

HER FOUNDATION PUBLISHES GROUNDBREAKING RESEARCH ON HG 2007-2024

- *GDF15, a hormone acting on the brain stem, has been implicated in the nausea and vomiting of pregnancy (NVP) including its most severe form, Hyperemesis Gravidarum (HG), but a full mechanistic understanding is lacking [1-4]. Here we report that fetal production of GDF15, and maternal sensitivity to it, both contribute substantially to the risk of HG. We confirmed that higher GDF15 levels in maternal blood are associated with vomiting in pregnancy and HG. Using mass spectrometry to detect a naturally-labeled GDF15 variant we demonstrate that the vast majority of GDF15 in the maternal plasma is derived from the feto-placental unit. By studying carriers of rare and common genetic variants we found that low levels of GDF15 in the non-pregnant state increase the risk of developing HG. Conversely, women with beta-thalassemia, a condition where GDF15 levels are chronically high [5], report very low levels of NVP. In mice, the acute food intake response to a bolus of GDF15 is influenced bi-directionally by prior levels of circulating GDF15 in a manner suggesting that this system is susceptible to desensitization. Our findings support a putative causal role for fetally-derived GDF15 in the nausea and vomiting of human pregnancy, with maternal sensitivity, at least partly determined by pre-pregnancy exposure to the hormone, being a major influence on its severity. They also suggest mechanism-based approaches to the treatment and prevention of HG. GDF15 is linked to maternal risk of nausea and vomiting during pregnancy. Nature. 2024*
- *Significant associations have been identified between hyperemesis gravidarum and multiple adverse outcomes. Maternal deaths owing to hyperemesis gravidarum continue to be reported, and hyperemesis gravidarum is associated with high fetal loss and termination rates. Hyperemesis gravidarum must be recognized early and treated aggressively with frequent monitoring. The gene, growth differentiation factor-15, which codes for a nausea and vomiting hormone produced by the placenta, is the greatest genetic risk factor for hyperemesis gravidarum. Pregnant, Miserable, and Starving in 21st Century America. AJOG Global Report, 2023.*
- *This study confirms GDF15 is the greatest genetic risk factor for HG. The new variants identified may have implications for prediction and diagnosis. The findings provide insight into the cause, and molecular mechanisms for developing therapeutics for HG. Whole-exome sequencing uncovers new variants in GDF15 associated with hyperemesis gravidarum. BJOG, 2022.*
- *HELP Score classified 92% of people reporting “nothing goes or stays down” as severe, compared to 58% using PUQE. People hospitalized for HG were more likely classified as severe using HELP. HELP performs better than PUQE in identifying patients with severe symptoms requiring intervention. This study validates a new and greatly needed tool designed by HER to measure severity of HG. HyperEmesis Level Prediction identifies patients with indicators of severe disease: a validation study. Geburtshilfe und Frauenheilkunde, 2021.*
- *The complexity of HG affects every aspect of a woman’s life during and after pregnancy. Without methodical intervention by knowledgeable and proactive clinicians, life-threatening complications may develop. Effectively managing HG requires an understanding of both physical and psychosocial stressors, recognition of potential risks and complications, and proactive assessment and treatment strategies using innovative clinical tools. Hyperemesis Gravidarum Strategies to Improve Outcomes. The Art and Science of Infusion Nursing, 2020.*
- *Article summarizing the state of knowledge on HG published in one of the most highly respected international journals includes tables and figures provided by HER. Nausea and vomiting of pregnancy and hyperemesis gravidarum. Nature Reviews Disease Primers, 2019.*
- *The free iPhone App developed by HER and UCLA improves accuracy in defining symptom level, communication between patients and providers, and treatment of Hyperemesis Gravidarum for both patient and providers. Performance of iPhone Hyperemesis Gravidarum Care App. Norcal Publications, 2019.*



