

HER FOUNDATION COLLABORATIVE HG RESEARCH 2021-2023 ABSTRACTS



1. [AJOG Global Report](#). 2023. doi: 10.1016/j.xagr.2022.100141

Pregnant, miserable, and starving in 21st Century America

Fejzo M, MacGibbon K, Wisner K

Abstract (abbreviated)

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. *(See article for recommendations on HG management: Early identification, increase awareness, offer resources like patient support, prescribe oral and IV vitamins, refer for supportive care and consults.)*



2. [BJOG](#). 2022. doi:10.1111/1471-0528.17129

Whole-exome sequencing uncovers new variants in GDF15 associated with hyperemesis gravidarum

Fejzo M, MacGibbon K, First O, Quan C, Mullin P

Abstract

Objective: A genome-wide association study (GWAS) linked the placenta and appetite hormone gene GDF15 to hyperemesis gravidarum (HG). This paradigm changing finding has shifted the field away from the prevailing hypotheses, but more evidence is needed. This study was performed to identify coding variants in addition to the non-coding variants implicated by GWAS.

Design: Case–control study. Population: Hyperemesis gravidarum cases requiring intravenous fluid treatment for disease (n = 926) and controls with normal or no nausea and vomiting of pregnancy (n = 660), from the USA.

Methods: Whole exome-wide sequencing and genome informatics were performed using the standard Regeneron pipeline. All variants were compared between cases and controls using dominant, recessive, and allelic models to identify variants with exome-wide significant p values ($p < 10^{-6}$). Odds ratios and associated p values were calculated for exome-wide significant allele(s) in subgroups of genetically predicted ancestries. Variants were filtered to identify rare pathogenic variants occurring in ≥ 10 cases and in no controls.

Results: A common coding variant in GDF15 was the only exome-wide significant association, and a rare coding variant in GDF15 was the only predicted disease causing variant occurring in 10 or more cases.

Conclusions: This study confirms the GWAS finding that 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.

3. [Geburtsh Frauenheilk.](#) 2021. doi:10.1055/a-1309-1997

HyperEmesis Level Prediction (HELP Score) Identifies Patients with Indicators of Severe Disease: a Validation Study

MacGibbon K, Kim S, Mullin P, Fejzo M

Abstract

Objective: Hyperemesis gravidarum (HG) severity can be underestimated resulting in undertreatment and adverse outcomes. This study was conducted to validate a tool (HELP Score) designed to score HG severity.

Materials and Methods: A survey link which included PUQE and HELP Score (HELP) tool questions posted on websites related to HG. HELP scores were compared to PUQE scores for indicators of severe disease.

Results: HELP classified 92% of women reporting “nothing goes or stays down” as severe, compared to 58% using PUQE. Women self-categorizing symptoms as severe were more likely categorized as severe using HELP. Women hospitalized for HG were more likely classified as severe using HELP. HELP performs better than PUQE in identifying patients with severe symptoms requiring intervention.

Conclusion: This study provides a novel tool that should be implemented to determine the need for intervention for NVP that may be overlooked using PUQE or empirical assessment.

4. [Journal of Infusion Nursing.](#) 2020. doi:10.1097/NAN.0000000000000363

Hyperemesis Gravidarum: Strategies to Improve Outcomes

MacGibbon K

Abstract

Hyperemesis gravidarum (HG) is a debilitating and potentially life-threatening pregnancy disease marked by weight loss, malnutrition, and dehydration attributed to unrelenting nausea and/or vomiting; HG increases the risk of adverse outcomes for the mother and child(ren). 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.

5. [Nat. Rev. Dis. Primers.](#) 2019. doi:10.1038/s41572-019-0110-3

Nausea and vomiting of pregnancy and hyperemesis gravidarum

Fejzo M, Trovik J, Grooten I, Sridharan K, Roseboom T, Vikanes Å, Painter R, Mullin P

Abstract (abbreviated)

Although no consensus definition is available for hyperemesis gravidarum (HG), it is typically viewed as the severe form of nausea and vomiting of pregnancy (NVP) and has been reported to occur in 0.3–10.8% of pregnant women. HG can be associated with poor maternal, fetal and child outcomes. Most women with NVP can be managed with dietary and lifestyle changes, but more than one-third of patients experience clinically relevant symptoms that may require fluid and vitamin supplementation and/or antiemetic. Ondansetron is commonly used to treat HG, but studies are urgently needed to determine whether it is safer and more effective than using first line antiemetics. Thiamine (vitamin B1) should be introduced following protocols to prevent refeeding syndrome and Wernicke encephalopathy. Recent advances in the genetic study of NVP and HG suggest a placental component to the aetiology by implicating common variants in genes encoding placental proteins (namely *GDF15* and *IGFBP7*) and hormone receptors (namely *GFRAL* and *PGR*). New studies on aetiology, diagnosis, management and treatment are under way. In the next decade, progress in these areas may improve maternal quality of life and limit the adverse outcomes associated with HG.

6. [AJOG](#). 2019: S585-S586.

