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Antihistamines and other prognostic factors for adverse outcome in hyperemesis gravidarum

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Abstract

Objective—The purpose of this study is to determine the frequency of adverse perinatal outcome in women with hyperemesis gravidarum and identify prognostic factors.

Study design—This is a case-control study in which outcomes of first pregnancies were compared between 254 women with hyperemesis gravidarum treated with intravenous fluids and 308 controls. Prognostic factors were identified by comparing the clinical profile of patients with hyperemesis gravidarum with a normal and an adverse pregnancy outcome. Binary responses were analyzed using either a Chi-square or Fisher exact test and continuous responses were analyzed using a t-test.

Results—Women with hyperemesis gravidarum have over a 4-fold increased risk of poor outcome including preterm birth and lower birth weight ($p < 0.0001$). Among maternal characteristics, only gestational hypertension had an influence on outcome ($p < 0.0001$). Treatment as an outpatient and/or by alternative medicine (acupuncture/acupressure/Bowen massage) was associated with a positive outcome ($p < 0.0089$). Poor outcomes were associated with early start of symptoms ($p < 0.019$), and treatment with methylprednisolone ($p < 0.0217$), promethazine ($p < 0.0386$), and other antihistamines [diphenhy- dramine (Benadryl), dimenhydrinate (Gravol), doxylamine (Unisom), hydroxyzine (Vistaril/Atarax), doxylamine and pyridoxine (Diclectin/Bendectin)] ($p < 0.0151$) independent of effectiveness. Among these medications, only the other antihistamines were prescribed independent of severity: they were

Conflict of interest
The authors report no conflict of interest.

effective in less than 20% of cases and were taken by almost 50% of patients with an adverse outcome.

Conclusion—Poor outcomes are significantly greater in women with HG and are associated with gestational hypertension, early symptoms, and antihistamine use. Given these results, there is an urgent need to address the safety and effectiveness of medications containing antihistamines in women with severe nausea of pregnancy.

1. Introduction

Hyperemesis gravidarum (HG), severe nausea and vomiting of pregnancy, accounts for over 285,000 hospital discharges in the US 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].

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

Two recent systematic reviews of published outcome data came to the conclusion that HG is significantly associated with low birth weight, small for gestational age, and preterm birth [10,11], but scant attention has been paid to identification of the underlying factors in women with HG that are linked to poor outcome. Studies have focused on comparison of factors between women with and without HG rather than comparing women with HG who do and do not have poor outcomes. Therefore, herein, we determine the risk of poor outcome in well-defined cases with HG compared to well- defined controls without HG. We then determine what factors are significantly associated with poor outcome among women with HG, by identifying factors that are significantly different in women with HG who have negative outcomes compared to those with positive outcomes.

2. Materials and methods

2.1. Sample and settings

This study is part of a larger investigation evaluating the genetics and epidemiology of HG. A total of 562 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, independent of hospitalization because some treatments were given to patients in an outpatient setting. 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 whose first pregnancies did not last beyond 20 weeks were excluded because fetal outcomes beyond 20 weeks gestation are the focus of this study.

Each case was asked to recruit a friend with at least 2 pregnancies that went beyond 20 weeks to participate as a control. Controls were eligible if they experienced normal (did not interfere with their daily routine) or no nausea/vomiting of pregnancy (NVP), no weight loss due to nausea/vomiting and no medical attention in their 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 254 HG patients and 308 control patients enrolled in the study. This study has been approved by Institutional Review Boards, USC IRB # HS-06-00056 and UCLA IRB # 09-08-122-01A.

2.2. 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 outcome following their due date.

2.3. 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. The survey instrument is included in the Appendix.

2.4. Statistical analyses

Respondents were categorized according to two binary response variables: reported HG/no HG, and adverse fetal outcome/healthy fetal outcome, for all reported pregnancies of at least 21 weeks. Chi-square and Fisher’s exact tests were performed to compare groups according to these binary responses, and t-tests were used to compare respondents according to continuous explanatory variables. Logistic regression was per- formed in order to derive estimated odds ratios corresponding to various maternal characteristics. 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.

