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Sickle cell disease and the incidence and etiology of preterm birth

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Title: Sickle cell disease and the incidence and etiology of preterm birth

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

Short title: Sickle cell disease and preterm birth

Word count: 3213

AJOG at a Glance:

A. Why was this study conducted?
   - Pregnant individuals with sickle cell disease (SCD) are at an increased risk of preterm birth, but the etiology has not previously been elucidated.

B. What are the 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 due to a hypertensive disorder of pregnancy, fetal growth restriction, or a complication of SCD.
   - In a small number of cases more than one medical indication was identified, most commonly a vaso-occlusive crisis and a hypertensive disorder of pregnancy.

C. What does this study add to what is already known?

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

Key Words

sickle cell disease

preeclampsia

preterm delivery

pregnancy

vaso-occlusive crisis

Abstract

Background:

Medically indicated delivery can be defined as delivery due to intervention for maternal or fetal well-being—most commonly due to preeclampsia or non-reassuring fetal status. Among the general population of the United States, approximately two-thirds of preterm deliveries are due to spontaneous labor and/or premature rupture of the membranes while the remaining one third are medically indicated. Despite the increased risk of preterm birth among women with sickle cell disease (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.

Objective:

To estimate the incidence and etiologies of preterm births (spontaneous vs medically indicated) in women with SCD.

Study Design:

This was a retrospective, IRB-exempt cohort study of deliveries greater than 20 weeks gestation in women with SCD at Duke University Hospital (2013-2020). We screened pregnancy-linked hospitalizations with SCD ICD-9/10 codes (n=373). We excluded cases of pregnancy less than 20 weeks gestation, multiple gestation, and unproven SCD. We limited inclusion to deliveries within Duke (n=66). We compared the proportion of preterm birth cases between the SCD cohort and overall Duke population (n=18,365), and the proportion of spontaneous vs medically indicated preterm births with 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 compared to 85.9% term (n = 15,771) and 14.1% preterm (n = 2,594) births in the Duke population as a whole. The SCD cohort was nearly 3 times more likely to

deliver preterm than the Duke cohort (risk ratio [RR] = 2.79, 95% confidence interval [CI] = 2.06, 3.77; p < 0.001). 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 U.S Black 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 had 2 times the risk of medically indicated preterm birth compared to the U.S. population cohort (RR = 2.00, 95% CI = 1.55, 2.59; p < 0.001).

Conclusion:

Maternal SCD confers nearly triple the risk of preterm birth which is twice as likely to be medically indicated.

Introduction

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 confers substantial morbidity and mortality to affected individuals.[1] As recently as the 1970's, median life expectancy for individuals with sickle cell disease 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 sickle cell disease now live well into their reproductive years and even beyond.

For people with SCD who live into their reproductive years, pregnancy presents unique risks. Based on a systematic review and meta-analysis by Oteng-Ntim, et al., pregnant individuals with SCD are at a four-fold increased risk of stillbirth and six-fold increased risk of maternal death compared to the general population.[3] They are also at a two-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 one in ten infants are born preterm.[5] The etiology of preterm birth falls into two main classifications: delivery due to spontaneous labor and/or premature rupture of the membranes and medically-indicated delivery. Medically indicated delivery is defined as delivery due to intervention for maternal or fetal well-being—most commonly due to preeclampsia or non-reassuring fetal status. Among the general population of the United States, approximately two-thirds of preterm deliveries are due to spontaneous labor and/or premature rupture of the membranes while 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.

In this study, our aim was 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 proportion of preterm birth cases between the Duke SCD cohort and the overall Duke population and compared the proportion who had spontaneous (defined as due to spontaneous labor and/or premature rupture of the membranes) versus medically-indicated (defined as due to an intervention for maternal or fetal well-being) preterm birth with a racially-matched U.S. population from a similar time period. See the description of *Subjects* below.

