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Prepregnancy maternal body mass index and venous thromboembolism: A population based cohort study

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Abstract

Objective: To assess the relationship between maternal body mass index (BMI) and pregnancy-related venous thromboembolism (VTE).

Design: Cohort study.

Setting & population: 2,449,133 women with singleton pregnancies who underwent delivery hospitalization in California between 2008 and 2012.

Methods: Association of prepregnancy BMI and the risk of an antepartum and postpartum VTE was examined using logistic regression, with normal BMI as reference.

Main outcome measures: Antepartum and postpartum VTE related hospitalization.

Results: The prevalences of antepartum and postpartum VTE increased with increasing BMI (antepartum: 2.3, 3.0, 3.8, 4.2, 4.7, and 10.6 per 10 000 women for underweight, normal BMI, overweight, obesity class I, II, and III, $P<0.001$. postpartum: 2.0, 3.1, 3.9, 5.6, 9.0, and 13.2 per 10 000 women, $P<0.01$). The adjusted odds of antepartum and postpartum VTE increased

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progressively with increasing BMI, and obesity class III women being at highest risk of pregnancy-related VTE compared with normal BMI women: adjusted odds ratio (OR) for antepartum VTE: 2.9; 95% CI 2.2–3.8 and adjusted OR for postpartum VTE: 3.6; 95% CI 2.9–4.6.

Conclusions: Our findings clearly demonstrate an increasing risk of pregnancy-related VTE with increasing BMI.

Tweetable abstract

Obesity was associated with increased odds of antepartum and postpartum venous thromboembolism.

Keywords

Antepartum; Body mass index; Delivery; Postpartum; Pregnancy; Venous thromboembolism

Introduction:

Venous thromboembolism (VTE) is a leading cause of maternal death in well-resourced countries. In the United States (US), VTE accounted for 9.2% of deaths between 2011 and 2013.¹ In the United Kingdom, VTE remains the leading cause of direct maternal deaths, accounting for 1.1 deaths per 100,000 maternities between 2013 and 2015.² Consequently, identifying women at risk for pregnancy-related VTE is a maternal health priority.

Prior epidemiological studies have identified obesity as a risk factor for antepartum VTE^{3–7} and postpartum VTE^{5–10}. Less clear is the independent effect of maternal BMI on VTE. This is of important clinical relevance because BMI-specific recommendations for VTE prevention are limited and inconsistent. For example, the Royal College of Obstetricians and Gynaecologists (RCOG) recommend postpartum thromboprophylaxis if obesity is present with 3 other VTE risk factors.¹¹ In contrast, the American College of Obstetricians and Gynecologists (ACOG) provide no recommendations for postpartum thromboprophylaxis according to maternal BMI.¹² Given these aforementioned concerns and the fact that a disproportionate number of deaths from VTE occur in obese or overweight women,¹³ a detailed examination of the independent effects of maternal BMI on antepartum and postpartum VTE risk would enhance current guidelines for VTE prevention. Furthermore, antepartum and postpartum VTE are uncommon occurrences in the US (incidence proportions = 6.7 per 10,000 deliveries⁵ and 1.6–5.9 per 10,000 deliveries^{5, 9, 14}, respectively), therefore observational studies using large population samples are ideal for examining the associations between maternal BMI and pregnancy-related VTE hospitalizations.

Our main objective was to assess the relationship between maternal BMI and pregnancy-related VTE in a large population-based cohort study. This study used linked maternal discharge data and birth certificate data from a large, diverse obstetric cohort comprising more than 2 million women who underwent delivery hospitalization in California between 2008 and 2012. Access to a large database comprising detailed maternal and obstetric data provides

Materials and Methods:

We performed a population-based cohort study using data from the Office of Statewide Health Planning and Development (OSHPD), under the California Health and Human Services Agency. We used linked hospital discharge data (comprising diagnosis and procedure codes) and vital statistics birth certificate data. We did not use a core outcome set in our analysis. Patients were not involved in the development of the research, and no funding was obtained for this study. We initially identified all women aged 15 to 50 years with singleton pregnancies who underwent delivery hospitalization in any one of the 301 hospitals across California between January 1, 2008 and December 31, 2012. Delivery hospitalization is defined as a delivery in a hospital. We excluded mothers whose admission date was missing; who delivered in military hospitals, birth centres, or at home; and mothers with height or weight outside of the expected range (height < 1.32 meters (52 inches) or > 1.93 metres (76 inches); weight < 34 kg (75 lbs) or > 204 kg (450 lbs)) (Figure 1). Using a unique, encrypted alphanumeric code specific to each mother/baby pair, we linked antepartum and postpartum admissions occurring in the 9 months prior to and after each delivery hospitalization using the same identifier for the mother based on data availability from OSHPD. The Stanford University institutional review board approved the study (IRB protocol: 14746).

