1. Introduction

Sickle cell disease (SCD) occurs in people homozygous for the β² globin gene (SS) or heterozygous for the β² allele and different abnormal β globin gene alleles, such as β² (SC), Sβ²thal or Sβ²thal.

Pregnant patients with SCD are known to be at high risk of obstetrical complications and perinatal mortality, as well as of sickle-related complications [1,2]. They are, however, now able to successfully complete pregnancy. Improvements result from active management beginning in early pregnancy by teams including obstetricians, hematologists, anesthesiologists and pediatricians, in institutions accustomed to managing SCD.

Prophylactic red-cell transfusions are commonly used, but no studies have reported their benefit over transfusions restricted to those indicated in emergency situations. Some retrospective studies have reported decreased rates of perinatal and maternal mortality, prematurity, intrauterine growth restriction, pain crises and hospitalization during pregnancies with the prophylactic transfusions [3–6]. Only one prospective randomized study, with only 36 subjects in each arm, has compared these two policies; it failed to demonstrate a significant benefit of prophylactic transfusions, except for the number of sickle-related pain crises [7].

The purpose of our study was to describe, in a large series, the characteristics of pregnancies complicated by SCD in patients receiving prophylactic red-cell transfusions and to compare them to a control group of women with normal hemoglobin (AA) and therefore without transfusions.

2. Materials and methods

Using a computerized database, we identified pregnancies among women with SCD (Hb SS or SC phenotypes) who received prenatal care and gave birth at one of three maternity units (CHI Créteil, Necker Hospital, and Port Royal Maternity, Paris, France) between January 1994 and December 2004. We reviewed all of the medical data available. All patients received prophylactic red-cell transfusions during pregnancy in one same referral center for hemoglobinopathies. Exclusion criteria were: fetal loss before 16 weeks of gestation or elective abortion, incomplete or unavailable medical files, and multiple pregnancy. Each HbS pregnancy was matched with the next HbAA pregnancy for ethnicity, parity, age, and hospital.
Women were seen alternately at the obstetric high-risk center and the hematology clinic every two weeks. All three centers used similar protocols for the care and management of these patients. Hemoglobin phenotypes were characterized by standard procedures including isoelectric focusing, acid-agar electrophoresis, cation exchange HPLC and PCR for the β^S^ gene. The phenotypes were characterized as SS, SC, and AA (normal control). Gestational age was determined by first-trimester ultrasound. Initial laboratory studies included complete blood counts, reticulocyte counts, urine analyses and cultures, liver enzymes, screening for red-cell antibodies, and hepatitis profiles, repeated monthly to detect any sickle cell complications, transfusion-related hepatitis or alloimmunization. A second fetal ultrasound examination was performed during the second trimester, and two in the third, to detect any intrauterine growth restriction. Around 37 weeks, patients with SS or SC phenotypes were hospitalized to facilitate monitoring of fetal well-being (amniotic fluid volume quantification, umbilical artery Doppler, and fetal heart rate monitoring) and to schedule the delivery. Labor was induced at 38 weeks to avoid late pregnancy complications.

The following data were recorded for each patient: age, parity, ethnicity, previous obstetric history, prenatal care with the number of scheduled obstetric and hematology visits and of emergency visits. Obstetric outcomes included: gestational age at delivery, route of delivery, preterm delivery (defined as a delivery <37 weeks), preterm premature rupture of membranes, pre-eclampsia (defined by a systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg with 24 h proteinuria >300 mg), eclampsia, HELLP syndrome (defined by platelet count <100,000/μL, elevated liver enzymes and hemolysis). Perinatal outcome included: birth weight, 5-min Apgar score, small-for-gestational-age status (SGA, defined as a birth weight <10th percentile for gestational age), and perinatal mortality. SCD-related complications were also recorded: maternal mortality, antepartum hospitalizations, pain crises (defined as acute pain episodes leading to hospitalization for intravenous analgesia and hydration), acute chest syndrome, pneumonia and pyelonephritis. Antepartum hospitalizations did not include either the prophylactic transfusions or the routine admission at 37 weeks that was part of the management protocol.

