HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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Original article

Maternal and perinatal outcomes in pregnant women with sickle cell disease: an update

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ARTICLE INFO

Article history:
Received 7 August 2020
Accepted 8 December 2020
Available online 9 March 2021

Keywords:
Maternal
Perinatal
Pregnancy
Sickle cell disease

ABSTRACT

Introduction: The aim of this study was to describe maternal and perinatal outcomes in pregnant women with sickle cell disease (SCD) followed at Santa Casa de Sao Paulo over a 10-year period (between 2010 and 2019).
Method: Fifty-five records of pregnancies were analyzed among 35 women with SCD.
Results: Among 29 newborns, 19 (65.5%) were full-term and 10 pre-term; 24 (82.7%) caesareans and 5 (17.2%) natural births were observed. The mean gestational age at birth and mother's age were 36.6 weeks (30–40) and 26.7 years (17–39), respectively. No maternal death was observed. The main maternal obstetric and non-obstetric complications were: pre-eclampsia and gestational diabetes, and vaso-occlusive crisis, urinary tract infection and acute chest syndrome, respectively. Twenty-six (47.0%) fetal deaths were observed, 24 being intrauterine fetal (14 early abortions, 10 late abortions and 2 stillbirths). Regarding the red blood cell transfusion history, 40 (72.7%) out of 55 pregnancies received transfusion. Pregnant women who received 6 or more transfusions throughout pregnancy had a significantly lower number of abortions, i.e., no cases of early abortion and only 1 case of late abortion, versus 14 and 9 cases in pregnancies with 0–5 transfusions, respectively. Despite advances in the management of SCD, pregnant women with SCD (particularly those with HbSS) are at a high risk for maternal and fetal complications, even though they are followed in reference centers.
Conclusion: The lower risk of intrauterine fetal death for those women who received more transfusions throughout pregnancy observed in the current study leads us once more to raise the need for prospective, multicenter, randomized trials to determine whether the potential benefits balance the risks of prophylactic transfusions.

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https://doi.org/10.1016/j.htct.2020.12.009

Introduction

Sickle cell disease (SCD) is an increasing global health problem and one of the most common genetic disorders worldwide, with varying clinical severity, potentially serious complications with high lifetime morbidity and premature mortality.[1,2] SCD is defined as an autosomal recessive hemoglobinopathy that includes sickle cell HbSS disease and various compound heterozygous genotypes (e.g., sickle cell HbSC disease or sickle cell beta-thalassemia disease [HbSßthal]).[1,2]

Although HbS polymerization, vaso-occlusion, and hemolytic anemia are central to the pathophysiology of SCD, they precipitate a cascade of pathologic events, which in turn lead to a wide range of complications. These processes include vascular–endothelial dysfunction, functional nitric oxide deficiency, inflammation, oxidative stress and reperfusion injury, hypercoagulability, increased neutrophil adhesiveness and platelet activation.[1] Chronic complications fall into two main groups: those related to large vessel vasculopathy (cerebrovascular disease, pulmonary hypertension, priapism and retinopathy) and those caused by progressive ischemic organ damage (hyposplenism, renal failure, stroke, bone disease and liver damage).[1]

A better quality of care for individuals with SCD over the last two decades has improved the survival and quality of life and thus, there are increasing numbers of women reaching the reproductive age. It is estimated that 300,000 children are born with the condition each year.[1] In Brazil, SCD has an incidence of 1/1000 births, there are 3500 deliveries with SCD each year and the number of pregnancies among women with SCD is yet unknown.[3]

Several reviews and meta-analyses of available evidence have found an increased risk of maternal deaths and obstetric and fetal complications, compared to controls.[4–11] Knowledge of these risks has contributed to the implementation of a multidisciplinary management program, including the early detection and treatment of complications during pregnancy and postpartum, appropriate pain management protocols and transfusion programs adapted to each pregnant patient. Emphasis must be placed on educating patients and providers on pregnancy-related complications and management, as well as the benefit of early prenatal protocol-driven care provided by a multidisciplinary team.[2,12]

Objectives

The aim of this study was to describe maternal and perinatal complications in pregnant women with SCD followed at Santa Casa de Sao Paulo (SCSP) over a 10-year period (from January 1, 2010, to December 31, 2019), as well as the impact of red blood cell (RBC) transfusion on maternal and fetal complications during pregnancy.