The primary exposure of interest, prepregnancy body mass index (BMI), was calculated from prepregnancy weight and height from the birth certificate. BMI was categorized using World Health Organization (WHO) Classification¹⁵: underweight (<18.5 kg/m²), normal BMI (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), obesity class I (30–34.9 kg/m²), obesity class II (35–39.9 kg/m²), and obesity class III (> 40 kg/m²). Our outcome (VTE) was classified by the presence of a principle *International Classification of Diseases, ninth revision, Clinical Modification* (ICD-9) diagnosis code for VTE (Table S1). Diagnostic codes have been shown to have moderate-to-high positive predictive value for VTE in administrative data.^{16, 17}

We developed three distinct study cohorts (hereafter referred to as the antepartum, delivery, and postpartum cohorts) to examine the associations of BMI with antepartum, delivery, and postpartum-related VTE, respectively. Our base population (denominator) in each study cohort were women who underwent delivery hospitalization. To identify antepartum and postpartum VTE events among women who underwent delivery hospitalization in California, we linked longitudinally delivery hospitalizations to hospitalizations occurring during the antepartum and postpartum periods. Postpartum hospitalizations were identified up to 9 months after delivery. We designated women with an antepartum or postpartum VTE if a principle ICD-9 VTE code was associated with an antepartum or postpartum hospitalization, respectively. We designated women as having no antepartum or postpartum VTE event if one of the following criteria were met: (1) no VTE code was associated with an antepartum or postpartum hospitalization, respectively, or (2) no antepartum or postpartum hospitalization was linked to a delivery hospitalization, respectively. To limit outcome misclassification, women with an antepartum VTE ICD-9 code were excluded from our delivery study cohort. Similarly, those with a VTE code associated with an antepartum or delivery hospitalization were excluded from our postpartum study cohort (Figure 1).

Statistical Analysis

Differences in VTE frequencies between BMI classes were examined using Chi-square test. Unadjusted and adjusted associations between BMI and antepartum and postpartum VTE were estimated by logistic regression using binary Generalized Estimating Equations (GEEs) with a logit link and independence correlation to account for a hospital clustering effect, which may be presented because of hospital culture and protocols, and provide robust standard errors. Because VTE is rare, estimated odds ratios were assumed to approximate estimates of relative risk. Using multivariable models, the associations between BMI and VTE were adjusted for: maternal age (15–19, 20–24, 25–29, 30–34, and 35–50 years), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian, Hispanic/Latina, and others), smoking during prenatal period (non-smokers and smokers), insurance class (private, government-assisted, self-pay or other), highest education level (less than high school, high school, some college, college and above), and parity (no prior live birth, and 1 or more prior live birth). Of note, socioeconomic class was considered as a potential confounder because it is negatively associated with obesity and VTE respectively and is not on the causal pathway. Because the percentage of women with missing BMI data among delivery hospitalizations was 7% and the percentage of missing values for all covariates in our primary analyses did not exceed 3.5%, we performed complete case analyses in our logistic models. As five different comparisons were made for BMI (underweight, overweight, obesity class I, II and III vs. normal body mass index) in each regression model, a conservative cut-off of $P < 0.01$ (Bonferroni correction) was chosen to account for type I error inflation due to multiple testing.

In our analysis of the BMI-antepartum VTE relation, we performed exploratory analyses where we considered pre-existing diabetes, chronic hypertension, chronic heart disease as potential effect modifiers. Similarly, for the BMI-postpartum VTE relation, we additionally considered gestational diabetes mellitus or pre-existing diabetes mellitus (hereafter referred to as diabetes), any hypertensive disease of pregnancy (gestational hypertension, pre-eclampsia, or eclampsia), chronic heart disease, and mode of delivery as effect modifiers. ICD-9 codes for these conditions are provided in Table S2. To assess effect modification, interactions between BMI and each variable were added to the full adjusted model in turn and a Wald test was used to decide statistical significance using $P < 0.05$.

