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ORIGINAL ARTICLE

Risk factors, treatments, and outcomes associated with prolonged hyperemesis gravidarum

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Objective: **To identify factors associated with prolonged Hyperemesis Gravidarum (HG).** ***Study Design:*** **About 395 women completed a survey regarding pre-existing conditions, treatments and outcomes. Responses were compared using two-sided *t*-tests or the *F*-test.** ***Results:*** **Participants with prolonged HG are slightly younger and weigh more. Pre-existing factors associated with prolonged HG include allergies and a restrictive diet. Prolonged HG is associated with hematemesis, dizziness, fainting and antiemetic treatment. Following pregnancy, those with prolonged HG reported more posttraumatic stress, motion sickness, muscle weakness and infants with irritability, severe colic and growth restriction.** ***Conclusion:*** **Multiple pre-existing conditions and poor maternal and infant outcomes were associated with prolonged HG. The most significant condition prior to pregnancy was allergies suggesting a possible autoimmune component affecting duration of HG. In addition, the most significant lifestyle choice linked to prolonged HG was a restrictive diet. Future research is needed to determine whether a change in diet prior to pregnancy may lead to a shorter duration of HG and its associated outcomes.**

Keywords: hyperemesis gravidarum; outcomes; risk factors, treatments

Condensation
This case: control study shows pre-existing conditions, most significantly, allergies and a restricted diet, antiemetic treatments, and poor maternal and infant outcomes, are associated with prolonged HG.

Introduction

Hyperemesis Gravidarum (HG) accounts for over 285,000 hospital discharges in the United States annually, with most authors reporting an incidence of 0.5–2% [1,2]. HG often results in dehydration, electrolyte disturbance and nutritional deficiency in many cases, mandating intravenous hydration and, in severe cases, the use of parenteral nutrition. If left untreated, HG can result in Wernicke's encephalopathy [3], central pontine myelinolysis [4], hepatic dysfunction [5] and renal failure [6]. The diagnosis of HG is also associated with low birth weight, intrauterine growth restriction, preterm delivery and fetal and neonatal death [7–9].

The most common treatment modalities include IV hydration and serotonin inhibitors [10]. However, treatment is not always effective, resulting in therapeutic termination in as many as 15.2% of cases [11] and extreme weight loss of more than 15% of prepregnancy weight in more than a quarter of cases [12]. Furthermore, prolonged hyperemesis, nausea and vomiting lasting beyond 27 weeks' gestation, is seen in as many as 22% of cases [12]. The cause of HG is unknown and although it is becoming increasingly clear that there is a genetic basis to the disease [13,14], other factors are likely to play a role. To our knowledge, there are no previous reports identifying factors that affect duration of symptoms. Herein we explore maternal factors prior, during and after pregnancy, as well as child outcomes associated with prolonged HG.

Materials and methods

Sample and settings

This study is part of a larger investigation evaluating the genetics and epidemiology of HG. A total of 395 women have been recruited. Eligible patients were primarily recruited through advertising on the Hyperemesis Education and Research (HER) Foundation Website at www.HelpHer.org. Another method of recruitment of affected individuals 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 cases were a diagnosis of HG and treatment with IV fluids and/or total parenteral nutrition (TPN)/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 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.

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Each case was asked to recruit a friend with at least two pregnancies that went beyond 27 weeks to participate as a control. Controls 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 excluded.

Because this is a study of duration of symptoms, only participants whose pregnancies lasted beyond the second trimester were included in the study and, for consistency, only first pregnancies were analyzed. Thus, any participants whose first pregnancy did not last beyond the second trimester were excluded.

Study procedures

Participants were asked to submit their medical records and complete an online survey regarding information on a variety of demographic characteristics (e.g. age, gender and ethnicity), pre-existing conditions, pregnancy symptoms and treatments and maternal and fetal outcomes. The survey instrument can be found at http://www.helpher.org/HER-Research/2007-Genetics/2007rsch-start.php. The majority of participants (cases and controls) joined the study and began the survey during one of their pregnancies and were sent a reminder to complete the survey pertaining to pregnancy outcome following their due date.

Table I. Demography.

Demographics	Control group (%)	HG-short group (%)	HG-long group (%)	*p*-value
Sample size	194	74	127	
Race (White)	184 (95)	66 (89)	117 (92)	0.284
Country (USA)	184 (95)	73 (99)	120 (94)	0.813
Cesarean/vaginal	16 (16)	16 (22)	31 (13)	0.361
Miscarriages[a]	36 (19)	24 (32)	25 (20)	0.726
Fertility treatment[b]	7 (4)	3 (4)	4 (3)	0.848
	Avg. (range)			
Weight of group (pounds)[c]	138.73 (95–285)	139.08 (92–230)	150.69 (98–295)	0.001
Age[d]	36 (25–53)	36 (25–54)	34 (23–51)	0.009
Height of group (inches)	64.63 (54–78)	65.42 (54–74)	64.8 (55–75)	0.803

[a]Number (percent) of miscarriages reported after index pregnancy.
[b]Number (percent) who reported fertility treatment for index pregnan cy.
[c]Weight in pounds (range in pounds) prior to index pregnancy.
[d]Current age.

