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Risk Factors for Infusions, Emergency Room Visits and Hospitalizations for Hyperemesis Gravidarum: New Data and Literature Review

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Purpose: Few factors have been identified that increase the risk of visits (hospital emergency room or inpatient stays) due to hyperemesis gravidarum (HG). The purpose of this study is to understand trends in HG management and identify variables increasing visit frequency so that strategies may be developed to reduce hospital utilization.

Study Design: An online survey was posted on the Hyperemesis Education and Research Foundation website and social media between June 2022 and May 2023. Participants had previous or current severe pregnancy nausea and vomiting. Respondents were asked about themselves and their HG experience, including weight loss, medications, infusion care, and visit frequency. Odds ratios, p-values, and 95% confidence intervals were calculated via MedCalc to analyze the significance of each factor, and Spearman rank correlations were analyzed via SPSS for associations of ondansetron usage with visits and weight loss. Microsoft Excel and SPSS were used to calculate treatment and visit frequencies.

Results: Survey data from 1220 respondents who reported a current or prior pregnancy with HG were included in this study. Respondents were primarily White, from the US, and had at least one visit due to HG. Participants with a visit were significantly more likely to be a person of color (POC), unable to work, have no children, and lose over 15 pounds (6.8 kg). Those who took medications as prescribed had fewer visits. No medication combination or dose was found to be significantly more effective in preventing weight loss or repeat hospital visits.

Conclusion: Risk factors predicting visits included POC, not having children, being too sick to work, and having extreme weight loss. Utilization of medication and nutritional therapies is inconsistent and inadequate in this population, which may increase visit frequency.

Keywords: hyperemesis gravidarum, hospitalization, ondansetron, preterm birth

Introduction

Approximately 80% of pregnant women experience some form of nausea and vomiting during pregnancy (NVP).[1] However, 0.3 to 10.8% suffer from a more severe form of NVP called hyperemesis gravidarum (HG), which is the second leading cause of hospitalization during pregnancy in the United States.[2] According to the international consensus Windsor definition for HG, criteria are nausea and vomiting, at least one of which is severe; onset before 16 weeks of gestational age; symptoms that strongly limit daily activities; an inability to eat and/or drink normally; and signs of dehydration (not mandatory).[3] Due to the severity of these symptoms, many women with HG experience serious health complications such as loss of >15% pre-pregnancy weight,[2] preeclampsia,[2] organ damage,[2] esophageal rupture,[2] Wernicke's encephalopathy,[2] electrolyte imbalances,[2] post-traumatic stress disorder (PTSD),[2] and suicidal ideation,[4] all of which can require multiple emergency room visits or inpatient hospitalizations over one or more trimesters.[5]

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HG pregnancies also pose risks for unfavorable child outcomes such as low birth weight, preterm birth, fetal demise, and neurodevelopmental delays,[2] demonstrating the significant repercussions of this disease on both the mother and child. Fejzo et al found a weight loss >15% of pre-conception body weight due to HG is associated with fetal growth restriction, preterm birth, and behavioral disorders, underscoring the need to prevent weight loss.[6] Further, a recent study on neurodevelopmental outcomes in adolescents exposed prenatally to HG found a greater incidence of neurodevelopmental delays, attention deficit disorder, sensory processing disorder, and autism, but did not find a significant association of these outcomes with prenatal medication exposure.[7] This suggests that HG presents greater risks than antiemetics and underscores the importance of intervening before nausea and vomiting are severe.

Individual risk factors associated with HG include first-time pregnancies, multiple gestation, a diet high in saturated fat, weight over 170 pounds (77 kg), untreated asthma, dysmenorrhea, and epilepsy.[8] However, the most significant factors linked to HG are a previous pregnancy with HG,[9,10] having a female relative with HG,[2] and high levels of hormone Growth and Differentiation Factor 15 (GDF15) in maternal blood and low blood levels of GDF15 prior to pregnancy.[11]

While dietary and lifestyle changes may successfully treat milder nausea and vomiting during pregnancy, HG patients require more intensive therapies such as intravenous fluids and antiemetics. Antiemetic prescribing and effectiveness vary,[1] and delays in treatment are common, likely contributing to increased hospital utilization.[12] Recent research strongly supports that the placenta and appetite hormone, GDF15, play a primary role in the etiology of HG symptoms,[13] but medications treating this novel pathway are still under investigation.

Current medications for HG predominantly involve those targeting serotonin pathways (eg, ondansetron), dopamine antagonists (eg, promethazine, metoclopramide), and antihistamines (eg, doxylamine, cyclizine), with serotonin antagonists found to be most effective.[2] Antihistamines are considered a first-line medication, including doxylamine, which is often combined with pyridoxine (vitamin B6) in a delayed-release tablet. A systematic review by O'Donnell et al[14] concluded that most treatments are better than placebo, and taking preparations of doxylamine with pyridoxine prior to pregnancy help reduce severity, ondansetron reduces nausea more than doxylamine with pyridoxine, IV fluids reduce symptoms, and day case treatment is feasible and as effective as inpatient care. They also found medication effectiveness was greatest for ondansetron, followed by promethazine, and then metoclopramide. Fiaschi et al[15] found ondansetron was prescribed most at discharge, while steroids were prescribed most following readmissions, and these prescribing practices varied little in the UK. Thiamin and folic acid were also prescribed after hospitalization.

