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Logistic Regression Models and Diagnostics for Adverse Outcomes in Patients with Hyperemesis Gravidarum

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Logistic Regression Models and Diagnostics for Adverse Outcomes in Patients with Hyperemesis Gravidarum

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of the requirements for the degree

Doctor of Philosophy in Statistics

by

Aromalyn Latag Magtira

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Abstract of the Dissertation

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Aromalyn Latag Magtira

Doctor of Philosophy in Statistics

University of California, Los Angeles, 2015

Professor Frederic Paik Schoenberg, Chair

Logistic regression has been widely employed in the life sciences where the response variable of interest is the presence or absence of some characteristic or condition. Despite the popularity of logistic regression approaches and the simplicity that comes with implementing methods in software, the tools in place for model evaluation remain rather limited. Here we explore goodness-of-fit assessment for logistic regression models. In particular, following a review of numerical summaries such as likelihood ratio tests, Hosmer-Lemeshow tests, information criteria, and residual deviance, we focus on plots of fitted versus actual percentages and explore how the power of such graphical tests appears to depend on the choice of bin size.

The dissertation of Aromalyn Latag Magtira is approved.

Marlena Fejzo

Ying Nian Wu

Stuart Schweitzer

Hongquan Xu

Frederic Paik Schoenberg, Committee Chair

University of California, Los Angeles

2015

To my mother,

who has carried the burdens of our family.

Ang tagumpay na ito, ay para sayo

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Vita

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Publications

Marlena Fejzo, Aromalyn Magtira, Frederic Schoenberg, Kimber MacGibbon, Patrick Mullin, Roberto Romero, KhalilTabsh. Antihistamines and other prognostic factors for adverse outcome in hyperemesis gravidarum. European Journal of Obstetrics and Gynecology. 2013; 28 May 2013 (10.1016/j.ejogrb.2013.04.017)

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CHAPTER 1

Introduction

1.1 Hyperemesis Gravidarum

Hyperemesis Gravidarum (HG) is a severe form of nausea and vomiting of pregnancy (NVP) which accounts for over 285,000 hospital discharges in the U.S. annually [1]. Often resulting in dehydration and nutritional deficiency, HG can also lead to Wernicke's encephalopathy and even maternal and fetal death if left untreated [2, 3, 4]. Affected patients are usually treated with intravenous (IV) hydration and antiemetic therapy; however, when ineffective, about 25% of HG patients can experience weight loss of more than 15% of pre-pregnancy weight while about 15% resort to therapeutic termination [5]. In 22% of cases, symptoms last the entire pregnancy [6].

The thalidomide treatment that resulted in the tragedy in the 1960's resulted in HG patients treated with thalidomide giving birth to infants with limb deformities [7]. Because of this, pharmaceutical companies have generally steered away from developing new therapies and studies of effectiveness. The Cochrane Review of interventions for NVP had concluded that there is a lack of high quality evidence to support the efficacy of any intervention that could effectively treat the risks of NVP. Little is known about the etiology of the disease, but the risk HG imposes on maternal and fetal health remains a very important question for any HG patient and their families.

Many theories on the cause of HG are tested every year; however, research still remains inconclusive. Past research has suggested that HG could be linked to toxins, ulcerations, or infection in a related organ or abnormalities of the female reproductive system [8]. In the early 20th century, a psychological cause was proposed by those subscribing to psychoanalytic theories [8]. Despite the lack of evidence to support claims of a psychoanalytic component to HG, and the fact that some early reports suggesting such a link have been effectively debunked, HG is still sometimes perceived as a psychological disorder among some medical professionals [9]. Despite the evidence showing many contributing factors to HG unrelated to psychological conflicts, this belief has permeated the community of health professionals, and has often led to a lack of appropriate care, even in severe cases.

The actual proportion of affected women in the US, as suggested by hospital records, is likely to be several times greater. Reported cases only account for those treated as inpatients, not those treated at home or in outpatient/urgent care facilities. The cost of health care can also be problematic during a pregnancy and can be the reason an HG patient is not admitted.

The lack of funding in hyperemesis research poses limitations in studies such as ours. Small sample sizes and sparse data sets can be a common challenge, making it difficult to conduct high-quality studies with decisive results. Our data is largely based off of self-reported internet survey questions which have the potential to be affected by many types of biases, including non-response bias, coverage problems, and a sample that is wealthier, more highly educated, and with more extreme symptoms than the overall population of HG sufferers. In order for studies to adequately represent the affected population of this understudied disease, there

is a need for larger studies and more sophisticated methods of data collection. The goal of our study is to investigate recurrence rates, symptoms, treatments, and risks that appear to be associated with HG so that they might be potential targets for future study.

However, new findings are now supporting the idea that HG is a complex disease that is likely caused by multiple factors. In Chapter 2 we present our findings for prognostic factors for adverse fetal outcomes (AFO) amongst HG patients and controls along with a follow up study. Studies have demonstrated psychiatric factors to not be a significant factor for HG. We explore this in the context of recurrence risk in Chapter 3.2. Chapters 4 and 5 provide the results of a child follow-up study on neurodevelopmental delays and long-term health effects in children exposed to HG in utero. Finally, Chapter 6 gives a general discussion of our algorithm applied to some of the variables used in our study as well as some concluding remarks on the direction of future work.

1.2 Data and Study Design

This study is part of a larger investigation evaluating the genetics and epidemiology of HG. Eligible patients were primarily recruited through advertising on the HER Foundation website at www.HelpHer.org between 2007 and 2014. The website receives over 80,000 unique visitors per month with the primary search term being hyperemesis gravidarum, making it one of the most visited sites on the disease and an excellent resource for recruitment. The inclusion criteria for cases were a diagnosis of HG in their first pregnancy and treatment with IV fluids and/or total parenteral nutrition (TPN)/nasogastric feeding tube, independent of hospitalization (because some treatments were given to patients in an outpatient setting). Each case was asked to recruit a friend with at least 2 pregnancies that

went beyond 20 weeks to participate as a control. Controls were eligible if they experienced normal (did not interfere with their daily routine) or no NVP, no weight loss due to nausea/vomiting and no medical attention due to NVP.

Relatives of participants were not included in the study as the case-controls study depends on non-relatedness of individuals in the study. Minors (under 18 years of age) were not included in the study because few teens are expected to fit the study criteria for controls of having had two pregnancies, and it would be difficult to justify the risks/benefits to normal control minors. Because multiple gestations or chromosome abnormalities may be associated with HG due to unique physiological pathways, women with these types of pregnancies were also excluded. Participants whose first pregnancies did not last beyond 20 weeks were also excluded because fetal outcomes beyond 20 weeks gestation are the focus of this study.

Participants were asked to submit their medical records and complete an online survey regarding symptoms, treatments, and outcomes. The majority of participants, both cases and controls, joined the study and began the survey during their pregnancies and were automatically prompted to complete the survey on outcome following their due date. All subjects are from the USA. This study has been approved by Institutional Review Boards, USC IRB # HS-06-00056 and UCLA IRB $\#09-08-122-01A$

The socioeconomic (SES) statuses of each subject were determined using the US Census Bureau site [10]. Only US residents were included. Subjects were categorized as low, medium, and high according to the zip code they provided. Subjects were considered to be of low SES if they lived in an area that had a median income below $35,000$, medium SES if the median income was between $'35,000$ and

75,000, and of high SES if the median income were at least 75,000. The sites `http://zipwho.com/` and `http://www.zipdatamaps.com/` were used to determine the median income of an area.

In the initial and follow-up adverse fetal outcomes studies the inclusion criteria were the following:

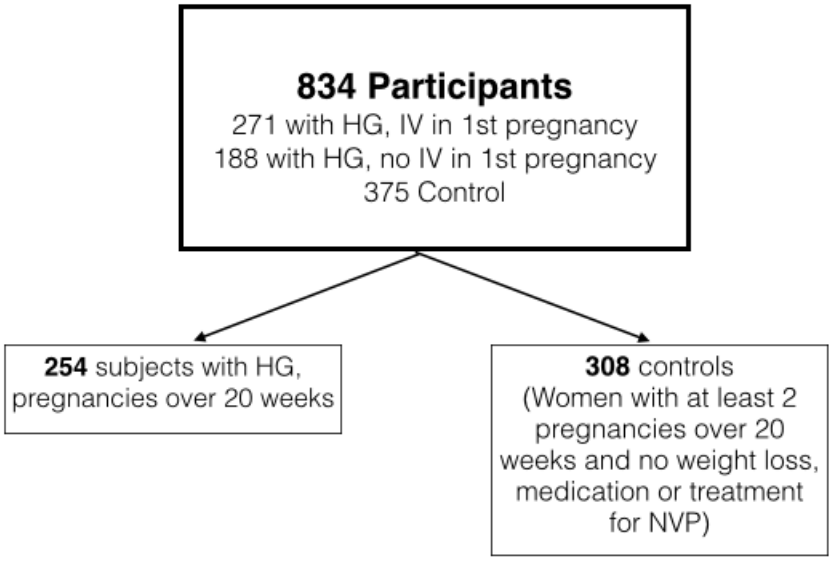


Figure 1.1: Sample for adverse fetal outcome studies

In our recurrence studies only women between the age of 18 and 50 who had at least two pregnancies that lasted beyond the second trimester and did not have multiple or chromosomally abnormal gestations were included in this analysis. In the survey, participants were asked to rate the severity of their NVP of each pregnancy by selecting a number from one to five, with five being the most severe, as follows:

1.No NVP

2.Very little NVP

3.Typical NVP

4.More severe morning sickness

5.HG

The inclusion criteria were those who required IV fluid treatment for dehydration due to HG and reported an NVP rating of 4 or 5 in their first pregnancy. Recurrent pregnancies, defined as having IV fluid treatment and an NVP rating of 4 or 5 in the second pregnancy, were compared to those who had no IV fluid treatment and an NVP rating of 1, 2, or 3 in the second pregnancy.

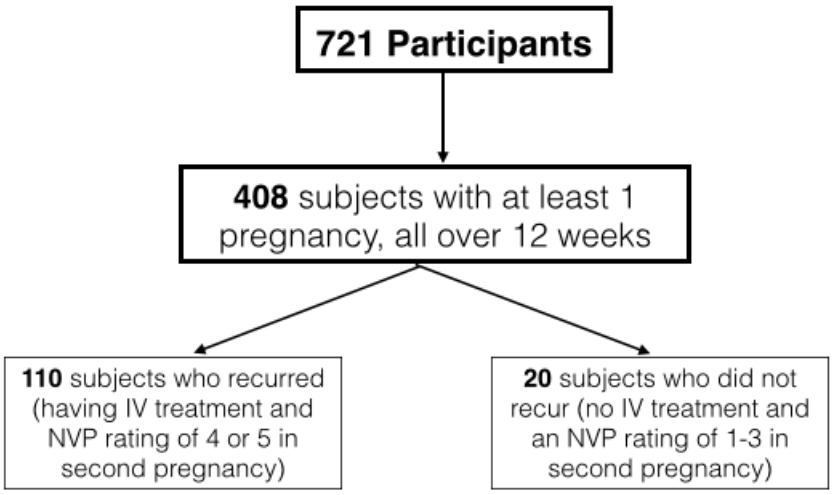


Figure 1.2: Sample for recurrence studies

Both child outcome studies used the same samples:

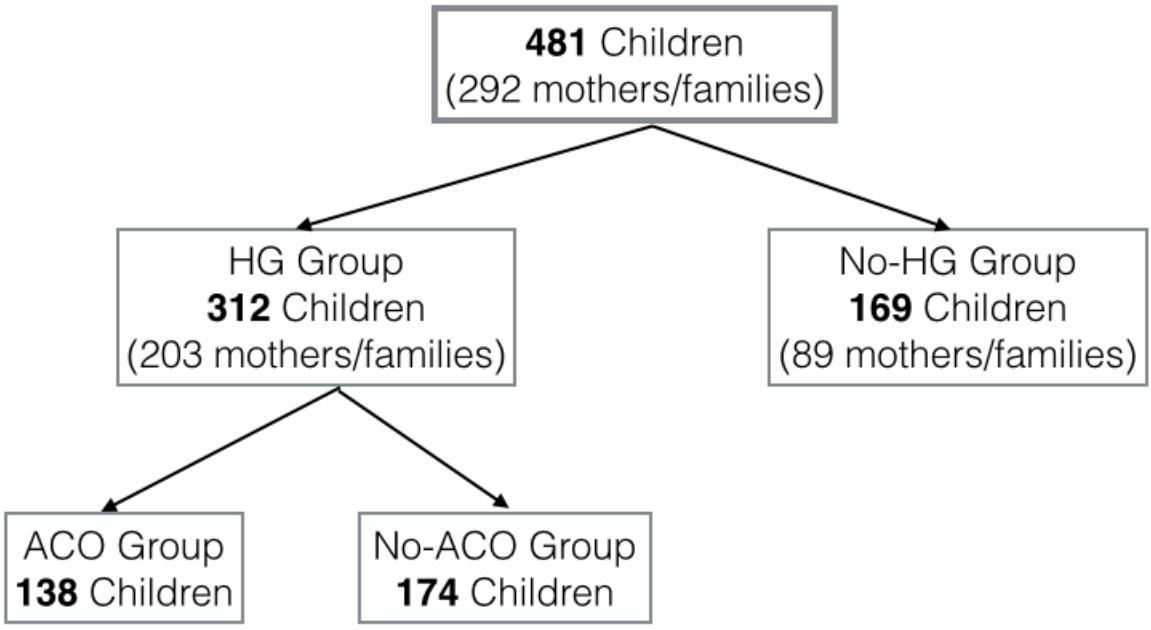


Figure 1.3: Sample for adverse child outcome studies

1.3 Logistic Regression

The popularity of logistic regression, especially in the life sciences, has increased over the last several years. By means of regression the influence of at least one predictor on a response variable, particularly the presence or absence of a condition, can be investigated. In our studies the response variables of interest were the presence of an adverse fetal outcome, recurrence of HG, and an adverse child outcome.

Goodness of fit tests help determine if a model is correctly specified. Common diagnostics for logistic regression models include the Hosmer-Lemeshow test, the Pearson Chi-Square statistics and deviance residuals, classification or contingency tables, and the Receiver Operating Characteristic (ROC) curve. In viewing residuals, we look at the difference between observed and expected values just like in linear regression. However, since the data and the residuals are discrete, plots

of raw residuals from a logistic regression are generally not useful. The binned residuals plot instead, after dividing the data into categories (bins) based on their fitted values, plots the average residual versus the average fitted value for each bin. This visual is usually viewed with a 95% bound in order to give insight on the classification of the model.

1.4 Power Analysis

In this study we explore an alternate way to view fitted values and observed proportions through a power analysis on a specific bin size. Instead of just viewing a plot of the entire data we select a particular bin and quantify the similarities through a power analysis to see if the given alternate model yielded predictions that were statistically significantly different than the observed data.

