

BMJ Open Association between vomiting in the first trimester and preterm birth: a retrospective birth cohort study in Wuhan, China

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ABSTRACT

Objective Although vomiting in the first trimester has been reported to be associated with preterm birth (PTB), findings supporting this association remain inconsistent. Our aim was to assess the association between vomiting and PTB, as well as evaluate if the association is modified by pre-pregnancy body mass index (BMI).

Design A retrospective cohort study.

Setting Wuhan, a central city of China.

Participants A total of 317 463 pregnant women who had a live, singleton newborn from 1 January 2010 to 23 May 2016 were enrolled in our study.

Main outcome measure PTB was defined as gestational age <37 gestational weeks. Gestational age was calculated using reports from mothers based on the first day of their last menstrual period. An ultrasound was routinely used to determine gestational age before 12 gestational weeks.

Results Of the 317 463 pregnant women, 29.88% (94 857) experienced vomiting in the first trimester and 5.00% (15 889) experienced a PTB. Vomiting in the first trimester increased the risk for PTB and the multivariable adjusted OR was 1.05 (95% CI 1.02 to 1.09). In the stratified analyses, the association of vomiting in the first trimester was significant among underweight women (adjusted OR=1.08, 95% CI 1.04 to 1.17) and normal pre-pregnancy BMI women (adjusted OR=1.06, 95% CI 1.02 to 1.11), but not in overweight women (adjusted OR=1.01, 95% CI 0.90 to 1.14) and obese women (adjusted OR=0.93, 95% CI 0.73 to 1.19).

Conclusions Our study indicates that vomiting in the first trimester was associated with PTB. Additionally, women with underweight and normal pre-pregnancy BMI who experienced vomiting are more likely to have a PTB.

INTRODUCTION

Nausea and vomiting in pregnancy (NVP) is a collection of symptoms composed of nausea alone or nausea in combination with vomiting.¹ This condition typically starts prior to 9 weeks of gestation and subsides by the end of the first trimester; however, this condition has been shown to continue into the second trimester in up to 25% of pregnant women

Strengths and limitations of this study

- The present study is a cohort study, which enrolled a large population of 317 463 pregnant women.
- This is the first study exploring the relationship between vomiting in the first trimester and preterm birth (PTB) in Chinese women by pre-pregnancy body mass index (BMI) status.
- Vomiting symptoms were based on self-reported data, which may be a possible source of bias.
- The prevalence of overweight and obesity was relatively low in our sample, and the relationship between vomiting and PTB in women with a high pre-pregnancy BMI needs to be further assessed.

and for 0.3%–2.3% into the third trimester.² NVP has an important effect on both individuals and society as it causes emotional distress, depression and can have a negative effect on a woman's activities and relationships.^{3,4} NVP also has been found to lead to loss of time at work and a decrease in job productivity.⁵ The aetiology of NVP remains unknown, although it is currently believed to be related to early pregnancy hormones.⁶

Almost 70% of women worldwide experience NVP.⁷ The average rate of vomiting only in early pregnancy is 47.1%, and the reported rates generally range from 22.3% to 63.5%.⁸ A Norwegian cohort investigation reported that the rate of NVP was 33% among 51 675 women.⁹ Källén *et al* studied the occurrence of NVP via questionnaires in 3675 Swedish pregnant women and observed that 38.3% of pregnant women reported vomiting in early pregnancy.¹⁰ One previous meta-analysis, which included 23 studies comprising 67 602 women,¹¹ estimated the rate of NVP in the USA to be as high as 68.6%. Meanwhile, studies on the rate of NVP in China are few and are limited by their small sample sizes.

