

In this study, outpatient management was effective in controlling nausea and vomiting during pregnancy and was associated with a reduced need for hospital or emergency room treatment as well as reduced costs.

Measuring Outpatient Outcomes of Emesis and Nausea Management in Pregnant Women

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ABSTRACT

Purpose: Nausea and vomiting during pregnancy (NVP) can create a significant clinical, psychological, and economic burden for patients, health care providers, and payers. The purpose of this analysis is to describe the clinical and economic outcomes of patients diagnosed with NVP utilizing an outpatient program of nursing support and pharmacologic treatment with subcutaneous metoclopramide (SMT).

Design: Women with singleton gestations who were experiencing NVP and whose physicians prescribed an outpatient program with SMT between January 2000 and February 2002 were identified from a database.

Methodology: Descriptive and statistical methods were used to ana-

lyze and report incidence of treatment failure, hospitalization/emergency room (ER) visits, degree of ketonuria, and Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score at program start/stop.

Principal findings: For a treatment duration of 26.9±20.8 days, 428 women were enrolled for outpatient SMT at 10.9±3.2 weeks' gestation. Improvement in NVP symptoms was achieved in 382 women with SMT (89.3 percent), while 46 (10.7 percent) required alteration of antiemetic therapy to subcutaneous ondansetron. The PUQE score at the start of SMT was 7.8±2.9, decreasing to 3.9±1.7 by therapy completion ($P<.001$). At treatment initiation, a PUQE score greater than or equal to 7 was reported by 63.1 percent of women versus 9.1 percent at the program's end ($P<.001$). Patients with ketonuria that was more than or equal to 1+ decreased from 36.2 percent to 1.4 percent ($P<.001$). The portion of patients with hospital/ER visits decreased from 65.4 percent to 3.3 percent during treatment ($P<.001$). Oral dietary improvement was noted in 78.7 percent of patients during treatment.

Conclusion: Outpatient management was effective in controlling NVP and was associated with a reduced need for hospital or emergency room treatment.

INTRODUCTION

Nausea and vomiting of pregnancy (NVP) is experienced by 50 to 80 percent of all pregnant women (Koren 2000). Symptom onset for NVP is usually between 4 and 8 weeks' gestation; the condition typically resolves by 14 to 16 weeks' gestation (Tierson 1986). Nevertheless, approximately 15 percent of women complain of nausea throughout their pregnancy, and 5 percent have emesis until delivery (Tierson 1986).

The most severe form of NVP, hyperemesis gravidarum (HG), occurs in 1 to 2 percent of pregnancies (Koren 2000). This is an especially debilitating problem that can lead to weight loss, dehydration, ketonuria, and the need for intravenous hydration and nutritional support.

Significant socioeconomic consequences are related to NVP. It is often a cause of much discomfort and concern for a pregnant woman and her family and can create significant disruption in their home and work lives.

NVP negatively affects job efficiency and attendance (Vellacott 1988, Gadsby 1993). It is the second most common reason for antepartum hospitalization, with more than 9 percent of all antepartum hospitalizations related to NVP (Gazmararian 2002). Hospitalization is costly, with inpatient treatment often required for several days or even

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weeks for some women. The average length of stay for an NVP-related hospitalization is 2.8 days at a mean cost of \$5,314 (HCUP 2001). Repeated hospitalizations that are attributable to symptom relapses are not uncommon for these women (Godsey 1991).

Numerous therapeutic interventions have been utilized to treat NVP, including pharmacotherapy, acupuncture, acupressure, and even pregnancy termination. The mainstays of NVP treatment consist of intravenous hydration and electrolyte replacement, nutritional counseling, psychosocial support, and antiemetic therapy (Naef 1995). The purpose of the present study is to describe the clinical and economic outcomes of patients who are diagnosed with NVP and are utilizing an outpatient program of nursing support and pharmacotherapy with subcutaneous metoclopramide (SMT).

