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No Increased Risk of Psychological/Behavioral Disorders in Siblings of Women with Hyperemesis Gravidarum (HG) unless their Mother had HG

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

No Increased Risk of Psychological/Behavioral Disorders in Siblings of Women with Hyperemesis Gravidarum unless their Mother had HG

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ABSTRACT

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

KEYWORDS: Genetic, Hyperemesis Gravidarum, Outcome, Depression, Bipolar, Anxiety

INTRODUCTION

Hyperemesis Gravidarum (HG), severe nausea and vomiting of pregnancy, accounts for over 285,000 hospital discharges in the U.S. annually.[1] Estimates of severe nausea and vomiting of pregnancy vary greatly and range from 0.3% in a Swedish registry to as high as 10.8% in a Chinese registry of pregnant women, with most authors reporting an incidence of approximately 0.5%.[2-4] HG can be associated with serious maternal and fetal morbidity such as Wernicke's encephalopathy,[5] fetal growth restriction, and even maternal and fetal death.[6,7]

Hyperemesis Gravidarum may be defined as persistent, unexplained nausea and vomiting resulting in more than a 5% weight loss, abnormal fluid and nutritional intake, electrolyte imbalance, dehydration, and ketonuria.[8]. Symptoms often extend beyond the first trimester and can last throughout the entire pregnancy in as many as one-third of cases, leading to extreme weight loss and possibly a state of malnutrition and extended dehydration of pregnancy.[9]

Many studies on the long term outcome of dehydration, starvation and/or anxiety in pregnancy in animal models and humans reveal adverse effects on exposed offspring including cardiovascular disease, obesity, diabetes, as well as neurodevelopmental, cognitive, emotional and behavioral disorders.[10-14] Given that HG can be a form of prolonged dehydration, starvation, and stress in pregnancy, it follows that long-term outcomes could possibly mimic those identified in these studies. Indeed, recently, we showed a 3.6-fold increased risk

of emotional/behavioral disorders in adult offspring exposed to HG in utero.[15] All cases and controls in the previous study had a family history of HG. However, scant attention has been paid to the family histories of women with HG in regard to links between HG and psychological or behavioral disorders. Herein, we compare the rates of emotional/behavioral disorders in cases with and without a family history of HG to determine whether emotional/behavioral predisposition is linked to HG, and to determine whether the rates of psychological/behavioral disorders reported in a previous study are increased due to the genetics of HG.

METHOD

Sample and Settings

This study is part of a larger investigation evaluating the genetics and epidemiology of Hyperemesis Gravidarum (HG). Eligible patients were primarily recruited through advertising on the Hyperemesis Education and Research Foundation Web site at www.HelpHer.org. Another method of recruitment of affected indivituals was a recruitment video on YouTube at http://www.youtube.com/watch?v=_92NFOwvAXcI which provided the rationale for starting this study, information about the study, and contact information. Some participants have also recruited their own affected acquaintances to participate and some participants heard about the study from articles, news stories, and pregnancy or parenting websites.

The inclusion criteria for affected individuals were a diagnosis of HG and

treatment with IV fluids and/or total parenteral nutrition/nasogastric feeding tube. Affected participants were asked to submit their medical records. Minors (under 18 years) were not included in the study because few teens are expected to fit the study criteria of having had two pregnancies and it would be difficult to justify the risks/benefits to minors who never experienced HG. Women over the age of 50 at the time of first contact were not included in a somewhat arbitrary attempt to limit the possibility of recall bias. Because multiple or chromosomally abnormal gestations may be associated with HG due to unique physiological pathways, women with these types of pregnancies were also excluded.

Each participant was asked to recruit a friend with at least 2 pregnancies that went beyond 27 weeks to participate. Unaffected friends were eligible if they experienced normal (did not interfere with their daily routine) or no nausea/vomiting in their pregnancy, no weight loss due to nausea/vomiting and no medical attention in their pregnancy due to nausea. Biological relatives of participants in the study were not included in the study as the case-control study depends on non-relatedness of individuals in the study. All participants who reported their mothers had HG were excluded to avoid reports of emotional/behavioral disorders related to in utero exposure to HG.

This study has been approved by Institutional Review Boards, USC IRB # HS-06-00056 and UCLA IRB # 09-08-122-01A.

