We think we have found a cause of pregnancy sickness, and it may lead to a treatment

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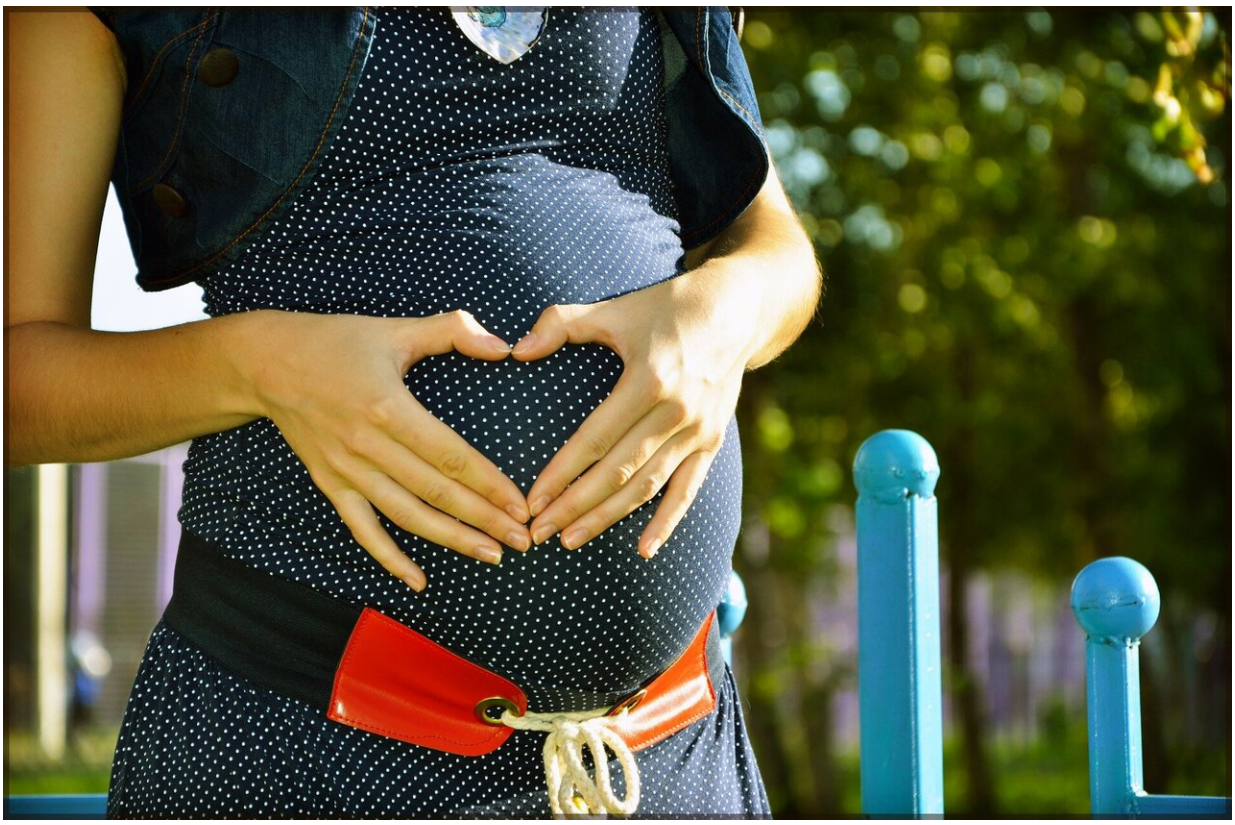

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Sickness in pregnancy, or hyperemesis gravidarum, is common and is thought to affect seven out of ten women at some time in their

pregnancy. But, until recently, very little has been known about why it happens.

New research by our team has identified sensitivity to a hormone made in abundance by the developing pregnancy, GDF15, as a contributor to the risk of pregnancy sickness.

