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Venous thromboembolism during pregnancy and the postpartum period: Incidence, risk factors, and mortality

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Objective: The purpose of this study was to estimate the incidence, risk factors, and mortality from pregnancy-related venous thromboembolism.
Study design: The Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality for the years 2000 to 2001 was queried for all pregnancy-related discharges with a diagnosis of venous thromboembolism.
Results: The rate of venous thromboembolism was 1.72 per 1000 deliveries with 1.1 deaths per 100,000. The risk of venous thromboembolism was 38% higher for women ages 35 and older and 64% higher for black women. Other significant risk factors included thrombophilia, lupus, heart disease, sickle cell disease, obesity, fluid and electrolyte imbalance, postpartum infection, and transfusion. The risk factor with the highest odds ratio, 51.8 (38.7-69.2) was thrombophilia.
Conclusion: The incidence of pregnancy-related venous thromboembolism was higher than generally quoted. Women ages 35 and older, black women, and women with certain medical conditions and obstetric complications appear to be at increased risk.

Pregnant women are 4 to 5 times more likely to develop venous thromboembolism than women who are not.[1] This predisposition to develop venous thromboembolism results from the hypercoagulable state of pregnancy that has likely evolved to protect women from hemorrhage during miscarriage and childbirth. While the leading cause of maternal death in the developing world is hemorrhage,[2] in the United States, where death from hemorrhage is prevented, the leading cause of maternal death is thromboembolic disease.[3] Besides death, venous thromboembolism can cause significant acute and chronic morbidity. In addition to the immediate morbidity associated with venous thromboembolism, there is long-term morbidity associated with the post-thrombotic syndrome. The majority of women who suffer from venous thromboembolism during pregnancy develop sequelae that range from edema and skin changes to recurrent thromboses and ulceration.[4]

In addition to the consequences to their own health, women who experience venous thromboembolism in pregnancy may be more likely to suffer poor pregnancy outcome. Recently, it has been suggested that women with inherited or acquired risk factors for thrombosis (thrombophilia) are at a greater risk of poor pregnancy outcome,

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Table I Frequency of venous thromboembolic events by type and timing in gestation

	DVT	PE	Both	Total (%)
Pregnancy admissions n = 9,058,162	5929	1033	215	7177 (50%)
Postpartum admissions n = 73,834	5397	1466	295	7158 (50%)
Total (%)	11,326 (79%)	2499 (17%)	510 (4%)	14,335 (100%)

Table II Rate of venous thromboembolic events by age

Age	No. of cases	Per 1000 deliveries	95% CI
<20	1399	1.47	(1.33-1.61)
20-24	3201	1.58	(1.50-1.66)
25-29	3667	1.67	(1.59-1.75)
30-34	3424	1.73	(1.63-1.83)
35-39	2067	2.13	(1.97-2.29)
40+	577	2.75	(2.36-3.14)

including placental abruption, preeclampsia, fetal growth restriction, stillbirth, and possibly recurrent miscarriage.[5,6]

Despite a growing interest in the role of thromboembolic disease in maternal and fetal health, there is little information about the epidemiology of pregnancy-related thromboembolic disease in the US. The purpose of this study was to estimate the incidence, identify risk factors, and estimate the mortality from pregnancy-related venous thromboembolic disease in the US.

Material and methods

Data for this study were obtained from the Nationwide Inpatient Sample (NIS), from the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ). The NIS contains data from 5 to 8 million hospital stays from about 1000 US hospitals and is the largest all-payer inpatient care database in the US. The NIS is a 20% stratified sample of all discharges and allows for national estimates. Included in the sample are general hospitals and academic medical centers. Excluded are rehabilitation hospitals, long-term hospitals, psychiatric hospitals, and alcoholism or chemical dependency treatment facilities. The hospitals are divided into strata based on ownership, bed size, teaching status, urban versus rural location and region. Sampling probabilities are proportional to the number of hospitals in each stratum. The sampling frame comprises 90% of all US hospital discharges.[7,8]

Information included in the NIS is what can be derived from a typical discharge abstract, with safeguards to protect the privacy of individual patients, physicians, and hospitals. Although the data are limited to discharge diagnoses and demographic information, the NIS is the most reliable source of data on hospital discharges. Reliability is supported by agreement between the NIS, a telephone survey, and the National Health Interview Survey (a national, door-to-door survey). Invalid or inconsistent diagnostic codes are flagged.[7,8]

Data may be utilized for the purposes of aggregate statistical reporting, analysis, and research. The NIS allows for the study of relatively rare conditions such as venous thromboembolism in pregnancy.[7,8]

The NIS was queried for all pregnancy-related discharge codes for the years 2000 to 2001 (the latest data available at the inception of the study). The pregnancy-related discharge records from that time period were classified as to whether they were from a pregnancy admission or from a postpartum admission. A pregnancy admission was defined as any discharge record with a pregnancy-related diagnosis (International Classification of diseases [ICD]-9 codes 630-648) or a delivery code (ICD-9 codes 74 for cesarean delivery and 72, 73, 75, v27, or 650-659 for vaginal delivery). A postpartum admission was defined as any discharge record that included a postpartum diagnosis (ICD-9 codes 660-677), but did not also include a delivery code.

