OBSTETRICS

Familial aggregation of hyperemesis gravidarum

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OBJECTIVE: This study was undertaken to determine whether there is familial aggregation of hyperemesis gravidarum (HG), making it a disease amenable to genetic study.

STUDY DESIGN: Cases with severe nausea and vomiting in a singleton pregnancy treated with intravenous hydration and unaffected friend controls completed a survey regarding family history.

RESULTS: Sisters of women with HG have a significantly increased risk of having HG themselves (odds ratio, 17.3; $P = .005$). Cases have a significantly increased risk of having a mother with severe nausea and vomiting; 33% of cases reported an affected mother compared to 7.7% of controls ($P < .0001$). Cases reported a similar frequency of affected second-degree maternal and paternal relatives (18% maternal lineage, 23% paternal lineage).

CONCLUSION: There is familial aggregation of HG. This study provides strong evidence for a genetic component to HG. Identification of the predisposing gene(s) may determine the cause of this poorly understood disease of pregnancy.

Key words: familial aggregation, genetic, hyperemesis gravidarum, nausea, pregnancy

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Hyperemesis gravidarum (HG), severe nausea and vomiting of pregnancy (NVP), hospitalizes >59,000 pregnant women in the United States annually, with most authors reporting an incidence of 0.5%.[1,2] Estimates of severe NVP vary greatly and range from 0.3% in a Swedish registry to as high as 10.8% in a Chinese registry of pregnant women.[3,4] Recent large population studies support ethnic variation in the incidence of HG. A Norwegian study of the medical birth registry of Norway from 1967 through 2005 defined HG as persistent NVP associated with ketosis and weight loss >5% of prepregnancy weight, and revealed an overall prevalence of 0.9%, but when broken down by ethnicity, found HG in 2.2% of 3927 Pakistani women and 1.9% of 1997 Turkish women, both more than twice the incidence of 0.9% in 798,311 Norwegian women.[5] A study of California birth and death certificates >20 weeks' gestation linked to neonatal hospital discharge data in 1999 with the primary diagnosis of hyperemesis found an incidence of 0.5% (2466 cases of 520,739 births), and women with HG were reportedly significantly less likely to be white or Hispanic compared to nonwhites or non-Hispanics.[6] A Canadian study found HG in 1270 (0.8%) of 156,091 of women with singleton deliveries from 1988 through 2002.[7] This rate was confirmed in a second Canadian study during the same time frame of the population-based Nova Scotia Atlee Perinatal Database of deliveries at 20 weeks' gestation, which found HG in 1301 (0.8%) of 157,922 pregnancies.[8] Asian populations tend to have higher incidence rates. For example, a Malaysian study identified 192 recorded cases (3.9%) of 4937 maternities.[9] Additionally, a study of 3350 singleton deliveries in an Eastern Asian population observed HG in 119 (3.6%) of the population.[10] As mentioned, a study of 1867 singleton live births revealed the highest rate of severe NVP in Shanghai, China, from 1986 through 1987, with an incidence of 10.8%. However, unlike the other studies mentioned, this study was based on a clinical record of severe vomiting on prenatal care cards, rather than hospitalization for HG; did not limit itself to a primary diagnosis of HG; and included, for example, women with chronic liver disease, chronic hypertension, chronic renal illness, and preeclampsia.[4] HG is the most common cause of hospitalization in the first half of pregnancy and is second only to preterm labor for pregnancy overall.[11] HG can be associated with serious maternal and fetal morbidity such as Wernicke encephalopathy,[12] fetal growth restriction, and even maternal and fetal death.[6,13]

A biologic component to the condition has been suggested from animal studies. Anorexia of early pregnancy has been observed in various mammals in-

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TABLE 1
Distribution of number of pregnant sisters (n = 317)

Variable	Controls (n = 110)	Cases (n = 207)	*P* value
No. of pregnant sisters, n (%)			.4854
1	74 (67.27)	146 (70.53)	
2	23 (20.91)	45 (21.74)	
≥3	13 (11.82)	16 (7.73)	

