PREVALENCE OF NAUSEA AND VOMITING OF PREGNANCY IN THE USA: A META-ANALYSIS

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ABSTRACT

Background
Nausea and vomiting of pregnancy (NVP) is the most common medical condition during gestation, carrying tremendous health burden, especially for the severe form, hyperemesis gravidarum (HG). The rates of NVP in the USA have not been systematically calculated.

Objectives
To estimate the rates of NVP and HG in the USA.

Methods
A meta-analysis was conducted of all peer-reviewed articles from the USA that provided rates of NVP in early or late pregnancy or HG. Medline, Embase and Cochrane databases were searched from inception through November 2012; reviews and articles were hand searched. Rates were combined across studies using a random effects model.

Results
Forty-eight articles were identified; 15 were rejected and 33 were included for analysis. Twenty-three studies of 67,602 women provided rates of NVP which had a meta-analytic rate of 68.6% ($CI_{95\%}$:64.4%-72.8%). Three of them (N=5034) reported nausea without vomiting in 28.6% and two studies (N=136) produced a rate for NVP during late pregnancy of 24.0%. HG occurred in 1.2% of the 2.1 million women in 12 studies.

Conclusions
We have summarized rates of NVP and HG, which are similar to those found in other parts of the world. Almost 70% of women suffer some form of the syndrome; 1.2% have the severe form, most of whom were hospitalized because of the HG. Future research should address issues of cost and resource utilization.

Key Words: *Nausea, vomiting, pregnancy, NVP, prevalence, USA, meta-analysis*

Nausea and vomiting in pregnancy (NVP) is the most common medical condition during gestation.[1] It usually begins between weeks 4-6 of gestation, peaking between weeks 8-12, then tapering down until it ceases, usually by week 20.[2,3] NVP can vary in severity from mild to incapacitating, the latter form being known as hyperemesis gravidarum (HG).[4,5] All forms of NVP exerts a huge burden on patients, caregivers and society.[6,7]

Guidelines have been published to assist practitioners and their patients in managing the problem.[1,8,9] However, there is very little high quality evidence quantifying its consequences in terms of clinical outcomes of treatment or economic burden.[1,8-10] A literature search of Medline and Embase located only three studies from the USA that quantified different aspects of this burden in terms of cost.[11-13]

As well, reviews of the topic during the last 10 years have taken a general viewpoint; none has focused on data specific to the USA. Prevalence estimates around the world have varied widely, from 50% to 85%.[14] A need exists for country specific information that provides a quantitative estimate that will allow an accurate determination of the resource and costs associated with this disease. Therefore, we undertook the present research. The objective of this study was to calculate point estimates and 95% confidence intervals for rates of early and late NVP as well as HG that have reported for women in the USA.

METHODS

To be included for analysis, articles must have been published original peer reviewed research on women in the USA. Articles must have presented rates of nausea and/or vomiting (or data from which they could be calculated) at any stage of pregnancy using any acceptable definition, providing it was clearly defined. No restrictions were placed on year or language of publication. Outcomes of interest included rates of NVP in early pregnancy (i.e., ≤12 weeks), rates of NVP in late pregnancy (i.e., >12 weeks), rates of nausea only (i.e., without vomiting or retching), and rates of HG. A systematic search was conducted using the Medline, Embase, and Cochrane Libraries databases from inception to November 1, 2012.

Data were combined into a single weighted rate using the random effects meta-analytic method presented by Einarson.[15] That method weights each rate both by within-study variance with larger sample sizes receiving greater weights and also by between-study variance. That approach allows for differences in study design or data collection methods, allowing incorporation of the maximum number of studies which yields the highest degree of representation of the population.

