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Women's health

Pregnancy sickness linked to hormone from fetus

Alice E. Hughes & Rachel M. Freathy

Maternal sensitivity to a hormone produced by the fetus might underlie the risk of severe nausea and vomiting in human pregnancy – a finding that could open up strategies for the treatment of this debilitating condition. **See p.760**

Nausea and vomiting are reported in about two-thirds of pregnancies[1]. Although pregnancy sickness is often mild and transient, some people experience persistent and severe nausea and vomiting that presents a serious health problem. This condition, known as hyperemesis gravidarum (HG), occurs in 0.3–3% of pregnancies[2] and can cause dehydration, nutrient deficiencies and weight loss. It frequently leads to hospitalization, and, at its most extreme, can result in termination of wanted pregnancies and maternal death. Even though excessive vomiting in pregnancy has been recognized for centuries[3,4], the cause of HG has remained elusive. On page 760, Fejzo *et al.*[5] describe a link between sickness during pregnancy and sensitivity to a hormone called growth differentiation factor 15 (GDF15). The findings open up potential avenues for research aimed at preventing or treating HG.

In 2018, a genome-wide analysis of more than 53,000 women identified a link between the *GDF15* gene and nausea and vomiting in pregnancy across the whole spectrum of severity[6]. Although GDF15 had not previously been implicated in pregnancy sickness, it was a promising candidate for investigation, because evidence suggested that it acts on a part of the brainstem that controls vomiting[7], and its overproduction had already been linked to chronic nausea and weight loss in people with cancer[8,9].

In the latest study, Fejzo and colleagues found that the levels of GDF15 in the maternal bloodstream increase steadily in the first 12 weeks of pregnancy, but are higher on average in women who experience nausea, vomiting and HG than in those who do not (Fig. 1a). These results were important because they confirmed observations from previous studies, which used a method of assessing the levels of GDF15 in the blood that was subsequently found to be unreliable[10]. Those measurements were confounded by the inability of the assays to detect a common genetic variant of *GDF15* known as H202D.

What makes the study by Fejzo *et al.* a major advance is that it goes beyond establishing a correlation between GDF15 and nausea and vomiting in pregnancy, and provides genetic evidence for a potential causal mechanism. Using the H202D genetic variant to their advantage, the authors developed a mass-spectrometry-based method to distinguish between GDF15 carrying a histidine (H) amino-acid residue at position 202 and the variant carrying an aspartate (D) residue at this position. They then studied pairs of mothers and babies in which the mother and the baby had different genotypes – for example, a mother who did not have the 'D' variant of the *GDF15* gene (an 'HH' genotype) and a baby who had one copy of the 'D' variant and one copy of the 'H' variant (an 'HD' genotype). In this way, the researchers could assess how much of the GDF15 in the mother's blood was maternal in origin, and how much was fetal. They found that most of the circulating GDF15 in pregnancy came from the fetus.

The team focused next on variants in or near the *GDF15* locus that are linked with a predisposition to HG. They showed that, in the blood of non-pregnant individuals, these genetic variants were associated with circulating levels of GDF15 that were lower – not higher, as might be expected – than those observed in people who did not have the HG-predisposing variants (Fig. 1b). The finding that a high risk of HG is related to genetic variants that are associated with low levels of GDF15 in the non-pregnant state is consistent with a causal relationship, because genotypes cannot be changed by lifestyle factors that might normally confound a correlation between exposure to something in the environment and a disease[11]. Furthermore,

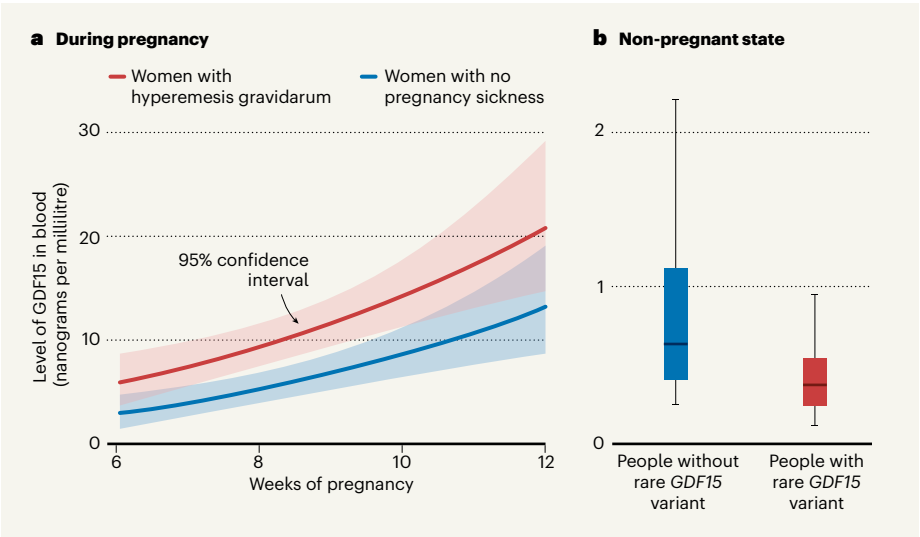

Figure 1 | The hormone GDF15 is responsible for excessive nausea and vomiting during pregnancy. **a**, Fejzo *et al.*[5] find that the levels of GDF15 in the mother's bloodstream increase during the first 12 weeks of pregnancy, and that most of this GDF15 originates from the fetus and placenta. Women with a condition called hyperemesis gravidarum (HG), who experience severe nausea and vomiting, have higher levels of GDF15 than those who don't experience pregnancy sickness – suggesting that high levels of GDF15 are linked to symptoms of HG. Graph adapted from Fig. 1c of ref. 5. **b**, People with a rare *GDF15* variant have lower basal levels of GDF15 than those who do not have the variant. Individuals with this genetic variant are predisposed to HG. Lower levels of GDF15 in the non-pregnant state could explain why these people are sensitive to the increase in GDF15 during pregnancy, and so experience HG. Graph adapted from Fig. 3c of ref. 5.

in a real-life example of how a genetic disease can inform understanding of human physiology, the authors showed that women with an inherited blood disorder called β-thalassaemia, who typically have high levels of GDF15, rarely report nausea and vomiting in pregnancy.