Statistical analyses

Responses from participants with HG, prolonged HG and the control group were compared for a number of variables including health issues of participants and offspring using two-sided *t*-tests, and variables included in demography, treatment and method of delivery were performed using the *F*-test. All data were analyzed using R. For significant factors analyzed prior, during and after pregnancy, only those reported in 10% or greater of at least one of the three samples are reported herein. All significant child outcomes regardless of percentage are presented.

Results

Demographic characteristics

About 201 women with HG pregnancies and 194 women without HG participated in the study. About 127 women reported HG lasting until birth and are included as the group "HG long" (prolonged HG). About 74 women reported HG symptoms that resolved before the end of the second trimester (27 weeks) and are included as the group "HG short." The 194 women who did not have HG were included as "Controls."

As shown in Table I, participants were primarily from the United States and are currently in their mid-30s, Caucasian, 65 inches and 139–151 pounds. No significant differences were found between the control group and the HG-short group for any characteristic. However, the HG-long group was significantly more likely to be younger and weigh more than the other groups. Participants were well matched for vaginal versus cesarean delivery, fertility treatment and miscarriages.

Treatments

Women with prolonged HG were significantly more likely to be treated with antiemetic therapies. Among eleven treatments for HG, seven were significantly more commonly prescribed for women in the HG-long group (Table II). These treatments included Seabands, (72%), Zofran (70%), Phenergan (66%), Antacids (56%), Reglan (49%), Compazine (20%) and Antimotion medications (20%). There was no significant difference in the use of vitamin B6, homeopathics, Tigan or TPN between the HG-short and HG-long (Prolonged HG) groups.

Factors associated with prolonged HG (significantly different between HG-short and HG-long).

Four factors prior to pregnancy were significantly different between HG lasting less than 27 weeks and HG lasting more than

Table II. Treatment.

Factor	Control group (%)	HG-short group (%)	HG-long group (%)	Control versus HG short *p*-value	Control versus HG long *p*-value	HG short versus HG long *p*-value
Sample size	194	74	127			
Treatment						
Reglan (Metoclopramide)	0	20	49	<0.0001	<0.0001	<0.0001
Phenergan (Promethazine)	0	41	66	<0.0001	<0.0001	0.0004
Zofran (Ondansetron)	0	45	70	<0.0001	<0.0001	0.0005
Compazine (Prochlorperazine)	0	8	20	0.0133	<0.0001	0.0109
Antacids	23	38	56	0.0200	<0.0001	0.0131
Seabands	4	55	72	<0.0001	<0.0001	0.0230
Antimotion medicine	0	9	20	0.0073	<0.0001	0.0393
Homeopathics	2	12	20	0.0054	<0.0001	0.1152
Vitamin B6 (Trimethobenzamide)	0	8	13	0.0133	<0.0001	0.3037
Tigan (Trimethobenzamide)	0	5	7	0.0447	0.0024	0.6313
Total parenteral nutrition	0	9	10	0.0073	0.0002	0.8589

Table III. Factors significantly different between HG short versus HG long (prolonged HG).

Factor	Control group	HG-short group	HG-long group	HG short versus HG long *p*-value	OR (confidence interval)
Sample size	194	74	127		
Demography					
Pre-pregnancy weight average (range)	138.73 (95–285)	139.08 (92–230)	150.69 (98–295)	0.0105	1.01 (1.0022, 1.0225)
Current age average (range)	36 (25–53)	36 (25–54)	34 (23–51)	0.0445	0.95 (0.9020, 0.9991)
Before first pregnancy					
Allergies	34	31	49	0.0124	2.12 (1.1672, 3.9112)
Restrictive diet	3	8	18	0.0342	2.51 (1.0266, 7.0706)
Mother during first pregnancy					
Vomiting blood	0	1	15	0.0001	12.84 (2.5771, 233.2709)
Dizzy	0	1	13	0.0007	10.52 (2.0784, 191.9589)
Fainting	2	1	10	0.0037	8.32 (1.6063, 152.8244)
Depression	1	5	18	0.0038	3.87 (1.4145, 13.6253)
GERD	2	9	24	0.0040	3.09 (1.3521, 8.0127)
Anxiety	1	7	18	0.0128	3.05 (1.1911, 9.4284)
Low blood pressure	1	7	18	0.0128	3.05 (1.1911, 9.4284)
Restrictive diet	4	8	20	0.0161	2.78 (1.1476, 7.7968)
Excessive saliva	0	27	41	0.0422	1.87 (1.0143, 3.5431)
Mother after pregnancy					
PTSD	0	1	13	0.0004	11.28 (2.2416, 205.4786)
Motion sickness	5	12	31	0.0011	3.20 (1.5053, 7.4652)
Muscle weakness	0.5	3	13	0.0032	5.56 (1.5331, 35.7611)
Anxiety	6	18	32	0.0231	2.16 (1.0876, 4.5064)
Outcome of children					
Irritability	3	5	18	0.0038	3.87 (1.4145, 13.6253)
Severe colic	0.5	1	8	0.0189	6.24 (1.1592, 115.6949)
Growth retardation	1	0	3	0.0451	Not applicable

