second question raised by the anti-rejection hypothesis is the more ultimate question of whether GDF15 production indicates embryo quality. The key unknown in this case is whether GDF15 production shows positive or

negative condition-dependence with respect to embryo chromosomal integrity. To borrow distinction used in behavioral ecology (Mock et al., 2011), investigation of the anti-rejection hypothesis must address whether GDF15 is a Signal of Quality (positive condition-dependence, i.e. high-quality embryos make more) as assumed by theories which take hCG as the emetogenic hormone because of its demonstrated relationship to embryo genetic integrity (Bruckner et al., 2012; Forbes, 2017), a Signal of Need (negative condition dependence, i.e. marginal-quality embryos make more to suppress abortion), a scenario modeled plausibly (Flaxman and Sherman, 2008) but not yet empirically demonstrated, or merely a "Signal of Want" reflecting that it is in the evolutionary interest of most embryos, unless of exceedingly low quality, to stave off spontaneous abortion any way they can, causing a loss of reliable indication between quality and signaling intensity (Crespi, 2024; Haig, 1990; McCoy and Haig, 2020). Because the relationship between serum GDF15 levels and maternal nausea is nonlinear due to the aforementioned fold-change sensing phenomenon (Fejzo et al., 2024), it is essential that evidence supporting or refuting these three scenarios measure fetal GDF15 production rather than maternal self-reported nausea, which considerably shrinks the scope of usable evidence from previous research. However, one study which directly measured blastocyst GDF15 levels showed that blastocysts fertilized by sperm from males with male factor infertility produced elevated GDF15 (McCallie et al., 2017), suggesting that negative condition-dependence deserves consideration.

Functional theories for the continued prevalence of pregnancy sickness in modernity

Epigraph: *Suffering is quite compatible with the belief in Natural Selection, which is not perfect in its action, but tends only to render each species as successful as possible in the battle for life with other species, in wonderfully complex and changing circumstances.*
(Darwin, 1958, p. 90)

If NVP-induced behavioral shifts are decoupled from the normal GDF15-induced sickness behavior, it is puzzling why selection has not acted also to decouple nausea and vomiting, and reduced the risk of severe hyperemesis gravidarum. Here, I provide three potential explanations.

Heritable hyperemesis gravidarum risk may be maintained by asymmetric selection

Benefits of NVP do not scale indefinitely. Hyperemesis gravidarum, characterizing about 0.5-2% of pregnancies (Verberg et al., 2005), is clearly detrimental to fitness. A genotype distribution which gives rise to individuals with deleterious traits can nevertheless be maintained by natural selection if the costly extremes "paid for" by positive benefits of moderate alleles, a phenomenon known as "cliff edge selection" (Mountford, 1968). The key requirement for such a scenario is that the fitness function is asymmetric, and the optimal distribution of genotypes in the population includes a tail of affected individuals falling into a pathological extreme, or falling off the metaphorical "cliff" (Vercken et al., 2012). This dynamic has been used to explain the persistence of slightly deleterious heritable traits such as risk of cephalopelvic disproportion (Mitteroecker et al., 2016) and schizophrenia (Mitteroecker and Merola, 2024; Nesse, 2004). Available evidence highly suggests that NVP risk, treated as a continuous quantitative trait, has an asymmetric fitness function, with increasing fitness benefits at low levels and a turning point at which hyperemesis gravidarum risk reduces fitness (**Figure 3**).

One property of asymmetric fitness functions is that a difference in optima between sexes makes the development of the pathological extreme trait more likely. In the case of obstructed birth, the fact that a smaller pelvis gives fitness benefits to both sexes, but females disproportionately bear its costs due to obstructed labor, increases the evolutionarily optimal proportion of individuals susceptible to cephalopelvic disproprtion beyond the optimum if both sexes were affected (Mitteroecker et al., 2016). Likewise, sensitivity to GDF15 is beneficial to both sexes in the case of pathogenic infection, but the costs of its activation during pregnancy are disproportionately paid by females. The fetus likely has a higher optimum for the maternal severity of NVP than the mother does, as the mother benefits more from preserving condition for future reproduction than the fetus. As such, the hypothetical quantitative trait of GDF15 sensitivity/NVP risk is likely to differ in its optimal distribution between maternal and paternal genotypes, or parent and offspring, which would increase the acceptable proportion of genotypes susceptible to hyperemesis gravidarum.