Venous thromboembolism was defined as deep vein thrombosis (DVT), pulmonary embolus (PE), or both. When both were present, and the record was assigned to 1 category, the record was assigned to PE. ICD-9 codes used for deep vein thrombosis included the pregnancy-related codes 671.3, 671.4, and 671.5 and the standard codes, 451-453. ICD-9 codes used for pulmonary embolus included the pregnancy-related codes 673.2 and 673.8 and the standard code, 415.

The analysis accounted for the cluster sampling utilized by the NIS. Data were weighted by the strata's primary sampling units (hospitals) and sampling weights based on the NIS sampling design. STATA 8.0 (Stata Corp LP, College Station, TX) and the SVY (survey data) commands utilizing these weights were used for both descriptive and inferential analyses. Two-way chi-square analyses yielded cell frequencies and their confidence intervals. Rates were computed from cell frequencies by dividing sample numbers. Logistic regression modeling was used to generate relative risk estimates for age and race.

The protocol was reviewed and approved by the Duke University Medical Center Institutional Review Board.

Results

During the period from 2000 to 2001, there were 9,058,162 pregnancy admissions and 73,834 postpartum admissions. Among the pregnancy admissions, there were 8,330,927 deliveries. Of these, 6,400,956 (77%) were vaginal and 1,929,971 (23%) were cesarean. There were 3375 arterial thromboembolic events (2850 strokes and 525 myocardial infarctions) in addition to

Table III Rate of venous thromboembolic events by race

Race	No. of cases	Per 1000 deliveries	95% CI
White	5943	1.75	(1.67-1.83)
Black	2184	2.64	(2.46-2.82)
Hispanic	1699	1.25	(1.13-1.37)
Asian	266	1.07	(.85-1.29)
Other	442	1.47	(1.27-1.67)

Table IV Medical conditions and the risk of venous thromboembolism

Complication (ICD-9 code)	Odds ratio (OR)	95% CI
Hypertension (401-405)	1.8	(1.4-2.3)
Heart disease (390-399, 412-417, 420-429)	7.1	(6.2-8.3)
Thrombophilia (273.8, 286.9, 289.8)	51.8	(38.7-69.2)
History of thrombosis (V12.51)	24.8	(17.1-36.0)
Antiphospholipid syndrome (286.5, 289.9, 795.79)	15.8	(10.9-22.8)
Sickle cell disease (282.4, 282.6)	6.7	(4.4-10.1)
Lupus (695.4, 710)	8.7	(5.8-13.0)
Diabetes (648.8, 250)	2.0	(1.4-2.7)
Obesity (278.0)	4.4	(3.4-5.7)
Smoking (305.1, V15.82)	1.7	(1.4-2.1)
Substance abuse (648.3, 305.2, 305.3, 305.5, 305.6, 305.7)	1.1	(0.7-1.9)

Table V Complications of pregnancy and delivery and risk of venous thromboembolism

Complication (ICD-9 code)	Odds ratio (OR)	95% CI
Multiple gestation (651)	1.6	(1.2-2.1)
Anemia (648.2, 285.0)	2.6	(2.2-2.9)
Thrombocytopenia (287.3)	0.6	(0.8-4.1)
Hyperemesis (643)	2.5	(2.0-3.2)
Disorders of fluid, electrolyte, and acid-base balance (276)	4.9	(4.1-5.9)
Preeclampsia and gestational hypertension (642)	0.9	(0.7-1.0)
Preterm labor (644)	0.9	(0.7-9.5)
Antepartum hemorrhage (640.9, 641.1, 641.2, 641.3, 641.8, 641.9)	2.3	(1.8-2.8)
Postpartum infection (670, 672)	4.1	(2.9-5.7)
Postpartum hemorrhage (666, 667, 669.1)	1.3	(1.1-1.6)
Transfusion (CPT codes 9900, 9902, 9904, 9907)	7.6	(6.2-9.4)
Cesarean vs vaginal delivery	2.1	(1.8-2.4)