Table IV. Restrictive diets.

	Control group	HG-short group	HG-long group	OR (confidence interval)
Total	6 (3.1%)	6 (8.1%)	23 (18.1%)	
Lactose intolerant	1	1	8	4.91 (0.8748, 91.9733)
Vegetarian	1	2	7	2.1 (0.4917, 14.3526)
Other (i.e., Kosher)	4	2	5	1.48 (0.3092, 10.4871)
Celiac disease	0	2	3	0.87 (0.1412, 6.7282)

27 weeks. These factors include allergies, a restrictive diet, greater weight, and younger age (Table III). The most common restrictive diets reported in the HG-long group included a lactose-free diet and a vegetarian diet (Table IV). Several symptoms occurring during pregnancy were reported significantly more often in the HG-long group compared with the HG-short group. The three most significant symptoms were hematemesis (15% of HG long), dizziness (13%) and fainting (10%). Differences in reported depression, gastroesophageal reflux disease (GERD), anxiety, low blood pressure, restrictive diet and excessive saliva during pregnancy were also significant.

After pregnancy, those with prolonged HG were significantly more likely to report several conditions including posttraumatic stress disorder (PTSD) (13%), motion sickness (31%), muscle weakness (13%) and anxiety (32%). Among 49 factors examined, three child outcomes found to be significantly different between the HG groups included irritability (18%), severe colic (8%) and growth restriction (3%).

Comment

Nausea and vomiting during pregnancy usually resolves by the end of the first trimester, but with HG, in as many as 22% of cases, symptoms can last until delivery [12]. Herein, several risk factors for prolonged HG have been identified, the most significant being allergies and a restrictive diet prior to the first pregnancy. The etiology of HG is unknown, but recently, several groups have investigated whether cytokines, which are central to the immune response to allergens, play a role in HG. The consistent finding has been an increased concentration of TNF-alpha [15]. TNF-alpha is involved in regulation of hCG production, suggesting a possible link to the hCG-hormone hypothesis, wherein HG is proposed to be caused by an abnormality in the hCG hormone-receptor pathway. The normal shift in pregnancy to Th2 over Th1 dominance has been reported to be more exaggerated in women with HG [16]. The increase in Il-4 secreting cells seen in this milieu also favors increased hCG production. Adenosine, which is thought to attenuate the oxidative burst of TNF-alpha is also increased in HG [17] as is its precursor catalytic enzyme 5′-nucleotidase [18]. These changes and the increase in hCG point to increased activity in the trophoblast cells at the maternal-fetal interface. Consistent with this is the finding of increased cell-free DNA in the plasma of women with HG, attributed to trophoblasts damaged or destroyed by a hyperactive maternal immune response [19]. Additionally, in a recent study of over 7000 women with rheumatoid arthritis, it has been found that women with a history of HG had a 1.7-fold increased risk of developing rheumatoid arthritis [20]. An autoimmune component to HG can also explain the "dramatic response" to corticosteroid therapy observed in some patients who did not respond to conventional antiemetic therapies [21]. Support for an autoimmune component

to HG comes from reports of either pre-existing or pregnancy onset Addison's disease [22–24], as well as pre-existing diabetes and pre-existing asthma linked to HG-risk [25]. However because not all women with a pre-existing autoimmune disease nor women with immune disorders that present during pregnancy, develop HG, an abnormal allergic response may effect duration of HG symptoms, but more work is needed to determine whether HG may in fact be classified as an autoimmune disease.

The identification of a restrictive diet linked to a 2.5-fold increased risk of prolonged HG is of particular interest because of its potential to lead to a safe dietary modification prior to pregnancy that may have an effect on duration of HG symptoms. To date, the only studies of pre-pregnancy lifestyle choices linked to HG are saturated fat intake and younger age, which increased the risk of HG [8,26], and maternal smoking and advanced maternal age, both independently linked to decreased risk of HG [25]. In this study, participants with prolonged HG were almost five-fold more likely to be on a lactose-free diet due to self-reported lactose intolerance and twice as likely to be vegetarian. These findings are consistent with the evidence that protein meals significantly reduce nausea compared to equally caloric non-protein meals in the first trimester of pregnancy [27].