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cluding monkeys.[14] In dogs, anorexia can be accompanied by vomiting and can be severe enough to require pregnancy termination.[15] Several lines of evidence support a genetic predisposition to NVP. Firstly, in the only study of NVP in twins, concordance rates were more than twice as high for monozygotic compared to dizygotic twins.[16] Secondly, several investigators have noted that siblings and mothers of patients affected with NVP and HG are more likely to be affected than siblings and mothers of unaffected individuals.[17,18] Thirdly, the higher frequency of severe NVP in patients with certain genetically determined conditions such as defects in taste sensation,[19,20] glycoprotein hormone receptor defects,[21-23] or latent disorders in fatty acid transport or mitochondrial oxidation,[24,25] suggests that some portion of HG cases may be related to discrete, genetically transmitted disease states that are unmasked or exacerbated in pregnancy. Finally, in a previous survey administered by the Hyperemesis Education and Research Foundation, approximately 28% of cases reported their mother had severe NVP or HG while pregnant with them. Of the 721 sisters with a pregnancy history, 137 (19%) had HG. Among the most severe cases, those requiring total parenteral nutrition (TPN) or nasogastric (NG) feeding tube, the proportion of affected sisters was even higher, 49 of 198 (25%). Nine percent of cases reported having at least 2 affected relatives including sister(s), mother, grandmother(s), daughter(s), aunt(s), and cousin(s). There is a high prevalence of severe NVP/HG among relatives of HG cases in this study population.[26] Overall, these data suggest that genetic predisposition may play a role in the development of NVP. However, to our knowledge, a case-control study of familial aggregation of severe NVP and HG has never been done. The goal herein is to determine whether there is familial aggregation of severe NVP and HG in a case-control setting.

TABLE 2
Summaries for several characteristics

Variable	Controls	Cases	*P* value
Age, y	37.92 (5.65)	35.77 (6.13)	.0016
Pregnancy losses	0.55 (0.88)	0.62 (1.43)	.7597
No. of living children	2.48 (1.00)	1.89 (1.07)	< .0001
Pregnancy termination	0.16 (0.44)	0.24 (0.74)	.0664
Currently pregnant, n (%)	9 (8.65)	36 (19.25)	.0166
Race, n (%)			.0346
White	107 (97.27)	181 (87.44)	
African American	0 (0.00)	10 (4.83)	
Asian	0 (0.00)	3 (1.45)	
Hispanic	2 (1.82)	4 (1.93)	
Other	1 (0.91)	9 (4.35)	

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Materials and Methods

Recruitment

The University of Southern California–Los Angeles and the University of California–Los Angeles are currently conducting a study of the genetics and epidemiology of HG, and >650 participants have been recruited, primarily through advertising on the Hyperemesis Education and Research Foundation World Wide Web site at www.HelpHer.org. The inclusion criteria for cases are a diagnosis of HG and treatment with intravenous (IV) fluids and/or TPN/NG feeding tube. Participants are asked to: (1) submit their medical records; (2) provide a saliva sample; and (3) complete an online survey regarding family history, treatment, and outcomes. Each case is asked to recruit a friend with at least 2 pregnancies that went >27 weeks to participate as a control. Controls are eligible if they experience normal (did not interfere with their daily routine) or no NVP, no weight loss due to NVP, and no medical attention in their pregnancy due to nausea. Eligibility questions for cases and controls are attached in the Appendix.

Survey

Participants were asked to report on the severity of NVP of their family members according to the following definitions:

1. **No nausea and vomiting**: never felt nauseated and never vomited in this pregnancy.
2. **Very little nausea and vomiting**: felt nauseated and/or vomited for a total of 1-7 days during this pregnancy.
3. **Typical nausea and vomiting**: may have nausea and/or vomiting in this pregnancy but (all of the following must be true): (1) did not lose weight from nausea/vomiting; and (2) was able to sustain normal daily routine most days with little change in productivity due to nausea/vomiting

most of the time; and (3) no need to consult health professional for medical treatment due to nausea and vomiting.

4. **More severe morning sickness:** (1) persistent nausea and vomiting that interfered with normal daily routine in this pregnancy but did not require IV hydration or TPN due to persistent nausea/vomiting; (2) may have consulted a medical professional to treat nausea and vomiting; and (3) may have lost a few pounds or 1 kg.
5. **HG:** persistent nausea and vomiting with weight loss that interfered significantly with daily routine, and led to need for: (1) IV hydration or nutritional therapy (feeding IV [TPN] or by tube [NG] through the nose); and/or (2) prescription medications to prevent weight loss and/or nausea/vomiting.
6. **Other or unsure:** please describe in text box at end of section.

The survey used for this study can be found at: http://www.helpher.org/HER-Research/2007-Genetics/.

Statistical methods

Characteristics were summarized for both the case group and the control group, and compared between the 2 groups. For the characteristics race and current pregnancy, the χ^2 test was used to compare the difference between the 2 groups. For the characteristics age, pregnancy losses, number of living children, and voluntary termination, Wilcoxon rank sum test was used to compare the 2 groups.