3. Results

3.1. Demographic characteristics

All participants were Caucasian, from the United States, and cases and controls were well-matched for age, socio-economic status, pre-existing hypertension, gestational diabetes, autoimmune disease, spontaneous labor, delivery method, and use of assisted reproduction

(Table 1). Participants with HG were more likely to have gestational hypertension, immune problems, anxiety, bipolar disorder, and depression. These significantly different characteristics were rare, as less than 80% of participants in either group reported any of these characteristics prior to their first pregnancy. Carrying a female fetus was significantly more common in women with HG.

3.2. Outcome

Women with HG were significantly more likely to report lower birth weight and prematurity (<37 weeks), and their overall rate of adverse fetal outcome was 16.93% compared to 4.55% in controls (Table 2). There is a 4.28-fold increased risk of adverse fetal outcome in women with HG (OR 4.28 [2.34–8.30], adjusted OR 4.00 [2.11–7.97]). There was no significant difference in the rate of birth defects, perinatal mortality, nor weight below the 10th percentile, although all these rare events were slightly more common outcomes in the HG group.

3.3. Factors associated with adverse fetal outcome in women with HG

All factors that were significantly different in women with HG compared to unaffected controls were analyzed in women with HG to determine whether those factors were also associated with poor outcome. With the exception of gestational hypertension, none of the significant maternal characteristics related to HG in Table 1, including psychiatric illness, immune problems and fetal gender, were found to have any significant influence on outcome in women with HG (Table 3).

To analyze potential associated factors further, we looked at the week symptoms began, the time of first treatment and treatment setting, and the week weight gain began. Among these, only nausea and vomiting symptoms beginning at gestational age 3–4 weeks were significantly associated with poor outcome. Treatment as an outpatient (and not by home health care nor inpatient hospitalization) was associated with a positive outcome (Table 4).

3.4. Medications/treatment and outcome/effectiveness

We explored this further by comparing use of various medications/treatments in the two groups (43 HG participants with an adverse outcome compared to 211 HG participants with a good outcome). Among 36 medications/treatments, only alternative medicine (acupuncture/acupressure/Bowen massage) was significantly associated with a positive outcome. Alternatively, promethazine, other antihistamines [diphenhydramine (Benadryl), dimenhydrinate (Gravol), doxylamine (Unisom), hydroxyzine (Vistaril/Atarax), doxylamine and pyridoxine (Diclectin/ Bendectin)], and methylprednisolone, were significantly associated with a poor outcome (Table 5).

We compared self-reported effectiveness of medications between those with adverse outcome and those with a favorable outcome to determine whether the medications were less effective for participants with poor outcome (which might suggest these cases are more severe and the poor outcome could be due to severity rather than the medication itself). (Table 5) The only treatments/medications self-reported to be effective in more than 50% of patients were cannabis, intravenous fluids, methylprednisolone, and ondansetron (Zofran),

and there was no significant association between self-reported medication effectiveness and outcome for any medication including the medications associated with poor outcome (Table 5).

3.5. Severity in factors associated with adverse outcome

We examined use of total parenteral nutrition (TPN) as well as mean weight loss in patients with and without factors associated with outcome, to determine whether these factors were also associated with severity (Table 6). Women treated as outpatients only (not inpatient nor home health care), were significantly less likely to be treated with TPN, suggesting this group is less severe and better associated outcomes may be related to milder symptoms for participants in this group. Participants treated with methylprednisolone were significantly more likely to be treated with TPN and women with HG taking promethazine lost significantly more weight, suggesting these patients may be more severely ill and that may be a factor in the link to poor outcome. No increased use of TPN nor increased weight loss were seen in the antihistamine group, in the gestational hypertension group, nor in the early NVP symptoms group, suggesting that disease severity (as defined by TPN treatment and/or weight loss) cannot explain the increased adverse fetal outcome in these groups.