the 14,335 venous thromboembolic events. Therefore, venous thromboembolic events were 4 times more common than arterial events. Among the venous thromboembolic events, 11,326 (79%) were deep vein thromboses and 3009 (21%) were pulmonary emboli or both. Seven thousand one hundred seventy-seven (50%) occurred during pregnancy and 7158 (50%) postpartum (Table I). The risk of DVT was 1.36 per 1000 deliveries and the risk of PE was 0.36 per 1000 deliveries, for an overall risk of venous thromboembolism of 1.72 per 1000 deliveries. Although the actual causes of death were not studied, there were 89 deaths associated with venous thromboembolism, for a risk of mortality of 1.1 per 100,000 deliveries. There were 73 deaths among the 3009 women with pulmonary embolus, for a case fatality rate of 2.4%.

The risk of venous thromboembolism increased with age and increased significantly after age 35 (Table II). The risk of venous thromboembolism was 1.64 per 1000 deliveries for women under age 35, but 2.27 per 1000 deliveries for women age 35 and older (38% higher).

Because data on race were missing from 30% of the records, univariate analyses in Table III were limited to the records for which race was known. The risk of venous thromboembolism was significantly lower for Asian women, with a rate of 1.07 per 1000 deliveries, and Hispanic women, with 1.25 per 1000 deliveries, than white women, with 1.75 per 1000 deliveries. The rate for black women, 2.64 per 1000 deliveries, was 64% higher than that for women of other races (1.61 per 1000 deliveries). At all ages, black women had a higher rate.

Table IV presents the univariate analyses for various medical conditions considered to be risk factors for pregnancy-related thrombosis. With the exception of substance abuse, all of the medical conditions queried were significantly associated with pregnancy-related venous thromboembolism. Hypertension, an important risk factor for arterial thromboembolism, was associated with only a 1.8-fold increased risk of venous thromboembolism. Medical conditions that were associated with a significantly increased risk of venous thromboembolism included heart disease, odds ratio (OR) 7.1 (6.2-8.3), thrombophilia, OR 51.8 (38.7-69.2), a history of thrombosis, OR 24.8 (17.1-36.0), the antiphospholipid syndrome, OR 15.8 (10.9-22.8), sickle cell disease, OR 6.7 (4.4-10.1) lupus, OR 8.7 (5.8-13.0), obesity, OR 4.4 (3.4-5.7) and smoking, OR 1.7 (1.4-2.1).

Table V presents the univariate analyses for venous thromboembolism and various complications of pregnancy and delivery. Pregnancy and delivery complications that were associated with a significantly increased risk of venous thromboembolism included multiple gestation, OR 1.6 (1.2-2.1), anemia, OR 2.6 (2.2-2.9), hyperemesis, OR 2.5 (2.0-3.2), disorders of fluid, electrolyte, and acid-base balance, OR 4.9 (4.1-5.9) antepartum hemorrhage, OR 2.3 (1.8-2.8) postpartum infection, OR 4.1 (2.9-5.7),

Table VI Pregnancy-related venous thromboembolism by age and race

Independent variables	Odds ratio	95% CI*	*P* value
Age (referent 15-19)			
20-24	1.1	(0.9-1.3)	.46
25-29	1.2	(1.0-1.4)	.07
30-34	1.2	(1.0-1.4)	.12
35-39	1.4	(1.2-1.8)	< .01
40+	1.7	(1.3-2.3)	< .01
Race (referent white)			
Black	1.4	(1.2-1.6)	< .01
Hispanic	0.8	(0.7-0.9)	.01
Asian	0.7	(0.5-0.9)	< .01

* Logistic regression models: venous thromboembolism or not = constant + age; venous thromboembolism or not = constant + race; venous thromboembolism or not = constant + race in combination with ≥35 or <35.

postpartum hemorrhage, OR 1.3 (1.1-1.6), and transfusion OR 7.6 (6.2-9.4). The OR for cesarean versus vaginal delivery was 2.1.

Table VI summarizes the significant findings from the outcome of the logistic regression analysis for age and race. When controlled for age, black race, OR 1.4 (1.2-1.6), remained a significant risk factor for venous thromboembolism.

