QUANTIFYING THE GLOBAL RATES OF NAUSEA AND VOMITING OF PREGNANCY: A META-ANALYSIS

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ABSTRACT

Background
Nausea and vomiting of pregnancy (NVP) is the most common medical condition in pregnancy, affecting women worldwide. It is unclear whether its prevalence and severity NVP are variable across different nations and races.

Purpose
To summarize global rates of NVP as reported in the literature using meta-analysis.

Methods
We searched Medline, Embase and Cochrane databases for all peer-reviewed articles reporting rates of NVP and/or hyperemesis gravidarum (HG). No restrictions were imposed on publication year or language. Numbers of women, studies and NVP rates were extracted and aggregated using a random effects model. Outcomes included: overall rates (i.e., women suffering any nausea or vomiting or both) in early and in late pregnancy, rates of nausea only, symptom severity, and HG rates.

Results
We identified 116 studies, rejecting 37 and accepting 79, of which 59 provided data for NVP (N=93,753 in 13 countries) and 26 for HG (N= 6,155,578). All developed regions of the world were represented (2 studies from Africa, 1 India; none from Latin America). Reported NVP rates varied from 35%-91% (median 69%); the meta-analytic average rate was 69.4% ($CI_{95\%}$:66.5%-72.3%). Among pregnant women, 32.7% had nausea without vomiting and 23.5% overall had NVP continuing into the third trimester. NVP was rated as mild in 40%, moderate in 46% and severe in 14% of cases. The prevalence of HG was 1.1% ($CI_{95\%}$:0.8%-1.3%), with a range of 0.3%-3.6%.

Conclusions
Almost 70% of women worldwide experience NVP, but reported rates vary widely. HG, the most severe form, affects 1.1%.

Key Words: *Nausea, vomiting, pregnancy, epidemiology, prevalence, burden of disease, meta-analysis*

Since the beginning of time, pregnant women have been reported to suffer from a syndrome variously known as morning sickness, pregnancy sickness, or nausea and vomiting of pregnancy (NVP).[1,2] Reported rates seem to vary widely as does the severity of symptoms. Some symptoms are so severe that women suffer life threatening dehydration and electrolyte imbalance requiring hospitalization, known as hyperemesis gravidarum (HG).[2-4]

All forms of NVP, especially HG, exert a negative impact on the quality of life of affected women.[5-8] As well, it impacts healthcare resources and their associated costs.[8-10] However, little information exists in the literature describing the burden of NVP and HG on healthcare systems. In

order to examine this burden, a precise estimate for the prevalence of each is required. Past reviews have summarized published studies, but none has provided such estimates.

The purpose of this research was therefore to quantitatively summarize reported rates of NVP in the peer-reviewed literature into a precise point estimate, along with a 95% confidence interval. Our objectives were to quantify the incidence of NVP by calculating the overall worldwide rates of a) NVP in early pregnancy and its severity, b) NVP in late pregnancy, c) women suffering from nausea only, and d) HG.

METHODS

Eligible were peer-reviewed articles that presented original research on pregnant women. We accepted papers in any language or published at any time. Posters or presentations at meetings were not accepted, nor were those presented only in abstract form or in books. The unit of analysis was the pregnancy, rather than births, since women could suffer NVP and subsequently experience a termination of that pregnancy; others could have multiple births from one pregnancy. Articles must have presented numbers of pregnant women and numbers who experienced NVP or HG.

For this research, the operational definition of NVP was the syndrome in pregnancy that involves any degree (or duration) of nausea with or without vomiting or retching at any time during pregnancy and which is not associated with other causal factors. HG, described as the most severe form of NVP, has been well recognized for thousands of years;[1] however, a precise definition has yet to be officially agreed upon.[11,12] Most definitions incorporate a constellation that includes severe persistent or intractable vomiting which occurs in early pregnancy and is not due to other factors.[11,13-18] Various cutoffs have been used for its timing such as <9 weeks,[14] <16 weeks,[15] and <20 weeks.[16] Not only are symptoms included in the constellation, but also associated outcomes that can be measured objectively including: dehydration,[14,16] electrolyte imbalance,[11,13,15-17] weight loss of >5%,[10,13,15,17,18] and a measure of starvation (ketonuria).[13,15,16-18] Hospitalization is often included, but is not an absolute requirement.[11,15,16] We therefore accepted all papers that claimed to examine HG using any reasonable definition.