As a means of improving VTE detection, we performed a sensitivity analysis by classifying women as experiencing VTE if a woman had a principle or secondary ICD-9 code for VTE.

Statistical analysis was performed using SAS 9.3 (SAS Institute Inc, Cary, NC) and STATA Version 14.0 (StataCorp., College Station, TX). Prior to data analyses, the statistical plan for the primary and secondary study aims was reviewed by all study investigators in June 2017.

Results:

We identified 2,449,133 women with singleton pregnancies. Patient characteristics are presented in Table S3. A flow diagram for the antepartum, delivery, and postpartum study cohorts is presented in Figure 1. The overall prevalences of VTE in the antepartum, delivery, and postpartum study cohorts were 0.04% (889/2,449,133), 0.01% (136/2,448,244), and

0.04% (1,033/2,448,108), respectively. Prevalences of antepartum, delivery-related, and postpartum VTE by BMI class are presented in Figure 2. The prevalence of antepartum VTE was lowest in the underweight group (0.02%), increased slowly to 0.047% in obesity class II group, and increased sharply to 0.11% in obesity class III group. The prevalence of postpartum VTE increased steadily from 0.02% in the underweight group to 0.13% in obesity class III group. Prevalences of antepartum and postpartum VTE increased with increasing BMI class ($P<0.001$), whereas prevalences of VTE associated with delivery hospitalizations did not significantly differ between BMI classes ($P=0.27$).

Among both antepartum and postpartum study cohorts, the risk of a VTE-related hospitalization increased monotonically with increasing BMI (Table 1). Based on our models, the adjusted odds of antepartum VTE were significantly higher for obesity class I and III women compared to normal BMI women (accounting for a Bonferroni correction). The adjusted odds of postpartum VTE were significantly higher for obesity class I, II, and III women than for normal BMI women. In our adjusted analyses, obesity class III had the highest odds of antepartum VTE (aOR=2.89; 95% CI=2.20–3.81) and postpartum VTE (aOR=3.64; 95% CI=2.92–4.55) compared to normal BMI women (Table 1). In our delivery cohort, in our unadjusted analysis, we observed no significant differences in the odds of VTE between any BMI class compared to normal BMI women. VTE events during delivery hospitalization could not be examined in a multivariable analysis because of the infrequency of these events. We failed to detect an interaction effect of BMI with chronic heart disease ($P=0.37$), pre-pregnancy diabetes ($P=0.05$) and chronic hypertension ($P=0.09$) for antepartum VTE. We detected a potential interaction effect of BMI with chronic hypertension for postpartum VTE ($P=0.02$). The stratified analyses are presented in Tables S4. We failed to detect any interaction effects of BMI with delivery mode ($P=0.73$), diabetes ($p=0.24$), hypertensive disorder ($p=0.81$), and chronic heart disease ($P=0.62$) for postpartum VTE.

In our sensitivity analysis, we re-ran our GEE models with antepartum and postpartum VTE identified by a principle or secondary ICD-9 VTE codes (Table S5). The odds of VTE for each BMI class were similar to those of our primary analysis.

Discussion:

Main Findings

Using data from a large cohort of women who underwent delivery hospitalization in California between 2008 and 2012, we found evidence of strong positive ‘dose-response’ relations between prepregnancy BMI with antepartum VTE and postpartum VTE, respectively. Because obesity class III women had the highest adjusted odds for antepartum VTE (aOR=2.89) and postpartum VTE (aOR=3.64), obesity class III should be considered as a major risk factor for antepartum and postpartum VTE. Our findings may inform recommendations for VTE preventive strategies in obese women who require hospitalization before or after delivery.

Our study found evidence of a strong dose-response effect between maternal BMI with antepartum and postpartum VTE. Although prior observational studies report that obesity is

a risk factor for antepartum³⁻⁷ and postpartum VTE,⁵⁻¹⁰ the independent association between maternal BMI and pregnancy-related VTE has been poorly studied. Larsen et al. reported that obese women had a 5.3-fold and 2.8-fold increased odds of antepartum and postpartum VTE, respectively.⁶ In a separate study, Blondel et al. observed a 'dose-response' between BMI and postpartum VTE.¹⁸ However, both these studies were case-control, therefore rates of VTE according to BMI class could not be determined. Plus both had substantially smaller study cohorts than our study.