RESULTS

We identified 48 articles that addressed the topic; however, 15 of them were rejected for reasons detailed (Table 1),[11,16-29] leaving 33 for analysis (Table 2). There were 23 studies of 67,602 women providing information on rates of NVP in early pregnancy.[3,30-51] Two studies provided information on NVP in late pregnancy (Table 3)[38,40] and three reported rates of nausea only (without any vomiting).[3,34,46] Finally, there were 12 papers that documented rates of HG.[13,39,46,52-60]

Twenty-three studies of 67,602 women provided rates of NVP which had a meta-analytic rate of 68.6% ($CI_{95\%}$:64.4%-72.8%). Three of them (N=5034) reported nausea without vomiting in 28.6% and two studies (N=136) produced a rate for NVP during late pregnancy of 24.0%. HG occurred in 1.2% of the 2.1 million women in 12 studies (Tables 2-3).

TABLE 1 Rejected Studies (n=15) from the USA and Reasons for Rejection

Outcome (number rejected)	Reason for rejection (number rejected)	First author (year)
NVP (8)	Duplicate publication (3)	Chan (2010)[16], Klebanoff (1986)[17], Weigel (1988)[18]
	Patients were recruited based on having NVP (3)	Attard (2002)[11], Fejzo (2008)[19], Munch (2011)[20]
	Review (1)	Flaxman (2000)[21]
	No data (1)	Corey (1992)[22]
Hyperemesis gravidarum (7)	Patients were recruited based on having NVP (6)	Depue (1987)[23], Godsey (1991)[24], Naef (1995)[25], Nageotte (1996)[26], Safari (1998)[27], Saha (2011)[28]
	Duplicate (1)	Franks (1999)[29]

TABLE 2 Summary of Published Rates of Nausea and Vomiting in Early Pregnancy in the USA

Outcome	First author (year)	Number reporting NVP	Total N	Rate
Overall NVP	Boneva (1999)[30]	1,173	4,027	70.9%
	Brandes (1967)[31]	5,117	7,027	72.8%
	Brown (1997)[32]	436	549	79.4%
	Chan (2011)[3]	2,130	2,407	88.5%
	Chou (2003)[33]	73	113	64.6%
	Crystal (1999)[34]	110	129	85.3%
	DiIorio (1985)[35]	44	78	56.4%
	Fawcett (1986)[36]	45	70	64.3%
	Fenster (1991)[37]	1,244	1,886	66.0%
	Jahangiri (2011)[38]	26	45	57.8%
	Klebanoff (1985)[39]	4,507	8,007	56.3%
	Lindseth (2005)[40]	76	109	69.7%
	Little (1979)[41]	151	210	71.9%
	Louik (2006)[42]	14,998	22,487	66.7%
	Milkovich (1976)[43]	6,305	10,205	61.8%
	O'Brien (1995)[44]	81	126	64.3%
	Pettiti (1986)[45]	1,318	1,933	68.2%
	Semmens (1957)[46]	1,091	2,500	43.6%
	Speert (1954)[47]	165	256	64.5%
	Tierson (1986)[48]	370	414	89.4%
	Weigel (1989)[49]	626	903	69.3%
	Werler (1989)[50]	182	268	67.9%
	Yerushalmy (1965)[51]	2,740	3,853	71.1%
	Total	44,689	67,602	66.1%
	Meta-analytic average (SE)			**68.8% (2.1%)**

TABLE 3 Summary of Published Rates of Nausea and Vomiting in Late Pregnancy and HG in the USA

Outcome	First author (year)	Number reporting NVP	Total N	Rate
Nausea only	Chan (2011)[3]	849	2405	35.3%
	Crystal (1999)[34]	58	129	45.0%
	Semmens (1957)[46]	155	2500	6.2%
	Total	1,062	5,034	21.1%
NVP in late pregnancy	Jahangiri (2011)[38]	4	28	14.3%
	Lindseth (2005)[40]	35	108	32.4%
	Total	39	136	28.7%
		Meta-analytic average (SE)	**24.0%**	**(0.9%)**
Hyperemesis gravidarum				
	Adams (1994)[52]	30	1,825	1.6%
	Bacak (2005)[53]	820	68,514	1.2%
	Bailit (2005)[13]	2,466	520,739	0.5%
	Bennett (1998)[54]	6,377	579,742	1.1%
	Gazmararian (2002)[55]	337	46,179	0.7%
	Hallak (1996)[56]	138	12,473	1.1%
	Klebanoff (1985)[39]	86	9,098	0.9%
	Peckham (1929)[57]	43	6,491	0.7%
	Reid (1938)[58]	176	27,275	0.6%
	Scott (1997)[59]	24,998	833,264	3.0%
	Semmens (1957)[46]	33	2,500	1.3%
	Tsang (1996)[60]	193	13,053	1.5%
		35,694	2,121,153	1.7%
		Meta-analytic average (SE)		**1.2% (0.2%)**