Dairy foods are not only an excellent source of protein, but also, calcium, magnesium, potassium, riboflavin, other nutrients and, when fortified, vitamin D. Therefore lactose-free diets may be deficient in these nutrients [28]. It is of particular interest that Asian women have an increased risk of HG and tend to be lactose intolerant and have diets low or deficient in dairy [13,28,29]. Vegetarian diets can also be similarly deficient leading to undernutrition or chronic energy deficiency [30]. The link with prolonged HG and a vegetarian diet is supported by the fact that Indian women residing in Norway (who more commonly than Norwegian women, have a vegetarian diet) are three times more likely to be diagnosed with HG as Western European women living in Norway [31]. Still, it is unknown whether this is due to genetics, diet, a combination of both, or other as yet unidentified factors.

Alternatively, the increased risk of prolonged HG linked to lactose-free and vegetarian diets may have nothing to do with nutritional deficiency, but may be caused by an increased intake of soy-based protein supplementation which contains high levels of phytoestrogens similar to 17-estradiol. Phytoestrogens have been implicated in the etiology of hormone-dependent cancers, menopausal symptoms, male infertility, and obesity [32]. This would be in line with the most widely studied theory that HG is caused by abnormal pregnancy hormone levels, variants, or pathways [2].

Although being underweight and obese are both associated with hyperemesis [33], pre-pregnancy eating disorders were included in the survey and were not reported by more than 10% of participants in any group. However, this study did reveal a significantly higher overall weight in the prolonged HG group, consistent with the findings that obesity may increase HG risk [33]. In addition, this study found that women with prolonged HG were significantly younger, consistent with the previous finding that women hospitalized for HG are more likely to be younger than patients without hospital admission for hyperemesis [8]. More research is needed to determine whether younger age may be due to the fact that women with extended duration of symptoms are more likely to limit family size compared to women in the other groups.

As one might expect, with a longer duration of symptoms, participants were significantly more likely to suffer from symptoms, most commonly, excessive saliva (41%) and GERD (24%), and to be treated with antiemetics, the most common being Zofran (Ondansetron) and Phenergan (Promethazine), used by 70 and 66% of the HG-long group, respectively. Surprisingly, the very aggressive treatment, TPN, was equally prescribed for both the HG-short and HG-long groups. One explanation for this could be that TPN is effective in reducing duration of symptoms. This would be in line with the findings herein that a restricted diet and possibly nutritional deficiency add to the duration of symptoms, but further study is needed.

The findings that prolonged HG is associated with significant maternal and neonatal outcomes including posttraumatic stress, motion sickness, muscle weakness and infants with irritability, severe colic, and growth restriction, indicate a critical need for more research on HG to identify better treatment options that effectively reduce duration of symptoms.

A major strength of this study stems from the collaboration with the HER Foundation, which allowed collection of data 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 maternal outcome. Thus, this study is the first case-control report of its kind.

Admittedly, this study has some methodological concerns. The participants were primarily Caucasian, older and with longer-lasting symptoms than the general affected population in the United States. This limitation may stem 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, in addition to the factors above, may represent women of higher education and income. We feel, however, our study remains generalizable since, thus far, to our knowledge, there is no evidence that neither race, age, education level nor income should have any effect on the findings related to having long-lasting symptoms presented herein. However, we cannot eliminate the possibility that affected women may have been more willing to search for information and participate if they are more severely affected than the general population.

Another limitation is that the study is based on self-reports, which can lead to misclassification of symptoms and outcomes. However, we believe it would be highly unlikely for women to misrepresent themselves, as the affected individuals are required to have been treated with IV therapy for severe nausea and vomiting and asked to send in medical records to confirm treatment. In addition, evidence suggests that individuals who encounter rare events (one might consider HG a "rare event," or even a "pregnancy" for any given women is "rare") compared to everyday occurrences can be recalled well [34].

In conclusion, multiple preexisting conditions and poor maternal and infant outcomes are associated with prolonged HG. Among 60 factors analyzed, the most significant condition prior to pregnancy was allergies suggesting a possible allergic or autoimmune component affecting duration of extreme nausea of pregnancy. In addition, the most significant lifestyle choice linked to HG lasting beyond the second trimester was a restrictive diet. Future research is needed to determine whether a modification in diet, via supplementation and/or reduction of soy-based protein prior to and during pregnancy, may shorten the duration of HG symptoms. Furthermore, studies that focus on the identification of genes associated with HG in addition to the factors effecting the duration of symptoms, such as those identified in this study, will result in elucidation of the currently unknown etiology of this common pregnancy disease.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. This study has been approved by Institutional Review Boards, USC IRB # HS-06-00056 and UCLA IRB # 09-08-122-01A.

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