ECONOMIC BURDEN OF NAUSEA AND VOMITING OF PREGNANCY IN THE USA

Charles Piwko[1], Gideon Koren[2,3], Vusal Babashov[1], Colin Vicente[1], Thomas R Einarson[2,3]

[1]PIVINA Consulting Inc., Mississauga, ON, Canada; [2]University of Toronto, Toronto, ON, Canada;
[3]Division of Clinical Pharmacology, Department of Pediatrics, Hospital for Sick Children, Toronto, Canada

Corresponding Author: *charles.piwko@utoronto.ca*

ABSTRACT

Background
Nausea and vomiting of pregnancy (NVP) is the most common medical condition during gestation, affecting 50%-90% of women during their first trimester, and many in the second and third trimester. NVP affects women's quality of life and exerts a large economic impact on patients, caregivers and society.

Objectives
To estimate the overall economic burden of illness of NVP in the USA.

Methods
A spreadsheet model was utilized to estimate this burden including direct and indirect costs. Costs are reported in 2012 US dollars and were estimated from the perspective of society. Cost centers included drug treatments for mild to severe NVP and hospitalizations for hyperemesis gravidarum (HG), as well as time lost from work and caregiver time. Clinical, epidemiologic, and economic data were obtained from the literature to populate the model. Rates of drug use were multiplied by unit costs and summed.

Results
The estimated total economic burden in 2012 in the USA was $1,778,473,782 which included $1,062,847,276 (60%) in direct costs and $715,626,506 (40%) in indirect costs. Overall, the average cost to manage one woman for NVP was $1827. Costs increased with increasing severity of NVP. The estimates were conservative, as not all applicable costs could be included.

Conclusions
NVP results in a significant economic impact, and hence effective therapy should be sought. Future prospective research should determine in more detail what resources are utilized in the USA to manage women with NVP.

Key Words: *Cost, burden, nausea, NVP, pregnancy, vomiting*

Nausea and vomiting of pregnancy (NVP) is the most common medical condition affecting 50%-90% of women during their first trimester and in many cases, even in later trimesters.[1,2] Fifty percent of pregnant women have both nausea and vomiting, 25% have nausea only, and 25% are unaffected.[3] Symptoms usually begin to manifest between weeks 4-6 of gestation, peaking between weeks 8-12, then tapering down until they cease, usually by week 20.[2,4]

However, some women experience NVP throughout their pregnancy.[5] The popular term "morning sickness" is misleading, as this condition often persists throughout the day.[6,7] Its severity can vary from mild to moderate to severe and even to extreme. This latter form is known as hyperemesis gravidarum (HG); it affects about 1% of women and commonly results in hospitalization.[8-11] Severe HG symptoms are the second most common reason for prenatal hospitalizations in the United

States, amounting to 11.4% of all non-delivery antenatal admissions.[12]

Research at the patient level has documented that NVP not only affects the quality of women's lives but also exerts an economic impact on them as well as their families, caregivers and society.[13-17] Approximately 35% of women suffering from NVP reported that they had lost time from work and reduced social life as a result.[13,14] However, none of these studies made projections to the population at large. In fact, only a few studies worldwide have examined the impact of NVP on resource utilization and costs.

The only paper to address NVP in general as well as HG was conducted in Canada in 2007.[15] However, the authors calculated only weekly costs and not the overall cost per patient, so projections to the population are difficult. As well, differences in healthcare systems between the countries complicate extrapolations to the USA.

HG has been examined in three additional papers. In the USA, Attard and colleagues[13] examined the burden of severe NVP, reporting a positive correlation between severity and resource utilization as well as time off work. Their results were quite similar to those of Piwko's group.[15] Bailit and associates estimated that the total burden of HG in California during 1999 was $18 million.[18] Similarly, Gadsby and Barnie-Adshead calculated that HG cost the National Health Service of England £36.5 million during 2003/2004.[19] Little else has been done for a condition that is so widespread.

Objectives

The objective of this study was to estimate, from the perspective of society, the economic burden of NVP in the USA during 2012, including direct and indirect costs.

METHODS

Model

A spreadsheet model was utilized to estimate the overall burden due to NVP in the USA from the perspective of society. Both direct and indirect costs were considered. Direct costs for NVP included drugs, medical care, healthcare professional fees, hospitalization and emergency room (ER) costs; indirect costs included time lost from work by the woman and her spouse and additional caregiver time. The same costs were calculated for HG as well as associated hospitalization costs.