All patients received prophylactic exchange red-cell transfusions to maintain the hemoglobin level at 9 g per deciliter or more and to reduce the level of HbS below 40%, according to experimental data studying rheological properties of various mixtures of normal and sickle red cells [4,8]. Phlebotomy was performed to remove 300–500 mL of blood, depending on the patient’s weight, and 2 or 3 units of phenotype-matched red-cell units were transfused. This prophylactic transfusion program was planned to begin between 22 weeks and 26 weeks. After the program began, the same transfusion procedure was repeated every three weeks until delivery. In addition, emergency transfusions were performed for severe anemia (hemoglobin concentration ≤6 g/dL) or severe complications such as pain crisis resistant to intravenous analgesia and hydration, and acute chest syndrome. All blood units were obtained from volunteer AA donors and processed according to standard blood-banking procedures. All transfused units were chosen for Rhesus D Cc Ee and Kell antigen compatibility. We analyzed the number of prophylactic and emergency transfusions, of units of red cells transfused, and of transfusion-related complications. Alloimmunization was defined as de novo detection of red-cell antibodies during the current pregnancy, with or without symptoms.

Data were analyzed with Stata 10 SE (SAS Institute Inc., Cary, NC, USA). The Pearson Chi square test was used to compare groups for the categorical outcomes. For instances in which there were too few subjects per cell for the Chi square test to be used, the Fisher exact test was used to compare discrete outcomes. For the continuous outcomes, data were analyzed with t tests for approximately normally distributed outcomes, and Wilcoxon rank sum tests for non-normally distributed outcomes. A p-value less than or equal to 0.05 was considered statistically significant.

3. Results

We identified 143 deliveries of 130 women in the database. Seven cases (deliveries and women) were excluded because their medical files were incomplete or not available, three cases were excluded because of early fetal loss or elective abortion, and five twin pregnancies with an SS genotype were excluded because twin pregnancies may affect obstetrical and perinatal outcomes. Finally, 128 singleton deliveries (95 deliveries of 83 women with SS and 33 deliveries of 32 women with SC) were matched with 128 deliveries of women with an Hb AA genotype. Table 1 summarizes the patients’ characteristics. Previous early fetal loss was more frequent for SS and SC patients compared to control subjects.

Obstetric and specific hemolytic follow-up are summarized in Table 2. Compared with the control group, SS patients were seen for the first time earlier and had more obstetrical visits. SS and SC patients had more and later antepartum admissions and more transfers to the intensive care unit. Compared with SC patients, SS patients were seen earlier by the hematologist, had more visits, more prophylactic transfusions, and received more red-cell units.

SS and SC patients did not differ significantly in their SCD-related complications (Table 3). Of the 52 patients who had pain

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the study population, comparison of SS + SC group versus AA group.</th>
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<tbody>
<tr>
<td>SS</td>
<td>SC</td>
</tr>
<tr>
<td>Age</td>
<td>29.4 ± 5.6</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>70 (73.7)</td>
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<tr>
<td>French Overseas Territories</td>
<td>24 (25.3)</td>
</tr>
<tr>
<td>Others</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Nullipara</td>
<td>69(78.9)</td>
</tr>
<tr>
<td>Previous early fetal loss</td>
<td>30 (31.6)</td>
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<tr>
<td>Previous IUD</td>
<td>3 (3.2)</td>
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</tbody>
</table>

All comparisons between SS + SC versus AA are not significant except for p < 0.05; data are given as mean ± SD or n (percent incidence). SD, standard deviation; IUD, intrauterine fetal death.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Prenatal obstetric and hematologic care.</th>
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<tr>
<td>SS</td>
<td>SC</td>
</tr>
<tr>
<td>GA at 1st obstetrical visit in weeks</td>
<td>14.8 ± 5.3^1^</td>
</tr>
<tr>
<td>Number of obstetrical visits</td>
<td>8.7 ± 2.7</td>
</tr>
<tr>
<td>Number of antepartum admissions</td>
<td>65 (68.4)^1^</td>
</tr>
<tr>
<td>Antepartum days of hospitalisation</td>
<td>6.5 ± 8.3</td>
</tr>
<tr>
<td>Transfer to intensive care unit</td>
<td>1 (11.6)^1^</td>
</tr>
<tr>
<td>GA at 1st hematologic visit in weeks</td>
<td>14.2 ± 6.1^1^</td>
</tr>
<tr>
<td>Number of hematologic visits</td>
<td>6.3 ± 2.2</td>
</tr>
<tr>
<td>Number of prophylactic transfusions</td>
<td>5.0 ± 2.0</td>
</tr>
<tr>
<td>Emergency transfusions</td>
<td>35 (37.2)</td>
</tr>
<tr>
<td>Units of red cells transfused</td>
<td>12.8 ± 5.2</td>
</tr>
<tr>
<td>HBs or HbS + C levels at delivery (%)</td>
<td>35.8 ± 12.1</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD or n (percentage incidence). GA, gestational age.