Medline, Embase, and Cochrane databases were searched from inception to November 1, 2012. As well, references from retrieved articles were hand searched as were reviews of the subject. Data extracted included author, date, country, number of pregnant women studied, number reporting NVP, and severity of NVP, including HG. Where multiple rates were presented or where there could be overlap (e.g., reporting nausea ± vomiting and vomiting ± nausea), only the highest one was used to avoid duplication.

We pooled data for the following outcomes: NVP (i.e., nausea ± vomiting) in early pregnancy, nausea without vomiting in early pregnancy, NVP in late pregnancy and HG. These rates were aggregated across studies using the meta-analytic method for rates described by Einarson.[19] That method uses inverse variance weighting, giving greater weight to larger studies as well as incorporating between-study variance. The output is the weighted average rate and its standard error, from which 95% confidence intervals can be constructed. Additional descriptive statistics were also calculated for summary rates, such as raw average rate (i.e., sum of NVP cases/ total number of pregnancies), minimum, maximum, and median. As well, when severity of NVP was reported (i.e., as mild, moderate or severe), data were simply aggregated across studies.

RESULTS

The literature search identified 107 potential articles, 39 of which (36%) were rejected for the reasons specified in Table 1.[5,12,17,18,20-52] Overall, 75 studies were used in this research. There were 72 studies accepted for the main analyses, of which 55 provided data for NVP and 21 for HG (4 studies provided data for both). The 55 NVP studies examined 83,253 women from around the globe. The largest number of studies (n=28; 47%) originated in North America, 21 (36%) from Europe, 5 (8%) from Asia, 3 (5%) from Australasia and 2 (3%) from Africa.

TABLE 1 Rejected Studies (n=37) and Reasons for Rejection

Outcome	Reason for Rejection	First Author (year)
NVP	Patients were recruited based on having NVP (8)	Chou (2006)20, Chou (2008)21, Emelianova (1999)22, Fejzo (2008)23, Kuo (2007)24, Locock (2008)25, Mazzotta (2000)26, Munch (2011)2
	No appropriate data presented (8)	Corey (1992)27, Dickens (1970)28, Markl (2007)29, Markl (2008)30, Pepper (2006)31, Smith (2000)32, Tylden (1968)33, Zhang (1991)34
	Duplicate/overlapping data (4)	Chan (2010)35, Gadsby (1997)12, Klebanoff (1986)36, Weigel (1988)37
	Review (1)	Flaxman (2000)38
Hyperemesis gravidarum	Purposively recruited women with hyperemesis gravidarum in order to study the disease (13)	Bashiri (1995)39, Borgeat (1997)40, Depue (1987)41, Godsey (1991)42, Naef (1995)43, Nageotte (1996)17, Jørgensen (2012)44, Kuru (2012)45, Safari (1998)46, Saha (2011)47, Tan (2010)48, Uguz (2012)49, van Stuijvenberg (1995)50
	Duplicate or overlapping data (3)	Franks (1992)51, Trogstad (2005)18, Vilming (2000)52

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

First author (year)	Country	N	Number reporting NVP	Rate
Abraham (1994)[53]	Australia	100	62	62.0%
Ananth (1993) [54]	India	2,500	875	35.0%
Biggs (1975) [55]	Australia	116	73	62.9%
Boneva (1999)[56]	USA	4,027	2,854	70.9%
Brandes (1967)[57]	USA	7,027	5,117	72.8%
Brown (1997)[58]	USA	549	436	79.4%
Chan (2010)[6]	Hong Kong	396	360	90.9%
Chan (2011)[59]	USA	2,407	2,130	88.5%
Chin (1989)[60]	Hong Kong	1,453	1,092	75.2%
Chou (2003)[61]	USA	113	73	64.6%
Chou (2008)[62]	Taiwan	243	188	77.4%
Crystal (1999)[63]	USA	129	110	85.3%
Davies (1986)[64]	UK	212	125	59.0%
Diggory (1962)[65]	UK	100	88	88.0%
DiIorio (1985)[66]	USA	78	44	56.4%
Drake (1988)[67]	Canada	20	13	65.0%
Evans (1986)[68]	UK	342	284	83.0%
Fairburn (1990)[69]	UK	50	35	70.0%
Fairburn (1992)[70]	UK	100	91	91.0%
Fawcett (1986)[71]	USA	70	45	64.3%
Fenster (1991)[72]	USA	1,886	1,244	66.0%