The familial aggregation of HG was examined by modeling the probability of having ≥1 sister with HG using the logistic regression method. The status whether a participant was a case or a control was assumed to affect the probability of having ≥1 affected sister through a logit fashion, in this way the effect of being a case on having at least 1 affected sister can be expressed in odds ratio (OR). If we use Y to denote the status whether a participant had ≥1 sister with HG, ie, Y = 1 if a participant has ≥1 affected sister, and Y = 0 otherwise, then the probability that a participant had ≥1 affected sister $\Pr(Y = 1)$ was modeled as follows:

$$\Pr(Y=1) = \frac{\exp(\beta_0 + \beta_1 X)}{\exp(\beta_0 + \beta_1 X) + 1} \quad (1)$$

Where, X denotes the status of whether a participant was a case or a control, ie, X = 1 if a participant was a case, and X = 0 if a participant was a control; β_0 is the regression intercept that was of little interest in this case; β_1 is the regression coefficient for variable X; and the exponential of the estimated β_1 is the estimated OR of being a case on having at least 1 affected sister, ie, the odds of having ≥1 affected sister for a case over the odds of having ≥1 affected sister for a control. In this analysis, 2 definitions were used to define that a sister had HG. In the first definition, a sister was said to have HG if she had severity 4, more severe morning sickness and severity 5, HG. In the second definition, a sister was said to have HG only if she had HG (severity 5). Since the cases and controls were not perfectly matched in terms of race and white was the dominating race in both case group and control group, analyses were also conducted only on white women for both definitions of HG.

This study was approved by institutional review boards at University of Southern California (HS-06-00056) and University of California–Los Angeles (09-08-122-01A).

TABLE 3
Distribution of affected sisters (all races, more severe nausea and vomiting of pregnancy and hyperemesis gravidarum)

Variable	Controls	Cases	*P* value
Affected sisters	9 (8.33%)	68 (33.83%)	< .0001
Unaffected sisters	99 (91.67%)	133 (66.17%)	

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RESULTS

Sisters

Cases and controls were well matched for distribution of the number of pregnant, and therefore informative, sisters, as shown in Table 1. In all, 207 cases and 110 controls had at least 1 sister with a pregnancy history and were included in the study of affected sisters. Age, race, and pregnancy characteristics of cases and controls with informative sisters are shown in Table 2. Cases were significantly more likely to report having a sister with more severe morning sickness or HG than controls (odds ratio [OR], 5.6; $P < .001$) (Table 3).

Because the cases and controls were not perfectly matched with respect to race, and the majority of participants were white, the analysis was repeated with whites only and the ORs were very similar (OR, 5.2; $P < .001$).

When excluding the less severe definition (more severe morning sickness) and looking at reports of sisters with HG only, cases were even more likely to report having a sister with HG than controls (OR, 17.3; $P = .005$) (Table 4). Again, the analysis was repeated with whites only and the ORs were very similar (OR, 17.9; $P = .005$). Very few cases and controls were missing data on the nausea and vomiting in pregnant sisters and the distribution of missingness was

TABLE 4
Distribution of affected sisters (all races, hyperemesis gravidarum)

Variable	Controls	Cases	*P* value
Affected sisters	1 (0.93%)	28 (13.93%)	< .0001
Unaffected sisters	107 (99.07%)	173 (86.07%)	

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TABLE 5
Distribution of missingness of affected sisters (all races)

Variable	Controls	Cases	*P* value
Missing	2 (1.82%)	6 (2.90%)	.7186
Not missing	108 (98.18%)	201 (97.10%)	

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TABLE 6
Distribution of missingness of affected sisters (white only)

	Controls	Cases	*P* value
Missing	2 (1.87%)	4 (2.21%)	1.000
Not missing	105 (98.13%)	177 (97.79%)	

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not significantly different between cases and controls as shown in Tables 5 and 6.

Mothers

In all, 469 cases and 216 controls were included in the analysis of mothers. Cases were significantly more likely to report an affected mother ($P < .0001$) as 33% of cases and only 8% of controls reported having a mother affected with HG or more severe morning sickness (Table 7). Cases and controls were well matched for distribution of missing data on affected and unaffected mothers (Table 8).

Maternal and paternal grandmothers

Cases and controls were not well matched with respect to missing data on second-degree relatives (maternal and paternal grandmothers) and therefore a comparison between cases and controls is not interpretable and is not included herein. However, 18% of cases reported an affected maternal grandmother and 23% of cases reported an affected paternal grandmother. Inheritance can pass through maternal and paternal lines and multiple generations as exhibited in the pedigree show in the Figure.

