Assessment of management approaches for hyperemesis gravidarum and nausea and vomiting of pregnancy: a retrospective questionnaire analysis

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Abstract

**Background:** Hyperemesis gravidarum is the most severe form of nausea and vomiting of pregnancy, or morning sickness. 2% of pregnancies in the United States are affected by hyperemesis gravidarum. The condition is characterized by severe vomiting in pregnant people, especially during the first trimester, often leading to hypovolemia and weight loss. The standard of care for hyperemesis and nausea and vomiting of pregnancy is commonly ineffective. We hypothesize that based on patient experience; the current treatment guidelines for hyperemesis are not clinically effective. Our objective was to identify the efficacy of the various management approaches that are currently in place for hyperemesis and nausea and vomiting of pregnancy.

**Methods:** A questionnaire was designed based on diagnostic criteria, standard demographic identifiers, and common medications for the treatment of hyperemesis gravidarum. This questionnaire was distributed online to through hyperemesis and nausea and vomiting of pregnancy support groups, personal social media, and institutional email.

**Results:** In our study, most participants diagnosed with hyperemesis gravidarum trialed at least three medications, most of which were ineffective and/or had severe side effects. The most used medication for treatment of hyperemesis gravidarum is ondansetron, a standard antiemetic, with fatigue and constipation being the most reported side effects. All data in the dataset was coded as categorical and analyzed using contingency tables using Mantel-Haenszel Chi square tests.

**Conclusions:** The data presented in this research provides insight into the suffering that patients with these diagnoses face day-to-day due to the lack of efficacious, well-tolerated treatment options. Establishing this gap in treatment can facilitate the development of effective treatments that will provide relief for thousands of patients.

Introduction

Nausea and vomiting of pregnancy (NVP) are extremely common, taking place in 70–80% of pregnancies. However, 0.3–3.6% of pregnant patients experience the most severe form of NVP known as Hyperemesis Gravidarum (HG), with debilitating symptoms. HG is characterized by intractable vomiting, especially during the first trimester that is difficult to treat and often leads to hypovolemia and weight loss. HG is the single largest cause of early pregnancy hospitalization. Patients with HG are commonly hospitalized due to weight loss that exceeds 5% of pre-pregnancy weight, dehydration, electrolyte imbalance, arrhythmias, and acid-base balance disturbance. HG can also be a driving factor in the development of metabolic disorders including acute kidney injury. However, there is currently no consensus on diagnostic criteria, which has impeded the care and research of HG along with stigma, inappropriate management, and lack of investment. Despite the prevalence and significant morbidity associated with HG, high-quality research is still lacking in its basic etiology, treatment, and prevention. Most studies are limited by a lack of a standard definition of HG, too few participants, biases, and
uncontrollable confounding variables. Most research specific to therapeutic and pharmacologic interventions for HG does not include randomized control studies, and cross-study comparison is made challenging by inconsistent diagnostic criteria. Available therapies have remained virtually unchanged over the past few decades, and affected patients only respond partially to the standard antiemetic medications that are currently recommended for HG treatment.

Many HG patients have experienced sub-optimal management of their condition, specifically due to a lack of support from their healthcare providers. A study on a large cohort of affected patients found that those who reported that their provider was either not attentive to or not aware of the severity of their condition were more likely to also report psychiatric sequelae such as feelings of anxiety and depression. Such approaches by providers may decrease the likelihood that patients seek care in a timely manner. Although providers face a challenging situation due to the scarcity and low quality of studies evaluating the efficacy of antiemetics for HG. The current lack of clinical attention, misinterpretation of symptoms, and delayed diagnosis and treatment of HG patients underlines a need to improve clinical care. In a study involving an online survey of 249 patients with severe NVP or a formal diagnosis of HG, one in four were denied medications such as doxylamine to treat their condition. Even when those with HG are treated with medications, the quality of evidence to support their use is slim. In a network meta-analysis and trial sequential analysis of randomized clinical trials of current drugs used to treat NVP, only ginger root had a moderate quality of evidence to support its use, and all other interventions had little evidence of efficacy. Clinical pharmacotherapy guidelines for both NVP and HG involve a significant amount of trial and error with multiple combinations of antiemetics, vitamins, and supplements all while the patient is suffering. Amalgamations of medications including doxylamine, dopamine antagonists, antihistamines, serotonin antagonists, phenothiazine medications, and vitamins/supplements are routinely used both in inpatient and outpatient settings to control symptoms of HG. However, it is well established that most of these medications come with side effects or potentially even birth defects.