First author (year)	Country	N	Number reporting NVP	Rate
Fitzgerald (1984)[73]	UK	86	63	73.3%
Gadsby (1993)[74]	UK	435	292	67.1%
Jahangiri (2011)[75]	USA	45	26	57.8%
Järnfelt-Samsioe (1983)[76]	Sweden	911	635	69.7%
Järnfelt-Samsioe (1985)[77]	Sweden	96	62	64.6%
Jinadu (1990)[78]	Nigeria	400	266	66.5%
Källén (2003)[79]	Sweden	3,675	2,906	79.1%
Klebanoff (1985)[80]	USA	8,007	4,507	56.3%
Kramer (2010)[81]	Canada	551	349	63.3%
Kricker (1986)[82]	Australia	429	303	70.6%
Kullander (1976)[83]	Sweden	6,578	4,599	69.9%
Lacasse (2009)[8]	Canada	367	288	78.5%
Lacroix (2000)[84]	Canada	160	118	73.8%
Lindseth (2005)[85]	USA	109	76	69.7%
Little (1979)[86]	USA	210	151	71.9%
Louik (2006)[87]	USA	22,487	14,998	66.7%
Masson (1985)[88]	UK	113	65	57.5%
McBride (1991)[89]	Canada	732	487	66.5%
Medalie (1957)[90]	Israel	100	71	71.0%
Meyer (1994)[91]	UK	1,513	1,195	79.0%
Milkovich (1976)[92]	USA	10,205	6,305	61.8%
Mori (1988)[93]	Japan	132	111	84.1%
O'Brien (1995)[94]	USA	126	81	64.3%
Paarlberg (1996)[95]	Netherlands	396	181	45.7%
Pettiti (1986)[96]	USA	1,933	1,318	68.2%
Robertson (1946)[97]	UK	100	57	57.0%
Semmens (1957)[98]	USA	2,500	1,091	43.6%
Speert (1954)[99]	USA	256	165	64.5%
Stewart (1988)[100]	UK	242	167	69.0%
Tierson (1986)[101]	USA	414	370	89.4%
Uddenberg (1971)[102]	Sweden	152	105	69.1%
Velacott (1988)[103]	UK	500	380	76.0%
Walker (1985)[104]	South Africa	1,771	1,070	60.4%
Weigel (1989)[105]	USA	903	626	69.3%
Werler (1989)[106]	USA	268	182	67.9%
Whitehead (1992)[107]	UK	984	827	84.0%
Wolkind (1978)[108]	UK	96	51	53.1%
Yerushalmy (1965)[109]	USA	3,853	2,740	71.1%

First author (year)	Country	N	Number reporting NVP	Rate
Total		93,753	62,623	66.8%
		Meta-analytic average rate		69.4%
			Standard error	1.5%
			Minimum	35.0%
			Maximum	91.0%
			Median	69%

NVP = nausea and/or vomiting of pregnancy

Table 2 summarizes published rates of nausea and vomiting in early pregnancy.[6,8,53-109] The meta-analytic summary rate of NVP was 69.4% ($CI_{95\%}$:66.5%-72.3%). That rate includes all women who suffered from any form of NVP, from mild nausea only to both severe nausea, vomiting and retching. Rates ranged from 35% to 91%, with a median of 69% (see Table 2). There was no correlation between sample size and NVP rate (r = -0.094, P = 0.497); neither sample size (r = 0.028, P = 0.839) nor NVP rate was related to publication year (r = 0.135, P = 0.332).

On the other hand, there were some geographical differences noted. The average of the rates reported from most of the developed countries fell within 5% of the meta-analytic average. That included Australia, Canada, Israel, Sweden, UK and USA. However, the countries in East Asia (i.e., Hong Kong, Taiwan and Japan) reported much higher rates ranging from 75% to91%. Two countries reporting exceptionally low rates were India (35%) and Netherlands (46%).

