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

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

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. 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. 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%. 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 associated morbidity and mortality in an otherwise difficult 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

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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 were 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 (66 SC) involving 111 fetuses were followed. Overall, 86% of the pregnancies ended in live births. Only one premature delivery, of twins, 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.

**Data analysis**

The number of successfully completed pregnancies, the maternal mortality rate, fetal death rate, and perinatal mortality rate were recorded. We also recorded the frequency and severity of SCD-related events, specific complications of pregnancy including spontaneous abortion (defined as spontaneous termination of the pregnancy before the 28th week of gestation), the frequency of *P. falciparum* malaria infection, and the causes of a worsening of anemia resulting in transfusion.

**Results**

Table 1 summarizes the characteristics of the patients enrolled in this study and Table 2 presents the overall maternal and fetal outcomes. A total of 108 pregnancies (42 homozygous SS and 66 SC) involving 111 fetuses were followed. Overall, 86% of the pregnancies ended in live births. Only one premature delivery, of twins, 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.

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>SS</th>
<th>SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Age (years): mean ± SD</td>
<td>28.0 ± 5.3</td>
<td>27.9 ± 4.6</td>
</tr>
<tr>
<td>Gestational age at inclusion, weeks: mean ± SD</td>
<td>18.3 ± 6.5</td>
<td>19.1 ± 8.3</td>
</tr>
<tr>
<td>Twin pregnancies</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Patients with previous unsuccessful pregnancy</td>
<td>9*</td>
<td>23†</td>
</tr>
<tr>
<td>Primigravidas</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Hemoglobin level at inclusion, g/dL, mean ± SD</td>
<td>20.0 ± 4.1</td>
<td>27.5 ± 10.0</td>
</tr>
<tr>
<td>Fetal hemoglobin (%), mean ± SD</td>
<td>6.4 ± 1.3</td>
<td>8.5 ± 1.6</td>
</tr>
<tr>
<td>Breakdown</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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.
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%). Atypical, 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. For all other patients, only one episode of infection.

Table 2. Maternal and fetal outcomes in SCD pregnancies actively managed

<table>
<thead>
<tr>
<th>Patients</th>
<th>n = 42</th>
<th>n = 66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous abortion</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fetal deaths</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Maternal deaths</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Birth weight, g, mean ± SD (only live birth) 2500 ± 540 2700 ± 430

Cesarean section 18 20

Patients not transfused during the study period 19* 44

Patients experiencing SCD-related painful crises (episodes of crises) 24 35

Patients with urinary tract infections 7 17†

Patients with pulmonary complications 2 0

*Plasmodium falciparum* malaria:

Patients with fever (total episodes) 10 (14) 11 (12)

Patients without fever (total episodes) 6 (11) 4 (7)

Patients with preeclampsia 0 2

*†Four patients had had transfusion before being included in the study.

‡Two episodes of urinary tract infections were recorded in one patient; all the other patients had only one episode of infection.

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.

Table 4. Hemoglobin and hematocrit levels, SCD-related complications, and outcome in patients who did not receive blood transfusion during the study period

<table>
<thead>
<tr>
<th>Patients</th>
<th>n = 19</th>
<th>n = 44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin concentration (Hb, g/dL, mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At inclusion*</td>
<td>7.0 ± 1.3 23.1 ± 4.0 9.2 ± 1.4 28.4 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>Before labor</td>
<td>8.2 ± 0.7 26.0 ± 2.7 9.8 ± 1.3 29.8 ± 4.0</td>
<td></td>
</tr>
<tr>
<td>Immediate post delivery</td>
<td>6.6 ± 1.4 21.5 ± 4.1 8.8 ± 1.4 27.3 ± 4.0</td>
<td></td>
</tr>
<tr>
<td>Day +15 post delivery</td>
<td>7.8 ± 0.9 25.0 ± 2.8 10.0 ± 1.3 30.6 ± 3.7</td>
<td></td>
</tr>
<tr>
<td>Patients with SCD-related pain crises (total episodes)</td>
<td>8</td>
<td>19</td>
</tr>
</tbody>
</table>

Patients with *P. falciparum* malaria (total episodes) 2 (4) 10 (15)

Delivery route

Vaginal 10 33

Cesarean section 8 10

Spontaneous abortion 1† 1

Fetal outcome:

Stillbirth 2‡ 1

Live birth 16 42

Maternal death 0 0

*Four patients had had blood transfusion before being included.

†This pregnancy was terminated at 26 weeks after a 3rd episode of *P. falciparum* malaria.

‡One of the fetuses presented with multiple malformations.

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⁺ gene frequency of about 25%. There are 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 4 shows the hemoglobin levels, SCD-related complications, and maternal/fetal outcomes of the 19 SS patients and 44 SC patients who did not receive a blood transfusion during the study period. Overall, hemoglobin level and hematocrit increased between inclusion and the end of the pregnancy for these patients. The increase was particularly marked for the SS patients (1.2 g/dL and 3%, respectively). However, 4 of the SS patients who were not given transfusions during the study period had been given 3 or more blood transfusions before their inclusion in this study. At first presentation, these patients had hemoglobin levels of 4.3, 5.8, 6.0, and 7.2 g/dL. Their hematocrit values were 15%, 18%, 19%, and 24%, respectively. There was a gradual and marked increase in hemoglobin level and hematocrit in these patients during the study, with no further transfusions. Their final hemoglobin levels were 8.7, 8.0, 8.8, and 8.7 g/dL, respectively. Their final hematocrit values were 29%, 25%, 27%, and 28%, respectively. Finally, fewer SCD-associated complications were observed in the group of 19 SS patients who were never transfused during the study period than for the study population as a whole. No maternal deaths occurred and all but 5 pregnancies (2 spontaneous abortions and 3 stillbirths) ended in live births. Only 2 of the nontransfused SS patients were found to have *P. falciparum* malaria.
due to local constraints. We found that many patients, when receive blood transfusions during the course of their pregnancy. women with SCD, particularly those who are homozygous (SS), through a multidisciplinary approach.\textsuperscript{11-14} The maternal mortal - many communities, SCD women surviving to reproductive age 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.\textsuperscript{11-14} 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\textsuperscript{2,5,6,8,13,14} and lower than the 9.2\% reported by Dare et al for Nigeria,\textsuperscript{7} 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.\textsuperscript{14,15} 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,\textsuperscript{14-18} 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.\textsuperscript{12} 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,\textsuperscript{19} 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 \textit{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 \textit{P falciparum} malaria during the pregnancy. Incidentally, fever is a major symptom of \textit{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 \textit{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\textsuperscript{6} or the United States.\textsuperscript{6} 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.

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References

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