Sensitivity to fetal hormone GDF15 drives maternal risk of nausea and vomiting during pregnancy

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To the Editor: Two-thirds of pregnant women experience nausea and vomiting during pregnancy (NVP) in their first trimester, with 0.3–10.8% of pregnant women developing a severe condition called hyperemesis gravidarum (HG). HG leads to dehydration, nutritional deficiencies, electrolyte imbalances, and stress. NVP dramatically reduces quality of life, causes substantial maternal morbidity, and can result in adverse pregnancy outcomes. However, the etiology and pathology of NVP have been poorly understood until recently.

Hormonal changes are considered potential drivers of NVP. In 2017, Fejzo *et al*[1] first linked growth/differentiation factor 15 (GDF15) to HG, identifying that genetic variant and circulating levels of GDF15 and insulin-like growth factor-binding protein-7 (IGFBP7) were significantly associated with HG in a genome-wide association study. Subsequently, O'Rahilly *et al*[2] demonstrated an association between NVP and circulating GDF15 levels in a nested case-control study. These studies support the conclusion that GDF15 levels correlate with NVP.[1–3] However, the underlying mechanism remains unclear. Recently, Fejzo and O'Rahilly co-authored a study concluding that maternal sensitivity to fetal-derived GDF15 underlies the risk of NVP [Figure 1A].[4]

GDF15 Involved in NVP: GDF15, a member of the transforming growth factor-β (TGF-β) family, can induce anorexia through nausea and vomiting, reduce food intake and body mass, and promote muscle energy consumption by binding to glial cell-derived neurotrophic factor family receptor alpha-like (GFRAL) and recruiting the receptor tyrosine kinase (RET) in the hindbrain [Figure 1B]. Previous clinical studies have reported correlations between GDF15 and NVP using various strategies.[3] In this study, circulating GDF15 levels were measured in pregnant women over 15 consecutive gestational weeks. GDF15 levels were higher in the 168 pregnant women with nausea and vomiting compared to the 148 pregnant women without symptoms. Furthermore, GDF15 levels were higher in the 57 pregnant women with HG than in the 56 pregnant women with mild nausea and vomiting. These results support the finding that circulating GDF15 levels are positively associated with severe NVP [Figure 1A].[3,4] However, circulating GDF15 is influenced by factors such as inflammation, cardiometabolic diseases, and drug use, which should be included in statistical analyses alongside age and body mass index.[5] Additionally, the interaction of other hormones, such as progesterone, requires further study. The progesterone receptor gene is strongly associated with NVP, and the interaction of progesterone with GDF15 is linked to changes in appetite, weight loss, reduced gastrointestinal motility, and gastric dysrhythmias.[6]

Fetal Origin Accounts for Most GDF15: Because both fetus and pregnant mother produce GDF15,[4,5] identifying the primary source of GDF15 poses a challenge.

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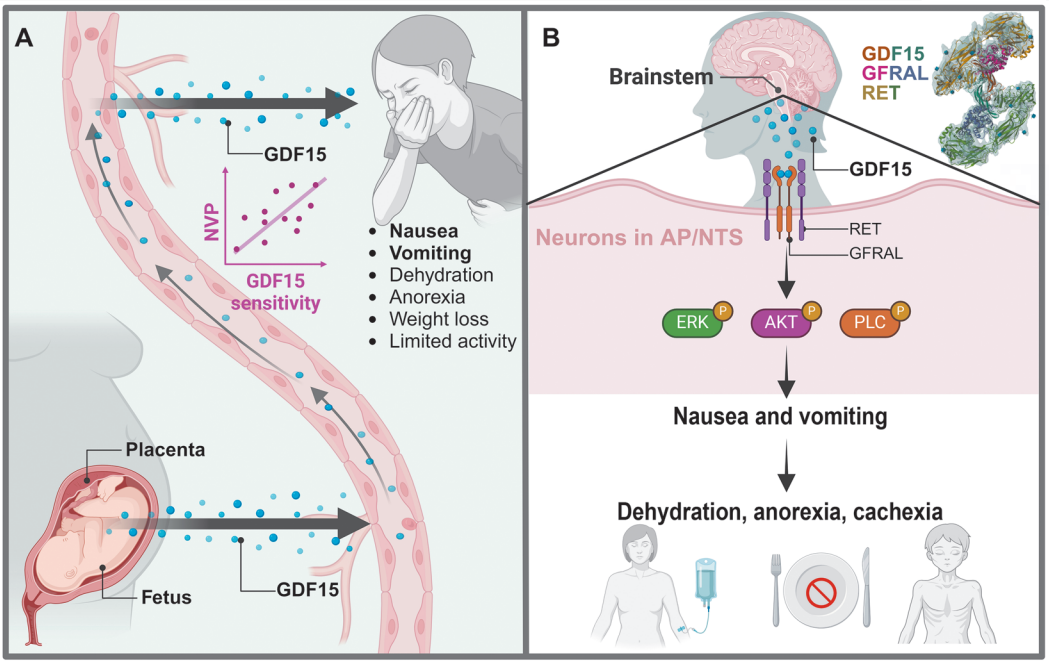

