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Risk of Postoperative Venous Thromboembolism Among Pregnant Women

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Venous thromboembolism (VTE) is a critical complication after surgery. Although pregnancy is a known risk factor of VTE, available data on the risk of postoperative VTE are scarce. Using the American College of Surgeons National Surgical Quality Improvement Program database between 2006 and 2012, we matched 2,582 pregnant women to 103,640 nonpregnant women based on age, race, body mass index, and modified Rogers score. Pregnant women, compared with matched nonpregnant women, experienced higher incidence of VTE (0.5% vs 0.3%; odds ratio 1.93, 95% confidence interval 1.1 to 3.37, p = 0.02). Pregnant women also showed higher risk of pneumonia, ventilator dependence ≥48 hours, bleeding, and sepsis than did the counterparts. In conclusion, pregnancy was associated with higher risk of VTE after surgery as well as other postoperative complications. The absolute risk difference was small, and careful evaluation against the potential risk and benefit should be given when surgical treatment is considered among pregnant women. **(Am J Cardiol 2017;120:479−483)**

Venous thromboembolism (VTE) is a critical complication after surgery. Although pregnancy increases the risk of VTE 4- to 5-fold,[1] there are scarce data on the risk of VTE among pregnant women undergoing surgery. Therefore, we examined the association of pregnancy with postoperative VTE by using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) data. We also examined the association with other postoperative complications because the risk of postoperative VTE may be induced by other complications (i.e., infections and bleeding) and vice versa.

Methods

An exemption from institutional review board review for the use of the NSQIP patient-level data was obtained at the University of California, Irvine Medical Center. We identified 269,104 women (including 3,719 pregnant women) who were aged <50 years and who underwent surgery using the NSQIP database between 2006 and 2012, when data on pregnancy are available (Figure 1). Clinical data on preoperative risk factors and laboratory values, type of surgery, and 30-day postoperative mortality and morbidity were collected by trained nurses at >500 hospitals across North America. After excluding patients with missing information for relevant clinical factors, we identified 192,554 patients including 2,596 pregnant women. We calculated modified Rogers score where we excluded hematocrit, serum bilirubin, and serum albumin from original Rogers score[2] because these factors are influenced by pregnant status, and hence considered intermediates rather than confounders. Primary outcome was postoperative VTE defined as either venous thromboses or pulmonary embolism during 30 days after surgery. Secondary outcomes included other postoperative complications such as surgical site infection, pneumonia, ventilator dependence >48 hours, bleeding, and sepsis (see Supplementary Text for detail). We estimated odds ratios (ORs) of postoperative complications using logistic regression. Age, race, and body mass index were adjusted for in the complete case analysis. Additionally, pregnant women were matched to nonpregnant women based on age, race, body mass index, and modified Rogers score by coarsened exact matching with Sturge's rule.[3−5] First, we coarsened age and modified Rogers score into categories using cut-points of 20 and 35 years and 3, 14, 16, and 19 points, respectively. We then sorted all patients by each stratum of the age category, race, and the modified Rogers score category. Within each stratum that included at least 1 patient in each group, pregnant patients were given a weight of 1, and nonpregnant women were given a weight that equalized the ratio of sum of weights in each group of the stratum to the ratio of total matched patients on each group in the complete case cohort. The comparison of clinical characteristics between matched cohort and unmatched cohort was listed in Supplementary Table 1. The association between pregnancy and each postoperative complication was then estimated in the matched cohort without adjustment. As a sensitivity analysis, we further added emergent surgery into matching variables.

Between-group differences were evaluated by standardized difference because of the large sample size of this study; 0.8, 0.5, and 0.2 in absolute values are considered

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See page 483 for disclosure information.

