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Venous thromboembolism in pregnant women with sickle cell disease: A retrospective database analysis ☆

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ABSTRACT

Introduction: The risk of venous thromboembolism (VTE) is higher during pregnancy, with an incidence between 0.05 and 0.2%, and among persons with sickle cell disease (SCD), yet the rates and risk factors, such as pneumonia, vasoocclusive crisis (VOC), and acute chest syndrome (ACS), associated with pregnancy-related VTE are not firmly established in SCD.
Methods: Inpatient hospital discharge data from 2007-2011 were obtained from the Pennsylvania Health Care Cost Containment Council to estimate the rate of VTE among African American delivery hospitalizations with SCD and to compare pregnancy complications and medical comorbidities among pregnant women with SCD.
Results: Among 212 hospitalized deliveries in African-American women with SCD, 6 (2.8%, 95% CI 1.0%-5.9%) had VTE compared to 0.05 to 2.0% in the general population. Risk factors for VTE included pneumonia and diabetes mellitus. Overall, the prevalence of VTE, among hospitalized deliveries in SCD women with pneumonia, VOC, and/or ACS, 6.6%, was significantly greater than among those without these conditions, 2.2%, $p < 0.001$.
Conclusion: Pregnancy-related VTE in women with SCD appears to be 1.5 to 5 times greater than pregnancy-related VTE in the general population. The higher prevalence of VTE among pregnant women with pneumonia, VOC, and/or ACS, and their potential clinical overlap, suggests that VTE may be missed in such women. We conclude that VTE in pregnant women with SCD may be more common than previously reported, and such women might be candidates for thromboprophylaxis.

Introduction

Sickle cell disease (SCD) and pregnancy are each individually associated with thrombosis. During pregnancy, women have a 4- to 5-fold increased risk of thromboembolism [1,2], and up to 80 percent of thrombotic events are venous [3]. Furthermore, 80% of pregnancy-associated venous thromboembolic events are due to deep venous thrombosis (DVT) with the remaining 20% percent due to pulmonary embolism (PE) [4,5]. The absolute risk of venous thromboembolism (VTE) during pregnancy is between 0.5 and 2.0 per 1000 deliveries and is associated with 1.1 deaths per 100,000 deliveries [6]. VTE risk is greatest in the postpartum period, increasing 20- to 80-fold during the first 6 weeks postpartum [1,2]. VTE risk during pregnancy is related to increased venous distention, decreased venous outflow, decreased mobility, and a decrease in anticoagulant proteins, such as protein S, with a simultaneous increase in procoagulant proteins, such as factor VIII, von Willebrand factor, and fibrinogen [7].

An association between SCD and VTE has been established in several studies. The incidence of PE in hospitalized SCD patients is 50- to 100-fold higher compared with the general population [8], and among hospitalized African-Americans with SCD, PE prevalence is 3.6-fold higher than in age-matched controls [9]. Further, among patients with acute chest syndrome (ACS), the prevalence of pulmonary artery thrombosis is 17% [10], and, at autopsy, PE is found in over a third, 38.1%, and microvascular pulmonary thrombi, although small (<1 millimeter) and undetected by computed tomography, are noted in over a quarter, 28.5% [11].

The risk of DVT and PE in pregnant women with SCD is not firmly established, but among pregnancy-related discharges, DVT and PE are more common, but not significantly so, in women with SCD, OR 2.5 (95% CI 1.5-4.1), than in women without SCD, OR 1.7 (95% CI 0.9-3.1), respectively [12]. Further, among delivery hospitalization, the prevalence of DVT and PE is more common in women with SCD, 2.0% and 1.1%, respectively, than among women without SCD, 0.3%, $p < 0.001$, and 0.1%, $p < 0.001$, respectively ($p <$ [13].

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Table 1
Pregnancy Complications and Medical Comorbidities in Women with Sickle Cell Disease.

