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Sickle cell disease and pregnancy: analysis of 34 patients followed at the Regional Blood Center of Ribeirão Preto, Brazil

Ana Cristina Silva-Pinto^{a,*}, Simery de Oliveira Domingues Ladeira^b,
Denise Menezes Brunetta^a, Gil Cunha De Santis^a, Ivan de Lucena Angulo^a,
Dimas Tadeu Covas^{a,b}

^a Hemocentro de Ribeirão Preto, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (USP), Ribeirão Preto, SP, Brazil

^b Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (USP), Ribeirão Preto, SP, Brazil

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ABSTRACT

Objective: The objective of this study was to verify the evolution of pregnancies in sickle cell patients followed at one institution over a period of 12 years (January 2000 to June 2012).

Methods: The study evaluated 34 pregnant women with sickle cell disease with a mean age of 23.9 ± 5.3 years. The incidence of obstetric complications, non-obstetric complications linked to sickle cell disease and complications in the newborn were analyzed.

Results: A total of 26% of the cases reported previous miscarriages, 20% had preterm labor, 10% had pre-eclampsia, and 5% had gestational diabetes. Forty-one percent of the deliveries were cesarean sections and 29% of patients required blood transfusions. In respect to sickle cell disease, 62% of patients had vaso-occlusive crises, 29% had acute chest syndrome, 23% had urinary tract infection, 15% had impaired cardiac function and 6% developed pulmonary hypertension. Only one patient died in the postnatal period due to acute chest syndrome. The mean gestational age was 37.8 ± 2.63 weeks, and mean newborn weight was 2.809 ± 643.8 g. There were seven fetal losses, including three stillbirths and four miscarriages. The impact of transfusion therapy on the incidence of maternal-fetal complications during pregnancy was evaluated.

Conclusions: Pregnancy in sickle cell patients is still associated with complications. Although no statistical difference was observed between transfused and non-transfused women, there were no deaths (fetal or maternal) in transfused patients whereas one maternal death and three stillbirths occurred in non-transfused women. A larger study of sickle cell pregnant women will be necessary to elucidate the actual role of transfusion during pregnancy in sickle cell disease.

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* Corresponding author at: Hemocentro de Ribeirão Preto, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (FMRP-USP), Rua Tenente Catão Roxo, 2501, Campus Universitário, Monte Alegre, 14051-140 Ribeirão Preto, SP, Brazil.

E-mail address: acristina@hemocentro.fmrp.usp.br (A.C. Silva-Pinto).

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Introduction

Sickle cell disease (SCD) comprises a group of diseases characterized by the presence of sickle hemoglobin (Hb S). It is classified as sickle cell anemia (Hb SS), hemoglobinopathy SC, hemoglobinopathy SD, S-beta thalassemia (Hb S-beta) and other associations of mutant hemoglobins with Hb S.

In situations of low oxygen tension, Hb S solubility decreases, resulting in the polymerization of these molecules. The intracellular formation of Hb S polymers affects the red cell structure, changing it into a sickle-shaped, thereby damaging the cell membrane, making it more rigid and exposing a greater number of adhesion molecules on the cell surface, thus increasing the adherence of red cells to the vascular endothelium.¹ This phenomenon, named sickling, is responsible for the premature destruction of red cells by the reticuloendothelial system, causing a chronic hemolytic anemia. Under stress situations, such as infections, deoxygenation of Hb molecules and sickling of a large number of red blood cells occur. These cells adhere to the vascular endothelium which may cause vessel occlusion and, consequently, tissue ischemia causes the painful crises that characterize one of the clinical features of this disease. Chronic hemolytic anemia and frequent vaso-occlusive crises cause damage to various organs and impair both the survival and the quality of life of patients with SCD.²

Until the 1970s, the management of sickle cell patients was poor and pregnancy was associated with high maternal and fetal mortality.³ Nowadays, with newborn screening and preventive measures such as vaccination and antibiotic prophylaxis since birth, patient survival has improved.⁴ Furthermore, the quality of obstetric and neonatal care has also corroborated to a significant reduction in the maternal mortality rate (from 4.1% to 1.7%) and improved fetal survival (from 60 to 80%).^{4,5} However, despite all the medical advances in recent decades, pregnancy in sickle cell patients is still associated with many clinical and obstetric complications compared to the general population.⁶⁻⁸

The physiological adaptations that occur in the circulatory, hematologic, renal, and pulmonary systems during pregnancy can overburden organs that already have chronic injuries secondary to SCD, increasing the rate of obstetric complications such as eclampsia and pre-eclampsia as well as the complications of the disease, such as worsening of vaso-occlusive crises and acute chest syndrome.⁷

Objective

The aim of this study was to assess the evolution of pregnancy in sickle cell patients followed at one institution, the Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (HC-FMRP-USP) in a 12-year period (January 2000 to June 2012), and discuss the impact of blood transfusion on pregnancy.

This study will contribute to the knowledge on the prevalence of maternal and fetal complications occurring in this population and show the impact of therapeutic measures used to control these complications during pregnancy.

