

**The impact of and risk factors for HG: treatment, genetics and epidemiology.**

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Abstract.

We discuss our past and present research into the impact, risk factors, epidemiology and genetics of hyperemesis gravidarum, using data collected by the Hyperemesis Education and Research Foundation [www.helpher.org](http://www.helpher.org).

Main findings have suggested a large impact on women. Eighty percent of women reported a negative psychosocial impact. This finding was twice as likely to be seen in women who reported an uncaring or unaware provider. Fifteen percent of women who wanted to remain pregnant terminated, with the primary reason being “no hope for relief”. This suggests a critical need for better treatment options. Treatment options indicate the use of Zofran and intravenous fluids. Only one third of women are offered vitamins, raising the concern for risk of Wernicke's Encephalopathy.

A study of the symptoms and outcomes of extreme weight loss showed women with greater than 15% pre-pregnancy weight loss (26% of cases) experienced multiple physical and emotional sequelae. Additionally, 22% reported symptoms lasting through pregnancy and 9.3% reported a behavioral disorder in their child.

Patients with a history of HG had similar symptoms during egg stimulation and were at increased risk of developing ovarian hyperstimulation syndrome. A link between HG and increased fertility suggests an ovarian component to HG. High prevalence among relatives of affected individuals suggests a genetic component to HG making it amenable to genetic studies.

Ongoing studies of our cohort include learning, emotional, and behavioral disorders in children and adults exposed to HG in utero, post-traumatic stress disorder, early treatment and outcome, and identification and analysis of susceptibility genes for HG.

A large cohort of women with HG revealed 15% of cases terminated wanted pregnancies with the primary reason being “no hope for relief,” suggesting a critical need for better treatment options.

Secular trends in the treatment of HG indicated Zofran and intravenous fluids are most effective. Only a third of women were treated with vitamins, raising the concern for risk of Wernicke's Encephalopathy.

Investigation into the psychosocial burden of HG showed 80% of women reported a negative psychosocial impact. This finding was twice as likely to be seen in women who reported an uncaring or unaware provider.

A study of the symptoms and outcomes of extreme weight loss in HG showed women with greater than 15% pre-pregnancy weight loss (26% of cases) experienced multiple physical and emotional sequelae. Additionally, 22% reported symptoms lasting through pregnancy and 9.3% reported a behavioral disorder in their child.

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Herein we review our analyses of survey data collected by the Hyperemesis Education and Research Foundation [www.helpsher.org](http://www.helpsher.org) and provide an update of our current progress in the Genetics and Epidemiology of Hyperemesis Gravidarum Study.

### **Pregnancy Termination**

Poursharif, Korst, MacGibbon, Fejzo, Romero, Goodwin (2007) determined the characteristics of women who terminated secondary to HG. Eight hundred and eight women from 23 countries participated in an online survey. The termination rate ranged from 14.4% in the United States to 19.2% in the United Kingdom, with 123 (15.2%) reporting at least one termination due to HG and 49 (6.1%) reporting multiple terminations. Among those who terminated, 39.8% reported between 2 and 10 terminations due to HG. Main reasons given were no hope for relief (87%), inability to care for the family and self (66.7%), emotional distress (60.2%), fear that they or their baby could die (51.2%), inability to work (39.8%), no help from healthcare provider (36.6%), no help from treatment (25.2%), and/or fear that the baby would be abnormal (22.0%). Women who terminated due to HG were three times as likely to state that their health care providers were uncaring or did not understand how sick they were, and were significantly less likely to be treated with ondansetron (Zofran). Finally, many women with HG had reported fewer problems in subsequent pregnancies, not only because they knew what to expect but also because they were treated much earlier. Lack of insurance coverage for HG hospitalizations and for medication (Zofran) was also raised by a number of women. These data suggest that there is a critical need for further education within the medical community and further research into effective affordable treatment options to avoid termination due to HG.