DISCUSSION

The overall rate of NVP found by us is very similar to the global rate of 73.4% previously reported by Gadbsy and Barnie-Adshead.[14] As well, our rate of HG falls within their range of 0.14%-1.3%. The rate of NVP in late pregnancy of 24.0% (6.3%-41.7%) warrants special focus, as many health care professionals tend to trivialize NVP as a condition that subsides by 12 weeks of gestation; the fact that a quarter of all women suffer throughout gestation will therefore have huge impact on burden.

The studies that were retrieved reflected practice over a very long period of time, which

could affect results. However, there was no correlation between year of publication and rate of NVP (Spearman's correlation =0.237, P=0.266) or HG (Spearman's correlation =0.045, P=0.880). Similarly, sample sizes were not related to rates (P>0.05).

Two reasonably large studies by Chan et al.[3] and Louik et al.[42] investigated the relationship between rates of NVP and age or race in the USA, finding no association. However, higher rates of NVP had been reported from countries in East Asia, including Japan,[61] Taiwan[62] and China.[63,64] If genetics is involved and rates are indeed higher amongst American women with roots in these countries, such elevated rates could only be detected with research specifically aimed at these groups of women. We found no such studies in the literature.

This review concentrated on nausea and vomiting; however there are other aspects of "pregnancy sickness" that we did not address. In a review of the subject in 2000, Flaxman and Sherman[65] pointed out that many women may also suffer from cravings and aversions. These anomalies may involve food, beverages or even chemicals.[34,66] Aversions and cravings may or may not be associated with NVP; the relationship appears to be complex.[67,68] Nonetheless, they do affect the pregnancies of those afflicted as well as the quality of their everyday lives.

This research demonstrates that a sizeable proportion of pregnant women suffer from NVP. However, few studies have actually quantified that impact in terms of costs or healthcare resource utilization. Attard and associates[11] examined the burden of severe NVP, reporting a positive correlation between severity and resource utilization as well as time off work. There was a significant negative correlation between severity and health-related quality of life. Little else exists in the literature to guide practitioners or their pregnant patients.

Fortunately, there are some effective treatments available. Reichmann and Kirkbride[12] have reviewed the cost-effective options in the USA. Since the time of that publication, a randomized controlled trial in the USA has demonstrated the efficacy of doxylamine-vitamin B6 (Diclectin®) for NVP.[69] The impact of these treatments on burden of illness requires further research.

CONCLUSIONS

Rates of NVP and HG in the USA have been summarized into point estimates with 95% confidence intervals, which were 68.6% and 1.2%, respectively. These estimates may be useful for further research into determining the overall resource and cost burden of NVP in the United States. Further research into the burden of NVP on healthcare systems and the impact of available treatments is warranted.

