Sickle cell disease and the incidence and etiology of preterm birth

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BACKGROUND: Medically indicated delivery can be defined as delivery owing to intervention for maternal or fetal well-being—most commonly because of preeclampsia or nonreassuring fetal status. Among the general population of the United States, approximately two-thirds of preterm deliveries are because of spontaneous labor and/or premature rupture of membranes, whereas the remaining one-third are medically indicated. Despite the increased risk of preterm birth among women with sickle cell disease, the specific etiologies have not been described in the medical literature. Without an understanding of the etiologies of preterm birth in women with sickle cell disease, it is difficult to develop preventative strategies.

OBJECTIVE: This study aimed to estimate the incidence and etiologies of preterm births (spontaneous vs medically indicated) in women with sickle cell disease.

STUDY DESIGN: This was a retrospective, institutional review board–exempt cohort study of deliveries at >20 weeks' gestation in women with sickle cell disease at Duke University Hospital (2013–2020). We screened pregnancy-linked hospitalizations with International Classification of Diseases-9/10 codes for sickle cell disease (n=373). We excluded cases of pregnancy with <20 weeks' gestation, multiple gestation, or unproven sickle cell disease. We limited inclusion to deliveries within Duke (n=66). We compared the proportion of preterm birth cases between the sickle cell disease cohort and the overall Duke population (n=18,365), and the proportion of spontaneous vs medically indicated preterm births between the sickle cell disease cohort and a racially matched US population.

RESULTS: Of the 66 pregnancies, 65 occurred in patients who self-described as Black (98.5%). There were 60.6% (n=40) term and 39.4% (n=26) preterm births vs 85.9% term (n=15,771) and 14.1% preterm (n=2594) births in the Duke population as a whole. The sickle cell disease cohort was nearly 3 times more likely to deliver preterm than the Duke cohort (risk ratio, 2.79; 95% confidence interval, 2.06–3.77; $P<.001$). Among the 26 preterm births in the sickle cell disease cohort, 30.8% (n=8) were spontaneous and 69.2% (n=18) were medically indicated. In the US Black population comparison cohort, 65.4% (n=392,984) of preterm births were spontaneous and 34.6% (n=207,614) were medically indicated. The sickle cell disease cohort had 2 times the risk of medically indicated preterm birth compared with the US population cohort (risk ratio, 2.00; 95% confidence interval, 1.55–2.59; $P<.001$).

CONCLUSION: Maternal sickle cell disease confers nearly triple the risk of preterm birth, which is twice as likely to be medically indicated.

Keywords: preeclampsia, pregnancy, preterm delivery, sickle cell disease, vaso-occlusive crisis

Sickle cell disease (SCD) is a hematological disorder in which abnormal sickle-shaped red blood cells disrupt the flow in small vessels, leading to distal tissue ischemia and inflammation, and conferring substantial morbidity and mortality to affected individuals.[1] As recently as the 1970s, median life expectancy of individuals with SCD largely precluded reproductive success. However, in the past 50 years the anticipated life expectancy has nearly quadrupled—from a median age of 14 in the 1970s to 48 for women by the early 2000s.[2] A significant proportion of individuals with SCD now live well into their reproductive years and even beyond.

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For people with SCD who live into their reproductive years, pregnancy presents unique risks. According to a systematic review and meta-analysis by Oteng-Ntim et al,[3] pregnant individuals with SCD are at a 4-fold increased risk of stillbirth and 6-fold increased risk of maternal death compared with the general population. They are also at a 2-fold increased risk of preterm birth and at an increased risk for a variety of perinatal complications that may lead to preterm birth, such as preeclampsia and fetal growth restriction.[4] In the United States, approximately 1 in 10 infants are born preterm.[5] The etiology of preterm birth falls into 2 main classifications: delivery owing to spontaneous labor and/or premature rupture of membranes and medically indicated delivery. Medically indicated delivery is defined as delivery owing to intervention for maternal or fetal well-being—most commonly owing to preeclampsia or nonreassuring fetal status. Among the general population of the United States, approximately two-thirds of preterm deliveries are owing to spontaneous labor and/or premature rupture of membranes, whereas the remaining one-third are medically indicated.[6,7] Despite the increased risk of preterm birth among women with SCD, the specific etiologies have not been described in the medical literature. Without an understanding of the etiologies of preterm birth in women with SCD, it is difficult to develop preventative strategies.

