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Impact of sickle cell disease and thalassemias in infants on birth outcomes

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ABSTRACT

Objective: The contribution of sickle cell disease (SCD) and other common thalassemias in infants to adverse birth outcomes is under-studied. We therefore sought to compare adverse birth outcomes in infants with and without hemoglobinopathy.

Study design: Retrospective cohort study utilizing a population-based dataset from Florida (1998–2007, n = 1,564,038). The primary outcomes were low birthweight (LBW), very low birthweight (VLBW), preterm birth (PTB), very preterm birth (VPTB) and small for gestational age (SGA). We used propensity scores to match infants with hemoglobinopathy to those without hemoglobinopathy on selected variables. To approximate relative risks, we generated adjusted odds ratios (AOR) and 95% confidence intervals (CI) from logistic regression models and accounted for the matched design using generalized estimating equations framework.

Results: Infants with SCD or thalassemia had a heightened risk for LBW (AOR = 1.58, 95% CI: 1.29–1.93), VLBW (AOR = 3.01, 95% CI: 2.12–4.25), PTB (AOR = 1.36, 95% CI: 1.12–1.65), VPTB (AOR = 2.70, 95% CI: 1.93–3.78), and neurological conditions (AOR = 2.04, 95% CI: 1.48–2.81) compared to infants without hemoglobinopathy.

Conclusion: Infants with SCD or thalassemia experience considerably higher risks for multiple infant morbidities. Our findings are potentially important in prenatal counseling, as well as for targeted care of affected pregnancies in the prenatal period.

1. Introduction

As the most common inherited hemoglobin disorders [1,2], sickle cell disease (SCD) and thalassemias represent major global health issues. Approximately 5% of the world's population are carriers of a gene for SCD or thalassemia [3]. Although the exact prevalence of thalassemia is unknown, the United States Centers for Disease Control (CDC) estimates about 1000 people live with beta thalassemia major (i.e., Cooley's anemia) in the US [4].

Although it is possible for many women with hemoglobin disorders to carry successful pregnancies [5,6], mothers with SCD and thalassemia are at increased risk of serious pregnancy complications [5–9]. Maternal SCD increases the risk of preterm delivery, low birthweight, placental previa, preeclampsia, and endometritis [5–10], whereas thalassemias heighten the risk of cardiac failure, alloimmunization, viral infection, thrombosis, endocrine and bone disturbances [10]. These conditions are related to the severity of the maternal anemia, dysfunction of red blood cells, and the resulting poor systemic oxygenation, as well as transfusion-related complications.

Compared to maternal hemoglobinopathies, the contributions of fetal SCD and other common fetal thalassemias have been insufficiently explored in relation to birth outcomes. As part of the Cooperative Study of Sickle Cell Disease, Brown and colleagues conducted a natural history study of mothers and infants with SCD [11]. While the authors did not find significant differences in poor birth outcomes and neonatal complications (i.e., jaundice, fetal distress, anemia, and respiratory distress) by infant hemoglobin phenotype, an association between maternal anemia and poor birth outcomes was observed [11].

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Despite the seminal contributions of Brown et al. on the understanding of maternal and infant hemoglobinopathies and birth outcomes, some important limitations regarding the study design and generalizability of the findings were apparent. Therefore, to provide further insight on the role of SCD and thalassemias on birth outcomes, we conducted a retrospective cohort study utilizing a population-based data from the state of Florida. We hypothesized that infants with SCD or thalassemia will have an increased risk of adverse birth outcomes (preterm birth, low birthweight, small-for-gestational age and neurological conditions) than infants without SCD or thalassemia.

2. Materials and methods

Data were derived using two linked databases: the Florida vital statistics birth records, which included abstracted maternal socio-demographic information, and the Florida Agency for Health Care Administration's Inpatient Hospital Discharge Data, which contains maternal and infant hospitalization information including diagnosis for thalassemia, sickle cell, and maternal pregnancy complications. All singleton births that occurred in the state of Florida over the study period (1998–2007) were included in the vital statistics birth records (1,700,734 live singleton births). The inclusion criteria for this study was as follows: singleton births with gestational age ranging from 20 to 44 weeks and with non-missing birthweight.

