Effect of active prenatal management on pregnancy outcome in sickle cell disease in an African setting

Mohamed C. Rahimy, Annick Gangbo, Roslyn Adjou, Chantal Deguenon, Stephanie Goussanou, and Eusebe Alihonou

Sickle cell disease (SCD) is associated with an increased risk of medical complications during pregnancy. In sub-Saharan Africa, fetal and maternal mortality rates are particularly high. This study evaluated the effect of an active prenatal management program on pregnancy outcome in patients with SCD in an African setting. Pregnant women with SCD attending the National Teaching Hospital in Cotonou (The Republic of Benin, West Africa) were recruited before the 28th week of gestation. Management was based on providing information and education about SCD and improving nutritional status, malaria prevention, early detection of bacterial infections, and restricted use of blood transfusion. Maternal and fetal mortality rates and SCD-related morbidity were the principal variables assessed. One hundred and eight patients (42 SS and 66 SC) with 111 fetuses were included in the study. Thirteen fetal deaths (from 9 SS and 4 SC mothers) were recorded and 2 deaths of SC mothers. The maternal mortality rate of 1.8% was comparable with the overall maternal mortality rate for this maternity unit (1.2%). Few SCD-related events were recorded. Plasmodium falciparum malaria infection was the major cause of morbidity. Sixty-three patients (19 SS and 44 SC) successfully completed their pregnancy (58.3%) without requiring transfusion. Providing pregnant SCD patients with relevant medical care based on simple cost-effective approaches can have a positive impact on SCD-associated morbidity and mortality in an otherwise difficult setting in Africa.

Introduction

Sickle cell disease (SCD) is associated with an increased risk of medical complications during pregnancy. The maternal risks include prepartum and postpartum painful crises, urinary tract infections, pulmonary complications, anemia, preeclampsia, and death. Fetal complications include premature delivery with its associated risks, intrauterine growth retardation (low birth weight), fetal distress during labor, and a high rate of perinatal mortality.1-8 The details of appropriate prenatal care and perinatal management for these patients is still a matter for debate in developed countries. However, studies have shown that there is a significant improvement in pregnancy outcome and that these women are able to complete pregnancy successfully if they are given appropriate prenatal care.9-13 Unfortunately, no such improvement has yet been observed in sub-Saharan countries, which have the highest prevalence of SCD and reported rates of maternal mortality exceeding 9%.7 Between July 1, 1993 and December 31, 1993, 15 pregnant women with SCD (7 SS patients and 8 SC patients) were referred to the Gynecology and Obstetrics Department of the National Teaching Hospital in Cotonou, the capital of the Republic of Benin (West Africa). The maternal and fetal outcomes for these patients were very poor, with both mother and fetus dying in 4 cases (3 SS patients and 1 SC patient), and fetal deaths in 2 other cases (1 SS and 1 SC mother). In contrast, the current overall maternal and fetal mortality rates in this maternity unit are 1.2% and 6.3%, respectively. The prevalence of infections (especially malaria), the frequent worsening of anemia, the limited health care facilities, and particularly the lack of adequate management during pregnancy are thought to be the major factors responsible for the observed poor maternal and fetal outcomes.5 In light of the potentially extreme consequences of pregnancy in SCD patients in Benin, we initiated a prospective study in February 1994 to evaluate the effect of active prenatal management on maternal and fetal outcomes at our hospital. The data presented here indicate that providing SCD patients with relevant medical care based on simple cost-effective approaches during their pregnancies can have a positive impact on associated morbidity and mortality in an otherwise hostile setting in Africa.

Patients and methods

Patients

The patients were pregnant women with SCD attending or referred to the National Teaching Hospital in Cotonou. About 3500 deliveries per year are carried out at this maternity unit. In most cases, SCD status was known before the pregnancy. However, the hemoglobin phenotype of each patient was confirmed by cellulose acetate and citrate agar electrophoresis (Helena Laboratories, Beaumont, TX).

Study design

The study was open and prospective in design. It was approved by the Faculty of Health Sciences Ethical Committee and was carried out between...
February 1, 1994 and December 31, 1997. Pregnant women with SCD who presented at the Gynecology and Obstetrics Department and were less than 28 weeks into gestation were enrolled in this study after they gave informed consent.

