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Jacobs Journal of Gynecology and Obstetrics

Letter to Editor

Antihistamines and Other Prognostic Factors for Adverse Outcome in Hyperemesis Gravidarum: A Follow-Up Study

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Received: 05/26/2015

Accepted: 06/30/2015

Published: 07/21/2015

Dear Editor,

Hyperemesis gravidarum (HG) may be defined as persistent, unexplained nausea and vomiting resulting in more than 5% weight loss, abnormal fluid and nutritional intake, electrolyte imbalance, dehydration, and ketonuria [1]. 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 [2]. The purpose of this letter is to report on whether the findings in our publication in EJOG "Antihistamines and other Prognostic Factors for Adverse Outcome in Hyperemesis Gravidarum [3]" are reproducible in a new population sample.

Participants with HG enrolled in the study between January, 2011 and October, 2014. This is a case-control study in which pregnancy-related factors were compared between 43 offspring exposed to HG with an adverse fetal outcome (AFO) and 413 offspring exposed to HG with no AFO. The inclusion criteria for HG cases were a diagnosis of HG and treatment with IV fluids and/or total parenteral nutrition/nasogastric feeding tube, independent of hospitalization. Participants whose pregnancies did not last beyond 20 weeks were excluded because fetal outcomes beyond 20 weeks gestation are the focus of this study. AFO was defined as preterm birth (<37 weeks), birth weight less than 10%, and/or perinatal mortality. However the majority of AFO was represented by preterm birth and associated low birth weight, as perinatal mortality was rare in this small sample. Participants were asked to submit their medical records and complete an online survey regarding symptoms, treatment, and outcomes. Our previous study comparing the clinical profile of patients with HG (enrolled in 2007-2008) with a normal and an adverse pregnancy outcome identified 7 statistically significant prognostic factors (and 1 factor, tube feeding that was nearly significant). These factors were the focus of the current study. Binary responses were analyzed using either a Chi-square or Fisher exact test and continuous responses were analyzed using a t-test.

Herein, 41 pregnancies resulted in an adverse fetal outcome. Nausea and vomiting beginning in weeks 3-4 of pregnancy, hospitalization as an outpatient only, and gestational hypertension were no longer associated with adverse outcome, in contrast to their significant association with AFO in the first study. Variables remaining significant in the second popu-

lation were methylprednisolone, promethazine, and other antihistamine use. While tube feeding showed only a trend toward significance in the previous study, the current study demonstrated a significant association between tube feeding and an adverse outcome. Alternative medicine was not significant when examining data from the second set, but relatively few women with HG relied on it as a treatment. with early symptoms, treatment with medications, and treatment with tube feeding is higher than the more recent study group.Our original study reported on results based on multiple comparisons and therefore a follow-up study was necessary to confirm the findings. In both studies, poor fetal outcome in women with HG was shown to be associated with the use of promethazine, other antihistamines, methylprednisolone, and tube feeding.

Table. Factors/early symptoms associated with adverse outcome.

	N=41 HG With AFO[a](%)	N=413 HG No AFO[a] (%)	P-value[a]	OR (a)	95% CI (a)	N=43 HG With AFO[b](%)	N=211 HG No AFO[b] (%)	P-value[b]	OR (b)	95% CI (b)
Factors/early symptoms associated with adverse outcome										
Week of nausea and vomiting of pregnancy (when symptoms began) Week 3-4	9 (22.00%)	81 (19.60%)	0.6846	1.15237	(0.46, 2.59)	17 (39.54%)	45 (21.33%)	0.019	2.4	(1.12, 5.07)
Hospitalization "Outpatient" only	7 (17.10%)	68 (16.50%)	1	1.04445	(0.38, 2.53)	7 (16.28%)	71 (33.65%)	0.029	0.38	(0.14, 0.93)
Demographic characteristic Gestational hypertension	4 (9.8%)	21 (5.1%)	0.2674	2.01403	(0.48, 6.43)	12 (27.91%)	21 (9.95%)	< 0.0001	3.479571	(1.41, 8.31)
Treatment/medication										
Alternative medicine (acupuncture, acupressure/Bowen massage)	1 (2.4%)	33 (8.00%)	0.3459	0.28839	(0.01, 1.82)	1 (2.33)	38 (18.01%)	0.0089	0.11	(0.00, 0.69)
Promethazine	23 (56.10%)	135 (32.70%)	0.0053	2.62519	(1.31, 5.35)	37 (86.05%)	149 (70.62)	0.0386	2.56	(1.00, 7.79)
Other Antihistamines	14 (34.10%)	84 (20.30%)	0.04735	2.02723	(0.94, 4.21)	24 (55.81%)	73 (34.60%)	0.0151	2.38	(1.16, 4.93)
Methylprednisolone	7 (17.10%)	12 (2.90%)	0.00066	6.82423	(2.13, 20.31)	10 (23.26%)	21 (9.95%)	0.0217	2.73	(1.05, 6.73)
TPN/TPPN (total IV nutrition or hyperalimentation)	8 (19.50%)	24 (5.80%)	0.00458	3.91104	(1.41, 9.92)	12 (27.91%)	32 (15.17%)	0.0741	2.16	(0.91, 4.89)
Ondansetron	20 (48.80%)	178 (43.10%)	0.512	1.25671	(0.63, 2.52)	37 (86.05%)	162 (77.25)	0.2264	1.81	(0.70, 5.57)

[a]Results from this study

[b] Results from previous study[3]

It is important to note that the original group with "no adverse outcomes" differs when comparing it to the more recent group of "no adverse outcome." The selection of the material is the same for both time periods, so one possible explanation is a change in the diagnosis of HG over time. Recently there is more awareness and possibly more diagnosis of HG with iv fluid treatment. It may be that in the earlier study period, women were more commonly diagnosed with HG when their cases were at the very severe end of the HG spectrum. This would explain why in the first study, the proportion of cases Factors not significant in the second study were nausea and vomiting starting at 3-4 weeks of pregnancy, hospitalization as an outpatient only, gestational hypertension, and alternative medicine. This study shows association but does not prove causation. For example, the association of tube feeding with poor fetal outcome can be related to severity of disease. For comparison purposes, we included the results from both studies for the commonly prescribed medication ondansetron. Ondansetron was not found to be associated with AFO in either study. Future studies should focus on identifying the biological

basis of HG so that safe and effective therapies can be identified to eliminate the increased risk of poor outcomes.

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