The picture emerging from the genetic data is that the risk of experiencing nausea and vomiting in pregnancy is greater if maternal levels of GDF15 before pregnancy are low, rather than high. By contrast, high levels of GDF15 during pregnancy (mostly originating from the fetus) are associated with increased nausea and vomiting. How can these seemingly contradictory findings both be true?

The authors hypothesized that people who have naturally low levels of GDF15 might be more sensitive to the rise in fetal GDF15 during pregnancy — and therefore more susceptible to its sickness-inducing effects — than are those with naturally high levels of GDF15. They tested this hypothesis in mice, using suppression of appetite as an indirect measure of nausea because mice do not vomit. They showed that mice that had been treated with a long-acting version of GDF15 were less likely to show suppressed appetite when given an acute dose of GDF15 than were mice that had not been pre-exposed in this way. Similarly, mice that had been genetically engineered to lack GDF15 were more sensitive to its effects than were mice that expressed GDF15 normally. Overall, the results support a mechanism in which the sensitivity of some mothers to fetally derived GDF15, as a result of their relatively low previous exposure to this hormone, is responsible for nausea and vomiting during pregnancy.

The authors' findings provide a scientific basis for HG that could be used to develop treatments for and preventive measures against severe nausea and vomiting during pregnancy. Blocking the action of GDF15 could relieve the symptoms of HG, and therapeutically increasing the levels of GDF15 in susceptible people before they become pregnant might even prevent the onset of symptoms. However, before any treatments can reach the clinic, experiments are needed to verify that humans who are exposed to GDF15 become desensitized to its nauseating effects, in the same way that appetite is affected in mice.

Interactions between the mother and the fetus are relevant to many other poorly understood health conditions in pregnancy, and the study by Fejzo *et al*. is of broad interest to researchers who are attempting to understand such interactions. The authors analysed data from 17 pregnancies of 6 mothers with a rare genetic variant that is associated with an increased risk of developing HG. They observed that the prevalence of HG was lower if the fetus had the same variant as the mother. This finding would need to be replicated in a study with a larger sample size, but it suggests that the risk of HG is lower when the fetus is genetically predisposed to producing less circulating GDF15. Because the risk of HG might be moderated by the genetics of the fetus, future studies that account for maternal, fetal and paternal genotypes would be a valuable addition to this work.

Besides the precise contribution of the fetus to pregnancy sickness, some interesting questions remain. Do factors other than GDF15 contribute to nausea and vomiting? Variation in a gene expressed in the placenta called *IGFBP7* has also been shown to be associated with HG[6], so the role of this gene is an avenue for future research. Finally, pregnancy sickness seems to be unique to humans[12]. Why did a physiological system that causes such extreme vomiting evolve? One theory is that this mechanism protects the developing fetus from poisoning[13].

The identification of a possible link between maternal sensitivity to GDF15 and HG reflects real progress in the understanding of a disease that causes misery for many. The work by Fejzo *et al*. is likely to prompt further investigations and an appetite for clinical trials in the field of pregnancy-related diseases.

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Cell biology

How plants iron out competing interests

Shanice S. Webster & Mary Lou Guerinot

Once a plant recognizes a pathogen, part of its defence strategy is to withhold iron. The mechanism involves suppression of root acquisition of iron by degrading a molecule that activates the iron-uptake pathway. **See p.750**

How do plants strike a balance between regulating iron uptake to promote their own growth and nourish their associated non-harmful microbes (commensal microbiome), while inhibiting pathogenic microorganisms? On page 750, Cao *et al*.[1] provide insights into a molecular mechanism of crosstalk between iron and immunity during iron deficiency, and highlight the complex interplay between plants and their commensal and pathogenic bacteria.

Iron is an essential micronutrient for plants and their associated microorganisms. Its ability to facilitate electron transfer makes it invaluable for key cellular processes such as photosynthesis and respiration, but excessive amounts of iron can be detrimental[2]. Plants must therefore control iron uptake and maintain a suitable level — this iron homeostasis allows plants to maximize benefits while minimizing adverse effects. Furthermore, because iron can aid the proliferation of microbes that cause disease, plants, in a similar way to animals, have evolved mechanisms to restrict iron availability as a defence strategy — a phenomenon called nutritional immunity.

Iron homeostasis is linked to plant immunity defences[3]; however, little is known about the mechanisms of crosstalk between iron deficiency and plant immunity defence signalling. Cao *et al*. demonstrate that flg22, a peptide fragment derived from the flagellin protein of a bacterial surface component called a flagellum, suppresses iron uptake through a process during which the peptide IMA1 is degraded. IMA1 is one member of the IMA family of mobile signalling peptides. These are evolutionarily conserved across flowering plants, and are expressed during iron deficiency to regulate iron uptake by preventing the turnover of transcription factor proteins needed to activate the iron-deficiency response[4]. The