Challenges in the management of sickle cell disease during pregnancy in Senegal, West Africa

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ABSTRACT

Objectives: The aim of this study was to evaluate the maternal and fetal complications in pregnant patients with sickle cell disease (SCD) and find risk factors of stillbirth.

Method: We conducted a prospective study in pregnant women with SCD. Demographic characteristics, maternal and fetal morbi-mortality, and outcome of pregnancies were described. Risk factors of fetal loss were evaluated by comparing the parameters of the pregnancies that led to a live birth with those interrupted.

Results: We included 70 pregnancies in 58 women with SCD. The average age was 29.3 years. The average gestational age at the start of follow-up was 13 weeks. The occurrence of acute complications was significantly higher during pregnancy compared to the year before (p < 0.05). Maternal mortality was 0%. Live birth rate was 80%. Fetal loss rate was 3.9 times higher in previous pregnancies that had not been monitored in hematology (71.8 versus 18.6%). Stillbirth was associated with nulliparity, high leukocytes or platelet counts (p < 0.05).

Conclusion: Pregnancy in SCD was associated with a high maternal morbidity and stillbirth. Nulliparity, high leukocytes or platelet count were identified as risk factors of fetal loss.

KEYWORDS
Sickle-cell disease; pregnancy; risk factors; morbidity; mortality; fetal loss

Introduction

Sickle cell disease (SCD) is a public health problem in Sub-saharan Africa. In Senegal, the prevalence of S hemoglobin is 11.1% in the general population and 1.9% of newborns are suffering from sickle cell anemia [1]. It leads to high mortality and morbidity [2]. The advances in management of this disease have significantly improved its outcome. They allow many patients to reach the age of procreation and have better fertility [3]. However, the occurrence of pregnancy in sickle cell women can be challenging because of an increasing risk of morbidity and mortality for patients and fetus despite a good management [4]. In a previous study conducted among 34 cases of pregnancies with SCD in our clinical unit [5], the rates of fetal loss and maternal death were, respectively, 14.6 and 3%. Since then, we have improved the hematologic management of patients by following a standard practice in the unit explained in the paragraph ‘Method’. The aim of this study was to evaluate maternal and fetal morbidity-mortality and find risk factors associated with stillbirth.

Patients

We included pregnancies of women with SCD who did at least two hematological visits during pregnancy. SCD was confirmed by both electrophoresis of hemoglobin and Sickling test. Pregnancies were confirmed by at least an obstetric echography.

Method

Hematologic management

The patients were seen every month since the announcement of the pregnancy. During these visits, clinical and biological examinations were performed. Folic acid was given during all pregnancy time at the dose of 10 mg daily. Iron at 1 mg/kg daily among patients who had not received transfusion. A simple transfusion was performed when occurred dyspnea due to an aggravation of anemia in order to increase hemoglobin level to above 8 g/dl. Chronic transfusion was done from the second trimester to delivery when hemoglobin level decreased below 8 g/dl in patients who had previous fetal losses. Partial red cell exchange was performed in severe acute vaso-occlusive complications such as acute chest syndrome (ACS) or prolonged vaso-occlusive crisis (VOC). These patients were hospitalized in the clinical hematology unit during acute complications of SCD. They were referred
to a gynecology and obstetrics unit during obstetrical problems. The follow-up was considered as regular if at least one visit was performed every trimester.

**Statistical analysis**

We described socio-demographic characteristics, maternal complications and pregnancy outcome. Maternal morbidity was evaluated by comparing the number of complications, transfusion and hospitalization during pregnancy with those of the year before. Risk factors of fetal loss were sought by comparing the parameters of the pregnancies that led to a live birth with those that ended in stillbirth. Data analysis was done using SPSS software version 18. Descriptive study was conducted by calculating frequencies and proportions for qualitative variables. For quantitative data, we calculated the averages with their 95% confidence intervals. The analytical analysis was done with cross tables. Chi-squared, Student or Fischer tests were used according to their applicability to compare parameters.