This study aimed to describe the incidence and cause of preterm birth in the population of women with SCD at Duke University Hospital.

Materials and Methods

Study design

This was a retrospective, institutional review board (IRB)–exempt cohort study of pregnancy outcomes at 20 and 0/7 weeks' gestation and beyond in pregnant individuals with SCD at Duke University Hospital from July 1, 2013 to January 1, 2020. We compared the

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Why was this study conducted?

Pregnant individuals with sickle cell disease (SCD) are at increased risk of preterm birth, but the etiology has not been elucidated previously.

Key findings

Maternal SCD confers nearly triple the risk of preterm birth, which is twice as likely to be medically indicated as opposed to spontaneous. Medically indicated preterm births were primarily owing to a hypertensive disorder of pregnancy, fetal growth restriction, or a complication of SCD. In a small number of cases >1 medical indication was identified, most commonly a vaso-occlusive crisis and a hypertensive disorder of pregnancy.

What does this add to what is known?

The findings provide additional insights into the etiology of preterm birth and raise the question of whether therapies that improve perfusion might decrease complications from SCD in pregnancy, including placenta-mediated complications.

proportion of preterm birth cases between the Duke SCD cohort and the overall Duke population, and the proportion of spontaneous (defined as due to spontaneous labor and/or premature rupture of membranes) vs medically indicated (defined as due to an intervention for maternal or fetal well-being) preterm births between the Duke SCD cohort and a racially matched US population from a similar time period. The participants are described further in the following section.

Participants

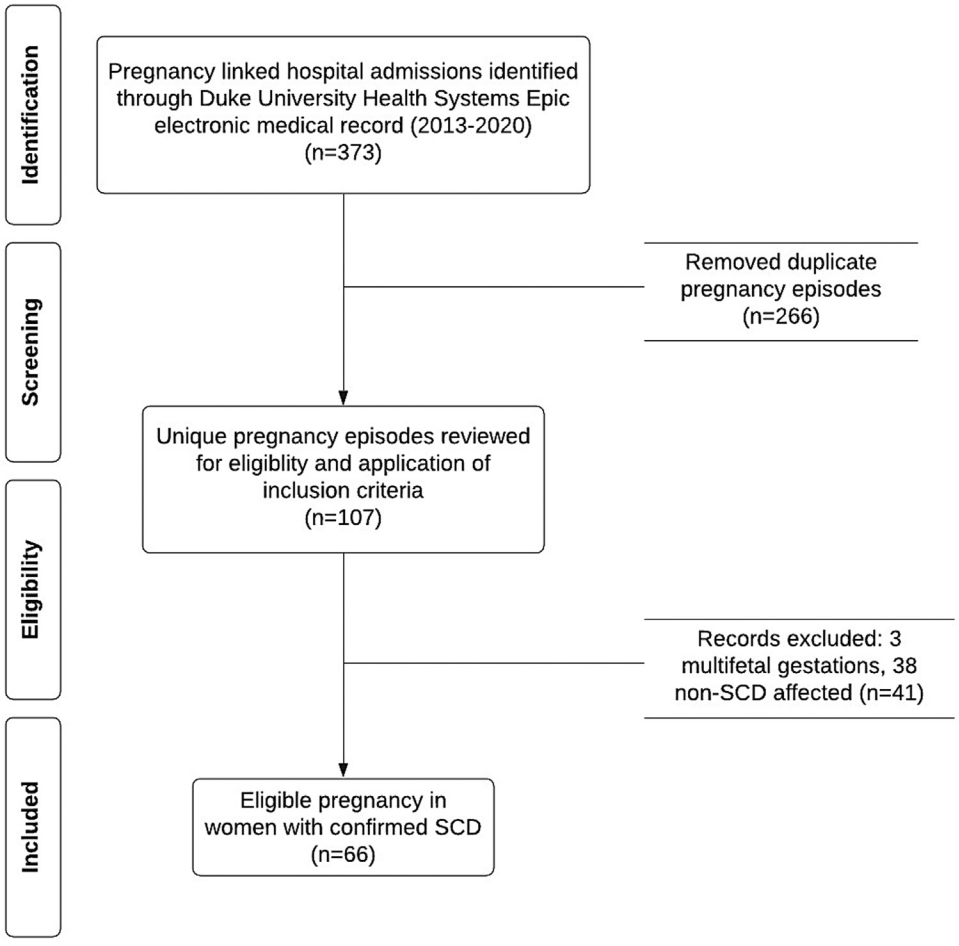
Pregnancies were identified from the electronic medical record (Epic Systems Corporation, Verona, WI) through a search performed by the Duke Departmental Analytics Resource Team (DART) that searched for pregnancy-linked admissions with an SCD diagnosis code (Figure). The date range for data collection extended from the implementation of the Epic electronic medical record system within the Duke University Health System (July 1, 2013) to the time of IRB submission (January 1, 2020). Pregnancy-linked hospital admissions with SCD International Classification of Diseases, Ninth/Tenth Revision (ICD-9/10) diagnosis codes were manually screened (n=373) by an obstetrics and gynecology–trained physician (V.F.). Pregnancy encounters were identified from the hospital admissions and subsequently reviewed for eligibility (n=107). Exclusion criteria were <20 weeks' gestation at delivery, multiple gestation, and absence of documented maternal SCD. Inclusion criteria included ≥20 weeks' gestation at delivery, maternal SCD confirmed by hemoglobin electrophoresis, and delivery within the Duke University Health System (n=66). During the study period, not all of the women with SCD who received their sickle cell care and/or their prenatal care at Duke, delivered at Duke. There were a small number of women who delivered at another institution, and their pregnancies were thus not captured by our search and were excluded from the study. There were an additional small number of patients who received their initial care outside the Duke Health System, but delivered at Duke and were thus included. During the study period, patients with SCD received individualized care based on their needs, but were generally cared for by both maternal-fetal medicine and the sickle-cell team. Most patients presented during pregnancy and had not received preconception counseling. During pregnancy, low-dose aspirin was routinely prescribed. Except for patients with multiple red cell antibodies, transfusions were administered monthly when necessary to maintain a hemoglobin of 8 g/dL. Hydroxyurea was not routinely prescribed. Fetal surveillance included monthly ultrasounds for growth in the third trimester and once or twice weekly antenatal testing starting at 32 weeks' gestation. Timing of delivery was planned for no later than 39 weeks and 37 weeks in patients with sickle SS genotype or a complicated prenatal course.