Our objective is to identify the subjective efficacy of the various management approaches that are currently in place for nausea and vomiting of pregnancy and hyperemesis gravidarum. The data presented in this research will provide insight into the suffering that patients with these diagnoses face day-to-day.

Methods

Data Acquisition and Study Population

All participants received informed consent and voluntarily elected to participate in this research. Before proceeding with the study, respondents were required to view and acknowledge written consent and were assured confidentiality. The questionnaire was administered via Google forms and each participant was asked to fill out one survey per child.
This questionnaire was distributed via institutional email, social media (including online HG support groups and personal social media pages), as well as the Hyperemesis Education and Research (HER) Foundation website. Participants were incentivized with a raffle for ten Amazon gift cards of various amounts. Inclusion criteria for this research included being assigned female sex at birth and birthing a child.

**Questionnaire Development**

The questionnaire was created using the diagnostic criteria used by the HELP Score Assessment from the HER Foundation. To correlate this diagnostic info with demographic and socioeconomic status at the time of the related pregnancy, we asked questions regarding age range, race, income level, education level, support system, the region in which they reside, and employment status. Participants were asked to answer 26 questions, consisting of multiple-choice, Likert scales, and free-response question formats. The study was approved by the Rocky Vista University Institutional Review Board.

**Statistical Analysis**

All data in the dataset was coded as categorical and was therefore analyzed using contingency tables. The dimensions of these tables were dependent on the number of levels for each category. Since counts in cells were small in some cases, we base our main testing on Mantel-Haenszel Chi square tests for being more robust using smaller samples than asymptotic Pearson's chi square tests. All data analyzes were performed using SAS/STAT v9.4 (SAS Institute Inc. Cary NC). Significance was declared at 95% confidence (P-value ≤ 0.05).

**Results**

A total of 786 participants responded to the survey and 1,002 pregnancies were analyzed. Voluntary respondents completed a survey for each living biological child. The survey screened for patients and symptoms congruent with HG, NVP, and asymptomatic as defined by the American College of Obstetricians and Gynecologists (ACOG) guidelines.

**Medication Usage**

Of those diagnosed with HG, 22.4% took three medications, 15.3% took four, and 19.4% took five or more (Figure 1). No associations were found between HG diagnosis and medication compliance (Figure 2). The most used medication by patients with HG was ondansetron. Other commonly used medications were pantoprazole, metoclopramide, diphenhydramine, prochlorperazine, promethazine, doxylamine, and vitamin B complex (Figure 3).

**Medication Side Effects**

Sixty eight percent of patients who took medication for HG experienced side effects. These side effects included fatigue, constipation, and headache, and for some, even included anxiety and depression.
This information, including individual pharmacotherapy data, can help us identify risk factors for HG and its widespread effects on patients' lives, which can be helpful for screenings, providing resources to patients, and developing further treatment options.

Discussion

This study was conducted to elucidate gaps in the current management of NVP/HG. As such, our data shows that over one-half (57.1%) of respondents diagnosed with HG have taken at least three different medications to alleviate their symptoms, some relying on more than five separate daily medications. As a result, over two-thirds (68%) of these patients experienced side effects from their treatment options, ranging from fatigue and constipation to depression and anxiety, for some. Our data suggests that we do not have an effective, well-tolerated treatment option for our NVP/HG patients. The Hyperemesis Education and Research (HER) Foundation has one of the most robust resources for management protocol of this disease, though it is often overlooked in clinical practice. ACOG also has a detailed management protocol for NVP/HG, which is more widely accepted amongst the Obstetrics community. However, even the evidence presented in the Practice Bulletin used to create the guidelines is limited.

Pyridoxine plus doxylamine is first-line pharmacologic therapy for NVP and HG and is shown to be safe and effective. However, around one-third of respondents taking this medication, reported central nervous system adverse effects (sleepiness/drowsiness). Another commonly used class of medications, dopamine antagonists, may lead to maternal extrapyramidal symptoms such as tardive dyskinesia, especially when combined with phenothiazine medications. Furthermore, the combination of serotonin antagonists and phenothiazine derivatives may result in QT prolongation with severe cardiac risk. Additionally, there is conflicting evidence regarding the formation of cleft palate birth defects with use of ondansetron (a serotonin antagonist) in early pregnancy. In brief, there are options for treatment, albeit these treatments have associated risks and little clinically proven efficacy.