Materials and methods

Study type

This was a retrospective and descriptive study that aimed to describe maternal and perinatal outcomes in pregnant women with SCD followed at SCSP over a 10-year period.

Study participants

The subjects were pregnant women with SCD regularly (at least three visit per year) followed in our outpatient unit of anemia at SCSP, a public hospital, as well as a reference center for patients with SCD. The inclusion criteria were one or more pregnancies in an SCD patient diagnosed by hemoglobin electrophoresis and/or high-performance liquid chromatography (HPLC).

According to the World Health Organization (WHO), early abortion was defined as abortion before 12 weeks of gestation and late abortion, as that in up to 22 weeks of gestation.

The on-demand RBC transfusion, defined as the transfusion instituted to treat complications, was indicated for pregnant patients if the hemoglobin (Hb) level fell below 8.0 g/dL or upon a 2-g/dL decrease in Hb in steady-state anemia (due to infection, increased hemolysis, renal disease, or multiorgan system failure) and in case of obstetric or acute SCD-related complications, such as stroke, acute chest syndrome, or acute splenic sequestration), regardless of the gestational age. Chronic transfusion therapy was maintained for those with an established chronic transfusion protocol before pregnancy (secondary prevention of stroke and/or acute chest syndrome) and was initiated from the diagnosis of pregnancy or in the first trimester of gestation for SCD patients with a history of late miscarriage and/or neonatal deaths, intrauterine growth retardation, or twin pregnancy. This protocol consisted of a simple or exchange transfusion every 3–4 weeks until delivery. The target Hb level was between 9.0 and 10.0 g/dL in patients with HbSS and HbS levels below 50.0% in those on long-term transfusion.

Design

Clinical data were obtained through a review of medical records from the hospital, with the confidentiality of information being preserved. Laboratory test results were obtained from the online hospital system, using our hospital software. These data were recorded on an Excel spreadsheet and later compiled for statistical analysis. The data collection was approved by the Santa Casa Medical Ethics Committee.

Data analysis

The data are presented as descriptive statistics with means and percentages. The Mann–Whitney nonparametric statistical test was used to compare the transfused with the non- or low-transfused groups. The data analysis was performed using the Epi Info™ 7 and Power BI 2.71 from July 19 to March 20.

Results

There were thirty-nine pregnant women with SCD followed at SCSP from January 1, 2010 to December 31, 2019. Four patients were excluded because of a lack of information. Fifty-

Table 1 – Characteristics of 35 patients according the SCD genotype and number of pregnancies.

SCD genotype	Number of women	Number of pregnancies
HbSS	26	39
HbSß$^+$thal	1	3
HbSß^{0}thal	2	3
HbSC	3	3
Other genotype[a]	3	7
Total	35	55

[a] HbSD (1, 3 pregnancies) and HbS/HPFH (2, 4 pregnancies).

five records of pregnancies were analyzed among 35 women with SCD. Tables 1 and 2 demonstrate the characteristics of the patients according to the SCD genotype, number of pregnancies and number of pregnancies and SCD genotype, respectively. Of the 55 pregnancies evaluated, 29 (53.0%) were submitted to the pre-natal at SCSP, 14 underwent an external pre-natal and 12 had not initiated the pre-natal. We observed 26 (47.0%) fetal deaths out of 55 pregnancies, of which 24 were intrauterine fetal, being 14 early abortions, 10 late abortions and 2 stillborn. The mean gestational age of fetal death was 14.35 weeks (4.0–29.8) and the mother's age, 23.8 years (17–41). Twelve out of the 26 abortions had not initiated the pre-natal.

Among the 29 newborns, 19 (65.5%) were full-term newborns and 10, pre-terms; 24 (82.7%) caesareans and 5 (17.2%) natural births were also observed. The mean gestational age and mother's age at birth were 36.6 weeks (30–40) and 26.7 years (17–39), respectively. As for the birthing, there were 21 (72.5%) birthings at SCSP and 8 external birthings. The two patients with stillborns underwent the pre-natal and birthing at SCSP. The main maternal obstetric complications were pre-eclampsia (3; 5.4%) and gestational diabetes (6; 10.9%). No maternal death was observed. Non-obstetric complications are shown in Table 3.