This condition can affect pregnant women's quality of life, even in so-called mild cases. Between 1% and 3% of women suffer from a severe form of pregnancy sickness when nausea and vomiting are so severe that they lose weight or become dehydrated, or both. In one study, this condition was the most common reason that women were admitted to hospital in the first three months of pregnancy.

It has been associated with worse pregnancy outcomes and its effect lasts beyond the end of pregnancy with some women reporting psychological distress and being reluctant to conceive again.

The fact that it develops in early pregnancy and invariably resolves when pregnancy ends strongly suggests that the cause of the sickness comes from the developing pregnancy. But the detail on how and why it happens has remained elusive. This dearth of understanding makes the development of treatments difficult and arguably contributes to the considerable stigma associated with this condition.

GDF15

GDF15 is a hormone that suppresses food intake in mice by acting, probably exclusively, on a small group of cells at the base of the brain which are also known to induce nausea and vomiting. As such, GDF15 has been under investigation as an obesity therapy.

Early trials confirm it suppresses appetite in people, but it also causes

nausea and vomiting. It has long been known that it is abundant in human placenta and is present at very high concentrations in the blood of healthy pregnant women. These factors make it a plausible cause, but a detailed understanding of if GDF15 affects the severity of sickness in pregnancy has been lacking.

We used a variety of methods to study how GDF15 increases the risk of pregnancy sickness. We measured GDF15 in the blood of pregnant women attending hospital due to sickness and those attending hospital for other reasons.

We found that women with pregnancy sickness did indeed have higher levels of GDF15. While this was in keeping with GDF15 contributing to the condition, levels of GDF15 in each group overlapped substantially. This suggests that factors other than the absolute amount of GDF15 coming from the developing pregnancy might determine the risk of sickness.

Natural variation in DNA of future mothers contributes to risk of pregnancy sickness. Previous studies have identified changes in DNA near GDF15 as the biggest determinants of risk of pregnancy sickness. In particular, one rare genetic mutation (present in around one in 1,500 people) that affects the make-up of the GDF15 protein in the blood, has a large effect on that risk.

To understand the potential impact of this genetic variant on GDF15 levels in the bloodstream, we studied its effects on the protein in lab-grown cells. We discovered that this mutated GDF15 molecule gets stuck inside cells. What's more, it actually stuck to and trapped "normal" GDF15—this creates a double hit that hinders the transport of GDF15 out of cells. Healthy people with this mutation have markedly lower levels of GDF15 in their blood, which is consistent with these findings.

We discovered that DNA changes near GDF15, which are prevalent in about 15 to 30% of people, lower the levels of the hormone. These changes increase the risk of pregnancy sickness by small amounts. Conversely, women with the blood disorder thalassaemia, who have very high levels of GDF15 throughout life, actually reported much less nausea and vomiting in pregnancy.

A roadmap to treatment

The conclusion of these studies is clear –- predisposition to higher levels of GDF15 when not pregnant reduces the risk of pregnancy sickness. At first glance, this is rather perplexing because how can having higher levels of a hormone that makes you sick protect against pregnancy sickness?

In fact, several hormone systems exhibit a phenomenon resembling memory, where the sensitivity to a hormone is influenced by previous exposure to that hormone. This seemed like the most plausible explanation for our results. Supporting this theory, mice with persistently high levels of GDF15 in their bloodstream were relatively unresponsive to an acute surge in GDF15 levels.

Our findings suggest that lower levels of GDF15 before pregnancy result in women being hypersensitive to the large amounts of GDF15 being released from the developing pregnancy. This poses two obvious approaches to treatment of this condition –- desensitizing women to GDF15 by increasing its levels before pregnancy or blocking its action during pregnancy.

The challenge now is to develop and test strategies to achieve these aims that are safe and acceptable to women at risk from this debilitating condition.

More information: M. Fejzo et al, GDF15 linked to maternal risk of nausea and vomiting during pregnancy, *Nature* (2023). DOI: 10.1038/s41586-023-06921-9