### **Trends in Treatment**

Goodwin, Poursharif, Korst, MacGibbon & Fejzo (2008) described the treatment of women with HG from 1985 to 2004. Overall 765 women from 26 countries

with HG pregnancies of at least 27 weeks duration reported usage and effectiveness of more than 20 treatment options for 1193 HG 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 more than 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. The least effective treatments (less than 20%) were trimethobenzamide and the majority of alternative approaches. Of particular concern, 67% of women with HG in the United States, and as many as 90% of women with HG in the United Kingdom, did not report being prescribed vitamins such as pyridoxine and thiamine during the critical period of fetal development when HG commonly presents. Pyridoxine is known to be safe and one of the few agents for which randomized controlled trials have confirmed its efficacy in reducing symptoms in general NVP (Sahakian, Rouse, Sipes, et al., 1991; Vutyavanich, Wongtra-ngan & Ruangsri, 1995). Thiamine has been recommended for all women with more than 3 weeks of daily vomiting because this is associated with Wernicke's encephalopathy (ACOG, 2004), which can lead to permanent maternal neurological dysfunction and death of the fetus or mother (Selitsky, Chandra & Schiavello, 2006). Although we found an increasing use of these vitamins from 17% in 1985–1989 to 33% in 2000–2004, there is still significant underutilization. More research regarding the safety and effectiveness of different medications for HG treatment and more education about the prevention of severe complications of HG with administration of vitamins/B6 therapy is warranted.

### **Psychosocial Burden**

Poursharif, Korst, MacGibbon, Fejzo, Romero & Goodwin (2007) described the

psychosocial impact of HG. Overall, 808 women from 23 countries reported on life changes secondary to HG in an online survey. Social isolation, problems relating to other family members and marital problems were frequently mentioned. Most women surveyed (76.0%) reported changes in their plans for future childbearing. Many (19.4%) developed a fear of pregnancy, and some specifically developed a fear of having sex. Over one-third (34.8%) changed their mind regarding or considered limiting the number of children they planned to conceive, and several used adoption or surrogacy to reach their family goals. Overall, 28.7% of women reported that their health-care providers were either uncaring or did not understand how sick they were. Overall, investigation into the psychosocial burden of HG showed 80% of women reported a negative psychosocial impact. This finding was twice as likely to be seen in women who reported an uncaring or unaware provider, and is confirmed by Munch & Schmitz (2006), who stated that a major factor in patient satisfaction was that caregivers understand and appreciate that HG is a disease state that was not caused by the patient herself. Given that the cause of HG is currently unknown and long-term outcome has not been well studied, insistence by caregivers that it is caused by pregnancy rejection, hysteria, or that the patient is “faking it” can only have a negative impact. Education of the medical community regarding sensitivity to patients is imperative and is likely to improve the psychosocial consequences of HG.

### **Extreme Weight Loss**

Fejzo, MacGibbon, Korst, Romero & Goodwin (2009) reported extreme weight loss and associated symptoms in a large cohort of women with HG. Among 819 women, 26% reported losing more than 15% of their pre-pregnancy weight (extreme weight loss). These women were twice as likely to be Hispanic or nonwhite, have symptoms lasting throughout the entire pregnancy, and to change doctors. They were also more likely to be hospitalized and use parenteral nutrition, and have multiple symptoms such as gallbladder and liver dysfunction, renal failure, and retinal hemorrhage.

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 less than 2500g. Among women with extreme weight loss, 9.3% reported having a child with a behavioral disorder. 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.

### **Hyperemesis and Ovarian Hyperstimulation Syndrome**

Fejzo, Romero & Goodwin (2009) described three interesting cases in a cohort of women with hyperemesis gravidarum. Three women with a history of HG experienced similar symptoms during egg stimulation, 22-30 mature oocytes in one cycle, high estrogen levels and ovarian hyperstimulation syndrome. There are several interesting points to be made with this case series. First, all three patients had symptoms similar to HG while not pregnant and before treatment with chorionic gonadotropin, suggesting that for these patients, the pregnancy state, and more notably, chorionic gonadotropin is not the likely cause of their severe nausea and vomiting during pregnancy. Second, all three patients reported that their surrogates had normal nausea during pregnancy. Thus, surrogates are not likely at an increased risk of severe nausea and vomiting while carrying a fetus with a maternal history of HG, even in the case of carrying female twins. This suggests a maternal genetic component, possibly ovarian rather than fetal or placental in origin, may be causal. Interestingly, the high number of mature follicles also suggests a new theory to explain why HG has not been removed by natural selection, despite its obvious reproductive disadvantage. Until the introduction of IV fluid treatment in the 1950s, HG was a common cause of maternal and fetal death, making its existence during pregnancy an evolutionary enigma. Perhaps extreme nausea during pregnancy is coupled with an increase in healthy follicles or ovarian reserve, resulting in an