Clinical, epidemiologic, and economic data were obtained from the literature to populate the model. To start, the number of pregnant women in the USA was determined. We then calculated the numbers that would be affected by NVP stratified by severity (i.e., mild, moderate and severe), the numbers who would be treated for it, and the numbers who would be hospitalized or visit the ER.

Clinical Inputs

The American Clinical Management Guidelines for Obstetrician-Gynecologists for NVP by the American College of Obstetrics and Gynecology (ACOG),[20] as well as published randomized controlled trials (RCTs) were utilized to determine patterns of treatment. Patterns included types of drugs used, dosages, frequencies, duration of treatment and their efficacy. To obtain clinical data, a literature search was conducted. Only peer reviewed articles were accepted that described original research on pregnant women in the USA. Articles must have involved RCTs in order for the treatment regimens to be included. A literature search was conducted using the OvidSP search platform in the following databases: Medline, Embase, EBMR, CDSR, EBMR CCTR and EBMR HTA as of December 2, 2012. Keywords used in the search strategy included terms such as: morning sickness, hyperemesis gravidarum, nausea, vomiting, pregnancy, economic, randomized controlled trials. No restriction was put on date of publication. Two researchers independently reviewed identified titles and/or abstracts to select potential references for full text review and data collection. Discrepancies were resolved via consensus discussion. A schematic presentation of the literature search is provided in Figure 1.