Hormone receptor genes PGR and GFRAL linked to hyperemesis gravidarum.

Fejzo M, MacGibbon K, Mullin P

Abstract (abbreviated)

Objective: Our recent genome-wide association (GWAS) and replication study identified the placenta, appetite, and cachexia genes *GDF15* and *IGFBP7* as being associated with HG. In our GWAS study, hormone receptor genes *PGR* and *GFRAL* were found to be significant. We performed a replication study to validate the genome-wide association linking to *PGR* and *GFRAL* to HG.

Study Design: DNA from 89 women treated for HG and 606 women with normal or no nausea and vomiting pregnancy were genotyped using a Taqman platform. Genotypes of risk alleles for *PGR* and *GFRAL* were compared between cases and controls.

Results: Replication results confirm risk alleles for *PGR* and *GFRAL* were significantly associated with HG.

Conclusion: Evidence suggests abnormal levels of the hormone *GDF15* are associated with HG. Validation of the *GDF15* receptor gene *GFRAL* as a genetic risk factor for HG provides further support that the *GDF15*-*GFRAL* pathway is involved in disease etiology. Additionally, the progesterone receptor *PGR*, like *GDF15*, plays a role in the developing placenta and gastrointestinal mobility. Our findings validate *PGR* as a genetic risk factor for HG. *GDF15* inhibitors have proven successful in restoring body weight and appetite in animal models of cachexia, making this a promising strategy for treating NVP and HG. Therapeutics targeting *GFRAL* and *PGR* should also be investigated.

7. [J Clinical Case Rep Case Stud](#). 2019: 53-59.

Performance of iPhone Hyperemesis Gravidarum Care App.

Korouri E, MacGibbon K, Chan C, Guba Leonides, Cruz LD

Abstract (abbreviated)

Introduction: Patients with HG often need help monitoring their care due to being ill throughout pregnancy. We created a mobile application to help HG patients track their symptoms and medications with the objective of improving care and communication.

Methods: The study was performed at the University of California, Los Angeles (UCLA). Interested participants were asked to use an iPhone app to record symptoms, intake, and medications for 7 days prior to their next prenatal appointment. Copies of data were given to their provider, and both the patient and provider completed an app success survey at the appointment. Feedback was requested from both the patient and provider on the App's effectiveness for defining symptom level, improving communication, and improving treatment of HG, as well as any suggestions for improvements for the HG Care App.

Results: Thirty-six patients participated in symptom tracking and provided feedback, and 6 providers gave feedback on the App. Data analysis showed that patients felt positive about the App's ability to accurately define symptom levels (92%), improve communication (66%), and improve care (61%). Providers unanimously thought the HG Care App was accurate in defining symptom levels and was useful in improving communication, and most (67%) found it useful in improving care. Common feedback regarding the App included: being tedious to fill out (22%), being able to more easily explain symptoms to one's provider (14%), and adding a daily reminder to input symptoms in future versions (11%).

Discussion: A majority of both patients and providers are proponents of using the HG mobile application for accurately defining symptom levels and improving quality of care and communication. Results indicate that mobile apps have potential to be effective tools towards treating HG and severe NVP.

8. [Geburtshilfe Frauenheilkd](#). 2019. doi:10.1055/a-0830-1346

Analysis of GDF15 and IGFBP7 in Hyperemesis Gravidarum Support Causality

Fejzo M, Fasching P, Schneider M, Schwitulla J, Beckmann M, Schwenke E, MacGibbon K, Mullin P

Abstract

Objective Hyperemesis gravidarum, severe nausea and vomiting in pregnancy, occurs in up to 2% of pregnancies and leads to significant weight loss, dehydration, electrolyte imbalance, and ketonuria. It is associated with both maternal and fetal morbidity. Familial aggregation studies and twin studies suggest a genetic component. In a recent GWAS, we showed that placentation, appetite, and cachexia genes GDF15 and IGFBP7 are linked to hyperemesis gravidarum (HG). The purpose of this study is to determine whether GDF15 and IGFBP7 are upregulated in HG patients.

Methods We compared serum levels of GDF15 and IGFBP7 at 12 and 24 weeks' gestation in women hospitalized for HG, and two control groups, women with nausea and vomiting of pregnancy (NVP), and women with no NVP.

Results We show GDF15 and IGFBP7 serum levels are significantly increased in women with HG at 12 weeks' gestation. Serum levels of hCG are not significantly different between cases and controls. At 24 weeks gestation, when symptoms have largely resolved, there is no difference in GDF15 and IGFBP7 serum levels.

Conclusion This study supports GDF15 and IGFBP7 in the pathogenesis of HG and may be useful for prediction and diagnosis. The GDF15-GFRAL brainstem-activated pathway was recently identified and therapies to treat conditions of abnormal appetite are under intense investigation. HG should be included.

9. [Reprod Toxicol](#). 2018 Dec 27;84:59-64. doi: 10.1016/j.reprotox.2018.12.009.

Analysis of neurodevelopmental delay in children exposed in utero to hyperemesis gravidarum reveals increased reporting of autism spectrum disorder.

