

Time to move on from the hCG hypothesis regarding nausea and vomiting of pregnancy and hyperemesis gravidarum

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Thank you for your letter¹ highlighting our study that implicates GDF15 and does not support a direct causal role for hCG in Hyperemesis Gravidarum (HG).² Both GDF15 and hCG are expressed in blastocysts and increase in the 1st trimester,² so any association between the two hormones in early pregnancy is not surprising and does not imply one controls expression of the other. While it is possible hCG plays a secondary role contributing to GDF15 levels, it is unlikely to be important for HG for the following reasons:

1. From Deruelle and Tranchant's letter,¹ "nausea and vomiting are not common side-effects of hCG," but are for GDF15.
2. Circulating hCG reaches its peak at 9-10 weeks,³ while GDF15 levels and HG symptoms do not.⁴
3. While the Petry et al. study mentioned by Deruelle and Tranchant shows GDF15 and hCG concentrations correlate, they failed to mention Petry also found that only GDF15 levels, and *not* hCG levels correlated with maternal antiemetic use and second trimester vomiting. Similarly, our study comparing GDF15 and hCG levels in pregnant patients hospitalized with HG compared to healthy pregnant controls also found an association with GDF15 levels, but *not* hCG.⁴
4. At least 14 studies, one including 4,372 pregnancies found no association between hCG and HG.⁴ While other studies find an association, continuing to spend limited resources attempting to prove an association, or a secondary relationship, while interesting, is unlikely to provide any clinically relevant finding regarding hCG and HG.
5. We recently presented a multi-ancestry meta-analysis of 7,197 HG cases and 178,953 controls that confirmed *GDF15* as the greatest genetic risk factor, but also replicated associations with placental genes insulin-like growth factor-binding protein 7 (*IGFBP7*) and progesterone receptor (*PGR*).⁵ Therefore, resources would be better spent determining whether *IGFBP7* and *PGR* alter GDF15 levels, and if not, elucidating their etiological role.
6. Both GDF15 and hCG are present in pregnancy directly because of the placental genes that code for them, and yet while the *GDF15* gene was the most significant locus in 4 individual GWASes,⁵ none identified any association with genes encoding hCG. If hCG plays a secondary role in HG through upregulating GDF15, genetic variation causing higher levels or overactive hCG should show up in larger GWASes -so far it has not.

The theory that hCG causes NVP and HG was a good one, and the lack of a genetic association was surprising. But the fascinating association with the nausea and vomiting hormone GDF15, a hormone

highly expressed by the placenta, and the discovery of a mutation in *GDF15* resulting in > 10-fold increased risk for HG, strongly implicates GDF15 as a causal factor.² This discovery leads to a potentially clinically relevant pathway for treatment of HG. Drugs that disrupt this pathway are currently in clinical trials to treat nausea and vomiting associated with cancer, and if safe in pregnancy, may be a game changer for HG. It is time to move on from hCG and focus on GDF15.

1. Deruelle and Tranchant's letter, in press.
2. Fejzo, M. S., MacGibbon, K. W., First, O., Quan, C., & Mullin, P. M. (2022). Whole-exome sequencing uncovers new variants in GDF15 associated with hyperemesis gravidarum. *BJOG : an international journal of obstetrics and gynaecology* , 129 (11), 1845–1852. <https://doi.org/10.1111/1471-0528.17129>
3. Rull, K., & Laan, M. (2005). Expression of beta-subunit of HCG genes during normal and failed pregnancy. *Human reproduction (Oxford, England)* , 20 (12), 3360–3368. <https://doi.org/10.1093/humrep/dei261>
4. Fejzo, M. S., Trovik, J., Grooten, I. J., Sridharan, K., Roseboom, T. J., Vikanes, Å., Painter, R. C., & Mullin, P. M. (2019). Nausea and vomiting of pregnancy and hyperemesis gravidarum. *Nature reviews. Disease primers* , 5 (1), 62. <https://doi.org/10.1038/s41572-019-0110-3>
5. Fejzo M., Mulin P., Pujol Gualdo N., Laisk T., E. Biobank Research Team, MacGibbon K.W., Wang X., Mancuso N. (2022). Large-scale genome-wide association study meta-analysis of Hyperemesis Gravidarum confirms the nausea and vomiting hormone gene GDF15 is the greatest genetic risk factor and identifies additional risk loci. ASHG, Los Angeles, CA.