Reasons for any of these discrepancies could not be determined. There were 10 studies of 11,155 women who reported rates of nausea only (i.e., without vomiting), that appear in Table 3.[6,59,60,63,73,74,88,93,98] The meta-analytic average rate was 32.7% ($CI_{95\%}$: 21.7%-43.7%). Six studies involving 1342 women presented results according to the severity of the symptoms, categorizing them as either mild, moderate, or severe[6,8,62,63,81,97](See Table 4). Overall, the majority (60%) of the women rated their NVP as either moderate or severe, which indicates a serious health burden. Table 5 lists the studies that provided data from 2512 women describing NVP in late pregnancy.[75,81,85,91,100,108] The weighted average was 23.5% ($CI_{95\%}$: 12.8%-34.2%). Finally, 25 studies provided rates of HG for more than 6.1 million women. They are summarized in Table 6.[2,3,53,55,60,80,98,110-127]

DISCUSSION

Perhaps the most comprehensive previous review was that by Gadsby and Barnie-Adshead, which is available online.[128] Those authors reviewed 26 articles on NVP involving 39,710 women and 18 articles that examined 13,489 with HG, but did not pool results into point estimates. The present analysis retrieved 59 studies of NVP with 93,753 women and 25 studies of HG with more than 6.1 million. Thus, we have added to the literature and provided precise estimates for these outcomes.

Rates on NVP varied widely, from 35% to 91%, with higher rates reported in East Asian countries. Some variations could reflect bias due to sampling, timing of data collection, or methods of data collection. On the other and, they could be reflecting real differences due to genetics, ethnic or cultural differences, healthcare systems (or lack thereof). In order to address such differences, we did use random effects which does account, at least in part, for some of the differences among studies. Therefore, depending on the focus of future research, it might be advisable to use country specific values. It is noteworthy that few studies were produced in the least developed areas of the world. Aside from a single paper from India, there has been nothing from south or south-east Asia. No studies described rates of NVP in South America, and there were only two from Africa and one from India, thus precluding the majority of women worldwide, and concentrating on the have's rather on the have-nots. This lack of research in developing countries is most bothersome, as women in these regions have

many other risk factors for adverse pregnancy outcome.

In examining the literature on this topic, we became aware of a lack of standard definitions for many terms used in researching this topic. Neither NVP nor HG has a standard definition that is universally accepted. Official organizations need to generate suitable definitions and that such definitions should be used in the future. As well, different authors have defined early and late pregnancy in a variety of ways. Furthermore, standard (precise) definitions are needed for the descriptors mild, moderate and severe.

Not only do definitions vary, but also presentation of results. The ideal would be to present results using all four categories: no NVP, mild, moderate, severe. However, authors often combined categories such as none/mild or mild/moderate or moderate/severe. Such categorizations tend to create more confusion than clarity and prevent the combination of results.

Only a few studies have examined the impact of NVP on resource utilization and costs. The only paper to address NVP in general as well as HG was a Canadian study done by Piwko and coworkers in 2005.[10] However, they calculated only weekly costs and not the overall cost per patient, so projections to the population are difficult. HG has been examined in three additional papers. In the USA, Attard and colleagues[9] found quite similar results to those of Piwko.[10] Bailit and colleagues estimated that the total burden of HG in California during 1999 was $200 million.[113] Similarly, Gadsby and Barnie-Adshead calculated that HG cost the National Health Service of England £36.5 million during 2003/2004.[128] Little else has been done for a condition that is so widespread.

In observational studies, several authors have noted that appropriate treatment for NVP, especially preventive, is associated with a decrease in the severity of symptoms.[8,129-131] A randomized controlled trial of doxylamine plus vitamin B6 Diclectin®) has confirmed these observations.[132] Therefore, more research is needed in this area, as very little is presently known about this relatively common medical problem.

CONCLUSIONS

Precise rates of NVP and HG have been calculated. NVP affects about 70% of all women and appears to exert a huge burden on healthcare budgets. However, rates in most developing countries are not available. Its impact requires further investigation, especially in poor countries where women face many other risk factors for poor pregnancy outcome. HG affects about 1.1% of pregnant women and has severe consequences, but is impact on resources and costs has seldom been addressed. More research is needed due the widespread nature of these problems

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TABLE 3 Reported Rates of Women Having Only Nausea in Early Pregnancy