Fejzo M, Kam A, Laguna A, MacGibbon K, Mullin P

Abstract

The purpose of this study was to follow up on the reporting of neurodevelopmental disorders in children exposed in utero to Hyperemesis Gravidarum (HG). This was an exploratory descriptive study whereby neurodevelopmental outcomes of 267 children delivered by 177 mothers with HG were compared to neurodevelopmental outcomes from 93 children delivered by 60 unaffected mothers. Similar to at age 8, the children (now 12) exposed in utero to HG had over 3-fold increase in odds of neurodevelopmental disorders including attention, anxiety, sensory, sleep difficulty, and social development delay/social anxiety. However, with the longer follow-up, there was also a significant increase in Autism Spectrum Disorder (ASD), reported in 22/267 (8%) of children exposed to HG in utero and no unexposed children. As early intervention for ASD can be critical to prognosis, larger studies are urgently needed to determine whether ASD is associated with exposure to HG.

10. [Geburtshilfe Frauenheilkd](#). 2018 Sep;78(9):866-870. doi: 10.1055/a-0661-0287. Epub 2018 Sep 14.

Evidence GDF15 Plays a Role in Familial and Recurrent Hyperemesis Gravidarum.

Fejzo MS, Arzy D, Tian R, MacGibbon KW, Mullin PM

Abstract

Introduction Hyperemesis gravidarum (HG), a pregnancy complication characterized by severe nausea and vomiting in pregnancy, occurs in up to 2% of pregnancies. It is associated with both maternal and fetal morbidity. HG is highly heritable and recurs in approximately 80% of women. In a recent genome-wide association study, it was shown that placentation, appetite, and the cachexia gene GDF15 are linked to HG. The

purpose of this study was to explore whether GDF15 alleles linked to overexpression of GDF15 protein segregate with the condition in families, and whether the GDF15 risk allele is associated with recurrence of HG.

Methods We analyzed GDF15 overexpression alleles for segregation with disease using exome-sequencing data from 5 HG families. We compared the allele frequency of the GDF15 risk allele, rs16982345, in patients who had recurrence of HG with its frequency in those who did not have recurrence. Results Single nucleotide polymorphisms (SNPs) linked to higher levels of GDF15 segregated with disease in HG families. The GDF15 risk allele, rs16982345, was associated with an 8-fold higher risk of recurrence of HG.

Conclusion The findings of this study support the hypothesis that GDF15 is involved in the pathogenesis of both familial and recurrent cases of HG. The findings may be applicable when counseling women with a familial history of HG or recurrent HG. The GDF15-GFRAL brainstem-activated pathway was recently identified and therapies to treat conditions of abnormal appetite are under development. Based on our findings, patients carrying GDF15 variants associated with GDF15 overexpression should be included in future studies of GDF15-GFRAL-based therapeutics. If safe, this approach could reduce maternal and fetal morbidity.

11. [Nat Commun](#). 2018 Mar 21;9(1):1178. doi: 10.1038/s41467-018-03258-0.

Placenta and appetite genes GDF15 and IGFBP7 are associated with hyperemesis gravidarum.

Fejzo MS, Sazonova OV, Sathirapongsasuti JF, Hallgrímsdóttir IB, Vacic V, MacGibbon KW, Schoenberg FP, Mancuso N, Slamon DJ, Mullin PM; 23andMe Research Team



Abstract

Hyperemesis gravidarum (HG), severe nausea and vomiting of pregnancy, occurs in 0.3-2% of pregnancies and is associated with maternal and fetal morbidity. The cause of HG remains unknown, but familial aggregation and results of twin studies suggest that understanding the genetic contribution is essential for comprehending the disease etiology. Here, we conduct a genome-wide association study (GWAS) for binary (HG) and ordinal (severity of nausea and vomiting) phenotypes of pregnancy complications. Two loci, chr19p13.11 and chr4q12, are genome-wide significant ($p < 5 \times 10^{-8}$) in both association scans and are replicated in an independent cohort. The genes implicated at these two loci are GDF15 and IGFBP7 respectively, both known to be involved in placentation, appetite, and cachexia. While proving the casual roles of GDF15 and IGFBP7 in nausea and vomiting of pregnancy requires further study, this GWAS provides insights into the genetic risk factors contributing to the disease.

12. [Mol Cell Endocrinol](#). 2017 Jan 5;439:308-316.

Genetic analysis of hyperemesis gravidarum reveals association with intracellular calcium release channel (RYR2).