Comment

This study demonstrates a remarkably high risk of more severe morning sickness and HG among relatives of HG cases as approximately one third of cases reported an affected mother and/or sister.

TABLE 7
Distribution of affected mothers

Variable	Controls	Cases	*P* value
Affected mothers	15 (7.73%)	143 (32.65%)	< .0001
Unaffected mothers	179 (92.27%)	295 (67.35%)	

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TABLE 8
Distribution of missingness of affected mothers

Variable	Controls	Cases	*P* value
Missing	22 (10.19%)	31 (6.61%)	.1233
Not missing	194 (89.81%)	438 (93.39%)	

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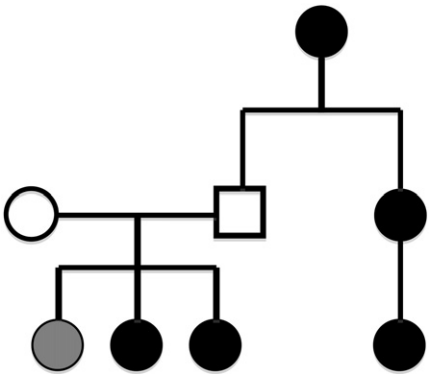
FIGURE
Maternal and paternal inheritance



Family A shows inheritance passes through maternal and paternal lines and multiple generations.

Black circles = hyperemesis gravidarum; *gray circle* = more severe morning sickness; *no fill* = not affected.

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The OR is highest (OR, 17) when comparing the proportion of affected sisters of cases to the proportion of affected sisters of controls using the most stringent definition of HG, rather than grouping HG and more severe morning sickness.

Although we realize that shared environmental risk factors can also contribute to the observed high prevalence of affected family members, to our knowledge no such factors have been identified. In addition, although sisters commonly have a similar in utero and childhood environment, it is unlikely that they share the same environment during their own pregnancy, when HG occurs. This study also suggests grandmothers, mothers, and daughters commonly share severe nausea of pregnancy and it is unlikely that this can be entirely explained by shared cross-generational environmental factors. Other reports of half-siblings reared in separate states and identical twins pregnant and diagnosed with HG while residing in different countries, although anecdotal, lend further support to a role for genetics.[26]

The pedigree presented in this study, the fact that mothers and sisters are commonly affected, and the similar frequency of maternal and paternal grandmothers affected suggest that HG may be

inherited in an autosomal dominant manner with incomplete penetrance, although other modes of inheritance in some families cannot be ruled out. Regardless of the mode of inheritance, this is the first case-control study of familial aggregation for HG and, in addition to previous studies showing higher concordance for NVP in monozygotic vs dizygotic twins[16] and a high prevalence of HG among family members of affected individuals,[26] provides strong support for a genetic contribution to severe NVP.

HG often leads to extreme weight loss and may result in a state of nutrient deprivation, malnutrition, and starvation for both the mother and the developing fetus. Fetal outcome remains controversial. Some studies suggest infants exposed to HG in utero are significantly more likely to be born earlier, weigh less, be small for gestational age, and die between 24-30 weeks' gestation than infants not so exposed.[6] Other studies show that these associated outcomes are only significant in cases with hyperemesis and low-pregnancy weight gain,[7] and that, if treated early, severe nausea may be associated with a protective effect against major malformations.[27] While few long-term studies of HG offspring have been conducted, there is a body of literature on starvation in pregnancy in human beings and animals, providing convincing evidence that nutritional deprivation in utero can have lasting or lifelong significance.[28] These data, along with the evidence of a familial component to HG, suggest that health care providers should be vigilant in identifying and treating women with a family history of HG.

While our data implicate a strong maternal genetic component, other observations suggest that additional risk factors may influence severity of NVP. An increased incidence of HG has been reported with multiple gestations, gestational trophoblastic disease, fetal chromosomal abnormalities, and central nervous system malformations, and for mothers of female offspring.[8,29]

While smoking during pregnancy was recently reported to decrease the risk of hyperemesis, smoking by the partner was reported to increase the risk.[4,8] Other than secondhand smoke, to our knowledge, no environmental factors have been identified that increase risk. Nongenetic maternal factors such as advanced maternal age have been associated with decreased risk, and adolescent pregnancy with increased risk for HG.[30,31] Finally, evidence for a paternal and fetal contribution was controversial.