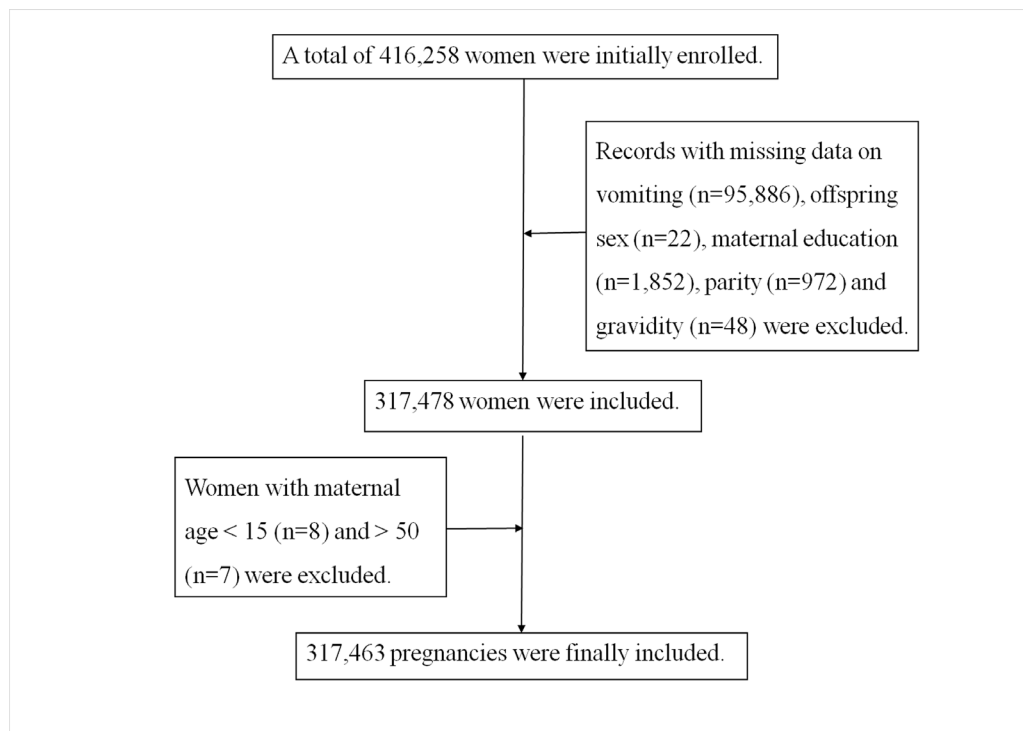


Figure 1 Flow chart of population selection.

Chin¹² conducted a study in a district hospital in Hong Kong in 1989 and found that the incidence of NVP was 74.9% among 1453 patients. Another cross-sectional study conducted in a university obstetric unit in Hong Kong revealed that the prevalence of NVP was 90.9% among 396 women.¹³

In previous studies, NVP was not found to be associated with primary maternal diseases such as gastrointestinal infections or allergies.⁸ Recently, there was a resurgence of interest in topics related to NVP, such as death,¹⁴ pregnancy complications¹⁵ and birth outcomes.¹⁶ Some studies reported that women with NVP were more likely to have a preterm birth (PTB) compared with symptom-free women.^{15 17 18} Still, other studies have found no association between this phenomenon.^{6 19} However, Czeizel and Puhó have suggested that women with NVP had a lower risk of PTB.²⁰ A Norway prospective cohort study involving 51 675 pregnant women found nausea to decrease the risk for PTB by 14% but did not find NVP associated with PTB.⁹

To our knowledge, there has been only one case-control study, which was conducted in Chinese pregnant women, that addressed the relationship between PTB and a severe form of NVP called *hyperemesis gravidarum*.¹⁹ Information about the association between vomiting in the first trimester and risk of PTB in China is unclear. Furthermore, there has not been a study in which the population was grouped according to pre-pregnancy body mass index (BMI) to determine its contribution to the identification of the association between NVP and risk of PTB. Thus, our objective in the present study is to explore the association between vomiting in the first

trimester and PTB as well as assess whether pre-pregnancy BMI modifies this association using a birth cohort study in Wuhan, China.