Fejzo MS, Myhre R, Colodro-Conde L, MacGibbon KW, Sinsheimer JS, Reddy MV, Pajukanta P, Nyholt DR, Wright MJ, Martin NG, Engel SM, Medland SE, Magnus P, Mullin PM

Abstract

Hyperemesis Gravidarum (HG), severe nausea/vomiting in pregnancy (NVP), can cause poor maternal/fetal outcomes. Genetic predisposition suggests the genetic component is essential in discovering an etiology. We performed whole-exome sequencing of 5 families followed by analysis of variants in 584 cases/431 controls. Variants in RYR2 segregated with disease in 2 families. The novel variant L3277R was not found in any case/control. The rare variant, G1886S was more common in cases ($p = 0.046$) and extreme cases ($p = 0.023$). Replication of G1886S using Norwegian/Australian data was supportive. Common variants rs790899 and rs1891246 were significantly associated with HG and weight loss. Copy-number analysis revealed a deletion in a patient. RYR2 encodes an intracellular calcium release channel involved in vomiting, cyclic-vomiting syndrome, and is a thyroid hormone target gene. Additionally, RYR2 is a downstream drug target of Inderal, used to treat HG and CVS. Thus, herein we provide genetic evidence for a pathway and therapy for HG.

13. *Auton Neurosci*. 2017 Jan;202:73-78.

Analysis of pre- and post-pregnancy issues in women with hyperemesis gravidarum.

Tian R, MacGibbon K, Martin B, Mullin P, Fejzo M

Abstract

The purpose of this study is to determine the frequency of reporting of both pre-pregnancy and post-pregnancy psychosocial and physical issues in women with hyperemesis gravidarum (HG). Conditions in 449 women with HG were compared to 459 unaffected women (controls). Binary responses were analyzed using either Chi-squared or Fishers Exact test. Continuous responses were analyzed using a t-test. Among 60 pre-pregnancy conditions surveyed, 10 common (>5%) maternal pre-pregnancy conditions were significantly more frequently reported by women with HG. Twenty rare (<5% controls) pre-pregnancy conditions with significantly increased reporting in the HG group were identified. Thirty (50%) pre-pregnancy conditions were similarly reported between cases and controls. Among 80 post-pregnancy factors surveyed, women with HG also showed significantly higher reporting for 7 common and 50 rare post-pregnancy outcomes. Women with HG are significantly more likely to self-report physical and psychosocial issues both before and after pregnancy.

14. *Reprod Toxicol*. 2016 Jul;62:87-91.

Ondansetron in pregnancy and risk of adverse fetal outcomes in the United States.

Fejzo MS, MacGibbon KW, Mullin PM

Abstract

This is an analysis of fetal outcome in pregnancies exposed to ondansetron to treat Hyperemesis Gravidarum (HG). In this retrospective cohort study, U.S. data on outcome were collected on 1070 pregnancies exposed to

ondansetron and compared to outcomes in two control groups: 771 pregnancies in women with a history of HG with no ondansetron exposure and 1555 pregnancies with neither a history of HG nor ondansetron exposure. Ventricular septal defects were reported in 2/952 of infants in the HG/Ondansetron-exposure group and 4/1286 in the No HG/No Ondansetron-exposure group. Cleft palate was reported in 1/952 live births in the HG/Ondansetron and 2/1286 in the No HG/No Ondansetron-exposure groups. Women with a history of HG who took ondansetron reported less miscarriages and terminations, and higher live birth rates. The overall results do not support evidence of teratogenicity of ondansetron.

15. *Women's Health & Gynecology*. 2015 Nov;1(2):011.

Mortality Secondary to Hyperemesis Gravidarum: A Case Report

MacGibbon K, Fejzo MS, Mullin P



Abstract

Background: Until the 1950's, maternal deaths were commonly caused by Hyperemesis Gravidarum (HG) [1]. Although maternal mortality secondary to HG has since decreased, herein we report a death occurring in the United States. We review a case of maternal death secondary to HG and resulting malnutrition.

Conclusion: Prompt treatment with parenteral vitamins, nutritional support, and methodical electrolyte replacement can prevent HG-related deaths. Clinician education and treatment protocols should be updated to proactively address the nutritional and metabolic requirements of pregnant women presenting with nausea, vomiting and malnutrition.

16. *Eur J Obstet Gynecol Reprod Biol*. 2015 Jun;189:79-84.

Neurodevelopmental delay in children exposed in utero to hyperemesis gravidarum.

Fejzo MS, Magtira A, Schoenberg FP, Macgibbon K, Mullin PM

Abstract

OBJECTIVE: The purpose of this study is to determine the frequency of emotional, behavioral, and learning disorders in children exposed in utero to hyperemesis gravidarum (HG) and to identify prognostic factors for these disorders.

STUDY DESIGN: Neurodevelopmental outcomes of 312 children from 203 mothers with HG were compared to neurodevelopmental outcomes from 169 children from 89 unaffected mothers. Then the clinical profiles of patients with HG and a normal child outcome were compared to the clinical profiles of patients with HG and a child with neurodevelopmental delay to identify prognostic factors.

RESULTS: Children exposed in utero to HG have a 3.28-fold increase in odds of a neurodevelopmental diagnosis including attention disorders, learning delay, sensory disorders, and speech and language delay ($P < 0.0005$). Among characteristics of HG pregnancies, only early onset of symptoms (prior to 5 weeks gestation) was significantly linked to neurodevelopmental delay. We found no evidence for increased risk of 13

emotional, behavioral, and learning disorders, including autism, intellectual impairment, and obsessive-compulsive disorder. However, the study was not sufficiently powered to detect rare conditions. Medications, treatments, and preterm birth were not associated with an increased risk for neurodevelopmental delay.