We start with the logistic model:

$$p(x) = P(Y = 1|x) = \frac{e^{\beta_0+\beta_1 x}}{1 + e^{\beta_0+\beta_1 x}} = \frac{1}{1 + e^{-(\beta_0+\beta_1 x)}}$$

The logit transformation is as follows, where $g(x)$ has the desirable properties of a linear regression model:

$$g(x) = \ln\left[\frac{p(x)}{1 - p(x)}\right] = \beta_0 + \beta_1 x$$

$g(x)$ here is continuous and depending on the range of the predictor, x, can take on any value from $-\infty$ to $+\infty$. We define the following:

- m: number of observations
- s: number of simulations
- u: proportion of interest

•h: bandwidth around u

•β_0, β_1: coefficients for the true model

•β_{0A}, β_{1A}: coefficients for the alternate model

•*obs.prop*: observed proportion of 1's in a particular bin, $u \pm h$:

$$\frac{\sum(y=1)[p^{(s)} \in (u \pm h)]}{length(p^{(s)} \in (u \pm h))}$$

•*reject*: number of rejections for true model

•$reject_A$: number of rejections for alternate model

$reject = 0$ and $reject_A$ are initialized to zero. To begin the power analysis we pick a bin, $u \pm h$. For the s^{th} simulation:

•Define the true model

–Using β_0 and β_1 generate $x_1^{(s)}, \ldots, x_m^{(s)}$ and $y_1^{(s)} \ldots, y_m^{(s)}$

•Define the alternate model.

–Using β_{0A} and β_{1A} we have $p_A(x) = \dfrac{e^{\beta_{0A}+\beta_{1A}x}}{1+e^{\beta_{0A}+\beta_{1A}x}} = \dfrac{1}{1+e^{-(\beta_{0A}+\beta_{1A})}}$

•On the true model:

–Perform a binomial test on $obs.prop = \dfrac{\sum(y=1)[p^{(s)} \in (u \pm h)]}{length(p^{(s)} \in (u \pm h))}$ on mean$(p^{(s)} \in (u \pm h))$

–If $p < 0.05$, $reject = reject + 1$

•To test the performance on the alternate model:

–Perform a binomial test on *obs.prop* using mean of the fitted values in the bin, mean$(p_A^{(s)} \in (u \pm h))$

–If $p < 0.05$, $reject_A = reject_A + 1$

After the s simulations are complete the rejection rates are then $\frac{reject}{s}$ for the true model and $\frac{reject_A}{s}$ for the alternate model. The effect the choice of parameters such as sample size, number of simulations, choice of coefficients has on the behavior of power is discussed in Chapter 6.

CHAPTER 2

Adverse Fetal Outcome

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

2.1.1 Abstract

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

Study design: This is a case-control study in which outcomes of first pregnancies were compared between 254 women with HG treated with IV fluids and 308 controls. Prognostic factors were identified by comparing the clinical profile of patients with HG 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 HG 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 (which includes acupuncture, acupressure, and Bowen massage) was associated with a positive outcome ($p < 0.0089$). Poor outcomes were associated with early an

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 over 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

2.1.2 Results

All participants were Caucasian. Cases and controls were well-matched for age, SES, pre-existing hypertension, gestational diabetes, autoimmune disease, spontaneous labor, delivery method, and use of assisted reproduction (Table 2.1). Participants with HG were more likely to have gestational hypertension, immune problems, anxiety, bipolar disorder, and depression. These significantly different characteristics were rare, as less than 80% of participants in either group reported any of these characteristics prior to their first pregnancy. Carrying a female fetus was significantly more common in women with HG.

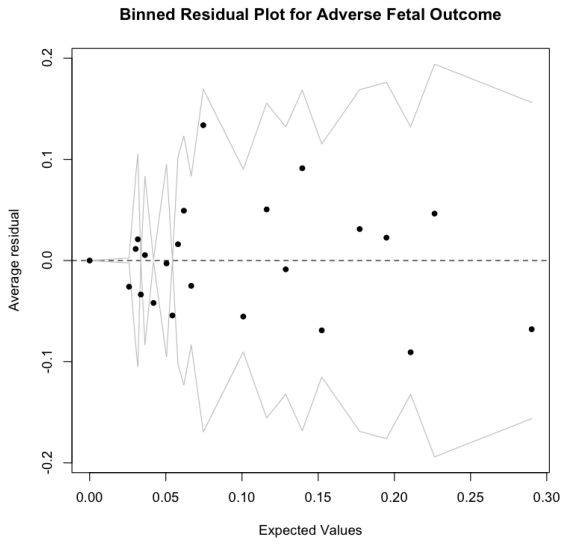
Response variables of interest were perinatal mortality, premature birth, fetal mortality, and adverse fetal outcome. AFO was defined as premature birth or births after 36 weeks where the baby was in the 10^{th} percentile for weight and/or

died at birth. The crude models used HG as a predictor:

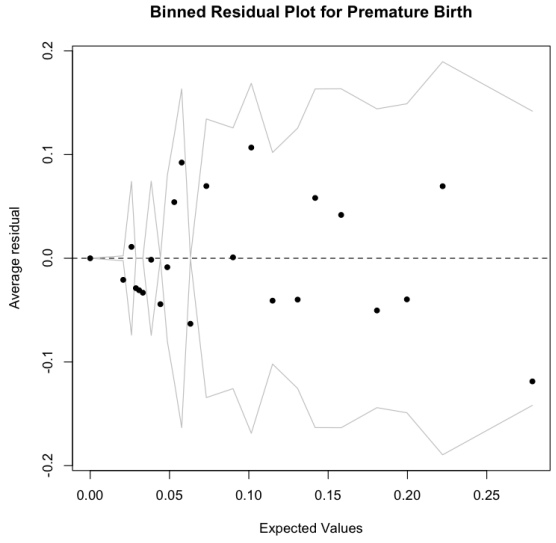
$$\widehat{logit(premature)} = -3.12 + 1.41 * HG \tag{2.1a}$$

$$\widehat{logit(AFO)} = -3.04 + 1.45 * HG \tag{2.1b}$$

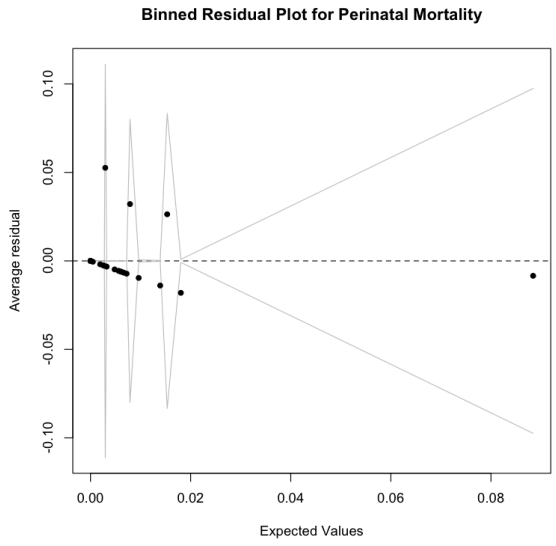
The adjusted models used HG, age, socioeconomic status, high blood pressure, diabetes, anxiety, bipolar disorder, depression, assisted reproduction, fetus gender as predictors. Binned plots of average fitted versus average residual values show about 95% of the data falling within two standard errors (Figures 2.2-2.4).


Binned Residual Plot for Adverse Fetal Outcome
Average residual
Expected Values
0.2
0.1
0.0
-0.1
-0.2
0.00
0.05
0.10
0.15
0.20
0.25
0.30

(2.2)


Binned Residual Plot for Premature Birth
Average residual
Expected Values
0.2
0.1
0.0
-0.1
-0.2
0.00
0.05
0.10
0.15
0.20
0.25

(2.3)


Binned Residual Plot for Perinatal Mortality
Average residual
Expected Values
0.10
0.05
0.00
-0.05
-0.10
0.00
0.02
0.04
0.06
0.08

(2.4)

Women with HG were significantly more likely to report lower birth weight and prematurity (< 37 weeks), and their overall rate of adverse fetal outcome AFO was 16.93% compared to 4.55% in controls (Table 2.2). There is a 4.28-fold increased risk of AFO in women with HG (OR 4.28 [2.34-8.30], adjusted OR 4.00 [2.11-7.97]). There was no significant difference in the rate of birth defects, perinatal mortality, nor weight below the 10th percentile, although all these rare events were slightly more common outcomes in the HG group.

All factors that were significantly different in women with HG compared to unaffected controls were analyzed in women with HG to determine whether those factors were also associated with poor outcome. With the exception of gestational hypertension, none of the significant maternal characteristics related to HG in Table 2.1, including psychiatric illness, immune problems and fetal gender, were found to have any significant influence on outcome in women with HG (Table 2.3).

To analyze potential associated factors further, we looked at the week symptoms began, the time of first treatment and treatment setting, and the week weight gain began. Among these, only NVP symptoms beginning at gestational age 3-4 weeks were significantly associated with poor outcome. Treatment as an outpatient (and not by home health care nor inpatient hospitalization) was associated with a positive outcome (Table 2.4).

We explored this further by comparing use of various medications and treatments in the two groups (43 HG participants with an adverse outcome compared to 211 HG participants with a good outcome). Among 36 medications/treatments, only alternative medicine was significantly associated with a positive outcome. Alternatively, promethazine, other antihistamines [diphenhydramine (Benadryl), dimenhydrinate (Gravol), doxylamine (Unisom), hydroxyzine (Vistaril/Atarax),

doxylamine and pyridoxine (Diclectin/Bendectin)], and methylprednisolone, were significantly associated with a poor outcome (Table 2.5).

We compared self-reported effectiveness of medications between those with adverse outcome and those with a favorable outcome to determine whether the medications were less effective for participants with poor outcome (which might suggest these cases are more severe and the poor outcome could be due to severity rather than the medication itself) (Table 2.5). The only treatments/medications self-reported to be effective in more than 50% of patients were cannabis, IV fluids, methylprednisolone, and ondansetron (Zofran), and there was no significant association between self-reported medication effectiveness and outcome for any medication including the medications associated with poor outcome (Table 2.5).

We examined use of TPN as well as mean weight loss in patients with and without factors associated with outcome, to determine whether these factors were also associated with severity (Table 2.6). Women treated as outpatients only (not inpatient nor home health care), were significantly less likely to be treated with TPN, suggesting this group is less severe and better associated outcomes may be related to milder symptoms for participants in this group. Participants treated with methylprednisolone were significantly more likely to be treated with TPN and women with HG taking promethazine lost significantly more weight, suggesting these patients may be more severely ill and that may be a factor in the link to poor outcome. No increased use of TPN nor increased weight loss were seen in the antihistamine group, in the gestational hypertension group, nor in the early NVP symptoms group, suggesting that disease severity (as defined by TPN treatment and/or weight loss) cannot explain the increased AFO in these groups.

2.1.3 Comment

This study focuses on the most extreme end of the NVP spectrum and shows a 4-fold increased risk of AFO in pregnancies complicated by HG. In line with these findings, two recent systematic reviews of published outcome data come to the same conclusion that HG is significantly associated with low birth weight, small for gestational age (SGA), and preterm birth [11, 12]. The risk of AFO reported in this study may be higher than other studies because this study may be biased toward women at the extreme end of the clinical spectrum of HG. Evidence for this comes from the high proportion of women (17%) treated with TPN. TPN is linked to a significant increase in serious complications including candida septicemia [13, 14], and in this study, though not quite reaching significance, 28% of TPN patients fell into the adverse outcome group compared to 15% in the control group. It is possible that TPN did not quite reach significance in this study because 85% of the women with HG were of middle or high income and thus more likely to have access to an advanced metabolic support team. While institutions lacking advanced metabolic support teams may have less favorable outcomes [13], we did not find a difference in AFO based on SES in this study (data not shown). Additionally, there is no universal standard in the medical community to determine when more aggressive nutritional therapy is recommended, possibly leading to variation in severity and TPN treatment. That being said, other indicators of severity, such as hospitalization and the week weight gain began, were also not found to be significant prognostic factors for adverse outcome: thus severity cannot completely explain the increased risk seen in this study. Of note, in a large study of HG and outcome from the Netherlands, Roseboom et al. also did not find any significant differences in outcome when restricting their analyses to the most severe cases that required hospitalization, and came to the conclusion that maternal characteristics largely explain the AFO in pregnancies affected by HG [15]. That study, however, adjusted for maternal characteristics by grouping

all characteristics (age, parity, SES, ethnicity, mode of conception, urbanization, substance abuse, hypertension, diabetes, psychiatric disease and sex of the baby) simultaneously. In our study we took each characteristic that was significantly different in our affected and unaffected groups separately and found that only the maternal characteristic gestational hypertension is significantly linked to adverse outcome. Our findings linking gestational hypertension to preterm birth are very similar to those of a recent publication by Spiegler et al. reporting on pregnancy risk factors for preterm birth, who found 28% hypertension in the adverse outcome group vs 8% in the control group (we find 28% vs 10%)[16]. Thus the connection between hypertension and HG pregnancies may explain, in part, the increased risk of poor fetal outcome.

Additionally, the study by Roseboom et al. reports a very similar percentage of adverse outcome in HG cases (16.9% in ours vs 17.9% in theirs)[15]. Therefore it appears that the difference between these two studies may not be in the cases but in the controls with adverse outcome (4.6% in our study vs 15.1% in theirs). In fact, the controls in our study are very similar to theirs with respect to percentages of perinatal mortality (0.65 vs 0.6), birth weight (3446 vs 3453 grams), and preterm births (4.22 vs 5.7). The only major difference is that in their study 9.8% weigh below the 10th percentile, compared to 0.97% in our study. Our findings are in line with another study from the Netherlands on perinatal outcome in women with eating disorders that reports $0.8 - 4.0\%$ of SGA in their cases and controls [17]. Thus, it is difficult to explain away our results by a comparison of the control group, which appears in agreement with recent reports.

This study is the first, to our knowledge, to identify prognostic factors for AFO in HG pregnancies not only by comparing cases affected with HG to unaffected controls, but also by comparing HG pregnancies with and without adverse outcomes.

Demographic characteristics, symptoms, medications, and treatments were all examined in patients with clinically defined HG to determine whether they are related to adverse outcome. Significantly better outcomes were seen in women who were treated as outpatients only (not hospitalized, nor treated in a home-health care setting). These participants were significantly less likely to be treated with TPN, suggesting the better prognosis in this group may be confounded by less severe disease. By contrast, patients treated with alternative medicine were also significantly more likely to have better outcomes, but in this group there was no difference in weight loss nor TPN treatment. This suggests the positive effects of alternative medicine on outcome identified in this study are not confounded by severity. It is important to note that while this treatment may significantly improve outcome, it was reportedly largely ineffective in improving HG symptoms in this study.

A history of gestational hypertension, and early start of HG symptoms (3-4 weeks) were both linked to adverse outcome, suggesting carers should be particularly attentive to patients with HG that fall into these categories. This study suggests that patients taking antihistamines, [diphenhydramine (Benadryl), dimenhydrinate (Gravol), doxylamine (Unisom), hydroxyzine (Vistaril/Atarax), doxylamine and pyridoxine (Diclectin/Bendectin)], are at particular risk for poor outcome. Of note, when analyzing adverse outcome for participants specifically taking doxylamine and pyridoxine (Diclectin/Bendectin), there was a trend toward adverse outcome, but not enough participants for statistical significance. These findings are of particular concern because of their increased use to treat HG worldwide. The use of antihistamines increased 100% between 2000 and 2004, and antihistamines were taken by over 50% of participants with adverse outcomes in this study [18]. A study of trends in treatment by country of residence reported that antihistamine treatment for HG is highest in the US (65%) and Canada (87.5%),

and notably lower in other countries such as the United Kingdom (18.5%) and Australia/New Zealand (26.3%) [18]. Therefore, the differences in outcome reported in this study compared to others may relate to differences in medications used for HG. Interestingly, pyridoxine, a component of Diclectin/Bendectin, is not linked to adverse outcome in this study, consistent with the findings that antihistamines are the causal factor. More research is needed to determine the mechanism whereby these medications may cause poor outcome in HG patients, but unlike what may be the case with promethazine and methylprednisolone, the cause and effect for some antihistamine use cannot be explained away by the severity of the disease, suggesting the medication itself is likely responsible for the link to adverse outcome identified in this study.