FIG. 1 Schematic of Literature Search

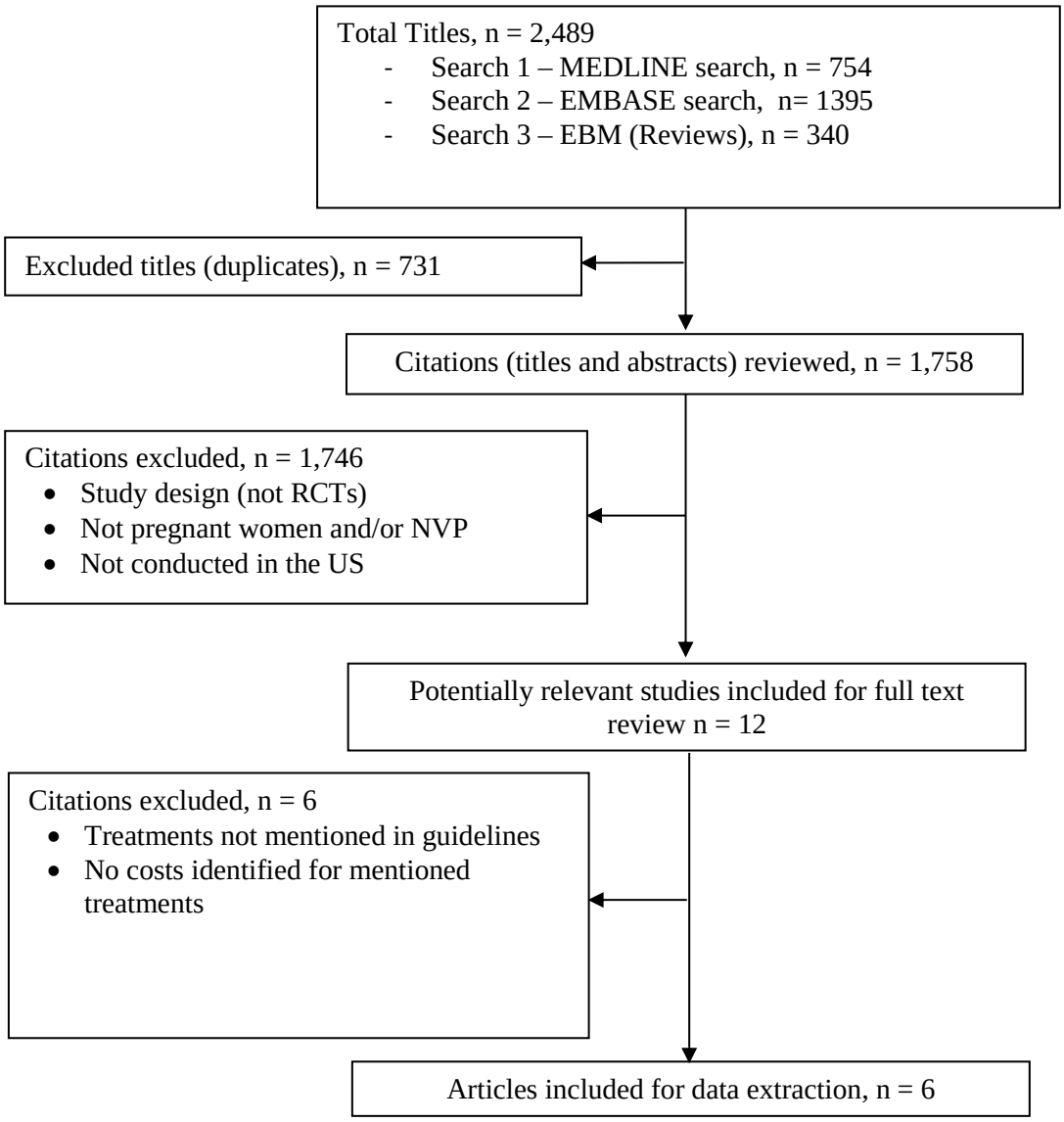
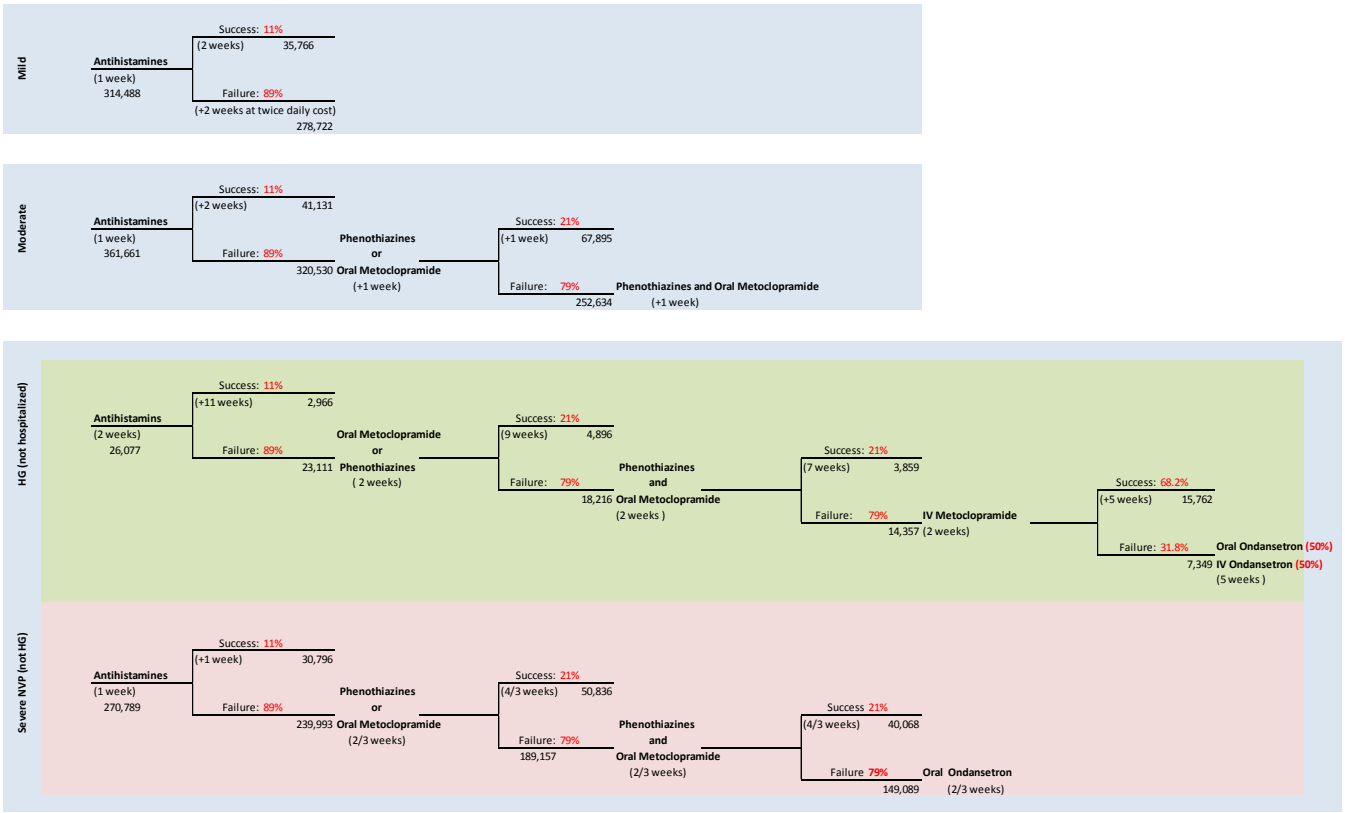


FIG. 2 Treatment Pathway* for Women with Mild, Moderate, and Severe NVP and HG



*failure: not responding to treatment, success; responding to treatment

Epidemiologic Inputs

For the epidemiology data, we used results from our previous research addressing this topic.[21] Included were rates of NVP, including stratification according to severity, as well as its duration and the proportion of treated women. We also determined rates of HG and associated hospitalizations. Prospective and/or retrospective collected data were utilized to estimate epidemiologic rates. In addition to the peer reviewed literature, also a "grey area" search was conducted to complement missing information.