CONCLUSION: Women with HG are at a significantly increased risk of having a child with neurodevelopmental delay. Common antiemetic treatments were not linked to neurodevelopmental delay, but early symptoms may play a role. There is an urgent need to address whether aggressive treatment that includes vitamin and nutrient supplementation in women with early symptoms of severe nausea of pregnancy decreases the risk of neurodevelopmental delay.

17. *J Obstet Gynaecol Res.* 2015 Apr;41(4):512-6.

Psychiatric factors do not affect recurrence risk of hyperemesis gravidarum.

Magtira A, Schoenberg FP, MacGibbon K, Tabsh K, Fejzo MS

Abstract

AIM: The aim of this study is to determine whether psychiatric symptoms affect recurrence risk of hyperemesis gravidarum (HG).

METHODS: The study sample included 108 women with HG treated with i.v. fluids in their first pregnancy. Women were divided into two groups based on recurrence of HG in their second pregnancy. Participants submitted medical records and completed a survey regarding pregnancy characteristics and psychiatric symptoms. The χ^2 -test and Student's t-test were performed to compare the two groups.

RESULTS: Eighty-four women (71%) had a recurrence of HG requiring i.v. fluid for dehydration, and were compared with 34 women (29%) who did not have a recurrence. There were no significant differences in obstetric history, although there was a trend toward greater time between first and second pregnancy in the recurrence group ($P = 0.08$). There were no differences in pre-existing psychiatric diagnoses including anxiety, depression, bipolar disorder, panic or eating disorders. Following the first HG pregnancy, participants in both groups were well matched for all post-traumatic stress symptoms.

CONCLUSION: This study is the first to analyze the relationship of psychiatric factors to risk of recurrence of HG. No factors were identified that increase the risk of recurrence including stress symptoms following a HG pregnancy. Psychological sequelae associated with HG are probably a result of the physical symptoms of prolonged severe nausea and vomiting, medication and/or hospitalization, and likely play no role in disease etiology.

18. *Eur J Obstet Gynecol Reprod Biol.* 2013 Sep;170(1):71-6.

Antihistamines and other prognostic factors for adverse outcome in hyperemesis gravidarum.

Fejzo MS, Magtira A, Schoenberg FP, MacGibbon K, Mullin P, Romero R, Tabsh K

Abstract

OBJECTIVE: The purpose of this study is to determine the frequency of adverse perinatal outcome in women with hyperemesis gravidarum and identify prognostic factors.

STUDY DESIGN: This is a case-control study in which outcomes of first pregnancies were compared between 254 women with hyperemesis gravidarum treated with intravenous fluids and 308 controls. Prognostic factors were identified by comparing the clinical profile of patients with hyperemesis gravidarum with a normal and an adverse pregnancy outcome. Binary responses were analyzed using either a Chi-square or Fisher exact test and continuous responses were analyzed using a t-test.

RESULTS: Women with hyperemesis gravidarum have over a 4-fold increased risk of poor outcome including preterm birth and lower birth weight ($p < 0.0001$). Among maternal characteristics, only gestational hypertension had an influence on outcome ($p < 0.0001$). Treatment as an outpatient and/or by alternative medicine (acupuncture/acupressure/Bowen massage) was associated with a positive outcome ($p < 0.0089$). Poor outcomes were associated with early start of symptoms ($p < 0.019$), and treatment with methylprednisolone ($p < 0.0217$), promethazine ($p < 0.0386$), and other antihistamines [diphenhydramine (Benadryl), dimenhydrinate (Gravol), doxylamine (Unisom), hydroxyzine (Vistaril/Atarax), doxylamine and pyridoxine (Diclectin/Bendectin)] ($p < 0.0151$) independent of effectiveness. Among these medications, only the other antihistamines were prescribed independent of severity: they were effective in less than 20% of cases and were taken by almost 50% of patients with an adverse outcome.

CONCLUSION: Poor outcomes are significantly greater in women with HG and are associated with gestational hypertension, early symptoms, and antihistamine use. Given these results, there is an urgent need to address the safety and effectiveness of medications containing antihistamines in women with severe nausea of pregnancy.

19. J Dev Orig Health Dis. 2012 Oct;3(5):375-9.

No increased risk of psychological/behavioral disorders in siblings of women with hyperemesis gravidarum (HG) unless their mother had HG.

