Glucocorticoid treatment, lower growth and differentiation factor 15 concentrations, and improved hyperemesis gravidarum symptoms

OBJECTIVE: Hyperemesis gravidarum (HG) is a severe form of nausea and vomiting in pregnancy associated with maternal and fetal morbidity. Recent evidence links HG to the emetic hormone, growth and differentiation factor 15 (GDF15), and affected individuals have significantly higher concentrations than unaffected individuals.[1,2] Thus, a medication-induced reduction in GDF15 concentrations may be a biologically plausible antiemetic response. In nonpregnant individuals, glucocorticoids lower circulating GDF15 concentrations in a dose-dependent manner.[3] While patient-reported survey data indicate that glucocorticoids are "very effective" for HG, their use is reserved for treatment-resistant cases due to possible maternal and fetal safety concerns.[4–8] Because the antiemetic mechanism is unknown in HG, we hypothesized that glucocorticoid effectiveness may be accompanied by a reduction in GDF15.

STUDY DESIGN: This retrospective cohort study included 22 patients with HG treated at The Morning Sickness Clinic. Institutional approval and ethics committee oversight was obtained, and all patients provided informed consent.

Since circulating GDF15 concentrations rise throughout early pregnancy, cases and controls were individually matched by gestational age.[2] The cohort comprised 11 cases with refractory symptoms who received glucocorticoids after failing other antiemetics and 11 controls managed with other antiemetics. Due to the retrospective nature, data on parity, prepregnancy body mass index, and HG history were unavailable, and patients were not matched for baseline severity.

Glucocorticoid treatment consisted of intravenous solumedrol (40 mg; Solu-Medrol) followed by a 19-day oral prednisone taper: 20 mg 3 times daily (3 days), 20 mg twice daily (3 days), 10 mg 3 times daily (3 days), 10 mg twice daily (3 days), 10 mg daily (3 days), and 5 mg daily (4 days). No patients required repeat courses. Controls received nonglucocorticoid antiemetics. Concomitant antiemetic therapy was comparable between groups, with ondansetron used in >50% of both cohorts.

Clinical data and blood were collected at initial visit (mean gestational age, 13 [standard deviation {SD}, 3] weeks for cases; 12 [SD, 2] weeks for controls) and follow-up visit (mean gestational age, 14 [SD, 2] weeks for cases; 14 [SD, 3] weeks for controls). While these represented follow-up intervals of 1 week for cases and 2 weeks for controls, both cohorts were assessed at an average of 14 weeks. Clinical data included circulating GDF15 concentrations, symptom scores, gestational age, and weight. For consistency, all blood draws were performed prior to intravenous fluid hydration.

GDF15 concentrations were quantified in duplicate using enzyme-linked immunosorbent assays (AnshLabs, AL-1014-r; sensitivity=2.2 pg/mL; dynamic range=15−2906 pg/mL; within-run and between-run variation <4.3% and <5.8%, respectively). Serum samples were diluted 1:15 to meet the assay's dynamic range, and results converted to ng/mL (1 ng=1000 pg). Symptom severity was measured using the 12-question HyperEmesis Level Prediction (HELP) tool (range, 0−60), categorized as mild (0−20), moderate (20−32), or severe (33−60).[9] Improvements were evaluated as a reduction in score from baseline since a threshold for clinically meaningful change has not been established.

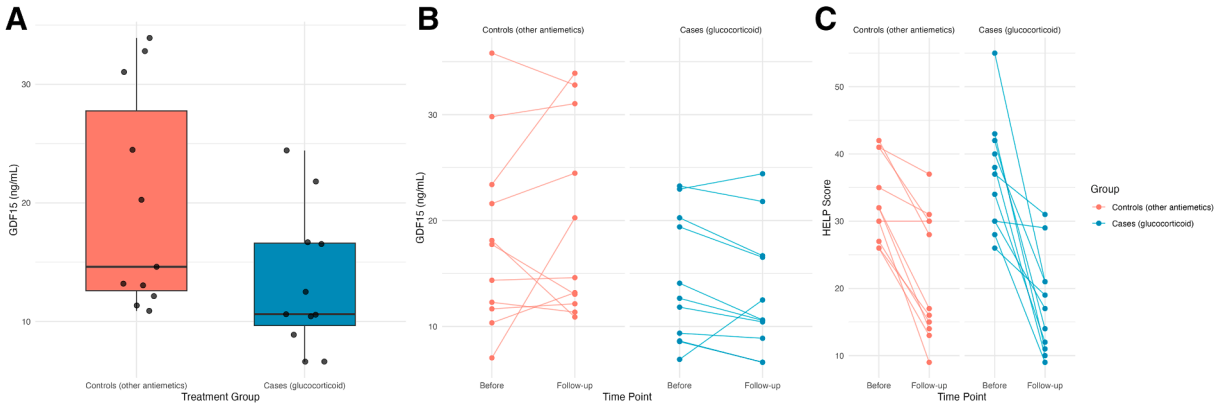
Between-group comparisons of GDF15 concentrations and symptom severity used independent 2-tailed *t* tests (normal) and Mann-Whitney U tests (non-normal). Within-group symptom changes used paired *t* tests due to their dependent nature and normality was confirmed by Shapiro-Wilk and visual inspection.