Maternal and fetal outcomes and transfusion history

Regarding the RBC transfusion history, 40 (72.7%) out of 55 pregnancies had received RBC transfusion during pregnancy: 1–3 transfusions in 9 (22.5%) patients, 4–6 transfusions in 11 (27.5%), 7–9 transfusion in 5 (12.5%), >10 in 8 (20%) and 7 pregnancies (17.5%) in women who had received transfusions, but did not know how many. Chronic transfusion therapy was maintained for the 3 patients with established chronic transfusion protocols before pregnancy (secondary prevention of stroke), was initiated and maintained until delivery, mostly in the first trimester of gestation, for SCD patients with a history of late miscarriage and/or neonatal deaths (7 patients, 11 pregnancies) and one twin pregnancy, as well as initiated at any time, regardless of gestational age, and maintained until delivery for those with vaso-occlusive crisis (VOC) (19 pregnancies), neurologic complication (2 pregnancies) and acute chest syndrome (7 pregnancies). Most of these two latter causes were associated most often with worsening anemia. The comparison of the number of intrauterine fetal and neonatal deaths associated with the number of transfusions (0–5 transfusions versus 6 or more transfusions) throughout pregnancy among 55 pregnancies is demonstrated in Table 4.

Table 3 – Maternal non-obstetric complications among 55 pregnancies.

Maternal non-obstetric complications	n (%)
Vaso-occlusive crisis	19 (34.5%)
Urinary tract infection	12 (21.8%)
Acute chest syndrome[a]	7 (12.7%)
Hospitalization in intensive care unit	5 (9.0%)
Neurologic complication[b]	2 (3.6%)
Hyperhemolytic syndrome	2 (3.6%)
Others[c]	3 (5.4%)

[a] All acute chest syndromes occurred in HbSS patients.
[b] 1 stroke, 1 convulsive crisis not classified as eclampsia.
[c] 2 leg ulcer, 1 osteoarthritis.

Table 4 – Comparison of intrauterine fetal and neonatal deaths in transfusion totals throughout pregnancy among 55 pregnancies.

Parameter	Group 1 (0–5 transfusions) (n = 40)	Group 2 (6 or more transfusions) (n = 15)	p
Early miscarriage	14	0	0.02
Late miscarriage	9	1	0.19
Neonatal death	1	1	1
Total	24	2	–

Discussion

Because of early diagnosis and improved pediatric care, more individuals with SCD are reaching reproductive age, thereby

Table 2 – Characteristics of 35 patients (55 pregnancies) according to the number of pregnancies and SCD genotype.

Number of gestations	Genotype				
	HbSS (n = 26)	HbSß^{0}thal (n = 2)	HbSß$^+$thal (n = 1)	HbSC (n = 3)	Other genotypes[a] (n = 3)
1	11	1	0	2	1
2	13	1	0	1	0
3	0	0	1	0	2
4	1	0	0	0	0
5	1	0	0	0	0

[a] HbSD (1; 3 pregnancies) and HbS/HPFH (2;1,3 pregnancies).

Table 5 – Comparison of maternal and fetal characteristics among three published studies and the current study.

Parameter	Current study n = 35[a] (%)	Elenga et al.[21] n = 62 (%)	Silva-Pinto et al.[15] n = 34 (%)	Leborgne-Samuel et al.[16] n = 58[d] (%)
Previous history of miscarriage	10 (38.4)	13 (21.0)	9 (26.6)	–
Gestational diabetes	6 (10.9)	0 (0)	2 (5.8)	–
Pre-eclampsia	3 (5.4)	11 (17.7)	4 (12.0)	7 (10.2)
Caesarean section	24 (82.7)[b]	33 (53.0)	14 (41.0)	30 (44.0)
Miscarriage	24 (43.6)[c]	4 (11.7)	4 (10.2)	4 (5.8)
Prematurity	10 (34.4)	18 (29.0)	8 (23.5)	16 (23.5)
Neonatal death	2 (3.6)	4 (6.4)	3 (7.7)	3 (4.4)
Maternal death	0 (0)	0 (0)	1 (2.9)	1 (1.4)

[a] 35 women and 55 pregnancies.
[b] 24 caesareans section out of 29 newborns.
[c] 24 intrauterine fetal deaths among 55 pregnancies.
[d] 58 patients and 68 pregnancies.

directing attention to improving reproductive health care and outcomes for pregnant women.[1,2,13,14] Despite improvements in health care over the last 4 decades, maternal and fetal morbidity and mortality remain high, with limited therapeutic interventions to improve pregnancy-related outcomes in women with SCD, particularly in those with the HbSS genotype.[2,14]