3.6. Comment

This study focuses on the most extreme end of the nausea and vomiting spectrum, hyperemesis gravidarum, and shows a 4-fold increased risk of adverse fetal outcome in pregnancies complicated by HG. In line with these findings, two recent systematic reviews of published outcome data come to the same conclusion that HG is significantly associated with low birth weight, small for gestational age, and preterm birth [10,11]. The risk of adverse fetal outcome reported in this study may be higher than other studies because this study may be biased toward women at the extreme end of the clinical spectrum of HG. Evidence for this comes from the high proportion of women (17%) treated with TPN. TPN is linked to a significant increase in serious complications including candida septicemia [12,13], and in this study, though not quite reaching significance, 28% of TPN patients fell into the adverse outcome group compared to 15% in the control group. It is possible that TPN did not quite reach significance in this study because 85% of the women with HG were of middle or high income and thus more likely to have access to an advanced metabolic support team. While institutions lacking advanced metabolic support teams may have less favorable outcomes [12], we did not find a difference in adverse fetal outcome based on socioeconomic status in this study (data not shown). Additionally, there is no universal standard in the medical community to determine when more aggressive nutritional therapy is recommended, possibly leading to variation in severity and TPN treatment. That being said, other indicators of severity, such as hospitalization and the week weight gain began, were also not found to be significant prognostic factors for adverse outcome: thus severity cannot completely explain the increased risk seen in this study. Of note, in a large study of HG and outcome from the Netherlands, Roseboom et al. also did not find any significant differences in outcome when restricting their analyses to the most severe cases that required hospitalization, and came to the conclusion that maternal characteristics largely explain the adverse fetal outcomes in pregnancies affected by hyperemesis [14]. That study, however, adjusted for maternal characteristics by grouping all characteristics (age, parity, socio-

economic status, ethnicity, mode of conception, urbanization, substance abuse, hypertension, diabetes, psychiatric disease and sex of the baby) simultaneously. In our study we took each characteristic that was significantly different in our affected and unaffected groups separately and find only the maternal characteristic gestational hypertension is significantly linked to adverse outcome. Our findings linking gestational hypertension to preterm birth are very similar to those of a recent publication by Spiegler et al. [15] reporting on pregnancy risk factors for preterm birth, who found 28% hypertension in the adverse outcome group vs 8% in the control group (we find 28% vs 10%). Thus the connection between hypertension and HG pregnancies may explain, in part, the increased risk of poor fetal outcome.

Additionally, the study by Roseboom et al. [14] reports a very similar percentage of adverse outcome in HG cases (16.9% in ours vs 17.9% in theirs). Therefore it appears that the difference between these two studies may not be in the cases but in the controls with adverse outcome (4.6% in our study vs 15.1% in theirs). In fact, the controls in our study are very similar to theirs with respect to percentages of perinatal mortality (0.65 vs 0.6), birth weight (3446 vs 3453 grams), and preterm births (4.22 vs 5.7). The only major difference is that in their study 9.8% weigh below the 10th percentile, compared to 0.97% in our study. Our findings are in line with another study from the Netherlands on perinatal outcome in women with eating disorders that reports 0.8–4.0% small for gestational age in their cases and controls [16]. Thus, it is difficult to explain away our results by a comparison of the control group, which appears in agreement with recent reports.