MATERIALS AND METHODS

Study population

A retrospective cohort study was conducted in Wuhan China, using data from the Wuhan Maternal and Child Health Management Information System (WMCHMIS). The WMCHMIS was introduced in our previous study.²¹ Enrolled women included every pregnant woman who had a live, singleton newborn from 1 January 2010 to 23 May 2016. The study has been approved by the Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital).

A total of 416 258 women were initially enrolled. We then excluded records with missing data on vomiting (n=95 886), offspring sex (n=22), maternal education (n=1852), parity (n=972) and gravidity (n=48). Moreover, we also excluded those with a maternal age less than 15 (n=8) and more than 50 (n=7). The final study population consisted of 317 463 pregnancies or 76.27% of the initial population.

Variables

Vomiting in the first trimester was assessed when pregnant women first visited the women and children health-care centres. Maternal age, education, parity, gravidity, pre-pregnancy weight and height were self-reported at their first antenatal care visit, whereas offspring sex and other obstetric information were provided by midwives

Table 1 Characteristics of women and infants

	Preterm (n=15 889, 5.00%)		Full-term (n=301 574, 95.00%)		p Value
	n	%	n	%	
Age at delivery					
<25	3091	3.62	82 224	96.38	<0.001
25–34	11 055	5.17	202 692	94.83	
≥35	1743	9.47	16 658	90.53	
Education level					
Less than high school	3519	4.55	73 737	95.45	<0.001
High school	5010	4.71	101 458	95.29	
College	7360	5.50	126 379	94.50	
Offspring sex					
Male	9188	5.41	160 671	94.59	<0.001
Female	6701	4.54	140 903	95.46	
Parity					
Nullipara	11 948	4.65	245 121	95.35	<0.001
Multipara	3941	6.53	56 453	93.47	
Gravidity					
<3	11 471	4.59	238 259	95.41	<0.001
≥3	4418	6.52	63 315	93.48	
Pre-pregnancy BMI (kg/m²)					
Underweight (<18.5)	3118	4.21	70 916	95.79	<0.001
Normal (18.5–23.9)	11 083	5.03	209 246	94.97	
Overweight (24–27.9)	1360	6.94	18 226	93.06	
Obese (≥28)	328	9.33	3186	90.67	
Vomiting					
Yes	4978	5.25	89 879	94.75	<0.001
No	10 911	4.90	211 695	95.10	

BMI, body mass index.

documented in WMCHMIS. Information was audited by clinicians and obstetric nurses, and a warning would be activated when illogical data were input into WMCHMIS.

Vomiting was dichotomised into yes and no response formats. Maternal age was categorised into three groups: younger than 25, 25–34 years and 35 years and older. A proxy for socioeconomic status was the maternal education which was categorised into three groups: less than high school, high school and college. By parity, women were dichotomised into nullipara and multipara. Regarding gravidity, it was divided into less than three times and three times and more. Pre-pregnancy BMI was calculated as weight/height² and grouped into four categories according to Chinese standard of weight for adults.²²

The main outcome variable was PTB. PTB was defined as gestational age <37 gestational weeks.²³ Gestational age was calculated using reports from mothers based on the

first day of their last menstrual period. An ultrasound was routinely used to determine gestational age before 12 gestational weeks.

Statistical analysis

Results were presented as frequencies (%). Difference between PTB group and full-term group was assessed by X² tests. A logistic regression model was used to estimate the association between vomiting in the first trimester and PTB. Results were adjusted for confounders including maternal age, education, parity, gravidity, pre-pregnancy BMI and offspring sex in accordance with previous studies.^{9 24} We also employed a stratified analysis by pre-pregnancy BMI, and the confounders adjusted in stratified analysis were maternal age, education, parity, gravidity and offspring sex. Crude and adjusted ORs statistics, as well as a 95% CI, were calculated. All statistical analyses were performed using SAS V.9.2 (SAS Statistical Institute).