A study by Erdal et al[16] found a decrease in gestational age and an increase in termination when metoclopramide utilization was reduced in Norway. As Clark et al[17] state, there are

> therapies that can be used when oral intake is not tolerated for prolonged time periods with ongoing weight loss. In refractory cases of hyperemesis gravidarum, the risks and benefits of these alternative forms of management must be considered, along with the risks of undertreated hyperemesis gravidarum and the overall effect of hyperemesis gravidarum on patients' quality of life.

Newer medications[17] are being trialed with some success for HG, including granisetron,[18] gabapentin,[19] mirtazapine[20] and olanzapine.[21] However, few studies exist to identify optimum dosing or regimens, and no studies have evaluated the possible role and safety of serotonin antagonists like palonosetron and neurokinin antagonists like aprepitant in managing HG.

Ondansetron is associated with a higher live birth rate and a lower rate of termination and miscarriage.[22] However, dosage rates vary greatly. Effectiveness studies for chemotherapy find that nausea is improved by 8 mg dosing every 6 hours, but vomiting does not improve between 24 and 32 mg.[23] Studies evaluating optimal dosing in HG are lacking, and many studies utilize lower dosing regimens like 4 mg of ondansetron every 8–12 hours.[24] The American College of Obstetrics and Gynecology recommends ondansetron 4 mg three times per day orally or 8 mg IV twice a day as a second-line treatment,[25] yet the maximum dose of ondansetron is 32 mg per day or 8 mg every six hours for other clinical indications. However, according to the updated RCOG Guidelines, the dose was reduced from a maximum of 24 mg per day to 16 mg per day.[26] Klauser et al[27] found subcutaneous ondansetron infusion therapy had immediate results and was overall superior to oral dosing, with doses up to 32 mg given daily. Symptom improvement was seen within three

days for half of patients. These substantial variations in ondansetron dosing reflect a lack of data on safe and effective dosing practices for HG.

In 2022, a study conducted by Nurmi et al[28] evaluated pregnancy outcomes and factors related to HG readmission in Finland. Researchers found that 60% of patients required outpatient or inpatient hospital care, with 33% having admissions after the first trimester, and multiple gestation, female sex of fetus, and parity of ≥5 were associated with higher odds of readmission. A similar study was conducted in England by Fiaschi et al,[9] and researchers found younger age, a lower socioeconomic status, being Asian or Black, carrying a female fetus, and multiple gestation significantly increased the risk of HG readmission. To our knowledge, no United States-based studies have been conducted to assess risk factors associated with readmission. This study aimed to evaluate lifestyle, demographic, and treatment factors that could predict the likelihood of HG mothers having one or multiple visits. For this study, the term "visit" was defined as inpatient or emergency care in a hospital facility. Those receiving treatment only from outpatient clinics, home care services, mobile infusion therapy, or urgent care centers were analyzed separately from the visit analysis.

Methods

Study Recruitment and Participants

This study utilized a 207-question survey through the Alchemer (SurveyGizmo) survey platform. The survey was described as a "Provider, Hospital, and ER Survey" and was posted on the Hyperemesis Education and Research (HER) Foundation website (www.hyperemesis.org) and related social media platforms (Facebook, Instagram, and Twitter). The survey was only administered in English and questions included explanations and definitions to ensure accurate interpretation. Responses were collected between June 2022 and May 2023 from 1746 participants. Participation was open to any person with a previous or current experience with HG or severe NVP. Formal diagnosis of HG by a physician was not required, but participants determined their HG status based on the Windsor definition defined in the survey if they did not have a diagnosis. Seventeen respondents were removed because they did not meet the criteria for HG based on their responses. An additional 502 responses were removed because they discontinued the survey after initial demographic questions and did not answer questions about their hospital visits and treatment, and 7 were disqualified because their data included conflicting numbers of visits or treatments received. For example, one participant stated they took ondansetron until 8 weeks gestation but listed the total days of ondansetron infusion as 90 which is greater than 8 weeks. A total of 1220 respondents were included for the final data analysis.

All survey visitors were allowed to respond, but completion of the survey questions was voluntary. Questions allowed the participant to choose not to respond by selecting "prefer not to answer" or "unsure". During the survey, not all questions were displayed to participants; some questions were conditioned based on prior answers (eg, questions about visits were only asked for those with a visit). IP address duplicate checking prevented participants from entering more than one response. To prevent spam responses, data was individually reviewed by researchers and clinicians with knowledge of the condition to check for validity and consistency.

This study complied with the Declaration of Helsinki, as the survey required their informed consent to publication of anonymized data prior to participating in the study. Answers were anonymous, and no identifiers were used to protect their identity. Therefore, this study (UP-22-00062) was designated exempt by the University of Southern California Institutional Review Board.

Descriptive and Statistical Analysis

Data were split into three major comparison groups for detailed analysis, no infusions or visits, outpatient/home infusion care only, and one or more visits. Demographic variables and data about HG treatments and hospitalization were summarized for all respondents and for each comparison group. Proportions, means, and/or medians were calculated for the answer to each survey question. Data was then compared between each group as appropriate. Visit analysis was only conducted on those who reported one or more visits.