Figure 1: Sensitivity to fetal hormone GDF15 drives nausea and vomiting during pregnancy. (A) GDF15 derived from the fetus and placenta is released into the maternal circulation, and maternal sensitivity to this hormone induces maternal nausea, vomiting, and other pregnancy symptoms. The severity of NVP is positively associated with maternal sensitivity to the fetal hormone GDF15. (B) In the brainstem, GDF15 binds to GFRAL and RET to form a hexamer on neurons in the AP and NTS, activating ERK/AKT/PLC signaling. This activation results in nausea and vomiting, which can cause dehydration, anorexia, cachexia, and other related syndromes in patients. AKT: Protein kinase B; AP: Area postrema; ERK: Extracellular-signal-regulated kinases; GDF15: Growth/differentiation factor 15; GFRAL: Glial cell-derived neurotrophic factor family receptor alpha-like; NTS: Nucleus tractus solitaries; NVP: Nausea and vomiting during pregnancy; PLC: Phospholipase C; RET: Receptor tyrosine kinase.

To address this, the authors designed a mass spectrometry-based method that could distinguish between the GDF15 (H202D) variant (D-peptide) and wild-type GDF15 (H-peptide),[4] based on their previous finding that the common H202D variant in GDF15 does not affect its bioactivity but can significantly interfere with the measurement of its circulating levels.[3] Maternal and fetal combinations of GDF15 dimers with H or D at the 202 position, such as maternal heterozygous (HD) and fetal homozygous (HH, DD) or maternal homozygous (HH) and fetal heterozygous (HD), were included to identify the source of the increased circulating GDF15 levels. The authors found that the circulating concentration of total GDF15 increased gradually during pregnancy, and the rate of increase varied at different stages. Moreover, the authors found that the fetal source of GDF15 was significantly higher than expected, confirming that the primary source of GDF15 in pregnant women is the fetal placenta [Figure 1A]. Since GDF15 is a stress response hormone and severe NVP can cause significant stress to maternal organs, GDF15 levels may be upregulated by physical and chemical changes in maternal organs in women predisposed to hypersensitivity to the rapid rise of the hormone in early pregnancy. In addition to the difficulty in monitoring and distinguishing between maternal and fetal GDF15 levels, the small number of patients included in the study limited the statistical power of these conclusions. Recent findings have revealed that human *GDF15* knockouts and heterozygous carriers who pass the *GDF15*-deficient allele to their fetuses suggest that GDF15 may not be required for pregnancy.[3] Thus, to confirm whether fetal GDF15 causes severe NVP, larger studies comparing maternal and fetal contributions in patients with and without HG and further genetic studies in animals are needed.