In terms of patient care, taking local infrastructure and environment constraints into account, we focused our attention on: (1) the provision of repeated information and education about SCD with particular emphasis on factors that may precipitate acute events; (2) suggesting ways to improve nutritional status, in particular, by drawing attention to affordable local products that have a high nutritional value but are often neglected; (3) systematic supplementation with iron, folate, and vitamins; (4) the provision of advice about maintaining hydration levels by a daily intake of fluid, to keep urine volume high; (5) *Plasmodium falciparum* malaria prophylaxis involving the prescription of chloroquine for intake on alternate days and advice to sleep under a mosquito net; (6) the early detection of bacterial infections (particularly urinary tract infections and pneumonia); and (7) the implementation of stringent criteria for blood transfusion indications.

**Patient care**

The staff included a senior hematologist, a gynecologist/obstetrician, and 4 specially trained midwives. On entry into the study, an exhaustive history was taken for each patient and physical/obstetric examinations were performed. Gestational age was estimated from the date of the last menstrual period or an ultrasound scan if the patient could afford to pay for it. Patients were evaluated fortnightly until the last month of their pregnancy, and weekly thereafter. At each prenatal visit, the importance of compliance and a healthy lifestyle to maternal and fetal health was emphasized. The women were advised to contact the clinicians involved in the study immediately if they experienced any unusual symptoms. Patients were admitted to the hospital when labor appeared imminent. Final evaluations were carried out 2 weeks and 6 weeks after the delivery. A friendly atmosphere was maintained throughout the follow-up, which was probably instrumental in achieving the excellent compliance observed.

Laboratory studies included a complete blood cell count, a reticulocyte count, urinalysis to detect asymptomatic bacteriuria, and blood smears for *P. falciparum* asexual parasite counts at each prenatal visit and whenever indications appeared. A chest x-ray was performed if pneumonia or any other pulmonary event was suspected and systematically at the 7th month of gestation to check for asymptomatic pulmonary events.

**Management of labor**

At the beginning of labor, the patient was hydrated by an intravenous infusion of 5% glucose (3000 mL/m² daily) with adjustment of electrolytes and acid–base balances. Intravenous bactericidal antibiotic treatment (amoxycillin and gentamycin) and quinine were also given and the whole protocol was maintained until the second day after delivery. Fetal heart rate was monitored throughout labor. Intravenous oxytocin was given to all patients at the start of labor, to reduce the duration of labor so as to decrease the level of delivery-associated blood loss. The delivery route (vaginal or cesarean section) depended on the usual obstetric indications. In our obstetric department, the rate of deliveries by cesarean section (for all cases) was recorded, at a gestational age of 34 weeks (for an SC patient). Overall, the mean birth weight of neonates from SS mothers was significantly lower than that for neonates from SC mothers (P = .03, Fisher exact test). However, both values were within the 25th and 10th percentiles of mean birth weight for 1200 neonates born to healthy AS and AC mothers in the same maternity unit over the same period. When observed, fetal death occurred at a gestational age of 32 to 39 weeks. No fetal deaths were recorded for patients with previous unsuccessful pregnancies. The maternal mortality rate was 1.8%. Two SC patients with pregnancies complicated by preeclampsia died from toxemia. No autopsy was performed in either case.

Most of the SCD patients had not been followed as part of a specific medical care program before this study. It was, therefore, difficult to obtain a precise past medical history for these patients. However, when interviewed, patients reported numerous past SCD-related acute events, and all but 15 (all SC) had had at least one transfusion. During the course of this study, over half the 108 patients experienced painful SCD crises (24 SS patients, 57%; 35 SC patients, 53%). These crises were mild in all cases, were treated essentially with aspirin and paracetamol, and did not require narcotics. A few patients (3 SS and 2 SC) had more than 2 episodes. Two SS patients had pulmonary complications; one of these patients experienced a severe acute chest syndrome with a fever over 40°C and respiratory distress requiring partial exchange transfusion. This patient was carrying twins and one fetus died soon after the onset of this episode.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SS</strong></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td><strong>Age (years): mean ± SD</strong></td>
</tr>
<tr>
<td><strong>Gestational age at inclusion, weeks: mean ± SD</strong></td>
</tr>
<tr>
<td><strong>Twin pregnancies</strong></td>
</tr>
<tr>
<td><strong>Patients with previous unsuccessful pregnancy</strong></td>
</tr>
<tr>
<td><strong>Primigravids</strong></td>
</tr>
</tbody>
</table>

| **Hemoglobin level at inclusion, g/dL, mean ± SD** | 18.3 ± 8.6 |
| **Fetal hemoglobin (%), mean ± SD** | 21.0 ± 1.0 |

*Eight patients had experienced 1 unsuccessful previous pregnancy and 1 patient had experienced 5 previous unsuccessful pregnancies.
†Number of previous unsuccessful pregnancies were 1 for 13 patients, 2 for 6 patients, and 3 or more for 4 patients.