Table 2 Association between vomiting and PTB and its association stratified by pre-pregnancy BMI

	Preterm, n (%)	Full-term, n (%)	Unadjusted OR (95% CI)	p Value	Adjusted OR (95% CI)*	p Value
Vomiting						
Yes	4978 (5.25)	89 879 (94.75)	1.08 (1.04 to 1.11)	<0.001	1.05 (1.02 to 1.09)	0.0048*
No	10911 (4.90)	211 695 (95.10)	1.00		1.00	
Underweight						
Vomiting						
Yes	810 (4.49)	17 216 (95.56)	1.08 (1.05 to 1.17)	0.0042	1.08 (1.04 to 1.17)	0.0082†
No	2308 (4.12)	53 700 (95.86)	1.00		1.00	
Normal						
Vomiting						
Yes	3610 (5.22)	65 485 (94.78)	1.06 (1.04 to 1.11)	0.0048	1.06 (1.02 to 1.01)	0.0058†
No	7473 (4.94)	143 761 (95.06)	1.00		1.00	
Overweight						
Vomiting						
Yes	462 (7.04)	6099 (92.96)	1.02 (0.91 to 1.15)	0.7012	1.01 (0.90 to 1.14)	0.8547†
No	898 (6.89)	12 127 (93.11)	1.00		1.00	
Obese						
Vomiting						
Yes	106 (8.95)	1079 (91.05)	0.93 (0.73 to 1.19)	0.5719	0.93 (0.73 to 1.19)	0.5508†
No	222 (9.53)	2107 (90.47)	1.00		1.00	

*Adjusted for maternal age, education, parity, gravidity, pre-pregnancy BMI and offspring sex.

†Adjusted for maternal age, education, parity, gravidity and offspring sex.

RESULTS

In 317 463 pregnancies included in our study (figure 1), gestational age ranged from 28 weeks to 43 weeks. Altogether, 94 857 out of 317 463 pregnant women (29.88%) reported vomiting in the first trimester. Further, 5.00% (15 889) of the births were delivered preterm. Maternal demographics and characteristics are shown in table 1. Women who were older than 35 years, had a college education, were multipara, had more than three times gravidity or had a higher pre-pregnancy BMI were more likely to have a PTB. PTB was observed to be more common in female babies than in male offspring.

When vomiting women were compared with non-vomiting women, we found that vomiting in the first trimester produced a significant increase in risk for PTB, with OR=1.08 and 95% CI 1.04 to 1.13. The relationship still persisted (OR=1.05, 95% CI 1.02 to 1.09, table 2) after adjustment for aforementioned confounders. In the additional stratified analyses, the results showed that vomiting in the first trimester was associated with PTB in underweight women (OR=1.08, 95% CI 1.04 to 1.17) and in women with a normal pre-pregnancy BMI (OR=1.06, 95% CI 1.02 to 1.11), but not among overweight and obese groups. After adjusting for the same set of confounders, no changes occurred in the results (table 2).

Additionally, we assessed the associations of maternal age, education, parity, gravidity, pre-pregnancy BMI and offspring sex with risk of PTB. PTB was associated with all of the evaluated exposures (online supplementary table S1).

DISCUSSION

NVP while pregnant has far reaching effects on the mental and physical health of mothers and their offspring. Little research has accrued on the association between NVP and PTB in China, especially taking into account pre-pregnancy BMI. This study showed that nearly 30% of Chinese pregnant women had experienced vomiting in the first trimester. The rate of vomiting in Chinese women was somewhat different than in other studies.^{9 11 25-27} A Norwegian cohort study reported that the rate of NVP was 33% among 51 675 women with 15 gestational weeks,⁹ which was higher than our findings. A previous meta-analysis estimated that the rate of NVP in the USA was 68.6% including 23 studies composed of 67 602 women.¹¹ Conflicting results can likely be explained by heterogeneity of populations, methods, definitions and confounders.

