OBSTETRICS

Contemporary outcomes of sickle cell disease in pregnancy

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BACKGROUND: Data regarding pregnancy outcomes in sickle cell disease are conflicting. Previous studies are limited by small sample size, narrow geographic area, and a wide range of resource availability.

OBJECTIVE: The purpose of this study was to examine the association between maternal sickle cell disease and adverse pregnancy outcomes in a contemporary North American cohort.

STUDY DESIGN: We performed a retrospective cohort study of 2,027,323 women with singleton pregnancies delivered in California from 2005–2008. Deliveries at <24 or >42 6/7 weeks of gestation were excluded. Women with sickle cell disease were compared with control subjects. Maternal outcomes of interest included preeclampsia, preterm delivery, placental abruption, oligohydramnios, and cesarean delivery; neonatal outcomes included small for gestational age, anomalies, stillbirth, neonatal death, and infant death.

RESULTS: The prevalence of sickle cell disease was 0.017%. Compared with control subjects, women with sickle cell disease were more likely to have limited prenatal care (7.4 vs 3.8%; *P*=.001), underlying chronic hypertension (2.3% vs 1.1%; *P*=.038), and fetal anomalies (14.0 vs 6.4%; *P*<.001). The increased odds of fetal anomalies persisted after adjustment for multiple confounders (odds ratio, 1.73; 95% confidence interval, 1.26–2.38). Women with sickle cell disease also had higher odds of severe preeclampsia (odds ratio, 3.75; 95% confidence interval, 2.21–6.38), preterm delivery (odds ratio, 2.50; 95% confidence interval, 1.93–3.21), small for gestational age (odds ratio, 1.96; 95% confidence interval, 1.18–3.25), and cesarean delivery (odds ratio, 1.93; 95% confidence interval, 1.40–2.67).

CONCLUSION: Women with sickle cell disease are at high risk of maternal and neonatal morbidity. Low rates of fetal and neonatal death may reflect improved antenatal surveillance and management as compared with previous studies. The association between sickle cell disease and fetal anomalies warrants further investigation.

Key words: fetal anomalies, outcome, pregnancy, sickle cell disease

Sickle cell disease (SCD) is one of the most common inherited genetic disorders in the world and is associated with significant lifelong morbidity.[1] Approximately 1 in 500 African American and 1 in 1200 Hispanic American births in the United States are affected by SCD, with important implications for both maternal and neonatal outcomes.[2,3] Maternal morbidity may occur secondary to acute SCD-related crises, in addition to venous thromboembolism, infection, or chronic end-organ dysfunction. Numerous studies have demonstrated significantly increased rates of intrauterine growth restriction, preterm delivery (PTD), and small for gestational age (SGA) infants in women with SCD, likely part to because of underlying hypertension and placental insufficiency. However, data regarding the association between SCD and gestational diabetes mellitus, preeclampsia, intrauterine fetal death (IUFD), neonatal death, and maternal death are conflicting, and estimates vary widely in regards to the magnitude of associated risk.[4-10]

A recent systematic review and meta-analysis of 19 studies from 9 different countries reported an increased risk of both IUFD and neonatal death in the setting of maternal SCD, with pooled odds ratios of 4.05 and 2.71, respectively.[7] A markedly increased risk of maternal death was seen among women with SCD compared with women without SCD; however, this effect was driven largely by data from low-income countries, in which the odds of maternal death were nearly 30 times higher than that of women without SCD.[11,12] Although maternal SCD status did not confer any significant additional risk for maternal death in high-income countries, such as the United States, previous studies have been limited similarly by small sample sizes, long periods of data accrual, and variations in clinical practice that may limit their generalizability.[7,13,14]

Given the significant impact and burden of disease associated with maternal SCD, additional data are needed regarding outcomes and risks of adverse pregnancy outcomes. We therefore sought to investigate outcomes of SCD in pregnancy in a contemporary North American cohort.

Methods

We performed a retrospective cohort study that included all singleton pregnancies delivered in the state of California from 2005–2008. The data were derived from linked mother-infant datasets from the California Vital Statistics Birth Certificate Data, infant Vital Statistics Death Certificate Data, California Patient Discharge Data, and Vital Statistics Fetal Death File. Data linkage is performed by the California Office of Statewide Health Planning and Development Healthcare Information Resource Center, under the California Health and Human Services Agency, which used a unique "record linkage number" specific to the mother-infant pair. The state of California maintains these linked datasets that include health information from maternal antepartum and postpartum hospital records for the 9 months before delivery and 1 year after delivery, as well as birth records and all infant admissions that occur within the

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first year of life. We obtained human subjects approval from the Institutional Review Board at Oregon Health & Science University, the California Office of Statewide Health Planning and Development, and the Committee for the Protection of Human Subjects. The linked dataset did not contain potential patient privacy/identification information, so informed consent was exempted.

