Growth Differentiation Factor-15 *versus* Human Chorionic Gonadotropin in Pathophysiology of Nausea and Vomiting of Pregnancy

Sir,

Nausea and vomiting of pregnancy (NVP) is defined as nausea and vomiting in pregnancy that starts before 16 weeks of gestation and when there is no identifiable cause. It affects almost 90% of pregnant women, being the second most common cause of hospital admission during pregnancy, with the stays lasting for about three to four days. Hyperemesis gravidarum (HG) is defined as an intense form of NVP that significantly interferes with the pregnant women's quality of life and their ability to eat and drink normally, which often results in loss of weight, loss of body water, nutritional deficiencies and electrolyte disturbances.[1] It affects approximately 0.3 to 3.6% of all pregnant women.[2]

For a long period of time in the field of obstetrics, it has been hypothesised that human chorionic gonadotropin (hCG) plays a central role in the pathophysiology of NVP.[1] This hypothesis can be attributed to the temporal relationship between NVP symptoms and hCG production, both having their peaks between the weeks 9 and 12 of gestation.[3] According to the recent guidelines published on The Management of Nausea and Vomiting in Pregnancy and Hyperemesis Gravidarum (Green-top Guideline No. 69) by the Royal College of Obstetricians and Gynaecologists, it is the vomiting hormone, called growth differentiation factor-15 (GDF15) that is related to the major mechanism of NVP and HG.[2]

GDF15 causes anorexia, nausea, vomiting, loss of weight, and taste aversion.[2] Both in families and in unrelated individuals, variation in the *GDF15* gene has been found to have an association with HG. Both GDF15 and hCG are made when placental genes are activated. Both hormones have their circulating peak levels in the first half of the pregnancy, but even in very large studies, no identifiable genetic variants in hCG have been found to be associated with HG. In hospitalised patients of HG, in patients having second-trimester vomiting, and in patients taking medications for NVP, it was GDF15 that had higher circulating levels and not the hCG hormone.[4] Therefore, hCG is unlikely to be the cause.[4] Genetic variants in GDF15 found in families having HG are identified to be the greatest risk factor in terms of genetic predisposition to HG[5] and are also related to the recurrence of HG in next pregnancies.

Despite the fact that NVP and HG are very common conditions, their pathophysiology has been poorly understood. In this article, sound evidence has been provided that the intensity of NVP is the consequence of GDF15 derived from the foetus. This has obvious implications for the future prevention and treatment of HG. For example, various therapies for lowering the risk of HG, by reducing the levels of GDF15 through desensitising the receptor before pregnancy, or antagonisation of its action during pregnancy, can usefully be evaluated for prevention or treatment of NVP, respectively.[6] A thorough understanding of the pathophysiology is essential for the health professionals. Further research is also warranted for a better and more detailed understanding of its treatment and prevention.

COMPETING INTEREST:
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SA: Conception and drafting of the manuscript, reviewing and editing.
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REFERENCES

1. Fejzo MS, Trovik J, Grooten IJ, Sridharan K, Roseboom TJ, Vikanes A, *et al*. Nausea and vomiting of pregnancy and hyperemesis gravidarum. *Nat Rev Dis Primers* 2019; **5(1)**:62. doi: 10.1038/s41572-019-0110-3.
2. Nelson-Piercy C, Dean C, Shehmar M, Gadsby R, O'Hara M, Hodson K, *et al*. The management of nausea and vomiting in pregnancy and hyperemesis gravidarum (Green-top Guideline No. 69). *BJOG* 2024; **131(7)**:e1-30.
3. Bustos M, Venkataramanan R, Caritis S. Nausea and vomiting of pregnancy - What's new? *Auton Neurosci* 2017; **202**:62-72. doi: 10.1016/j.autneu.2016.05.002.
4. Fejzo M, Rocha N, Cimino I, Lockhart SM, Petry C, Kay RG, *et al*. Fetally-encoded GDF15 and maternal GDF15 sensitivity are major determinants of nausea and vomiting in human pregnancy. Available from: http://doi.org/10.1101/2023.06.02.542661.
5. Fejzo MS, MacGibbon KW, First O, Quan C, Mullin PM. Whole-exome sequencing uncovers new variants in GDF15 associated with hyperemesis gravidarum. *BJOG* 2022; **129(11)**:1845-52. doi: 10.1111/1471-0528.17129.
6. Fejzo M, Rocha N, Cimino I, Lockhart SM, Petry CJ, Kay RG, *et al*. GDF15 linked to maternal risk of nausea and vomiting during pregnancy. *Nature* 2024; **625(7996)**:760-7. doi: 10.1038/s41586-023-06921-9.

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