Matern Child Health J (2011) 15:122–127
DOI 10.1007/s10995-009-0548-0

Maternal Influences on Nausea and Vomiting in Early Pregnancy

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Published online: 11 December 2009

Abstract Symptoms of nausea and vomiting in early pregnancy (NVP) are common among pregnant women, but whether some women are more likely than others to experience these symptoms has not been well established. We examined potential risk factors for NVP symptom severity, timing of onset, and duration. We included 2,407 newly pregnant women who participated in a prospective cohort study on early pregnancy health between 2000 and 2004 in three U.S. cities. Data on NVP and other health information were collected through telephone interviews, early gestation ultrasound, and medical record abstractions. Generalized linear models were used to model possible risk factors for each NVP characteristic. Eighty-nine percent of women had NVP; for 99% of these, symptoms started in the first trimester. None of the characteristics examined were associated with having NVP. Among those with NVP, increasing risk of delayed symptoms onset was associated with advancing maternal age; increased risks were also seen among non-Hispanic Black [Risk ratio (RR) = 4.3, 95% confidence interval (CI): 1.6,11.6] and Hispanic women (RR = 2.3, 95% CI:0.4,11.5). NVP symptoms for multigravidae were more likely to last beyond the first trimester with each additional pregnancy. Most pregnant women experienced NVP. Nearly all of them, regardless of characteristics examined, had symptoms beginning in the first trimester. Maternal age, race/ethnicity, and gravidity were associated with delayed onset and symptoms that persisted into the second trimester.

Keywords Gravidity · Maternal nausea and vomiting · Pregnancy

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Introduction

Symptoms of nausea and vomiting in early pregnancy (NVP) affect 50–90% of women [1, 2], and often are the first indicator to a woman that she is pregnant. Timing of onset, duration and severity of symptoms differ among women and among individual pregnancies of the same women. NVP can begin as early as the second week of gestation [3, 4], often peaking in intensity between 8 and 12 weeks [5] and subsiding by the twentieth week of gestation [4, 6], yet 20–30% of pregnant women continue to experience symptoms beyond 20 weeks' gestation [3, 7, 8],

Hyperemesis gravidarum is the most severe form of NVP, which causes maternal weight loss, electrolyte imbalance, and dehydration [9] and is one of the most common reasons for hospitalization in pregnant women [10]. The etiology of NVP remains unclear, but rises in human chorionic gonadotropin (hCG) and estrogens are likely contributors [1, 2, 11–13], with thyroxine [11], prostaglandin E_2 [3], and prolactin [13] as possible additional contributing factors.

Risk factors or markers for NVP have not firmly been established. Some studies found that presence of NVP is associated with older maternal age, employment as manual or service workers, maternal cigarette smoking, and infant gender [14–16], although other studies have not replicated some of these associations [17, 18]. Hypertension, liver and renal diseases [14], vitamin use [15], and stress [16] have been shown to be related to the risk of NVP. Reproductive history including increasing gravidity [17], plurality [17, 19, 20], and having multiple prior miscarriages [17] have also been reported to increase the risk for NVP. Cigarette or marijuana smoking [21], being less educated [17], being African–American [17], being older, having higher parity, and gaining less weight during pregnancy [17] have been found to be associated with having late/delayed symptom onset. Few studies have examined risk factors and markers for long symptom duration, but one study found that long symptom duration, defined as symptoms that lasted more than 4 months (independent of timing of onset), was more common among younger women, women with multiple gestations, and among multigravidae [17]. As part of a prospective pregnancy cohort study, we investigated potential risk factors for the characteristics of NVP symptoms involving severity, timing of onset and duration.

Methods

Study Design and Population

Data for this study were collected from 2000 to 2004 as part of a prospective cohort epidemiologic study of drinking water disinfection by-products and spontaneous abortion (SAB). Details of this study are described elsewhere [22–24]. We recruited pregnant women from multiple community settings and prenatal care clinics in three US cities, who (1) were $\geq$18 years old and were $\leq$12 weeks' gestation or (2) were between 18 and 45 and trying to conceive a pregnancy for no more than 6 months, and subsequently became pregnant. Endovaginal ultrasound assessments were used to confirm the gestational age and the viability of the fetus around 8 weeks' gestation. Two telephone interviews were conducted, to ascertain information on maternal health behavior and current and past medical and reproductive histories, including NVP symptoms. This study was reviewed and approved by The UNC-Chapel Hill Public Health Institutional Review Board (study #06-0285).