**Results**

We included 70 pregnancies among 58 women with SCD. The homozygous SS were 59 cases (84.3%), heterozygous SC and S/β-thalassemia, respectively, seven cases (10%) and four cases (5.7%). The average age at start of pregnancy was 29.3 years [95% IC: 28.2–30.5]. The most represented age group was 30–35 years (35.7%). The youngest was 18 years old, the oldest 39 years old. Baseline characteristics of patients are in Table 1. The number of followed pregnancies had significantly increased during the 5 last years. It represented 80% of all cases versus 20% during the 10 first years. We observed a significant increase of acute complications, transfusion and hospitalization during pregnancy compared to the year before (p < 0.05) (Table 2). The average level of baseline hemoglobin decreased from 8.7 [95%IC: 8.4–9] before pregnancy to 7.6 g/dl [95%IC: 7.3–8], meaning an average reduction in 1.1 g/dl. The most frequent obstetric complication was spontaneous stillbirth (18.6% of pregnancies). Nine (12.9%) occurred during the 2nd trimester of pregnancy, four (5.7%) during the 3rd one. Live birth rate was 80%. Delivery was done by cesarean in 58.8% of cases (Table 3). Fetal loss risk factors were the nulliparity, high leukocytes count and high platelet count (Table 4). Maternal mortality was 0%.

**Table 1. Baselines characteristics of patients.**

| Parameters                                      | Values          |
|------------------------------------------------|-----------------|
| Average age at start of pregnancy (years)      | 29.3 [IC 95%: 28.2–30.5] |
| Unemployed patients (n = 70)                   | 44 (62.8%)      |
| Hematologic follow-up before pregnancy (n = 70)| 54 (77.1%)      |
| Start of the pregnancy follow-up (n = 70)      |                 |
| 1st trimester                                  | 40 (57.2%)      |
| 2nd trimester                                  | 22 (31.4%)      |
| 3rd trimester                                  | 08 (11.4%)      |
| Average gestational age at start of management (week) | 13 [IC 95%: 11.5–15 SA] |
| Distribution of phenotypes (n = 70)            |                 |
| SS                                             | 59 (84.3%)      |
| SC                                             | 7 (10%)         |
| S/β-thalassemia                                | 4 (5.7%)        |
| Chronic complications (n = 70)                 |                 |
| Necrosis of the coxo-femoral joint             | 6 (8.6%)        |
| Glomerular nephropathy                         | 5 (7.1%)        |
| Cardiac valvulopathy                           | 1 (1.4%)        |
| Gravity per woman (n = 70)                     |                 |
| n = 1                                          | 34 (48.6%)      |
| n > 1                                          | 36 (51.4%)      |
| Parity (n = 70)                                |                 |
| Nulliparity                                    | 52 (74.3%)      |
| Primiparity                                    | 14 (20%)        |
| Multiparity                                    | 4 (5.7%)        |
| Outcome of the previous pregnancies not monitored (n = 78) |          |
| Live births                                    | 22 (28.2%)      |
| Stillbirths                                     | 56 (71.8%)      |

**Discussion**

This work has revealed the difficulties associated with the occurrence of pregnancy in women with SCD. It was characterized by an increase of maternal morbidity and fetal loss. Nulliparity, high level of leukocytes or platelet count seemed to increase fetal loss risk. Hematologic management led to reduce the rate of stillbirth.

The number of pregnancies associated with SCD had significantly increased in our clinical unit during the last 5 years. It represented 80% of all cases versus 20% during the 10 first years. The progress in the management of SCD has allowed patients to reach the age of procreation with a better fertility [6]. However, morbidity was significantly increased during pregnancy, marked by a higher rate of VOC, acute anemia, and hospitalizations (p < 0.05). Similar results were found by several authors [5,7–9]. It could be due to negative physiological interactions between the pregnancy and SCD among which the increase of cell adhesion, polymerization of Hemoglobin S, hypoxemia and immune deficiency [10]. We obtained a rate of live births of 80%, lower than in the developed countries. Oteng-Ntim et al. in the United Kingdom had obtained a rate 97.2% [11]; Rajab et al. 94.6% in Bahrain [12], Leborgne-Samuel et al. 92.6% in Guadeloupe [13] and Al Kahtani 95.2% in Saudi Arabia [7]. This difference seemed to be related to the better conditions of management in these countries. Fetal loss rate (18.6%) was 3.9 time lower in the managed cases compared to previous ones which had no follow-up (71.8%). The favorable impact of management in outcome of pregnancies was also reported by Oteng-Ntim et al. [11]. Cesarean section was the most common mode of delivery (58.8% of cases). Most of physicians preferred elective cesarean because they considered that the association of SCD and pregnancy led to a high-risk for women and fetus [14]. Nevertheless the experts recommend to allow normal childbirth if there are no contraindications such as retinopathy, heart disease or narrow pelvis [15]. Nulliparity
appeared as a risk factor for stillbirth. Several authors reported same result such as The ‘Still birth Collaborative Research Network Writing Group’ [16], Richard et al. [17], Legendre et al. [18]. According to their findings, this high risk could be due to the increase of stress in these patients. High level of leukocytes or platelet counts was associated with an increasing risk of fetal loss too. In patients with SCD circulating leukocytes and platelets have an activated phenotype and may contribute to increase cell adhesion and inflammatory vasculopathy [19]. This may affect the placenta causing areas of fibrosis, villous necrosis, infarction and restricted uteroplacental blood flow [3]. The occurrence of acute complications of SCD was not associated with fetal loss as Thame et al. found in [20], probably because of the early start of management of patients during acute problems. The mechanism of fetal loss was not found in this study because of the lack of obstetric information. Wilson et al. [21] found that in pregnant women with SCD, spontaneous stillbirths are more related to the deceleration of placental blood flow, maternal chronic anemia and pre-eclampsia.