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REFERENCES

1. ACOG Practice Bulletin number 52: nausea and vomiting of pregnancy. Obstet Gynecol 2004;103:803-13.
2. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. Br J Gen Pract 1993;43:245-8.
3. Chan RL, Olshan AF, Savitz DA, et al. Maternal influences on nausea and vomiting in early pregnancy. Matern Child Health J 2011;15:122-7.
4. Goodwin TM. Hyperemesis gravidarum. Obstet Gynecol Clin North Am 2008; 35:401-17.
5. Clark SM, Costantine MM, Hankins GD. Review of NVP and HG and early pharmacotherapeutic intervention. Obstet Gynecol Int 2012;2012:252676. Epub 2011 Nov 24.
6. Mazzotta P, Stewart D, Atanackovic G, Koren G, Magee LA. Psychosocial morbidity among women with nausea and vomiting of pregnancy: prevalence and association with anti-emetic therapy. J Psychosom Obstet Gynaecol 2000;21:129-36.
7. Smith C, Crowther C, Beilby J, Dandeaux J. The impact of nausea and vomiting on women: a burden of early pregnancy. Aust N Z J Obstet Gynaecol 2000;40:397-401.
8. Arsenault MY, Lane CA. The management of nausea and vomiting of pregnancy. J Obstet Gynaecol Can 2002;24:817-31.
9. Einarson A, Maltepe C, Boskovic R, Koren G. Treatment of nausea and vomiting in pregnancy: an updated algorithm. Can Fam Physician 2007;53:2109-11.
10. Matthews A, Dowsell T, Haas DM, Doyle M, O'Mathúna DP. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev 2010, Issue 9. Art. No.: CD007575. DOI: 10.1002/14651858.CD00575.pub2.
11. Attard CL, Kohli MA, Coleman S, Bradley C, Hux M, Atanackovic G, Torrance GW. The burden of illness of severe nausea and vomiting of pregnancy in the United States. Am J Obstet Gynecol 2002;186(5 Suppl Understanding):S220-7.
12. Reichmann JP, Kirkbride MS. Nausea and vomiting of pregnancy: cost effective pharmacologic treatments. Manag Care 2008;17:41-5.
13. Bailit JL. Hyperemesis gravidarium: Epidemiologic findings from a large cohort. Am J Obstet Gynecol 2005;193(3 Pt 1):811-4.
14. Gadsby R, Barnie-Adshead AM. Nausea and vomiting of pregnancy: clinical information about nausea and vomiting of pregnancy and its relation to various aspects of womens' personal and obstetric histories and other significant factors related to nausea and vomiting of pregnancy or hyperemesis gravidarum. A literature review. Available at: http://www.pregnancysicknesssupport.org.uk/documents/NVP-lit-review.pdf
15. Einarson TR. Pharmacoeconomic applications of meta-analysis for single groups: antifungal onychomycosis lacquers as example. Clin Ther 1997;19:559-69.
16. Chan RL, Olshan AF, Savitz DA, et al. Severity and duration of nausea and vomiting symptoms in pregnancy and spontaneous abortion. Hum Reprod 2010;25:2907-12.
17. Klebanoff MA, Mills JL. Is vomiting during pregnancy teratogenic? Br Med J (Clin Res Ed) 1986;292:724-6.
18. Weigel MM, Weigel RM. The association of reproductive history, demographic factors, and alcohol and tobacco consumption with the risk of developing nausea and vomiting in early pregnancy. Am J Epidemiol 1988;127:562-70.
19. Fejzo MS, Ingles SA, Wilson M, et al. High prevalence of severe nausea and vomiting of pregnancy and hyperemesis gravidarum among relatives of affected individuals. Eur J Obstet Gynecol Reprod Biol 2008;141:13-7.
20. Munch S, Korst LM, Hernandez GD, Romero R, Goodwin TM. Health-related quality of life in women with nausea and vomiting of pregnancy: the importance of psychosocial context. J Perinatol 2011;31:10-20.
21. Flaxman SM, Sherman PW. Morning sickness: a mechanism for protecting mother and embryo. Q Rev Biol 2000;75:113-48.
22. Corey LA, Berg K, Solaas MH, Nance WE. The epidemiology of pregnancy complications and outcome in a Norwegian twin population. Obstet Gynecol 1992;80:989-94.
23. Depue RH, Bernstein L, Ross RK, Judd HL, Henderson BE. Hyperemesis gravidarum in relation to estradiol levels, pregnancy outcome, and other maternal factors: a seroepidemiologic study. Am J Obstet Gynecol 1987;156:1137-41.
24. Godsey RK, Newman RB. Hyperemesis gravidarum. A comparison of single and multiple admissions. J Reprod Med 1991;36:287-90.
25. Naef RW, Chauhan SP, Roach H, Roberts WE, Travis KH, Morrison JC. Treatment for hyperemesis gravidarum in the home: an

