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

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ABSTRACT

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

1. Introduction

Hyperemesis Gravidarum (HG) 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 [2,3]. HG can be associated with serious maternal and fetal morbidity such as Wernicke's encephalopathy [4], fetal growth restriction, and even maternal and fetal death [5,6].

While there is no international consensus on the definition, Hyperemesis Gravidarum may be defined as persistent, debilitating, unexplained nausea and vomiting resulting in more than a 5% weight loss, abnormal fluid and nutritional intake, electrolyte imbalance, dehydration, and ketonuria [7]. 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 prolonged dehydration of pregnancy [8].

Published data has demonstrated pregnancy complications associated with HG. Two systematic reviews showed HG is significantly associated with low birth weight, small size for gestational age, and preterm birth [9,10]. While there is less information, on outcomes of children exposed to HG in utero, mounting evidence supports a role for

Hyperemesis Gravidarum and adverse fetal brain development [11]. In our past study of children exposed to HG in utero at approximately 8 years of age, we found a 3.3-fold increased risk of neurodevelopmental delay in children [12]. Herein, we repeat the study collecting data on maternal reports of children's diagnoses at approximately 12 years of age.

2. Materials and methods

2.1. Sample and settings

This study is part of a larger investigation evaluating the genetics and epidemiology of Hyperemesis Gravidarum (HG). Briefly, cases affected by HG and unaffected acquaintance controls who participated in the original genetics and epidemiology study between 2007 and 2017 were contacted in 2018 to participate in this follow-up study and self-report on child outcomes.

2.1.1. Cases

Originally, eligible cases were primarily recruited through advertising on the Hyperemesis Education and Research Foundation Web site at www.HelpHer.org between 2007 and 2017. The inclusion criteria for

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cases were a diagnosis of HG and treatment with IV fluids and/or total parenteral nutrition/nasogastric feeding tube. Minors (under 18 years) 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. Women were eligible to participate whether they were pregnant or postpartum. Women over 50 at the time of enrollment were excluded from the study because of difficulty in recall with respect to their pregnancies. 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 who have no children were excluded because child outcomes are the focus of this study.

2.1.2. Controls

Each case was asked to recruit an acquaintance with at least 2 pregnancies to participate as a control at the time of enrollment into the genetics and epidemiology of Hyperemesis Gravidarum (HG) study. Like cases, controls were required to be between 18–50 years old at the time of enrollment. The rationale for using acquaintances was to increase similarity of demographic characteristics between cases and controls. The rationale for 2 pregnancies in controls was to exclude women who had normal nausea and vomiting of pregnancy in one pregnancy and HG in the next, an important issue to keep our control group as homogeneous with respect to disease status as possible for the genetic study. Controls were eligible if they experienced either no nausea/vomiting in pregnancy or normal nausea/vomiting that did not interfere with their daily routine, no weight loss due to nausea/vomiting and no medical attention in any pregnancy due to nausea. Blood relatives of participants in the study were not included in the study as the genetic study depends on non-relatedness of individuals in the study.

This study has been approved by the Institutional Review Board at UCLA, IRB # 11-001681.

2.2. Study procedures

Participants were asked to submit their medical records and complete an online survey regarding symptoms, treatment, and outcomes. The medical records were only used to confirm the clinical criteria of IV fluid treatment for HG for case eligibility, and all remaining data, both on the mother and child were based on maternal self-report by survey. If cases and controls began the survey during their pregnancies, they were automatically prompted to complete the survey on fetal outcome following their due date.

In 2018, all cases and controls enrolled in the original study were notified by email to update child outcomes. Specifically, all participants were sent an email that said "We are evaluating child outcome again. Please use the study ID number at the top of this email to fill out the **CHILD FOLLOW UP SURVEY** at

http://www.helpher.org/HER-Research/opportunities.php for all of your children, **whether or not you had HG**."

The survey was not limited to neurodevelopmental diagnoses and the participants were not aware of the aims of the study. All children under 3 years of age were excluded from the analysis, as the focus of this study is on child neurodevelopmental diagnoses, which are difficult to ascertain under age 3. There was no maximum age at which mothers could enroll their children.

