Does the placenta and appetite hormone GDF15 cause NVP and HG?

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In the past, the cause of Hyperemesis Gravidarum (HG) was thought to be elevated levels of hCG. However, decades of research failed to find an association. More recent evidence points to a more likely candidate, a hormone called GDF15. In the first genome-wide association study (GWAS) of nausea and vomiting of pregnancy (NVP) and HG, GDF15 was found to be the greatest genetic risk factor. Replication studies have now confirmed that 2 unlinked variants in GDF15, as well as a variant in its receptor GFRAL, are associated with HG. No variants in hCG, nor its receptor were associated with HG. The NVP/HG GWAS also does not support the unproven theory that anxiety/neuroticism/depression are associated with HG as none of 176 genes from 37 studies associated with anxiety/neuroticism nor 44 variants associated with major depression overlapped with any of the genes found associated with NVP or HG. GDF15 variants are also associated with blood protein levels of GDF15, periodontitis, and taste preference (ie milk vs dark chocolate). GDF15 is produced by the placenta and decreases prior to miscarriage. Serum levels of GDF15, but not hCG, are abnormally high in women hospitalized for HG and in women taking antiemetics in the 2nd trimester. GDF15 variants associated with higher levels of GDF15 segregate with the disease in HG families and are associated with recurrence. GDF15 activates the nausea and vomiting center of the brain in the least shrew, but surprisingly, does not cause vomiting. It causes cancer cachexia, a disease with symptoms similar to HG, and a GDF15 inhibitor successfully reverses weight loss in animal models. Finally, GDF15 is upregulated by TSH and, also, in response to prolonged nutritional deficiency. This may contribute to a rapid downward spiral in some HG patients. Taken together, these studies strongly support GDF15 as a predominant causal factor involved in the pathogenesis of HG. Future work should focus on exploring the role of GDF15 in pregnancy and whether the GDF15/GFRAL pathway can be used to design novel therapies that are safe and effective in treating NVP and HG.