alternative to hospitalization. J Perinatol 1995;15:289-92.
26. Nageotte MP, Briggs GG, Towers CV, Asrat T. Droperidol and diphenhydramine in the management of hyperemesis gravidarum. Am J Obstet Gynecol 1996;174:1801-6.
27. Safari HR, Alsulyman OM, Gherman RB, Goodwin TM. Experience with oral methylprednisolone in the treatment of refractory hyperemesis gravidarum. Am J Obstet Gynecol 1998;178:1054-8.
28. Saha S, Manlolo J, McGowan CE, Reinert S, Degli Esposti S. Gastroenterology consultations in pregnancy. J Womens Health (Larchmt) 2011;20:359-63.
29. Franks AL, Kendrick JS, Olson DR, Atrash HK, Saftlas AF, Moien M. Hospitalization for pregnancy complications, United States, 1986 and 1987. Am J Obstet Gynecol 1992;166:1339-44.
30. Boneva RS, Moore CA, Botto L, Wong LY, Erickson JD. Nausea during pregnancy and congenital heart defects: a population-based case control study. Am J Epidemiol 1999;149:717-25.
31. Brandes JM. First-trimester nausea and vomiting as related to outcome of pregnancy. Obstet Gynecol 1967;30:427-31.
32. Brown JE, Kahn ES, Hartman TJ. Profet, profits, and proof: do nausea and vomiting of early pregnancy protect women from "harmful" vegetables? Am J Obstet Gynecol 1997;176(1 Pt 1):179-81.
33. Chou FH, Lin LL, Cooney AT, Walker LO, Riggs MW. Psychosocial factors related to nausea, vomiting, and fatigue in early pregnancy. J Nurs Scholarsh 2003;35:119-25.
34. Crystal SR, Bowen DJ, Bernstein IL. Morning sickness and salt intake, food cravings and food aversion. Physio Behav 1999;67:181-7.
35. DiIorio C. First trimester nausea in pregnant teenagers: incidence, characteristics, intervention. Nurs Res 1985;34:372-4.
36. Fawcett J, York R. Spouses' physical and psychological symptoms during pregnancy and the postpartum. Nurs Res 1986;35:144-8.
37. Fenster L, Eskenazi B, Windham GC, Swan SH. Caffeine consumption during pregnancy and spontaneous abortion. Epidemiology 1991;2:168-74.
38. Jahangiri F, Hirshfeld-Cytron J, Goldman K, Pavone ME, Gerber S, Klock SC. Correlation between depression, anxiety, and nausea and vomiting during pregnancy in an in vitro fertilization population: a pilot study. J Psychosom Obstet Gynaecol 2011;32:113-8.
39. Klebanoff MA, Koslowe PA, Kaslow R, Rhoads GG. Epidemiology of vomiting in early pregnancy. Obstet Gynecol 1985;66:612-6.
40. Lindseth G, Vari P. Nausea and vomiting in late pregnancy. Health Care Women Int 2005;26:372-86.
41. Little RE, Hook EB. Maternal alcohol and tobacco consumption and their association with nausea and vomiting during pregnancy. Acta Obstet Gynecol Scand 1979;58:15-7.
42. Louik C, Hernandez-Diaz S, Werler MM, Mitchell AA. Nausea and vomiting in pregnancy: maternal characteristics and risk factors. Paediatr Perinat Epidemiol 2006;20:270-8.
43. Milkovich L, van den Berg BJ. An evaluation of the teratogenicity of certain antinauseant drugs. Am J Obstet Gynecol 1976;125:244-8.
44. O'Brien B, Zhou Q. Variables related to nausea and vomiting during pregnancy. Birth 1995;22:93-100.
45. Petitti DB. Nausea and pregnancy outcome. Birth 1986;13:223-6.
46. Semmens JP. Hyperemesis gravidarum evaluation and treatment. Obstet Gynecol 1957;9:586-94.
47. Speert H, Guttmacher AF. Frequency and significance of bleeding in early pregnancy. J Am Med Assoc 1954;155:712-5.
48. Tierson FD, Olsen CL, Hook EB. Nausea and vomiting of pregnancy and association with pregnancy outcome. Am J Obstet Gynecol 1986;155:1017-22.
49. Weigel MM, Weigel RM. Nausea and vomiting of early pregnancy and pregnancy outcome. An epidemiological study. BJOG: Int J Obstet Gynaecol 1989;96:1304-11.
50. Werler MM, Pober BR, Nelson K, Holmes LB. Reporting accuracy among mothers of malformed and nonmalformed infants. Am J Epidemiol 1989;129:415-21.
51. Yerushalmy J, Milkovich L. Evaluation of the teratogenic effect of meclizine in man. Am J Obstet Gynecol 1965;93:553-62.
52. Adams MM, Harlass FE, Sarno AP, Read JA, Rawlings JS. Antenatal hospitalization among enlisted servicewomen, 1987-1990. Obstet Gynecol 1994;84:35-9.
53. Bacak SJ, Callaghan WM, Dietz PM, Crouse C. Pregnancy-associated hospitalizations in the United States, 1999-2000. Am J Obstet Gynecol 2005;192:592-7.