Pivot tables in Excel were used to tabulate the data and conduct descriptive analyses. For further analysis, odds ratio tests for statistical significance were applied to binary responses. Analysis was performed on a range of questions,

including demographic/lifestyle information, treatment types, and medications taken. Multiple questions included answers such as "Unknown", "Not Applicable", or "Unsure", and these responses were either included or excluded in final calculations based on the variable of interest. Odds ratios, p-values and 95% confidence intervals were calculated for these variables using Med Calc.[29] A Spearman rank correlation was additionally calculated in SPSS to analyze ondansetron dosing and weight loss data.

Results

Participant Demographics and Characteristics

A total of 1220 responses from participants who reported they were previously or currently pregnant at the time of the survey were included in the final analysis. Basic demographic characteristics are shown in Table 1. Respondents ranged from 16 to 47 years of age (median: 31 years) at the beginning of their most recent pregnancy, and a majority were White (80%) and resided in the United States (69%). About one-third (34%) of participants were currently pregnant, and among 552 people who reported the week they delivered, 17.6% reported a pre-term delivery which is defined as a live birth before 37 full weeks of pregnancy. Total number of responses to the question of pregnancy loss was very low (6%), so the data were unreportable. More than half of respondents (58%) had a child or multiple children to care for at the time of their pregnancy, and among those who knew the biological sex of the fetus, about 53% of pregnancies resulted in a female offspring.

A diagnosis of HG was reported by about 90% of respondents, and the remaining 10% stated that they had HG but were not yet diagnosed (HG was defined according to the Windsor criteria[3] which was listed in the survey question). Most respondents (92%) reported experiencing weight loss below their pre-pregnancy weight due to nausea and vomiting during their pregnancy (Table 1), and about 42% who lost weight reported losing more than 15 pounds (6.8 kg) below their pre-pregnancy weight.

A small proportion of respondents (36%) reported starting either a non-prescription or prescription treatment within one week of symptoms starting, with 90% of those participants taking prescription medications first (eg, ondansetron, metoclopramide, doxylamine, and promethazine). The median gestational age when starting a prescription antiemetic was 6 [range 2–13] weeks and the median for stopping prescription antiemetics was 25 [range 4–41] weeks gestation. The 28% of respondents who reported taking non-prescription medications listed vitamin B6 (30%), antihistamines

Table 1 Summary of Demographic Data for Study Participants

Demographic Variable	Yes (%) (n=1220)	No (%) (n=1220)	Median
Country of residence – United States	837 (69%)	383 (31%)	
Race: White	971 (80%)	249 (20%)	
Pregnant at time of study	418 (34%)	802 (66%)	
Had children at time of study	720 (58%)	500 (41%)	
*Sex of baby: Female	522 (53%)	469 (47%)	
Lost weight below pre-pregnancy weight	1121 (92%)	99 (8%)	
Height (Inches)			65
Weight (Pounds)			153
BMI			26
Age at beginning of pregnancy			31
Year of most recent delivery			2021
Number of children to care for at time of survey			1

Note: *Data was only calculated for participants who knew the biological sex of the fetus in their most recent pregnancy (n=991).

(29%), cannabis (2.3%), ginger (13%), acid reflux medication (eg, famotidine, lansoprazole) (1.5%), and antacids (eg, calcium carbonate) (6.2%) as the primary non-prescription medications taken.

No Outpatient Infusions, Emergency Visits, or Inpatient Visits

One hundred and seventy-eight participants had no infusion care nor emergency or inpatient visits, and a median gestational age of 13 weeks among the 46% pregnant during the survey. Sixty-eight percent had a diagnosis of HG by a physician, and the remaining 32% stated they met the stated criteria for HG but were not yet diagnosed. Eighty-two percent of respondents reported losing weight, and 17% of this group lost over 15 pounds (>6.8 kg). Preterm birth (live birth before 37 weeks) was reported by 17% of 59 participants who reported their gestational age at delivery. General characteristics of this group are further described in Table 2.

Participants were prescribed a median of 2 antiemetic medications in the first trimester, ranging from 0 to 9 medications. When asked if they took a prescription or non-prescription medication first, 87% responded that a prescription was used first, with 46% taking ondansetron, 25% taking a doxylamine and pyridoxine combination, 8% metoclopramide, 6% promethazine, and 16% other medications. Seventy-four percent reported taking their medications as prescribed, but 9% reported that they were unable to keep their medication down. Among non-prescription medications reported, 56 participants (31%) took one or more of the following: pyridoxine, antihistamine, cannabis, ginger, acid reflux medication, or antacids.

Nearly half (49%) of 120 responses stated medications were offered in a non-pill (eg, oral disintegrating, IV, suppository) format. Among 93 patients reporting ondansetron dosing, the average dose was 15 mg [range 4–32 mg], and 67% reported dosage of 16 mg or less. Ondansetron usage started at a median of 6 weeks and stopped at a median of 30 weeks. For dosing frequency, 36% were prescribed 1–2 doses per day, 31% were prescribed 3 doses per day, 11% were prescribed 4 or more doses per day, and 22% were taking ondansetron as needed. About half (52%) of patients received 8 mg per dose.

Over a third of participants (36%) with no visits reported they were not satisfied with the care they received from their obstetrician/gynecologist throughout their whole pregnancy, and 72% reported there was nothing they would recommend that their doctor did that helped them.