Mullin PM, Bray A, Vu V, Schoenberg-Paik F, MacGibbon K, Romero R, Goodwin TM, Fejzo MS

Abstract

Hyperemesis gravidarum (HG), severe nausea and vomiting of pregnancy, is characterized by prolonged maternal stress, undernutrition and dehydration. Maternal stress and malnutrition of pregnancy are linked to poor neonatal outcome and associated with poor adult health, and we recently showed that in utero exposure to HG may lead to increased risks of psychological and behavioral disorders in the offspring. In addition, we have shown familial aggregation of HG, which is strong evidence for a genetic component to the disease. In this study, we compare the rates of psychological and behavioral disorders in 172 adults with and 101 adults without a sibling with HG. The rate of emotional/behavioral disorders is identical (15%) in both groups. The results suggest that the etiology of HG is not likely to include genetic factors associated with emotional and behavioral disorders. In addition, this study provides evidence that the increased incidence of psychological/behavioral

disorders among offspring of women with HG is attributable to the HG pregnancy itself, rather than to confounding genetic factors linked to HG.

20. *J Matern Fetal Neonatal Med.* 2012 Aug;25(8):1241-5.

Change in paternity and recurrence of hyperemesis gravidarum.

Fejzo MS, Ching C, Schoenberg FP, Macgibbon K, Romero R, Goodwin TM, Mullin PM

Abstract

OBJECTIVE: To determine whether change in paternity changes recurrence risk of hyperemesis gravidarum (HG).

STUDY DESIGN: Survey data on recurrence of HG was compared between cases who had a paternity change between pregnancies and cases who did not.

RESULTS: The percentage of HG pregnancies in women with the same partner for all pregnancies was not significantly different from the percentage of HG pregnancies in women who changed partners for at least one pregnancy (78% vs 71%, $p > 0.05$). Participants who did and did not change partners between their first and second pregnancies, were asked to rate their first and second pregnancy in regards to symptoms of HG. Neither the ratings nor the change in rating between pregnancies was significantly different between the two groups.

CONCLUSION: Women reported HG in over 70% of their pregnancies regardless of a paternity change. Paternal genes expressed through the fetus do not have a significant effect on incidence or recurrence of HG. This study supports a strong maternal genetic factor involved in HG. However, because the recurrence risk is not 100%, other factors play a role. Identification of the predisposing gene(s) and other factors will determine the cause of this poorly understood complication of pregnancy.

21. *J Matern Fetal Neonatal Med.* 2012 Jun;25(6):632-6.

Risk factors, treatments, and outcomes associated with prolonged hyperemesis gravidarum.

Mullin PM, Ching C, Schoenberg F, MacGibbon K, Romero R, Goodwin TM, Fejzo MS

Abstract

OBJECTIVE: To identify factors associated with prolonged Hyperemesis Gravidarum (HG).

STUDY DESIGN: About 395 women completed a survey regarding pre-existing conditions, treatments and outcomes. Responses were compared using two-sided t-tests or the F-test.

RESULTS: Participants with prolonged HG are slightly younger and weigh more. Pre-existing factors associated with prolonged HG include allergies and a restrictive diet. Prolonged HG is associated with hematemesis, dizziness, fainting and antiemetic treatment. Following pregnancy, those with prolonged HG

reported more posttraumatic stress, motion sickness, muscle weakness and infants with irritability, severe colic and growth restriction.

CONCLUSION: Multiple pre-existing conditions and poor maternal and infant outcomes were associated with prolonged HG. The most significant condition prior to pregnancy was allergies suggesting a possible autoimmune component affecting duration of HG. In addition, the most significant lifestyle choice linked to prolonged HG was a restrictive diet. Future research is needed to determine whether a change in diet prior to pregnancy may lead to a shorter duration of HG and its associated outcomes.

22. *J Dev Orig Health Dis.* 2011 Aug;2(4):200-4.

Prenatal exposure to hyperemesis gravidarum linked to increased risk of psychological and behavioral disorders in adulthood.

Mullin PM, Bray A, Schoenberg F, MacGibbon KW, Romero R, Goodwin TM, Fejzo MS

Abstract

Hyperemesis gravidarum (HG), severe nausea and vomiting of pregnancy, is characterized by long-term maternal stress, undernutrition and dehydration. While maternal stress and malnutrition of pregnancy are linked to poor neonatal outcome and associated with poor adult health, long-term outcome of fetal exposure to HG has never been explored. The purpose of this study is to determine whether long-term emotional and behavioral diagnoses may be associated with fetal exposure to HG. Emotional and behavioral diagnoses of adults born of a pregnancy complicated by HG were compared to diagnoses from non-exposed controls. Offspring exposed to HG in utero were significantly more likely to have a psychological and behavioral disorder (OR = 3.6, P < 0.0001) with diagnoses primarily of depression, bipolar disorder and anxiety. In utero exposure to HG may lead to increased risks of psychological and behavioral disorders in the offspring.

23. *J Matern Fetal Neonatal Med.* 2011 Nov;24(11):1307-11.

Posttraumatic stress symptoms following pregnancy complicated by hyperemesis gravidarum.

Christodoulou-Smith J, Gold JI, Romero R, Goodwin TM, Macgibbon KW, Mullin PM, Fejzo MS

Abstract

OBJECTIVE: Hyperemesis gravidarum (HG) can be accompanied by severe physical and emotional distress. Most studies have focused on the physical and psychological stress associated with this condition during the affected pregnancy. This study explores posttraumatic stress symptoms (PTSS) and negative life outcomes following HG pregnancies.