Data Collection and Classification of NVP Symptoms

A woman was considered to have experienced symptoms of nausea if she reported "nausea or feeling sick to her stomach at any time" during the index pregnancy and to have experienced vomiting episodes if she "had nausea so bad that she vomited". Timing of onset (start of NVP symptoms) and ending dates were collected separately (month, day, and year) for symptoms of nausea and vomiting episodes. For those who were unable to recall the exact day of onset, we collected timing information with respect to "week in the month" and we imputed the day as the midpoint of the week.

For the purposes of this study, symptom severity was classified into no symptoms, nausea only, and nausea symptoms with vomiting episodes. Timing of onset was subdivided into "typical onset", defined in our study as symptom onset that took place prior to the start of the second trimester ($\leq$13 weeks gestation) and "delayed onset", which was defined as symptoms that started after the first trimester (>13 weeks gestation). Symptom duration was classified as symptoms in first trimester only and symptoms lasting beyond one trimester. Self-reported last menstrual period (LMP) was used to date the onset of pregnancy as we found the self-reported LMP in this cohort to be highly reliable and consistent with LMP dates assessed by ultrasound [23, 24], onset and duration of NVP symptoms are presented in gestational weeks, as calculated based on a woman's self-reported LMP .

Information on a wide range of potential risk factors for NVP was collected during the telephone interviews. Maternal characteristics included maternal age, maternal race/ethnicity, marital status, and education. Maternal health behaviors included cigarette smoking and alcohol use during pregnancy; reproductive and medical histories included age at menarche, gravidity and pregnancy loss history. We collected information on infant gender from medical records abstractions of women with live births.

Statistical Analysis

Because NVP symptoms are quite common, we estimated risk ratios (RRs) instead of odds ratios (ORs) [25] because the OR would overestimate the RR when greater than one or underestimate the RR when it is less than one. We used the modified Poisson regression with robust error variance [26] models in SAS 9.1 (SAS Institute Inc., Cary, NC) to generate the RRs for risk factors in relation to the timing of onset and two NVP symptoms outcomes.

Bivariate analyses were first conducted to examine each covariate and each outcome in order to reduce a list of potential risk factors for NVP; covariates were entered into the final models if they had a p-value of $p \leq 0.2$ or risk ratios (RR) of greater than two. Based on our strategies, variables retained in the three final models to predict NVP symptom severity, timing of onset, and duration included maternal age, maternal race and ethnicity, education, marital status, smoking, alcohol use, age at menarche, and pregnancy loss history. In a second set of analysis, we restricted the analysis to women with live births in order to examine the effects of infant gender on the characteristics of NVP.

Results

We enrolled 2,766 women into the study, with approximately 10% ($n = 252$) recruited before they became pregnant. Of the 2,766 women, 32 withdrew from the study. We excluded 227 women for reasons including ineligibility due to being greater than 12 weeks' gestation at the time of enrollment, being lost-to-follow-up, or relocating outside the study areas. We further excluded women with second or third study pregnancies to retain independence of observations ($n = 69$), with invalid key data elements for pregnancy dating ($n = 8$), or with multiple gestation pregnancies ($n = 23$), leaving 2,407 women for the final analysis.

The majority of the study participants were recruited from Raleigh (45.2%) or Memphis (37.3%). The mean age at enrollment was 27.8 years, and the mean gestational age at enrollment was 54.8 days. Non-Hispanic White women made up over 50% of the study population and 32% were non-Hispanic Black; nine percent were of Hispanic ethnicity with the majority of those (75.6%) from the Galveston area. Our study population consisted mostly of women who were college graduates (49.0%), married (66.0%), and non-smokers (94.5%) or did not consume alcohol during pregnancy (97.6%). Roughly half were primigravidae (49.5%).