While one study suggested that HG recurrence decreases with a change in partner, suggesting paternal genes expressed in the fetus may play a role, this conclusion was recently refuted by a separate study.[32,33] Additionally, a consanguinity study also found no increased risk of HG, suggesting recessive fetal genes may not be involved in HG risk.[5]

A major strength of this study stems from the collaboration with the Hyperemesis Education and Research Foundation, which allowed collection of family history information on a large sample of women affected by HG. To date, most studies of HG have been small case series or population studies relying on hospital databases with no information on family history. Thus this study is the first case-control report of its kind.

Admittedly, this study has some methodological concerns. One potential limitation arises from the use of an Internet-based survey. While Internet-based research is quickly becoming scientifically recognized as a reliable recruiting tool, the study population consists only of cases with Internet access, and thus may represent women of higher education and income. We believe, however, that the generalizability of our study results should be reasonably good since we have no reason to suspect that education level and income would affect the likelihood of having a family history of HG.

Another limitation is that family history of HG was based on self-reports, which can lead to misclassification of disease status and/or family history. However, we believe it would be highly unlikely for women to misclassify disease status of affected family members as they are given definitions to classify disease in family members and are required themselves to have been treated with IV therapy for severe nausea and vomiting.

Finally, the control group (friends of cases) was not perfectly matched for several characteristics. The controls were significantly older and had more living children than the cases, which is likely due to the fact that while cases were eligible with only 1 pregnancy affected with HG, controls had to have completed at least 1 pregnancy and 2 trimesters of a second pregnancy without experiencing HG. The fact that controls on the whole were slightly older should not have any affect on the affected status of family members and sisters, in particular, because the number of pregnant and therefore informative sisters was similar for cases and controls. Cases were also more likely to be currently pregnant, which is likely due to the fact that some case patients searched the Internet when they were given the diagnosis of HG and found the study information at that time. Again, we cannot think of a reason that this would bias the results. However, the cases were not well matched for race and this was of particular concern as genetic factors can be linked to race. We addressed this issue by repeating the analysis with the race that represented the majority for cases and controls (white) and the results were very similar, suggesting that the differences in race do not affect the results of this study.

Because the incidence of HG is most commonly reported to be 0.5% in the population and the sisters of cases have as much as an 18-fold increased familial risk for HG compared to controls, this study provides strong evidence for a genetic component to extreme NVP. In summary, this study demonstrates that maternal genetic susceptibility plays a role in the development of severe NVP.

Future work should focus on reproducing these results in other populations and on the identification of genetic variants that may contribute to HG susceptibility. Identification of genetic factors will elucidate the biology of NVP and allow novel therapeutics to be developed to treat the cause of the disease rather than the symptoms. ■

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APPENDIX:
Cases eligibility questions

Thank you for contacting me. I know you may have already answered some of these questions, but for my records, please answer the following questions in capital letters next to each question to determine your eligibility, and email it back to me.

0a. How did you hear about the study?
0b. Are you currently living in the US?
1. Did you have severe nausea and vomiting in a singleton (not twins or multiples) pregnancy?
2. Were you treated with IV and/or TPN (total parenteral nutrition) or other form of feeding tube (ie nasogastric feeding tube) in this pregnancy due to nausea and vomiting?
3. Did your HG pregnancy have an abnormal outcome such as molar pregnancy, Down Syndrome, or any other chromosomal abnormalities or malformations?
   If yes, please explain.
4. Do you think you will be able to identify an unaffected friend **of the same race/ethnicity** (not a family member) with at least 2 pregnancies that went beyond 27 weeks to participate in the study as a control?
5. To the best of your knowledge, are any of your relatives enrolled in this study?
6. Are you between the age of 18-50?

I will email you back shortly to tell you whether you are eligible to participate and then we can set up a phone appointment to consent and enroll you.

Thank you for your time!

Marlena

Controls eligibility questions

Thank you for your interest in serving as a control in this study. For my records, please answer each of the following questions in all capital letters by each question and email back to me to determine your eligibility to serve as a control.

Are you living in the US?

How did you hear about this study?

Are you related to the person who referred you?

This is a study to identify epidemiologic and genetic factors involved in HG. There is no cost to you or travel needed to participate in this study. You will be asked to 1) answer a risk factor and out-

comes survey, and 2) submit a saliva sample for DNA analysis. If you are still interested in participating, please answer the following questions for my records to determine eligibility:

1) Have you had at least 2 pregnancies that went beyond 27 weeks?
2) Did you have a) no nausea and vomiting or b) mild (meaning that it did not interfere with your daily routine) in all of your pregnancies?
3) Did you have any weight loss due to nausea and vomiting in any pregnancy?
4) Did you seek medical attention to treat symptoms of nausea and/or vomiting in any pregnancy?
5) Are you between the age of 18-50?

Thank you for your time!
Marlena