54. Bennett TA, Kotelchuck M, Cox CE, Tucker MJ, Nadeau DA. Pregnancy-associated hospitalizations in the United States in 1991 and 1992: a comprehensive view of maternal morbidity. Am J Obstet Gynecol 1998;178:346-54.
55. Gazmararian JA, Petersen R, Jamieson DJ, Schild L, Adams MM, Deshpande AD, Franks AL. Hospitalizations during pregnancy among managed care enrollees. Obstet Gynecol 2002;100:94-100.
56. Hallak M, Tsalamandris K, Dombrowski MP, Isada NB, Pryde PG, Evans MI. Hyperemesis gravidarum. Effects on fetal outcome. J Reprod Med 1996;41:871-4.
57. Peckham CH. Observations on 60 Cases of hyperemesis gravidarum. Am J Obstet Gynecol 1929;17:776-88.
58. Reid DE, Teel HM. The treatment of the vomiting of early pregnancy. N Eng J Med 1938;218:109-13.
59. Scott CL, Chavez GF, Atrash HK, Taylor DJ, Shah RS, Rowley D. Hospitalizations for severe complications of pregnancy, 1987-1992. Obstet Gynecol 1997;90:225-9.
60. Tsang IS, Katz VL, Wells SD. Maternal and fetal outcomes in hyperemesis gravidarum. Int J Gynecol Obstet 1996;55:231-5.
61. Mori M, Amino N, Tamaki H, Miyai K, Tanizawa O. Morning sickness and thyroid function in normal pregnancy. Obstet Gynecol 1988;72(3 Pt 1):355-9.
62. Chou FH, Chen CH, Kuo SH, Tzeng YL. Experience of Taiwanese women living with nausea and vomiting during pregnancy. J Midwifery Womens Health 2006;51:370-5.
63. Chin RK. Antenatal complications and perinatal outcome in patients with nausea and vomiting-complicated pregnancy. Eur J Obstet Gynecol Reprod Biol 1989;33:215-9.
64. Chan OK, Sahota DS, Leung TY, Chan LW, Fung TY, Lau TK. Nausea and vomiting in health-related quality of life among Chinese pregnant women. Aust N Z J Obstet Gynaecol 2010;50:512-8.
65. Flaxman SM, Sherman PW. Morning sickness: a mechanism for protecting mother and embryo. Q Rev Biol 2000;75:113-48.
66. Hook EB. Dietary cravings and aversions during pregnancy. Am J Clin Nutr 1978;31:1355-62.
67. Weigel MM, Coe K, Castro NP, Caiza ME, Tello N, Reyes M. Food aversions and cravings during early pregnancy: association with nausea and vomiting. Ecol Food Nutr 2011;50:197-214.
68. Bayley TM, Dye L, Jones S, DeBono M, Hill AJ. Food cravings and aversions during pregnancy: relationships with nausea and vomiting. Appetite 2002;38:45-51.
69. Koren G, Clark S, Hankins GD, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. Am J Obstet Gynecol 2010;203:571 e1-7.