Table 1 – Characteristics of the patients according to their sickle cell genotype.

	Hb SS	Hb S/beta ⁰	Hb SC
Number of patients	24	7	3
Mean age (years)	22.6	22.0	25.0
Previous HU use – n (%)	5 (21)	2 (28)	1 (33)
Blood transfusion – n (%)	5 (21)	4 (57)	1 (33)
Obstetric complications – n (%)	14 (58)	1 (14)	1 (33)
Sickle cell complications – n (%)	18 (75)	6 (85)	2 (67)

Methods

This was a retrospective study that aimed at analyzing the evolution of pregnancies in sickle cell patients during the period covered by the study (January 2000 to June 2012).

Study participants

The subjects comprised sickle cell patients followed at the Hospital das Clínicas, Universidade de São Paulo (USP) in Ribeirão Preto. Patient inclusion criteria were having a diagnosis of SCD (Hb SS, Hb S-beta or Hb SC) by hemoglobin electrophoresis and having had one or more pregnancies from January 2000 to June 2012. The patients were then divided in two groups in order to evaluate the impact of blood transfusions on sickle cell complications during pregnancy.

Design

Clinical data was obtained through a review of medical records from the hospital with the confidentiality of information being preserved. The results of laboratory tests were obtained through the online hospital system using the ATHOS program. The clinical and laboratory data were recorded on a data collection form and later compiled for statistical analysis of the prevalence of maternal and fetal complications.

Statistical analysis

Data are presented as descriptive statistics including means and percentages. The Mann-Whitney non-parametric statistical test was used to compare the transfused and non-transfused groups as the samples did not have a Gaussian (normal) distribution.

Results

The study evaluated 34 pregnant women with SCD; 24 (70.5%) had Hb SS, seven (20.5%) Hb S⁰-thalassemia and three (8.8%) Hb SC. The mean age was 23.9 ± 5.3 years and 20 (59%) were followed from the first trimester of pregnancy in the High-risk Pregnancy Outpatient Service of the hospital, nine (25%) started this follow-up in the last trimester, and five (15%) did not have any follow-up in this service. The characteristics of the patients according to the type of SCD are shown in Table 1.

Hb SS patients had more obstetric complications (three stillbirths, three miscarriages and eight pre-term labors and one maternal death) than the other two genotypes (S/beta⁰ with one miscarriage and Hb SC with one pre-term labor). Most

Table 2 – Maternal obstetric complications during pregnancy.

Obstetric complications	n (%)
Previous miscarriage	9 (26.6)
Preterm labor	8 (23.5)
Pre-eclampsia	4 (12.0)
Gestational diabetes	2 (5.8)
Cesarean section	14 (41.0)
Transfusion in peripartum period	10 (29.4)

Table 3 – Non-obstetric maternal complications during pregnancy.

Non-obstetric complications	n (%)
Vaso-occlusive crises	21 (61.7)
Acute chest syndrome	10 (29.4)
Urinary tract infection	8 (23.5)
Impaired cardiac function	5 (14.7)
Maternal death	1 (2.9)

of the patients in all three groups experienced complications related to SCD during pregnancy.

Obstetric complications

The patients had many obstetric complications, such as previous miscarriage, preterm labor, pre-eclampsia, and gestational diabetes (Table 2). Some patients required blood transfusions in the peripartum period for clinical complications such as acute chest syndrome, recurrent vaso-occlusive crises and one had hyper-hemolytic syndrome.

Non-obstetric complications

The incidence of sickle cell complications during pregnancy is shown in Table 3. Only one patient died two days after delivery due to acute chest syndrome.

Characteristics and complications of the newborn

The main characteristics of the newborns are shown in Table 4. There were seven fetal losses, including three stillbirths and four miscarriages.

Table 4 – Analysis of the characteristics of the newborn infants.

Characteristic	
Mean gestational age (weeks) – mean $\pm$ SD	37.8 $\pm$ 2.63
Average weight (g) – mean $\pm$ SD	2809 $\pm$ 643.8
First minute Apgar <7 – n (%)	11 (27.5%)
Stillbirth – n (%)	3 (7.7%)
Miscarriage – n (%)	4 (10.2%)
SD: standard deviation.	

The impact of transfusion therapy during pregnancy was also evaluated. The evolution of pregnancy, type of delivery, fetal characteristics and maternal complications were compared between transfused and non-transfused pregnant women. Approximately one third (10/34) of the patients were submitted to transfusion during pregnancy and the results of this analysis are presented in Table 5.

The indications for transfusion during pregnancy were: acute chest syndrome (six patients), and repeated vaso-occlusive crises (three patients); one patient was already on a transfusion program due to cerebral vasculopathy.

Discussion

This study shows that despite the medical advances in recent decades, pregnancy is still associated with many clinical and obstetric complications in patients with SCD, resulting in a higher maternal and infant mortality than in patients with the sickle cell trait (Table 6). All deaths (maternal and fetal) occurred in Hb SS patients, the most severe genotype of SCD.