www.hyperemesis.org
info@hyperemesis.org
Fax: 503.296.2220
Phone: 833.224.2844

HER Foundation
10117 SE Sunnyside Road
Suite F #8
Clackamas, OR 97015

- GDF15 hormone levels are abnormally high in HG pregnancies, providing more evidence GDF15 may cause HG. *Analysis of GDF15 and IGFBP7 in Hyperemesis Gravidarum support causality. Geburtshilfe und Frauenheilkunde, 2019.*
- Along with larger studies published by others, this study adds to mounting evidence that HG increases risk for having a child diagnosed with autism. Overall, 52% of children exposed to HG in utero were diagnosed with an emotional and/or behavioral condition, compared to 26% of unexposed children. This corresponds to a combined 3.2-fold increase in odds of neurodevelopmental delay in children from pregnancies complicated by HG. *Analysis of neurodevelopmental delay in children exposed in utero to hyperemesis gravidarum reveals increased risk of autism spectrum disorder. Repro Toxicol, 2019.*
- Groundbreaking study shows the placenta, appetite, and cachexia hormone GDF15 likely plays a role in causing HG. *Placenta and appetite genes GDF15 and IGFBP7 are associated with hyperemesis gravidarum. Nature Communications, 2018.*
- Sequencing of HG families identifies mutations in RYR2, an intracellular calcium release channel gene involved in vomiting, cyclic-vomiting syndrome, and a thyroid hormone target gene. *Genetic analysis of Hyperemesis Gravidarum reveals association with intracellular calcium release channel (RYR2). Molecular and Cellular Endocrinology, Mol Cell Endocrinol, 2017.*
- Among 80 post-pregnancy factors, people with HG showed significantly higher reporting for 7 common and 50 rare post-pregnancy outcomes. People with HG are significantly more likely to report physical and psychosocial issues both before and after pregnancy. *Analysis of pre- and post-pregnancy issues in women with hyperemesis gravidarum, Auton. Neurosci, 2016.*
- Summary of recent deaths secondary to HG lead to urgent appeal for prompt testing and treatment followed by frequent follow-up until symptoms subside to prevent HG-related deaths. *Why are women still dying from nausea and vomiting of pregnancy? Gyn and Obstetrics Case Report. Insight Medical Publishing Journals, 2016.*
- 1070 HG pregnancies exposed to ondansetron reveal no evidence of teratogenicity. People with HG who took ondansetron reported less miscarriages and terminations, and higher live birth rates. *Ondansetron in pregnancy and risk of adverse fetal outcomes in the United States. Reprod Toxicol, 2016.*
- We report on a maternal death due to Wernicke's encephalopathy and osmotic demyelination syndrome. *Mortality Secondary to Hyperemesis Gravidarum: A Case Report, Women's Health & Gyn., 2015.*
- People with HG have a 3.28-fold increased risk of having a child with neurodevelopmental delay including attention disorders, learning delay, sensory disorders, and speech and language delay. *Neurodevelopmental delay in children exposed in utero to hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol, 2015.*
- Poor outcomes (primarily preterm births) are 4 times more common in people with HG and are associated with gestational hypertension, early symptoms, and antihistamine use. *Antihistamines and other prognostic factors for adverse outcome in hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol, 2013.*
- Offspring exposed to HG in utero were significantly more likely to have a psychological or behavioral disorder (OR=3.6, p=0.0001) with diagnoses primarily of depression, bipolar disorder, and anxiety. *Prenatal exposure to hyperemesis gravidarum linked to increased risk of psychological and behavioral disorders in adulthood. J Dev Orig Health Dis, 2011.*
- More than 80% of people who had HG in their 1st pregnancy reported having HG in their next pregnancy. *Recurrence Risk of Hyperemesis Gravidarum. J Midwifery and Women's Health, 2011.*



www.hyperemesis.org
 info@hyperemesis.org
 Fax: 503.296.2220
 Phone: 833.224.2844

HER Foundation
 10117 SE Sunnyside Road
 Suite F #8
 Clackamas, OR 97015

- HG causes full criteria PTSD in 18% of people, especially when symptoms last the entire pregnancy. People may also experience post-traumatic stress symptoms without full criteria PTSD. *Posttraumatic Stress Symptoms (PTSS) following Hyperemesis Gravidarum (HG)* J Matern Fetal Neonatal Med, 2011.
- Those with prolonged HG reported more posttraumatic stress, motion sickness, muscle weakness, and infants with irritability, severe colic and growth restriction. Multiple pre-existing conditions and poor maternal and infant outcomes were associated with prolonged HG. *Risk factors, treatments, and outcomes associated with prolonged hyperemesis gravidarum.* J Matern Fetal Neonatal Med, 2012.
- HG runs in families suggesting a genetic component. If your sister has HG, you have a 17-fold increased risk of having it too. *Familial Aggregation of Hyperemesis Gravidarum.* AJOG, 2011.
- 26% of people report extreme weight loss (>15%) and 22% report symptoms lasting the entire pregnancy suggesting HG can be a form of prolonged starvation in pregnancy. For some, symptoms continued postpartum and included food aversions, muscle pain, nausea, and posttraumatic stress. Among those with severe weight loss, 17% of babies were born prematurely (33% of all participants), and 8% reportedly weighed <2500 g (16% of all participants). *Symptoms and pregnancy outcomes associated with extreme weight loss among women with hyperemesis gravidarum.* J Women's Health, 2009.
- 83% reported HG caused negative psychosocial changes (socioeconomic changes, attitude changes regarding future pregnancies, and psychiatric sequelae which for some continued postpartum - especially if their provider was uncaring). *The psychosocial burden of hyperemesis gravidarum.* J Perinatol, 2008.
- 15% reported therapeutic terminations of wanted pregnancies due to HG due to no hope for relief and uncaring providers. *Voluntary termination in a large cohort of women with hyperemesis gravidarum.* Contraception, 2007.

NOTE: Access FULL-TEXT articles on www.hyperemesis.org/research.



www.hyperemesis.org
 info@hyperemesis.org
 Fax: 503.296.2220
 Phone: 833.224.2844

HER Foundation
 10117 SE Sunnyside Road
 Suite F #8
 Clackamas, OR 97015