This study is the first, to our knowledge, to identify prognostic factors for adverse fetal outcome in HG pregnancies not only by comparing cases affected with HG to unaffected controls, but also by comparing HG pregnancies with and without adverse outcomes. Demographic characteristics, symptoms, medications, and treatments were all examined in patients with clinically defined HG to determine whether they are related to adverse outcome. Significantly better outcomes were seen in women who were treated as outpatients only (not hospitalized, nor treated in a home-health care setting). These participants were significantly less likely to be treated with TPN, suggesting the better prognosis in this group may be confounded by less severe disease. By contrast, patients treated with alternative medicine (acupuncture/ acupressure/Bowen massage) were also significantly more likely to have better outcomes, but in this group there was no difference in weight loss nor TPN treatment. This suggests the positive effects of alternative medicine (acupuncture/ acupressure/Bowen massage) on outcome identified in this study are not confounded by severity. It is important to note that while this treatment may significantly improve outcome, it was reportedly largely ineffective in improving HG symptoms in this study.

A history of gestational hypertension, and early start of HG symptoms (3–4 weeks) were both linked to adverse outcome, suggesting carers should be particularly attentive to patients with HG that fall into these categories. This study suggests that patients taking antihistamines, [diphenhydramine (Benadryl), dimenhydrinate (Gravol), doxylamine (Unisom), hydroxyzine (Vistaril/ Atarax), doxylamine and pyridoxine (Diclectin/ Bendectin)], are at particular risk for poor outcome. Of note, when analyzing adverse outcome for participants specifically taking doxylamine and pyridoxine (Diclectin/ Bendectin), there was a trend toward adverse outcome, but not enough participants for

statistical significance. These findings are of particular concern because of their increased use to treat HG worldwide. The use of anti- histamines increased 100% between 2000 and 2004 [17], and antihistamines were taken by over 50% of participants with adverse outcomes in this study. A study of trends in treatment by country of residence reported that antihistamine treatment for HG is highest in the US (65%) and Canada (87.5%), and notably lower in other countries such as the United Kingdom (18.5%) and Australia/ New Zealand (26.3%) [17]. Therefore, the differences in outcome reported in this study compared to others may relate to differences in medications used for HG. Interestingly, pyridoxine, a component of Diclectin/Bendectin, is not linked to adverse outcome in this study, consistent with the findings that antihistamines are the causal factor. More research is needed to determine the mechanism whereby these medications may cause poor outcome in HG patients, but unlike what may be the case with promethazine and methylprednisolone, the cause and effect for some antihistamine use cannot be explained away by the severity of the disease, suggesting the medication itself is likely responsible for the link to adverse outcome identified in this study.

The findings reported herein are surprising given the large body of evidence on the safety of antihistamine use in pregnancy [18]. The majority of these, however, as well as most studies of antiemetic use in pregnancy, focus on teratogenic potential [19], and the major adverse outcome reported herein is preterm birth (<37 weeks). One study of the Swedish Medical Birth Registry found a beneficial effect on delivery outcome for antihistamine use [20]. In this study 3% of women took antihistamines for nausea in pregnancy and an earlier report by the same author reports the prevalence of HG to be 0.3% [3]. The author suggests that the reported outcome is likely related to the positive association of early pregnancy nausea on pregnancy outcome and not due to the medication. Therefore, the beneficial effects of normal nausea may have masked the adverse outcomes associated with more severe nausea (HG) and antihistamine use in their study. A Hungarian study by Czeizel and Puho [21] supports this theory because their study of 3869 women with severe nausea and vomiting of pregnancy (10.1%) excludes 90 women (0.2%) hospitalized for HG, and finds overall longer gestational age in the severe nausea group compared to controls without severe nausea. In this study, in line with the findings herein, the group that used vitamin B6 showed the lowest proportion of preterm birth and the group using dimenhydrinate and thiethylperazine had the highest proportion of preterm birth. This suggests the adaptive function of nausea in pregnancy may mask the findings of an association of certain medications with preterm birth in studies that are not specific to the extreme end of the nausea spectrum. Therefore it would be very interesting to see whether the women hospitalized for HG that were excluded from the Hungarian study, and the women who specifically had HG in the Swedish study, showed similar findings to those reported here.