METHODS

Patients were identified from a large perinatal database comprising of women receiving outpatient nursing services for pregnancy-related conditions through Matria Healthcare. These services were prescribed by the patient's health care provider and were adjunctive to routine prenatal care. Per the requirements of their insurance carriers, patients previously had failed traditional management of NVP.

At initiation of outpatient treatment, informed consent was obtained, including permission for anonymous publication of data for research purposes. Patients acknowledged receipt of information relative to the potential lack of safety and efficacy of SMT during pregnancy. The Investigational Review Board at Central Baptist Hospital approved this retrospective analysis.

Included in this analysis were singleton pregnancies at less than 24

weeks' gestation enrolled for NVP management services with SMT between January 2000 and February 2002.

SMT was not the first-line treatment for any patient and was prescribed after other treatments had failed to provide relief from NVP symptoms. Patients received individualized instruction in their homes by skilled perinatal nurses on diet modification, device operation, infusion-site selection, and emergency procedures.

SMT was initiated using a protocol that included a 10mg loading dose administered intramuscularly or intravenously followed by continuous subcutaneous administration using a portable, programmable micro-infusion pump. The infusion rate was titrated based on the patient's symptoms, then held steady once NVP symptoms abated. As the patient's ability to take oral food and fluids increased, the continuous infusion rate was decreased as tolerated.

Daily and PRN telephonic nursing assessments of maternal weight, urine ketones, oral intake, and side effects of antiemetic medications were conducted. During the nursing assessment, the patient's Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score was calculated. The

PUQE score was defined using the length of nausea per day in hours, the number of daily retching episodes, and the number of daily vomiting episodes (Table 1) (Koren 2002). A PUQE score between 4 and 6 is considered mild NVP, a score between 7 and 12 is considered moderate NVP, and a score that exceeds 13 represents severe NVP.

Emotional support and counseling were provided PRN, as were additional home visits. A medication profile was maintained for documentation of adjuvant NVP treatments received in addition to SMT.

Maternal characteristics and treatment information were analyzed. The primary outcome was resolution of NVP symptoms during the treatment period. Treatment failure was defined as a transition from SMT to another agent due to continued severe NVP symptoms or the patient's inability to tolerate SMT due to extrapyramidal side effects. Statistical analysis was by McNemar's χ^2 . Student paired *t*-tests, and Wilcoxon Signed Rank, with significance defined as *P*<.05.

RESULTS

Four hundred twenty-eight patients were identified with NVP who received SMT. Maternal characteristics are presented in Table 2. The

TABLE 1 Pregnancy-Unique Quantification of Emesis and Nausea scoring system

1. In the last 12 hours, for how many hours have you felt nauseated?					
Response	None at all	1 hour or less	2-3 hours	4-6 hours	>6 hours
Points given	1	2	3	4	5
2. In the last 12 hours, have you vomited?					
Response	Did not vomit	1-2 times	3-4 times	5-6 times	≥7 times
Points given	1	2	3	4	5
3. In the last 12 hours, how many times have you had retching or dry heaves without emesis?					
Response	None at all	1-2 times	3-4 times	5-6 times	>7 times
Points given	1	2	3	4	5

SOURCE: KOREN 2002

mean length of enrollment in the outpatient program was 26.7±20.8 days. Improvement of symptoms occurred in 382 women (89.3 percent), with 34.5 percent (132) of those with improvement requiring treatment for 14 days or less. Forty-six women (10.7 percent) failed to gain relief of NVP symptoms with SMT and required transition to continuous subcutaneous ondansetron.

Those individuals failing SMT had higher mean PUQE scores at the start of outpatient management than those who were successfully treated (10.0±3.0 vs. 7.6±2.8, respectively, *P*<.001), were more likely to have a PUQE score equal to or greater than 13 (21.7 percent vs. 5.5 percent, *P*<.001), had an earlier gestational age at the start of SMT (9.7±2.9 weeks vs. 11.4±3.2 weeks, *P*=.005), and were more likely to require adjunctive intravenous hydration (91.3 percent vs. 65.2 percent, *P*<.001).