Our primary exposure of interest was a diagnosis of SCD in pregnancy. The following International Classification of Diseases, 9th Revision (ICD-9) codes were used: 282.60 (sickle cell disease, unspecified), 282.61 (Hg-S disease), 282.62 (Hg-S with crisis), 282.64 (Hg-S with vaso-occlusive pain). Three hundred forty-four cases were compared with 2,026,979 control pregnancies. Patients with sickle trait and other hemoglobinopathies were excluded, as were deliveries at <24or >42 6/7 weeks of gestation. To avoid the confounding of complications linked to multifetal gestations, we excluded these pregnancies for both the cases and the controls. Analyses were conducted with Stata software (version 12; Stata Corporation, College Station, TX). Outcomes of interest that were examined were also determined retrospectively through the use of ICD-9 codes and included preeclampsia, severe preeclampsia, eclampsia, abruption, IUFD, PTD <37 weeks of gestation, PTD <32 weeks of gestation, SGA, gestational diabetes mellitus, neonatal death, and infant death.

Our analytic approach was first to conduct bivariate analyses of women with and without the exposure of interest for each of the outcomes of interest. Statistical comparisons of categoric variables were made with the use of chi-squared tests. We then conducted multivariable logistic regression models to control for potential confounding. Potential confounders that were assessed included maternal age (≥35 years old and <20 years old), maternal education (>12 years vs ≤12 years), insurance status (private insurance vs public insurance or no insurance), race/ethnicity, parity, diabetes mellitus mellitus, chronic hypertension, and gestational diabetes mellitus. Additionally, we excluded those variables that were used as the outcome of interest when appropriate. For example, we did not adjust for preeclampsia when evaluating preeclampsia as an outcome. Adjusted odds ratios were calculated for all outcomes of interest. Statistical significance was determined by a probability value of <.05 and/or 95% confidence intervals.

TABLE 1
Maternal demographic characteristics

Characteristic	Sickle cell disease (n=344), n (%)	Control (n=2,026,979), n (%)	*P* value
Maternal age, y			.08
≤20	31 (9.0)	191,244 (9.4)	
21-34	266 (77.3)	1,485,717 (73.3)	
≥35	47 (13.7)	350,018 (17.3)	
Maternal race			<.001
African American	264 (76.7)	103,359 (5.1)	
White	13 (3.8)	538,457 (26.6)	
Hispanic	43 (12.5)	1,102,700 (54.5)	
Asian/Pacific Islander	10 (2.9)	241,760 (11.9)	
Other/unknown	14 (4.1)	38,370 (1.9)	
Highest education level			.13
High school or less	170 (49.4)	1,085,946 (53.6)	
Some college or graduate degree	165 (48.0)	882,097 (43.5)	
Unknown	9 (2.6)	58,936 (2.9)	
Nulliparous	159 (46.2)	806,593 (39.8)	.011
Limited prenatal care	26 (7.4)	77,392 (3.8)	.011
Public insurance	183 (53.2)	981,322 (48.4)	.076
Tobacco use	7 (2.0)	13,039 (0.6)	.001
Chronic hypertension	8 (2.3)	23,075 (1.1)	.038

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Results

A total of 2,027,323 pregnancies met inclusion criteria, among which 344 cases of SCD were identified. Maternal demographic characteristics are shown in Table 1. The prevalence of SCD was 0.017%. Compared with control subjects, women with SCD were more likely to be African American (76.7% vs 5.1%; *P*<.001), to be nulliparous (46.2% vs 39.8%; *P*=.011), to have underlying chronic hypertension (2.3% vs 1.1%; *P*=.038), and to have limited prenatal care, as defined by <5 visits (7.4% vs 3.8%; *P*=.001). A trend toward higher rates of public insurance was noted in the SCD group, although this was not statistically significant (53.2% vs 48.4%; *P*=.07). Maternal educational status and the relative percentages of women aged <20 years or ≥35 years at time of delivery were also similar between groups.

In univariate analyses, SCD was associated with a statistically significant increase in rates of preeclampsia, PTD, and SGA (Figure). Women with SCD had higher rates of both mild preeclampsia (10.2% vs 3.0%; *P*<.001) and severe preeclampsia (5.4% vs 0.9%); however, no difference in the rates of eclampsia were noted between women with or without SCD (0.0% vs 0.07; *P*=.62; data not shown). The incidence