The current study, like many observational ones already published,[15,16,21] confirmed this high complication rate in terms of maternal and fetal complications. We observed no maternal deaths, but rather, a higher rate of previous history of miscarriage, gestational diabetes, caesarean section, miscarriage and prematurity, compared to other published studies (Table 5).[15,16,21]

The higher rate of caesarean section for the resolution of childbirth is a phenomenon that has been occurring all over the world. According to the Brazilian Ministry of Health, the percentage of caesarean deliveries in Brazil varies between 30% and 50%, with higher rates of assisted deliveries in public health services, well above the rate of caesarean section with clinical indication recommended by the World Health Organization, which is up to 15%.[22,23] In the case of patients with SCD, in addition to the obstetric decision, based on the scientific knowledge of the specialty, there are certainly several orders of factors involved, including the understanding, or lack thereof, in relation to the underlying disease itself, as well as its complications (anemia, VOC and acute chest syndrome), the lack or failure of information about the types of delivery and its risks to the pregnant woman in prenatal care, the obstetric care offered, that is, the obstetrician in prenatal care is often not the same professional who assists the patient at the time of delivery, facilitating the decision for caesarean section, especially in the presence of clinical-obstetric complications, factors related to the evolution of labor and, undoubtedly, to the abuses of medical intervention.[22,23]

Spontaneous abortion is the most common obstetric complication; it is estimated that up to 20% of pregnancies progress to abortion before 20 weeks and of these, 80% of spontaneous abortions occur by the 12th week of pregnancy. In Brazil, despite the lack of indicators that allow for the measurement of the total number of occurrences of abortions in the general population, it is estimated that in every ten pregnancies, two do not come to term.[22,23] It is known that the abortion rate in patients with SCD is higher than the rate of the female population in general; the current study observed a higher number of abortions in relation to other studies (Table 5). Possible explanations for the data found are: 74.2% of the patients studied were of the SS genotype, 5 (14.2%) patients had a obstetric history of 3 or more pregnancies, 3 patients had had 3 or more abortions without laboratory evidence of thrombophilia, difficulty in accessing the health service and/or lack of sufficient economic resources to seek medical care at the appropriate time.

Although studies have showed that prophylactic RBC transfusions may reduce perinatal mortality, neonatal deaths and adverse pregnancy outcomes in pregnant women with SCD, corroborating the likely beneficial role of transfusion during pregnancy,[2,13,15–20] the use of chronic transfusion therapy prophylactically throughout pregnancy remains controversial because data are lacking, and clinical studies are limited by methodological problems.[2,14]

The current study is retrospective and did not aim to evaluate the benefit of transfusion among prophylactically transfused pregnant women versus non-transfused pregnant women, however, we observed that 40 (72.7%) out of 55 pregnancies received transfusion for different reasons, most of them associated with SCD complications. Analyzing the relationship between maternal obstetric and non-obstetric complications and transfusion, as one would expect, the number of complications observed were higher for transfused pregnancies (Table 4). On the other hand, when we analyzed the number of transfusions during pregnancy and the occurrence of abortion and stillbirth, we observed that pregnant women who received 6 or more transfusions had a significantly lower number of abortions, i.e., no cases of early abortion and only 1 case of late abortion versus 14 and 9 cases in pregnancies with 0–5 transfusions, respectively. The number of stillbirths between the two groups was not different. These data suggest that the higher the number of transfusions equal to or greater than 6, regardless of the indication (complication related to SCD and/or pregnancy), the lower the risk of intrauterine fetal death. This observation leads us once more to question the likely beneficial role of transfusions during pregnancy in patients with SCD observed in many other

studies, a period prone to an increase in the percentage of maternal and fetal complications.

Conclusion

Despite advances in the management of SCD, pregnant women with SCD (particularly those with HbSS) are at a high risk for maternal and fetal complications, even though they are followed in reference centers. We observed a lower risk for intrauterine fetal death for those women who received 6 or more transfusions throughout pregnancy, regardless of the indication. This observation leads us once more to raise the need for prospective, multicenter, randomized trials to determine whether the potential benefits balance the risks of prophylactic transfusions.

Contributors

All authors contributed equally to the writing of the manuscript and approved the final version.

Funding

Not applicable.

Conflicts of interest

The authors declare no conflicts of interest.

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