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Review

The protective effects of nausea and vomiting of pregnancy against adverse fetal outcome—A systematic review

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ABSTRACT

Studies have suggested that nausea and vomiting of pregnancy (NVP) may confer favorable pregnancy outcome, when compared to women not experiencing NVP. However, this was never examined systematically.

Methods: We systematically reviewed all human studies examining potential effects of NVP on rates of miscarriage, intrauterine growth restriction, congenital malformations, prematurity and developmental achievements.

Results: Our analysis reveals a consistent favorable effect of NVP on rates of miscarriages, congenital malformations, prematurity, and developmental achievements. The effect size was clinically important for miscarriage, malformations and prematurity. In a few studies the protective effects were more prominent in women with moderate–severe NVP than among those with mild or no NVP.

Conclusions: NVP is associated with favorable fetal outcome, and therefore studies of drug exposure in pregnancy should either match their exposed and control cases for existence and severity of NVP, or adjust for these confounders in their multivariate analysis.

Contents

1. Introduction

Nausea and vomiting of pregnancy (NVP) affects up to 85% of pregnant women, ranging from mild to the extremely severe form of hyperemesis gravidarum (HG) [1]. NVP is treated symptomatically with different antiemetics and antacid medications [2]. This condition typically starts before 9 weeks of gestation and subsides by the end of the first trimester, although, in up to 25% of women it continues into the second trimester and for a few into the third

Abbreviations: NVP, nausea and vomiting of pregnancy; aOR, adjusted odds ratio; OR, odds ratio; CI, confidence interval; SGA, small for gestational age.

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trimester or in severe cases it often subsides only when the placenta is delivered.

In the past, some studies suggested that women experiencing NVP may have favorable pregnancy outcome [3]. However, presently no systematic review has been conducted examining different teratological outcomes. The objective of the present study was to review the available evidence in order to verify which, if any, pregnancy outcome is affected by NVP.

2. Methods

A search was conducted using PubMed-Medline and EMBASE from inception to January 10, 2014, to identify all epidemiological studies which analyzed the potential effects of NVP on rates of adverse pregnancy outcomes. The terms used in the search were: NVP, morning sickness, pregnancy, congenital malformations, congenital defects, congenital anomalies, prematurity, miscarriages, spontaneous abortions, development, and developmental delay. Accepted papers had to adjust in their analysis for potential confounders among those who received or did not receive antiemetic treatment for NVP. Inclusion criteria included cohort or case–control studies, in any language, comparing rates of any adverse pregnancy outcome between a group of women experiencing NVP vs. a group not experiencing it.

Abstracts were reviewed for inclusion by two independent reviewers. Accepted studies were reviewed and summarized as to the existence, or lack of, relationship between NVP and the different pregnancy outcomes, and the epidemiological characteristics of these relationships. Pregnancy outcomes included miscarriages, preterm delivery, intrauterine growth restriction, major congenital malformations and long term neuro-developmental outcome.

3. Results

A total of 2387 articles were retrieved, and out of them 16 papers were reviewed. Ten publications met the inclusion criteria, measuring different parameters of fetal outcomes as listed in Table 1.

3.1. NVP and miscarriage rates

Chan et al. [4] examined the severity and duration of NVP symptoms in relation to the occurrence of miscarriage. The study analyzed data from 2407 pregnant women collected in three US cities between 2000 and 2004 through interviews, ultrasound assessments and medical records. Lack of NVP symptoms was associated with increased risk for miscarriage [adjusted odds ratio (aOR) = 3.2, 95% confidence interval (CI) = 2.4–4.3], compared with pregnant women having any NVP symptoms. When analyzing the

Table 1
Summary of the studies systematically reviewed for the effect of nausea and vomiting of pregnancy on fetal outcome.

Author and year [reference]	Number of pregnancies analyzed	Type of fetal outcome studied	Main results
Chan et al., 2010 [4]	2407 pregnant women	Miscarriage (spontaneous pregnancy loss)	Protective effect of NVP symptoms in ≥35 years age group for miscarriage [OR = 0.2, 95% CI: (0.1, 0.8)]; increased risk for miscarriage [adjusted odds ratio (OR) = 3.2, 95% (CI): (2.4, 4.3)] with lack of NVP symptoms.
Weigel et al., 2006 [5]	849 pregnant women	Miscarriage	Protective effect of nausea only (aOR = 0.45, 95% CI = 0.22–0.94) or nausea with vomiting (aOR = 0.66, 95% CI = 0.46–0.99) on miscarriage
Czeizel et al., 2006 [6]	22,843 cases with congenital abnormality: 1713 cases, mothers had severe NVP; matched population controls: 3777 had mothers with severe NVP from Hungarian Case-Control Surveillance Registry for Congenital Malformations	25 different congenital abnormalities	Protective effect of NVP in early pregnancy (mothers of cases with congenital abnormalities were 26% less likely to have severe NVP in early pregnancy than the mothers of population controls without congenital abnormalities).
Asker et al., 2005 [7]	29,804 pregnant women with 31,130 infants with reported use of antiemetic drugs from Swedish Medical Birth Register	Congenital abnormalities, low birth weight, prematurity, SGA	Reduced neonatal risk for adverse pregnancy outcome in pregnancies where any antiemetic was used for NVP.
Kallen et al., 2003 [8]	16,536 delivery outcomes of women exposed to meclozine and 540,660 controls	Congenital abnormalities, low birth weight, prematurity, SGA, small head circumference, short body length	Reduced neonatal risk for adverse pregnancy outcome in pregnancies exposed to meclozine for NVP.
Kallen et al., 2002 [9]	17,266 women with 17,776 deliveries and 18,197 infants exposed to antihistamines during pregnancy for NVP or allergies	Congenital abnormalities, low birth weight, prematurity, SGA	Reduced risk for adverse fetal outcomes in pregnancies exposed to antihistamines because of NVP compared to those with allergies.
Seto, 1992 [10]	170,000 cases exposed to antihistamines in the first trimester, a meta-analysis of 24 studies	Major congenital malformations	Reduced risk from major malformations summary OR = 0.76 (95% CI: 0.60–0.94)
Anderka et al., 2012 [11]	4524 cases and 5859 controls from National Birth Defects Prevention study	Nonsyndromic cleft lip with or without cleft palate [CL/P], cleft palate alone [CP], neural tube defects, and hypospadias	Reduced risk for CL/P (aOR = 0.87, 95% CI, 0.77–0.98) and for hypospadias (aOR = 0.84, 95% CI, 0.72–0.98) in pregnancies with NVP.
Czeizel et al., 2004 [12]	38,151 controls, 3869 of them with NVP from Hungarian Case-Control Surveillance Registry for Congenital Malformations	Preterm birth and low birth weight	Reduced risk for preterm birth OR = 0.76 (95% CI, 0.65–0.89) among mothers with NVP. No statistical difference between studied groups for low birth weight.
Nulman et al., 2009 [13]	45 born to mothers who had NVP and were exposed to Diclectin®, 47 with mothers who had NVP but no Diclectin® exposure, and 29 born to mothers without NVP	Long term child development	Children exposed to NVP scored significantly higher on performance IQ ($P < 0.02$), NEPSY verbal fluency ($P < 0.003$) and phonological processing ($P < 0.004$), and McCarthy numerical memory ($P < 0.004$).

SGA = small for gestational age.