It is important to note that in this study, medications are self- reported and may or may not have been taken with other treatments/medications, and therefore controlled single agent treatment/medication vs. placebo studies are necessary to confirm the findings. Additionally, long-term outcome studies are imperative to determine whether there are any adverse effects on children exposed to medications for HG in pregnancy, as this study only looks at fetal outcome. Self-reported information may result in significant recall bias in the group of mothers with positive outcomes, possibly leading to exaggerated findings. However, the fact

that other commonly used medications (with greater effectiveness) such as ondansetron (Zofran), were not significantly linked to poor perinatal outcome in this study, provides evidence that some medications used to treat HG may result in a better prognosis than others, and any potential recall bias would have to be unique to certain medications. When weighing in the link between antihistamine use and adverse fetal outcome, in addition to its reportedly low effectiveness in treating HG compared to other medications such as ondansetron, this study provides evidence there are both safer and more effective treatments. Given these results, there is an urgent need to address the safety and effectiveness of medications containing antihistamines in women with severe nausea of pregnancy. In addition, studies should focus on identifying the cause of HG so that safe and effective therapies can be identified to eliminate the fourfold increased risk of poor outcomes associated with HG.

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Table 1

Demographic characteristics

Demographic characteristics	HG[a]	No HG	P-value
N	254	308	
Age (SD[c])	27.7	27.2	0.1215
	(4.66)	(4.31)	
SES[d]-low	15.66%	10.78%	0.1155
SES - medium	75.10%	77.78%	0.5222
SES-high	9.24%	11.44%	0.4817
Pre-existing hypertension (HBP[b])	2.58%	0.80%	0.1039
Gestational hypertension	12.55%	5.07%	0.0003
Gestational diabetes	3.94%	1.30%	0.0574
Autoimmune disease (prior to first pregnancy)	16.21%	10.71%	0.0606
Immune problems (prior to first pregnancy)	12.20%	5.19%	0.0034
Auxietv (prior to first pregnancy)	17.32%	4.55%	<0.0001
Bipolar disorder (prior to first pregnancy)	1.57%	0.00%	0.0412
Depression (prior to first pregnancy)	18.11%	7.47%	0.0002
Assisted reproduction	3.54%	5.19%	0.4136
Spontaneous labor	65.32%	66.79%	0.7759
Vaginal delivery	81.00%	81.72%	0.9079
Female gender child	57.87%	47.23%	0.0138

[a]Hyperemesis grayidarum.

[b]High blood pressure.

[c]Standard deviation.

[d]Socioeconomic status.

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Table 2

Pregnancy outcome

Pregnancy outcomes	HC[b]	No HG	P-value	Crude OR[c]	95% CI[d]	Adjusted OR	95% CI
N	254	308					
Birth defects	2.76%	1.62%	0.5279				
Perinatal mortality (deaths after 20 weeks gestation to 1 week after birth)	1.18%	0.65	0.8283	1.83	0.30–13.96	2.29	0.36–17.85
Birth weight (grams)	3236.69	3446.01	<0.0001				
Preterm birth(<37 weeks)	15.35%	4.22%	<0.0001	4.12	2.20–8.19	4.05	2.08–8.30
Weight below 10th percentile	2.76%	0.97%	0.1976	2.88	0.79–13.47	2.05	0.50–10.23
AFO[a]	16.93%	4.55%	<0.0001	4.28	2.34–8.30	4.00	2.11–7.97

[a] Adverse fetal outcome = birth weight less than 10%, perinatal mortality, and/or preterm birth (<37 weeks).

[b] Hyperemesis gravidarum.

[c] Odds ratio.

[d] Confidence interval.

Table 3

Gestational hypertension associated with adverse outcome.