Table 2 Characteristics by Comparison Group

Characteristics	No Visits (n=178)	Non-hospital infusion care (n=115)	≥1 hospital visit (n=927)
Mean maternal age	32	31	29
Median gestational age at time of study	13	21	38
Median BMI	25.2	26.3	26.0
HG diagnosis by physician	68%	85%	94%
% who reported female fetus	56%	52%	52%
% with children at home requiring care during pregnancy	67%	71%	52%
% too sick to work due to HG	29%	42%	43%
% with >15 lb (6.8kg) *pg wt loss	17%	28%	48%
% preterm birth	17% (n=59)	4% (n=53)	20% (n=440)
Median infusion days	n/a	24.5	40
% who took any medications within 1 week of symptoms starting	38%	48%	35%
% who began taking medications after 8 weeks of symptoms starting	9%	9%	12%

Note: *pg wt loss = pregnancy weight loss.

For those who were satisfied with their care, however, 25% said they would recommend their doctor's counsel to work from home, be proactive about utilizing medications (especially ondansetron) to alleviate HG symptoms, and practice compassionate care (ie, listening and believing them about their symptoms). Over half (56%) of respondents said they had sufficient support at home to rest when needed, but 42% reported that they only received support occasionally or not at all.

Non-Hospital Infusion Care Only

Excluded from the visit analysis are 115 respondents that did not report hospital-based care and received intravenous or subcutaneous infusion care from home care services (37%), outpatient clinics or mobile infusion services (46%), or urgent care facilities (40%). Median gestational age was 21 weeks among the 42% pregnant during the survey. Preterm birth was reported by 2 of the 53 participants who had already delivered, and among those who lost weight during pregnancy, 28% experienced a weight loss greater than 15 pounds (6.8 kg). Additional characteristics of this group are listed in Table 2.

Over 84% reported taking a prescription medication as their first medication, with 46% prescribed ondansetron, 20% taking a doxylamine and pyridoxine combination, 12% metoclopramide, and 10% promethazine. Among 97 receiving medications, 48% began medication within 1 week of symptom onset. Of the 44 patients reporting infusion duration and medication(s), the median number of infusion days was 24.5 with about 43% of patients reporting more than 45 days of home infusion care for 1 or more of the following: ondansetron (50%), metoclopramide (14%), intravenous fluids (86%), multivitamins (41%), and B vitamins (36%). Thirty respondents reported starting infusions at a median of 8 weeks, and 25 reported stopping infusions at a median of 22 weeks. Of 53 respondents who reported total outpatient/mobile infusion events, there was a median of 6 events with a range of 1 to 65 total events. Similarly, for the 46 respondents reporting total urgent care infusion events, the median number of events was 2 with a range of 1 to 20.

One or More Hospital Emergency or Inpatient Visits

A total of 927 participants had one or more emergency room (ER) or inpatient hospital visits with a median gestational age of 38 weeks among the 31% pregnant during the survey. Ninety-four percent of participants were diagnosed with HG by a physician, and preterm birth was reported by 20% of the 440 participants who reported their gestational age at delivery. Of those respondents, 20% were less than 30 weeks gestation.

Of 843 respondents answering 'yes' or "no" to weight loss prior to hospitalization, 799 (95%) lost weight, and 48% lost over 15 pounds (6.8 kg). Those with a high BMI (>29.9) had an average of 8 visits and were significantly more likely to have greater than 2 visits compared to those with a BMI of <29.9 who averaged 6.7 visits (OR: 1.7, 95% CI: 1.2229 to 2.4161, $p = 0.0018$). Additional characteristics of this group are in Table 2.

Diagnosis of their condition was reported to be difficult, and the criteria varied. Multiple respondents stated their symptoms were diagnosed as HG by some providers but dismissed by others, and a few stated they were diagnosed in one pregnancy but not in others. One respondent stated that they were "heavily medicated" and thus did not vomit; therefore, they were not given a diagnosis of HG.

Respondents were asked to specify the first medication taken to manage symptoms of NVP. Of 754 responses, 26% took ondansetron 4 mg, 21% took ondansetron 8 mg, 14% took a doxylamine and pyridoxine combination, 8% took promethazine, and 7% took metoclopramide. The median number of medications taken over the course of pregnancy was 2, and the median number of doses taken per day for all medications was 3. Specifically, 18% were prescribed medications as needed, 24% were prescribed dosages of twice or three times a day, and 22% were prescribed dosages of four or more times per day.

Prior to First Hospitalization Visit

927 respondents were then asked to identify all the medications prescribed to them before their first hospital visit. Most respondents (69%) were prescribed medications prior to their first visit and took them as prescribed (65%), but 29% were not prescribed any medications. Only 4% of participants did not take their medications or did not take them as prescribed, citing various reasons such as lack of instructions on how to take their medication. One respondent was prescribed all medications as needed and reported none worked. Similarly, others reported discontinuing medication because it was not

working, or they could not keep it down. Some respondents stated they did not receive a refill on their medication or received no prescription so had to take fewer doses or discontinue their medication(s).

In response to a question about which prescription medications were taken, 847 (91%) responded and selected ondansetron (53%), a doxylamine and pyridoxine combination (21%), metoclopramide (11%), and/or promethazine (8%). It was found that over 50% of respondents who took an antihistamine and acid reflux medication lost over 15 pounds, and these results were similar for those taking an antihistamine, dopamine antagonist, and ondansetron combination (see Table 3 for the most frequent medication combinations taken and the average number of visits associated with each). Dosing was inconsistent and participants reported being unable to access medications consistently or keep medications down, so comparisons could not be made regarding the effectiveness of medications in reducing hospital stays or weight loss.