Most study participants (88.5%) reported experiencing some form of NVP symptoms, with 35.3% having nausea symptoms only and 53.2% having nausea symptoms with vomiting episodes. Characteristics were similar in many respects for women who experienced any NVP symptoms and those who experienced no symptoms. No measured maternal sociodemographic, behavioral characteristics, reproductive, or medical histories were associated with having either nausea alone or nausea with vomiting (Table 1).

Among women with NVP symptoms, symptom onset for nausea and for vomiting was mostly concentrated between the second and the tenth week gestation [median = 5 weeks (nausea); median = 7 weeks (vomiting)], with only 1.1% ($n = 23$) reporting onset of symptoms after the first trimester (>13 weeks gestation) (data not shown).

Among women reporting any symptoms, the risk of delayed symptom onset increased in a dose–response manner with advancing maternal age [RR = 1.3, 95% CI: 0.4, 4.2 (30–34 years old); RR = 1.7, 95% CI: 0.4, 6.9 (≥35 years old), p for trend < 0.5] (data not shown), compared to women with typical symptom onset. The risk for delayed symptom onset was elevated, but imprecise, for non-Hispanic Black (RR = 4.3, 95% CI: 1.6, 11.6) and Hispanic women (RR = 2.3, 95% CI: 0.4, 11.5) (p for trend < 0.5). Women who began menstruating at 12 and 13 years old were almost three times (RR = 2.6, 95% CI: 0.7, 8.7) as likely as women who began menstruating at a later age (≥14 years old) to have delayed symptom onset. Effects by gravidity were not observed.

The median duration for NVP symptoms was 8 weeks. Few characteristics were associated with symptoms lasting beyond the first trimester (data not shown). Modified Poisson regression analysis showed that older (≥35 years old) (RR = 0.7, 95% CI: 0.6, 1.0), and non-Hispanic Black women (RR = 0.8, 95% CI: 0.7, 0.9) were less likely to experience symptoms that lasted beyond the first trimester. Conversely, the risk for longer symptom duration increased with gravidity [RR = 1.1, 95% CI: 1.0, 1.2 (gravidity = 2); RR = 1.2, 95% CI: 1.1, 1.3 (gravidity = 3); RR = 1.3, 95% CI: 1.1, 1.5 (gravidity ≥ 4)]. Additional analysis of the joint effects of symptom severity and duration found no associations in the effect estimates (data not shown).

To examine the effects of infant gender on the characteristics of NVP, we restricted the analysis to include women with singleton live births ($n = 2,149$). Infant gender (female baby compared to male baby) was not associated with symptom severity [OR = 1.0, 95% CI: 1.0, 1.1 (nausea); OR = 1.1, 95% CI: 1.0, 1.1 (nausea and vomiting)], delayed symptom onset (OR = 1.0, 95% CI: 0.9, 1.1), or symptom duration [OR = 1.0, 95% CI: 1.0, 1.1 (symptoms restricted to first trimester); OR = 1.1, 95% CI: 1.0, 1.3 (symptoms lasting beyond first trimester)].

Discussion

Eighty-nine percent of our study cohort reported having experienced symptoms of nausea with or without vomiting, which is higher than previously reported in prospective or retrospective cohort [5, 13, 27] and case–control studies [17]. This study, and one other prospective cohort study that captured a high prevalence of NVP [21], recruited and interviewed very early in pregnancy, which may have better captured early pregnancy conditions.

Table 1 Selected maternal characteristics by NVP symptoms, adjusted risk ratios (RR) and 95% confidence interval (CI) on maternal characteristics in relation with symptom severity: right from the start (2000–2004), $n = 2{,}407$