Cost Inputs

Prospectively and/or retrospectively collected data were utilized to estimate the overall average costs as reported in the literature. Unit costs for drugs were taken from the Redbook and from published articles.[10,22] Hospital costs and ER visits were taken from the Healthcare Cost and Utilization Project (HCUP).[23,24] We included data for all hospitalizations associated with ICD-9 CM codes 643.01-643.93. ER visits from 2010 were taken from AHRQ[24] and projected to 2012, pro-rating by the birth rates.[25] Costs of ER visits were obtained from Chatterjee et al.[26] Number of physician visits, physician costs and other healthcare professional fees for severe NVP were obtained from Attard et al.[13] and Laugesen et al.[27] Physician costs for mild and moderate NVP were derived from Piwko et al.[15] All costs were estimated in 2012 US dollars; those from other years were adjusted using the Consumer Price Index.[28]

We followed the ACOG treatment recommendations and algorithm to estimate the treatment costs.[20] Figure 2 describes treatment pathways (including the numbers of treated

women, treatment regimens, success rates, and treatment durations) for women suffering from mild, moderate, and severe NVP, respectively, as well as HG. Treatment success and failure rates were obtained from the Mazotta and Magee[29] and Reichmann and Kirkbride reviews.[30] The duration of NVP was approximately 12 weeks, as reported by Gadsby et al.[19], and 13 weeks for HG, as reported by Goodwin et al.[9] We assumed that drugs would be taken for approximately 3 weeks to manage NVP (data obtained from IMS[31]), and for the full 13 weeks in the case of HG.[9,19]

A conservative approach was taken to estimate indirect costs and included time lost from work by the woman and her partner as well as additional caregiver costs due to minding children or household maintenance.[2,13,15] The average number of days was multiplied by the average US wage for 2012, then all indirect costs were summed to produce a total indirect cost.[32] We also calculated the average cost per woman treated and per pregnant woman.

Cost Calculations

With the above mentioned input parameters we calculated the economic burden by using the following formulas:

1. Cost of treatment for NVP = Number of pregnant women during 2012 * Rate of NVP * Rate of treatment * Cost of treatment
2. Cost of managing HG = Number of pregnant women during 2012 * Rate of HG * Rate of treatment * Cost of treatment + Costs associated with hospitalizations and ER visits
3. Overall burden = Σ Costs of drug treatment for NVP + Σ Costs of drug treatment for HG + ΣHospitalization and ER costs + Σ Indirect costs

RESULTS

Literature Search

The literature search resulted in a total of 2489 references. Of those, 731 were duplicates and therefore removed, leaving 1758 references for screening. After screening titles and abstracts, 1736 studies were excluded since these were not RCTs, did not report on pregnant women and/or NVP, or were not conducted in the US. A total of 22 references met the eligibility criteria and were included in the full text review. From those, 12 studies provided data that could potentially be used for data extraction (See Table 1). For the purposes of this analysis, data from 6 studies were used,[33-38] reporting on treatment regimens as per the ACOG guidelines.[20] Table 1 presents the treatment regimens identified in RCTs. A schematic of the results from the literature search is provided in Figure 1.

TABLE 1 Treatment Options Tested in Published Randomized Controlled Trials

Author	Year of publication	Treatment Option
Sahakian et al.[33]	1991	Vitamin B6 (pyridoxine hydrochloride)
Evans et al.[50]	1993	Sensory afferent simulation
Belluomini et al.[43]	1994	Acupressure
Sullivan et al.[34]	1996	Ondansetron & promethazine
Safari et al.[35]	1998	Methylprednisolone & promethazine
Steele et al.[44]	2001	P6 acupressure by sea-bands
Keating et al.[51]	2002	Ginger syrup
Bsat et al.[36]	2003	Pyridoxine–metoclopramide & prochlorperazine & promethazine
Rosen et al.[52]	2003	Nerve stimulation
Yost et al.[53]	2003	Methylprednisolone & prednisone
Adamczak et al.[37]	2007	Solumedrol® & Phenergan®
Koren et al.[38]	2010	Doxylamine succinate & pyridoxine hydrochloride