Our results showed that sociodemographic factors, such as age, education level, parity and gravidity, might influence PTB. Previous studies have indicated that women with advanced maternal age were associated with increased risk of PTB.^{28 29} Araya *et al* reported that age >35 years, delivery of more than two fetuses and <8 years of education were risk factors for PTB.²⁹ Women aged >35 years had longer exposure times to chronic pathologies and unhealthy lifestyles³⁰ and higher prevalence of maternal obesity in older mothers, which were associated with risk factors for PTB.³¹ Several studies demonstrated that the lower the socioeconomic and education level, the

higher the probability of developing infection, and that was clearly associated with PTB before 30 weeks of gestation.^{32 33}

In this large cohort study conducted among Chinese women, we have found an association between vomiting in the first trimester and PTB before 37 weeks of gestation. When compared with non-vomiting pregnant women, women who experienced vomiting were at an increased risk of PTB. Our results were inconsistent with that of other studies.^{15 18 34 35} For example, Czeizel and Puhó indicated that there was a significant association of vomiting with a decreased risk of PTB,²⁰ and Naumans *et al* found that vomiting was not associated with PTB.²⁷ The differences found among these studies may be attributed to race, definition or classification of vomiting and the differential sample sizes of the populations mentioned above.

The possible causal link between vomiting and PTB remains elusive. The most common hypothesis proffered to explain the harmful effects of vomiting is based on the fact that vomiting leads to abnormal digestive function, which results in a lower nutrient intake of pregnant women.^{14 36} Vomiting may also affect maternal and fetal physiology through dehydration and the modulation of stress-related risk factors.^{37 38} Moreover, vomiting may cause low maternal weight gain during pregnancy, which has been associated with PTB as reported by Canadian research.⁶

Additionally, our results reveal that vomiting was a risk factor for PTB in women with underweight and normal pre-pregnancy BMI, but not in overweight and obese women. Previous studies have estimated the risk factors for vomiting and PTB separately and found different effects of pre-pregnancy BMI on vomiting and PTB.^{39–41} No study has assessed the association between vomiting and PTB by pre-pregnancy BMI. The biological mechanisms underlying the associations with maternal pre-pregnancy BMIs remain unclear. Shaw *et al* indicated that the relationship between pre-pregnancy BMI and risk of PTB was complex.²³ Although it was not statistically significant, a trend towards lower risk for PTB in obese women with vomiting was observed. We speculate that vomiting may have relatively few impacts on the nutrition of obese women due to their increased capacity for energy storage.

Strengths of this study are as follows. First, this is the first study exploring the relationship between vomiting in the first trimester and PTB in Chinese women while assessing the association between PTB and vomiting by pre-pregnancy BMI status. Second, the data were collected from the large population-based cohort and linked to the WMCHMIS, providing thorough and detailed access to pregnancy and birth outcomes. Third, with such a large cohort size, many significant associations tend to appear, and the merit of these in the clinical setting is notable. However, there are two limitations. One is the reliance on self-reported data on vomiting. Retrospective evaluation of vomiting symptoms has been reported as a possible source of bias.⁴² The other is that the prevalence

of overweight and obesity was relatively low in our sample (6.17% and 1.10%, respectively), and the relationship between vomiting and PTB in women with a high pre-pregnancy BMI needs to be further assessed.

CONCLUSION

This study showed that vomiting presented an increased risk for PTB based on a large cohort study in China, although the effect was small. Vomiting was a risk for PTB in women who were underweight and normal weight based on their pre-pregnancy BMI. Although no significant association between vomiting and PTB in overweight and obese women was observed, clinicians should give all women suitable guidance for dealing with vomiting to ensure improved pregnancy outcomes. Finally, we recognise the need for greater clarity with respect to the association between vomiting and PTB and encourage researchers to build on our findings.

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Contributors RH, YC and BZ designed the research. YC, YZ and ML analysed the data. RH, YC and YL drafted the manuscript. ZQ, MG, SX, TZ and BZ revised the manuscript.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The Institutional Review Board of Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital) received and approved this study (approved on 13 October 2016).

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