The comparison group for the proportion of women that had a preterm birth was the overall Duke population. That cohort was developed by retrospective review of all deliveries at >20 weeks' gestation from a similar time period (from March 2014 to July 2020) and has been described elsewhere.[8] The comparison group for the proportion of women that had medically indicated preterm births was generated from US singleton natality data for Black women from the latest data that had been compiled and published as such for the United States as a whole (2000).[7]

Procedures

An electronic case report was created for each eligible pregnancy (n=66). Thus, women with >1 pregnancy may have contributed >1 case. Case report forms were saved in the REDCap secure web application (Vanderbilt University, Nashville, TN) to create an administrative database. Decisions regarding classification of clinical data were made with strict adherence to the American College of Obstetricians and Gynecologists clinical definitions for fetal growth restriction[9] and hypertensive disorders of pregnancy.[10] Demographic data included age, gravidity and parity, marital status, self-described race and ethnicity, and the number of documented prenatal care visits. Assessment of maternal health characteristics included SCD genotype, prepregnancy body mass index, and tobacco use. Pregnancy outcome at birth, interpregnancy intervals, pregnancy complications, and mode of delivery were also recorded. The case reports concluded with neonatal outcomes such as gestational age, birthweight, 5-minute Apgar scores, length of hospitalization, need for admission to the neonatal intensive care unit (NICU), and neonatal mortality within 28 days of life. Five-minute

FIGURE
Pregnancy case selection



SCD, sickle cell disease.

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rather than 1-minute Apgar scores were chosen because of their higher predictive value for long-term cognitive outcomes.[11]

Analysis

Maternal demographics, health characteristics, delivery characteristics, and neonatal outcomes were described. Continuous variables were reported as either mean (standard deviation [SD]) or median (Q1=25th percentile, Q3=75th percentile), as appropriate, and range. Categorical variables were reported as frequency (percentage).

The proportion of women that had a preterm birth in the SCD cohort was compared with that of the overall Duke population. Among the preterm births, the proportion that were medically indicated in the Duke SCD cohort were compared with that reported in the US singleton natality data for Black women. The Pearson chi-square test was used for both comparisons. Risk ratios (RR), 95% confidence intervals (CIs), and *P* values were reported. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC) at a 2-tailed significance level of .05.