Subjects

Pregnancies were identified from the electronic medical record (Epic – Verona, WI) through a search performed by the Duke Departmental Analytics Resource team (DART) who searched for pregnancy-linked admissions with an SCD diagnosis code. The date range for data collection extended from the implementation of the Epic electronic medical record system within the Duke University Heath System (July 1, 2013) and terminated at the time of IRB submission (January 1, 2020). Pregnancy-linked hospital admissions with SCD ICD-9/10 diagnosis codes were manually screened (n = 373) by an OBGYN-trained physician (VF). Pregnancy encounters were identified from the hospital admissions and subsequently reviewed for eligibility (n = 107). Exclusion criteria were pregnancy less than 20 weeks gestation at delivery, multiple gestation, and maternal SCD not documented. Inclusion criteria included pregnancy equal to or greater than 20 weeks 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. Since they did not deliver at Duke, their pregnancies were 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. Since they delivered at Duke, they were 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 planned for 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 greater than 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 U.S. singleton natality data for Black women from the latest data that had been compiled and published as such for the U.S. as a whole (2000).[7]

Procedures

An electronic case report was created for each eligible pregnancy (n = 66). Thus, a woman with more than one pregnancy may have contributed more than one case. Case report forms were saved in the Research Electronic Data Capture (REDCap) secure web application to create an administrative

database. Decisions regarding classification of clinical data were made with strict adherence to the American College of Obstetrics and Gynecology (ACOG) 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, pre-pregnancy 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 neonatal intensive care unit (NICU), and neonatal mortality within 28 days of life. (Five-minute APGARs were chosen over one-minute Apgar scores due to 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 (percent).

The proportion of women that had a preterm birth in the SCD cohort was compared to the overall Duke population. Among the preterm births, the proportion that were medically indicated in the Duke SCD cohort were compared with the U.S. singleton natality data for Black women. Pearson's chi-square test was used for both comparisons. Risk ratios (RR), 95% confidence intervals (CI), and p values were reported. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC) at a two-tailed significance level of 0.05.

Results

There were 66 eligible pregnancies in the Duke SCD cohort. There were a total of 54 unique patients who had 66 pregnancies which were analyzed. Seven had two pregnancies, one had three pregnancies and one had four pregnancies. The mean (SD) age of parturients was 27.9 (5.4) years. There were 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 one patient who did not report race, self-identified as Black or African American. One patient additionally identified as Hispanic. (See Table 1).

With regards to maternal health characteristics (see 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 then other genotypes (6.1%; n = 4). Most pregnancies were in women of either normal weight (39.4%; n = 26) or overweight (30.3%; n = 20) prior to pregnancy. Fewer than 10% (n = 5) were underweight prior to pregnancy. Nearly 20% (n = 12) of pregnancies were in women who were obese with a body mass index of 30 kg/m2 or greater. 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 prior to pregnancy. Ten percent (n = 7) were in women who reported tobacco use during pregnancy. All but one 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 (see Table 3). In the Duke comparison cohort, there were 85.9% (n = 15,771) term and 14.1% (n = 2,594) preterm births (see Table 4). The SCD cohort was nearly three-times more likely to deliver preterm compared to the Duke comparison cohort (RR = 2.79; 95% CI = 2.06, 3.77; $p < 0.001$). 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 U.S 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; $p < 0.001$). The median (Q1,

Q3) interpregnancy interval for term births was 3.8 years (1.1, 5.6), for spontaneous preterm births was 4.5 years (2.7, 5.0), and for medically indicated preterm births was 2.6 years (1.0, 7.2).

Medically indicated preterm births were primarily due to a hypertensive disorder of pregnancy, fetal growth restriction, or a complication of SCD (Table 3). In a small number of cases more than one 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 due to 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 more than 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 due to the placental-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 were by cesarean, whereas only 35% (n = 14) of term deliveries were by cesarean.

Neonatal outcomes are outlined in Table 5. The median (Q1, Q3) gestational age and birthweight was 37 0/7 (36 0/7, 39 0/7) weeks and 2600 (2250, 3165) grams, respectively. Birthweight was lower for babies born preterm compared to term, but was remarkably lower for babies born preterm for a medical indication compared to those born preterm as a result of spontaneous labor (median birthweight 1918 grams vs 2395 grams) despite the same median gestation 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 to those born after a spontaneous preterm birth (6.7 days vs 5.7 days), despite the same median gestational age. Admission to the neonatal intensive care unit (NICU) occurred after