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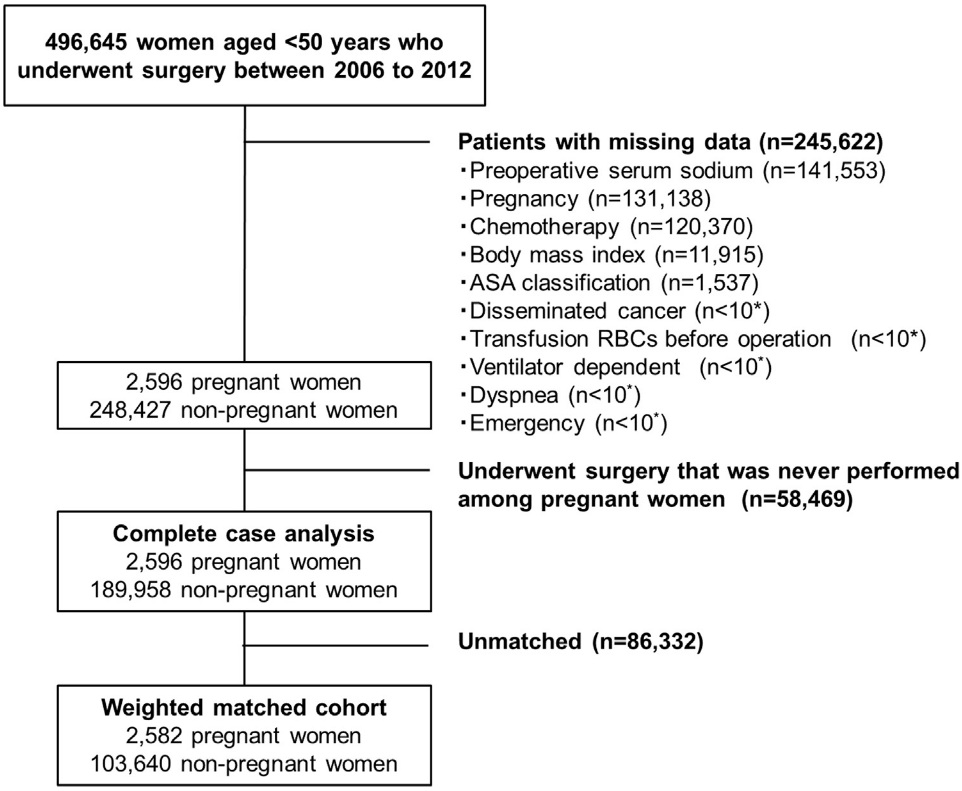

Figure 1. Patient selection criteria. *Not shown because of a limited number of patients as per the NIQIP policy. ASA = American Society of Anesthesiology; RBCs = red blood cells.

large, medium, and small differences.[6,7] Statistical significance was defined as a p value of <0.05. All analysis was performed using Stata 13.1 (StataCorp LP, College Station, Texas).

Results

Among 2,596 pregnant and 189,958 nonpregnant women in the complete case cohort, 2,582 (99.5%) pregnant women were matched to 103,640 nonpregnant women. There were large differences in age, body mass index, and modified Rogers sore between pregnant versus nonpregnant women in the complete case cohort, and these differences were diminished in the weighted matched cohort (Table 1). Among the components of modified Rogers score, pregnant women had lower preoperative serum sodium levels and higher prevalence of emergent surgery in both the entire and weighted matched cohort. The incidence of VTE among pregnant and nonpregnant patients was 0.5% versus 0.4% in the complete case cohort and 0.5% versus 0.3% in the matched cohort, respectively (Table 2). After matching, the incidence of other postoperative complications also decreased among nonpregnant women.

Pregnant women, compared with nonpregnant women, showed higher risk of VTE and other complications except for surgical site infection after adjustment for age, race, and body mass index in the matched cohort (Figure 2). Consistent associations were observed in the matched cohort (OR 1.93, 95% confidence interval [CI] 1.11 to 3.37, p = 0.02 for VTE; OR 1.79, 95% CI 1.06 to 3.00, p = 0.03 for pneumonia; OR 2.24, 95% CI 1.49 to 3.35, p <0.001 for ventilator dependency >48 hours; OR 2.36, 95% CI 1.79 to 3.10, p <0.001 for bleeding; and OR 1.52, 95% CI 1.11 to 2.07, p = 0.009 for sepsis). Sensitivity analyses including emergent surgery as a matching factor showed an attenuation in the risk of pneumonia, ventilator dependency, and sepsis, but the risk of VTE and bleeding remained significant (OR 2.26, 95% CI 1.29 to 3.97, p = 0.004; and OR 2.25, 95% CI 1.70 to 2.98, p <0.001, respectively).