Evolutionary mismatch

A major class of diseases are those exacerbated by the "transition to modernity", or the transition to sterile living environments. Costly immunity defenses, greedy metabolic systems, and antagonistic pleiotropic adaptations for early life fecundity (Byars and Voskarides, 2020) were acceptable trade-offs in a past environment characterized by high communicable disease risk, food and resource scarcity, and high extrinsic mortality (Corbett et al., 2018). In a modern environment lacking all three of these properties, these traits contribute to pathology, including allergy and autoimmunity (Strachan et al., 1996), obesity, and diseases of aging.

Severity of NVP is correlated with the difference between pre-pregnancy levels of GDF15 and its level during pregnancy rather than absolute serum GDF15 (Fejzo et al., 2024). By extension, the exposure of individuals to immune challenge during normal life before pregnancy decreases the severity of NVP and the likelihood of progressing to hyperemesis gravidarum. Among other immune challenges, GDF15 is elevated by parasitic infection (Reyes and Yap, 2023). It follows that individuals living in environments with higher pathogen burden would have higher probabilities of elevated GDF15. This effect would be protective against NVP, due to a smaller change in circulating GDF15 between non-pregnant and pregnant states. With respect to the evolutionary origin of NVP, this would suggest that when NVP first evolved, hyperemesis gravidarum was a less common occurrence, and has become more prevalent in post-industrial society (Emmott, 2024). If GDF15 induction by parasitic infection was consistently higher in ancestral environments than in modern sterile living conditions, this would be accentuated (**Figure 4**).

The mismatch explanation for NVP prevalence can be tested by cross-cultural comparison. 27 world populations, mostly small hunter-gatherer or subsistence farming communities, have been documented not to experience NVP (Flaxman and Sherman, 2000). A mismatch explanation for NVP suggests that 1) populations with higher parasite load should have lower incidence of NVP and 2) that populations in which NVP is reportedly completely absent should have significantly higher pathogen burdens than those with reported NVP. Previous analysis suggested that these differences are due to high levels of corn and low levels of meat in the diet, thus decreasing selection for behavioral avoidance of potentially contaminated meats (Flaxman and Sherman, 2000). Environmental pathogen prevalence has been quantified across more than 30 countries and been shown to correlate with sociocultural factors such as risk aversion (Tybur et al., 2016): the mismatch hypothesis predicts that epidemiological incidence of hyperemesis gravidarum should follow a similar trend.

The prophylactic hypothesis for NVP suggests that it is precisely in early human history (Pleistocene) that NVP first evolved, to promote avoidance of toxic substances, and that with current technological means to sanitize food, the trait is vestigial and obsolete (Profet, 1988). This reasoning is repeated in current calls to medically intervene in NVP, with the justification that NVP no longer serves the useful function it once did (Fejzo, 2024). The specific timing of its origin – in the Pleistocene – is incorrect: as I will describe below, it is clear that placental GDF15 production, and likely NVP itself, is a synapomorphy of catarrhine primates, which diverged in the Oligocene at least 28 million years ago. Nevertheless, it is undeniable that in the absence of modern sanitation and public health, parasite load during almost all of catarrhine evolution was substantially higher than current levels. One implication of the mismatch hypothesis is that the fold-change sensing mechanism of GDF15 is to blame for a current higher incidence of hyperemesis gravidarum than in early humans. A second, more extreme implication is that in order for pregnancy sickness behaviors to be fully dispensable/vestigial in modern life, the published evidence for fitness advantages of mild NVP by reduced fetal mortality would need to be explained as an artifact, such as an effect of developmentally defective embryos which lead to miscarriage also being incapable of inducing nausea (Emmott, 2024).

Parent-offspring conflict

Conflict is a recurrent phenomenon in mammalian reproduction. It is reviewed extensively elsewhere (Haig, 1993; Trivers, 1974). The premise relevant to the puzzle of NVP is that fetal and maternal, or paternal and maternal, evolutionary optima of investment into current versus future offspring are not entirely aligned, and the evolution of hormones to slightly shift the physiology of pregnancy towards one or the other's evolutionary optimum can escalate, leading to precarious physiological states with increased risk of pathology, such as gestational diabetes or pre-eclampsia. Conflict does not serve as a mechanistic, phylogenetic, or developmental explanation of NVP, but we can consider whether hyperemesis gravidarum is a disease exacerbated by conflict.