	Symptom severity[a]				
	No symptoms ($n = 279$)	Having nausea only ($n = 852$)		Having both symptoms of nausea and vomiting ($n = 1{,}274$)	
	n (%)	*n* (%)	Adj. RR[a,b] (95% CI)	*n* (%)	Adj. RR[b,c] (95% CI)
Maternal age					
<25 years old	76 (27.2)	159 (18.7)	1.0 (0.8, 1.3)	490 (38.5)	1.1 (1.0, 1.2)
25–29 years old	84 (30.1)	281 (33.1)	1.0 Reference	380 (29.7)	1.0 Reference
30–34 years old	70 (25.1)	279 (32.5)	1.0 (0.8, 1.2)	305 (23.9)	1.0 (0.9, 1.1)
≥35 years old	49 (17.6)	134 (15.7)	0.9 (0.8, 1.2)	99 (7.8)	0.8 (0.7, 0.9)
Race/ethnicity					
Non-Hispanic White	137 (49.1)	555 (65.2)	1.0 Reference	662 (51.2)	1.0 Reference
Non-Hispanic Black	112 (40.1)	213 (25.0)	0.9 (0.8, 1.0)	437 (34.4)	0.9 (0.9, 1.0)
Hispanic	22 (7.9)	56 (6.6)	0.9 (0.8, 1.1)	130 (10.1)	1.0 (0.9, 1.1)
Asian/other	8 (2.9)	27 (3.1)	1.0 (0.8, 1.2)	54 (4.3)	1.1 (1.0, 1.2)
Education					
<12 years	94 (33.7)	172 (20.2)	0.9 (0.8, 1.0)	446 (35.0)	1.0 (0.9, 1.1)
≥12 to <16 years	47 (16.9)	159 (18.7)	1.0 (0.9, 1.1)	310 (24.4)	1.1 (1.0, 1.2)
≥16 years	138 (49.5)	521 (61.2)	1.0 Reference	517 (40.6)	1.0 Reference
Marital status					
Married	169 (60.6)	658 (77.3)	1.0 Reference	758 (59.5)	1.0 Reference
Other	110 (39.4)	193 (22.7)	0.9 (0.8, 1.0)	516 (40.36)	1.0 (0.9, 1.0)
Smoking[b]					
Any	16 (5.8)	30 (3.5)	–	85 (6.7)	–
None	263 (94.3)	822 (96.5)	–	1,189 (93.3)	–
Alcohol use					
Any	11 (4.0)	22 (2.6)	0.8 (0.7, 1.1)	25 (2.0)	0.9 (0.7, 1.1)
None	266 (96.0)	830 (97.4)	1.0 Reference	1,249 (98.0)	1.0 Reference
Age at menarche					
≤11 years old	59 (21.5)	177 (21.0)	1.1 (1.0, 1.2)	295 (23.3)	1.0 (1.0, 1.1)
12–13 years old	132 (48.0)	460 (54.5)	1.1 (1.0, 1.2)	664 (52.4)	1.1 (1.0, 1.1)
≥14 years old	84 (30.7)	207 (24.5)	1.0 Reference	308 (24.3)	1.0 Reference
Pregnancy loss (SAB) history					
No prior SAB	88 (31.5)	244 (28.6)	1.0 Reference	387 (30.4)	1.0 Reference
≥1 pregnancy with no SAB	150 (53.8)	426 (50.0)	1.0 (0.9, 1.1)	601 (47.2)	1.0 (1.0, 1.1)
≥1 pregnancy with ≥1 SAB	41 (14.7)	182 (21.4)	1.1 (1.0, 1.2)	286 (22.5)	1.1 (1.0, 1.2)
Gravidity[b]					
Primigravid	93 (33.3)	251 (29.5)	–	403 (31.6)	–
2	89 (31.9)	282 (33.0)	–	373 (29.3)	–
3	45 (16.1)	170 (20.0)	–	254 (19.9)	–
≥4	52 (18.6)	149 (17.5)	–	244 (19.2)	–
Infant gender[d]					
Female baby	77 (42.1)	318 (46.5)	1.0 (1.0, 1.1)	582 (51.2)	1.1 (1.0, 1.1)
Male baby	106 (57.9)	366 (53.5)	1.0 Reference	554 (48.8)	1.0 Reference

NVP Nausea and vomiting during early pregnancy

[a] Cannot determine severity for $n = 2$ women

[b] Model adjusted for maternal age, race/ethnicity, education, marital status, alcohol use, age at menarche, and pregnancy loss history; smoking and gravidity were not retained in the final model based on pre-determined selection criteria outlined in "Methods" section

[c] Compared to women with no nausea and vomiting symptoms

[d] Analysis of infant gender was restricted to women with singleton live births ($n = 2{,}149$)

We found little to no association between all characteristics we examined and the risk for having symptoms of NVP, which supports some earlier studies reporting no association with younger maternal age [15, 17, 18, 28] and infant gender [17, 29], but inconsistent with other reports implicating infant gender [14, 18] and a history of miscarriages [17, 29].