Results

There were 66 eligible pregnancies in the Duke SCD cohort. There were a total of 54 unique patients who had 66 pregnancies that were analyzed. Seven had 2 pregnancies, 1 had 3 pregnancies, and 1 had 4 pregnancies. The mean (SD) age of parturients was 27.9 (5.4) years. There was a median (Q1−Q3) of 9 (5−12) prenatal care visits per pregnancy. The median (Q1−Q3) for gravidity and parity of parturients was 2 (1−4) and 1 (0−1), respectively. In half of the pregnancies, parturients were married at the time of delivery. All except 1 patient who did not report race self-identified as Black or African American. One patient additionally identified as Hispanic (Table 1).

With regard to maternal health characteristics (Table 2), the most common sickle cell genotype was HbSS (50.0%; n=33), followed by HbSC (27.3%; n=18), HbSB+ (16.7%; n=11), and other genotypes (6.1%; n=4). Most pregnancies were in women with either normal weight (39.4%; n=26) or overweight

TABLE 1
Maternal demographics

Characteristic	Total (N=66)
Age (y)	
Mean (SD)	27.9 (5.4)
Range	(17.0−40.0)
Number of prenatal care visits	
Median (Q1−Q3)	9 (5−12)
Range	(0−16)
Gravida	
Median (Q1−Q3)	2 (1−4)
Range	(1−10)
Parity	
Median (Q1−Q3)	1 (0−1)
Range	(0−5)
Marital status	
Married	33 (50.0%)
Single	31 (47.0%)
Separated	1 (1.5%)
Divorced	1 (1.5%)
Race	
Black or African American	65 (98.5%)
Unknown or not reported	1 (1.5%)
Ethnicity	
Not Hispanic or Latina	65 (98.5%)
Hispanic or Latina	1 (1.5%)

SD, standard deviation; *Q1−Q3*, 25th percentile to 75th percentile.

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(30.3%; n=20) before pregnancy. Fewer than 10% (n=5) were underweight before pregnancy. Nearly 20% (n=12) of pregnancies were in women who were obese with a body mass index of ≥30 kg/m^2. Information regarding maternal tobacco use was available for 91% of cases. Almost 75% (n=48) of pregnancies were in women who did not use tobacco. An additional 8% (n=5) were in women who quit tobacco use before pregnancy, and 10% (n=7) were in women who reported tobacco use during pregnancy. All but 1 delivery resulted in a live birth (n=65).

In the full cohort of 66 pregnancies, there were 60.6% (n=40) term and 39.4% (n=26) preterm births (Table 3). In the Duke comparison cohort, there were 85.9% (n=15,771) term and 14.1% (n=2594) preterm births (Table 4). The SCD cohort was nearly 3 times more likely to deliver preterm compared with the Duke comparison cohort (RR, 2.79; 95% CI, 2.06−3.77; *P*<.001). Among the 26 preterm births in the SCD cohort, 30.8% (n=8) were spontaneous and 69.2% (n=18) were medically indicated. In the US population comparison cohort, 65.4% (n=392,984) of preterm births were spontaneous and 34.6% (n=207,614) were medically indicated. The SCD cohort was twice as likely to have a medically indicated preterm birth (RR, 2.00; 95% CI, 1.55−2.59; *P*<.001). The median (Q1−Q3) interpregnancy interval was 3.8 years (1.1−5.6) for term births, 4.5 years (2.7−5.0) for spontaneous preterm births, and 2.6 years (1.0−7.2) for medically indicated preterm births.

Medically indicated preterm births were primarily because of a hypertensive disorder of pregnancy, fetal growth restriction, or a complication of SCD (Table 3). In a small number of cases >1 medical indication was identified, most commonly a vaso-occlusive crisis and a hypertensive disorder of pregnancy. Nearly 50% (n=8) of all medically indicated preterm births were because of a hypertensive disorder of pregnancy. Preeclampsia was the diagnosis in two-thirds (n=5) of the cases of a hypertensive disorder of pregnancy. Fetal growth restriction accounted for >20% (n=4) of medically indicated preterm deliveries. Worsening SCD was the medical indication for preterm birth in an additional 20% (n=4) of cases. Another 10% (n=2) were delivered preterm for cholestasis of pregnancy. An additional 17% (n=3) were delivered because of the placenta-mediated complications of oligohydramnios (n=2) and placental abruption (n=1). Cesarean delivery was the most common mode of delivery for both medically indicated and spontaneous preterm births. Nearly 60% (n=14) of preterm deliveries and only 35% (n=14) of term deliveries were by cesarean delivery.