Among the 26% reporting their first non-prescription medication, 27% reported taking a non-prescription antihistamine or pyridoxine, 17% reported cannabis, 16% reported ginger, and 11% reported either antacids or acid reflux medication. Vitamin usage prior to the first visit was reported by 63% of respondents, and vitamins taken included prenatal multivitamins, folic acid, vitamin B6, vitamin D, iron, potassium, magnesium, and others. Participants, however, reported being unable to keep them down or only took them as tolerated.

Only 35% of participants reported being offered any medication (prescription or non-prescription) within 1 week of symptoms starting and 20% reported being offered medication within 2 weeks. Among patients with a BMI of 30 or greater, 28% were offered medication within 1 week of symptom onset, while 21% were offered medications within 2 weeks. In this same group, ondansetron was taken by 50% of participants and started at 7 weeks compared to 6 weeks for normal BMI participants.

There were 202 participants that identified as POC (a person of color identifying as Black, Asian, Hispanic/Latino, Native Hawaiian/Pacific Islander, American Indian/Alaskan Native (AI/AN), or Other) and 123 (61%) reported being

Table 3 Medication Combinations Taken by Participants with One or More Hospital Visits

*Medication Combination	Number of Participants (n=754)	Proportion of Participants Who Lost >15 Lbs (6.8kg) (%) in Each Med Combo	Average Emergency Room Visits	Average Total of Visits
a[a]	94	30 (32%)	4	5
b[b]	39	13 (33%)	5	7
c[c]	52	30 (58%)	6	8
e[d]	104	40 (38%)	5	7
ab	24	11 (46%)	4	6
ac	35	18 (51%)	7	10
ae	53	18 (34%)	4	5
abe	50	28 (56%)	6	8
ace	27	6 (22%)	2	4
abce	50	30 (60%)	4	6
be	44	28 (64%)	5	7
bce	30	13 (43%)	5	7
ce	26	12 (46%)	5	7

Note: *The medication combinations listed above (egs ab, ac, ae) are combinations of the following medications: [a]a = antihistamine (egs doxylamine, cyclizine) [b]b = dopamine antagonists (egs promethazine, prochlorperazine, metoclopramide) [c]c = non-Rx (egs famotidine, proton pump inhibitor) [d]e = ondansetron.

prescribed medications and taking their medications as prescribed. Of 718 White participants prescribed medications, 66% took them as prescribed. This difference was statistically insignificant.

Weight loss of over 10 pounds (4.5 kg) occurred prior to the first visit in 34%, and a weight loss of 15 pounds (6.8 kg) occurred during the pregnancies of nearly half of respondents with one or more visits. Those with a weight loss over 15 pounds were significantly more likely to have visits than those with a loss of 1 to 15 pounds (OR: 4.48, 95% CI: 2.8533 to 7.0262, $p < 0.0001$). Among 675 White participants who lost weight below their pre-pregnancy weight due to nausea and vomiting, a significantly greater proportion (66%) lost >10 pounds compared to 141 (49%) of 285 POC respondents (OR: 0.41, 95% CI: 0.31 to 0.55, $p < 0.0001$).

During First Hospitalization Visit

Half (468) of respondents reported both an emergency room and inpatient visit with a median gestational age for the first visit at 7 weeks. Respondents selected one or more reasons for the first emergency visit/hospitalization which included: could not eat/keep food down (92%), could not drink/keep fluid down (93%), could not swallow/keep medication down (49%), frequent vomiting (90%), dehydration (93%), and losing weight due to nausea/vomiting (66%). Non-pill (eg, oral disintegrating tablets) options were prescribed for 78%.

Emergency room (ER) visits were reported by 878 (95%) of participants with a median of 3 ER visits and a range of 1 to 56 visits. Only 18% reported a single visit and 82% reported multiple visits, with 90% reporting their first visit occurred prior to 14 weeks. The majority reported having an ER visit during the first trimester (53%) compared to the second (44%) or third trimester (27%).

Among 521 respondents reporting inpatient hospitalization, the median number of inpatient visits was 2, and the median number of total hospital days was 7. Inpatient admission decreased each trimester with 33% reporting visits in the first trimester, 32% reporting visits in the second trimester, and 22% reporting visits in the third trimester.

The primary treatments in the ER/hospital for the first visit were intravenous medications including fluids (96%), ondansetron (68%), and electrolytes (47%). Only 25% were given vitamins, parenteral nutrition (4%), or enteral nutrition (1%). While 49% had no change in weight during hospitalization, 21% reported losing weight in the hospital during their first visit.

In addition to hospital care, 253 (27%) participants also received a median of 40 days of intravenous or subcutaneous infusions at home with 89% receiving intravenous fluids, 79% ondansetron, 53% multivitamin infusion, 33% one or more B vitamins (eg, B6, B1, B complex), 28% metoclopramide, 27% acid reflux medication, and 12% steroids. Over 57% of these patients reported receiving more than 30 days of infusions and 38% more than 60 days.