---

For personal use only on April 15, 2017 by guest from www.bloodjournal.org
Urinary tract infections, with *Escherichia coli* as the most frequent causative pathogen, were recorded in 7 SS patients (16.7%) and 17 SC patients (25.7%). Despite our preventive measures, *P. falciparum* malaria was diagnosed in 16 SS patients (38.0%) and 15 SC patients (22.7%). Atypically, we found that many patients presented with high parasitemia and severe anemia (hemoglobin levels > 40% below the steady-state level) but without fever (rectal temperature, 37.5°C). Indeed, 40.9% of the episodes of *P. falciparum* malaria infection were not associated with fever (11 episodes in 25 SS patients, 44.0%; 7 episodes in 19 SC patients, 36.8%).

Forty-five patients (41.7%) had a blood transfusion during the study period (23 SS patients, 54.8%; 22 SC patients, 33.3%). All except 2 SS patients and 1 SC patient had transfusions before enrollment. One SS patient had an emergency partial exchange transfusion because of severe pneumonia. In the initial phase of the study, scheduled partial exchange transfusions were given once each to 2 SS patients and twice to another patient as recommended in the literature. Similarly, systematic “top-up” transfusions in case of cesarean section or prelabor transfusion for a hemoglobin level lower than 8 g/dL were given to 3 SS patients and to 4 SC patients. These 10 patients with scheduled transfusions also had transfusions during pregnancy for worsening of anemia. For all the other cases, in the later phase of the study, transfusion was administrated only when anemia was not tolerated clinically. Table 3 lists the different etiologies associated with the worsening of anemia in these patients. The 2 maternal deaths involved women belonging to that group. It is noteworthy that in 45.6% of the transfusions given to SS patients, *P. falciparum* malaria was the causative factor. No immediate adverse reactions to transfusion were reported.

Table 3. Etiology of the worsening of anemia in transfused patients

<table>
<thead>
<tr>
<th>Causes</th>
<th>SS</th>
<th>SC</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. falciparum</em> malaria</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>Aplastic crisis</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Severe anemia of unknown cause</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Toxemia</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Postpartum bleeding</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

*Table does not include the cases of partial exchange transfusions and “top-up” transfusions described in the text. Values correspond to total number of transfusions performed for each cause.*

Discussion

The Republic of Benin, West Africa, has a high prevalence of SCD. Although precise data about the incidence of pregnancies in women with SCD are not available in Benin, it is clear that they are not by far as frequently encountered as might be expected from a *β*^s^ gene frequency of about 25%. There are
several reasons for this. First, the clinical presentation is generally severe and more than 50% of affected children do not reach their 5th birthday. Survivors suffer rapid progressive organ damage, which reduces life expectancy. Thus, many patients die before reaching the reproductive age. Second, the fact that the outcome of pregnancy in women with SCD is often poor is widely known by the population and it is common belief that pregnancy is the main cause of death in women with SCD who have survived childhood events. Indeed, our experience before this study, with maternal and fetal mortality rates of 27% and 40%, respectively, clearly illustrates the high level of risks associated with pregnancy in SCD patients in Benin. Thus, in many communities, SCD women surviving to reproductive age are advised to avoid becoming pregnant. In developed countries, improvements in the pregnancy outcome have been achieved through a multidisciplinary approach. The maternal mortality rate after implementation of the active prenatal program described here was 1.8%, a figure within the range of the 0.45 to 2% reported for developed countries and lower than the 9.2% reported by Dare et al for Nigeria, a neighboring country. This mortality rate of 1.8% is to be compared to the current overall maternal mortality rate at our hospital (1.2%). It suggests that, with appropriate medical care, pregnancy could be equally well tolerated by SCD patients in an African setting as in developed countries.

In designing this pilot study, we focused our attention on environmental factors associated with the African setting that might seriously affect the clinical course of SCD. Other than one severe pulmonary complication in a patient bearing twins, few SCD-related events were observed and those that did occur were mild. In this respect, it is notable that the mean fetal hemoglobin level in our SS patients was only 2.1%. Thus, probably, the poor pregnancy outcomes previously reported for SCD patients in West Africa reflect inadequate management of these patients rather than the intrinsic severity of the disease. Both the women who died had SC disease. This is consistent with previous findings that women with this genotype have a relatively benign course when not pregnant but are genuinely at risk in late pregnancy. Because these patients do not normally suffer from severe acute events, they may be less concerned about the possible harmful complications of pregnancy. This may result in a lower level of compliance with the preventive measures proposed during the antenatal period. This series consisted of cases from a single institution, followed prospectively; thus, we cannot rule out some possible selection bias. However, if there were bias, it would probably result from the selection of more complicated cases because peripheral maternity hospitals generally refer eventful cases to our university hospital.