The findings reported herein are surprising given the large body of evidence on the safety of antihistamine use in pregnancy [19]. The majority of these, however, as well as most studies of antiemetic use in pregnancy, focus on teratogenic potential, and the major adverse outcome reported herein is preterm birth (< 37 weeks)[20]. One study of the Swedish Medical Birth Registry found a beneficial effect on delivery outcome for antihistamine use [21]. In this study 3% of women took antihistamines for nausea in pregnancy and an earlier report by the same author reports the prevalence of HG to be 0.3%[22]. The author suggests that the reported outcome is likely related to the positive association of early pregnancy nausea on pregnancy outcome and not due to the medication. Therefore, the beneficial effects of normal nausea may have masked the adverse outcomes associated with more severe nausea (HG) and antihistamine use in their study. A Hungarian study by Czeizel and Puho supports this theory because their study of 3869 women with severe NVP (10.1%) excludes 90 women (0.2%) hospitalized for HG, and finds overall longer gestational age in the severe nausea group compared to controls without severe nausea [23]. In this study, in line with the findings herein,

the group that used vitamin B6 showed the lowest proportion of preterm birth and the group using dimenhydrinate and thiethylperazine had the highest proportion of preterm birth. This suggests the adaptive function of nausea in pregnancy may mask the findings of an association of certain medications with preterm birth in studies that are not specific to the extreme end of the nausea spectrum. Therefore it would be very interesting to see whether the women hospitalized for HG that were excluded from the Hungarian study, and the women who specifically had HG in the Swedish study, showed similar findings to those reported here.

It is important to note that in this study, medications are self reported and may or may not have been taken with other treatments/medications, and therefore controlled single agent treatment/medication vs. placebo studies are necessary to confirm the findings. Additionally, long-term outcome studies are imperative to determine whether there are any adverse effects on children exposed to medications for HG in pregnancy, as this study only looks at fetal outcome.

Self-reported information may result in significant recall bias in the group of mothers with positive outcomes, possibly leading to exaggerated findings. However, the fact that other commonly used medications (with greater effectiveness) such as ondansetron (Zofran), were not significantly linked to poor perinatal outcome in this study, provides evidence that some medications used to treat HG may result in a better prognosis than others, and any potential recall bias would have to be unique to certain medications. When weighing in the link between antihistamine use and AFO, in addition to its reportedly low effectiveness in treating HG compared to other medications such as ondansetron, this study provides evidence there are both safer and more effective treatments. 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. In addition, studies

should focus on identifying the cause of HG so that safe and effective therapies can be identified to eliminate the four fold increased risk of poor outcomes associated with HG.

2.1.4 Tables

Demographic characteristics	HG	No HG	P-value
N	254	308	
Age (SD[a])	27.7 (4.66)	27.2 (4.31)	0.1215
Miscarriage/fetal death in 1st pregnancy	3.57%	2.94%	1.00
SES - low	15.66%	10.78%	0.1155
SES - medium	75.10%	77.78%	0.5222
SES - high	9.24%	11.44%	0.4817
Pre-existing hypertension (HBP[b])	2.58%	0.80%	0.1039
Gestational hypertension	12.55%	5.07%	0.0003
Gestational diabetes	3.94%	1.30%	0.0574
Autoimmune disease (prior to first pregnancy)	16.21%	10.71%	0.0606
Immune problems (prior to first pregnancy)	12.20%	5.19%	0.0034
Anxiety (prior to first pregnancy)	17.32%	4.55%	< 0.0001
Bipolar disorder (prior to first pregnancy)	1.57%	0.00%	0.0412
Depression (prior to first pregnancy)	18.11%	7.47%	0.0002
Assisted reproduction	3.54%	5.19%	0.4136
Spontaneous labor	65.32%	66.79%	0.7759
Vaginal delivery	81.00%	81.72%	0.9079
Female gender child	57.87%	47.23%	0.0138

Table 2.1: Demographic Characteristics

[a] Standard deviation

[b] High blood pressure

Pregnancy outcomes	HG	No HG	P-value	Crude OR[a]	95% CI[b]	Adjusted OR	95% CI
N	254	308					
Birth defects	2.76%	1.62%	0.5279				
Perinatal mortality (deaths after 20 weeks gestation to 1 week after birth)	1.18%	0.65%	0.8283	1.83	0.30-13.96	2.29	0.36-17.85
Birth weight (grams)	3236.69	3446.01	< 0.0001				
Preterm birth(< 37 weeks)	15.35%	4.22%	< 0.0001	4.12	2.20-8.19	4.05	2.08-8.30
Weight below 10th percentile	2.76%	0.97%	0.1976	2.88	0.79-13.47	2.05	0.50-10.23
AFO	16.93%	4.55%	< 0.0001	4.28	2.34-8.30	4.00	2.11-7.97

Table 2.2: Pregnancy Outcomes

[a] Odds ratio

[b] Confidence interval

Demographic characteristics	HG with AFO	HG No AFO	P-value
N	43	211	
Gestational hypertension	27.91%	9.95%	< 0.0001
Female gender child	48.84%	59.72%	0.2355
Prior to first pregnancy:			
Immune problems	6.98%	13.27%	0.3149
Anxiety	23.26%	16.11%	0.2717
Bipolar disorder	2.33%	1.42%	0.5261
Depression	20.93%	17.54%	0.6639

Table 2.3: Gestational hypertension, child gender, and other factors prior to first pregnancy associated with adverse outcome

Demographic characteristics	HG with AFO	HG No AFO	P-value
N	43	211	
Week of NVP (when symptoms began)			
Week 1-2	6.977%	8.531%	0.973
Week 3-4	39.535%	21.327%	0.019
Week 5-6	48.837%	53.081%	0.734
Week 7-8	4.651%	14.692%	0.125
Week 9-10		1.896%	
Week 11-12		0.474%	
Time of first treatment			
Inpatient admission: weeks pregnant at your first inpatient visit	11.867	9.752	0.132
Home health care visit: weeks pregnant at first home health care visit for nausea/vomiting	13.067	11.438	0.365
Outpatient visit: weeks pregnant at your first outpatient visit for nausea/vomiting?	9.080	9.105	0.983
Hospitalization			
Inpatient (paired with anything else)	72.093%	57.820%	0.089
Home health care (paired with anything else)	37.209%	31.754%	0.481
Outpatient only	16.279%	33.649%	0.029
Weight gain			
Week they began gaining weight	17.618	19.684	0.100

Table 2.4: Early symptoms associated with adverse outcome

	N = 43	N = 211			Answered Effective		
N	43	211					
Treatment/medication	HG With AFO (%)	HG No AFO (%)	P-Value	*n* who had tx/med	HG Adverse outcome (%)	HG No adverse outcome (%)	P-value
Alternative medicine	2.33	18.01	0.0089	39	0.00	10.53	1
Antacids	67.44	52.61	0.0925	140	0.00	10.20	0.1722
Antibiotics (for Heliobater pylori)	2.33	1.42	0.5261	4	0.00	0.00	1
Antidepressants/Antianxiety	13.95	11.85	0.7979	31	33.33	16.67	0.7321
Antihistamines	55.81	34.60	0.0151	97	35.20	16.21	0.3265
Anti-motion sickness medications	16.28	18.48	0.8307	46	0.00	5.13	1
Azemet	0.00	3.32	0.606	7	0.00	28.57	
B6 injection	18.60	9.95	0.1161	29	0.00	14.29	0.6549
Cannabis/Marijuana	4.65	2.37	0.3377	7	50.00	75.00	1
Compazine/stemetil/buccastem	18.60	20.38	1	51	12.50	9.52	1
Motilium	2.33	0.47	0.3105	2	0.00	0.00	0
Emend	0.00	0.00	1	0	Not taken		
Gastric pacing	2.33	0.47	0.3105	2	Not taken		
Herbal medicine	11.63	10.90	0.7955	28	0.00	4.17	1
Homeopathics	6.98	18.48	0.0727	42	0.00	2.56	1
IV fluids	100.00	100.00	1	254	53.49	41.63	0.2079
Inapsine (droperidol)	0.00	0.47	1	1	0.00	0.00	
Kytril (granisetron)	0.00	1.42	1	3	0.00	0.00	
Solumedrol (methylprednisolone)	23.26	9.95	0.0217	31	55.56	45.00	0.9008
Nasal to stomach tube feedings	4.65	0.95	0.1342	4	0.00	0.00	
Phenergan/lergigan/avomine (promethazine)	86.05	70.62	0.0386	186	19.44	18.37	1
Peripherally inserted central catheter (PICC)	25.58	23.70	0.8451	61	36.36	48.00	0.7136
Physical therapy	4.65	1.90	0.2688	6	0.00	50.00	1
Psychotherapy/counseling	6.98	9.48	0.775	23	0.00	0.00	
Protonix/prevacid (lansoprazole)	13.95	10.90	0.599	29	0.00	13.64	0.9302
Reglan/maxeran/maxolone (metoclopramide)	62.79	53.08	0.3133	139	7.41	9.82	0.9852
Scopolamine (scopolamine hydrobromide)	6.98	3.32	0.3802	10	0.00	14.29	1
SeaBands/relief bands	67.44	65.88	1	168	0.00	1.45	1
Special diet (bland, low fat),	60.47	65.88	0.4894	165	0.00	10.87	0.1637
Tagamet (cimetidine)	4.65	1.90	0.2688	6	0.00	0.00	
Thorazine (chlorpromazine),	6.98	1.42	0.0626	6	33.33	0.00	1
Tigan/Vomet (trimethobenzamide)	6.98	8.53	1	21	0.00	16.67	1
TPN/TPPN or	27.91	15.17	0.0741	44	36.36	31.25	
Vitamins (taken orally)	41.86	34.60	0.3862	91	0.00	1.43	1
IV Vitamins	27.91	25.59	0.8488	66	9.09	9.09	1
Zofran (ondansetron)	86.05	77.25	0.2264	200	59.46	49.08	0.338

Table 2.5: Medications/treatments vs outcome and effectiveness.

	N	AFO (%)	P-value	Mean % weight loss	P-value	TPN (%)	P-value
Gestational hypertension	33	36.36	0.0033	12.58	0.982	18.18	0.81
No gestational hypertension	221	14.03		12.55		17.19	
NVP began week 3-4	62	27.42	0.0194	12.85	0.687	22.58	0.2466
Other	192	13.54		12.45		15.63	
Outpatient only	78	8.97	0.0385	12.06	0.622	2.56	< 0.0001
Other	176	20.45		12.76		23.86	
Acupuncture	39	2.56	0.0179	11.62	0.281	20.51	0.6452
No acupuncture	215	19.53		12.71		16.74	
Methylprednisolone	31	32.26	0.0298	14.22	0.097	41.94	0.0005
No methylprednisolone	223	14.80		12.31		13.90	
Promethazine	186	19.89	0.0582	13.34	5E-04	19.89	0.0917
No promethazine	68	8.82		10.37		10.29	
Antihistamines[a]	93	23.66	0.0456	12.31	0.746	19.35	0.606
No antihistamines	161	13.04		12.70		16.15	

Table 2.6: Severity in factors associated with adverse outcome

[a] Antihistamines include Benadryl (diphenhydramine), Gravol (dimenhydrinate), Unisom (doxylamine), Vistaril/Atarax (hydroxyzine), Diclectin/Bendectin (doxylamine and pyridoxine).

2.2 Follow Up Study

We repeated part of the previous analysis discussed in Chapter 2.1 to see if our results were reproducible in a new sample (Table 2.8). We compared between 43 offspring exposed to HG with an AFO and 413 offspring exposed to HG with no AFO. Follow-up patients were enrolled between 2011 and 2014. The inclusion criteria for cases were the same as our previous study, a diagnosis of HG and treatment with IV fluids and/or TPN/nasogastric feeding tube, independent of hospitalization. Participants with pregnancies less than 20 weeks were excluded. AFO was defined as preterm birth (< 37 weeks), birth weight less than 10%, and/or perinatal mortality.

Because perinatal mortality was rare in this small sample, the majority of AFO was represented by preterm birth and associated low birth weight. For this study we focused on the seven statistically significant prognostic factors identified in our previous study where we compared the clinical profile of HG patients (enrolled in 2007 to 2008) 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.

Herein, 41 pregnancies resulted in an AFO. NVP beginning in weeks 3-4 of pregnancy, hospitalization as an outpatient only, and gestational hypertension were no longer associated with adverse outcome, in contrast to their significant association with AFO in the first study. Variables remaining significant in the second population were methylprednisolone and promethazine use. Other antihistamine use continued to be associated with AFO, though here the association was not quite statistically significant ($p = 0.0642$). Unlike the previous study, tube feeding came out to be significantly associated with an adverse outcome in this study. Alternative medicine was not significant when examining data from the second set, but relatively few women with HG relied on it as a treatment.

It is important to note the differences of the "no AFO" groups from both studies. Recently there is more patient and doctor awareness of HG which could lead to more diagnosed cases of HG with IV fluid treatment. In the first study there was a higher proportion of cases with early symptoms, treatment with medications, and treatment with tube feeding. A possible explanation of this is that those women were more commonly diagnosed at the very severe end of the HG spectrum.

In both studies, poor fetal outcome in women with HG was shown to be associated

with the use of promethazine, other antihistamines, methylprednisolone, and tube feeding. Factors not significant in the second study were NVP starting at 3-4 weeks of pregnancy, hospitalization as an outpatient only, gestational hypertension, and alternative medicine. This study suggests association between the factors and outcomes but does not imply causation. There are other confounding factors which need to be accounted for when interpreting such results. For instance, the association between tube feeding and poor fetal outcome could be a result of the severity of disease. Ondansetron, one of the most commonly prescribed medications during pregnancy, was not found to be associated with AFO in either study. There is a need for future studies to focus on identifying the biological basis of HG so that safe and effective therapies can be identified to eliminate the risk of poor outcomes.

	N=41	N=413			
	HG, AFO	HG, No AFO	P-value	OR	95% CI
Factors/early symptoms associated with adverse outcome					
NVP began Week 3-4	9 (22.00%)	81 (19.60%)	0.6846	1.1524	(0.46, 2.59)
Outpatient only	7 (17.10%)	68 (16.50%)	1	1.0445	(0.38, 2.53)
Gestational hypertension	4 (9.8%)	21 (5.1%)	0.2674	2.0140	(0.48, 6.43)
Treatment/medication					
Alternative medicine	1 (2.4%)	33 (8.00%)	0.3459	0.2884	(0.01, 1.82)
Promethazine	23 (56.10%)	135 (32.70%)	0.0053	2.6252	(1.31, 5.35)
Other Antihistamines	14 (34.10%)	84 (20.30%)	0.0474	2.0272	(0.94, 4.21)
Methylprednisolone	7 (17.10%)	12 (2.90%)	0.0007	6.8242	(2.13, 20.31)
TPN/TPPN	8 (19.50%)	24 (5.80%)	0.0046	3.9110	(1.41, 9.92)
Ondansetron	20 (48.80%)	178 (43.10%)	0.512	1.2567	(0.63, 2.52)

Table 2.7: Results of follow-up study from patients recruited 2011-2014

N=43	N=211				
HG, AFO	HG, No AFO	P-value	OR	95% CI	
Factors/early symptoms associated with adverse outcome					
NVP began Week 3-4	17 (39.54%)	45 (21.33%)	0.019	2.4	(1.12, 5.07)
Outpatient only	7 (16.28%)	71 (33.65%)	0.029	0.38	(0.14, 0.93)
Gestational hypertension	12 (27.91%)	21 (9.95%)	< 0.0001	3.4796	(1.41, 8.31)
Treatment/medication					
Alternative medicine	1 (2.33%)	38 (18.01%)	0.0089	0.11	(0.00, 0.69)
Promethazine	37 (86.05%)	149 (70.62%)	0.0386	2.56	(1.00, 7.79)
Other Antihistamines	24 (55.81%)	73 (34.60%)	0.0151	2.38	(1.16, 4.93)
Methylprednisolone	10 (23.26%)	21 (9.95%)	0.0217	2.73	(1.05, 6.73)
TPN/TPPN	12 (27.91%)	32 (15.17%)	0.0741	2.16	(0.91, 4.89)
Ondansetron	37 (86.05%)	162 (77.25%)	0.2264	1.81	(0.70, 5.57)

Table 2.8: Continuation of Results of follow-up study from patients recruited 2011-2014

CHAPTER 3

Risk Recurrence

3.1 Motivation

Our original goal with this analysis was to be the first study to analyze the relationship of multiple factors to risk of recurrence of HG. In our sample, many factors that have been shown to be potentially associated with HG did not show to an effect on risk of recurrence. Participants who reported amenorrhea, birth defects, scoliosis, or inner ear problems prior to their first pregnancies had significantly lower recurrence rates. Several pre-existing health issues were also significantly associated with a lower risk of recurrence.

Because the small sample in our study was a limitation, this analysis was slightly modified. We looked at psychiatric factors and found that, in our sample of women, was not a significant predictor of recurrence. The original analysis is included in Section 1 of this chapter. The final publication is printed in the sections thereafter.

3.1.1 Abstract

Introduction: The aim of this study is to identify factors that reduce the risk of recurrence of HG. The diagnosis of HG is associated with a-4 fold increased risk of adverse outcome including low birth weights, preterm delivery, and fetal and neonatal death.

Methods: Participants were asked to submit medical records and complete an online survey regarding demographic characteristics, preexisting conditions, pregnancy symptoms and treatments, and maternal and fetal outcomes. The inclusion criteria were those who had clinically defined HG in their first pregnancy. Logistic regression, chi-square tests, Fisher's exact tests, and t-tests were performed to compare groups who had a recurrence of HG in their second pregnancy and those who did not. The ROC curve was plotted to evaluate model performance.

Results: Participants who reported amenorrhea, birth defects, scoliosis, or inner ear problems prior to their first pregnancies had significantly lower recurrence rates. Recurrence risk was not associated with demographic characteristics, family history, special diets, or certain health issues (gastric disorders, mental health issues, thyroid disorders, immune dysfunction, allergies, and motion sickness). Additionally, severity of first pregnancy, time between pregnancies, and post traumatic stress symptoms (PTSS) all were not significantly linked to risk of recurrence.

Discussion: This study is the first to analyze the relationship of multiple factors to risk of recurrence of HG. Interestingly, no factors were identified that increase the risk of recurrence, but several pre-existing health issues are associated with a lower risk of recurrence. Many of the predictors found here to be statistically significant may be hormonally related. The association between these conditions, hormones, and HG recurrence suggests that this link warrants further study.

3.1.2 Introduction

Several lines of evidence support a genetic predisposition to NVP. In the only study of NVP in twins, concordance rates were more than twice as high for monozygotic compared to dizygotic twins [24]. Approximately one-third of women affected with HG have an affected mother and 1 out of 5 have an affected sister [25]. Such data suggest that a genetic predisposition may play a role in the development of HG and explains the high recurrence risk independent of change in partner [26].

Based on a website survey sponsored by the HER Foundation, the risk for recurrence can be as high as 81% [27]. Understanding the risk for recurrence has implications for both counseling, treatment, and disease etiology for women, especially because of the high percentage of women who change reproductive plans (37%) due to their experiences with HG [27]. The aim of this study is to identify risk factors linked to recurrence for HG patients. These results could potentially lead to better methods to predict recurrence and prepare for an HG pregnancy.

3.1.3 Sample and Settings

In order to focus on recurrence, only women between the age of 18 and 50 who had at least two pregnancies that lasted beyond the second trimester and did not have multiple or chromosomally abnormal gestations were included in this analysis. In the survey, participants were asked to rate the severity of their NVP of each pregnancy by selecting a number from one to five, with five being the most severe, as follows:

1.No NVP

2.Very little NVP

3.Typical NVP

4.More severe morning sickness

5.HG

The inclusion criteria were those who required IV fluid treatment for dehydration due to HG and reported an NVP rating of 4 or 5 in their first pregnancy. Recurrent pregnancies, defined as having IV fluid treatment and an NVP rating of 4 or 5 in the second pregnancy, were compared to those who had no IV fluid treatment and an NVP rating of 1, 2, or 3 in the second pregnancy.

3.1.4 Study Procedures

Using the data gathered from the participants medical records and the online survey results, 130 respondents were included in the recurrence study and categorized according to the binary response variable of recurrence as defined previously. Chi-square and Fisher's exact tests were performed to compare groups according to these binary responses, and t-tests were used to compare respondents according to continuous explanatory variables.

Logistic regression was initially used to explore potential combinations of explanatory variables of interest, particularly symptoms and complications experienced prior to or during the first pregnancy, as shown in the four models in Table 3.1.8.

To assess goodness of fit, a chi-squared test was used to test the significance of the residual deviances of each model. The Hosmer-Lemeshow statistic was used as an additional approach for comparison. Moreover, a Receiver Operating Characteristic curve (ROC curve) was plotted for each model to evaluate performance.

3.1.5 Results

Demographic Characteristics

Table 3.1 compares the demographic characteristics of the two groups. All participants were from the United States. Cases who recurred and those who did not recur were well matched for race, age, height, weight, spontaneous labor, number of pregnancies begun, and delivery method (Table 3.1).

Family History

To look into the possibility of inherited or familial components affecting the likelihood of recurrence we looked at those who had a mother, sister, or had a partner whose sister had HG (Table 3.2). Our results did not show that those who had a family history were more likely to recur. None of the differences between the groups were statistically significant.

Health Issues/Lifestyle Prior to First Pregnancy

Table 3.3 shows fifty health conditions (prior to the first pregnancy) that were compared. Conditions such as having amenorrhea or scoliosis prior to the first pregnancy, or being born with a birth defect were rare, as 15% or less in either group reported having these characteristics, but nonetheless still came out to be significantly more common among those who did not experience a recurrence of HG (Table 3.3). Many health issues/lifestyles previously associated with HG, including gastric disorders, mental health issues, thyroid disorders, immune dysfunction, allergies, motion sickness, and special diets, all showed no evidence of any effect on recurrence risk.

Severity and Outcome of First Pregnancy

Severity of disease and fetal outcomes can affect maternal recovery time and there-

fore we investigated whether severity factors and fetal outcomes have an effect on recurrence [28, 29]. We compared factors such as the week of pregnancy at the first inpatient visit, total weight loss in pregnancy, pregnancy outcomes, and PTSS. These factors were closely matched for both groups (Table 3.5, Table 3.6). The biggest differences observed (though not statistically significant) was that those who did recur tended to have an AFO in their first pregnancies and tended to take more time between pregnancies.

Model Comparison and Regression

Of all factors in Tables 3.3 - 3.6 that were compared between the two groups, amenorrhea, birth defects, inner ear problems, and scoliosis came out to be significant (or close to statistically significant, $P < 0.07$). These were looked at together in a logistic regression model (Model 3.1a) and then separately with related medical or health conditions (e.g. amenorrhea, PMS, gynecological disorders, and irregular periods were in one model, inner ear problems, motion sickness, migraine, and nausea in another model) in other models. A backwards stepwise logistic regression was then performed on each of these separate models, with the resulting models (Models 3.1b-3.1d) shown in Table 3.1.8 with corresponding coefficients and p-values. After examining amenorrhea with other related conditions (PMS, irregular period, gynecological disorders, and special diet) only gynecological disorders and amenorrhea remained, with amenorrhea being significant (Model 3.1b). We looked at associated health conditions with inner ear problems and scoliosis as separate covariates in Model 3.1c and 3.1d, respectively. After performing a backward stepwise logistic regression with inner ear problems with motion sickness, vertigo, migraine, dizziness, balance, and chronic nausea the best model came out to be inner ear problems and migraine as predictors (Model 3.1c). The same was done with scoliosis, examined with arthritis, muscular or skeletal pain, amenorrhea, special diet, and joint pain. Scoliosis and amenorrhea came out to

be the only two covariates in the model after backward stepwise logistic regression (Model 3.1d).

$$\begin{aligned} logit(\widehat{recur}) = \beta_0 - 2.76 * Amenorrhea - 18.92 * BirthDefects - \\ 3.04 * InnerEar - 2.76 * Scoliosis \end{aligned} \tag{3.1a}$$

$$logit(\widehat{recur}) = \beta_0 - 2.52 * Amenorrhea + 0.83 * GynDisorders \tag{3.1b}$$

$$logit(\widehat{recur}) = \beta_0 - 2.45 * InnerEar - 0.56 * Migraine \tag{3.1c}$$

$$logit(\widehat{recur}) = \beta_0 - 2.43 * Scoliosis - 2.43 * Amenorrhea \tag{3.1d}$$

The coefficients for the statistically significant covariates in all the models in Table 3.1.8 are negative, showing that in our population recurrence tends to be less likely when these respective conditions are present prior to the first pregnancy. The first model examined only the significant variables associated with health issues and lifestyle prior to the first pregnancy. Three of the four variables were found to be significant predictors (amenorrhea, inner ear, and scoliosis). Subjects who recurred were less likely to have experienced these conditions (OR less than 0.06).

The values of the residual deviances of each model varied in value, with Model 3.1a having the smallest (85.23) and Model 3.1c having the largest (106.52). The residual deviance was tested for significance using a chi-squared test and all yielded p-values greater than 0.05, thus indicating no evidence that any of the models had a significant lack of fit. Calculating the Hosmer-Lemeshow statistic showed consistent results of a good fit for each model with p-values also all above 0.05. Figure 1 shows receiver operating characteristic (ROC) curves, which indicate the predictive capacity of each of the 4 logistic regression models in Table 3.1.8. Model 3.1a showed to be the best choice here, with an area under the curve (AUC) of 0.73 (Table 3.1.8).

3.1.6 Comments

This study focuses on examining factors that could possibly affect one's chance of an HG recurrence. Our findings show certain medical and health conditions to be more strongly associated with a decreased risk of recurrence. Most observed factors were closely matched between the group reporting recurrence of HG and the group not reporting recurrence. We did not find any significant link between recurrence risk and demographic characteristics, family history of HG, or severity of disease. The most significant findings were that patients that did not recur were more likely to have pre-existing conditions of probably hormonal etiology including scoliosis and amenorrhea.

Our results showed a limited amount of factors to be significantly different between the two groups so we looked into possible associations between those significant factors (amenorrhea, birth defects, inner ear problems, and scoliosis) to see if any of these conditions were related. In Model 3.1a birth defects was the only variable that was not significant. Amenorrhea, inner ear problems, and Scoliosis were significantly associated with those who did not have the recurrence of HG in their second pregnancies. A possible association between amenorrhea and scoliosis could be exercise and calorie intake. Previous studies have shown that women athletes who perform considerable amounts of exercise and/or do not consume enough calories can be more at risk of developing hypothalamic amenorrhea [30]. Bone disorders have also been associated with amenorrhea as physical exertion can play a major role in how ones bone mass can change. Bone loss rather than an increase in bone density can result from considerable amounts of exercise on a regular basis in women with amenorrhea [31]. A study by Warren et al. (1986) examined the risk of developing scoliosis in young athletes with delayed menarche. They found that the benefit of physical activity on maintaining a healthy bone density can be overridden by other factors with prolonged strenuous activities in women who

are already suffering from amenorrhea because the risk of developing osteoporosis can increase by the incidence of scoliosis, stress fractures, and amenorrhea [31, 32].

A possible alternative explanation to these factors being associated with non-recurrence could be hormonal variation between pregnancies. Possible associations with hypothalamic amenorrhea, where certain hormones are suppressed and altered by exercise and can affect estrogen and progesterone levels, are long-term consequences that can include infertility, a reduced bone density, and stress fractures [33]. It is believed that various hormones, primarily estrogens play a role in the onset and development of scoliosis [34]. In addition, a link between estrogen and the auditory system has been well established [35].

Model 3.1b, 3.1c, and 3.1d are consistent with Model 3.1a in that amenorrhea, inner ear problems, and scoliosis were significantly associated with a decreased risk of recurrence. Though gynecological disorders (Model 3.1b) and migraines (Model 3.1c) did not come out to be significant, there are possible hormonal associations between the conditions to examine further in a future study. For example, some women who are affected by migraines and Meniere's disease, a condition in the inner ear that can affect balance and hearing, are believed to experience aggravated symptoms during their premenstrual period due to the hormonal stress that the premenstrual period can have on the inner ear [36]. In addition, catamenial migraines are commonly associated with fluctuations in estrogen levels [37]. Thus the link between hormones, scoliosis, amenorrhea, inner-ear disorders, migraines, and non-recurrent hyperemesis is intriguing. The results of this study indirectly support the hypothesis that estrogen dysregulation may play a role in recurrence risk.

This study has serious limitations, as in particular the sample sizes are small and

the subjects are not randomly sampled from the overall population of HG sufferers. For example, coefficient estimates for certain variables may be unstable due to the small sample size, especially for covariates, such as birth defects, for which the number of women with birth defects experiencing recurrence in the second pregnancy was zero. Nevertheless, the results of this study have implications for counseling. Many factors were explored for the first time in this study and showed no evidence of any effect on the risk of recurrence of HG, including gastric disorders, mental health issues, thyroid disorders, immune dysfunction, allergies, motion sickness, and special diets. Thus therapeutic interventions or diet changes to treat these problems are not likely to alter the risk of recurrence. There is a trend toward a longer duration (3.2 years vs 2.7 years) between pregnancies and increased recurrence risk, which is consistent with findings from a previous study, but this trend was not statistically significant in either study [38]. The findings presented herein suggests that unless HG patients have had amenorrhea, birth defects, scoliosis, or inner ear problems, one should expect a recurrence risk of over 80%.

The significant findings that certain hormonally driven pre-existing conditions are linked to a lower risk of recurrence, indicate possible promising directions for future research. Further study is needed to determine whether the significant predictors identified here do in fact reduce the risk of recurrence. In addition, many of the predictors found here to be statistically significant may be hormonally related, and the association between these conditions, relevant hormones, and HG warrants serious further attention in the future.

3.1.7 Figures

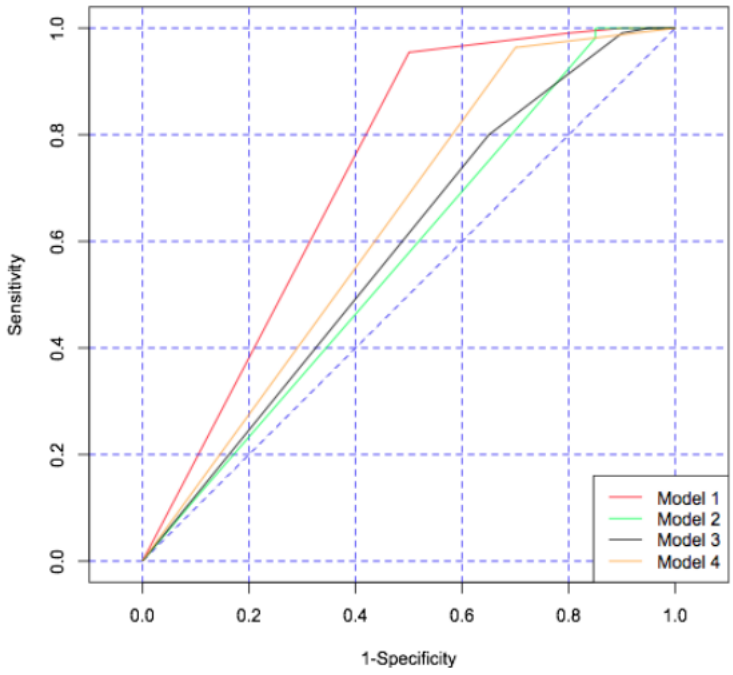


Figure 3.1: AUC for models 1-4 were 0.73, 0.57, 0.58, and 0.63, respectively. For the chi-squared tests on residual deviances, Model 3.1a had the smallest at 85.23, Model 3.1c had the largest at 106.52. Hosmer-Lemeshow statistics showed consistent results of a good fit for each model (all p-values above 0.05)

3.1.8 Tables

Demographics	Recurrence in 2nd pregnancy	No Recurrence in 2nd pregnancy	P-value
Sample size	110	20	
Vaginal Delivery	94.06%	85.00%	0.17
Miscarriage/fetal death	3.64%	5.00%	0.57
Fertility treatment	2.75%	0.00%	1.00
Had same partners for 1st and 2nd pregnancy	74.55%	80.00%	0.78
Number of pregnancies begun (including current)	2.38	2.75	0.11
Singleton pregnancy	96.36%	100.00%	1.00
Spontaneous labor	54.55%	55.00%	1.00
Had Labor (no C-section or Labor)	94.06%	85.00%	0.17
Race (white)	91.81%	100%	1.00
	Avg., SD, (range)		
Weight of group (pounds)	148.4, 34.61 (90-250)	142.25, 32.39 (110-230)	0.45
Age (at end of first pregnancy)	26.67, 4.40 (14-38)	27.6, 4.40 (19-39)	0.49
Height (inches)	65.78, 6.45 (55-72)	64.66, 2.39 (60, 69)	0.20

Table 3.1: Demographics

Variable 2nd pregnancy	Recurrence in 2nd pregnancy	No Recurrence in	P-value
Had mother with HG/more severe morning sickness	34.55%	30.00%	0.89
Had a sister with HG /more severe morning sickness	37.25%	50.00%	0.70
Partner's sister(s) had HG /more severe morning sickness	1.72%	0.00%	1.00
Had relatives that had NVP but not HG	48.18%	45.00%	0.81

Table 3.2: Family History

Variable	Recurrence in 2nd pregnancy	No Recurrence in 2nd pregnancy	P-value
Time between 1st and 2nd pregnancies	3.24 (2.73)	2.7 (1.30)	0.18
Weeks pregnant at first inpatient visit	9.15 (4.05)	7.75 (2.05)	0.08
Changed doctors during pregnancy	22.02%	20.00%	1.00
Mean % Weight Loss	3.01%	3.42%	0.57
Low Blood Pressure during 1st pregnancy	20.00%	15.00%	0.76

Table 3.5: Severity of 1st Pregnancy

Variable	Recurrence in 2nd pregnancy	No Recurrence in 2nd pregnancy	P-value
Allergies	40.00%	40.00%	1.00
Amenorrhea	1.82%	15.00%	0.03
Anxiety	12.73%	15.00%	0.73
Arthritis	3.64%	5.00%	0.57
ADD	2.73%	0.00%	1.00
Bipolar	1.82%	5.00%	0.40
Birth Defects	0.00%	10.00%	0.02
Chronic Constipation	7.27%	10.00%	0.65
Chronic Diarrhea	3.64%	5.00%	0.57
Chronic Fatigue	5.45%	5.00%	1.00
Chronic Infection	2.73%	5.00%	0.5
Chronic Nausea	1.82%	10.00%	0.11
Dental Cavities	35.45%	20.00%	0.21
Depression	12.73%	10.00%	1.00
Eating Disorder	6.36%	5.00%	1.00
Fainting	6.36%	0.00%	0.59
Fibromyalgia	1.82%	5.00%	0.37
GERD	6.36%	5.00%	1.00
Gynecologic Disorder	13.64%	10.00%	1.00
Hearing Disorder	0.91%	0.00%	1.00
High Blood Pressure	3.64%	0.00%	1.00
Hypoglycemia	6.36%	10.00%	0.63
Immune Disorder	10.00%	15.00%	0.45
Infertility	6.36%	10.00%	0.63

Table 3.3: Health Issues/Lifestyle Prior to First Pregnancy

Variable	Recurrence in	No Recurrence in	P-value
2nd pregnancy	2nd pregnancy		
Inner Ear	0.91%	10.00%	0.06
Irregular Periods	13.64%	30.00%	0.09
Irritable Bowel Syndrome	12.73%	15.00%	0.73
Joint Abnormality	1.82%	0.00%	1.00
Learning Difficulties (e.g. dyslexia)	4.55%	0.00%	1.00
Migraine	19.09%	30.00%	0.37
Motion Sickness	39.09%	50.00%	0.46
Other Dental Issues	0.91%	0.00%	1.00
Muscle or Skeletal Pain	2.73%	0.00%	1.00
Panic Disorder	7.27%	10.00%	0.65
Polycystic Ovarian Syndrome	4.55%	0.00%	1.00
PMS	25.45%	40.00%	0.19
Raynauds	2.73%	10.00%	0.17
Scoliosis	1.82%	15.00%	0.03
Seizures	0.91%	0.00%	1.00
Special Diet	6.36%	10.00%	0.63
Ulcer	6.36%	0.00%	0.59
Tachycardia	1.82%	5.00%	0.40
Thyroid Disease	4.55%	5.00%	1.00
TMJ	17.27%	20.00%	0.75
Chronic Dizziness	4.55%	5.00%	1.00
Vertigo	7.27%	10.00%	0.65
Fertility treatments	2.75%	0.00%	1.00
Months trying to get	> year: 0	> year: 2	
pregnant before conceiving	0-3: 85	0-3: 14	
	4-6: 6	4-6: 1	0.41
	7-9: 4	7-9: 3	
	10-12: 4	10-12: 0	
Autoimmune disorder	20.00%	20.00%	1.00

Table 3.4: Continuation of Health Issues/Lifestyle Prior to First Pregnancy

Variable	Recurrence in 2nd pregnancy	No Recurrence in 2nd pregnancy	P-value
Live birth	87.27%	95.00%	0.46
Miscarriage fetal death	3.64%	5.00%	0.57
Termination	7.27%	0.00%	0.61
Stillbirth	0.91%	0.00%	1.00
Baby died after birth	0.91%	0.00%	1.00
AFO *(< 37 weeks and ≥37 weeks that are < p10 and/or died)*	24.55%	10.00%	0.25

Table 3.6: Outcome of First Pregnancy

	Variable	Coefficient Estimates	P-value	AUC ROC
Model 1	Amenorrhea	-2.7568	0.0045*	0.73
	Birth Defects	-18.9174	0.99110	
	Inner Ear	-3.0445	0.0164*	
	Scoliosis	-2.7568	0.0045*	
Model 2	Amenorrhea	-2.5238	0.0138*	0.57
	Gynecological Disorders	0.8258	0.3686	
Model 3	Inner Ear	-2.4533	0.0515*	0.58
	Migraine	-0.5615	0.3167	
Model 4	Scoliosis	-2.4298	0.0110*	0.63
	Amenorrhea	-2.4298	0.0110*	

Table 3.7: Regression Coefficients

3.2 Psychiatric factors do not affect recurrence risk of Hyperemesis Gravidarum

3.2.1 Abstract

Aim: The aim of this study is to determine whether psychiatric symptoms affect recurrence risk of HG.

Methods: The study sample included 108 women with HG treated with IV 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 chi-squared test and Student's t-test were performed to compare the two groups.

Results: Eighty-four women (71%) had a recurrence of HG requiring IV 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 PTSS.

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 NVP, medication and/or hospitalization, and likely play no role in disease etiology.

3.2.2 Introduction

Several lines of evidence support a genetic predisposition to NVP. In the only study of NVP in twins, concordance rates were more than twice as high for monozygotic compared with dizygotic twins [24]. Approximately one-third of women affected by HG have an affected mother, and one out of five have an affected sister [25]. Such data suggest that a genetic predisposition may play a role in the development of HG and explains the high recurrence risk independent of change in partner [26].

Based on a website survey sponsored by the HER Foundation, the risk for recurrence can be as high as 81% [27]. Understanding the recurrence risk has implications for counseling, treatment and disease etiology for women, especially because of the high percentage of women who change reproductive plans (37%) due to their experiences with HG [27]. Severe nausea and vomiting has been attributed historically to psychological conflicts, albeit with lack of supporting scientific evidence [39]. The theory that HG is psychological is due primarily to the fact that a biological cause for HG has yet to be identified. If HG is caused by psychological factors, we predict that psychiatric symptoms will positively correlate with recurrence risk. Therefore, the aim of this study is to determine whether psychiatric symptoms are linked to risk of recurrence for HG patients. These results could potentially lead to better methods to predict recurrence and prepare for a HG pregnancy.

3.2.3 Methods

A variety of demographic characteristics, pre-existing conditions, pregnancy symptoms and treatments, and maternal and fetal outcome are reported in Tables 3.8-3.10. The majority of the subjects joined the study at the time they were pregnant and were sent a reminder to complete the survey pertaining to their respective pregnancy outcome following their due dates.

In order to focus on recurrence, only women between the age of 18 and 50 years who had at least two pregnancies that lasted beyond the second trimester were included in this analysis.

The clinical criteria were all participants who required IV fluid treatment for dehydration due to HG in their first pregnancy. Participants with recurrent pregnancies, defined as having IV fluid treatment for HG in the second pregnancy, were compared with participants who had no IV fluid treatment for HG and self-reported that they did not have HG in the second pregnancy.

Using the data gathered from the participants medical records and online survey results, 118 respondents were included in the recurrence study and categorized according to the binary response variable of recurrence as defined previously. Self-reported medically diagnosed emotional/behavioral disorders were collected via online survey and answers were compared between the recurrence group and the non-recurrence group. Post-HG-pregnancy stress symptoms were drawn from questions (shown in Table 3.10) assessing the three post-traumatic stress disorder symptom categories and compared between the recurrence and non-recurrence group: (i) re-experiencing;(ii) avoidance/numbing; and (iii) hyperarousal. The chi-squared test was performed to compare groups according to these binary re-

sponses, and Students t-test was used to compare respondents according to continuous explanatory variables.

3.2.4 Results

Eighty-four women (71%) who had a recurrence of HG requiring IV fluid treatment for dehydration were compared with 34 women (29%) who did not have severe NVP in their second pregnancy. Table 3.8 compares the pregnancy characteristics of the two groups. Cases who recurred and those who did not recur were well matched for obstetric history (Table 3.8); there were no significant differences in obstetric history, although there was a trend toward greater time between first and second pregnancy in the group that recurred (P=0.08) and a trend toward more pregnancies in the group that did not recur (P=0.06)

Table 3.9 shows psychiatric health conditions (prior to the first pregnancy) that were compared. There were no differences in pre-existing psychiatric diagnoses including anxiety, depression, bipolar disorder, panic or eating disorders. Pre-existing psychiatric conditions do not play a role in risk of recurrence of HG.

Table 3.10 shows PTSS following HG pregnancies. Participants in both groups were well matched for all PTSS . There is no increased risk of recurrence in patients with PTSS following HG pregnancies.

3.2.5 Discusion

This study focuses on examining psychological factors that could possibly affect ones chance of a HG recurrence. Our findings show pre-existing psychological conditions and post-pregnancy stress symptoms have no impact on the risk of a

recurrence of HG. Most observed factors were closely matched between the group reporting recurrence of HG and the group not reporting recurrence. There is a trend toward a longer duration (3.2 vs 2.7 years) between pregnancies and increased recurrence risk, which is similar to findings from a previous study, but this trend was not statistically significant in either study [38].

This study has limitations, particularly that sample sizes are small and the subjects are not randomly sampled from the overall population of HG sufferers. Nevertheless, the results of this study have implications for counseling. One should expect a recurrence risk of over 70% independent of pre-pregnancy psychiatric diagnoses. As many as 18% of women with HG experience full criteria stress symptoms following a HG pregnancy, but it should provide some comfort to these women that PTSS are unlikely to increase the risk of recurrence [40].

The cause of HG is unknown. Studies continue to focus on a psychiatric etiology despite the fact that no cause and effect have ever been scientifically proven and more and more studies refute this hypothesis [9]. Studies in support of a psychological etiology are primarily based on the fact that women with HG have increased risk of depression and anxiety while suffering from HG. However, this is more likely the result of prolonged physical symptoms, dehydration, malnutrition, medication and hospitalization, rather than causal. Control groups never include women who are currently suffering from similar physical symptoms and thus are not comparable. One would not compare the emotional/behavioral symptoms of cancer patients to a control group of healthy patients and presume an increase in depression and anxiety in the cancer group is evidence that depression and anxiety cause cancer, but this is done over and over in publications on HG [41].

Herein, for the first time, both our cases and controls have suffered from HG in

their first pregnancy, and we show that there is no correlation between either pre or post-pregnancy psychiatric conditions and recurrence of HG. This study provides strong scientific evidence against a psychogenic etiology by showing that psychological factors do not play a role in risk of recurrence. Avoiding a recurrent HG pregnancy is a critical topic to women who have already experienced a HG pregnancy. Future studies are imperative to decipher the etiology of HG and should focus on analyzing genetic and environmental factors associated with the disease, and identify factors that minimize the risk of recurrence.

3.2.6 Tables

Pregnancy History	Recurrence in 2nd pregnancy	No Recurrence in 2nd pregnancy	P-value
Sample Size	84	34	
Number of pregnancies	2.29	2.59	0.06
Miscarriage/fetal death in 1st pregnancy	3.57%	2.94%	1.00
Fertility treatment in 1st pregnancy	3.61%	2.94%	1.00
Vaginal delivery in 1st pregnancy	93.67%	84.85%	0.26
Spontaneous labor in 1st pregnancy	53.57%	50.00%	0.88
Labor (and not C section no labor) in 1st pregnancy	93.67%	84.85%	0.26
	Average (SD)		
Age at end of 1st pregnancy (pounds)	27.11 (4.36)	26.88 (4.36)	0.82
Age at end of 2nd pregnancy (pounds)	30.52 (4.38)	29.58 (4.38)	0.35
Time (years) between 1st and 2nd pregnancy	3.42 (2.68)	2.71 (1.62)	0.08

Table 3.8: Pregnancy History

Variable	Recurrence in 2nd pregnancy	No Recurrence in 2nd pregnancy	P-value
Anxiety	14.29%	17.65%	0.86
Bipolar	1.19%	2.94%	1
Depression	13.10%	12.73%	1
Eating Disorder	7.14%	5.88%	1
Panic Disorder	5.95%	8.82%	0.87

Table 3.9: Psychiatric Diagnoses Prior to First Pregnancy

Variable	Recurrence in 2nd pregnancy	No Recurrence in 2nd pregnancy	P-value
Had nightmares about it or think about it when you did not want to? (Y/N)	34.52%	50.00%	0.38
Tried hard not to think about it or went out of your way to avoid situations that reminded you of it? (Y/N)	33.33%	38.24%	0.09
Were constantly on guard, watchful or easily startled? (Y/N)	15.48%	20.59%	0.67
Felt numb or detached from others, activities or your surroundings? (Y/N)	14.29%	17.65%	0.46
How long did HG affect you emotionally? (number months, years, ongoing, describe)	No answer: 5 Months: 33 Ongoing: 36 Years: 10	No answer: 2 Months: 12 Ongoing: 15 Years: 5	0.88

Table 3.10: PTSS following first pregnancy

CHAPTER 4

Neurodevelopmental delay in children exposed in utero to hyperemesis gravidarum

4.1 Abstract

Objective: The purpose of this study is to determine the frequency of emotional, behavioral, and learning disorders in children exposed in utero to 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. Binary responses were analyzed using either a Chi-square or Fisher Exact test and continuous responses were analyzed using a t-test.

Results: Children exposed in utero to HG have a 3.28-fold increase in odds of a neurodevelopmental diagnosis including attention disorders, learning difficulties and delays (LDD), sensory integration disorder/sensory processing disorders (SID/SPD), and speech and language impairment/delay (SLI). The p-value for these conditions combined were less than 0.0005. Among characteristics of HG pregnancies, only early onset of symptoms (prior to 5 weeks gestation) was signif-

icantly 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.

4.2 Introduction

Published data has demonstrated pregnancy complications associated with HG. Two systematic reviews showed HG is significantly associated with low birth weight, SGA, and preterm birth [11, 12]. There is less information, however, on outcomes of children exposed to HG in utero [15, 42]. Recently we found a 3.6-fold increased risk of emotional and behavioral disorders in adults exposed to HG in utero [43, 44]. Herein, we determine the risk for emotional, behavioral, and learning disorders in children from well-defined cases with HG compared to well-defined controls without HG. Factors significantly associated with neurodevelopmental delay in children exposed to HG in utero were also identified.

4.3 Materials and Methods

An online survey was used to obtain information on a variety of demographic characteristics, pre-existing conditions, pregnancy symptoms and treatments, and maternal and fetal outcomes [8]. A follow-up survey was administered to report on the diagnosis of childhood emotional, behavioral, and learning disorders [8].

Respondents were categorized according to two binary responses in each table. Table 4.1 compared maternal and child characteristics between all of the children who were exposed to HG in utero to those children who were not. In order to account for genetic or familial traits these two groups were compared as families in Table 4.2. Proportions of families in each group that had diagnosis in at least one child per family were compared. Tables 4.3 and 4.4 both looked at children who were exposed to HG in utero, comparing those who had an adverse child outcome versus those who had a healthy child outcome. To evaluate differences amongst the groups Chi-square and Fishers exact tests were used for categorical variables and t-tests were used for numerical variables. Logistic regression was performed in order to derive estimated odds ratios and confidence intervals corresponding to various diagnoses found in families.

The variables weeks pregnant at first home health care visit, and weeks pregnant at first outpatient visit had missing response rates of 4.5% and 4.8%, respectively. All other variables had missing response rates below 1.4%. For each of the tests performed and models considered, observations with missing responses for any of the variables in the corresponding model were omitted.

4.4 Results

Cases and controls were well-matched for mean maternal age, spontaneous labor, delivery method, and use of assisted reproduction (Table 4.1). Children of cases and controls were well-matched for gender and age, with the average age between 8 and 9 years old. Participants with HG had fewer children overall (1.54 on average for cases with HG compared to 1.9 for the control group) and were significantly more likely to have a child born premature (before 37 weeks).

Women with HG were significantly more likely to report a diagnosis of attention deficit disorder/attention deficit hyperactivity disorder (ADD/ADHD), learning delays, sensory integration/sensory processing disorder, social development delay or social anxiety, and speech or language delay in at least one of their children (Table 4.2). There was no significant difference in the reported rates of autism spectrum disorder, bipolar disorder, central auditory processing disorder, conduct disorder, depression, dysgraphia, dyslexia, intellectual impairment, memory impairment, obsessive compulsive disorder, self-control issues, self-mutilation, or visual/spatial skill impairment. However, a larger sample size is needed in order to have sufficient power to discriminate adequately between the HG group and the control group with regard to rare conditions such as autism spectrum disorder.

There was a trend toward more mothers with HG reporting at least one child born preterm, but it was not significant ($p = 0.07$). Overall, 49% of women with HG reported at least one child with an emotional, behavioral, or learning disorder, compared to 22% of women without HG. This corresponds to a combined 3.28-fold increase in odds of neurodevelopmental delay in children from pregnancies complicated by HG (OR 3.28, 95% CI $= [1.89 - 5.92]$).

To analyze potential factors associated with neurodevelopmental delay in children exposed in utero to HG, we looked at the gestational age symptoms began, time of first treatment, treatment setting, and the gestational age weight gain began. Among these, only NVP symptoms beginning at gestational age of 1-4 weeks were significantly associated with neurodevelopmental delay (Table 4.3). The pregnancy characteristics, gestational hypertension, ptyalism, and preterm birth rate (< 37 weeks) were also compared between women with HG and a child diagnosed with neurodevelopmental delay and women with HG and no children diagnosed with neurodevelopmental delay. Neither were associated with the diagnoses seen in this study.

We also explore the influence of various medications and treatments on child outcome in the two groups (138 children exposed to HG with neurodevelopmental delay compared to 174 children exposed to HG with a good outcome). Among 37 medications/treatments, none were significantly associated with neurodevelopmental delay (Table 4.4).

4.5 Comment

This study shows a 3.28-fold increase in odds of a neurodevelopmental diagnosis in children born from pregnancies complicated by HG. This finding is not surprising given that previously, we found 3.6-fold increased risk of a behavioral or emotional disorder in adults exposed to HG in utero [43, 44]. Other studies on nausea and vomiting and pregnancy and neurodevelopment have somewhat conflicting results on the effects of NVP and neurodevelopment. Martin et al. showed nausea beyond the first trimester was associated with lower task persistence at age 5 and more attention and learning problems at age 12, while Nulman et al.

showed higher intelligence scores in NVP-exposed children [45, 46]. Consistent with Nulman et al., we find no evidence for intellectual impairment. Consistent with Martin et al., our results support the finding that HG may have an effect on the emotional/behavioral development of exposed individuals as well as learning, speech, and language delay, most likely independent of overall intelligence.

The mechanism for exposure to HG and abnormal neurodevelopment is unknown, but there are several hypotheses offered in the literature. Maternal anxiety and stress are common during HG pregnancies [47, 48]. Maternal stress, primarily during the first and second trimesters, has been linked to permanent changes in neuroendocrine regulation and behavior in offspring. Neuroendocrine regulation is regarded as an important factor underlying both ADD/ADHD and depression. Interestingly, animal studies convincingly show that stress during pregnancy results in offspring with increased anxiety and depressive behavior possibly by altered fetal development of the Hypothalamicpituitaryandrenal (HPA) axis and alterations of regulatory and neurotransmitter systems in the brain [49, 50].

More than a quarter of HG pregnancies result in greater than 15% weight loss and symptoms persist until term in over 20% of pregnancies. This suggests HG can be a form of prolonged starvation [6]. Studies of the Dutch and Chinese famine reveal that in addition to significant low birth weight, smaller head circumference, and cardiovascular disease, there are more schizophrenia spectrum disorders, congenital anomalies of the central nervous system and antisocial personality disorders among people exposed to famine in the first half of gestation. It is proposed that stunted brain development underlies these associations. Among people exposed in-utero to famine in mid or late gestation, affective disorder occurred more frequently, possibly due to abnormal programming of the HPA-axis [51].

While the cause of HG is unknown, hormone dysregulation is widely believed to be the most plausible explanation. Hormones, estrogen in particular, have been linked to development of the central nervous system in murine models [52]. While abnormal maternal serum leptin levels are a marker of HG, neonatal hyperleptinaemia has been associated with an increased level of anxiety developing in adult rats [53, 54, 55]. The findings described by our data, therefore, may be the result of exposure to abnormal hormone levels during fetal development.

HG can also have substantial physical and psychological effects on the mother and can be a financial burden postpartum [28]. Women with extreme weight loss due to HG are more likely to have longer recovery times, postpartum digestive problems, muscle pain, gall bladder dysfunction, and PTSS. A child with a behavioral disorder was reported by 9.3% of these women [28]. It is possible that these conditions may have a negative effect on maternal-infant bonding which in turn may contribute to the behavioral abnormalities seen later in life. This theory is supported by rodent studies that show maternal care in the first week after birth results in epigenetic modification of genes expressed in the brain that shape neuroendocrine and behavioral stress responsivity throughout life [56].

Lastly, severe cases of HG can lead to vitamin deficiency syndromes such as maternal Wernickes Encephalopathy caused by thiamine deficiency and fetal intracranial hemorrhage caused by vitamin K deficiency [2, 57]. Reports have linked early neonatal vitamin K deficiency to impaired neuronal migration and cortical dysplasia [58, 59]. Specific nutritional deficiencies in pregnancy such as deficits of folate and vitamin B12 have been linked to disruptions in myelination and inflammatory processes in infants and a greater risk of depression in adulthood [60]. In animal models, prenatal vitamin D deficiency is linked to adverse neuropsychiatric outcomes [61]. While we cannot identify the specific cause of the neurodevelopmental

delay in this study, the finding that early symptoms are significantly associated with neurodevelopmental delay supports the theory that very early nutritional deficiencies may play a critical role. Future studies to determine whether earlier maternal/fetal supplementation can minimize the increased risk of neurodevelopmental delay are needed.

Admittedly there are limitations to the study. The participants were not assessed for certain factors that may increase risk of neurodevelopmental delay such as maternal smoking, alcohol consumption, and recreational drug use during pregnancy [62, 63]. However, maternal smoking is inversely correlated to HG and participants with HG in this study required iv fluid treatment due to low fluid intake [64]. Thus, if cases and controls are not well matched for smoking and/or alcohol consumption, it would likely bias toward the null. Another limitation to the study is that the childhood diagnoses are self-reported and therefore may not be accurate. However, the rates of diagnoses in the control population (with an average age of 8) are consistent with rates reported in the published literature, for example, ADD/ADHD 5.6% here versus 7.6% reported for ages 5-11; ODD 4.5% here versus 4.6% reported for ages 3-17, suggesting accurate self-reporting [65, 66]. Also, because of the small sample size, we combined all significant adverse outcomes to analyze factors linked to neurodevelopmental delay. Although we found no evidence linking combined neurodevelopmental diagnoses to specific medications or treatments, time to first treatment, severity of disease, pytalism, preterm birth, nor to gestational hypertension, this study cannot detect whether these factors may be related to individual diagnoses.

Interestingly, the only factor significantly linked to neurodevelopmental delay is early onset of symptoms, which was also found in a previous study to be linked to AFO [67]. It can be of some comfort for women to know that while antihis-

tamines, which are commonly used to treat HG, were linked to preterm birth in HG pregnancies, there was no evidence of antihistamine exposure being linked to neurodevelopmental delay in children [67]. Consistent with our findings, in a recent study, Larrimer et al. also found no evidence linking adverse neurobehavioral outcomes to common antiemetics, promethasizine, and ondansetron, in pregnancy [68].

Our finding that early onset of symptoms are linked to neurodevelopmental delay suggests early onset HG may be considered a negative prenatal exposure leading to adverse health outcomes. There is increasing evidence across species, including humans, that there are developmental origins of health and disease including neuropsychiatric disease [69]. Early exposure to altered nutrition and stress during development can lead to epigenetic alterations that can persist into adulthood and extend beyond a single generation. More research in this area is critical and should focus on whether early nutritional supplementation in HG patients overrides potentially adverse epigenetic modification and subsequent adverse neurodevelopmental outcomes.

One of the strengths of this study comes from the long-standing collaboration with the HER Foundation that resulted in a unique opportunity to identify a large group of women affected by HG and the ability to collect long-term outcome data. In addition, the study design allowed for a significantly well-matched study population. Furthermore, by limiting the second part of the study to survey participants with HG, the study was able to control for potential confounding genetic factors contributing to HG that may also contribute to the child outcome disorders.

In conclusion, a significant increase in neurodevelopmental and behavioral disor-

ders in children exposed to HG in utero was demonstrated which suggests HG may be linked to life-long effects on the exposed fetus. The cause for this association is unknown, but may be due to maternal stress, abnormal hormone levels during fetal development and/or maternalnewborn bonding after birth, or malnutrition and vitamin deficiency. In addition to the findings reported herein, increasing evidence support long-term adverse outcomes associated with HG exposure including higher baseline cortisol concentrations, reduction of insulin sensitivity, and greater risk of testicular cancer in adulthood [70, 71]. HG is an understudied and undertreated condition of pregnancy that can result in not only short-term maternal physical and mental health problems, but also potentially life-long consequences to the exposed fetus, especially for those exposed to early symptoms.

4.6 Tables

	N = 312	N = 169	P-value
	Children exposed to HG	Children not exposed to HG	
Mean maternal age	28.89	27.27	0.2132
Maternal race (caucasian)	92.4%	95.7%	0.5408
SES (Low)	10.6%	11.6%	1
SES (Medium)	78.2%	81.2%	0.7482
SES (High)	11.3%	7.2%	0.5027
Spontaneous labor	60.08%	70.31%	0.1717
Vaginal delivery	83.40%	84.38%	0.9995
Assisted reproduction	7.69%	3.53%	0.2677
Female gender child	54.81%	51.47%	0.7142
Mean childrens age	8.1333	8.5966	0.4378
Preterm birth	13.46%	7.10%	0.0502
Mean number of children per family	1.54	1.9	0.0015

Table 4.1: Maternal and child characteristics

	N = 203 HG	N = 89 families No HG	P-value	OR	95% CI
ADD/ADHD	18.72	5.62	0.0064	3.8691	(1.56, 11.55)
LDD	12.32	3.37	0.0297	4.0262	(1.36, 17.24)
SID/SPD	19.70	8.99	0.0355	2.4847	(1.17, 5.94)
Social Development Delay or Social Anxiety	10.34	2.25	0.0333	5.0192	(1.43, 31.83)
SLI	24.14	11.24	0.0178	2.5136	(1.43, 31.83)
ADD/ADHD, LDD, SID or SPD, social development delay or social anxiety, and SLI (combined)	48.77	22.47	< 0.0005	3.2841	(1.89, 5.92)
Preterm birth	18.23	8.99	0.0663	2.2568	(1.05, 5.42)

Table 4.2: Increased risk of neurodevelopmental delay (diagnosis in at least one child reported per family) in children exposed to HG.