	ICD-9 codes	SCD and VTE	SCD and no VTE	*p* value
Number of admissions	-	7 (0.4%)	251 (12.8%)	
Age	-	26.9 ± 3.2	25.5 ± 6.0	0.561
Length of stay	-	8.3 ± 8.5	5.1 ± 7.1	0.247
Inpatient mortality	-	0 (0.0%)	0 (0.0%)	-
Pregnancy Complications				
Preeclampsia/gestational HTN	642.0-642.5, 642.7, 642.9	1 (14.3%)	49 (19.5%)	0.999
Eclampsia	642.6	0 (0.0%)	0 (0.0%)	-
Gestational diabetes mellitus	648.8	1 (14.3%)	6 (2.4%)	0.177
Placental abruption	641.2	0 (0.0%)	1 (0.4%)	0.999
Preterm labor	644	1 (14.3%)	33 (13.1%)	0.999
Caesarean delivery	74	3 (42.9%)	74 (29.5%)	0.429
Intrauterine fetal death	656.4	0 (0.0%)	19 (7.6%)	0.999
Intrauterine fetal growth restriction	656.5	0 (0.0%)	6 (2.4%)	0.999
Postpartum infection	670, 672-677	1 (14.3%)	19 (7.6%)	0.436
Medical Complications				
Obesity	278, 649.1	0 (0.0%)	4 (1.6%)	0.999
Smoking	305.1, 649.0, V1582	0 (0.0%)	19 (7.6%)	0.999
Hypertension	401-405	0 (0.0%)	5 (2.0%)	0.999
Hyperlipidemia	272.4	0 (0.0%)	0 (0.0%)	-
Diabetes mellitus	250, 648.0, 648.8	2 (28.6%)	9 (3.6%)	***0.031***
Myocardial infarction	411-415	0 (0.0%)	1 (0.4%)	0.999
Stroke	431, 434, 436, 674.0	0 (0.0%)	0 (0.0%)	-
Cardiomyopathy	425, 648.5	0 (0.0%)	0 (0.0%)	-
Renal failure	586	0 (0.0%)	0 (0.0%)	-
HIV infection	42	0 (0.0%)	0 (0.0%)	-
Pneumonia	480-486	2 (28.6%)	11 (4.4%)	***0.043***
Sepsis	995.91-995.92	0 (0.0%)	1 (0.4%)	0.999
Anemia	280-281, 648.2	5 (71.4%)	243 (96.8%)	***0.026***
Vasooclusive crisis	282.62	4 (57.1%)	62 (24.7%)	0.073
Acute chest syndrome	517.3	1 (14.3%)	6 (2.4%)	0.177

HTN is hypertension.

An increased risk of VTE in SCD and pregnancy is consistent with the potential causal role of thrombosis in SCD. Nearly every component of hemostasis is altered in SCD, in the direction of a procoagulant phenotype [14], including enhanced platelet function, and procoagulant, anticoagulant, and fibrinolytic systems [14]. The pathogenesis of SCD involves all three aspects of Virchow's triad: increased coagulability, endothelial dysfunction, and impaired blood flow, resulting in a thrombogenic environment [15].

Based on these findings, we hypothesize that the risk of VTE is increased in pregnant women with SCD, and that VTE contributes to the complications of SCD, including pneumonia, vasooclusive crisis (VOC), and ACS, which may be indistinguishable from VTE.

Therefore, we obtained inpatient hospital discharge data for the most recent 5-year period available, 2007-2011, from the Pennsylvania Health Care Cost Containment Council (PHC4) to estimate the prevalence of pregnancy-related VTE in SCD and the prevalence of other pregnancy complications, medical comorbidities, and mortality among hospitalized deliveries in African-American women with SCD [16].

Methods

Inpatient hospital discharge data for hospitalized pregnancies in African American women with SCD for the most recent 5-year period available, 2007-2011, were obtained from the PHC4. The PHC4 is an independent agency that collects inpatient hospital discharge data and ambulatory/outpatient procedure records each year from hospitals and freestanding ambulatory surgery centers in Pennsylvania in order to assess rapidly growing health care costs [16]. An independent broker removed all patient identifying information from PHC4 abstracted data. We estimated the prevalence of VTE among African-American women with SCD with a hospitalized delivery. The time frame for each delivery included the entire antepartum and 3 months postpartum. ICD-9 codes were used to define the following: pregnancy 630-639 (ectopic and molar pregnancy and other pregnancy with abortive outcome), 640-648 (complications mainly related to pregnancy), 650-659 (normal delivery, and other indications for care in pregnancy, labor, and delivery), 670-677 (complications of the puerperium), V27, V270-277, and V279 (outcome of delivery), and 72-74 (delivery); SCD 282.60-282.64 and 282.68-282.69; and VTE 415.11, 415.19, 451.1-451.2, 671.3-671.4, and 673.2. Individuals with more than one hospital admission for VTE were counted only once.

To assess risk factors for VTE and differential outcomes, we compared age, medical comorbidities, the prevalence of pregnancy complications, length of stay, and mortality among hospitalized deliveries in African-American women with SCD with and without VTE beginning with the onset of pregnancy until 3 months postpartum (length of stay refers to the delivery hospitalization only). These variables were also evaluated among hospitalized deliveries in African-American women with SCD according to the presence or absence of pneumonia (ICD-9 codes 480-486), VOC (ICD-9 code 282.62), and ACS (ICD-9 code 517.3), beginning with the onset of pregnancy until 3 months postpartum. Pregnancy complications included any diagnosis of preeclampsia/gestational hypertension, eclampsia, gestation diabetes mellitus, placental abruption, preterm labor, caesarean delivery, intrauterine fetal growth restriction, intrauterine fetal death, and postpartum infection. Medical comorbidities included any diagnosis of obesity, smoking, hypertension, hyperlipidemia, diabetes mellitus, myocardial infarction, stroke, cardiomyopathy, renal failure, HIV infection, pneumonia, sepsis, anemia, VOC, and ACS (Table 1). Additionally, given the shared clinical characteristics of pneumonia, VOC, and ACS with VTE, we estimated the prevalence of VTE among hospitalized deliveries in women with SCD with and without pneumonia, VOC, and/or ACS.

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