overall fertility advantage that surpasses the hereditary disadvantage historically caused by maternal and fetal death, extreme weight loss, malnutrition, prolonged dehydration, Wernicke's encephalopathy, and fetal growth restriction. Several lines of evidence support a genetic predisposition to nausea and vomiting during pregnancy. It is therefore possible that in finding the genes predisposing to HG, one may simultaneously identify genes that contribute to increased fertility and more successful ovarian stimulation. Finally, practitioners and caretakers of patients undergoing follicle stimulation for HG should be wary of ovarian hyperstimulation syndrome in patients with a history of HG. A family history of HG should also be taken into consideration, as HG has been shown to cluster in families. Overall, this case series provides lessons in IVF for women with a history of HG and their surrogates, as well as insight into the cause of HG and its potential role in fertility.

Genes predisposing to HG and their potential link to increased fertility merit further investigation.

### **Genetics of HG**

Mounting evidence suggests a genetic component to HG. Firstly, in the only study of NVP in twins, concordance rates were more than twice as high for monozygotic compared to dizygotic twins (Corey, Berg, Solaas, & Nance, 1992). Secondly, several investigators have noted that siblings and mothers of patients affected with NVP and HG are more likely to be affected than siblings and mothers of unaffected individuals (Gadsby, Barnie-Adshead & Jagger, 1997; Vellacott, Cooke & James, 1988). Thirdly, the higher frequency of severe NVP in patients with certain genetically determined conditions such as defects in taste sensation (Sipiora, Murtaugh, Gregoire & Duffy, 2000; Bartoshuk, Duffy, Reed & Williams, 2002), glycoprotein hormone receptor defects (Rodien, Bremont, Raffin Sanson, et al., 1998; Akerman, Zhenmin, Rao & Nakajim, 2000; Rodien, Jordan, Lefevre, et al., 2004), or latent disorders in fatty acid transport or mitochondrial oxidation (Innes, Seargeant, Balachandra, et al., 2000; Outlaw & Ibdah, 2005),

suggests that some portion of HG cases may be related to discrete, genetically transmitted disease states that are unmasked or exacerbated in pregnancy. A high risk of recurrence after a previous HG pregnancy as well as evidence for a 3-fold increased risk for HG in daughters of mothers with a history of HG are studies consistent with a genetic component to HG (Fejzo, MacGibbon, Romero & Goodwin, in press; Vikanes, Skjaerven, Grijbovski, Gunnes, Vangen & Maguns, 2010). Additionally, we find, approximately 28% of cases reported their mother had severe nausea and vomiting or hyperemesis gravidarum while pregnant with them (Fejzo et al., 2009). Of the 721 sisters with a pregnancy history, 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, 25%. Nine percent of cases reported having at least two affected relatives including sister(s), mother, grandmother, daughters, aunt(s), and cousin(s). And more recently, in a case-control study using a separate dataset, we found sisters of women with Hyperemesis Gravidarum have a significantly increased risk of having Hyperemesis Gravidarum themselves (OR=17.3, p=0.005; Zhang, Cantor, MacGibbon, Romero, Goodwin, Mullin & Schoenberg Fejzo, in press).

To conclude, through extensive online surveys conducted on a large cohort of women with HG, we have shown there is a critical need for more education of the medical community and increased research to identify the cause and ultimately more effective treatments for HG. Our study on the Genetics and Epidemiology of HG is underway to identify the predisposing genes and environmental risk factors resulting in this devastating disease in pregnancy. In this study, we are collecting saliva samples and survey data on 1,000 cases and 1,000 controls. Currently we have been contacted by over 2,100 potential participants, among which we have identified over 1,000 eligible cases who have referred over 500 eligible controls. Enrollment is ongoing. Future work includes a genome-wide association study of affected and unaffected women and analysis of survey data. Projects in the recent future include long-term outcome of HG-exposed offspring,

risk factors for Post-Traumatic Stress Disorder (PTSD) in women with HG, and potential effect of pre-existing conditions and time of first treatment on duration of symptoms and maternal and fetal outcomes.

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