Randomized studies have shown no significant beneficial effect of prophylactic blood transfusions in pregnant women with SCD, and the appropriate timing of their use is still a matter of debate. Apart from emergency transfusion for acute anemia (< 5 g/dL hemoglobin), the recommended indications for blood transfusion include toxemia, twin pregnancy, previous history of perinatal mortality, septicemia, acute renal failure, acute chest syndrome, a recent neurologic event, hypoxemia, and preparation for surgical intervention. Thus most pregnant women with SCD, particularly those who are homozygous (SS), receive blood transfusions during the course of their pregnancy. In this study, we set out to limit the use of blood transfusion during pregnancy. We were forced to restrict its use even further due to local constraints. We found that many patients, when closely monitored, had well-tolerated anemia, regardless of the level of hemoglobin, and that many were able to complete their pregnancy successfully without transfusion, regardless of the route of delivery. Thus, as stated by El-Shafei et al, a policy of restricted blood transfusions can be followed safely without compromising maternal or fetal well-being, with the additional benefit of reducing blood transfusion-associated complications. These findings have major implications in Africa where safe blood products are not always available.

In this series, 23 SS women (54.7%) and 22 SC women (33.3%) had transfusions. Analysis of the factors responsible for the worsening of anemia that led to transfusion indicated that the percentage of women transfused could probably be reduced further because P. falciparum malaria, a preventable infection, was the root cause of 45.6% of the transfusions in SS women. In contrast, only 2 of the nontransfused SS women had P. falciparum malaria during the pregnancy. Incidentally, fever is a major symptom of P. falciparum malaria. However, we observed that several patients presented with high parasitemia and life-threatening anemia (hemoglobin < 40% of steady-state levels), but without fever. The pathophysiology of this condition is unclear, but the prevention of P. falciparum malaria remains an essential goal in the management of pregnant women with SCD in environments in which this infection is endemic.

The 11.9% rate of fetal loss late in pregnancy is exactly the same in this study as that reported in Jamaica or the United States. Still, it is higher than for the hospital maternity unit as a whole (6.3%). The limited laboratory facilities in our hospital have hampered attempts to investigate the causes of these fetal deaths in more detail. However, retrospective analysis suggested that at least 4 of the 13 fetal deaths (3 from SS mothers and 1 from an SC mother) might have been prevented by inducing labor earlier. These fetuses were aged over 37 weeks and all were alive during the 3 days preceding the onset of labor. It is possible that, in these patients who may have chronic organ damage, uterine blood flow and placental volume may not have been sufficient to meet the metabolic exchanges and growth requirements of the enlarging fetus, resulting in sudden fetal death as the pregnancy neared completion. An evaluation of when and how to induce labor in SCD patients is underway.

In conclusion, we have shown that in an African setting, the clinical status of most SS and SC patients is not seriously affected by pregnancy if these women benefit from active prenatal management. The Republic of Benin is one of the least developed countries of sub-Saharan Africa. Its gross annual per capita income was estimated to be US $287 in 1994, with less than 5% of its budget dedicated to health services. The care regime described herein is based on simple low-cost approaches and does not require any significant increase in health care expenditure. Instead, emphasis is placed on education and frequent medical follow-up. It is therefore suitable for application in most African settings. The improvement we have seen in maternal and fetal outcomes suggests that the widespread tradition in Benin of advising patients with SCD to avoid pregnancy requires reassessment.

**Acknowledgments**

We would like to thank Drs F. Guedou, E. Papiernik, R. Krishnamoorthy, and J. Elion for their help in the preparation of this manuscript.
References

Effect of active prenatal management on pregnancy outcome in sickle cell disease in an African setting

Mohamed C. Rahimy, Annick Gangbo, Roslyn Adjou, Chantal Deguenon, Stephanie Goussanou and Eusebe Alihonou

Updated information and services can be found at:
http://www.bloodjournal.org/content/96/5/1685.full.html

Articles on similar topics can be found in the following Blood collections
  Clinical Trials and Observations (4514 articles)
  Red Cells (1159 articles)

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml