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Neurodevelopmental delay in children exposed in utero to hyperemesis gravidarum

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ABSTRACT

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

Study design: Neurodevelopmental outcomes of 312 children from 203 mothers with HG were compared to neurodevelopmental outcomes from 169 children from 89 unaffected mothers. Then the clinical profiles of patients with HG and a normal child outcome were compared to the clinical profiles of patients with HG and a child with neurodevelopmental delay to identify prognostic factors. 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 delay, sensory disorders, and speech and language delay ($P < 0.0005$). Among characteristics of HG pregnancies, only early onset of symptoms (prior to 5 weeks gestation) was significantly linked to neurodevelopmental delay. We found no evidence for increased risk of 13 emotional, behavioral, and learning disorders, including autism, intellectual impairment, and obsessive-compulsive disorder. However, the study was not sufficiently powered to detect rare conditions. Medications, treatments, and preterm birth were not associated with an increased risk for neurodevelopmental delay.

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

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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, 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, debilitating, 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 prolonged dehydration of pregnancy [9].

Published data has demonstrated pregnancy complications associated with HG. Two systematic reviews showed HG is

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significantly associated with low birth weight, small size for gestational age, and preterm birth [10,11]. There is less information, however, on outcomes of children exposed to HG in utero [12,13]. Recently we found a 3.6-fold increased risk of emotional and behavioral disorders in adults exposed to HG in utero [14,15]. 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.

Materials and methods

Sample and settings

This study is part of a larger investigation evaluating the genetics and epidemiology of Hyperemesis gravidarum (HG). A total of 292 women have been recruited. Eligible patients were primarily recruited through advertising on the Hyperemesis Education and Research Foundation Web site at www.HelpHer.org between 2007 and 2011. The inclusion criteria for cases were a diagnosis of HG in their first pregnancy 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. 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.

Each case was asked to recruit an acquaintance with at least 2 pregnancies to participate as a control. 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. 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. There were 203 HG patients and 89 control patients enrolled in the study. This study has been approved by the Institutional Review Board at UCLA, IRB no. 09-08-122-01A.

Study procedures

Participants were asked to submit their medical records and complete an online survey regarding symptoms, treatment, 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 fetal outcome following their due date.

In 2012, participants who met the study criteria were notified by email to update child outcomes. Women with HG reported on the diagnosis of emotional, behavioral, and learning disorders in 312 children exposed to HG in utero. Controls reported on the diagnosis of emotional, behavioral, and learning disorders in 169 children who were not exposed to HG in utero.

Online survey

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 [16]. A follow-up survey was administered to report on the diagnosis of childhood emotional, behavioral, and learning disorders [16].

Statistical analyses

Respondents were categorized according to two binary responses in each table. Table 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 2. Proportions of families in each group that had diagnosis in at least one child per family were compared. Tables 3 and 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 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 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.

Results

Demographic characteristics

All participants were from the United States, and cases and controls were well-matched for mean maternal age, spontaneous labor, delivery method, and use of assisted reproduction (Table 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 before 37 weeks.

Outcome

Women with HG were significantly more likely to report a diagnosis of attention deficit disorder/attention deficit hyperactivity disorder, 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 2). There was no significant difference in the reported rates

Table 1
Maternal and child characteristics.

	N = 312	*N* = 169	*P*-value
	Children exposed to HG[a]	Children not exposed to HG	
Mean maternal age	28.89	27.27	0.2132
Maternal race (caucasian)	92.4%	95.7%	0.5408
SES[b] (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 children's age	8.1333	8.5966	0.4378
Preterm birth	13.46%	7.10%	0.05019
Mean number of children per family	1.54	1.9	0.0015

[a] Hyperemesis gravidarum.
[b] Socio-economic status.

Table 2
Increased risk of neurodevelopmental delay (diagnosis in at least one child reported per family) in children exposed to HG.

	N = 203	*N* = 89 families	*P*-value	Odds ratios	95% Confidence interval
	Families with children exposed to HG[a] (%)	Families with children not exposed to HG (%)			
Diagnosis					
ADD/ADHD[b]	18.72	5.62	0.0064	3.8691	(1.56, 11.55)
LDD[c]	12.32	3.37	0.0297	4.0262	(1.36, 17.24)
SID/SPD[d]	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[e]	24.14	11.24	0.01783	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)

[a] Hyperemesis gravidarum.
[b] Attention deficit disorder/attention deficit hyperactivity disorder.
[c] Learning difficulties delays.
[d] Sensory integration disorder/sensory processing disorder.
[e] Speech or language impairment/delay.

Table 3
Early symptoms associated with neurodevelopmental delay.

	ND[a]	No ND	*P*-value
	N = 138	*N* = 174	
HG[b] characteristics			
Week of NVP[c]			
Week 1–4	42.75%	30.46%	0.0332
Week 5–8	52.90%	66.09%	0.0245
Week 9–15	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

[a] Neurodevelopmental delay.
[b] Hyperemesis gravidarum.
[c] Nausea and vomiting of pregnancy.

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]).

Factors associated with neurodevelopmental delay in children exposed to HG in utero

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 nausea and vomiting symptoms beginning at gestational age of 1–4 weeks were significantly associated with neurodevelopmental delay (Table 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.

Medications/treatment and outcome

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).