**Conclusion**

Pregnancy in SCD was associated with a high maternal morbidity with a significant increase of the frequency of VOC and anemia. For the fetus it increased the rate of spontaneous stillbirth. Nulliparity, high leukocytes and platelet count was identified as risk factors of fetal loss. An appropriate management could lead to a favorable outcome for most of patients. Better results could be obtained in multidisciplinary conditions of management.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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**Table 2.** Comparison of sickle cell disease morbidity before and during pregnancy.

| Parameters        | During the year before (n = 70) | During pregnancy (n = 70) | p-value |
|-------------------|--------------------------------|--------------------------|---------|
|                   | Number | Frequency (%) | Number | Frequency (%) |         |
| VOC               | 18     | 25.7         | 34     | 48.6          | 0.0051  |
| ACS               | 1      | 1.4          | 5      | 7.1           | 0.095   |
| Infections        | 8      | 11.4         | 11     | 15.7          | 0.459   |
| Acute anemia      | 11     | 15.7         | 23     | 32.8          | 0.018   |
| Transfusion       | 27     | 38.6         | 45     | 64.3          | 0.0023  |
| Glomerular nephropathy | 2    | 2.8         | 2      | 2.8           | 0.999   |
| Emergency admission | 38   | 54.3         | 73     | 104.3         | 0.000   |
| Hospitalization for 1 day | 10 | 14.3        | 50     | 71.4          | 0.0001  |
| Hospitalization > 1 day | 4   | 5.7          | 23     | 32.8          |         |

Note: Bold values indicate p-values which are <0.05.

**Table 3.** Obstetrical complications and outcome of followed pregnancies.

| Parameters                             | Number | Frequency (%) |
|----------------------------------------|--------|---------------|
| Obstetrical complications (n = 70)      |        |               |
| Threat of abortion                     | 1      | 1.4           |
| Pre-eclampsia                          | 1      | 1.4           |
| Eclampsia                              | 1      | 1.4           |
| Oligoanomnios                          | 3      | 4.3           |
| Spontaneous stillbirth                 | 13     | 18.6          |
| Live births (n = 51)                   |        |               |
| Premature birth                        | 6      | 11.8          |
| Full-term birth                        | 45     | 88.2          |
| Type of delivery (n = 51)              |        |               |
| Vaginal delivery                       | 21     | 41.2          |
| Cesarian                               | 30     | 58.8          |
| Pregnancies in progress at the end of study | 6  | 8.6            |

**Table 4.** Risk factors of stillbirth.

| Parameters                                         | Stillbirths (n = 13) | Live births (n = 51) | p-value |
|----------------------------------------------------|----------------------|----------------------|---------|
| Average age at start of pregnancy (years)           | 30.31                | 28.9                 | 0.35    |
| Start of management beyond 12th week of gestation   | 7                    | 24                   | 0.49    |
| Average gestational age at start of management (week) | 11.5                | 13.3                 | 0.40    |
| Irregular follow-up                                 | 7                    | 19                   | 0.22    |
| Phenotype of SCD                                    | 11                   | 43                   | 0.67    |
| SS                                                  | 0                    | 6                    | 0.24    |
| SC                                                  | 2                    | 2                    | 0.18    |
| S/B0-thalassemia                                    | 13                   | 49                   | 0.63    |
| Acute complications of SCD during pregnancy         |                      |                      |         |
| Nulliparity                                         | 13                   | 36                   | 0.02    |
| Average level of hemoglobin during pregnancy (g/dl) | 7.3                  | 7.7                  | 0.28    |
| Average level of platelets count (10³/mm³)          | 506.7                | 354.0                | 0.001   |
| Average level of leukocytes count (10³/mm³)         | 12.6                 | 10.1                 | 0.025   |
| Number of patients who received transfusion         | 9                    | 34                   | 0.57    |

Note: Bold values indicate p-values which are <0.05.
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