It is known that pregnancy induces a number of physiologic changes that affect the hematologic indices, and patients with SCD may experience worsening of the anemia and other sickle cell complications.⁹

Oxygen demand during pregnancy increases to support the metabolic requirements of the placenta and fetus. As the maternal oxygen reserve may be compromised during pregnancy due to the increased oxygen consumption and decreased functional residual capacity, patients may be predisposed to hypoxemia, with exacerbation of sickling and its complications.¹⁰ These changes during pregnancy highlight

Table 5 – Comparison of maternal-fetal characteristics between pregnant women with sickle cell disease transfused and non-transfused during pregnancy.

	Non-transfused (n = 24)	Transfused (n = 10)	p-value
Median age (years) – mean (range)	23 (19–37)	22 (18–32)	0.79
Pre-gestational Hb (g/dL) – mean (range)	8.45 (6.6–10.0)	8.2 (7.6–11.6)	1
Mean gest. age (weeks)	39.6	37.5	0.87
Mean 1st minute Apgar score	7.3	7.8	0.79
Mean weight at birth (g)	2850 (1415–3063)	2710 (1745–3335)	0.22
Mean weight of placenta (g)	512.5	450.0	0.25
C. section/normal delivery	6/15	5/6 ^a	0.47
Miscarriage – n (%)	3 (12.5)	1(10.0)	0.68
Stillbirth – n (%)	3 (12.5)	–	0.14
Maternal death – n (%)	1 (2.9)	–	0.25
Total deaths (maternal and fetal)	4/48	0/20	0.31

^a One patient had two pregnancies.

Table 6 – Comparison of maternal-fetal characteristics between two published studies and the current study.

	Koshy et al. ¹¹	Nomura et al. ⁸		Current study
	Hb SS	Hb SS + Hb SC	Sickle cell trait	Hb SS + Hb S/beta + Hb SC
Number of patients	100	51	56	34
Gestational age (weeks)	37.5	35.2	37.9	37.8
Weight <2500 g (%)	41.7	62.7	17.9	25.0
Previous miscarriage (%)	36.0	25.5	25.0	26.6
Perinatal death (%)	7.6	11.8	1.8	7.7
Cesarean section (%)	–	84.3	73.2	41.1
Pre-eclampsia (%)	18.0	21.6	14.3	12.0
Gestational diabetes (%)	–	2.0	12.5	6.0
Maternal death (%)	1.7	3.9	0	2.9

the need for a multidisciplinary team of experts to monitor pregnant sickle cell women in a tertiary hospital.

When our results are compared to a Brazilian study published in 2010 by Nomura et al. (Table 6), the maternal death rate was similar despite differences in the obstetric complication rate (pre-eclampsia, gestational diabetes and cesarean section).⁸ The largest difference occurred in the analysis of fetal characteristics such as gestational age at delivery, weight lower than 2500 g at birth and perinatal death. The gestational age and perinatal death rate in this study were similar to the publication by Koshy et al.¹¹

In another recently published retrospective study, the authors analyzed 68 SCD patients. Almost all of the patients had at least one sickle cell complication during pregnancy, but a lower rate of obstetric complications (15/68) compared to the current study.¹² In relation to newborn outcomes, a study performed at a university hospital in the West Indies analyzed perinatal outcomes such as admission to a nursery ward, birth weight less than 2.5 kg, 5-min Apgar score less than 7, cesarean section for fetal distress, and perinatal death or death before discharge from nursery ward of 19 newborn babies. A total of 47% of the subjects had adverse outcomes.¹³

The need for transfusion during pregnancy for either acute anemia or obstetric emergencies is common in SCD patients. On the other hand, the use of prophylactic transfusions is still polemic.¹⁴ According to Koshy et al., there is no need for prophylactic transfusions during a non-complicated pregnancy.¹⁵ The authors performed a randomized controlled trial evaluating the benefits of prophylactic transfusions during pregnancy and found that maternal and fetal outcomes were similar in the transfused and non-transfused group. Subsequent retrospective cohort studies evaluating the efficacy of prophylactic transfusions also failed to show a substantial decrease in obstetric and fetal complications.^{16,17} Conversely, prophylactic erythrocytapheresis in the third trimester has been associated with a reduction in adverse maternal and fetus outcomes.¹⁸

Although no statistical difference was observed between transfused and non-transfused patients, there were no deaths (fetal or maternal) in transfused women, whereas in non-transfused patients, there was one maternal death and three stillbirths. This observation leads us to question again the role of transfusions in sickle cell patients during pregnancy, a period prone to an increase in the percentage of maternal and fetal complications. Perhaps the current study did not detect any statistical significance between the two groups due to the

limited number of pregnant women analyzed. A randomized multicenter study should be performed urgently to evaluate a larger number of pregnant sickle cell women in order to better elucidate this issue.

Conclusions

This study shows that pregnancy is still associated with many clinical and obstetric complications in patients with SCD and so patients should be followed by a multidisciplinary team in a tertiary hospital.

The actual role of transfusion during pregnancy in SCD remains to be determined however it seems that it should be adopted more liberally.

Conflicts of interest

The authors declare no conflicts of interest.

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