METHODS: A total of 610 women (HG = 377 and control = 233) were recruited and completed an online survey. χ -square analyses were used to compare the HG and control groups on various life outcome variables.

RESULTS: Eighteen percent of women with HG reported full criteria PTSS (n = 68). Negative life outcomes regarding financial and marital status, career, as well as psychological and physical well-being differed significantly for the HG groups compared to the control group ($0.001 < p < 0.05$).

CONCLUSIONS: PTSS is common following HG pregnancies and is associated with negative life outcomes including inability to breastfeed, marital problems, financial problems, and inability of self-care.

24. *J Midwifery Womens Health*. 2011 Mar-Apr;56(2):132-6.

Recurrence risk of hyperemesis gravidarum.

Fejzo MS, Macgibbon KW, Romero R, Goodwin TM, Mullin PM

Abstract

INTRODUCTION: The purpose of this study is to describe the recurrence risk for hyperemesis gravidarum.

METHODS: Women who registered on a Web site sponsored by the Hyperemesis Education and Research Foundation as having had one HG-complicated pregnancy were contacted to follow-up on a subsequent pregnancy. Participants completed an online survey.

RESULTS: One hundred women responded. Fifty-seven had become pregnant again, 2 were trying to conceive, 37 were not willing to get pregnant again because of HG, and 4 did not have a second pregnancy for other reasons. Among the 57 women who responded that they had become pregnant again, 81% reported having severe nausea and vomiting in their second pregnancy. Among the women reporting recurrent HG, 98% reported losing weight and taking prescribed medication for HG, 83% reported treatment with intravenous fluids, 20% reported treatment with total parenteral nutrition or nasogastric tube feeding, and 48% reported hospitalization for HG.

DISCUSSION: This study demonstrates both a high recurrence rate of HG and a large percentage of women who change reproductive plans because of their experiences with HG.

25. *Am J Obstet Gynecol*. 2011 Mar;204(3): 230.e1-7.

Familial aggregation of hyperemesis gravidarum.

Zhang Y, Cantor RM, MacGibbon K, Romero R, Goodwin TM, Mullin PM, Fejzo MS

Abstract

OBJECTIVE: This study was undertaken to determine whether there is familial aggregation of hyperemesis gravidarum (HG), making it a disease amenable to genetic study.

STUDY DESIGN: Cases with severe nausea and vomiting in a singleton pregnancy treated with intravenous hydration and unaffected friend controls completed a survey regarding family history.

RESULTS: Sisters of women with HG have a significantly increased risk of having HG themselves (odds ratio, 17.3; $P = .005$). Cases have a significantly increased risk of having a mother with severe nausea and vomiting; 33% of cases reported an affected mother compared to 7.7% of controls ($P < .0001$). Cases reported a similar

frequency of affected second-degree maternal and paternal relatives (18% maternal lineage, 23% paternal lineage).

CONCLUSION: There is familial aggregation of HG. This study provides strong evidence for a genetic component to HG. Identification of the predisposing gene(s) may determine the cause of this poorly understood disease of pregnancy.

26. *J Womens Health (Larchmt)*. 2009 Dec;18(12):1981-7.

Symptoms and pregnancy outcomes associated with extreme weight loss among women with hyperemesis gravidarum.

Fejzo MS, Poursharif B, Korst LM, Munch S, MacGibbon KW, Romero R, Goodwin TM

Abstract

OBJECTIVE: To report the weight loss and associated symptoms experienced by a large cohort of women with hyperemesis gravidarum (HG).

METHODS: Data were obtained from an HG website registry, where women with HG were recruited on-line. Respondents were included if they experienced at least 1 live birth >27 weeks' gestation. Extreme weight loss was defined as a loss of >15% of prepregnancy weight.

RESULTS: Of the 819 women surveyed, 214 (26.1%) met criteria for extreme weight loss. These women were twice as likely to be Hispanic or nonwhite. Extreme weight loss ($p < 0.001$) was associated with indicators of the severity of HG, such as hospitalization and use of parenteral nutrition, and with multiple symptoms during pregnancy, such as gallbladder and liver dysfunction, renal failure, and retinal hemorrhage. Among all women surveyed, 22.0% reported that symptoms lasted throughout pregnancy; this finding was nearly twice as likely among women with extreme weight loss: 63 of 214 (29.4%) vs. 117 of 605 (19.3%) (OR=1.73, 95% CI 1.2-2.5, $p=0.003$). For some women, symptoms continued postpartum and included food aversions, muscle pain, nausea, and posttraumatic stress. Approximately 16% of babies were born prematurely, and 8% reportedly weighed <2500 g. Among women with extreme weight loss, 9.3% reported having a child with a behavioral disorder.

CONCLUSIONS: Extreme weight loss is common among women with HG, suggesting that HG is a form of prolonged starvation in pregnancy and that the long-term effects of this condition on women and their offspring warrant further investigation.

27. *Eur J Obstet Gynecol Reprod Biol*. 2008 Nov;141(1):13-7.