Maternal Sensitivity to GDF15: In addition to GDF15 levels, maternal sensitivity to GDF15 and their interactions drive NVP severity. In the absence of pregnancy, GDF15 (C211G) heterozygous mutations lead to a significant reduction in GDF15 secretion. Carrying the C211G variant in the mother increases the risk of NVP; however, the risk of NVP may decrease if the fetus also carries the variant. While low levels of GDF15 before pregnancy do not achieve desensitization, fetuses carrying the same variant as the mother tend to produce less GDF15, instead of reducing the risk of HG in the mother during pregnancy. Similarly, two common variants, rs45543339 and rs1054221, have been shown to significantly reduce GDF15 secretion, and high levels of GDF15 before pregnancy may reduce the risk of developing NVP during pregnancy.[4] These results support the finding that fetal GDF15 increases NVP risk and suggest that agonist GDF15-induced desensitization determines susceptibility to GDF15-mediated NVP, a mechanism validated in animals. When administered with a high dose of GDF15, the mice ate substantially less and lost weight, with symptoms similar to those of NVP in pregnant women. In contrast, mice pre-exposed to long-acting GDF15 maintained normal body weight when administered GDF15 at a high dose, and knockout mice were more sensitive and had reduced food intake when treated with low-dose GDF15 compared to wide-type mice. These findings confirmed the hypothesis that prior exposure to GDF15 can induce

desensitization to GDF15 and reduce the risk of NVP. A real-world example is pregnancy with β-thalassemia, characterized by life-long elevated levels of GDF15,[3] and a strikingly lower prevalence of NVP symptoms.[4] Thus, GDF15 desensitization may reduce the risk of NVP. However, regarding rare variations in *GDF15*, the authors included only a few cases. Additionally, the animals used by the authors were not pregnant mice; therefore, they do not fully represent an animal model of NVP. Moreover, fertility is impaired in women with β-thalassemia and it remains to be demonstrated whether the reduced risk of NVP in these patients is due to other factors that may have been mistaken for prolonged exposure to GDF15. Other factors are known to affect the secretion and sensitivity of GDF15 during pregnancy, including fetal sex, twin pregnancy, disease, and receptor status.[4] The mechanism of desensitization is still unclear.

GDF15-Based Treatment and Management of NVP: As previously mentioned, pre-exposure to a safe dose of GDF15 or activation of the GDF15/GFRAL signaling axis before pregnancy in women who are deficient in GDF15 or at high risk of NVP may lead to desensitization of the GDF15/GFRAL system.[5,6] Thus, LY3463251, a newly identified long-acting GDF15 receptor agonist, can be further tested for its potential to desensitize the GDF15 receptor GFRAL/RET before pregnancy, thereby reducing NVP risk. Alternatively, considering the elevated GDF15 levels in women, GDF15 neutralization may be another potential therapeutic option for alleviating symptoms and improving health. In non-human primates, the effectiveness of GDF15 neutralization with the monoclonal antibody (mAB1) has been demonstrated in anorexia and emesis induced by platinum-based chemotherapies.[5] These two strategies may hold promise for reducing the incidence of NVP during pregnancy. Furthermore, GDF15 deficiency has been shown to hinder human trophoblast invasion, highlighting the need to consider the physiological function of fetal/placental GDF15 in mediating pregnancy loss.[7] Since the occurrence of HG is related to changes in GDF15 levels before and during pregnancy, as well as maternal sensitivity to GDF15, it is possible to develop models for the early prediction and management of HG risk in pregnant women after accumulating sufficient data. Additionally, GDF15 levels are a promising biomarker for many lung diseases, are associated with the prognosis of cardiovascular diseases, and have been studied as predictors of preeclampsia, gestational diabetes, and other conditions. The role of GDF15 in maternal and fetal health needs to be fully explored. A better understanding of the expression of GDF15 in maternal and fetal diseases is also urgently needed. Establishing criteria for the upper and lower limits of GDF15 concentration and determining the appropriate dose of GDF15 pre-exposure are problems to be addressed in the near future.

Overall, Fejzo and O'Rahilly utilized a smart study design to gain insights into the causal relationship between GDF15 and maternal NVP. They showed that basal GDF15 levels determine maternal sensitivity to acute increases in GDF15 levels and the risk of NVP. This study improves our understanding of NVP and represents a promising reference for future clinical interventions. It also presents a useful paradigm for patient-based translational research.

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Conflicts of interest

None.

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