Transition to subcutaneous ondansetron occurred after a mean of

14.0±18.4 days of SMT. These patients remained on subcutaneous ondansetron for a mean of 22.3±20.2 days.

In addition to SMT, 77.6 percent of patients received adjuvant therapy in the home: 68.0 percent received intravenous hydration, 28.3 percent received antiemetics other than metoclopramide, 5.6 percent received H₂ blockers, and 2.1 percent received total parenteral nutrition (TPN). The majority of patients, 61.0 percent, reported no adverse events related to SMT. Of those reporting adverse events, the most commonly reported were drowsiness, headache, and restlessness. One patient experienced extrapyramidal side effects.

Primary treatment outcomes are presented in Table 3. During treatment, the reported mean PUQE score, number of patients reporting ketonuria equal to or greater than 1+, and need for hospitalization declined. Of the 14 women with hospital admission, 7 had a 1-day length of stay.

One woman required more than 1 hospitalization during outpatient therapy. Mean weight gain during treatment was 1.9±5.4 pounds. Increased oral intake and reduced dietary restrictions were reported in 78.7 percent of women.

The mean gestational age at delivery was 37.9±4.7 weeks, with 54.7 percent of infants being female. Twelve women experienced spontaneous or elective abortion. There was one stillbirth at 32 weeks. The preterm birth rate was 12.6 percent, with 6.3 percent of infants having low birth weight (<2500 g).

At \$145 per day for the outpatient NVP program with SMT and \$380 per day if the patient received subcutaneous ondansetron following SMT failure, the average program cost per patient was approximately \$4,432. This is equivalent to 2.9 days of hospital management. Overall, subcutaneous antiemetics (SMT or ondansetron) were received for a mean of 26.7 days per patient. If these extremely ill women were hospitalized in lieu of outpatient management, hospital charges would be approximately \$40,050 per patient (Figure).

TABLE 2 Maternal characteristics

Data presented as mean ± SD, or percentage, as indicated

	N=428
Age (years)	28.6±5.4
Married	87.4%
Tobacco user	1.6%
Primigravid	26.2%
Maternal BMI at start or program	25.6±6.2
GA at start of program (week)	10.9±3.2
GA at end of program (week)	14.8±4.4

BMI=body mass index, GA=gestational age.

TABLE 3 Outcome of treatment (n = 428)

Data presented as mean ± SD, or percentage, as indicated

	Program start	Program stop	P-value
PUQE score	7.8±2.9	3.9±1.7	<.001
PUQE score >7	63.1%	9.1%	<.001
Ketonuria ≥ 1+	36.2%	1.4%	<.001
Hospital/ER visits	65.4%	3.3%	<.001

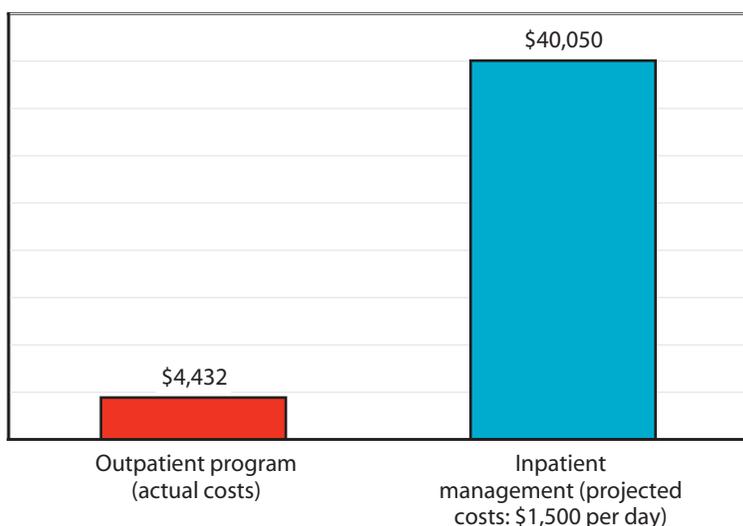
ER=emergency room, PUQE=Pregnancy-Unique Quantification of Emesis and Nausea