The majority (54%) reported that their primary outpatient obstetrician/midwife did not see them nor communicate with hospital staff during their first visit, and 35% did not have a follow-up appointment scheduled with an obstetrician or midwife when they were discharged. It was only within one week of the first visit that 43% managed to schedule an appointment with an obstetrician or midwife, and 39% were able to do so in one to two weeks. Eighty-nine percent of participants who had a follow-up scheduled were able to attend their appointment.

Following First Hospitalization Visit

At discharge, a median of 1.5 medications were prescribed, and dosing was as needed (29%), one or two times a day (22%), three times a day (27%), or four or more times a day (17%). In addition, 55% were offered non-pill options for medication, and 3% were given continuous infusions. Ondansetron was the most prescribed medication at discharge (64%). Instructions for care following discharge were followed by 69% of respondents, with 55% reporting taking medications as prescribed and 18% reporting they did not take their medications due to unacceptable side effects.

Among participants with visits, 37% reported being unsatisfied with their ER/hospital care. Common reasons for dissatisfaction included not being believed, listened to, or taken seriously by their physician regarding the pain and discomfort they were feeling; not receiving adequate treatment or information to manage HG; and being discharged while still very sick. Consequently, among 765 who were employed, over half (53%) were too sick to return to work in the month following their 1st visit.

Among those with a return visit, the majority (77%) returned to the same hospital. Similar reasons were given for the return visit, including 91% could not keep fluid down, 88% could not eat/keep food down, 87% had frequent vomiting, 69% were losing weight, and 55% could not keep medications down.

The majority (70%) reported there was nothing they would recommend that helped them in their 2nd visit, while 29% had various recommendations that primarily involved getting intravenous fluids, being prescribed ondansetron, and ensuring that the doctor takes the condition seriously. Eleven percent of respondents recommended sharing HER Foundation resources and support information.

Factors Significantly Associated with Having One or More Hospital Visits

To investigate potential predictive factors for hospital visits, we compared participant responses between those who had one or more visits versus those who had no visits (Table 4). Participants who identified as POC had higher odds of having one or more hospital visits compared to White participants (OR: 1.87, 95% CI: 1.18 to 2.95, p = 0.0074). Participants who had no children were also more likely to have hospital visits compared to those who had children to care for during their HG pregnancy (OR: 2.12, 95% CI: 1.29 to 3.02, p < 0.0001). Those too sick to work because of HG symptoms had higher odds of going to the emergency room or having an inpatient visit (OR: 1.77, 95% CI: 1.23 to 2.56, p = 0.0023).

Almost half of total respondents (42%), regardless of the number of visits, reported a greater than 15-pound (6.8 kg) weight loss below their pre-pregnancy weight during pregnancy. However, for those with at least one visit, 48% of respondents lost more than 15 pounds compared to 17% of respondents with no visits. Ultimately, it was found that those who lost more than 15 pounds had higher odds of having one or more visits compared to those who lost less than 15 pounds below their pre-pregnancy weight (OR: 4.00, 95% CI: 2.56 to 6.29, p < 0.0001).

Most participants (65%) reported being prescribed medications by a healthcare professional and taking them as prescribed, and it was found that those who took medications as prescribed had lower odds of having one or more hospital visits compared to those who did not take medications as prescribed (OR: 0.61, 95% CI: 0.41 to 0.90, p = 0.014).

Factors Not Significantly Associated with Having One or More Hospital Visits

Additional factors that were additionally found to not have significantly higher odds of visits occurring were the sex of the baby being female (OR: 1.17, 95% CI: 0.80 to 1.73, p = 0.42) and the first prescription medication taken being ondansetron (OR: 1.33, 95% CI: 0.94 to 1.87, p = 0.11). Those who took vitamins had lower odds of having one or more hospital visits compared to those who did not take vitamins, but this data was found to be statistically insignificant (OR: 1.30, 95% CI: 0.92 to 1.85, p = 0.14). (See Table 5)

Table 4 Factors That Were Significantly Different Between Participants with One or More Hospitalization Visits Compared to Those with No Visits

Factor	1+ Visits (%) (n=927)	No Visits (%) (n=178)	Significance (1+ Visits vs No Visits)	Odds Ratios	95% CI
Race: POC	209 (23%)	24 (13%)	***P=0.0074**	1.87	1.18 to 2.95
No children	437 (47%)	51 (29%)	***P<0.0001**	2.12	1.29 to 3.02
Too sick to work	394 (43%) (n=926)	46 (29%) (n=156)	***P=0.0023**	1.77	1.23 to 2.56
15+ lb weight loss	420 (48%) (n=875)	25 (17%) (n=146)	***P<0.0001**	4.00	2.56 to 6.29
Was prescribed medications and took as prescribed	599 (65%) (n=924)	112 (75%) (n=149)	***P=0.014**	0.61	0.41 to 0.90

Note: *Statistically significant = p-value <0.05.

Table 5 Factors That Were Not Significantly Different Between Participants with One or More Hospitalization Visits Compared to Those with No Visits

Factor	1+ Visits (%) (n=927);	No Visits (%) (n=178)	Significance (1+ Visits vs No Visits)	Odds Ratios	95% CI
Sex of baby: Female	405 (52%) (n=775)	69 (56%) (n=123)	P=0.42	1.17	0.80 to 1.73
Took vitamins	556 (60%) (n=922)	100 (63%) (n=160)	P=0.14	1.30	0.92 to 1.85
First prescription medication: ondansetron	450 (53%) (n=847)	71 (46%) (n=154)	P=0.11	1.33	0.94 to 1.87

Analysis of Ondansetron Usage

Ondansetron, usually considered a second-line medication, was found to be the most prescribed and used first-line medication, likely because it has been reported to be more effective than other medications.[22] Due to these findings, further analysis was completed to look at prescribing patterns of ondansetron.