Primary analysis employed Ordinary Least Squares regression to assess the association between glucocorticoid treatment and circulating GDF15 concentrations, adjusting for baseline weight to control for the influence of body mass on GDF15 concentrations. Because raw GDF15 values violated assumptions of normality and homoscedasticity, concentrations were log-transformed prior to modeling. Coefficients and 95% confidence intervals were subsequently back transformed to express the treatment effect as a percentage reduction. Model integrity was verified through visual and analytic diagnostic tests (Supplemental Note 1). Sensitivity analyses were also performed to evaluate the inclusion of additional baseline covariates and the impact of influential outliers. A *P* value <.05 was considered statistically significant.

RESULTS: At first clinic visit, the groups did not have significant differences in baseline characteristics. Mean GDF15 concentrations were 14.4 (SD, 6.1) ng/mL in cases compared to 18.4 (SD, 8.7) ng/mL in controls (*P*=.23), and mean HELP scores were 36.6 (SD, 8.4) and 32.9 (SD, 6.1), respectively (*P*=.25).

Follow-up assessments at an average of 14 weeks' gestation showed circulating GDF15 concentrations were significantly lower in the glucocorticoid group (median, 10.6 ng/mL; 95% confidence interval [CI], 8.9−16.7 vs 14.6 ng/mL; 95% CI, 12.1−31; *P*=.04) (Figure 1A). Visual inspection of individual trajectories showed a consistent downward trend following

FIGURE
Lower GDF15 concentrations and symptom resolution in glucocorticoid treated cases



(**A**) Significantly lower GDF15 concentrations in cases at follow-up. (**B**) Individual trajectories show a consistent downward trend in cases, not controls. (**C**) Symptom improvement in controls and treatment-resistant cases.

GDF15, growth and differentiation factor 15.

glucocorticoids, whereas controls exhibited marked variability (Figure 1B).

In the primary regression, glucocorticoid treatment was associated with a 35.4% mean reduction in GDF15 concentrations compared with controls (95% CI, 7.7%−54.7%; P=.02) (Supplemental Table 1). This reflects a significant proportional GDF15 reduction following intervention. Higher baseline weight also significantly predicted lower follow-up GDF15 concentrations (P=.02). Sensitivity analyses supported these findings (Supplemental Note 2, Supplemental Tables 2 and 3).

With respect to symptom severity, glucocorticoids were associated with a larger mean HELP score reduction than controls (−19 vs 11 points; mean difference, −8; 95% CI, −16.1 to 0.3). Although this between-group difference was near-threshold significance (P=.06), the standardized effect size was large (Cohen d=0.87). Visual analysis of individual trajectories (Figure 1C) confirms a more uniform decline in symptoms for cases compared to higher symptom persistence and variability in controls. These findings are supported by a significant within-group improvement in the glucocorticoid cohort, whose HELP scores decreased from 37 (95% CI, 31−42.3) to 18 (95% CI, 12.6−22.6) between visits (P<.001).

CONCLUSION: In treatment-resistant HG, glucocorticoid therapy was associated with significant reduction in circulating GDF15 concentration and was accompanied by symptom improvement compared with other antiemetics. However, these findings are limited by small sample size, retrospective design, single-clinic setting, and confounding by indication, as corticosteroid treatment was reserved for refractory cases. Furthermore, residual confounding remains possible due to unmeasured/unmatched variables, variable antiemetics, variations in management, and differences in follow-up intervals. Albeit hypothesis generating, this study is the first to demonstrate a clinical association between glucocorticoid treatment, decreased GDF15 concentrations, and treatment response in refractory HG. Given concerns with glucocorticoid exposure, investigation is warranted to determine whether therapeutics targeting GDF15 could provide a safer alternative in HG management.