Most of these medications have at least proven to more effective than placebo when treating NVP/HG. Although, ACOG Practice Bulletin #189 states that “no single approach has been proved to be more effective than the other.”

HG has far-reaching implications that outlast the physical illness. In a cross-sectional population-based study conducted in Norway, respondents suffering from more severe symptoms were found to have a physical quality of life close to that among patients with breast cancer, and a mental quality of life comparable to that seen among mothers with postpartum depression. In an online survey of 377 patients who experienced HG, 18% met the criteria for posttraumatic stress syndrome. In a study of over 800 patients with HG, 15% of participants had terminated a pregnancy due to the severity of their HG symptoms. Two of five (40%) of participants in a separate Norwegian study expressed that they had contemplated abortion, and 8 subjects had a minimum of one elective abortion because of HG. 19% of subjects switched their doctor because they were not receiving satisfactory HG treatment. These patients...
also expressed confusion about their prescribed pharmacological regimens, and 87.9% used one or more complementary and alternative medicines, but only 12.8% of whom reported any positive effect on HG symptoms. More than half of the interviewees believed their general practitioner had no knowledge of HG.

The limitations of this study include the retrospective and subjective nature of our data collection. We relied on the mothers’ memories of pregnancies that may have happened decades in the past. Furthermore, we had did not have the resources to verify the claims of diagnoses of Hyperemesis Gravidarum or Nausea and Vomiting in Pregnancy or the treatments of said diagnoses. We cannot rule out a self-selection bias due to respondents who have been severely affected with NVP/HG potentially being more willing to participate, therefore leading to the potential overestimation of severity. The use of the internet to disseminate the questionnaire may also isolate a population who do not have access to the internet or have low internet-literacy, though web-based recruitment has been shown to be valid in terms of study design.

Conclusions

Despite the grave ramifications of this condition, many healthcare providers do not meet the needs of their HG patients. This is evident not only from the sheer number of medications that patients are trialing as shown in our data, but also from several studies regarding lessened quality of life and even PTSD. Furthermore, we discovered that more than half of the patients who are prescribed medication for their symptoms are experiencing a plethora of side effects. It is vital to reverse this trend; health care providers need to be aware of the high burden NVP/HG and its current treatment places on these patients.

Support and high-quality care are essential for this vulnerable population. However, the lack of a unified standard of care for NVP/HG patients prevents the condition from being widely recognized and downplays the need for effective interventions. By emphasizing the lack of efficacious, well-tolerated treatment, we hope that this research will inspire the obstetrics community to better understand NVP/HG, including treatments and outcomes. Though pregnant people are a controversial study population, high-quality research is necessary to bridge this gap. Effective therapeutics for NVP/HG will give patients a better experience in pregnancy, an improved relationship with their healthcare providers, and a higher quality of life during and after pregnancy.

Abbreviations

ACOG: American College of Obstetricians and Gynecologists

HG: Hyperemesis Gravidarum

NVP: Nausea and Vomiting of Pregnancy

PTSD: Post-Traumatic Stress Disorder
Declarations

Ethics approval & consent to participate:

The study was approved by the Rocky Vista University Institutional Review Board (IRB#:2020-0094). Information about the study was presented to the respondents before they could enter the online questionnaire. This included the study objectives, the participants’ right to withdraw at any time, and contact information to members of the research group. All participants provided their written informed consent to participate in the study. All methods were carried out in accordance with relevant guidelines and regulations or declaration of Helsinki.

Availability of data & materials:

The datasets used and/or analyzed during the current study are not made public because of privacy concerns but can be made available from the corresponding author on reasonable request.

Consent for Publication:

Not applicable.

Competing Interests:

The authors declare they have no competing interests.

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Authors’ Contributions:

RM, HS, and BB conceived and designed the questionnaire. RM, HS, BB, and AM collected and curated the data. IZ performed the statistical analysis. All authors contributed to the interpretation of results, the drafting the manuscript, and all have approved the final version of the manuscript.

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**Figures**
Figure 1

Number of medications women took depending on their diagnosis status.

Figure 2

Three key questions from the survey were evaluated using contingency tables where pairwise associations were determined using Mantel-Haenszel Chi-square tests.
Figure 3

Commonly used medications frequency among surveyed women users formally diagnosed with HG.