Comment

We found a higher incidence of pregnancy-related venous thromboembolism, 1.72 per 1000 deliveries, than has been previously reported. While none of the reports are from the US, and none have included as many cases, the previously published figures for the incidence of pregnancy-related venous thromboembolism range from 0.71 to 1.25 per 1000 deliveries.[9-14]

Data from the Nationwide Inpatient Sample are limited to information derived from discharge abstracts. Consequently, detailed and precise information on diagnosis and treatment are not available. A potential confounder, therefore, is the difference in the availability and utilization of various imaging or other diagnostic modalities among institutions. A number of cases may go undiagnosed. For that reason, our estimate of the incidence of pregnancy-related venous thromboembolism, although higher than others, may be an underestimate. Improved diagnosis has been shown to increase, rather than decrease, the reported incidence of pregnancy-related thromboembolism.[12] Additionally, in a study measuring the accuracy of coding for thromboembolism, the diagnostic codes for thromboembolism were found to be both sensitive (97%) and specific (74%).[15]

A reason our estimate may be too high is that some patients may have been admitted more than once. While the discharge record should only include current diagnoses, it is possible that some patients were readmitted with the same diagnosis. On the other hand, because data were derived only from inpatients, and because from 2000 to 2001 some pregnant patients were being treated as outpatients,[16] our estimate could be an underestimate.

Half of pregnancy-related venous thromboembolism occurred postpartum. This is similar to the proportion in other series, in which one third to two thirds of cases occurred postpartum.[1,14,16,17]

We estimated the mortality rate from pregnancy-related venous thromboembolism to be 1.1 per 100,000 deliveries. This is lower than the previously reported 2 to 3 per 100,000 deaths,[18,19] but these reports included cases of amniotic fluid embolism as well as pulmonary embolus. We found the case fatality rate for pulmonary embolus to be 2.4%. This is one tenth what has been previously reported.[20] The probable explanation is that pregnant and postpartum patients are not representative of those who suffer from pulmonary emboli, the majority of whom are likely to be older or have life-threatening comorbidities such as cancer.

The medical conditions with the highest ORs for pregnancy-related venous thromboembolism, not surprisingly, included known thrombophilia, OR 51.8 (38.7-69.2), a history of thrombosis, OR 24.8 (17.1-36.0), and the antiphospholipid syndrome, OR 15.8 (10.9-22.8). Other conditions with more than a 5-fold increased risk were lupus, OR 8.7 (5.8-13.0), heart disease, OR 7.1 (6.2-8.3), and sickle cell disease, OR 6.7 (4.4-10.1). The presence of these comorbidities may warrant consideration for thromboprophylaxis.

The complication of pregnancy or delivery with the highest OR was transfusion, OR 7.6 (6.2-9.4). Danilenko-Dixon et al also identified transfusion as a possible risk factor for pregnancy-related venous thromboembolism.[21] Transfusion may be associated with venous thrombosis because of the conditions for which the transfusion is indicated, such as anemia, antepartum hemorrhage, or postpartum hemorrhage, or may reflect the severity of a patient's condition. There is evidence, however, that storage and preservation of red blood cells increases their aggregability,[22] which may contribute to an increased risk of thrombosis.

Disorders of fluid, electrolyte, and acid-base balance, OR 4.9 (4.1-5.9), not obvious risk factors for thrombosis, were likely present in critically ill patients who were at risk of thrombosis because of their underlying condition.

We found that postpartum infection increased the risk of thrombosis 4-fold, paralleling findings from Hauth et al, who reported a 4-fold increased risk of venous thromboembolism among women with chorioamnionitis who underwent cesarean delivery.[23]

We found that cesarean delivery increased the risk of thrombosis 2-fold. Despite recommendations for thromboprophylaxis for women undergoing cesarean delivery,[24] a 2-fold increased risk may not be sufficient to

justify thromboprophylaxis unless other risk factors are present.

The risk of pregnancy-related venous thromboembolism increased with age. This is not surprising because the risk of venous thromboembolism is known to increase with age.[25] The increased incidence of pregnancy-related venous thromboembolism among women age 35 and older may be partly explained by an increased prevalence of risk factors, such as cesarean delivery, hypertension, heart disease, and obesity. With more women over age 35 becoming pregnant,[26] there may be implications for thromboprophylaxis.

When controlled for age, black race remained a significant risk factor for pregnancy-related venous thromboembolism. While current research has focused on the identification of genetic mutations and polymorphisms associated with thrombosis, most of these studies have been conducted in northern Europe. We found, however, that African-American women were at a higher risk for venous thromboembolic events. This increased incidence may be explained by an increased prevalence of risk factors such as hypertension, heart disease, obesity, and sickle cell disease, or by as yet unidentified environmental or genetic factors. The incidence of pregnancy-related venous thromboembolism may not be reduced in the US until such risk factors are identified, especially among women of African descent.

Current recommendations for thromboprophylaxis during pregnancy and postpartum[27] are stratified based on a history of thrombosis or the presence of thrombophilia. While thrombophilia and a history of thrombosis are important risk factors, age, race, certain medical conditions and complications of pregnancy are also important and should be factored into decisions regarding the prevention of pregnancy-related venous thromboembolism.

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