Strengths and Limitations

The main strengths of our study include the large study population comprising a diverse, contemporary obstetric cohort and unique maternal information made available from linkage of birth certificate and maternal discharge data. The availability of these data allowed us to investigate the presence and the extent of a 'dose-response' relation between BMI with antepartum and postpartum VTE, whilst controlling for relevant confounding factors. Analyses for confounding and effect modification may not be possible in smaller studies with less granular data.

We also explored whether interactions exist between BMI and potential effect modifiers. We found no evidence of interaction between BMI and delivery mode in our postpartum cohort. This was unexpected because the risk of postpartum VTE is higher after caesarean delivery compared with vaginal delivery.^{9, 19} However, we did find evidence of interaction effects between chronic hypertension with BMI in our postpartum cohorts. Because our examination of interaction effects was exploratory, future studies are needed to ascertain the combined influence of obesity and each comorbid state, including delivery mode, on VTE risk.

Our study has a number of limitations inherent to a retrospective, observational study design. Because we relied upon ICD-9 codes to identify VTE events, misclassification is a potential concern. Small rates of misclassification has been shown to lower the positive predictive value of ICD-9 codes specific for pregnancy-related VTE.¹⁷ However, the prevalences of antepartum and postpartum VTE in our study are in line with those reported in prior studies of examining VTE related hospitalization.^{5, 14} Also, the sensitivity of VTE ICD-9 codes is likely non-differential across BMI classes which would bias our results to the null. Furthermore, our estimates of risk were similar in each of our sensitivity analysis suggesting our main findings are robust. The reliability of BMI data recorded on birth certificates has been previously examined. Bodnar et al. demonstrated good agreement between prepregnancy BMI categorization between birth certificate data and medical record data.²⁰ Chen et al. reported a high correlation (0.9) between self-reported and recorded prepregnancy BMI using 1988 National Maternal and Infant Survey data.²¹ We likely underestimated the frequency of VTE because outpatient diagnoses are not captured in our datasets. Pharmacy data was not available therefore we could not account for the use of anticoagulants for thromboprophylaxis or VTE treatment. Rates of postpartum mechanical or thromboprophylaxis among obese women are higher after caesarean delivery compared to vaginal delivery (42% vs. 5.9%).^{22, 23} However, the likelihood of obese patients receiving any prophylaxis is only marginally higher compared with non-obese patients,²³ and rates of

prophylaxis according to BMI among women undergoing antepartum or postpartum hospitalization are unknown.²⁴ We based our analysis on women who delivered in California hospitals, and thus are not able to obtain antepartum or postpartum hospitalization data for out of state women who delivered in California. We also did not account for antepartum VTE events in women who underwent termination of pregnancy or who miscarried. As our data are episodic, we could not ascertain the timing of each VTE episode during the delivery hospitalization or differentiate women who had a pre-existing VTE from those who were diagnosed with a VTE at or during the hospital admission. In any observational study, residual confounding remains a concern. Unmeasured confounders may include lupus, infection, and prolonged immobility. However, any effect from these potential confounders would need to be substantial and non-differential to fully explain the observed association between BMI class and VTE. Lastly, there was a low number of VTE cases in each BMI class during the delivery hospitalization, therefore we could not examine the association between BMI-VTE accounting for confounders and effect modifiers. However, one would expect that a high proportion of obese women would receive postpartum mechanical or thromboprophylaxis whilst in hospital. This may partially explain why rates of VTE were very low in all BMI classes.