Demographic characteristics	ND[a]	No ND	P-value
N	138	174	
HG characteristics Week of NVP			
Week 1-4	42.75%	30.46%	0.0332
Week 5-8	52.90%	66.09%	0.0245
Week 9-12	4.35%	2.87%	0.6949%
Time of first treatment as			
Inpatient	10.16	9.94	0.7967
Home health care visit:	10.57	11.54	0.36
Outpatient visit:	9.03	9.7	0.4451
Time (weeks) to first treatment after nausea began	4.63	4.06	0.3182
Hospitalization			
Inpatient (paired with anything else)	50.72%	46.55%	0.5363
Home health care (paired with anything else)	55.80%	54.60%	0.9228
Outpatient only	22.46%	27.01%	0.4297
Weight gain			
Week they began gaining weight	20.14	19.05	0.2274
Other			
Gestational hypertension	7.97%	7.47%	1
Ptyalism	35.51%	35.06%	1
Preterm birth	13.77%	13.22%	1

Table 4.3: Early symptoms associated with neurodevelopmental delay

Treatments and medications	N = 138	N = 174	
	HG with ND (%)	HG no ND (%)	P-value
Allergy	1.45	0.00	0.3794
Antacids	58.70	51.72	0.2651
Antibiotics	2.17	1.15	0.7934
Antidepressants/Antianxiety	12.32	9.20	0.4804
Antimotion sickness meds	19.57	16.09	0.5157
Anzemet (Dolasetron)	3.62	2.30	0.7236
B6 injection	6.52	9.77	0.4095
Bedrest	64.49	52.30	0.0404
Prochlorperazine	21.01	13.22	0.0925
Domperidone	1.45	0.57	0.8398
Herbal medicine	13.04	11.49	0.8093
Homeopathics	12.32	11.49	0.9621
IV Therapy	81.88	79.31	0.6704
Methylprednisolone	9.42	8.05	0.8211
PICC	23.19	14.94	0.0867
Promethazine	54.35	51.15	0.6543
Lansoprazole	10.87	5.75	0.1484
Metoclopramide	44.20	50.57	0.3149
Seabands/relief bands	53.62	48.85	0.4694
SpecialDiet (bland, low fat, low acid)	54.35	48.85	0.3949
Chlorpromazine, Haloperidol	0.72	1.72	0.785
Tigan/Vomet (trimethobenzamide)	6.52	3.45	0.3202
TPN/TPPN	15.22	10.92	0.3384
Acupuncture	12.32	16.67	0.3602
Vitamins (taken orally-pyridoxine, etc.)	43.48	40.23	0.6438
Vitamins (IV)	26.09	20.69	0.3229
Ondansetron	71.74	65.52	0.2936

Table 4.4: Treatments and Medications Child was Exposed to in Utero

CHAPTER 5

Long-term health effects in children exposed in utero to hyperemesis gravidarum

5.1 Abstract

Objective: Previously we reported on the increased risk of adverse neurodevelopmental outcomes in children exposed in utero to HG. The purpose of this study is to determine the frequency of non-neurodevelopmental long-term health effects in children exposed in utero to HG and to identify prognostic factors for these disorders.

Study Design: Long-term outcomes of 312 children from 203 mothers with HG were compared to outcomes from 169 children from 89 unaffected mothers. The clinical profiles of patients having a child with an adverse outcome were then compared to the clinical profiles of patients having a child with a normal outcome to identify prognostic factors. Proportion tests were used to compare outcomes between variables with binary responses. Continuous responses were analyzed using a t-test.

Results: Children exposed in utero to HG have a 3.82-fold increase in odds of being diagnosed with a long-term health effect including allergies, chronic constipation, GERD, growth restriction (height and weight below 20th percentile), lactose intolerance, chronic respiratory or ear infections, or sleep difficulties ($p < 0.0005$).

Among HG patients, women who took promethazine during pregnancy or began gaining weight later in their pregnancy (after 20 weeks) were more likely to have a child that was diagnosed with allergies. Those who took antidepressants while pregnant were more likely to have a child with chronic constipation. Metoclopramide use during pregnancy was protective against having a child diagnosed with GERD. Preterm delivery and anti-motion sickness medications were both significantly linked to growth restriction in a child. Both herbal medicine and homeopathics were also significantly linked to growth retardation as well as sleep difficulties. PICC and Dolasetron use were linked to having a child with respiratory or ear infections.

Conclusion: Women with HG are at a significantly higher risk of having a child with long-term health effects. This study demonstrates the need for further analyses to address whether HG itself or certain herbal and prescribed medications taken during pregnancy are responsible for the increased risk.

5.2 Introduction

Published data has demonstrated pregnancy complications associated with HG. Two systematic reviews showed HG is significantly associated with low birth weight, SGA, and preterm birth [11, 12]. There is less information, however, on outcomes of children exposed to HG in utero [15, 70]. In the past, we found a 3.6-fold increased risk of neurodevelopmental disorders in adults exposed to HG in utero [43, 44]. In a more recent study we found that children exposed to HG in utero show a 3.28-fold increase in odds of having a neurodevelopmental diagnosis including attention disorders, learning delay, sensory disorders, and speech and language delay [72]. Herein, we determine the risk for non-neurodevelopmental

long-term health effects in children from well-defined cases of HG compared to well-defined controls. Factors such as pregnancy characteristics, treatments, and medications taken during pregnancy that were significantly associated with adverse outcomes in children exposed to HG in utero were also identified.

5.3 Materials and Methods

Maternal and child characteristics were compared between children who were exposed to HG in utero and those who were not (Table 4.1). Children were then separated based on whether or not there was a family history of HG (Table 5.1). To account for genetic or familial traits, proportions of families in each group that had diagnosis in at least one child per family were compared. To evaluate differences amongst the groups, proportion tests were conducted for categorical variables and t-tests were used for numerical variables. Logistic regression was performed in order to derive estimated odds ratios and confidence intervals corresponding to various diagnoses found in families (Table 5.1).

Pregnancy characteristics (such as the week NVP and weight gain began), hospitalization data, preterm birth, treatments, and medications taken during pregnancy were compared between those who had a child with a long term health effect versus those who had a healthy child outcome (Table 5.2). Within the HG group, we examined potential factors linked to adverse outcomes such as treatments and medications received during pregnancy, NVP characteristics, and preterm births. To see if a treatment, medication, or symptom affected the probability of having a child with an adverse outcome, a proportion test on the presence of each long-term effect was performed.

Lastly, to detect any clustering or groupings of characteristics in the HG group,

the child data set was transformed into a binary data set to represent the presence and absence of each condition. After applying non metric multi-dimensional scaling, hierarchical clustering, and k-means clustering to the child dataset, we found no apparent clustering or groupings of diagnoses in the HG group.

5.4 Results

All participants were from the United States. Cases and controls were well matched for mean maternal age, race, SES, spontaneous labor, delivery method, and use of assisted reproduction (Table 4.1). The children of both groups were also well matched for gender and age, with the average age between 8 and 9 years old. HG patients tended to have fewer children (1.54 on average for cases with HG compared to 1.9 for the control group) and were significantly more likely to have a child born premature (before 37 weeks).

HG patients were significantly more likely to report a child that had a diagnosis of allergies, chronic constipation, GERD, growth restriction (weight and height below the 20th percentile), lactose intolerance, chronic respiratory or ear infections, or chronic sleep difficulty in at least one of their children (Table 4.2).

Among other physical issues including asthma, eczema, motor delays, vision problems, weight issues, excessive bruising, cleft palates, cavities, cyclic vomiting syndrome, and abnormalities in the skin, face, ligaments, joints, limbs, and extremities, there were no significant differences with the reported rates between the cases and controls. A larger sample size would be needed to ensure precise and accurate estimates between groups, especially for rare conditions.

Preterm birth, though not statistically significant (p = 0.07), was more common among HG families. Overall, 84% of HG patients reported at least one child with a long-term health effect, compared to 57% of women without HG. This corresponds to a combined 3.82-fold increase in odds of having a child diagnosed with an adverse physical condition from pregnancies complicated by HG (OR 3.82, 95% CI = [2.20, 6.77]).

We compared gestational age at which NVP began, time of first treatment for NVP, treatment setting, gestational age at which weight gain began for the mother, rates of gestational hypertension, ptyalism, preterm birth, and treatments and medications taken during pregnancy within the HG group (Table 5.2). Those who took an anti-motion medication and had IV therapy were more likely to have a child that had at least one adverse physical outcome listed in Table 5.1. Later weight gain as well as being a home health care patient were also significant indicators of having a child with an adverse physical outcome.

Forty different treatments and medications were explored to look for possible links to individual adverse outcomes significantly increased in families with children exposed to HG compared to controls. Our sample included 232 children that were exposed to HG with a long-term health effect and 80 children who were exposed to HG with a good outcome. Patients who took promethazine were more likely to have a child with allergies. Antidepressants were linked to having a child with chronic constipation. Homeopathy, herbal and anti-motion sickness medications were linked to having a child that experienced growth restriction. Having IV therapy was linked to having a lactose intolerant child. Dolasetron and having treatment through a PICC were linked to higher rates of having a child with respiratory/ear infections. Lastly, homeopathy and herbal medication were both significantly associated with a higher rate of having a child that had chronic sleep

difficulties.

5.5 Comment

This study focuses on the most extreme end of NVP in which symptoms are prolonged and intractable. Women affected with HG show a 3.82-fold increase in odds of having a child diagnosed with an long-term health effect later in life. Failure to gain enough weight during pregnancy puts the child at risk for intrauterine growth restriction, which then may put the child at greater risk for other neurodevelopmental and physical problems later in life compared to infants of normal weight. Our data supports this, showing that HG mothers have a 3.14-fold increase in odds of having a child who suffers from growth failure [73].

The specific mechanism linking exposure to HG and abnormal physical development is unknown, however several studies have shown significant associations between HG and physical developmental problems in children. Higher rates of diagnoses with undescended testicles, hip dysplasia, and down syndrome were reportedly associated with HG according to a cohort study done in Sweden [22]. In utero, vitamin D deficiency has recently been linked to an increased risk of asthma, allergy, and acute lower respiratory infections in early childhood [74, 75]. Neonatal vitamin A deficiency has been associated with an increased risk of ear and respiratory infections [76]. Herbal medicine, when used during the first trimester, which was found to be linked to a higher rate of growth failure in our study, has been found to be significantly associated with congenital malformations [77].

In more than a quarter of HG pregnancies, patients experience at least a 15% loss in body weight. HG symptoms persist until the end of the pregnancy in over 20%

of cases. This lack of nutrition and hydration suggests HG can be a form of prolonged starvation [4]. The Dutch Famine of 1944 demonstrated the detrimental effects of prenatal exposure to undernutrition. The Dutch Famine Birth Cohort Study not only found that the children whose mothers lived during the Dutch famine of 1944 were at higher risk for health problems, but the children of these children were thought to be smaller than average, suggesting a possible epigenetic characteristic was passed down to the next generation [78].

In our sample, the intake of antidepressants were linked to having a child with chronic constipation. While there have been adverse outcomes associated with exposure to selective serotonin reuptake inhibitors (SSRI) such as lower Apgar scores and delayed motor development reported previously, more recent studies have not demonstrated any significant birth defects associated with their use [79, 80]. Future studies are needed to determine whether such medications can increase the risk for any long-term health effects.

There are limitations to the study. Participants were not assessed for common factors associated with adverse or delayed physical outcomes such as maternal smoking, alcohol consumption, and recreational drug use during pregnancy [62, 63]. However, maternal smoking is inversely associated with HG, and the HG participants in this study required IV fluid treatment due to low fluid intake. Thus, if cases and controls were not well matched for these characteristics, the results would likely bias toward the null.

Because this was an online survey, all the conditions were self-reported which presents the possibility of inaccurate findings, and a potential source of response bias. However rates of diagnoses in our control population are consistent with rates reported in the published literature. In our sample 35.96% of mothers re-

ported that at least one of their children had allergies. According to the American Academy of Allergy, Asthma, and Immunology the population proportion of school children who are reactive to common allergens is approximately 40% [81]. In March 2015 the American Academy of Otolaryngology published that an estimated 5-8% of adolescent children have GERD, which is consistent with the 7.87% of our controls that reported at least one child with GERD [82].

Our small sample size is also another limitation. We examined as a response variable the collection of all significant adverse outcomes in order to search for potential predictors and found significantly higher rates of adverse physical outcomes amongst those who took anti-motion medications, had IV fluid treatment, were home health care patients, and began gaining weight after week 20. However, for particular individual response variables, especially rarely observed outcomes such as chronic sleep difficulties or chronic constipation, our study has insufficient power to detect significant predictors. Further, in this study we are performing numerous simultaneous tests in order to investigate potential links between HG and associated treatments with a variety of outcomes. We report individual p-values and these should be interpreted qualitatively as summaries of the strength of the observed correlation, but further study is needed to determine if these associations definitively exist in the overall population. In addition, we certainly cannot infer causal links between treatments and adverse consequences based on the observed associations from this observational study.

One of the strengths of this study comes from the long-standing collaboration with the HER Foundation that provided a unique opportunity to involve a large group of women affected with HG to contribute important data. In addition, the design allowed for a significantly well-matched study sample. By limiting the second part of our analysis to HG patients only, we were able to control for potential

confounding factors contributing to HG that could possibly also contribute to adverse child outcomes.

Adverse physical outcomes are significantly associated with children who were exposed to HG, which suggests that such exposure could have long-term effects on a child. The cause for this association is unknown, but may be due to certain medications/treatments, maternal stress, abnormal hormone levels during fetal development, malnutrition, or vitamin deficiency. The nutrition the child receives in utero and immediately after birth from its mother is vital for physical development. When the mother's health, nutrition, and hormone balance is compromised, so is the health of the baby. HG is an understudied and undertreated condition of pregnancy that not only results in maternal physical and mental health problems, but also potentially long term health consequences to the exposed fetus.

5.6 Tables

	N = 203	N = 89 families	P-value	OR	95% CI
Diagnosis	HG	No HG			
Allergies	51.72%	35.96%	0.02	1.9085	(1.15, 3.21)
Chronic Constipation	22.17%	8.99%	0.0116	2.8837	(1.36, 6.86)
GERD	26.11%	7.87%	0.0007	4.1390	(1.91, 10.36)
Growth Retardation	15.76%	5.62%	0.0273	3.1439	(1.28, 9.45)
Lactose Intolerance	24.14%	11.24%	0.0178	2.5136	(1.25, 5.50)
Chronic Respiratory/Ear Infections	29.56%	16.85%	0.0322	2.0699	(1.12, 4.01)
Sleep Difficulties	20.69%	5.62%	0.0023	4.3826	(1.82, 13.04)
Allergies, Chronic Constipation, GERD, Growth Retardation, Lactose Intolerance, Chronic Respiratory or Ear Infections, or Sleep Difficulties	83.74%	57.30%	< 0.0005	3.8179	(2.20, 6.77)
Preterm birth	18.23%	8.99%	0.0663	2.2568	(1.05, 5.42)

Table 5.1: Increased risk of long-term health effects (diagnosis in at least one child reported per family) in children exposed to HG.