In all four of the functional theories for NVP summarized above, there are opportunities for parent-offspring conflict. In the prophylactic hypothesis, foods which provide great amounts of nutrition for the mother at the cost of a teratogenic potential disproportionately affecting the more vulnerable fetus, such as meat, may be "worth the risk" to the maternal genotype, whereas from the fetus's perspective they are better off avoided, and as such the optimal level of food sensitivity should be greater in the fetus than in the mother. Under the catabolic hypothesis, the optimal amount of blood glucose will differ between the two, and the induction of a catabolic state in the mother to increase blood glucose could be primarily driven by conflict, akin to gestational diabetes (Crespi, 2024). Under the autocrine placental growth hypothesis, placental growth can occur at the expense of maternal allocation to future offspring, and as seen in the Dutch famine cases, even at the expense of the embryo itself. Finally, under the anti-rejection hypothesis, while autoimmune rejection is in the interest or neither parent nor offspring, the optimal threshold for which embryos to reject if a quality control assessment is being conducted will differ between parent and offspring. Embryos of low quality which will nevertheless survive to adulthood would be selected to suppress their own rejection (Flaxman and Sherman, 2008; Kozlowski and Stearns, 1989). Due to the potential to contribute to many evolutionary scenarios for the origin of NVP, the presence or absence of conflict can be treated as an orthogonal question to that of the adaptive function of placental GDF15. Nevertheless, conflict is a potential explanation for the continued persistence of NVP and hyperemesis gravidarum risk in modern humans.

Phylogeny: How come?

This discovery of GDF15 as the causal hormone of nausea and vomiting of pregnancy has major implications for evolutionary theories. Unlike hCG, the gene encoding GDF15 is widely conserved among mammals, as is the neuroendocrine circuit of GDF15-mediated sickness behaviors. Behavioral changes during NVP could previously only be investigated by psychological surveys, and led to the assumption that NVP is a human-specific phenomenon (Profet, 1988). Causal linkage of NVP to an easily-quantifiable hormone allows insight into its mechanistic underpinnings in non-human animals. Production of GDF15 by the placenta is absent in rodents such as mouse and rat, previously only reported in humans and non-human primates (Klein et al., 2023). This raises the question of, how far does a homologous process to human NVP reach?

Placental (syncytiotrophoblast) production of prodigious GDF15 evolved in Old World monkeys, and perhaps elephants

GDF15 expression in the placenta is phylogenetically restricted, with the only published examples being humans and non-human primates (Klein et al., 2023). RNA sequencing of placentas from across the mammalian tree supports this claim, with extreme levels of *GDF15* only detected in catarrhine primates (Old World monkeys): human, chimpanzee, and macaque, with lower transcription in the spider monkey, a New World or platyrrhine primate **(Figure 5)** (Armstrong et al., 2017; Berkebile et al., 2021; Eidem et al., 2016). Curiously, the lineage showing the second greatest level of placental GDF15 is the elephant, evolutionarily distant from Old World primates but sharing with humans life history traits such as a singleton birth and high investment in offspring. Further investigation into the role of GDF15 in elephant pregnancy, and the metabolic changes involved therein, is warranted.

To date, the cis-regulatory elements driving placental-specific *GDF15* expression in primates have not been identified. Previous multi-species genome alignment suggested that the cis-regulatory regions of primate GDF15 had diverged from their ancestor with rodents, with primates having a unique enhancer region which binds GATA1, TAL1, KLF1, and NFE2 transcription factors and is active in hematopoietic cells (Ulirsch et al., 2014). Whether the same or different enhancer elements are used to drive GDF15 expression in other taxa such as elephants would be worth investigating.

How can we investigate pregnancy sickness behavior in model organisms?

Functional hypotheses for NVP suggest that sickness behaviors such as food avoidance are beneficial to pregnant individuals and/or their offspring. Nevertheless, placental GDF15 production is phylogenetically rare. Is there a possibility that pregnancy sickness behaviors in other species have arisen by convergent evolution, induced by different intermediate mechanisms?

Three relevant covariates to NVP are the ability to vomit at all (most rodents cannot vomit), anorexia during pregnancy, and geophagy (consumption of dirt, salt, or inedible matter) during pregnancy. Two patterns are readily apparent. First, the ability to vomit is widespread, much more so than placental GDF15 production, certainly ancestral to placental mammals and possibly older (Horn et al., 2013), with its absence in rodents being a secondary loss (**Figure 5**). The evolution of vomiting itself therefore cannot explain the evolution of NVP. Second, anorexia in pregnancy exists in species without placental production of *GDF15* (**Figure 5**). It has been speculated that anorexia in reproducing dogs, snakes, chickens, octopuses and other animals may be homologous to human NVP (Fejzo, 2024). Macaques, which produce human-like levels of *GDF15*, have been reported to reject food in gestational weeks 3 to 5 out of 23 (Czaja, 1975). However, they also are reported to do so during the peri-ovulatory period of the menstrual cycle, suggesting a cause related to maternal rather than fetal pregnancy hormones (Czaja, 1975). Pregnant dogs exhibit anorexia during weeks 3 to 5 of their 9-week gestation, to the extent that the behavior has been used as a sign of pregnancy (Lewis et al., 1987), although available transcriptomic data suggest that the dog placenta does not produce appreciable levels of *GDF15* (**Figure 5**). It is therefore doubtful that reports of anorexia during pregnancy – which are often anecdotal or otherwise not rigorously demonstrated – can be used as a reliable indicator for cross-species comparison.