Study Procedures

Participants were asked to complete an online survey regarding information on a variety of demographic characteristics and medical conditions in their siblings, including all diagnosed and/or treated emotional/behavioral disorders. The survey instrument can be found at http://www.helpher.org/HER-Research/2007-Genetics/2007rsch-start.php.

A total of 162 participants with HG, confirmed their mother did not have HG while pregnant with their siblings and reported on health complications in 172 siblings that were not exposed to HG in utero. This group of 172 non-exposed siblings of participants who had HG themselves, represents the CASES in this study because they have a family history (sibling with HG, mother not affected).

A total of 95 unaffected friends of participants with HG, confirmed their mother did not have HG while pregnant with their siblings and reported on health complications in 101 siblings that were not exposed to HG in utero. This group of 101 non-exposed siblings of participants who did not have HG themselves, represents the CONTROLS in this study because they have no family history of HG (no affected mother or sister).

Data Analysis

The 257 survey participants were compared for a number of variables including number of siblings, age, ethnicity, and education. Ethnicity and

education were compared using a two-tailed Fisher's exact test, number of siblings and age of siblings were compared using Wilcoxson rank-sum test (Mann-Whitney U or robust t-test) in addition to the conventional t-tests and kolmogorov-smirnov tests.

We report on the psychological/behavioral diagnoses and other health complications are not included herein. The frequency of diagnoses was compared among the cases with a family history of HG (sister with HG) and the controls (no family history) using two-sided Fisher's exact test. Some cases and controls had more than one diagnosis in a given group and therefore the overall affected rate is the number of affected siblings out of the total number of siblings rather than the number of diagnoses out of the total number of siblings.

This study has been approved by Institutional Review Boards, USC IRB # HS-06-00056 and UCLA IRB # 09-08-122-01A.

RESULTS

Matched-Pairs Analysis

Respondents were primarily white and born in the mid-1970s. On average, over 50% had a college degree. At the time of the survey, female and male siblings were primarily in their mid-30s. Respondents were well matched for all variables tested; no significant differences were found between groups (Table 1).

Psychological/Behavioral Disorders

Psychological and behavioral disorders reported by participants on behalf of their siblings are listed in Table 2. Fifteen percent of participants were reportedly diagnosed and treated for an emotional/behavioral disorder regardless of a family history (sister) affected with HG.

DISCUSSION

This is the first study to explore emotional and behavioral issues in families with HG compared to families without HG. Herein adults with a sibling affected with HG were no more likely to have emotional/behavioral disorders including depression, bipolar disorder, and anxiety, than adults with no affected sibling. The cause of HG is unknown, but is reported to have a genetic basis, [16,17]most likely of hormonal etiology.[2] Currently the existence of a psychological component is accepted by the scientific community to be the result of the burden of prolonged physical illness rather than a causal factor.[18—21] Unfortunately, a few methodologically flawed studies have suggested a psychological etiology in the past,[19] leading to skepticism among health care providers and causing a lack of timely and appropriate treatment resulting in more severe symptoms and outcomes.[18-22]

While in this study 15% of adults with and 15% without a sibling with HG were affected with emotional/behavioral disorders, this is in stark contrast to the thirty-eight percent reported to have a behavioral or emotional disorder in adults whose mother's had HG while pregnant with them. The cause for this association

is unknown, but may be due to common factors relating to HG pregnancies such as prolonged maternal stress, malnutrition and vitamin deficiency, abnormal hormone levels during fetal development, and/or maternal-newborn bonding after birth.[15]

Admittedly, there are multiple limitations to this study. For example, the study includes a retrospective component, and self-reporting of maternal HG-status and sibling diagnoses, as well as the fact that our well-matched analysis and diagnosis comparison were conducted on two different pairs of groups. However, the survey respondents appear to have been well matched for all factors studied and reported a similar occurrence of other outcomes not presented herein (ie autoimmune disorders and cancer). Therefore, we can think of no reason why one group would be more likely to have a greater reporting or recall bias than another with respect to the diagnoses reported here.

One of the strengths of this study comes from the long-standing collaboration with the Hyperemesis Education and Research Foundation that resulted in a unique opportunity to identify a large group of individuals 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.