Demographic characteristics	HG[b] with AFO[a]	HG No AFO	P-value
N	43	211	
Gestational hypertension	27.91%	9.95%	<0.0001
Immune problems (prior to first pregnancy)	6.98%	13.27%	0.3149
Anxiety (prior to first pregnancy)	23.26%	16.11%	0.2717
Bipolar disorder (prior to first pregnancy)	2.33%	1.42%	0.5261
Depression (prior to first pregnancy)	20.93%	17.54%	0.6639
Female gender child	48.84%	59.72%	0.2355

[a] Adverse fetal outcome.

[b] Hyperemesis grayidarum.

Table 4

Early symptoms associated with adverse outcome.

	AFO[a]	No AFO	P-value
N	43	211	
Week of NVP[b] (when symptoms began)			
Week 1–2	6.977%	8.531%	0.973
Week 3–4	39.535%	21.327%	0.019
Week 5–6	48.837%	53.081%	0.734
Week 7–8	4.651%	14.692%	0.125
Week 9–10		1.896%	
Week 11–12		0.474%	
Time of first treatment			
Inpatient admission: Weeks A pregnant at your first inpatient visit	11.867	9.752	0.132
Home health care visit: Weeks pregnant at first home health care visit for nausea/vomiting	13.067	11.438	0.365
Outpatient visit: weeks pregnant at your first outpatient visit for nausea/vomiting?	9.080	9.105	0.983
Hospitalization			
“Inpatient” (paired with anything else)	72.093%	57.820%	0.089
“Home health care” (paired with anything else)	37.209%	31.754%	0.481
“Outpatient only” Weight gain	16.279%	33.649%	0.029
Week they began gaining weight	17.618	19.684	0.100

[a] Adverse fetal outcome.

[b] Nausea and vomiting of pregnancy.

Table 5

Medications/treatment vs outcome and effectiveness.

Treatment/medication	N = 43 HG With AFO (%)[a]	N = 211 HG No AFO (%)	P-Value	Total number who hadtx/med	Those who answered "Effective" HG Adverse outcome (%)	HG No adverse outcome (%)	P-value
Alternative medicine (acupuncture/acupressure/Bowen massage)	2.33	18.01	0.0089	39	0.00	10.53	1
Antacids [e.g. Zantac (Ranitidine), Pepcid (Famotidine)]	67.44	52.61	0.0925	140	0.00	10.20	0.1722
Antibiotics (for Heliobaterpylon)	2.33	1.42	0.5261	4	0.00	0.00	1
Antidepressants/Antianxietv[b]	13.95	11.85	0.7979	31	33.33	16.67	0.7321
Antihistamines[c]	55.81	34.60	0.0151	97	35.20	16.21	0.3265
Anti-motion sickness medications[d]	16.28	18.48	0.8307	46	0.00	5.13	1
Azement (Dolasetron)	0.00	3.32	0.606	7	0.00	28.57	
B6 injection [see oral vitamins below]	18.60O	9.95	0.1161	29	0.00	14.29	0.6549
Cannabis Marijuana Dronabinol (Marinol)	4.65	2.37	0.3377	750.00	75.00	1	
Compazine/stemetil/buccastem (prochlorperazine)	18.60	20.38	1	51	12.50	9.52	1
Motilium (domperidone)	2.33	0.47	0.3105	2	0.00	0.00	0
Emend (aprepitant)	0.00	0.00	1	0			
Gastric pacing	2.33	0.47	0.3105	2			
Medicine not taken at all							
Herbal medicine	11.63	10.90	0.7955	28	0.00	4.17	1
All marked - unsure Homeopathics	6.98	18.48	0.0727	42	0.00	2.56	1
IV fluids	100.00	100.00	1	254	53.49	41.63	0.2079
Inapsine (droperidol)	0.00	0.47	1	l	0.00	0.00	
Kytril (granisetron)	0.00	1.42	1	3	0.00	0.00	
Solu-medrol/medrol (methyprednisolone)	23.26	9.95	0.0217	31	55.56	45.00	0.9008
NG (nasal to stomach) tube feedings	4.65	0.95	0.1342	4	0.00	0.00	
Phenergan/lergigan/avomine (promethazine)	86.05	70.62	0.0386	186	19.44	18.37	1
PICC [peripherally inserted central catheter)	25.58	23.70	0.8451	61	36.36	48.00	0.7136
Physical therapy	4.65	1.90	0.2688	6	0.00	50.00	1
Psychotherapy/counseling	6.98	9.48	0.775	23	0.00	0.00	