High prevalence of severe nausea and vomiting of pregnancy and hyperemesis gravidarum among relatives of affected individuals.

Fejzo MS, Ingles SA, Wilson M, Wang W, MacGibbon K, Romero R, Goodwin TM

Abstract

OBJECTIVE: The goal of this study was to determine the prevalence of severe nausea and vomiting of pregnancy/hyperemesis gravidarum among relatives of affected individuals.

STUDY DESIGN: Family history data were obtained on 1224 self-reported cases of hyperemesis gravidarum. Cases completed an online survey administered by the Hyperemesis Education and Research Foundation between 2003 and 2006.

RESULTS: Approximately 28% of cases reported their mother had severe nausea and vomiting or hyperemesis gravidarum while pregnant with them. Of the 721 sisters with a pregnancy history, 137 (19%) had hyperemesis gravidarum. Among the most severe cases, those requiring total parenteral nutrition or nasogastric feeding tube, the proportion of affected sisters was even higher, 49/198 (25%). Nine percent of cases reported having at least two affected relatives including sister(s), mother, grandmother, daughters, aunt(s), and cousin(s).

CONCLUSION: There is a high prevalence of severe nausea and vomiting of pregnancy/hyperemesis gravidarum among relatives of hyperemesis gravidarum cases in this study population. Because the incidence of hyperemesis gravidarum is most commonly reported to be 0.5%, this study provides strong but preliminary evidence for a genetic component to extreme nausea and vomiting of pregnancy.

28. *Am J Perinatol.* 2008 Mar;25(3):141-7.

Secular trends in the treatment of hyperemesis gravidarum.

Goodwin TM, Poursharif B, Korst LM, MacGibbon KW, Romero R, Fejzo MS

Abstract

The purpose of this study was to describe the treatment of women with hyperemesis gravidarum (HG). Women with HG pregnancies of at least 27 weeks duration occurring between 1985 and 2004 described their treatment on an HG website from 2003 to 2005. The usage and effectiveness of > 20 treatment options were reported by 765 women for 1193 pregnancies. The women who used intravenous (IV) hydration, serotonin inhibitors, and parenteral nutrition (PN) reported the highest rates of effectiveness, with 84%, 83%, and 79% reporting that these respective treatments may have contributed to decreased nausea/vomiting. The use of conventional treatments increased from 20 to 30% to > 60% between 1985 and 1989 and 2000 and 2004; serotonin inhibitor use increased to 55% after its introduction in the 1990s. Over the past 20 years, multiple treatments have been used for women with HG, with a trend toward treatment with reportedly more effective modalities, such as IV hydration and serotonin inhibitors.

29. *Contraception.* 2007 Dec;76(6):451-5. Epub 2007 Nov 9.

Elective pregnancy termination in a large cohort of women with hyperemesis gravidarum.

Poursharif B, Korst LM, Macgibbon KW, Fejzo MS, Romero R, Goodwin TM

Abstract

BACKGROUND: This study was conducted to describe characteristics of women who terminated their pregnancies secondary to hyperemesis gravidarum (HG).

STUDY DESIGN: Data were obtained from a survey provided on an HG Web site from 2003 to 2005.

RESULTS: Of 808 women who completed the survey, 123 (15.2%) had at least one termination due to HG, and 49 (6.1%) had multiple terminations. Prominent reasons given for the terminations were inability to care for the family and self (66.7%), fear that they or their baby could die (51.2%), or that the baby would be abnormal (22.0%). These same women were three times as likely to state that their health care providers were uncaring or did not understand how sick they were [64/123 (52.0%) vs. 168/685 (24.5%), odds ratio 3.34 (95% CI 2.21-5.05), $p < .001$].

CONCLUSION: These data suggest that the physical and psychological burden of HG has been underestimated, and that further education within the medical community may be warranted.

30. *J Perinatol.* 2008 Mar;28(3):176-81. Epub 2007 Dec 6.

The psychosocial burden of hyperemesis gravidarum.

Poursharif B, Korst LM, Fejzo MS, MacGibbon KW, Romero R, Goodwin TM

Abstract

OBJECTIVE: To describe the psychosocial burden of hyperemesis gravidarum (HG) in a large cohort of affected women, focusing on previously unreported problems.

STUDY DESIGN: Women with HG described their pregnancy history in an open-ended survey administered internationally through an HG website during 2003 to 2005.

RESULT: Of the 808 participants, 626 (77.5%) were American. A large majority (82.8%) reported that HG caused negative psychosocial changes, consisting of (1) socioeconomic changes, for example, job loss or difficulties, (2) attitude changes including fear regarding future pregnancies and (3) psychiatric sequelae, for example, feelings of depression and anxiety, which for some continued postpartum. Women who reported that their health-care provider was uncaring or unaware of the severity of their symptoms were nearly twice as likely to report these psychiatric sequelae (odds ratio 1.86, 95% confidence interval 1.06 to 3.29, $P = 0.032$).

CONCLUSION: Over 80% of a large cohort of women with HG reported that HG caused a negative psychosocial impact.