In conclusion, our evidence suggests that women with HG do not have an increased familial risk of emotional/behavioral disorders in their siblings, only in their children. The significance of this is two-fold. Firstly, it provides further confirmation that HG leads to a 3.6-fold increased risk of emotional/behavioral disorders in offspring born of pregnancies affected by HG because both women

with and without a sibling history of HG reported a 15% disorder rate suggesting this is the true background rate in this population, and the 38% of affected participants whose mothers had HG while pregnant with them represents a significant increased risk.

Secondly, this study provides further evidence in refutation of the spurious claim of a link between pre-existing emotional/behavioral factors and HG. 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. Recently, HG was linked to adverse pregnancy outcomes including an increased risk of spontaneous preterm birth[23] and a smaller head circumference, and it was concluded that studies designed to assess the long-term consequences of HG should be given high priority.[24,25] This study lends further support to a 3.6-fold increased risk of long-term emotional/behavioral disorders in offspring of HG pregnancies and supports current evidence against a psychological etiology. The increased psychological sequelae noted in past studies in women with HG are likely to be the result of an HG pregnancy while their mothers were pregnant with them, or due to persistent physical symptoms from a previous or current HG pregnancy, rather than causes of HG. Understanding the etiology of HG and its associated outcomes will lead to more effective therapies or a cure for this debilitating disease of pregnancy.

ACKNOWLEDGEMENTS

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TABLE 1. Participants reporting on cases (CASES) and participants reporting o

	MOM HG	CASES	CONTROLS
Race White	98%	91%	96%
Degree College	63%	54%	60%
Mean reporter year born	1975	1975	1973
Mean sister age	34.3	33.3	36
Mean brother age	33.4	33.7	35.6

* all comparisons tested yielded p > .05.

TABLE 2. Psychological/Behavioral Diagnoses

Diagnosis	MOM HG	CASES	CONTROLS	P-Value A/B/C
ADHD	3	4	0	
OCD	3	3	1	
depression	14	5	9	
bipolar	7	3	2	
learning disorder	3	3	0	
dyslexia	2	0	0	
ADD	1	4	0	
alcoholism/drug addiction	3	2	1	
anxiety	6	4	2	
Rett syndrome	1	0	0	
aspergers	2	1	0	
delayed sleep phase syndro	1	0	0	
schizophrenia	1	0	1	
speech delay	1	0	0	
emotional disorder	1	0	0	
Tourettes Syndrome	0	0	1	
autism	0	1	1	
Total # siblings	87	172	101	
Affected Rate	0.38	0.15	0.15	0.000002

MOM HG-offspring from a pregnancy complicated by HG
CASES-offspring from a pregnancy NOT complicated by HG but do have a positive family
CONTROLS-offspring from a pregnancy NOT complicated by HG and do NOT have a fami

n controls (CONTROLS) are well-matched for all demographic variables tested.

/ history of HG (sister with HG)
ly history of HG

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ORIGINAL ARTICLE

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

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

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Key words: anxiety, bipolar, depression, hyperemesis gravidarum, outcome

Introduction

Hyperemesis gravidarum (HG), severe nausea and vomiting of pregnancy, accounts for over 285,000 hospital discharges in the United States annually.[1] Estimates of severe nausea and vomiting of pregnancy vary greatly and range from 0.3% in a Swedish registry to as high as 10.8% in a Chinese registry of pregnant women, with most authors reporting an incidence of 0.5%.[2–4] HG can be associated with serious maternal and fetal morbidity such as Wernicke's encephalopathy,[5] fetal growth restriction and even maternal and fetal death.[6,7]

HG may be defined as persistent, unexplained nausea and vomiting resulting in more than a 5% weight loss, abnormal fluid and nutritional intake, electrolyte imbalance, dehydration and ketonuria.[8] Symptoms often extend beyond the first trimester and can last throughout the entire pregnancy in as many as one-third of cases leading to extreme weight loss and possibly a state of malnutrition and extended dehydration of pregnancy.[9]