2.3. Online surveys

An original 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 [13]. A follow-up survey was administered to report on the diagnosis of childhood health outcomes [13]. The Child Outcome Survey asked the

mother to fill in the circle if the diagnosis is not seen in the child, or if it is seen, when the diagnosis was made. Diagnostic criteria for each ND diagnosis were not individually obtained nor reviewed in this study, and medical records to confirm childhood diagnoses were not collected, with the exception of Autism Spectrum Disorder (ASD), where medical records of ASD diagnosis were requested. The diagnoses are based on self-report by the mother.

For example, for autism, the survey is written as follows and the mother fills the circle for when the diagnosis was made (ie before age 5, etc):

Autism Spectrum Disorder. Please indicate which diagnosis if known. (e.g. Aspergers)

- ⚪ Not seen in child
- ⚪ At Birth
- ⚪ Before Age 5
- ⚪ As Child/Teen
- ⚪ As Adult

The complete Child Outcome Survey can be found in the Supplement (S1).

2.4. Statistical analyses

Maternal and child characteristics were compared between mothers and their children exposed to HG in utero to those mothers/children who were not. Diagnoses in children who were exposed to HG in utero to diagnoses in unexposed children were compared. Pregnancy characteristics from women with HG who subsequently had a child with an ASD diagnosis were compared to pregnancy characteristics in women with HG who did not go on to have a child with an ASD diagnosis. The factors maternal inpatient hospitalization and maternal total parenteral nutrition as treatment for HG were used as proxies for severity of disease to determine whether there may be evidence for a relationship between severity of HG and ASD. In addition, vitamin intake, early symptoms, and medications (ondansetron, promethazine, and metoclopramide) were also compared between the groups to assess whether these factors may be associated with ASD. Sex of the child was included as a control because it has already been determined that male children have an increased risk of ASD compared to female offspring.

To evaluate differences amongst the groups Chi-square and Fisher's 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.

3. Results

3.1. Demographic characteristics

Among 1035 H G cases and 705 controls emailed the link to the child outcome survey, 177 H G patients and 60 control patients participated in this child follow-up study. Women with HG reported on the diagnosis of emotional, behavioral, and learning disorders in 267 children exposed to HG in utero. Controls reported on the diagnosis of emotional, behavioral, and learning disorders in 93 children who were not exposed to HG in utero (Fig. 1).

Cases and controls had a mean maternal age of 41 and 42 respectively, and were primarily Caucasian. Children of cases and controls were approximately 12 years old and cases and controls had similar numbers of children > 3 years of age, and similar reports of preterm birth (Table 1).

3.1.1. Outcome

Women with HG were significantly more likely to report a diagnosis of attention deficit disorder/attention deficit hyperactivity disorder,
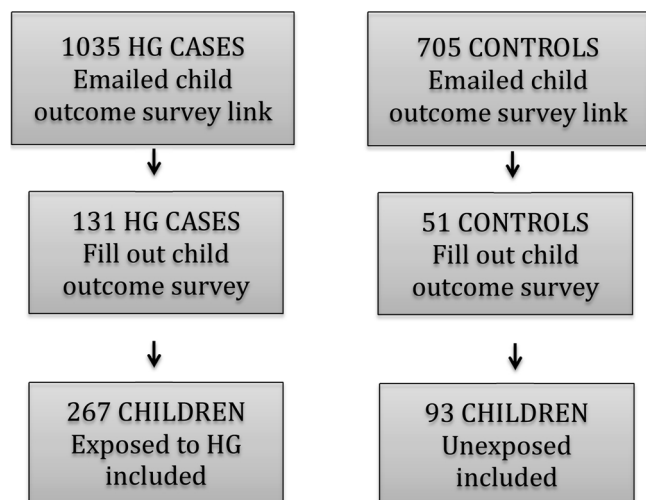
Fig. 1. Flow chart of study participation.

Table 1
Maternal and Child Characteristics.