Discussion

This study demonstrated the association of pregnancy with increased risk of postoperative VTE. The risk of other postoperative complications (i.e., pneumonia, ventilator dependency >48 hours, bleeding, and sepsis) was also significantly higher among pregnant patients than nonpregnant female patients.

The absolute rate of postoperative VTE in this study was consistent with previous studies.[8–10] A recent US population-based study by Abbasi et al[9] also showed that among pregnant women who developed acute appendicitis during the hospital stay for delivery, the risk of postoperative VTE was 60% higher than nonpregnant women after adjustment for age, race, obesity, income, insurance, and hospital type. Our study included all types of surgical procedures that were ever performed for pregnant women during the antepartum period, and confirmed the association between pregnancy and postoperative VTE even after matching on factors related to VTE.

Previous studies also showed that pregnant women had higher risk of postoperative adverse events including

Table 1
Clinical characteristics in complete case analysis and weighted matched cohort

Variables	Complete case cohort (n=192,554)			Weighted matched cohort (n=106,222)		
	Pregnant (n=2,596)	Non-pregnant (n=189,958)	Standardized difference*	Pregnant (n=2,582)	Non-pregnant (n=103,640)	Standardized difference*
Age, mean ± SD, (years)	29 ± 6	37 ± 9	1.12	29 ± 6	29 ± 6	0
Body mass index, median (IQR), (kg/m^2)	27.9 (24.0, 32.9)	30.4 (24.4, 39.4)	-0.33	27.9 (24.0, 32.9)	27.9 (23.7, 32.9)	0
Race						
White	1,651 (64%)	130,354 (69%)	0.11	1,644 (64%)	70,494 (68%)	0.09
Black	422 (16%)	29,526 (16%)	-0.02	419 (16%)	14,505 (14%)	-0.06
Asian	81 (3%)	4,673 (2%)	-0.04	81 (3%)	2,668 (3%)	-0.03
Other + Unknown	442 (17%)	25,408 (13%)	-0.10	438 (17%)	15,973 (15%)	-0.04
Modified Rogers score	8 (6, 9)	8 (6, 10)	-0.14	8 (6, 9)	8 (6, 9)	0
ASA classification	2 (2, 2)	2 (2, 3)	-0.08	2 (2, 2)	2 (1, 2)	0.25
Work relative value unit	12 (9, 12)	12 (10, 18)	-0.51	12 (9, 12)	12 (10, 14)	-0.18
Disseminated cancer	10 (0.4%)	1,868 (1%)	0.07	<10[†]	614 (0.6%)	0.04
Chemotherapy for malignancy within 90 days of operation	<10[†]	2,269 (1%)	0.10	<10[†]	794 (0.8%)	0.06
Serum sodium >145 mEq/L	<10[†]	913 (0.5%)	0.06	<10[†]	558 (0.5%)	0.07
Transfusions RBCs before operation	15 (0.6%)	660 (0.3%)	-0.03	14 (0.5%)	394 (0.4%)	-0.02
Ventilator dependent	20 (0.8%)	631 (0.3%)	-0.06	16 (0.6%)	284 (0.3%)	-0.05
Wound class (clean /contaminated)	1,284 (49%)	88,230 (46%)	-0.06	1,278 (49%)	50,930 (49%)	-0.01
Dyspnea	54 (2%)	13,187 (7%)	0.24	50 (2%)	3,201 (3%)	0.07
Emergent surgery	1,425 (55%)	31,425 (17%)	-0.87	1,419 (55%)	27,651 (27%)	-0.60
Type of surgery						
Integument	1,809 (70%)	122,041 (64%)	-0.12	1,805 (70%)	75,886 (73%)	0.07
Respiratory and hemic	169 (7%)	26,475 (14%)	0.25	167 (6%)	9,692 (9%)	0.11
Hernia	103 (4%)	12,810 (7%)	0.12	102 (4%)	5,249 (5%)	0.05
Mouth, palate	13 (0.5%)	2331 (1.2%)	0.08	13 (0.5%)	1168 (1.1%)	0.07
Thoracoabdominal aneurysm, embolectomy/thrombectomy, venous reconstruction, and endovascular repair	24 (0.9%)	1,972 (1.0%)	0.01	19 (0.7%)	1,022 (1.0%)	0.03
Stomach, intestines	<10[†]	950 (0.5%)	0.02	<10[†]	828 (0.8%)	0.06
Aneurysm	<10[†]	158 (0.1%)	-0.04	<10[†]	51 (0.0%)	-0.05
Laboratory tests[‡]						
Hematocrit, mean ± SD, (%)	34.1 ± 4.2	38.0 ± 4.2	0.93	34.1 ± 4.2	37.8 ± 4.2	0.87
Serum bilirubin, median (IQR), (mg/dl)	0.5 (0.3, 0.7)	0.5 (0.7, 0.8)	-0.06	0.5 (0.3, 0.7)	0.5 (0.3, 0.7)	-0.14
Serum albumin, mean ± SD, (g/dl)	3.4 ± 0.7	4.0 ± 0.6	0.89	3.4 ± 0.7	4.0 ± 0.6	0.88