Despite the fact that it is the most common cause of hospitalization in the first half of pregnancy and is second only to preterm labor for pregnancy overall,[10] there are very few studies on child outcome of HG and no studies, to our knowledge, on adult outcome, with the exception of two studies on subsequent cancer risk.[11,12] However, many studies on the long-term outcome of dehydration, starvation and/or anxiety in pregnancy in animal models and humans reveal adverse effects on exposed offspring including cardiovascular disease, obesity, diabetes, neurodevelopmental, cognitive, emotional and behavioral disorders.[13–17] Given that HG can be a form of prolonged dehydration, starvation and stress in pregnancy, it follows that long-term outcomes could possibly mimic those identified in these studies. To explore this possibility, we compare adulthood physical, emotional and behavioral diagnoses between individuals exposed to HG *in utero* and non-exposed controls.

Method

Participants

This study is part of a larger investigation evaluating the genetics and epidemiology of HG. Eligible participants were primarily recruited through advertising on the Hyperemesis Education and Research Foundation Web site at www.HelpHer.org. The inclusion criteria for participants with HG were a diagnosis of HG and treatment with intravenous (i.v.) fluids and/or total parenteral nutrition/nasogastric feeding tube. Because multiple or abnormal gestations may be associated

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with HG due to unique physiological pathways, women with these types of pregnancies were excluded.

Procedure: part 1

In the first part of the study, participants with HG were asked to submit their medical records confirming diagnosis and treatment with i.v. fluids and/or parenteral or nasogastric tube feeding, and complete an online survey (survey 1, http://www.helpher.org/HER-Research/2007-Genetics/) regarding family history, treatment and outcomes. A total of 279 women with an HG diagnosis completed the survey. In the family history section of survey 1, participants answered the following question:

In her most severe (with respect to nausea) pregnancy, did your biological *mother* have..?

(1) no nausea and vomiting
(2) very little nausea and vomiting
(3) typical nausea and vomiting
(4) more severe morning sickness
(5) HG
(6) other or unsure (please describe in text box)
(7) unknown

Immediately preceding the question, the following definition was given to them to refer to for their mother's pregnancy: HG-persistent nausea and vomiting with weight loss that interfered significantly with daily routine, and led to need for (i) i.v. hydration or nutritional therapy [feeding by an iv (TPN) or tube (NG) through the nose] and/or (ii) prescription medications to prevent weight loss and/or nausea/vomiting.

Procedure: part 2

In the second part of the study, all 279 participants who completed survey 1 were then asked to fill out a second survey (survey 2), in order to (i) confirm a positive or negative diagnosis of HG in their mother while pregnant with each sibling, as reported for at least one pregnancy in the family history section of survey 1 and (ii) report on health complications in their siblings. Among the 117 participants who reported HG in their mothers in survey 1, 55 responded to survey 2, confirmed HG in their mothers, and reported on health complications in 87 siblings who were exposed to HG *in utero*. This group of 87 HG-exposed siblings represents the cases in this study.

Among the 162 participants with HG who reported that their mothers did not have HG, 95 completed survey 2, confirming their mother did not have HG while pregnant with their siblings and reporting on health complications in 172 siblings who were not exposed to HG *in utero*. This group of 172 non-exposed siblings of participants, who had HG themselves, represents the control group in this study, and controls for the potential confounding factor of family history of HG.

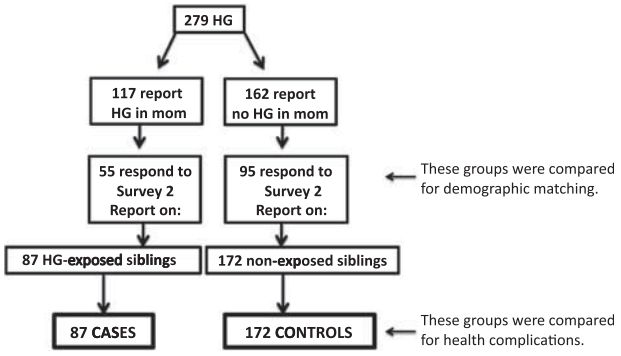

Fig. 1. Study design.