Of the 93 participants who reported no visits and either oral or IV ondansetron dosing, 52% were given 8 mg doses. The median week started was 6 weeks gestation, and median end week was 30. Frequency of dosing was as needed (22%), 1 or 2 times per day (36%), 3 times per day (31%), and 4 or more times per day (11%). The average dose per day was 15 mg, and 67% received less than 16 mg or less per day, while 38% reported ≤12 mg per day.

In the visit group, 438 respondents with 1 or more visits received oral or IV ondansetron beginning at a median of 6 weeks gestation and ceasing at a median of 33 weeks. Over half started either 4 mg or 8 mg doses of ondansetron after 8 weeks of nausea and vomiting symptoms. At least 3 respondents stated that ondansetron did not work but were prescribed only 4 mg per day.

Prior to their first visit, 56% were given 4 mg per dose, while 44% were given 8 mg per dose. Dosing was prescribed as needed (20%), 1 to 2 times a day (29%), 3 times a day (25%), and 4 or more times a day (26%). Only 22% received the maximum dose of 32 mg per day. Among the 331 prescribed ondansetron one or more times per day prior to their first visit, only 3% did not lose weight on an average dose of 14 mg/day, 60% lost 1–10 pounds (<4.5 kg) on an average dose of 16 mg/day, and 32% lost over 10 pounds (4.5 kg) on an average of 19 mg/day. Using Spearman's rho, the correlation between pre-visit weight loss and ondansetron dose was calculated and found to be insignificant with a correlation coefficient of 0.066. Total dosing of ondansetron was compared to the number of visits, and a small but statistically significant relationship was found between ondansetron dosage and number of visits ($r = 0.131$, $p = 0.014$) which suggests that a higher dosage of ondansetron is associated with a greater number of visits.

Discussion

Hyperemesis gravidarum (HG) results in hospital and emergency department visits for many patients, while others seek infusion care outside the hospital setting. As our study found, there is a high frequency of outpatient infusion visits in addition to repeat hospital or emergency visits, with visits and medication usage continuing past the first trimester and often into late pregnancy. As costs of hospital-based care in the United States continue to increase,[30] it is imperative that risk factors associated with hospitalization are identified to establish timely and effective treatments that prevent future visits or readmission and complications such as hepatic and renal injury.[31,32]

Similarly, recognizing factors influencing risk of hospital and emergency visits and symptom severity are crucial to reducing the misery and costs associated with HG. Consistent with other studies,[12] we found that pregnant people suffering from HG who were obese or identified as POC had a greater number of hospital visits. Prior studies found that POC was less likely to receive antiemetic medications,[33] but this study found that a similar proportion of the White and POC groups were prescribed antiemetic medications and adhered to the dosing instructions.

Visits for emergency or inpatient care were less likely in those who received and took prescription medication as prescribed. Visits were found to be more common in those who did not have children at home, were too sick to work, or lost over 15 pounds (6.8 kg). However, this study was not able to determine the cause of this effect. Possible reasons might include higher severity of illness due to age or parity effect, prior severe symptoms with pregnancy termination, lack of early access to effective outpatient care, or declining to seek hospital-based care due to child needs at home.

Among those with visits, many were also receiving infusion care for over a month, which indicates significant need for more effective treatment. This is evidenced, too, by the preterm birth rate of 20% among our participants with visits, double the US average of 10%,[34] which results in significant psychosocial impact on families plus financial burdens in the short and long term.

Given 30% of patients with a visit were not given medication prior to their visit, the criteria for diagnosing early HG may be unclear to healthcare providers, and signs like incremental weight loss may be dismissed if multiple health professionals provide primary obstetrical care for an individual. This highlights the importance of trending weight changes and suggests a tool like the validated HELP Score to quantify HG severity may be helpful in the clinical setting.[35]

Those with infusion care only had a lower median number of infusion days compared to those with visits and fewer lost over 15 pounds (6.8 kg). Significant weight loss over 15 pounds (6.8 kg) occurred among nearly half of those with 1+ visits and was significantly associated with more visits, thus weight loss is a critical indicator of more severe symptoms and greater risk for hospital care. Because weight loss and severe symptoms are associated with numerous adverse outcomes, it is important that guidelines be updated to reflect more optimized dosing of medications so there is consistent prescribing, patient education about HG treatment, and payer coverage of medications.

The fact that nearly all participants lost weight is concerning, considering a 2020 study conducted by Meinich et al found that "inadequate total maternal weight gain" and being unable to restore pre-pregnancy weight by weeks 13–18 were both independent risk factors that led to deliveries of smaller babies by gestational age.[36] Furthermore, the study found that not achieving adequate weight gain during the first trimester was directly correlated with adverse fetal outcomes. Thus, nutritional therapy and monitoring of weight gain/loss during the first trimester should be a priority in HG pregnancies to improve fetal outcomes and prevent hospital visits.