^1 p < .05 SS versus AA.
^2 p < .05 SS versus SC.
^3 p < .05 SC versus AA.
cises, the crisis chronology was available for 45 (36 with SS and 9 with SC). Only 21 of them (46.6%) had a crisis after the transfusion program began. Despite prophylactic transfusions, 11 SS patients (11.6%) had severe anemia that led to emergency transfusion, four patients had an acute chest syndrome, one patient had pulmonary embolism, two had acute renal failure related to papillary necrosis and one had bacterial pneumonia. Alloimmunization complicated the pregnancy of five SS patients (5.3%). One severe case caused intravascular hemolysis, severe anemia, transfer to intensive care and finally intrauterine fetal death within 24 h, at 29 weeks. There were no maternal deaths.

Table 4 summarizes obstetrical and perinatal outcomes. Pre-eclampsia was more frequent and more severe in patients with SS than among control women, none of whom had any complications of pre-eclampsia. Of the nine SS patients with pre-eclampsia, three had HELLP syndrome and another eclampsia. All four had severe SCD, severe anemia, and pain crises. One had an acute chest syndrome in the antepartum period, and two received their first transfusion during the first trimester of pregnancy. Three had emergency transfusions, receiving in total 8, 11 and 10 red-cell units during pregnancy, having emergency cesarean deliveries. These admissions lasted 19, 13 and 23 days. The patient with eclampsia had her first transfusion at 12 weeks, had two emergency transfusions and received 14 red-cell units in all during pregnancy. She had a cesarean section at 33 weeks and an acute chest syndrome in the postpartum period, resulting in a hospitalization that lasted 39 days.

Four intrauterine fetal deaths (IUFDs) occurred in the SS group. Two occurred at 23 and 24 weeks. Another, as described above, occurred at 29 weeks, after a severe transfusion-related complication with intravascular hemolysis. The patient was asymptomatic at the time of prophylactic transfusion but her Hb was 7.5 g/dL and her HbS at 86.1%. The final IUFD occurred at 30 weeks. That patient had severe anemia and two severe pain crises during pregnancy despite the prophylactic transfusions. The fetus had severe intrauterine growth restriction (birth weight was 480 g at 30 weeks). The final perinatal mortality rate was 2.1% in the SS group. There were no neonatal deaths.

4. Comment

We report here the outcome in a large series of pregnant patients with SCD who received prophylactic red-cell transfusions, and compare these outcomes with a control group of women with no blood diseases. Our patients were homogenous. They were all followed in one center specializing in hereditary red-cell diseases and in three maternity units that applied the same clinical protocol for these cases. Nevertheless, our study has some limitations. It is retrospective and the control group is not optimal. Our study does not compare patients receiving prophylactic transfusions to patients with SCD without prophylactic transfusion, since in the participating institutions, all pregnant patients with SCD received prophylactic transfusions. Our purpose was to describe the outcome of this policy. In order to evaluate the elevated risk of obstetrical complications in these patients, a control group was necessary. Women with SCD are known to have a higher risk of pregnancies involving preterm delivery, pre-eclampsia, intrauterine growth restriction, and IUFD [9–14]. It is also known that women of African and Caribbean descent have a higher risk of pre-eclampsia, preterm birth and IUFD than white women [15–20]. Moreover, the incidence of pre-eclampsia can vary according to age and parity [21]. Therefore, to minimize the bias linked to age, parity and ethnicity, we chose to compare our patients with SCD to patients without any blood disease, matched for those items.

Previous studies report maternal mortality rates ranging from 0.45% to 3.7% and perinatal mortality rates from 2% to 12% [9–14]. There were no maternal deaths in our study. The perinatal mortality rate was 2.1% in the SS group, including two IUFDs after 28 weeks and no neonatal deaths.

In our series, 40% of patients had at least one pain crisis during pregnancy, half after the beginning of the transfusion program. Koshy et al. found that the incidence of pain crises decreased significantly in women with prophylactic transfusions compared with women with emergency transfusions (14% versus 50%, p < 0.01) [7]. Previous studies reported pain crises in 20–88% of SS patients without prophylactic transfusion [9–14]. In those series, 41–68% of SS patients received emergency transfusions. In a retrospective study of patients undergoing prophylactic red-cell partial exchanges beginning at 28 weeks, Morrison et al. observed these crises in 5% [4]. A more recent retrospective study by the same authors found the incidence of pain crises to be significantly higher in patients with emergency compared with systematic transfusions (21% versus 8%, p < .05) [6], while other authors have failed to demonstrate any difference between the two policies [10,22]. Unfortunately, these differences cannot be accurately compared from one study to another, since the definition of pain crisis varies from one team to another.