Procedure: summary

In summary, the study design is shown in Figure 1: the offspring of the participants are currently too young to obtain long-term data on the effects of *in utero* exposure to HG. However, because HG runs in families,[18] a large proportion of participants have a mother who had HG, and therefore, were able to report on the current health of their adult siblings exposed to HG during their mother's affected pregnancy. Thus, participants, with HG provided information about their mother's obstetric history, and the presence ($n = 117$) or absence ($n = 162$) of HG (using definitions from survey 1) with each pregnancy involving their siblings. A second questionnaire (survey 2) was then used to collect information about the participants' siblings. Cases are defined as offspring from a pregnancy reported to have been complicated by HG. Controls are defined as offspring from a pregnancy NOT complicated by HG. A total of 87 cases and 172 controls were identified.

Data analysis

The 279 participants who filled out survey 1 were compared for a number of variables including response rate, number of siblings, age, ethnicity and education. Response rate, ethnicity and education were compared using a two-tailed Fisher's exact test, number of siblings and age of siblings were compared using the Wilcoxson rank-sum test (Mann-Whitney *U* or robust *t*-test) in addition to the conventional *t*-tests and kolmogorov–smirnov tests.

We report on the psychological and behavioral diagnoses and other health complications are not included herein. The frequency of diagnoses was compared among the cases exposed to HG and the controls using two-sided Fisher's exact test. Some cases and controls had more than one diagnosis in a given group and therefore the overall affected rate is the number of affected siblings out of the total number of siblings rather than the number of diagnoses out of the total number of siblings.

This study has been approved by Institutional Review Boards (IRBs), University of Southern California IRB no. HS-06-00056 and University of California, Los Angeles IRB no. 09-08-122-01A.

Results

Matched-pairs analysis

Response rate to survey 2 regarding sibling diagnoses was close to 50% for all participants. Respondents were primarily White and born in the mid-1970s. On average, over 50% had a college degree. At the time of the survey, female and male siblings were primarily in their mid-30s. Respondents were well matched for all variables tested; no significant differences were found between groups (Table 1).

Table 1. *Survey participants are well matched*

	Mother having HG	Mother not having HG
Response rate	0.47	0.59
Race – White	0.98	0.91
College degree and above	0.63	0.54
Median reported year of birth	1976	1975
Median age of the sister age	33.5	34
Median age of the brother	33	33.75

HG, hyperemesis gravidarum.
P-values for all: >0.05; no significant difference was found between groups.

Psychological and behavioral disorders

Psychological and behavioral disorders reported by participants on behalf of their siblings are listed in Table 2. In all, 38% of cases are reported to have a psychological and behavioral disorder, as compared to 15% of controls. In this study, adults exposed to HG *in utero* are significantly more likely to have a psychological and behavioral disorder than non-exposed adults (OR = 3.57, $P = 0.000035$, 95% CI = 1.87–6.9). Analysis of the two largest subcategories independently reveals that depression and bipolar are both significantly more common in the HG-exposed group (for depression OR =6.35, $P = 0.0002$ and for bipolar OR = 4.90, $P = 0.0338$).

Table 2. *Psychological or behavioral diagnoses*

Diagnosis	Cases	Controls
ADD	1	4
ADHD	3	4
Alcoholism/drug addiction	3	2
Anxiety	6	4
Aspergers	2	1
Autism	0	1
Bipolar	7	3
Delayed sleep phase syndrome	1	0
Depression	14	5
Dyslexia	2	0
Emotional disorder	1	0
Learning disorder	3	3
OCD	3	3
Rett syndrome	1	0
Schizophrenia	1	0
Speech delay	1	0
Tourettes syndrome	0	0
Total number of siblings	87	172
Overall diagnosis rate[a]	0.38	0.15

ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; OCD, obsessive-compulsive disorder.
$P = 0.000035$, OR = 3.57, 95% CI = 1.87–6.9.
[a] Cases or controls with more than one diagnosis were counted only once.

Discussion

To our knowledge, this is the first study to explore fetal exposure to HG and adult emotional and behavioral outcomes. Herein fetal exposure to HG is significantly correlated to an increased risk of emotional or behavioral disorders in adulthood including depression, bipolar disorder and anxiety. Thirty-eight percentage of exposed offspring are reported to have a behavioral or emotional disorder. Previous studies on nausea and vomiting and pregnancy and neurodevelopment have somewhat conflicting results on the effects of nausea and vomiting of pregnancy (NVP) and neurodevelopment. Martin *et al.*,[19] showed that nausea beyond the first trimester was associated with lower task persistence at the age of 5 years and more attention and learning problems at the age of 12 years, whereas Nulman *et al.*,[20] showed that higher intelligence scores in NVP-exposed children. Although we did not address intelligence in our study, consistent with Martin *et al.*,[19] our results suggest HG may have an effect on the emotional or behavioral development of exposed individuals, perhaps independent of intelligence.