Hannah Thompson
Hyperemesis Education and Research Foundation
Clackamas, OR
hannahthompson24@gmail.com

Zainab H. Neemuchwala
Department of Population and Public Health Sciences
Keck School of Medicine
University of Southern California
Los Angeles, CA

Kimber W. MacGibbon, RN
Hyperemesis Education and Research Foundation
Clackamas, OR

Andrew Housholder, MD
The HG & Morning Sickness Clinic
Birmingham, AL

Marlena Fejzo, PhD
Department of Population and Public Health Sciences
Keck School of Medicine
University of Southern California
Los Angeles, CA

A.H. is a paid consultant for NGM Bio. M.S.F. has a grant from the EQT Foundation, is a paid consultant for, and holds stock options from NGM

Bio, a company testing a GFRAL antagonist antibody in patients with HG. She was a paid consultant for Harmonia Healthcare and Materna Biosciences. M.S.F. has received honoraria for speaking at the 12th Naval Academy Science and Engineering Conference, NGM Bio Conference, Glendale Community College, Drug Discovery Chemistry, Award Lecture, AAAS BII Innovations in Women's Health Prize, and Yale Center for Molecular and Systems Metabolism Seminar Series. She has received travel support for Keystone Symposium, Fortune Most Powerful Women Next Gen, SciFoo Camp, 12th Naval Academy Science and Engineering Conference, NGM Bio, University of Pennsylvania, HLTH, Burroughs Wellcome Fund, and Drug Discovery Chemistry; Award Lecture, AAAS BII Innovations in Women's Health Prize, Yale Center for Molecular, and Systems Metabolism Seminar Series; Keynote Speaker, Harvard Medical School: BBS Program in Genetics and Genomics, American Diabetes Association 85th Scientific Sessions. She has participated on a Data Safety Monitoring Board for a trial on mirtazapine for HG. She is a HER Foundation Board Member, Morning Sickness Clinic CSO, and Foundation for Women's Health Board Member. H.T., Z.H.N., and K.M. report no conflict of interest.

This study was funded, in part, by a grant from the BIKKJA Trust.

Click Supplemental Materials and Video under article title in Contents at ajog.org

REFERENCES

1. Fejzo MS, MacGibbon KW, First O, Quan C, Mullin PM. Whole-exome sequencing uncovers new variants in GDF15 associated with hyperemesis gravidarum. BJOG 2022;129:1845–52.

2. Fejzo M, Rocha N, Cimino I, et al. GDF15 linked to maternal risk of nausea and vomiting during pregnancy. Nature 2024;625:760–7.

3. Melvin A, Chantzichristos D, Kyle CJ, et al. GDF15 is elevated in conditions of glucocorticoid deficiency and is modulated by glucocorticoid replacement. J Clin Endocrinol Metab 2020;105:1427–34.

4. Wills L, Hsiao HF, Thomas A, Kay-Smith C, Henry A, Grzeskowiak LE. Assessing the burden of severe nausea and vomiting of pregnancy or hyperemesis gravidarum and the associated use and experiences of medication treatments: an Australian consumer survey. PLoS One 2025;20:e0329687.

5. Bandoli G, Palmsten K, Forbess Smith CJ, Chambers CD. A review of systemic corticosteroid use in pregnancy and the risk of select pregnancy and birth outcomes. Rheum Dis Clin North Am 2017;43:489–502.

6. Grooten IJ, Vinke ME, Roseboom TJ, Painter RC. A systematic review and meta-analysis of the utility of corticosteroids in the treatment of hyperemesis gravidarum. Nutr Metab Insights 2016;8(Suppl 1):23–32.

7. Desai RJ, Bateman BT, Huybrechts KF, et al. Risk of serious infections associated with use of immunosuppressive agents in pregnant women with autoimmune inflammatory conditions: cohort study. BMJ 2017;356:j895.

8. Skorpen CG, Lydersen S, Gilboe IM, et al. Influence of disease activity and medications on offspring birth weight, pre-eclampsia and preterm birth in systemic lupus erythematosus: a population-based study. Ann Rheum Dis 2018;77:264–9.

9. MacGibbon KW, Kim S, Mullin PM, Fejzo MS. HyperEmesis level prediction (HELP Score) identifies patients with indicators of severe disease: a validation study. Geburtshilfe Frauenheilkd 2021;81:90–8.

© 2026 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies. https://doi.org/10.1016/j.ajog.2026.03.017