ASA = American Society of Anesthesiology; RBCs = red blood cells.
* 0.8, 0.5, and 0.2 in absolute values are considered large, medium, and small differences.
† Not shown because of a limited number of patients as per the NSQIP policy.
‡ Missing frequency was 2%, 27%, and 31% for hematocrit, bilirubin, and serum albumin.

Table 2
Incidence of postoperative complications among pregnant versus nonpregnant women

Variable	Complete case cohort (n= 192,554)		Weighted matched cohort (n= 106,222)	
	Pregnant women (n=2,596)	Non-pregnant women (n=189,958)	Pregnant women (n=2,582)	Non-pregnant women (n=103,640)
Venous thromboembolism	13 (0.5%)	742 (0.4%)	13 (0.5%)	271 (0.3%)
Surgical site infection*	83 (3%)	6,597 (3%)	82 (3%)	2,939 (3%)
Pneumonia	16 (0.6%)	924 (0.5%)	15 (0.6%)	338 (0.3%)
Ventilator >48 hours	28 (1%)	1,195 (0.6%)	25 (1%)	451 (0.4%)
Bleeding	57 (2%)	2,141 (1%)	55 (2%)	948 (0.9%)
Sepsis	42 (2%)	2,567 (1%)	42 (2%)	1,117 (1%)

* Surgical site infection is defined as superficial surgical site infection, deep surgical site infection, organ/space surgical site infection, or wound disruption.

infection, sepsis, pneumonia, and mortality.[8,9] Patients with severe complications, especially those who are ventilator dependent, usually require complete bed rest, and immobility is a major cause of postoperative VTE.[11] Additionally, infection and systemic inflammation may increase the risk of VTE through Virchow triad (i.e., stasis of