50% (n = 4) of spontaneous preterm birth 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 three times more likely to deliver preterm compared to 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 greater than 0, late or limited prenatal care, and extremes of maternal age. Among the women who delivered preterm, however, they were twice as likely to have a medical indication for preterm delivery compared to the Black women who delivered preterm in the U.S. as a whole. Qualitative and quantitative analysis of the etiologies of the medically indicated preterm deliveries revealed mechanisms that were overwhelmingly placental-mediated. Two-thirds of all medically indicated preterm deliveries were due to a hypertensive disorder of pregnancy (including preeclampsia), or fetal growth restriction. In addition, another 20% of medically indicated preterm deliveries were due to 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 more than 26,000 women with SCD, Oteng-Ntim et al found, as did we, a two-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 also reported a two-fold increased risk of preeclampsia in women with SCD. The rate of preeclampsia in the U.S is approximately 2-8%. 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,[3,4,12,13] but the disproportionate contribution of hypertensive disorders of pregnancy and fetal growth restriction to the incidence of preterm delivery, conditions which are placental-mediated, and the contribution of worsening SCD, have not been described previously. Preterm labor arises from one or more pathological processes that activate a mechanism or mechanisms that lead to parturition.[14] These pathological 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, appears 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 we recognize as preeclampsia. While our understanding of preeclampsia and the hypertensive disorders of pregnancy has become more refined,[17] the basic paradigm remains intact. Preeclampsia is an endothelial disease. In SCD, the endothelium is already chronically activated or otherwise in a state of dysfunction.[18] It should not be a surprise then 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 previously been described. Furthermore, prior large studies were

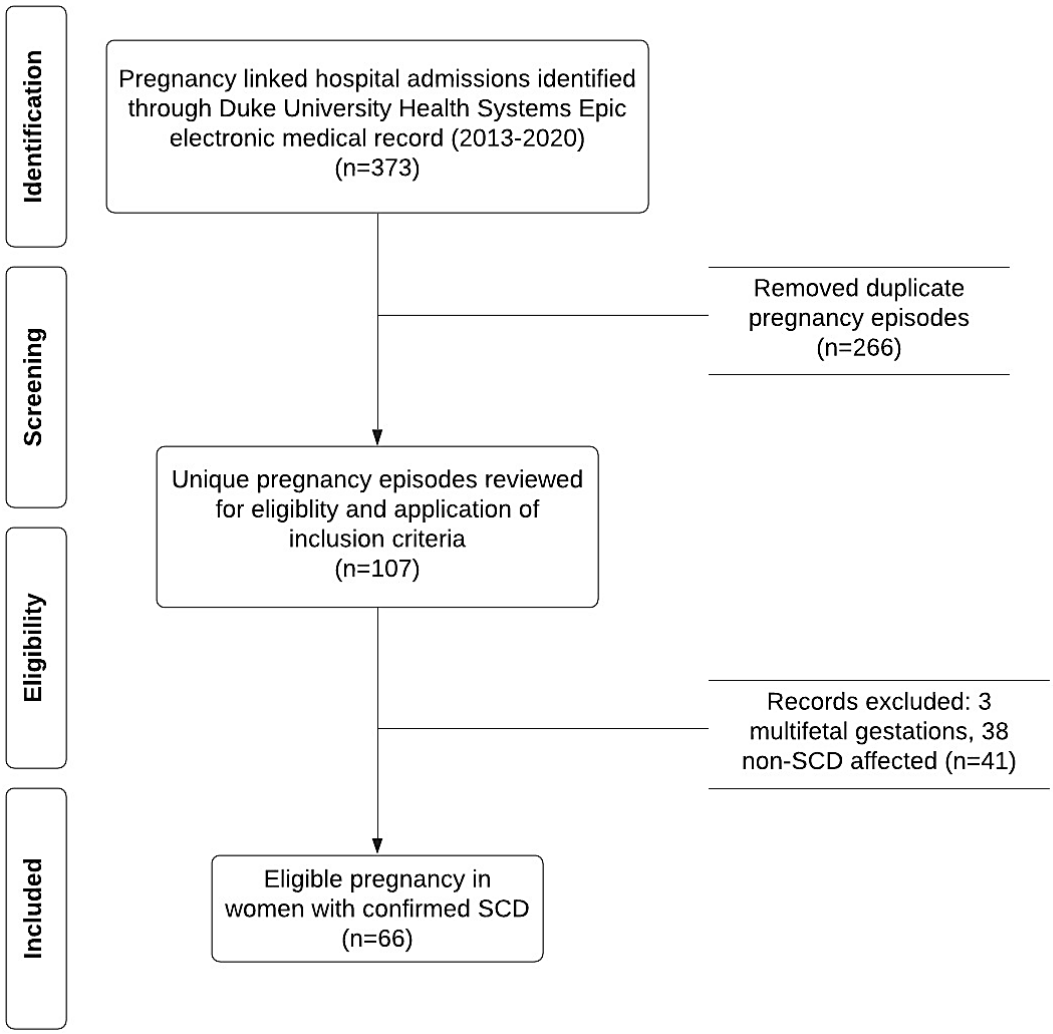
279 from administrative databases. In contrast, in this study each patient record and the peripartum course
280 of each patient in the SCD cohort was manually reviewed. There was very little missing patient data for
281 the parameters examined. The detailed review of patients' characteristics and their clinical course
282 permitted inferences about etiologies of preterm birth.