Comment

This study focuses on the most extreme end of the nausea and vomiting spectrum, Hyperemesis gravidarum, and 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 [14,15]. Other 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. 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 [17,18]. Consistent with Nulman et al., we find no evidence for intellectual impairment. Consistent with Martin et al.,

Table 4
Medications/Treatments taken during first and/or second trimester not linked to neurodevelopmental delay.

Treatments and medications	*N* = 138		*N* = 174		
	HG[a] with ND[b] (%)	*N*	HG no ND (%)	*N*	*P*-value
Allergy	1.45	2	0.00	0	0.3794
Antacids [e.g. Zantac (Ranitidine), Pepcid (Famotidine)]	58.70	81	51.72	90	0.2651
Antibiotics (for *Heliobater pylori*)	2.17	3	1.15	2	0.7934
Antidepressants/Antianxiety[c]	12.32	17	9.20	16	0.4804
Antihistamines[d]	34.78	48	35.06	61	1
Antimotion sickness medications[e]	19.57	27	16.09	28	0.5157
Anzemet (Dolasetron)	3.62	5	2.30	4	0.7236
B6 injection	6.52	9	9.77	17	0.4095
Bedrest	64.49	89	52.30	91	0.0404
Compazine/stemetil/buccastem (prochlorperazine)	21.01	29	13.22	23	0.0925
Diclectin	7.97	11	8.62	15	1
Motilium (domperidone)	1.45	2	0.57	1	0.8398
Emend (aprepitant)	0.00	0	0.57	1	1
Gastric pacing	0.72	1	0.57	1	1
Herbal medicine	13.04	18	11.49	20	0.8093
Homeopathics	12.32	17	11.49	20	0.9621
Intravenous Therapy	81.88	113	79.31	138	0.6704
Kytril (granisetron)	0.72	1	0.57	1	1
Solu-medrol/medrol (Methylprednisolone)	9.42	13	8.05	14	0.8211
NG° (nasal to stomach) tube feedings	1.45	2	1.72	3	1
PICC (peripherally inserted central catheter)	23.19	32	14.94	26	0.0867
Physical Therapy	0.72	1	0.57	1	1
Psychotherapy/counseling	7.25	10	7.47	13	1
Phenergan/lergigan/avomine (promethazine)	54.35	75	51.15	89	0.6543
Protonix/prevacid (lansoprazole)	10.87	15	5.75	10	0.1484
Reglan/maxeran/maxolone (metoclopramide)	44.20	61	50.57	88	0.3149
Scopolamine (scopolamine hydrobromide)	5.07	7	5.17	9	1
Seabands/relief bands	53.62	74	48.85	85	0.4694
SpecialDiet (bland, low fat, low acid)	54.35	75	48.85	85	0.3949
Tagamet (cimetidine)	2.90	4	2.87	5	1
Thorazine (chlorpromazine), Haldol (haloperidol)	0.72	1	1.72	3	0.785
Tigan/Vomet (trimethobenzamide)	6.52	9	3.45	6	0.3202
TPN/TPPN (total IV nutrition or hyperalimentation)	15.22	21	10.92	19	0.3384
Acupuncture	12.32	17	16.67	29	0.3602
Vitamins (taken orally-pyridoxine, etc.)	43.48	60	40.23	70	0.6438
Vitamins (taken intravenously-i.v.)	26.09	36	20.69	36	0.3229
Zofran (ondansetron)	71.74	99	65.52	114	0.2936

[a] Hyperemesis gravidarum.
[b] Neurodevelopmental delay.
[c] Prozac (fluoxetine), Wellbutrin (bupropion), Zoloft (sertraline), Paxil (paroxetine), Ativan (lorazepam).
[d] Benadryl (diphenhydramine), Gravol (dimenhydrinate), Unisom (doxylamine), Vistaril/Atarax (hydroxyzine), Diclectin/Bendectin (doxylamine and pyridoxine).
[e] Marezine (cyclizine), Dramamine (dimenhydrinate), Bonine/Antivert (meclizine).

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 [19,20]. 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–andrenal (HPA) axis and alterations of regulatory and neurotransmitter systems in the brain [21,22].

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 [9]. 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 [23].

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 [24]. While abnormal maternal serum leptin levels are a marker of HG [25,26], neonatal hyperleptinaemia has been associated with an increased level of anxiety developing in adult rats [27]. 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 [9]. 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 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 [28].

Lastly, 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 [29,30]. Reports have linked early neonatal vitamin K deficiency to impaired neuronal migration and cortical dysplasia [31,32]. 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 [33]. In animal models, prenatal vitamin D deficiency is linked to adverse neuropsychiatric outcomes [34]. 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 [35,36]. However, maternal smoking is inversely correlated to HG [37] and participants with HG in this study required iv fluid treatment due to low fluid intake. 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 [38,39]. Also, because of the small sample size, we combined all significant adverse outcomes to analyze factors linked to neurodevelopmental delay. Thus although we found no evidence linking combined neurodevelopmental diagnoses to specific medication/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 adverse fetal outcome [40]. 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, there was no evidence of antihistamine exposure being linked to neurodevelopmental delay in children [40]. 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 [41].

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 [42]. 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 Hyperemesis Education and Research 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 disorders 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 maternal–newborn 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 [43,44]. 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.

Conflict of interest statement

The authors report no conflict of interest.

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