Mothers	N = 177 Children exposed to HG[a]	N = 60 Children not exposed to HG	P-value
Mean Maternal Age	41.04	42.14	0.2631
Maternal Race (Caucasian)	82.44%	86.27%	0.553
Children	N = 267 Children exposed to HG	N = 93 Children not exposed to HG	P-value
Mean children's age	11.66	12.33	0.315
Preterm Birth	9.33%	8.60%	0.8342
Mean number of children > 3 yrs	1.49	1.55	0.7727

[a] Hyperemesis gravidarum.

anxiety disorder, autism spectrum disorder, sensory integration/sensory processing disorder, sleep difficulty, and social development delay or social anxiety (Table 2). There was no significant difference in the reported rates of oppositional/defiant disorder, bipolar disorder, central auditory processing disorder, depression, dysgraphia, dyslexia, dysphagia, dyspraxia, learning difficulties/delays, intellectual impairment, memory impairment, obsessive-compulsive disorder, self-mutilation/harm, self-control/impulsivity, speech/language impairment, or

visual/spatial skill impairment.

Overall, 52% of children exposed to HG in utero were diagnosed with an emotional and/or behavioral condition, compared to 26% of unexposed children. This corresponds to a combined 3.2-fold increase in odds of neurodevelopmental delay in children from pregnancies complicated by HG (OR 3.17, 95% CI = [1.88–5.35]).

3.2. Factors associated with ASD in children exposed to HG in utero

There was a diagnosis of autism spectrum disorder in 8.2% of children exposed to HG and none of the unexposed children. Among medical records collected, ASD diagnoses were made by psychiatrist, neurologist, or developmental pediatrician. With respect to the time of diagnosis, 16/22 children were diagnosed at a young age, while the remaining 6/22 were diagnosed as pre-teens/teens. Pregnancy characteristics were available for 118/245 pregnancies resulting in no autism diagnosis in women exposed to HG and in 15/22 pregnancies resulting in an autism diagnosis in women exposed to HG. The difference in missingness of pregnancy characteristics between the groups is not significant. To analyze potential factors associated with ASD in children exposed in utero to HG, we looked at maternal hospitalization, total parenteral nutrition, vitamin intake, early start of symptoms, and first trimester use of the three most common antiemetic treatments, ondansetron, promethazine, and metoclopramide. None of these were significantly different. By comparison, an autism diagnosis was significantly more common in male offspring (Table 3).

3.3. Comment

This study focused on the most extreme end of the nausea and vomiting spectrum, Hyperemesis Gravidarum, and showed there may be a 3.2-fold increase in odds of a neurodevelopmental diagnosis in approximately 12-year old children born from pregnancies complicated by HG. This finding was not surprising given that previously, we found a 3.3-fold increased risk of neurodevelopmental delay in 8-year children, and a 3.6-fold increased risk of a behavioral or emotional disorder in adults exposed to HG in utero [12,14,15]. However, in this study, the diagnosis of autism spectrum disorder may have been significantly increased in children exposed to HG. Among 267 children approximately 12 years of age exposed to HG in utero, 22 (8.2%) were reported by their mothers to be diagnosed with ASD. The current ASD prevalence is less than 1.7%, consistent with our control population of 93 children, where there were no ASD diagnoses [16]. Recently, two other studies have also identified an association between severe nausea and vomiting of pregnancy (NVP) and ASD. One retrospective case-control study of 287 children in the Western Australian Autism Biological Registry showed that increasing frequency and severity of NVP in the mother

Table 2
Comparison of neurodevelopmental diagnoses in children exposed to HG in utero and unexposed children.

	267 children HG[a]	93 children no HG	P-value	OR	95% CI
Diagnosis					
ADD/ADHD[b]	22.85%	11%	0.013	2.458	1.201 to 5.027
Anxiety	29.96%	21.51%	0.01	2.225	1.207 to 4.100
Autism Spectrum Disorder	8.24%	0.00%	0.048	–	–
SID/SPD[c]	20.22%	8.60%	0.013	2.694	1.230 to 5.899
Sleep Difficulty[d]	16.10%	6.45%	0.024	2.784	1.144 to 6.774
Social Development Delay/Anxiety	13.86%	4.30%	0.018	3.579	1.240 to 10.334
Preterm Birth	9.36%	8.60%	0.827	1.098	0.477 to 2.526
Combination[*]	52.43%	25.81%	< 0.0001	3.1693	1.879 to 5.346

[a] Exposed to Hyperemesis gravidarum in utero.
[b] Attention deficit disorder/attention deficit hyperactivity disorder.
[c] Sensory integration disorder /sensory processing disorder.
[d] Chronic/Frequent Irregular Sleep Patterns.
[*] ADD/ADHD, Anxiety, Autism Spectrum Disorder, SID/SPD, and Social Development Delay or Social Anxiety (combined).