According to population statistics from the Index Mundi website as well as the American Pregnancy Association and a recently published article, there were about 6,520,328 pregnancies in 2012 in the USA, of whom 4,427,303 (67.9% of pregnant women) suffered from NVP.[25,29,40]

According to Einarson et al., 40% of US women suffer from mild, 46% from moderate, and 14% from severe NVP.[21] Based on published data reporting on 7923 women, we estimated that about 17.8% of women affected by mild and moderate NVP used drugs.[16,41,42] Based on expert opinion, we estimated that 50% of affected women would take drugs for severe NVP and HG; the total treated would be 973,015.

Treatment Regimens for NVP and HG in the USA and Costs

Table 2 summarizes the treatment regimens included in this analysis and daily costs associated with the management of NVP and HG.

TABLE 2 Unit Cost of Treatments Included in the Analysis

Line of treatment	Class	Drug Name	Cost per day ($)*
First	Antihistamine	Dimenhydrinate	0.37[10]
	Antihistamine	Diphenhydramine	1.01[10]
	Antihistamine	Doxylamine	0.52[10]
	Vitamin	Pyridoxine	0.16[10]
	Antihistamine	Hydroxyzine	8.41[29]
	Antihistamine	Meclizine	1.97[10]
	Unknown†	Trimethobenzamide	7.07[29]
Second	Dopamine Antagonists	Metoclopramide (oral)	2.77[10]
	Dopamine Antagonists	Phenothiazines/ Promethazine	2.34[10]
	Dopamine Antagonists	Metoclopramide (IV)	154.62[10]
Third	Serotonin 5-HT3 Antagonists	Ondansetron (oral)	83.52[29]
	Serotonin 5-HT3 Antagonists	Ondansetron (IV)	405.22[10]

*All costs are in 2012 USD

†Probably acts at the chemoreceptor trigger zone

TABLE 3 Estimated Average Treatment Costs for the Management of NVP and HG in 2012

Severity Level	Number of Women Taking Treatment	Total Cost of Treatment	Average Cost per Treated Woman
Mild NVP	314,488	$12,669,508	$40
Moderate NVP	361,661	$20,619,329	$57
Severe NVP	270,789	$72,250,838	$267
Total NVP	946,938	$105,539,677	$111
HG	26,077	$184,851,479	$7,089
Total NVP and HG	973,015	$290,391,156	$298

HG, hyperemesis gravidarum; NVP, nausea and vomiting of pregnancy

Cost of Drug Treatment

Table 3 summarizes the cost of drugs used to manage NVP in the USA (also see Figure 2 for more details). The estimated total burden associated with treatment was $290,391,156 in 2012. Estimated costs for medical care correlated with severity of symptoms, from $40 for mild, $57 for moderate to $267 for severe and highest for women suffering from HG ($7,089).

Cost of Hospitalization and Emergency Room Visits

Based on HCUP data, there were 26,077 women hospitalized due to HG in 2012 in the USA.[32] The estimated total hospital cost associated with HG was $324,906,000 for that year, resulting in an average of $12,453 per patient admission. There were an estimated 241,829 ER visits,[24] each costing $1035, for a total of $250,293,036. Thus, the overall cost of hospital and ER was $575,199,036.

Cost of Healthcare Professionals

Based on published literature, the total healthcare provider cost for severe NVP was $322.26.[13,27] Health care provider costs for moderate and mild NVP were derived from Piwko et al.[15] and estimated at $254.82 and $26.98 for moderate and mild NVP, respectively. As with drugs, costs increased with increasing symptom severity.

Indirect Costs

Based on studies published by Attard and Piwko[13,15] we calculated an average of 23 days lost from work. Partners' absence from work and caregiver time was estimated from Piwko et al.[15] See Table 4 for details.

Overall Economic Burden

The 2012 estimated total economic burden was $1,778,473,782 which comprised $1,062,847,276 (60%) in direct costs and $715,626,506 (40%) in indirect costs. The average cost was $1827 for a woman treated for NVP and $402 per women suffering from NVP (treated and untreated). That amounted to $273 per pregnancy. For more details see Table 5.