Interpretation

Our findings have potentially important clinical relevance for informing obstetric societies' guidelines for VTE prevention in obese women because current recommendations are limited and inconsistent. The American College of Chest Physicians (ACCP) recommend post-cesarean thromboprophylaxis for all obese women (BMI ≥ 30 kg/m²) with at least one additional VTE risk factor e.g., preeclampsia, thrombophilia or emergency cesarean section.²⁵ However the guidelines are silent if obese women require antepartum or postpartum thromboprophylaxis. The RCOG recommend antepartum or postpartum thromboprophylaxis if obesity is present with 3 or 2 other VTE risk factors, respectively.¹¹ For women requiring antepartum hospitalization, the RCOG recommend thromboprophylaxis irrespective of BMI. Similarly, the National Partnership for Maternal Safety recommend thromboprophylaxis for all women requiring antepartum hospitalization for > 72 hrs.²⁶ In contrast, beyond stating that obesity is a risk factor for VTE, ACOG do not provide BMI-specific recommendations for antepartum or postpartum thromboprophylaxis in outpatients or inpatients.¹² In a recent review of guidelines for thromboprophylaxis, Palmerola et al. reported that, among a typical population of women undergoing caesarean delivery, 85% would receive prophylaxis with RCOG guidelines vs. 1% under ACOG guidelines.²⁷ Given the marked differences in obstetric societies' guidelines, further clinical, decision-analysis and cost-effectiveness studies are needed to clarify optimal prophylaxis regimens according to BMI class. In addition, our findings may be useful for providers who provide preconception counseling to overweight and obese women about the risks of obesity in pregnancy.

The strong 'dose-response' association between maternal BMI and pregnancy-related VTE may be mediated through a number of different pathways. Evidence suggests that obesity is linked to impaired fibrinolysis. Humans with central adiposity display upregulation of plasminogen-activator inhibitor-1 (PAI-1) expression.²⁸ Plasma levels of PAI-1 are also elevated in patients with obesity.²⁹ Platelet hyperactivity has also reported in patients with

metabolic syndrome, a condition closely linked with obesity; the hyperactivity may be induced by insulin resistance, dyslipidemia, oxidative stress, adipokines, and inflammation.³⁰ Furthermore, obesity has as a proinflammatory phenotype which may lead to activation of prothrombotic signaling pathways in vascular cells and coagulation thereby increasing thrombotic risk.^{29, 31, 32} To further attenuate the risk of VTE related to obesity, preventive strategies beyond the use of thromboprophylaxis may need to consider these important pathways.

Conclusion

In conclusion, a high prepregnancy BMI, compared with normal BMI, was associated with a statistically significant increased odds of antepartum VTE and postpartum VTE. Our findings may have important implications for future work to examine the effect of strategies to prevent antepartum and postpartum hospitalizations for VTE in obese women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow Diagram for the Study Cohort Examining the Relations between Maternal Body Mass Index and Antepartum Venous Thromboembolism

Figure 2.
Prevalences of VTE among antepartum, delivery and postpartum cohorts

Univariable and multivariable analyses examining the relations between maternal body mass index with venous thromboembolism occurring in the antepartum and postpartum periods.

Table 1.

	Antepartum Study Cohort			Postpartum Study Cohort		
	n/N*	Crude OR (95% CI)	Adjusted OR (95% CI) [†]	n/N*	Crude OR(95% CI)	Adjusted OR(95% CI) [†]
Underweight	21/91,115	0.76 (0.44–1.31)	0.86 (0.50–1.49)	18/91,090	0.64 (0.40–1.01)	0.70 (0.45–1.11)
Normal BMI	339/1,120,417	Ref	Ref	346/1,120,025	Ref	Ref
Overweight	224/589,507	1.26 (1.03–1.53) [‡]	1.27 (1.04–1.54)	229/589,252	1.26 (1.06–1.49) [‡]	1.21 (1.02–1.43)
Obesity class I	122/288,939	1.40 (1.14–1.70) [‡]	1.37 (1.11–1.68) [‡]	161/288,799	1.81 (1.50–2.17) [‡]	1.74 (1.43–2.12) [‡]
Obesity class II	56/118,368	1.56 (1.15–2.12) [‡]	1.40 (1.01–1.93)	107/118,302	2.93 (2.39–3.59) [‡]	2.70 (2.16–3.36) [‡]
Obesity class III	73/69,160	3.49 (2.69–4.53) [‡]	2.89 (2.20–3.81) [‡]	91/69,080	4.27 (3.46–5.27) [‡]	3.64 (2.92–4.55) [‡]

* n=number of VTE events; N=total number of women in each body mass index class

[†] Adjusted for maternal age, race/ethnicity, education, insurance, smoking, and parity

[‡] p<0.01

BMI = body mass index; CI = confidence intervals; OR = odds ratio