First author (year)	Country	N*	Number reporting nausea only	Rate
Chan (2010)[6]	Hong Kong	396	136	34.3%
Chan (2011)[59]	USA	2,405	849	35.3%
Chin (2008)[60]	Hong Kong	1,453	165	11.4%
Crystal (1999)[63]	USA	129	58	45.0%
Fitzgerald (1984)[73]	UK	86	39	45.3%
Gadsby (1993)[74]	UK	266	75	28.2%
Källén (2003)[79]	Sweden	3,675	1,443	39.3%
Masson (1985)[88]	UK	113	37	32.7%
Mori (1988)[93]	Japan	132	69	52.3%
Semmens (1957)[98]	USA	2,500	155	6.2%
Total		11,155	3,026	27.1%

Meta-analytic average rate	32.7%
Standard error	5.6%
Minimum	6.2%
Maximum	52.3%
Median	35%

TABLE 4 Reported Severity of Nausea and Vomiting in Early Pregnancy*

Author	N	mild	%	moderate	%	severe	%
Chan (2010)[6]	360	149	41%	205	57%	6	2%
Chou (2008)[62]	188	70	37%	88	47%	30	16%
Crystal (1999)[63]	110	35	32%	47	43%	28	25%
Kramer (2010)[81]	349	113	32%	132	38%	104	30%
Lacasse (2009)[8]	278	145	52%	126	45%	7	3%
Robertson (1946)[97]	57	31	54%	17	30%	9	16%
Total	1,342	543	40%	515	46%	184	14%

TABLE 5 Summary of Published Rates of Nausea and Vomiting in Late Pregnancy

First author (year)	Country	N	Number with NVP	Rate
Jahangiri (2011)[75]	USA	28	4	14.3%
Kramer (2010)[81]	Canada	575	261	45.4%
Lindseth (2005)[85]	USA	108	35	32.4%
Meyer (1994)[91]	UK	1,463	446	30.5%
Stewart (1988)[100]	England	135	32	23.7%
Stewart (1988)[100]	Scotland	107	9	8.4%
Wolkind (1978)[108]	UK	96	8	8.3%
		2,512	795	31.6%
		Meta-analytic average rate		23.5%
			Standard error	5.5%
			Minimum	8.3%
			Maximum	45.4%
			Median	23.7%

TABLE 6 Summary of reported rates of hyperemesis gravidarum

First author (year)	Country	Number with hyperemesis	Total number of women	Rate
Abraham (1994)[53]	Australia	2	100	2.0%
Adams (1994)[112]	USA	27	1,825	1.5%
Askling (1999)[113]	Sweden	8,186	1,027,213	0.8%
Bacak (2005)[114]	USA	820	68,514	1.2%
Bailit (2005)[115]	USA	2,466	520,739	0.5%
Bennett (1998)[116]	USA	6,377	579,742	1.1%
Biggs (1975)[56]	Australia	2	116	1.7%
Cedergren (2008)[117]	Sweden	7,938	781,725	1.0%
Chin (1989)[61]	Hong Kong	5	1,453	0.3%
Fairweather (1968)[2]	England	337	91,139	0.4%
Fell (2006)[118]	Canada	1,301	157,922	0.8%
Fischer-Rasmussen (1990)[119]	Sweden	30	6,700	0.4%
Fitzgerald (1956)[120]	Scotland	305	51,854	0.6%
Gadsby (1993)[75]	England	2	363	0.55%
Gazmararian (2002)[121]	USA	337	46,179	0.7%
Hallak (1996)[122]	USA	138	12,473	1.1%
Jimenez (2000)[123]	Canada	254	19,839	1.3%
Källén (1987)[124]	Sweden	3,068	989,073	0.3%
Källén (2003)[80]	Sweden	39	3,675	1.1%
Klebanoff (1985)[81]	USA	86	9,098	0.9%
Matsuo (2007)[125]	Japan	119	3,350	3.6%
Peckham (1929)[3]	USA	43	6,491	0.7%
Reid (1938)[126]	USA	176	27,275	0.6%
Scott (1997)[127]	USA	24,998	833,264	3.0%
Semmens (1957)[100]	USA	33	2,500	1.3%
Tsang (1996)[128]	USA	193	13,053	1.5%
Vikanes (2008)[129]	Norway	8,383	900,074	0.9%
		65,665	6,155,941	1.1%
			Meta-analytic average	1.0%
			Standard error	0.1%
			Minimum	0.3%
			Maximum	3.6%
			Median	0.9%

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