The mechanism for exposure to HG and abnormal neurodevelopment is unknown, but there are several hypotheses offered in the literature. First, maternal anxiety and stress are common during HG pregnancies.[21,22] 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 attention-deficit hyperactivity disorder 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 hypothalamic–pituitary–adrenal (HPA) axis and alterations of regulatory and neurotransmitter systems in the brain.[13,14]

Second, 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 that HG can be a form of prolonged starvation.[9] Studies of the Dutch and Chinese famine reveal that among those exposed to famine

during mid to late gestation, there is significantly lower birth weight, smaller head circumference and affective disorder. Those exposed to famine in the first half of pregnancy not only had significantly increased risk of obesity and coronary heart disease, but also reduced cognitive ability and significantly more schizophrenia spectrum disorders, congenital anomalies of the central nervous system and antisocial personality disorders. It is proposed that stunted brain development and abnormal programming of the HPA axis underlies these associations.[15–17]

Third, severe cases of HG can lead to vitamin deficiency syndromes such as maternal Wernicke's encephalopathy caused by thiamine deficiency and fetal intracranial hemorrhage caused by vitamin K deficiency.[23,24] Specific nutritional deficiencies in pregnancy such as deficits of folate and vitamin B_{12} have been linked to disruptions in myelination and inflammatory processes in infants and a greater risk of depression in adulthood.[25] In animal models, prenatal vitamin D deficiency is linked to adverse neuropsychiatric outcomes.[26]

Although 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.[27] In addition, abnormal maternal serum leptin levels are a marker of hyperemesis gravidarum,[28,29] and neonatal hyperleptinemia is associated with an increased level of anxiety in adult rats.[30] Thus, the results described herein may be the result of exposure to abnormal hormone levels during fetal development.

Lastly, HG can also lead to physical, psychological and a financial burden postpartum.[9] Women with extreme weight loss due to HG were more likely to have longer recovery times, postpartum digestive problems, muscle pain, gall bladder dysfunction and post-traumatic stress disorder. A child with a behavioral disorder was reported by 9.3% of these women.[9] 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.[31]

Admittedly, there are multiple limitations to this study. There is an incomplete response rate for survey 2. The reason that approximately half of the participants that responded to the first survey did not respond to the second survey is unknown, but may have to do with a change in email address or the fact that the majority of women joined the study while they were currently pregnant and ill with HG, and the second survey was sent out at a later date when original participants may have been busy caring for infants. However, because both groups had similar response rates (and the non-responders were well-matched to the responders, data not shown), we do not believe this has an effect on the comparison between the two groups of responders. Other limitations to the study include its retrospective component and self-reporting of maternal HG status and sibling diagnoses, as well as the fact that our well-matched analysis and diagnosis comparison were conducted on two different pairs of groups. Therefore rates of diagnoses in each group should be treated with caution. However, the highly significantly increased risk identified in this study between cases and controls should reflect a valid comparison because the survey respondents were well matched for all factors studied and reported a similar occurrence of other outcomes not presented herein (i.e. autoimmune disorders and cancer). Therefore, we can think of no reason why one group would be more likely to have a greater reporting or recall bias than another with respect to the diagnoses reported here.

Recently, HG was linked to adverse pregnancy outcomes including smaller head circumference, and it was concluded that studies designed to assess the long-term consequences of HG should be given high priority.[32,33] One of the strengths of this study comes from the long-standing collaboration with the Hyperemesis Education and Research Foundation that resulted in a unique opportunity to identify a large group of individuals whose mothers were 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 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 outcome disorders.

In conclusion, a highly significant increase in neurobehavioral disorders in adults exposed to HG *in utero* was shown, which suggests that 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, malnutrition and vitamin deficiency, abnormal hormone levels during fetal development and/or maternal–infant bonding after birth. 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.

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