Table 3

Factors in pregnancy with HG[a] with autistic child compared to pregnancy with HG without autistic child.

	No Autism N = 118	Autism N = 15	P-value	OR	95% CI
Male child	42%	73%	0.03	3.87	(1.16, 12.88)
Inpatient	56%	40%	0.25	1.90	(0.64, 5.69)
Total Parenteral Nutrition	13%	20%	0.44	1.72	(0.43, 6.80)
Vitamins	59%	53%	0.66	1.28	(0.43, 3.75)
Early symptoms (< 5 wks)	32%	27%	0.66	1.31	(0.39, 4.37)
Ondansetron (1st trimester)	82%	73%	0.41	1.68	(0.49, 5.79)
Promethazine	64%	53%	0.41	1.58	(0.54, 4.67)
Metoclopramide	47%	33%	0.33	1.75	(0.56, 5.42)

[a] Hyperemesis gravidarum.

correlated with increasing severity of ASD symptoms in the child [17]. Another study of 8760 children with ASD and 26,280 matched controls in the Military Health System Database in the United States identified maternal HG as a risk factor for ASD [18].

Other studies on nausea and vomiting and pregnancy and neurodevelopment had somewhat conflicting results on the effects of nausea and vomiting of pregnancy (NVP) and neurodevelopment. Martin et al. [19], 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. [20], showed higher intelligence scores in NVP-exposed children [29,20]. Consistent with Nulman et al. [20], we found no evidence for intellectual impairment. Consistent with Martin et al. [19], our results supported the finding that HG may have an effect on the emotional/behavioral development of exposed individuals, including increased risk of attention deficit disorder/attention deficit hyperactivity disorder, anxiety disorder, autism spectrum disorder, sensory integration/sensory processing disorder, sleep difficulty, and social development delay or social anxiety, 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. Recently, our genome-wide association study (GWAS) of HG identified the placenta and appetite genes GDF15 (macrophage inhibitory cytokine-1) and IGFBP7, are significantly associated with HG ($p = 2.4 \times 10^{-41}$, $p = 9.2 \times 10^{-24}$) [21]. Studies have also linked dysregulation of maternal inflammation and fetal inflammation genes to abnormal fetal brain development [22,23]. It is therefore of interest that both GDF15 and IGFBP7 may play a role in signaling immune system changes in early pregnancy, suggesting abnormal levels of these proteins in HG pregnancies could have an effect on fetal brain development. Notably, IL-6 which is upregulated by GDF15, has a variant linked to neurodevelopmental delay at age 2 [23,24]. And, blocking IL-6 results in substantial elimination of autism-like behaviors in a rodent model of maternal immune activation and autism behaviors [25]. GDF15 has also been shown to enhance mouse neural stem cell proliferation and differentiation and promote synaptic activity, suggesting a role in fetal brain development and functioning [26]. In addition, *IGFBP7* was the top association signal in a GWAS of variants influencing prenatal brain development [27].

Another factor could be maternal stress. Maternal anxiety and stress are common during HG pregnancies [28,29]. And, prenatal bereavement stress has been linked to increased risk of ASD [30]. Maternal stress, primarily during the first and second trimesters, has been associated with permanent changes in neuroendocrine regulation and behavior in offspring. Neuroendocrine regulation has been regarded as an important factor underlying both attention deficit hyperactivity disorder and depression. Interestingly, animal studies convincingly showed that stress during pregnancy results in offspring with increased anxiety and depressive behavior possibly by altered fetal development

of the Hypothalamic-pituitary-andrenal (HPA) axis and alterations of regulatory and neurotransmitter systems in the brain [31,32].

Maternal starvation may also play a role. More than a quarter of HG pregnancies resulted in greater than 15% weight loss and symptoms persist until term in over 20% of pregnancies. This suggested HG can be a form of prolonged starvation [8]. Studies of the Dutch and Chinese famine revealed that in addition to significant low birth weight, smaller head circumference, and cardiovascular disease, there were 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 was 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 [33]. Additionally, maternal diet during pregnancy has been associated with an increased ASD risk, which offers another explanation for the association between HG and autism risk [34]. Moreover, a rodent model of ASD showed that maternal protein malnutrition, a common feature of HG, caused ASD-like symptoms in offspring [35].