Geophagy is also widespread in non-human vertebrates compared to emesis: Young and colleagues (2011) identify evidence for geophagy in some 240 species. Animals which cannot vomit, like rodents, detoxify via geophagy instead: ingested substances protect the integrity of the gut mucosa and inhibit bacterial growth (Young and Miller, 2019), and toxin-induced morbidity is reduced by ingestion of clay in rats and parrots (Gilardi et al., 1999), as the adsorptive properties of clay reduce bioavailability of the toxin. Geophagy is inducible by the same GDF15-dependent neuroendocrine pathways as nausea and vomiting: administration of recombinant human GDF15 to rats, which cannot vomit, induces geophagy behavior, whereas administration to musk shrews, which can vomit, induces vomiting (Borner et al., 2020). Observational data of geophagy seldom mentions the sex or pregnancy status of the individual, as most accounts come from observations of nutrient or salt licks where the assumption is that geophagy functions solely for nutritional supplementation (Young et al., 2011). Pregnant phyllostomid bats (Bravo et al., 2010, 2008) and chacma baboons (Pebsworth et al., 2012) have been shown

to spend more time at geophagy sites than their non-pregnant conspecifics. Like anorexia, however, available reports are phylogenetically spotty.

Benefits of geophagy to the fetus or the mother have not been demonstrated: if anything, the effects appear to be detrimental. Kaolin, also known as “white dirt,” is a clay commonly consumed by humans either recreationally or due to a pica disorder (Forrester et al., 2015). A study which introduced 20% kaolin clay to the diet of pregnant rats before and throughout gestation found that the kaolin-fed rats had ~10% reduced fetal birthweights and signs of maternal anemia (Patterson and Staszak, 1977). A human study of 26 geophagic and 79 non-geophagic participants found no association of geophagy with fetal birth weight (Poirier et al., 2021). While kaolin consumption has been shown to lead to increase levels of heavy metals such as lead, arsenic, and cadmium in blood serum (Akah et al., 2020) and decreased levels of calcium and potassium, it has also been linked to a dose-dependent elevation of plasma glucose (Zeigbo et al., 2020) which could benefit placental growth at the expense of maternal health, as predicted by the metabolic hypothesis for NVP (Crespi, 2024). An effective test of this hypothesis would be to test whether geophagy during pregnancy is, like during the Dutch famine, associated with increased *placental* weight.

Due to its likely homology with NVP, geophagy of pregnancy can serve as a useful proxy to identify NVP in non-human species. The kaolin pica test is a quantitative empirical measure of nausea developed for rodents, which involves measuring the amount of kaolin clay an animal consumes in response to a stimulus (Mitchell et al., 1976). One could conduct the kaolin pica test in multiple species with pregnancy stage taking the place of the emetogenic agent. If early-gestation females consume more kaolin, the species may possess a form of pregnancy sickness.

Relevance to clinical practice: So what?

The discovery of GDF15 as a proximate cause of NVP and hyperemesis gravidarum has been a major advance in the diagnosis and treatment of severe morning sickness. Proposed interventions to avoid at-risk individuals from experiencing hyperemesis gravidarum have included blockage of GDF15's main receptor GFRAL, inhibition of serum GDF15 (eg by monoclonal antibody), and leverage of the fold-change sensing phenomenon by pre-treating individuals intending to become pregnany with recombonant GDF15 in anticipation of the pregnancy spike.

If one of the GFRAL-dependent hypotheses for placental GDF15's selected function are true, such as the prophylactic or catabolic hypothesis, it can be expected that GFRAL inhibition may cause side effects on fetoplacental nutrient uptake or, via maternal behavior, on fetal toxin exposure. As pointed out by recent authors, if the prophylactic hypothesis explains the origin of NVP but its function is obsolete in modern humans due to sanitization and nutritional counseling, then GFRAL-mediated induction of NVP would be a vestigial trait which can be safely inhibited without maternal consequence (Fejzo, 2024). If the selected role of placental GDF15 is paracrine rather than endocrine, as in the placental growth and anti-rejection hypotheses, one can expect GFRAL inhibition to be without severe consequence, and indeed to be a superior target over GDF15 itself to alleviate symptoms without affecting yet uncharacterized local functions.