The main exposures of interest – either thalassemia or SCD – were abstracted from the hospital discharge data using ICD-9-CM codes [12]. The primary endpoints were fetal growth outcomes, which included low birthweight (LBW: $<$2500 g), very low birthweight (VLBW: $<$1500 g), preterm birth (PTB: $<$37 weeks of gestation), very preterm birth (VPTB: $<$33 weeks of gestation), and small for gestational age (SGA: birthweight $<$10th percentile for gestational age using population reference standards [13]). Birthweight was measured immediately after birth and documented in grams. Gestational age was based on a clinical estimate calculated by the physician. A second method involved taking the interval between the date of last menstrual period reported by the mother at first prenatal visit and the date of delivery. We generated results in the study for each method of computation of gestational age for the purpose of sensitivity analysis.

The secondary outcome consisted of a composite variable for central nervous system (CNS) conditions/neurological outcomes among infants, including: cephalhematoma; intracranial hemorrhage, seizure, and other CNS defects; facial nerve injury; brachial plexus injury; feeding difficulty; fetal distress; and cerebral depression in the neonatal period. Infants in the study were followed through the first year of life for diagnosis of these neurological outcomes since these conditions are rarely diagnosed at delivery.

We considered the following maternal socio-demographic characteristics as covariates: maternal age, maternal race, maternal education, maternal marital status, maternal prenatal smoking, adequacy of prenatal care and parity. Maternal age was dichotomized as women who were of advanced age ($\geq$35 years old) or $<$35 years old. Maternal race was grouped into four categories: white, black, Hispanic or other. Maternal education was categorized as those without a high school degree ($\leq$12 years of education) and those with at least a high school degree ($\geq$12 years of education). Mothers with missing and unknown educational information were grouped under the latter category (i.e., without a high school degree). Maternal marital status was grouped as either: married or unmarried, with all persons divorced, widowed, or of unknown marital status classified as unmarried. Prenatal smoking was categorized as yes (smokers) or no (non-smoker). In order to describe the level of prenatal care utilization, we used the revised graduated index algorithm (R-GINDEX) [14,15]. The index assesses the adequacy of care based on the trimester of prenatal care initiation, the number of visits, and the gestational age of the infant at birth. Inadequate prenatal care was defined as either missing prenatal care information, had prenatal care but the level was considered suboptimal (fewer visits as compared to the length of pregnancy), or mothers had no prenatal care at all. Parity was dichotomized as nulliparous or multiparous. We also performed crude frequency comparisons with respect to common pregnancy complications that included: anemia, gestational and pre-gestational diabetes mellitus, hypertensive disorders of pregnancy, preeclampsia, eclampsia, placental abruption, placenta previa, alcohol and drug abuse.

2.1. Statistical analysis

Baseline characteristics between women in the study were compared using the Chi-square test. The test results showed that the two groups of women (i.e., exposed and unexposed) might be significantly different from each other with respect to baseline characteristics. To balance the exposed and the unexposed groups with respect to these baseline variables, we used the propensity scoring algorithm defined as the probability of a woman being assigned to an exposed group given a set of baseline variable [16]. For each computed propensity score, women were selected from the candidate comparison group based on the closest absolute propensity score – the "nearest neighbor" [17]. We conducted the selection process without replacement and matched one exposed woman to four unexposed women (1:4 ratio) [17,18].

After matching, the risk of infant morbidity and neurological outcomes among the exposed group were compared to the unexposed group using conditional generalized estimating equations (GEE) since the dataset included matched cases and controls [19]. We used a clinical estimate of gestational age for each type of exposure. We performed a subgroup analysis using race/ethnicity as the stratifying variable. The procedure involved the construction of separate regression models for each racial/ethnic group to generate risk estimates for adverse birth outcomes. In all the models, white infants without SCD or thalassemia served as the referent category. Regression models and goodness-of-fit were assessed using aggregates of residuals [20]. The GENMOD procedure in SAS (SAS Institute, Inc., Cary, NC, version 9.2) was used to conduct this analysis. All tests of hypothesis were two-tailed with a type 1 error rate fixed at 5%. Prior to initiation, the study was approved by the Institutional Review Board of the University of South Florida.

3. Results

A total of 1,564,038 singleton births with gestational age 20–44 weeks and documented birthweight values were recorded during the study period. Prior to propensity score matching, there were significant differences in sociodemographic characteristics and selected common medical and obstetric complications between mothers of children with SCD/thalassemia and those without SCD/thalassemia. Mothers of infants with SCD/thalassemia were more likely to be black and unmarried and to present with anemia, diabetes, abruption and preeclampsia/eclampsia. Mothers of children without SCD/thalassemia were more likely to be at least 35 years old, smoke cigarettes, complete high school, and to have adequate prenatal care than their counterparts with infants with SCD/thalassemia [data not shown]. Because of the imbalance in baseline characteristics, we utilized propensity score matching by selecting four controls for each case. The 892 women in the