Nausea or vomiting, for nearly all women with symptoms (99%), began at some point within the first trimester, primarily between the second and tenth week of gestation, and the few with later (delayed) onset were more likely to be non-Hispanic Black and women of Hispanic ethnicity, which agree with findings from an earlier study [17]. Our findings suggested a modest increase in risk for delayed symptom onset for women who began their menarche at 12 and 13 years old, a group that is over represented in our study population. While no earlier study had examined a woman's age at menarche and timing of NVP onset, our findings merit a further look to uncover the possible influences of having an earlier ($\leq$11 years old) or later ($\geq$14 years old) age of menarche on late pregnancy NVP symptom onset. All findings regarding delayed onset were imprecise, in part due to the small number of women with this condition. Our findings of elevated risk among multigravidae and among younger women (<25 years old), though marginal, supported the findings of one [17], but not another study [7].

One strength of this work is the use of data from a prospective cohort study of reproductive age women who were identified early in pregnancy or who were trying to conceive. This allowed us to collect information on maternal behaviors, reproductive and medical histories, and information on symptoms of nausea and vomiting early in pregnancy. Unlike most previous studies, we captured more precisely dates relating to NVP symptoms because we collected onset and ending dates independently for symptoms of nausea and vomiting episodes, by the month, day, and year around the time that the symptoms occurred, rather than having women recall them at a later time.

The information we collected allowed us to examine risk factors and markers for specific NVP symptom characteristics including severity, timing, and duration. Although no biologic specimens were collected, we were able to examine effects of important potential maternal and obstetric risk factors within the NVP subgroups.

Despite our enhanced protocol and intense effort to recruit women early into our study from communities and prenatal care clinics, limitations still exist with data collection. Although we interviewed 97% of the study cohort to assess NVP information prospectively and 3% retrospectively, we still had to impute the "day" for approximately one-fourth of women with NVP symptoms for either their onset and/or ending dates based on the responses provided for the "week in the month", introducing some error.

A woman's experience with nausea symptoms is inherently more subjective, while her experience with vomiting episodes is more objective. Therefore, some women with nausea symptoms may have been misclassified as having no symptoms and vice versa, though these classification errors for experiencing any vomiting seem unlikely. Our study did not measure the changes in forms of NVP symptoms; once a woman reported having either nausea only or nausea symptoms with accompanying vomiting episodes, we made the assumption that her symptom severity to be constant throughout the pregnancy (i.e. always nausea only or always both symptoms).

In this study, we collected a limited amount of information concerning medical treatment and weight loss and weight gain as a result of NVP; thereby we were unable to evaluate hyperemesis gravidarum, a relatively rare event. From our data, only 20% of 2,149 women with NVP symptoms ($n = 430$) self-reported having contacted their clinicians and only 30 of 430 women (7%) reported being hospitalized for NVP symptoms. Some of these cases, if furthered investigated, may have been classified as hyperemesis gravidarum.

We collected limited data on antiemetic treatment. Roughly 16% ($n = 344$) reported using antiemetic treatments, with a higher report on prescription medication use ($n = 200$) than over-the-counter medication ($n = 144$). While women who used antiemetic treatments at some point during their pregnancy had a slightly shorter duration of NVP symptoms (median = 9.8 weeks without use; median = 9.1 weeks with use), the effect of antiemetic treatments on the duration of NVP cannot be evaluated, given no information is available on the timing of antiemetic treatments.

Our study found a higher NVP prevalence in pregnant women than previously reported and that a few, if any, characteristics of pregnant women placed them at a greater risk for its occurrence. Further studies may shed more light on risk factors for a small percentage who experienced delayed onset or longer symptom duration. While NVP in pregnancy is a natural phenomenon, findings from this study provided some more understanding on the potential risk factors associated with these pregnancy symptoms and may help health care providers to better educate pregnant women about NVP and treatment options.

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