Neonatal outcomes are outlined in Table 5. The median (Q1−Q3) gestational age and birthweight were 37 0/7 (36 0/7−39 0/7) weeks and 2600 (2250−3165) g, respectively. Birthweight was lower for preterm infants than for term infants, but was remarkably lower for infants born preterm for a medical indication than for those born preterm as a result of spontaneous labor (median birthweight, 1918 vs 2395 g), despite the same median gestational age of 35 0/7 weeks. The median 5-minute Apgar scores were similar between term, spontaneous preterm, and medically indicated preterm births. The median length of stay in the hospital was shorter for neonates born at term. Neonates born after a medically indicated preterm birth, however, had a longer median hospital stay compared with those born after a spontaneous preterm birth

TABLE 2
Health characteristics of subjects

Characteristic	Total (N=66)
Sickle cell disease genotype	
HbSS	33 (50.0)
HbSC	18 (27.3)
HbSB+	11 (16.7)
Other or unknown	4 (6.1)
Prepregnancy body mass index	
Underweight	5 (7.6)
Normal	26 (39.4)
Overweight	20 (30.3)
Obese	12 (18.2)
Unknown	3 (4.5)
Tobacco use during pregnancy	
No	48 (72.7)
Yes	7 (10.6)
Quit	5 (7.6)
Unknown	6 (9.1)
Pregnancy outcome	
Liveborn	65 (98.5)
Fetal demise	1 (1.5)

Data presented as number (percentage).

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(6.7 vs 5.7 days), despite the same median gestational age. Admission to the NICU occurred after 50% (n=4) of spontaneous preterm births and after 61% (n=11) of medically indicated preterm births. Fewer than 20% (n=7) of neonates born at term required NICU admission. Two neonatal deaths occurred, one in each preterm group.

Discussion

Principal findings

We found that the SCD cohort was nearly 3 times more likely to deliver preterm compared with the Duke cohort, despite the fact that the women with SCD had low rates of other risk factors for preterm birth such as smoking, close-interval pregnancy for those with parity >0, late or limited prenatal care, and extremes of maternal age. However, those who delivered preterm were twice as likely to have a medical indication for preterm delivery compared with Black women who delivered preterm in the United States as a whole. Qualitative and quantitative analysis of the etiologies of the medically indicated preterm deliveries revealed mechanisms that were overwhelmingly placenta-mediated. Two-thirds of all medically indicated preterm deliveries were because of a hypertensive disorder of pregnancy (including preeclampsia) or fetal growth restriction. In addition, another 20% of medically indicated preterm deliveries were because of placental compromise manifest by either oligohydramnios or placental abruption.

Results in the context of what is known

In a systematic review and meta-analysis of 21 studies describing >26,000 women with SCD, Oteng-Ntim et al[3] found, as did we, a 2-fold increased risk of preterm delivery in women with SCD. However, the results of the systematic review and meta-analysis did not differentiate between spontaneous and medically indicated preterm delivery, nor has this been reported elsewhere. Oteng-Ntim et al[3] also reported a 2-fold increased risk of preeclampsia in women with SCD. The rate of preeclampsia in the United States is approximately 2% to 8%. The rate of any hypertensive disorder of pregnancy among our SCD cohort was 15%.

Clinical and research implications

The increased risk of preterm delivery is recognized among women with SCD,[3,4,12] as is the increased risk of preeclampsia[3,4] and fetal growth restriction or small-for-gestational-age neonates.[3,4,12,13] However, the disproportionate contribution of hypertensive disorders of pregnancy and fetal growth restriction (conditions that are placenta-mediated) and the contribution of worsening SCD to the incidence of preterm delivery have not been described previously. Preterm labor arises from ≥1 pathologic processes that activate a mechanism or mechanisms that lead to parturition.[14] These pathologic processes may include deregulation of the immune system and an exaggeration of inflammatory processes,[14] both of which are more likely to be present in women with SCD[1,15] and contribute to an increased incidence of spontaneous preterm labor. An even greater contributor to the increased incidence of preterm delivery, however, seems to be placental ischemia. Poor placental perfusion results in stillbirth, fetal growth restriction, oligohydramnios, placental abruption, and preeclampsia. In 1989, Roberts et al[16] proposed that a poorly perfused placenta releases factors into the maternal systemic circulation that damage endothelial cells, setting in motion a cascade of coagulation, vasoconstriction, and intravascular fluid redistribution that results in the clinical syndrome that we recognize as preeclampsia. Although our understanding of preeclampsia and the hypertensive disorders of pregnancy has become more refined,[17] the basic paradigm remains intact. Preeclampsia