The only proposed intervention compatible with all selected scenarios is anticipatory pre-dosing with GDF15 (Fejzo et al., 2024). This proposed intervention would allow paracrine levels to remain high during pregnancy. If the mismatch hypothesis for NVP is true, this intervention can be likened to the proposed benefits of helminthic extracts ("worm therapy") for autoimmune disorders: mimicry of an ancestral high pathogen load to restore physiological states which were optimized to that state.

The safety and efficacy of these and other interventions will and must be sorted out in the clinic. That said, research into the evolutionary proximate and ultimate causes of NVP have clear implications for the design of smart medical interventions. Especially when evolutionary arguments are made when proposing interventions (Fejzo, 2024), it is appropriate to consider whether those arguments are sound, and the opportunity exists for clinical researchers and evolutionary biologists to engage in productive exchange. While there are other drawbacks of GDF15 pre-dosing, primarily that it is preventative rather than ameliorative and therefore cannot be used in a patient already suffering hyperemesis gravidarum and would likely have to be targeted to women with high hereditary risk or previous incidence, its compatibility across all four leading evolutionary/mechanistic hypotheses for NVP is appealing. Among the proposed ameliorative treatments, GFRAL inihbition rather than GDF15 suppression would allow for local utero-placental effects of GDF15 to proceed uninhibited. In this case, a phylogenetic perspective is essential – that the absence of infertility in *Gdf15*$^{-/-}$ mice, which lack the trait of placental GDF15 production, does not mean that a primate-specific role for GDF15 in pregnancy does not exist. With recent advances, the potential for transformative treatment of hyperemesis gravidarum in the light of not just new molecular knowledge, but also by their intersection with evolutionary thought, appears bright.

Conclusions

In summary, proximate and ultimate questions of nausea and vomiting of pregnancy must be considered together to offer a complete account of the phenomenon. Major advances in recent years have demonstrated its etiology to depend upon brain stem reception of the hormone GDF15. The next breakthroughs in revising the evolutionary narrative of NVP will

depend upon whether paracrine (non-GFRAL) mechanisms of action of GDF15 act at the fetal-maternal interface. Specifically, it will be crucial to test whether GDF15 exerts direct (non-behavioral) changes on maternal metabolism, and whether the gain of high placental GDF15 production in Old World primates (Catarrhini) is associated with evolutionary changes to the placenta beyond the scope of maternal behavior, and whether NVP has evolved convergently in any other mammalian group, with the best candidates being elephants.

Beyond its status as a public health concern, NVP is also an attractive test system for the evolution of complex behaviors. NVP research promises insight into the poorly-understood interplay between physiological and behavioral mechanisms of host defense. More than a curiosity of human evolution, further research into the pregnancy sickness phenomenon has the opportunity to provide a unique window into the genotype-phenotype map and modularity of heritable behaviors.

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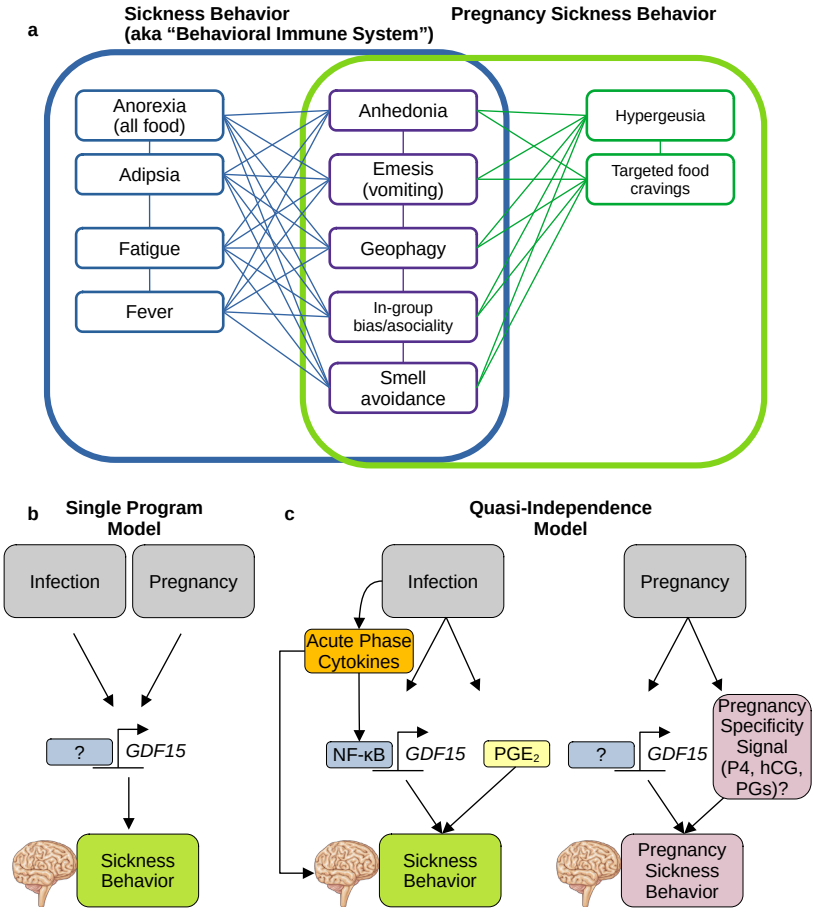