This point is underscored by the factor that 75% of respondents with a visit did not receive vitamins or nutritional therapy despite being unable to eat, and half of those with visits lost over 15 pounds (6.8 kg). Of those hospitalized, half did not gain weight and 21% lost weight during their visit. Further, few were able to tolerate oral vitamins and prenatal multivitamins, increasing their risk of complications such as Wernicke's encephalopathy[37] and fetal vitamin K embryopathy.[38] Nutritional support such as thiamine supplementation, intravenous vitamins, electrolytes, enteral feedings, and total parenteral nutrition are underutilized in this population and are needed when significant weight loss is present to prevent potentially life-altering complications for mother and child. However, it is imperative that interventions be given methodically to avoid complications such as refeeding syndrome[2] and osmotic demyelination syndrome.[39]

Importantly, the management of HG in our study varied greatly and continued throughout much of pregnancy for many patients, with infusion care, medications, and visits continuing into the third trimester. While acid reducing medication helps decrease nausea and prevents erosion of the esophagus and teeth, only 153 respondents with visits reported taking famotidine or a proton pump inhibitor like lansoprazole.

Less than 20% of our population had only 1 visit, indicating that ER and inpatient visits rarely cure HG and often are inadequate to control symptoms. Dosing on many prescribed medications was often as needed or twice daily, when the recommended dosing frequency for most medications is 3–4 times per day. Thus, many patients are not receiving adequate medication benefits throughout the day, likely leading to more severe symptoms. Adequate prescribing before visits and prior to discharge should be standard practice.

The maximum dose of ondansetron is 32 mg per day or 8 mg every 6 hours, yet most respondents received less than 16 mg or less per day or were told to take it as needed. Only 22% of those with visits received the maximum dose. We also found that over half of respondents began ondansetron over two months after symptoms began, which may make symptoms refractory.[33] Interestingly, those who began taking ondansetron within a week of symptom onset were more likely to have subsequent visits compared to those who began taking ondansetron during later weeks of symptoms. This counterintuitive finding may be explained by the fact that patients with a more severe presentation of HG may be

prescribed ondansetron therapy earlier than those with milder symptoms, or the medication is ineffective in some patients. However, ondansetron has been found in other studies to reduce the duration of hospital stays,[33] although this could not be compared in this study as duration of each stay was not measured.

Additionally, of 40 different medication combinations reported, none was found to be highly effective in preventing weight loss or visits despite the high rate of medication compliance reported. Only about half of respondents took their medications as prescribed after their first visit, however. Differences in treatment effectiveness is likely explained in large part by reports of widely varying dosing regimens and schedules, unmanaged side-effects, difficulty with transportation to the pharmacy, prohibitive costs of medication, too few doses and refills of their prescription, confusion about dosing schedules, inability to keep medication down, utilization of various forms of medication (IV, oral disintegrating), and varying gestational ages when treatment began, making it impossible to determine an ideal treatment regimen. Those on higher doses or multiple medications may also have experienced more severe and treatment resistant symptoms or delays in receiving care.

Lack of communication with their primary obstetrical provider during their first visit and delays in follow-up visits likely led to the dissatisfaction expressed in this survey. More treatment guidance and support early in pregnancy will likely improve patient satisfaction and adherence to treatment. Importantly, reported challenges related to communication, getting diagnosed, timely and consistent intervention, and adequate medication access also suggest continuity of care may significantly influence treatment utilization and thus could possibly affect both weight loss and number of visits. This highlights the need for more prospective studies to determine optimal management practices for HG to prevent weight loss and adverse child outcomes while reducing the enormous costs of treatment and lost productivity.

The most significant limitations in this study were that the data were self-reported by the participants and some questions were not reported by all participants for comparison. Because 66% of participants had already delivered, there is a risk of recall bias regarding details related to treatments and visits, although the median year of delivery was 2021. Furthermore, there may have been a bias towards participation by respondents with visits because the words "hospital" and "ER" were in the survey title. However, the fact that several risk factors overlap with those identified in other studies increases confidence in the results reported herein. A strength of the study is the large number of participants and global participation. The significant findings could also have arisen by chance due to the large number of statistical tests done.

Conclusion

In conclusion, most respondents in this survey reported weight loss during pregnancy, and those who lost more than 15 pounds were more likely to have one or more visits. Based on prior research, we know that severe NVP symptoms contribute greatly to maternal morbidity and weight loss, preterm birth and adverse child outcomes, as well as high utilization of hospital, emergency and infusion care.

We found care for HG is inconsistent and inadequate to control symptoms for most patients. This study was unable to reach a conclusion on a regimen of care that is most effective and further investigation is urgently needed. We recommend that dosing guidelines and clinical practice be re-evaluated to optimize dosing and delivery of treatment to reduce symptom severity and the burden of healthcare costs. Education and clinical resources for health professionals to improve recognition of early indicators of HG may reduce visits and the impact of HG.

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Disclosure

Author (M.S.F.) is Chief Scientific Officer, shareholder, and a paid consultant of Harmonia Healthcare and is a paid consultant for NGM Biosciences. Author (M.S.F.) is also a Board Member and Research Director for the Hyperemesis Education and Research Foundation and a Board Member for the Foundation for Women's Health.

Author (K. W. M.) is a shareholder and a paid consultant of Harmonia Healthcare. The authors report no other conflicts of interest in this work.

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