TABLE 4 Average Estimated Indirect Cost

Cost Item	Days	Cost
Work days lost	23.0[13]	
Partner work days lost	3.5[15]	
Caregiver time	9.8[15]	
Total	36.3	**$6,445***
Women treated for NVP		973,015
Proportion working	56.7%[2]	552,179
Proportion taking time off	20.1%[2]	111,044
Total indirect cost in 2012		**$715,626,506**

*The average 2012 US income per day ($177.59) was multiplied by the total days lost by the woman (23.0 days) + spouse/partner (3.5 days) + caregiver time (9.8 days). [13,15,32]

TABLE 5 Economic Burden of NVP in the USA 2012

Group	Number of women	Direct* cost/ woman	Indirect† cost/ woman	Total cost/ woman
All pregnant women	6,520,328	$163	$110	$273
All women with NVP	4,427,303	$240	$162	$402
Mild NVP	1,770,921	$14	$404	$418
Moderate NVP	2,036,560	$17	$351	$368
Severe NVP	619,822	$1105	$1155	$2260
All treated women	973,015	$1,092	$735	$1,827
Mild NVP	314,488	$79	$2,276	$2,355
Moderate NVP	361,661	$95	$1,979	$2,074
Severe NVP	270,789	$2,530	$2,623	$5,153
HG	26,077	$19,908	$27,443	$47,351
Total economic burden (all women)	**6,520,328**	**$1,062,847,276**	**$715,626,506**	**$1,778,473,782**

HG, hyperemesis gravidarum; NVP, nausea and vomiting of pregnancy
*These costs include hospitalizations, emergency room visits, physician visits, and drugs
†Includes time lost from work by the woman and her spouse as well as caregiver time and child minding.

DISCUSSION

We estimated that the overall economic burden of NVP to third party payers in the USA was almost $1.8 billion in 2012. The approach taken in this study was rather conservative, as for all included treatment regimens, the lowest price was always used. Additionally, costs for procedures such as acupressure and acupuncture were not included, despite having been studied in RCTs[43,44] as they were not part of the US treatment guidelines.[20] Other drugs or vitamins taken were also not included due to a lack of precise information. Costs for treating dehydration were not included, which would also impact the bottom line. Therefore, our estimate may be somewhat low.

For the indirect cost items, only time lost from work and caregiver time were included. The amount of time lost from work (the main indirect cost item) was consistently reported in published articles was around 23 days.[2,13,15] However, little else was identified in the peer reviewed literature and further research is warranted.

Although this is not the first paper to estimate the burden of NVP in the USA, it is the most comprehensive and current. Bailit and coworkers[18] estimated that HG was responsible for $19 million in expenditures for hospital care in California during 1999. That would amount to about $36 per pregnancy in 2012 dollars, as opposed to our estimate of about $50 per pregnancy. Similarly, the National Health Service in England spent £36,481,745 during 2003-2004 on hospital care for HG, equivalent to $89 per pregnancy (2012 USD). Both of those studies estimated only hospital costs; neither included outpatient treatments nor indirect costs such as time lost from work.

Theoretically, the management of NVP should begin with prevention.[20] Studies have found that fewer women who were taking a multivitamin at the time of conception needed less medical attention for vomiting.[45] Therefore, it is reasonable to advise women with a history of NVP or HG to take a multivitamin at the time of the next conception.[20] Also, research has suggests that pre-emptive treatment with antinauseants can reduce the severity of HG[46,47] as well as the duration of hospitalization and need for intravenous fluids.[48] Since data for this research were not collected prospectively, various assumptions had to be made and all model inputs had to be derived from the published literature. One factor that could potentially impact the economic burden is the duration of NVP. Some women suffer from NVP for much longer than only 12 weeks, as assumed in this study and may take pharmacological treatments for longer than only 3 weeks. This study also assumed that only women with HG were hospitalized and received IV treatments, which may underestimate the total costs.

The only USA study that categorized women by the severity of their NVP was that by Crystal et al.[49] Those authors reported that 32% of US women suffered from mild, 43% from moderate, and 25% from severe NVP.[49] However, that study reported the proportion of women suffering from nausea separately from those suffering from vomiting, and did not combine them as NVP. Therefore, we used 40%, 46% and 14% for women with mild, moderate and severe NVP, respectively, as calculated in our meta-analysis.[21]

In conclusion, NVP results in a significant economic impact to women, payers and society. The impact increases with increasing severity of NVP. There are some strategies available to assist in reducing this burden, such as early diagnosis, change in diet and treatment. However, additional evidence-based options are still needed. This field suffers from a lack of research, which needs to be addressed. Future research should estimate cost centers in more detail, in order to more precisely estimate the economic burden of NVP.

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