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Original article

Clinical complications in pregnant women with sickle cell disease: prospective study of factors predicting maternal death or near miss

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ABSTRACT

Objective: To evaluate complications in pregnant women with sickle cell disease, especially those leading to maternal death or near miss (severe obstetric complications).
Methods: A prospective cohort of 104 pregnant women registered in the Blood Center of Belo Horizonte (Hemominas Foundation) was followed up at high-risk prenatal units. They belonged to Group I (51 hemoglobin SS and three hemoglobin S/β^0-thalassemia) or Group II (49 hemoglobin SC and one hemoglobin S/β^+-thalassemia). Both groups had similar median ages. Predictive factors for 'near miss' or maternal death with p-value ≤ 0.25 in the univariate analysis were included in a multivariate logistic model (significance set for p-value ≤ 0.05).
Results: Group I had more frequent episodes of vaso-occlusive crises, more transfusions in the antepartum and postpartum, and higher percentage of preterm deliveries than Group II. Infections and painful crises during the postpartum period were similar in both the groups. The mortality rate was 4.8%: three deaths in Group I and two in Group II. One-third of the women in both the groups experienced near miss. The most frequent event was pneumonia/acute chest syndrome. Alpha-thalassemia co-inheritance and β-gene haplotypes were not associated with near miss or maternal death. In multivariate analysis predictors of near miss or death were parity above one and baseline red blood cell macrocytosis. In Group I, baseline hypoxemia (saturation < 94%) was also predictive of near miss or death.
Conclusion: One-third of pregnant women had near miss and 4.8% died. Both hemoglobin SS and SC pregnant women shared the same risk of death or of severe complications, especially pulmonary events.

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Introduction

The first case description of sickle cell disease (SCD) dates back to over a century ago. Since then, medicine and related areas have built a large body of knowledge on the disease. SCD probably arose on the African continent and in the Middle East with the slave trade being responsible for its spread to the New World. It has become one of the most common genetic diseases in the world.[1]

Sickle cell anemia, or SS hemoglobinopathy, is the result of sickle cell gene homozygosis. SCD also includes hemoglobin (Hb) S interactions with Hb variants other than normal Hb A. The most common Hb variants are C (SC hemoglobinopathy), D-Punjab, and the co-inheritance of the beta thalassemia trait (Hb S/β-thalassemia).[1–3]

Early diagnosis through newborn screening, prevention and treatment of complications have increased the life expectancy of individuals with SCD. This also accounts for SCD women reaching the fertile age and becoming pregnant.[3,4] The extreme variability of SCD clinical phenotypes makes it very difficult to predict the course of most pregnancies.[5] The incidence of severe complications is high not only because of biological aspects inherent to SCD, but also because the disease is poorly understood by healthcare staff ('lack of visibility'), it is rarely discussed beyond the academic arena, and there are few well-designed studies that would lead to developing appropriate protocols.

In non-pregnant women, less severe clinical forms such as SC hemoglobinopathy and S/β^+-thalassemia co-inheritance may pass unnoticed for these individuals are usually asymptomatic or oligosymptomatic and have hemoglobin concentrations near to or within the normal range. During pregnancy, however, these women may undergo complications as severe as those associated with the Hb SS genotype.[5,6]

Several studies have reported complications in pregnant women with SCD, but focused only upon perinatal outcomes.[7–13] This study aims at the following: (i) gaining an in-depth understanding of the profile of pregnant women assisted by hematologists at the Blood Center of Belo Horizonte (Hemominas Foundation) and by obstetricians at high-risk maternities in Belo Horizonte, Minas Gerais State, Brazil; (ii) describing the morbi-mortality of pregnant women with SCD; and (iii) investigating the causes of the most severe complications that led do death or near miss.

Methods

The study is built on a prospective cohort of pregnant women with SCD followed up at the Blood Center of Belo Horizonte (Hemominas Foundation) from December 2007 to November 2011. The population comprised pregnant women with SCD registered in the 'Project Aninha', who were treated at the Hemominas Foundation and high-risk maternities in Belo Horizonte. Project Aninha was created in 2007 to provide a multidisciplinary team to support pregnant women with SCD at the Educational and Support Center for Hemoglobinopathies (Cehmob), a center coordinated by the Unit for Newborn Screening and Genetic Diagnosis (Nupad) of the Medicine School of the Universidade Federal de Minas Gerais (UFMG), and the Hemominas Foundation.

The sample included a total of 104 pregnant women, 51 with the Hb SS genotype, 49 with SC hemoglobinopathy, three with Hb S/β^0-thalassemia, and one with Hb S/β^+-thalassemia. All cases were confirmed by hemoglobin electrophoresis. The Hb SS genotype was distinguished from Hb S/β^0-thalassemia by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) using the *Ddel* restriction enzyme.

Both hematological and obstetrical complications were investigated, but this report focuses on hematological complications. The analysis included investigating both maternal death and the most severe complications that could lead to maternal death (near miss). The inclusion criteria required that the patients were pregnant at the medical appointment, had been followed up by one of the Project Aninha participants, and had signed an informed consent to participate in this study. The investigation was approved by Ethics Committees recognized by the Brazilian Committee for Research Ethics (CONEP) and was carried out in accordance with the Declaration of Helsinki (revised as of 2008).

The initial statistical analysis involved data such as age, hemoglobinopathy type (genotype), age at menarche, number of pregnancies, number of abortions, clinical comorbidities, and baseline phenotypic characteristics, including hypoxemia (baseline finger oxygen saturation < 94%) identified during a medical appointment despite a lack of symptoms, painful crises or infections. Asymptomatic hypoxemia was confirmed by more than one evaluation at distinct clinical appointments. Baseline hematologic values were calculated as the average of three measurements in patients without blood transfusions three months prior to the tests. Alloimmunization was investigated in the patients' transfusion records before pregnancy. The β-globin gene haplotypes were determined by PCR-RFLP; alpha-thalassemia genotypes were determined by multiple gap PCR to detect the seven most common alpha-globin gene deletions.

The following clinical events were recorded during pregnancy and during the first 42 days postpartum: infections, vaso-occlusive crises (exclusively those episodes which required emergency care for intravenous hydration and the administration of analgesia), pulmonary complications/acute chest syndrome (pulmonary symptoms and signs associated with new pulmonary infiltration as observed through chest imaging), number of blood transfusions, and number of hospitalizations (days of stay). Symptomatic urinary infection was defined as urinary symptoms associated with pyuria and a positive urine culture (>100,000 colony forming units). Positive urine culture without urinary symptoms was interpreted as asymptomatic bacteriuria. Both symptomatic urinary infection and asymptomatic bacteriuria were grouped together for statistical analysis.

Variables that might have contributed to maternal death or severe clinical complications (near miss) were included in the prognostic factors analysis. These variables were classified according to the adapted criteria for near miss.[14,15] The criteria for near miss included admission to the intensive care unit, obstetric hemorrhage with hemodynamic