Treatment/medication	N = 43 HG With AFO (%)[a]	N = 211 HG No AFO (%)	P-Value	Those who answered "Effective" Total number who hadtx/med	HG Adverse outcome (%)	HG No adverse outcome (%)	P-value
Protonix/preyacid (lansoprazole)	13.95	10.90	0.599	29	0.00	13.64	0.9302
Reglan/maxeran/maxolone (metoclopramide)	62.79	53.08	0.3133	139	7.41	9.82	0.9852
Scopolamine (scopolamine hydrobromide)	6.98	3.32	0.3802	10	0.00	14.29	1
SeaBands/reliefbands	67.44	65.88	1	168	0.00	1.45	1
Special diet (bland, low fat, low acid)	60.47	65.88	0.4894	165	0.00	10.87	0.1637
Tagamet (cimetidine)	4.65	1.90	0.2688	6	0.00	0.00	
Thorazine (chlorpromazine), Haldol (haloperidol)	6.98	1.42	0.0626	6	33.33	0.00	1
Tigan/Vomet(tritmethobenzamide)	6.98	8.53	1	21	0.00	16.67	
TPN/TPPN (total IV nutrition or hyperalimentation)	27.91	15.17	0.0741	44	36.36	31.25	1
Vitamins (taken orally- pyridoxide, etc.)	41.86	34.60	0.3862	91	0.00	1.43	1
Vitamins (taken intravenously-i.v.)	27.91	25.59	0.8488	66	9.09	9.09	1
Zofran (ondansetron)	86.05	77.25	0.2264	200	59.46	49.08	0.338

[a] Adverse fetal outcome.

[b] Prozac (fluoxetine), Wellbutrin (bupropion), Zoloft (sentraline), Paxil (paroxetine), Ativan (lorazepam).

[c] Benadryl (diphenhydramine), Gravol (dimenhydrinate), Vistaril/Atarax (hydroxyzine), Diclectin/Bendectin (doxylamine and pyridoxine), Marezine (cyclizine).

[d] Dramamine (dimenhydrinate), Bonine/Antivent (meclizine).

Table 6

Severity in factors associated with adverse outcome.

	N	AFO (%)[a]	P-value	Mean % weight loss	P-value	TPN (%)[c]	P-value	
Gestational hypertension	33	36.36	0.0033	12.58	0.982	18.18	0.81	
No Gestational hypertension	221	14.03		12.55		17.19		
NVI[b] began week 3–4	62	27.42	0.0194	12.85	0.687	22.58	0.2466	
Other	192	13.54	12.45	15.63 Outpatient only	78	8.97	0.0385	12.06
Other	176	20.45		12.76		23.86		
Acupuncture	39	2.56	0.0179	11.62	0.281	20.51	0.6452	
No acupuncture	215	19.53	12.71	16.74 Methylprednisolone	31	32.26	0.0298	14.22
No methylprednisolone	223	14.80	12.31	13.90 Promethazine	186	19.89	0.0582	13.34
No promethazine	68	8.82	10.37	10.29 Antihistamines[d]	93	23.66	0.0456	12.31
No antihistamines[d]	161	13.04		12.70		16.15		

[a] Adverse fetal outcome.

[b] Nausea and vomiting of pregnancy.

[c] Total parenteral nutrition.

[d] Antihistamines include Benadryl (diphenhydramine), Gravol (dimenhydrinate), Unisom (doxylamine), Vistaril/Atarax (hydroxyzine), Diclectin/Bendectin (doxylamine and pyridoxine).