			P-value
Allergies	Gained weight $\geq$ 20 weeks	Gained weight before 20 weeks	
	50%	34.51%	0.0126
	Promethazine	No Promethazine	
	48.17%	5.81%	0.0365
Chronic Constipation	Time of first treatment as Inpatient 5 weeks or after	Time of first treatment before 5 weeks	
	17.93%	80.00%	0.0045
	Antidepressants	No Antidepressants	
	30.30%	13.98%	0.0289
GERD	Metoclopramide	No Metoclopramide	
	13.42%	25.15%	0.0136
Growth Retardation	Preterm Birth	No Preterm Birth	
	26.19%	9.26%	0.0033
	Anti-motion sickness medication	No Anti-motion sickness medication	
	20%	9.73%	0.0534
	Herbal	No Herbal	
	26.32%	9.49%	0.0056
	Homeopathy	No Homeopathy	
	29.73%	9.09%	0.0006
Allergies, Chronic, Constipation, GERD, Growth Retardation, Lactose Intolerance, Chronic Respiratory or Ear Infections, or Sleep Difficulties	Anti-motion sickness medication	No Anti-motion sickness medication	
	89.09%	71.21%	0.0097
	IV	No IV	
	78.49%	57.38%	0.0013
	Seabands	No Seabands	
	81.13%	67.32%	0.0077
	Home Health Care	No Home Health Care	
	83.84%	69.95%	0.0133
	Gained weight $\geq$ 20 weeks	Gained weight before 20 weeks	
	80.31%	69.28%	0.0493

Table 5.2: Pregnancy characteristics, NVP symptoms, treatments and medications taken during pregnancy within the HG group

CHAPTER 6

Results

One of the most fundamental ways to asses model performance in regression is to view the actual data against the predicted values. This was the motivation behind the power analysis, more particularly to explore how graphical methods can be interpreted by the choice of bin size. Is there a way to determine an optimal bin size, such that we can identify where power is relatively high for smaller bin sizes? In this analysis we observed the behavior of power with respect to bin size through the use of a null and alternative model. In all the cases discussed all models have only one predictor.

In 1980 David Hosmer and Stanley Lemeshow proposed grouping cases together according to predicted values derived from the logistic regression model. These values were ordered in increasing order then separated into groups of approximately equal size depending on the number of observations (10 is the standard recommended number of groups). A limitation with this standard is the variability of results produced, as it can vary greatly depending on the number chosen, and there is no theoretical base to guide the optimal choice of that number. In this analysis, our attempt to finding a bin size begins with graphical explorations of bin size on parameters such as the distribution of predictors, number of observations, iterations, and coefficients chosen for both the original and alternative models we apply the power analysis to.

We quickly revisit the parameters defined in Chapter 1.4:

•m: number of observations

•s: number of simulations

•u: proportion of interest

•h: bandwidth around u

•β_0, β_1: coefficients for the true model

•β_{0A}, β_{1A}: coefficients for the alternate model

•*obs.prop*: observed proportion of 1's in a particular bin, $u \pm h$:

$$\frac{\sum(y = 1)[p^{(s)} \in (u \pm h)]}{length(p^{(s)} \in (u \pm h))}$$

•$reject$: number of rejections for true model

•$reject_A$: number of rejections for alternate model

6.1 Standard Normal Case

We first start with the case where $s = 1000, m = 5000$, and $x \sim N(0, 1)$. The coefficients for the null model were: $\beta_0 = 1, \beta_1 = 2$, and for the alternate model: Alternate model: $\beta_{0A} = 1, \beta_{1A} = -1$

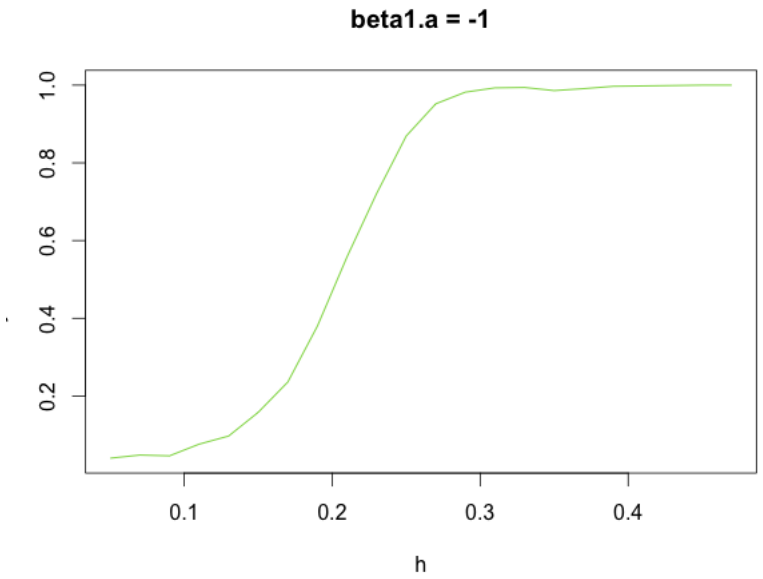


Figure 6.1: Power as a function of h for standard normal

Modifying the example above by only changing the alternate model where $\beta_{0A} = -4$ and $\beta_{1A} = 2$, it is shown in Figure 6.1 that power is slightly hampered by the change in coefficients when h is greater than 0.2.

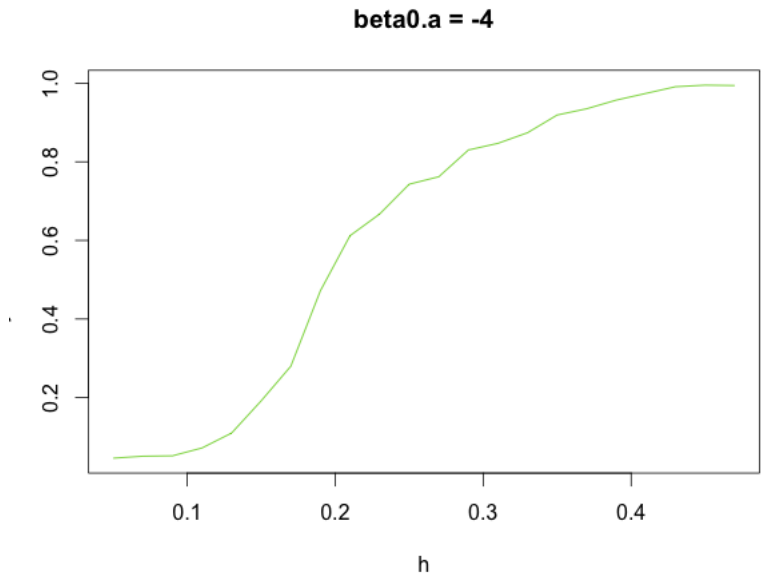


Figure 6.2: Power vs h for Standard Normal Case, $\beta_{0A} = -4$ and $\beta_{1A} = 2$

Aside from varying the coefficients for the alternate model, the analysis was also run for different sample sizes (m). Smaller values of m (close to 100), were problematic for $h < 0.15$. A smaller amount of observations increased the chances of capturing a bin with no observations whereas for $m = 1000$ and $m = 5000$, h can be as low as 0.015 and 0.005 respectively. Simulating the analysis with values of m between 100 and 5000 affected the power by less than 5%.

6.2 Uniform Case

The more the coefficients for the alternate model deviated from the null, the smaller the range was for the fitted values which limited the number of bins observations would lie. For simplicity, the deviations in the coefficients were decreased so as not to completely skew the results of the fitted values. The second series of results presented here came from applying the power test with a predictor following the uniform distribution, $x \sim Unif(0, 1)$. In Figure 6.3, $s = 1000$

and $m = 5000$. The null model was assigned $\beta_0 = 0.5$ and $\beta_1 = 0.7$, and the alternate model was assigned $\beta_{0A} = 0.8$ and $\beta_{1A} = 0.7$. Compared to the previous simulation that used a Normal distribution, power increased at a much faster rate.

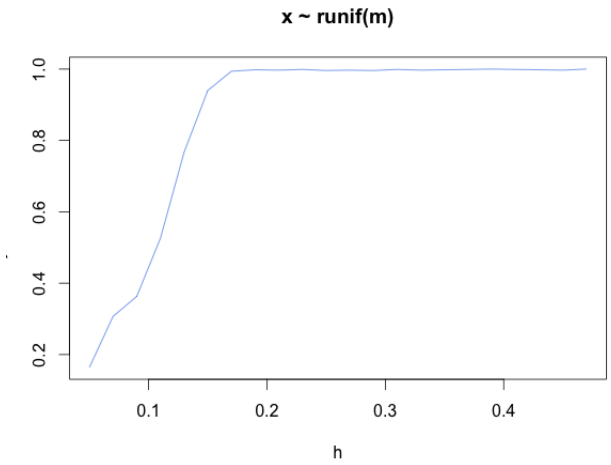


Figure 6.3: Power vs. h for Standard Uniform Case

Modifying only the number of observations to $m = 400$ shows an increase in power for $0 < h < 0.1$, however it appears to remain constant at around 0.85 as shown in Figure 6.4.

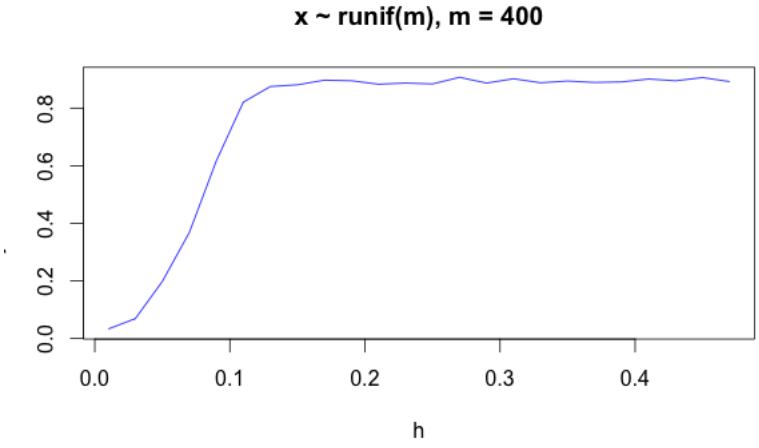


Figure 6.4: Power vs. h for Standard Uniform Case, $m = 400$

The power analysis was applied to the mean percent weight loss variable used in the first HG study on adverse fetal outcomes which followed a Uniform distribution ($Unif(0, 0.2)$). Though the sample size here was $m = 562$, higher than the previous case, the power was considerably lower. This is likely due to the larger difference in coefficients between the null and alternate model. The power fluctuated greatly between 27% and 35%.

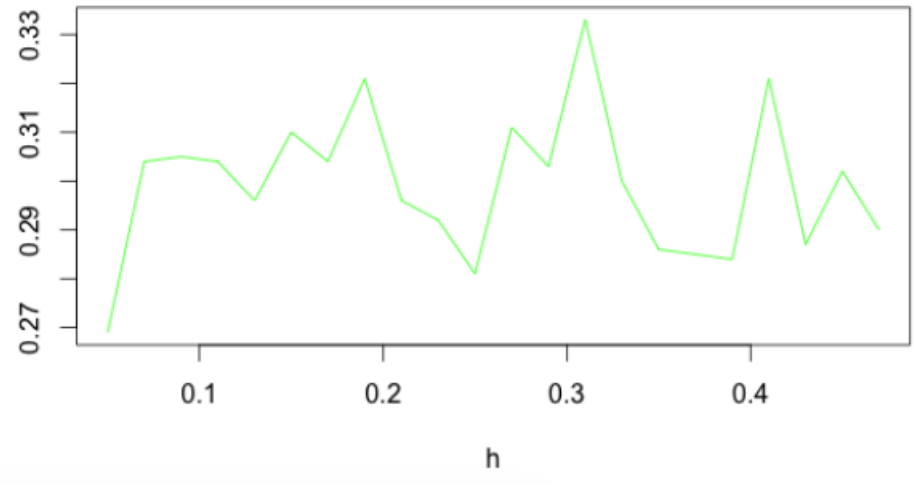


Figure 6.5: Power vs. h for Mean Percent Weight Loss, $m = 562$

Holding the coefficients (from the mean percent weight loss simulation) constant and increasing the sample size yielded a significant improvement in power. Here the null model is assigned $\beta_0 = 0.5$ and $\beta_1 = 0.7$ and the alternate model is assigned $\beta_{0A} = 0.4, \beta_{1A} = 0.2$. Power is significantly higher in this case, showing a spike at approximately $h = 0.05$, and staying well above 98% thereafter.

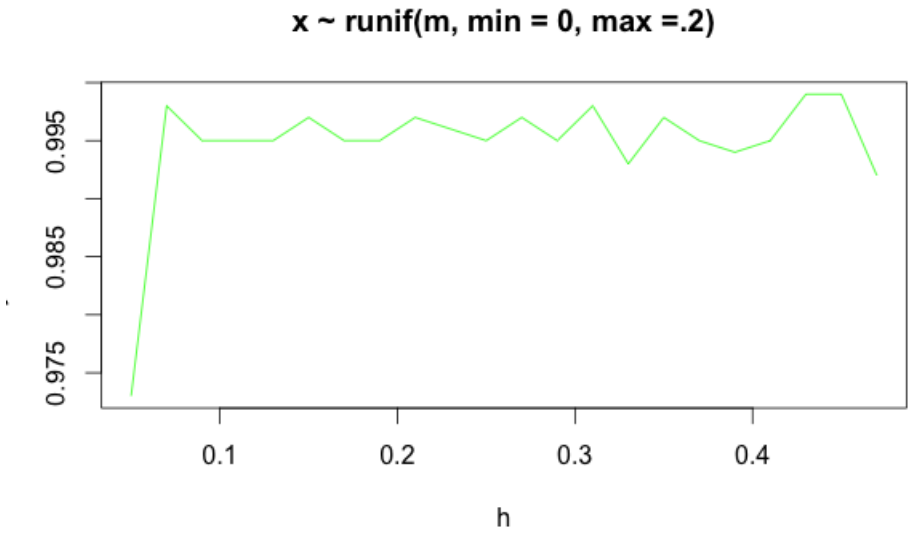


Figure 6.6: Power vs. h, $m = 5000$

CHAPTER 7

Discussion and Future Work

This work presents an alternate way to view the results of a logistic regression, specifically with the characteristics of the HG dataset we used in our studies. The results of the power analysis has its sensitivities with parameters, especially with varying distributions of the predictor. In the Standard Normal cases, there were slight variation in power when the coefficients for the alternate model were changed, and even less variation with very different values of m. Power performed consistently when h was between 0.2 and 0.3 despite changes with the alternate model. In the Uniform distribution case, power was much more sensitive to m and performed better than with a normally distributed predictor. Unlike the Normal case, smaller values of h, as shown in the previous chapter where we compared the results of $Unif(0, 1)$ vs $Unif(0, 0.2)$, had higher power. From the analysis done it is clear that the results can vary greatly with minor changes in the parameters chosen. A direction this can continue to go forward would be to continue the simulations and observe how power changes with respect to different distributions to better define optimal ranges for h.

One area that was not accounted for was the possibility of selecting a bin with no observations. A possible alternative to this problem would be to divide the data into k bins of approximately equal size (number of observations) instead of dividing the axis into a specific bin size. This would also accommodate observations that wouldn't otherwise be picked up if only bin size were being selected.

The datasets used in our HG studies are unique in a sense that the majority of the variables analyzed were categorical (mostly binary), and in some cases very sparse. In many of our studies we also looked at adjusted models that had multiple predictors. Extending this analysis to account for such predictors will give a deeper understanding of how distributions affect the power of a particular bin, as well as provide new insight when multiple distributions need to be accounted for.

Aside from identifying future directions this diagnostic tool can take on with the HG dataset, another goal in this field of study would be to see improvements in the data collection process. Having more follow up studies, controlled studies, and extending the data collection beyond conducting internet surveys are just some of the ways to produce results that are more representative of the general HG population. This, combined with implementing innovative statistical methodologies will have a positive and direct impact on the field of HG research.

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