Figure 1. Overlap of pregnancy sickness behaviors with generic sickness behaviors induced by viral, bacterial, or parasitic infection. a. While sickness behaviors and pregnancy sickness behaviors have considerable overlap, behaviors unique to one or the other are also present. If differences between pregnancy sickness and generic sickness behavior are due to two separately-adapted underlying modules of behaviors, correlation networks of symptoms should show a modular structure. **b.** If both infection-induced GDF15 production and placental GDF15 production induce the same sickness behaviors, symptoms of each should be highly similar and differences may reflect experimenter bias (e.g. only testing for food cravings vs. geophagy) **c.** If sickness behaviors and pregnancy sickness behaviors are developmentally decoupled, their inductive signaling must differ as well. As GDF15 is implicated in both, a combinatorial pattern may be present, where additional pregnancy-specific hormones modulate the effects of GDF15 on behavior. PG: prostaglandin; P4: progesterone; hCG: human chorionic gonadotropin.

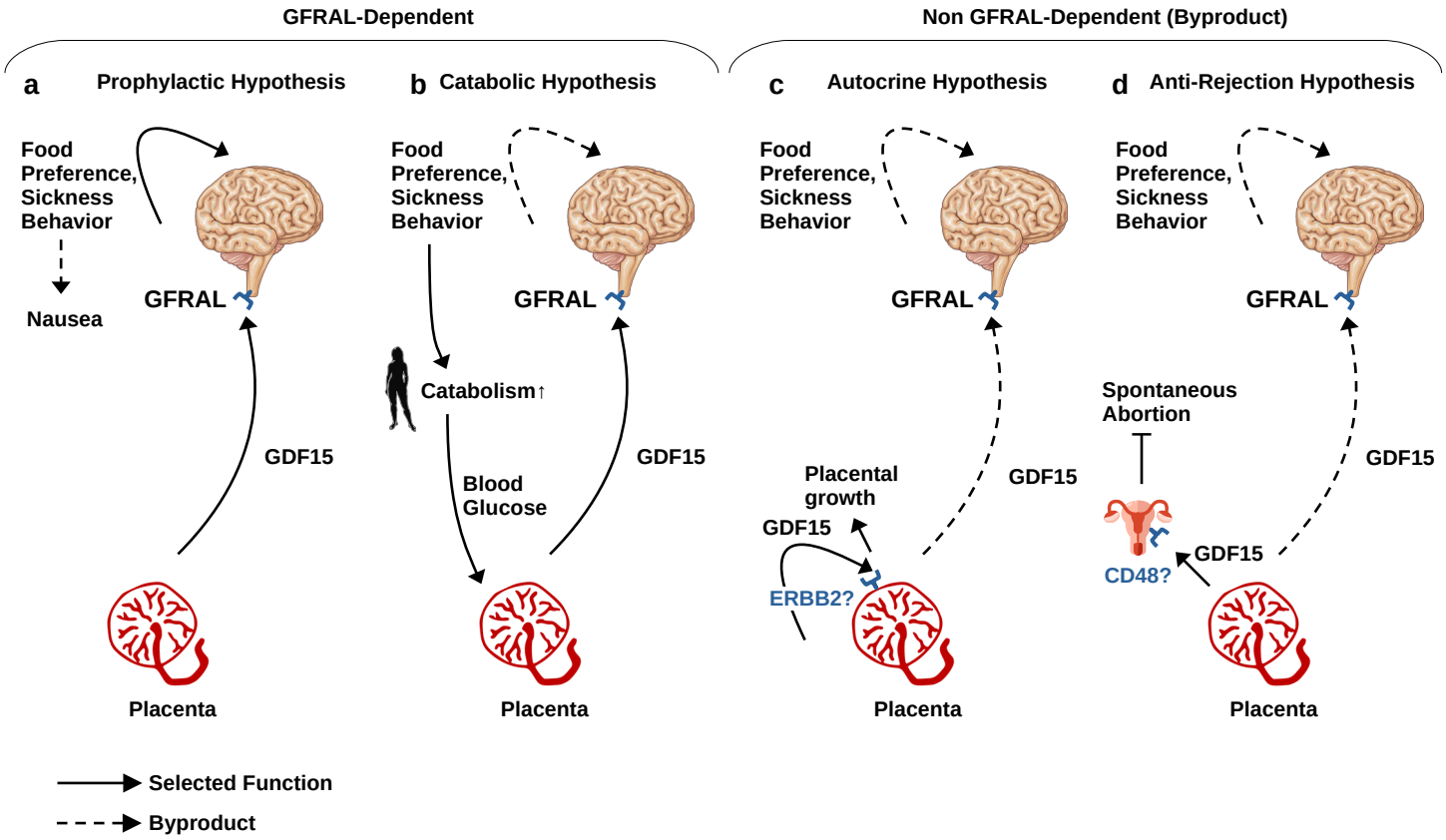

Figure 2. Leading hypotheses for the proximate and ultimate causes of NVP, given the GDF15 mechanism. Functions which were directly selected for are marked with continuous arrows, and byproduct effects are marked by dashed arrows. **a.