DISCUSSION

Although the cause of NVP remains unclear, numerous theories exist. Among the possible causes are atypical human chorionic gonadotropin levels or metabolism, hormonal dysfunctions, liver abnormalities, gastric hypofunction, and vitamin B deficiencies (Abell 1992).

Treatment for NVP can be divided into supportive, unconventional, and conventional therapies. Supportive therapy includes recumbent rest, dietary changes, and relaxation techniques, whereas unconventional measures include hypnosis, acupuncture, and acupuncture. Conventional measures include medical management with pyridoxine (vitamin B6), antihistamines, phenothiazines, and

FIGURE Mean cost per patient for management of nausea and emesis of pregnancy



other antiemetics — trimethobenzamide, metoclopramide, steroids, and ondansetron (Peleg 1997).

The above-mentioned drug classes have many different mechanisms of action and have been variably effective in treating NVP (Cowan 1996, Goodwin 1998). SMT has been shown to be effective in controlling gastroparesis and emesis induced by chemotherapy (McCallum 1991, Bruera 1988).

Metoclopramide reduces nausea in multiple ways. This medication acts on the central chemoreceptor trigger zone, which affects the vomiting center of the brain and also increases the resting tone of the lower esophageal sphincter, leading to decreased reflux. Additionally, metoclopramide shortens gastric emptying time (Cowan 1996). In a study of 646 women with hyperemesis who received SMT, 63.9 percent had complete resolution of symptoms (Buttino 2000).

Metoclopramide is considered a pregnancy risk factor B_M drug (Briggs 2002). Reproductive studies in mice, rats, and rabbits at doses up to 250 times the human dose have revealed

no evidence of impaired fertility or fetal harm as a result of the drug (Reglan PI 1997).

Long-term evaluation of infants exposed *in utero* to metoclopramide has been reported in a single study only. A 1981 study by Martynshin and colleagues mentioned normal infant development for up to 4 years, but no details were provided. Per the entry on metoclopramide in the most recent edition of *Drugs in Pregnancy and Lactation*, no congenital malformations or other fetal or newborn adverse effects attributable to the drug have been observed (Briggs 2002).

Severe NVP may necessitate frequent or prolonged hospitalization of the patient (Cowan 1996, Naef 1995, Godsey 1991). As such, the costs associated with NVP are significant. In a study of 140 patients with HG, almost 30 percent of women had multiple hospital admissions. The average inpatient length of stay per admission was 4.2 days for women with a single admission and 5.5 days for those with multiple admissions (Godsey 1991).

In a study comparing the cost of

inpatient (n=47) versus outpatient (n=50) intravenous hydration for women with HG, the mean number of hospital days for the inpatient group was 13, with 57 percent of patients requiring readmission due to relapse of symptoms (Naef 1995). More recent data from a national managed care organization revealed hyperemesis to be the second most common reason for antepartum hospitalization, with a mean length of stay of 3.0 days and a mean cost of \$4,167 per admission (Gazmararian 2002).

Data from the Agency for Healthcare Research and Quality, Healthcare Cost and Utilization Project, Nationwide Inpatient Sample revealed a mean length of stay per HG admission of 2.8 days and a mean cost of \$5,314.

At a cost of \$1,898 per inpatient day, one hospital admission for HG averaging 2.8 days is approximately equivalent to 36 outpatient treatment days with SMT at \$145 per day. Outpatient disease management programs and newer therapies such as SMT may reduce the need for hospitalization and may be clinical and cost-effective methods for managing patients with NVP.

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