TABLE 3
Delivery data

Aspects of pregnancy and delivery	Term birth (N=40)	Spontaneous preterm birth (N=7)	Medically indicated preterm birth (N=18)	Total (N=65)
Interpregnancy interval (y), among those with parity >0				
Missing	6/22 (27.3%)	0/6 (0.0%)	0/8 (0.0%)	6/36 (16.7%)
Median (Q1–Q3)	3.8 (1.1–5.6)	4.5 (2.7–5.0)	2.6 (1.0–7.2)	3.9 (1.2–5.7)
Range	(0.5–14.5)	(2.6–12.4)	(0.4–13.0)	(0.4–14.5)
Pregnancy complications providing medical indications for delivery				
Hypertensive disorder of pregnancy	6 (15.0%)	0 (0.0%)	8 (44.4%)	14 (21.5%)
Gestational hypertension	4 (66.7%)	0 (0.0%)	0 (0.0%)	4 (28.6%)
Preeclampsia	2 (33.3%)	0 (0.0%)	5 (62.5%)	7 (50.0%)
Eclampsia	0 (0.0%)	0 (0.0%)	2 (25.0%)	2 (14.3%)
HELLP syndrome	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (7.1%)
Intrahepatic cholestasis	3 (7.5%)	0 (0.0%)	2 (11.1%)	5 (7.7%)
Fetal growth restriction	3 (7.5%)	0 (0.0%)	4 (22.2%)	7 (10.8%)
Vaso-occlusive crisis	16 (40.0%)	0 (0.0%)	4 (22.2%)	20 (30.8%)
Other pregnancy complications at delivery	3 (7.5%)	2 (28.6%)	3 (11.1%)	8 (12.3%)
Delivery mode				
Cesarean	14 (35.0%)	4 (57.1%)	10 (55.6%)	28 (43.1%)
Spontaneous vaginal	22 (55.0%)	3 (42.9%)	8 (44.4%)	33 (50.8%)
Operative vaginal	4 (10.0%)	0 (0.0%)	0 (0.0%)	4 (6.2%)

HELLP, Hemolysis, Elevated Liver enzymes and Low Platelets; *Q1–Q3*, 25th percentile to 75th percentile.

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TABLE 4
Incidence of preterm birth in Duke and US populations

Type and timing of birth	Sickle cell cohort	Duke cohort[a]	Populationdata[b]	Relative risk (95% confidence interval)	*P* value
Term birth (≥37 wk)	40 (60.6%)	15,771/18,365 (85.9%)	—	—	—
Preterm birth (<37 wk)	26 (39.4%)	2594/18,365 (14.1%)	—	2.79 (2.06–3.77)	<.001
Spontaneous preterm birth (<37 wk) out of all preterm births	8 (30.8%)	—	392,984/600,598 (65.4%)	—	—
Medically indicated preterm birth (<37 wk) out of all preterm births	18 (69.2%)	—	207,614/600,598 (34.6%)	2.00 (1.55–2.59)	<.001

[a] This sample was collected between March 2014 and July 2020; [b] US singleton natality data for Black women from 2000.[7]