Despite the prophylactic transfusions, pre-eclampsia was higher in the SS group than among controls (9.4% versus 2.3%, p = 0.3). Previous studies have reported pre-eclampsia rates from 8% to 12.7% in populations receiving emergency transfu-
In our study, the rate of SGA babies was also higher in the SS group than among controls but remained low in comparison with rates observed in previous studies—ranging from 11.6% to 46% [9,10,12,13]. Patients with the SS genotype are known to have a higher incidence of abnormal velocimetry in the uteroplacental circulation [23], which may be related to the sickling process in the uteroplacental vessels and to abnormal blood viscosity. Some authors assessed the change in placental vascular resistance following partial exchange transfusion in HbSS patients and found that prophylactic transfusions had no effects on uteroplacental waveforms [24]. This is consistent with the persistence of higher rates of pre-eclampsia and SGA babies in HbSS patients.

Preterm delivery was significantly higher in the SS group than among controls, but was low compared with that in earlier studies in which it ranged from 21% to 45% in patients without prophylactic transfusions [9–14].

We found a low rate of alloimmunization (5.3%). One was associated with an IUFD at 29 weeks, while the four other cases occurred without any clinical complications. There were no transfusion-related hepatic complications. Koshy et al. reported a 29% alloimmunization rate [7], and El Shafei et al. a 23.6% rate of transfusion-related complications [22]. Today, it is recommended that only phenotype-matched red-cell units be transfused [25].

The survival of patients with SCD certainly depends on the availability of matched blood, but transfusion-related complications are not an argument against prophylactic transfusion since our alloimmunization rate was higher than the rate obtained with emergency transfusions. It is known that SC patients have lower mortality and morbidity rates than SS patients [26,27]. Their childhood growth and development are almost normal with usually mild complications, and their median age for irreversible organ dysfunction is 10–35 years later [27]. Pregnancy outcome in SC disease is reported to be generally benign compared with SS disease. In a cohort study followed from birth, Sergeant et al. showed that pregnancy outcome in SC disease did not differ from that of AA controls for the prevalence of pre-eclampsia [28]. They also found fewer miscarriages, more live births and greater birth weight in the SC compared with the SS group, but the rates of sickle-related complications were similar. Our data too showed better obstetrical outcomes for SC than SS patients. There were no significant differences in obstetrical complications and perinatal outcomes between SC and AA patients, except for the route of delivery (number of cesareans) and labor induction after 37 weeks. In our study too, SC and SS patients were comparable for sickle-related complications.

While indications for emergency transfusion are well defined [1,22], the question of prophylactic transfusions has not been answered definitively and transfusion regimens vary from one team to another. The most recent study describing the pregnancy outcomes of SS patients receiving only selective transfusion found high rates of complications: 47% of sickle crisis, 32% of anemia requiring transfusion, 9% of pre-eclampsia, 28% of infection, 32% of prematurity and 18% of IUGR [29]. The most recent study which compared selective prophylactic transfusions to emergency transfusions found decreased rates of preterm delivery and pain crisis in the patients who received prophylactic transfusions, but this study was a retrospective cohort and had a small number of patients [30]. The only prospective randomized study had a sample size inadequate for analysis of perinatal outcomes (36 patients in each arm) [7].

Our purpose here was to describe maternal and fetal outcomes in pregnant patients managed according to a policy of prophylactic transfusion started in our institutions a long time ago. We began to adopt this policy in the 1980s for three reasons: first, the number of pregnancies was low and very few maternity units were used to caring for such clinical situations; second, our experience with maternal mortality at that time was worrying, mainly related to bad follow-up; third, the literature gave encouraging data for maternal mortality rates in series in which transfusion was either programmed or without restriction [4]. Our policy led to a structured organisation of care between the maternity units and the Sickle Cell Centre and to a better follow-up of those pregnancies. This study describes the results of such a choice. We found higher rates of pre-eclampsia, IUGR and prematurity in patients with sickle cell SS disease compared to the control group. Despite prophylactic transfusion, we found persistence of high rates of pain crisis in women with SCD. Alloimmunization was low but was associated in one case with an IUFD. SCD remains a complicating factor in pregnancy and further studies with randomized trials comparing prophylactic red-cell transfusions to emergency transfusions are needed.

References

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