Additionally, severe cases of HG have lead to vitamin deficiency syndromes such as maternal Wernicke's Encephalopathy caused by thiamine deficiency and fetal intracranial hemorrhage caused by vitamin K deficiency [36,37]. Reports have linked early neonatal vitamin K deficiency to impaired neuronal migration and cortical dysplasia [38,39]. 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 [40]. In animal models, prenatal vitamin D deficiency was linked to adverse neuropsychiatric outcomes [41]. Future studies to determine whether maternal/fetal supplementation can minimize the increased risk of neurodevelopmental delay are needed.

Finally, HG can also have substantial physical and psychological effects on the mother, and can be a financial burden postpartum [8]. 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 [8]. 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 showed maternal care in the first week after birth resulted in epigenetic modification of genes expressed in the brain that shaped neuroendocrine and behavioral stress responsivity throughout life [42].

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 [43,44]. However, maternal smoking is inversely correlated to HG [45] and participants with HG in this study required intravenous fluid treatment due to low fluid intake. Thus if cases and controls were not well matched for smoking and/or alcohol consumption, it would likely bias towards the null. Another limitation to the study was that the childhood diagnoses were self-reported and therefore may not be accurate. However, the rates of diagnoses in the control population (with an average age of 12) were consistent with rates reported in the published literature, for example, ADD/ADHD 11% here versus 13.6% reported for ages 12–17 [46] (http://www.chadd.org/understanding-adhd/about-adhd/data-and-statistics/general-prevalence.aspx); anxiety 21.51% here versus 25.1% for ages 13–18 [47], and SPD 8.6% here vs 5–16% in school-aged children [48], and the prevalence of preterm birth was 9%, equivalent to the preterm birth rate in white women in the US [49], suggesting accurate self-reporting in the control group. Cases and controls that responded to the child outcome survey were well-matched with respect to the descriptive factors analyzed which included maternal age, race, mean child age, and preterm birth. We acknowledge that there may be

biases in reporting, but as controls reported outcomes at similar rates to reported rates for healthy controls, these biases are not likely to be related to selection bias between the original and the follow-up study.

Admittedly, there may have been differences in reporting between mothers who experienced HG and healthy controls. Significantly more cases responded to the child outcome survey than controls, which may also add to biases in reporting. Additionally, while both the maternal and child ages were not significantly different between cases and controls, it is possible that the inclusion of both retrospective and prospective children of cases and controls may have lead to inaccuracies in prevalence or incidence. Finally, adjustments were not made for multiple comparisons. While this may be preferable in some settings [50], the findings reported herein should be considered with caution until confirmed by other studies with more robust study designs.

It can be of some comfort for women to know that while antihistamines, which are commonly used to treat HG, were linked to preterm birth in HG pregnancies, herein, in this small study, there was no evidence to support antihistamine (promethazine) exposure, (nor ondansetron or metoclopramide) were associated with ASD diagnosis in children [51]. In addition, women with HG who reported a child diagnosed with ASD were not significantly more likely to be hospitalized and/or treated with total parenteral nutrition (TPN) for HG than women with HG and no diagnosis of ASD. This may suggest that the sickest mothers with HG, those that require hospitalization and/or TPN, were not at a significantly increased risk of having a child with ASD.

In conclusion, a significant increase in neurodevelopmental and behavioral disorders, and notably autism spectrum disorder, in children exposed to HG in utero may have been demonstrated by this study, which might suggest HG may be linked to life-long effects on the exposed fetus. The cause for this association is unknown, but may be due to abnormal placental *GDF15* and *IGFBP7* expression during fetal development, maternal stress, nutritional deficits, and/or maternal-newborn bonding after birth. In addition to the findings reported herein, increasing evidence has supported 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 [52,53]. HG is an understudied and undertreated condition of pregnancy that may result in not only short-term maternal physical and mental health problems, but also potentially life-long consequences to the exposed fetus. As this was a small exploratory descriptive study, larger studies with validated clinical criteria are now warranted to confirm these findings.

Conflict of interest

The authors report no conflict of interest.

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