** The prophylaxis hypothesis (Flaxman and Sherman, 2000; Hook, 1974; Profet, 1988) proposes that behavioral changes due to NVP are directly selected for due to avoidance of ingesting environmental toxins. **b.** The catabolic hypothesis (Crespi, 2024; Huxley, 2000) holds that GDF15's effects on the brain are selected for, but due to downstream induction of catabolism in maternal tissues which increase blood glucose. **c.** The autocrine growth hypothesis holds that GDF15 has local effects on placental growth and that all maternal effects, including NVP, are a byproduct. **d.** The anti-rejection or embryo selection hypothesis (Forbes, 2017, 2002) predicts that the causative hormone of NVP has local effects on the endometrium which determine whether pregnancy continues and may be a part of maternal quality-control mechanisms.

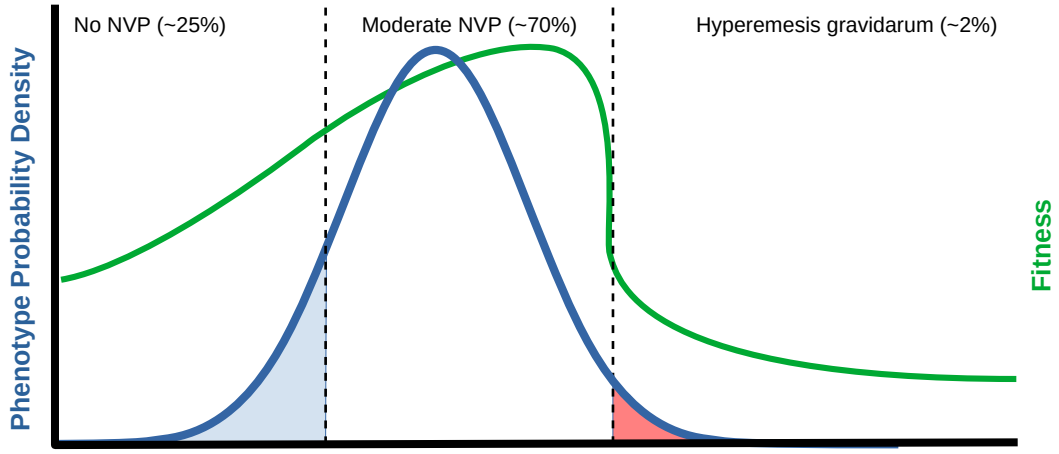

Figure 3. Asymmetric selection explanation for hyperemesis gravidarum risk in modern populatons. Putative fitness distribution of NVP severity during the first trimester is plotted in green, showing a gradual increase until the threshold for triggering of hyperemesis gravidarum, at which point the fitness function declines. Assuming that the population phenotype distribution must be normally distributed, the optimal distribution (maximizing mean fitness) is plotted in blue. An overhang of individuals with maladaptive extreme phenotypes (red shaded region), representing the approximately 2% of pregnancies with hyperemesis gravidarum. After Mitteroecker and Merola (2024).