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TABLE 5
Neonatal outcomes

Outcome	Term birth (N=40)	Spontaneous preterm birth (N=8)	Medically indicated preterm birth (N=18)	Total (N=66)
Gestational age (wk)				
Median (Q1–Q3)	38.0 (37.0–39.0)	35.0 (32.0–36.5)	35.0 (33.0–36.0)	37.0 (36.0–39.0)
Range	(37.0–40.0)	(20.0–37.0)	(23.0–36.0)	(20.0–40.0)
Birthweight (g)				
Median (Q1–Q3)	2990.0 (2622.5–3439.9)	2395.0 (1800.1–2595.0)	1917.6 (1632.1–2340.0)	2599.9 (2250.1–3164.9)
Range	(2059.9–4035.0)	(370.0–2800.1)	(375.9–2554.9)	(370.0–4035.0)
5-min Apgar score				
Median (Q1–Q3)	9.0 (9.0–9.0)	8.0 (6.0–9.0)	9.0 (8.0–9.0)	9.0 (9.0–9.0)
Range	(3.0–9.0)	(0.0–9.0)	(1.0–9.0)	(0.0–9.0)
Length of hospitalization				
Missing	1 (2.5%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Median (Q1–Q3)	2.5 (1.9–3.6)	5.7 (1.9–19.9)	6.7 (3.7–11.2)	3.1 (2.1–6.7)
Range	(1.2–27.8)	(0.2–31.0)	(0.2–160.0)	(0.2–160.0)
NICU admission	7 (17.5%)	4 (50.0%)	11 (61.1%)	22 (33.3%)
Neonatal death (≤28 d of life)	0 (0.0%)	1 (12.5%)	1 (5.6%)	2 (3.0%)

NICU, neonatal intensive care unit; *Q1–Q3*, 25th percentile to 75th percentile.

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is an endothelial disease. In SCD, the endothelium is already chronically activated or otherwise in a state of dysfunction.[18] Thus, it should not be surprising that pregnant women with SCD are particularly vulnerable to the adverse endothelial consequences of a poorly perfused placenta.

Strengths and limitations

Although previous studies have described the increased rates of prematurity and the increased risk of preeclampsia and fetal growth restriction in women with SCD, the specific etiologies of preterm birth in women with SCD have not been described previously. Furthermore, previous large studies were from administrative databases. In contrast, in this study each patient record and the peripartum course of each patient in the SCD cohort were manually reviewed. There were very little missing patient data for the parameters examined. The detailed review of patients' characteristics and their clinical course permitted inferences about etiologies of preterm birth.

Limitations of this study are primarily related to its retrospective nature and the relatively small sample size. Given the small sample size, all comparisons were unadjusted. Furthermore, the numbers were insufficient to draw any conclusions about differences in outcomes by sickle cell genotype, and there were not enough pregnancies in the SCD cohort to adequately evaluate trends in outcomes over time. As described, the cohort was obtained from a single center by retrospective review. Unlike data collected from patients enrolled in a prospective study, the data in this study were collected retrospectively from documentation made in the course of clinical care. Thus, the structure and consistency of the documentation differed from that expected in a prospective study. Clinical care was not dictated by a study protocol, and during the course of the data collection period (2013–2020) there may have been changes in clinical practice at the institutional and national levels. Among the preterm births, the proportion that were medically indicated was compared between the Duke SCD cohort data and the most recently published US singleton natality data for Black women from 2000. It would have been optimal to compare the proportion of medically indicated preterm births between the Duke SCD cohort data and contemporaneous US data (2013–2020). Furthermore, multiple pregnancies occurred within the same patients, in both the Duke SCD cohort and presumably in the Duke comparison cohort, and would not technically be considered "independent," an important underlying assumption of many statistical tests, including otherwise uncomplicated unadjusted analyses as were done in this study. Women were not bound to deliver at Duke. Not all of the women with SCD who received their sickle cell care and/or their prenatal care at Duke, delivered at Duke. Consequently, their pregnancies were excluded from the study. A small number who received their initial care outside the Duke Health System, delivered at Duke and were included. Nonetheless, the vast majority of the patients both received their care and delivered at Duke. It should be noted that although the

sample size was small, this SCD cohort represents a large series for this rare condition in pregnancy and allowed for a detailed review of each individual case, which would not have been possible in a larger, database study.

Conclusions

What may not have been considered previously is that impaired vascular perfusion in SCD will lead to maternal organ impairment and placental ischemia, resulting in complications from SCD, and placenta-mediated adverse pregnancy outcomes such as preeclampsia, other hypertensive disorders of pregnancy, fetal growth restriction, oligohydramnios, placental abruption, and stillbirth. The findings provide additional insights into the etiology of preterm birth and raise the question of whether therapies that improve perfusion might decrease complications from SCD in pregnancy, including placenta-mediated complications. The same mechanisms that result in acute and chronic organ damage in SCD likely result in perinatal inflammation and placental ischemia, and the same therapies that decrease inflammation and improve perfusion in SCD will likely improve pregnancy outcomes for both women with SCD and their unborn infants in the future. ■

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