283 Limitations of this study relate primarily to the retrospective nature of the study and the
284 relatively small sample size. Given the small sample size, all comparisons were unadjusted.
285 Furthermore, the numbers were insufficient to draw any conclusions about differences in outcomes by
286 sickle cell genotype, nor were there enough pregnancies in the SCD cohort to adequately evaluate
287 trends in outcomes over time. As described, the cohort was obtained from a single center by
288 retrospective review. Unlike data collected from patients enrolled in a prospective study, the data in this
289 study was collected retrospectively from documentation made in the course of clinical care. Thus, the
290 structure and consistency of the documentation differed from that expected in a prospective study.
291 Clinical care was not dictated by a study protocol and during the course of the data collection period
292 (2013-2020) there may have been changes in clinical practice at the institutional and at the national
293 level. Among the preterm births, the proportion that were medically indicated in the Duke SCD cohort
294 were compared with the most recently published U.S. singleton natality data for Black women (from
295 2000). It would have been optimal to compare the proportion that were medically indicated in the
296 Duke SCD cohort with contemporaneous US data (2013-2020). Also, multiple pregnancies occurred
297 within the same patient, in both the Duke SCD cohort and presumably in the Duke comparison cohort,
298 and would not technically be considered "independent," an important underlying assumption of many
299 statistical tests, including otherwise uncomplicated unadjusted analyses as were done in this study.
300 Women were not bound to deliver at Duke. Not all of the women with SCD who received their sickle cell
301 care and/or their prenatal care at Duke, delivered at Duke. Consequently, their pregnancies were
302 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 while 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 previously may not have been considered is that impaired vascular perfusion in SCD will lead to maternal organ impairment and placental ischemia resulting in complications from SCD, and placental-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 that therapies which improve perfusion might decrease complications from SCD in pregnancy, including placental-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 babies in the future.



320
321 **Figure 1**. Pregnancy case selection.

Table 1. Maternal demographics	
	Total (N=66)
Age (years)	
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%)

Table 2. Health characteristics of subjects	
	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%)
Pre-pregnancy 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%)

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Table 3. Delivery data				
	Term birth (N=40)	Spontaneous preterm birth (N=7)	Medically indicated preterm birth (N=18)	Total (N=65)
Interpregnancy interval (years), 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%)

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Table 4. Incidence of preterm birth in Duke and US populations					
	Sickle cell cohort	**Duke cohort****	**Population data†**	**Relative risk (95% confidence interval)**	**P value**
Term birth (≥ 37 weeks)	40 (60.6%)	15,771/18,365 (85.9%)	---	---	---
Preterm birth (< 37 weeks)	26 (39.4%)	2594/18,365 (14.1%)	---	2.79 (2.06, 3.77)	<0.001
Spontaneous preterm birth (< 37 weeks) out of all preterm births	8 (30.8%)	---	392,984/600,598 (65.4%)	---	---
Medically indicated preterm birth (< 37 weeks) out of all preterm births	18 (69.2%)	---	207,614/600,598 (34.6%)	2.00 (1.55, 2.59)	<0.001

**This sample was collected between March and July of 2014-2020

†US singleton natality data for Black women from 2000[7]

Table 5. Neonatal outcomes				
	Term birth (N=40)	Spontaneous preterm birth (N=8)	Medically indicated preterm birth (N=18)	Total (N=66)
Gestational age (weeks)				
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 (grams)				
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 minute APGARs				
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 days of life)	0 (0.0%)	1 (12.5%)	1 (5.6%)	2 (3.0%)

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