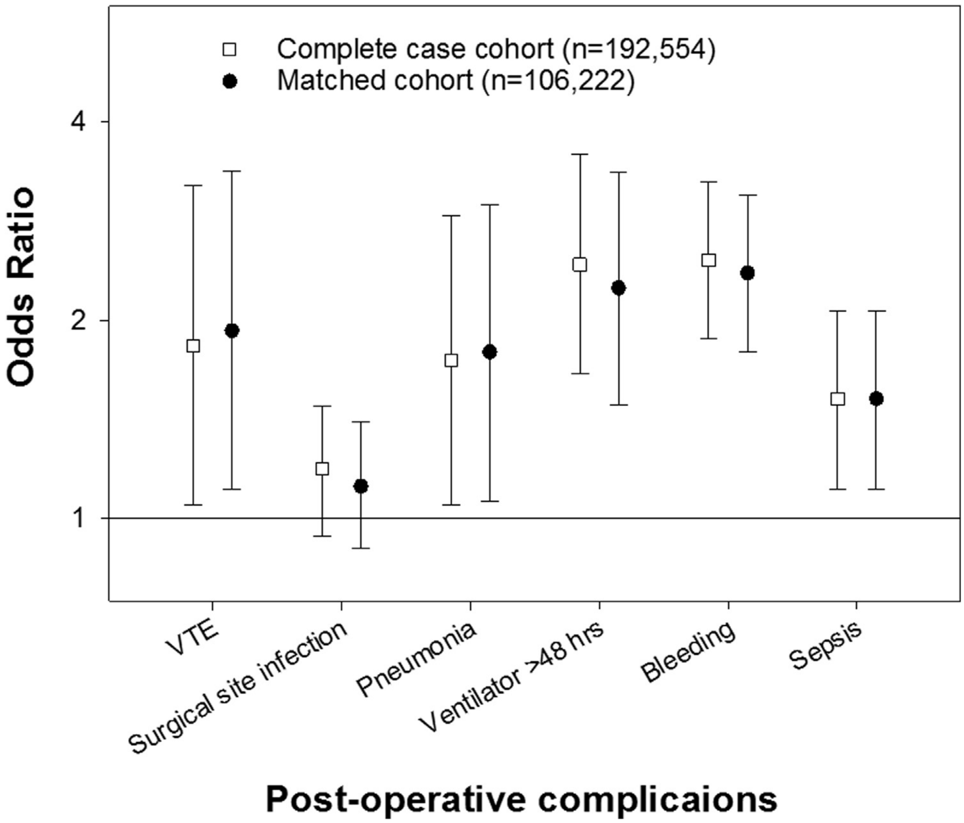

Figure 2. Risk of postoperative complications among pregnant women. Odds ratios in the complete case cohort were adjusted for age, race, and body mass index.

blood flow, endothelial injury, and hypercoagulability).[12,13] Bleeding activates coagulation system, and transfusion may also increase the risk of VTE.[14–16] Meanwhile, pulmonary embolism may cause other complications including respiratory dysfunction and sepsis in turn, and anticoagulant therapy increases bleeding risk, creating a vicious cycle among these complications.

Hypernatremia is an index of dehydration which may lead to postoperative VTE,[17] as included in Rogers score.[2] Despite the physiological increase in body fluid during the antepartum period as partly reflected by lower serum sodium levels, pregnancy was associated with postoperative VTE. These results suggested the involvement of other factors such as increased procoagulant factors (i.e., fibrinogen, factor VIII, and von Willebrand factor)[18] and reduced anticoagulant factors (i.e., protein C and protein S),[19] as well as venous compression by enlarged uterus.[2]

The higher prevalence of emergent surgery among pregnant women may reflect an effort of physicians to avoid surgical complications. However, delayed treatment may result in adverse consequences. Abbasi et al[9] reported that conservative treatment was more common than expected and associated with septic shock, peritonitis, and VTE among pregnant women. We also found that the risk of pneumonia, ventilator dependence, and sepsis was attenuated after adding emergent surgery into matching variables, suggesting the contribution of preoperative conditions to these complications. The postoperative VTE risk remained significant, but the absolute rate difference was 0.2%. Therefore, surgical procedures for pregnant women should be considered with the risk-benefit balance between surgical versus conservative treatment on an individual basis. Further studies are necessary to identify high-risk patients who need careful monitoring and aggressive prophylaxis.

Several limitations should be noted. First, there may be residual confounding and/or effect modification by type of surgery.[20] However, type of surgery was contained in Rogers score,[2] and we selected those ever performed in pregnant women. Second, there may also be unmeasured confounding by hereditary thrombophilia (i.e., antithrombin, protein C, or protein S deficiency),[21] smoking, a history of VTE, and the use of prophylactic and therapeutic drugs and devices. Third, the incidence of VTE may be underestimated in this study because the NSQIP database contains only clinically observed outcomes within 30 days after surgery. Indeed, a previous study showed that the risk of VTE among middle aged women was substantially increased in the first 12 postoperative weeks.[10] Finally, gestational period was not recorded in the NSQIP database. The incidence rate of venous thromboses may be consistent across the trimesters,[22] but the physiological changes in the course of pregnancy may alter the risk of VTE among pregnant women, which need further investigation.

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Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2017.04.053.

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