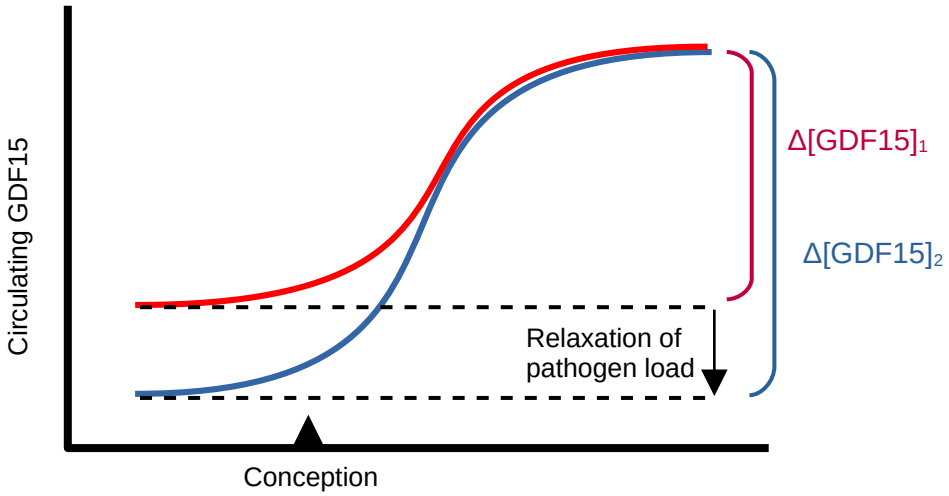

Figure 4. Mismatch model of NVP severity in modern populations. Severity of NVP is determined by the change between pre-pregnancy and post-pregnancy levels of circulating GDF15. In individuals with high parasitic load (red line), pre-pregnancy circulating GDF15 is more likely to be elevated above the levels in non-infected individuals in sterile living environments (blue line). The magnitude of the pregnancy GDF15 spike (Δ[GDF15]) is therefore increased in the non-parasitized group.

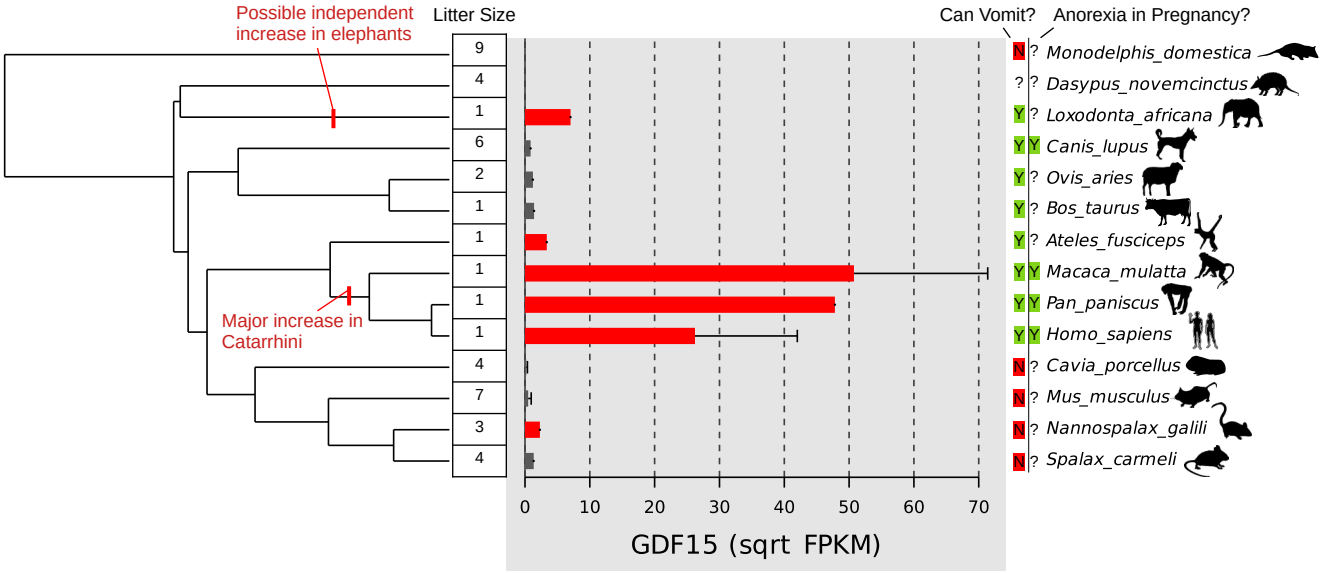

Figure 5. Extreme placental GDF15 production evolved in Catarrhine primates. Phylogenetic distribution of whole-placental *GDF15* mRNA expression (square-root fragments per kilobase-million). Expression data are compiled from Armstrong et al. (2017), Eidem et al. (2016), and Berkebile et al. (2021), with litter size values from AnAge (Tacutu et al., 2018) and vomiting and anorexia in pregnancy status from sources cited in main text.