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ORIGINAL ARTICLE

Management of sickle cell disease during pregnancy: experience in a third-level hospital and future recommendations

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ABSTRACT

Objective: To describe the outcomes of sickle-cell disease in pregnancy according to the different treatments adopted before and during pregnancy and to propose a systematic approach to treat sickle-cell disease (SCD) during pregnancy.

Methods: A retrospective descriptive study compared pregnancy outcomes among women with SCD who stopped hydroxyurea (HU) once pregnant (Group 1), were never treated before and during pregnancy (Group 2) or were treated by HU before conception who received prophylactic transfusion during pregnancy (Group 3). For each group we recorded the population's characteristics and the transfusion-related, obstetrical, perinatal and SCD complications.

Results: We found 11 patients for group 1 (9/11 with at least 3 painful crises during the 12 months before conception), 4 for group 2 (3/4 with no sickle-cell complications during the year before pregnancy) and 2 for group 3 (one with previous multiorgan failure (MOF), one with previous stroke). No transfusion-related complication occurred. Group 1 and 2 developed SCD complications and a high number of acute transfusions and hospital admissions. Group 3 showed none of these complications, but one patient developed preeclampsia and preterm birth. Several obstetrical and perinatal complications occurred in group 1.

Conclusion: Not treating sickle-cell during pregnancy increases maternal and perinatal morbidity, even in mildly affected women. All sickle-cell pregnancies should be treated, according to the treatment adopted before but also to patient's SCD-history. We propose chronic transfusion to women with previous stroke or MOF or already under transfusion program, and HU for severely and mildly affected patients, respectively from the second and third trimesters. Additional prospective studies are needed to validate the results of the proposed protocol.

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Introduction

Sickle cell disease (SCD) is the most common genetic condition worldwide due to a hemoglobin (Hb) disorder. It is associated with lifelong morbidity and reduced life expectancy. With advances in patient care and population movements from high to low HbS-frequency areas, more and more patients reach reproductive age, thereby increasing SCD prevalence during pregnancy to 4.83/10,000 pregnancies worldwide [1]. Sickle cell pregnancy is a life-threatening condition, for both mother and fetus (Figure 1). The physiological changes occurring during pregnancy (hypercoagulability, immune tolerance, increased metabolic demand, increased pulmonary resistance, etc.) increase the incidence of SCD-related complications [2], especially during the third trimester and early postpartum [3]. Endothelial damage and vaso-occlusive crisis (VOC) can also occur in the placenta, leading to an impaired uteroplacental circulation. For these reasons, sickle cell pregnancies have been linked to higher rates of maternal and perinatal complications such as preeclampsia, eclampsia, pregnancy-induced hypertension, intrauterine growth restriction (IUGR), abortion, placenta abruption, intrauterine fetal death (IUFD), emergency cesarean section, preterm birth, small for gestational age (SGA) infants, low birth weight, neonatal intensive care unit (NICU) admission, 5-min Apgar score <7, perinatal mortality, with a maternal mortality 6 times that of the general population [4–6].

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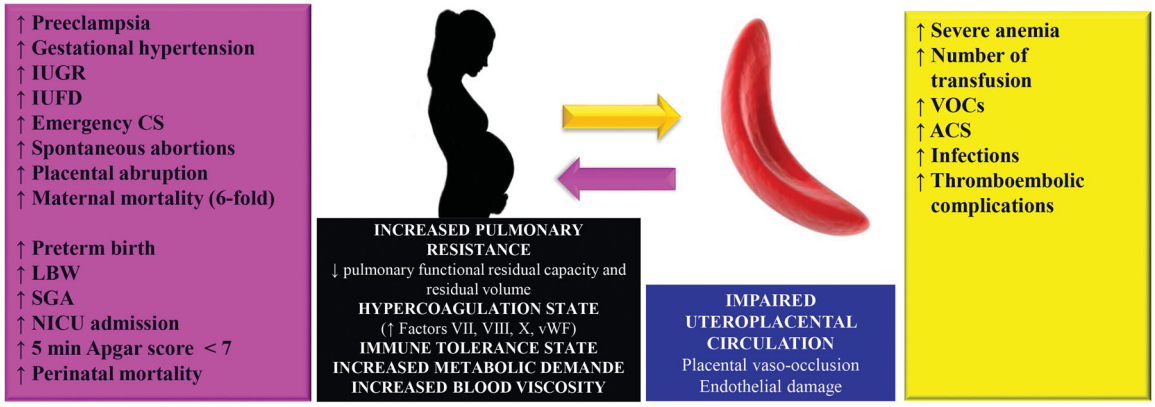

Figure 1. Pathophysiology of sickle cell pregnancy. IUGR: intrauterine growth restriction; IUFD: intrauterine fetal death; CS: cesarean section; LBW: low birth weight; SGA: small for gestational age; NICU: neonatal intensive care unit; VOCs: vaso-occlusive crisis; ACS: acute chest syndrome.

The management of sickle cell pregnancy is a challenge. The only two treatments (hydroxyurea [HU] and chronic prophylactic red-cell transfusion) recognized as disease-modifying are not recommended during pregnancy. As it inhibits HbS polymerization, HU is currently the only US Food and Drug Administration-approved medication that modifies the course of the disease in adults and children [7]. It is strongly recommended not only for severely affected adults with at least 3 painful crises over the prior 12 months or recurrent acute chest syndrome (ACS), but also for patients with common clinical symptoms that interfere with daily activities and for children after the age of 9 months, regardless of clinical symptoms [8]. However, it is recommended to stop HU at least 3 months before pregnancy and restart it after the end of breastfeeding [9,10], since it is teratogenic in a wide variety of animal models [11]. Equally, the role of chronic red cell transfusion is still controversial. In SCD, red cell transfusion decreases the proportion of HbS and its benefits have been established for stroke prophylaxis and protection of organs from ongoing damage in cases of multiorgan failure (MOF) [8,12]. In sickle cell pregnancy, chronic red cell transfusion has been proposed to reduce the extent of sickling in both the maternal and placental circulation [13]. However, although it seems to reduce maternal and perinatal morbidity and mortality [14], there is currently no sufficient evidence to recommend its use prophylactically [15].

The purpose of our study was to evaluate the outcomes related to sickle cell pregnancy (transfusion-related, obstetrical, perinatal and sickle cell complications), according to the different treatments of the disease adopted before and during pregnancy. Using our results and literature data, our ultimate goal is to propose a systematic way to treat SCD during pregnancy, using HU treatment or chronic prophylactic red cell transfusion.

Materials and methods

This was a retrospective descriptive study involving pregnancy among women with SCD, who delivered at the University Hospital Brugmann, Université Libre de Bruxelles, in Brussels, Belgium between January 2006 and October 2019. The study was approved by the Local Ethics Committee (Number: CE 2020/40). Exclusion criteria were: fetal loss before 14 weeks, elective abortion, incomplete or unavailable medical files and multiple pregnancy. Women were seen alternately at the obstetric high-risk unit and the hematology clinic every 2–3 weeks. Hemoglobin genotypes were characterized by standard electrophoresis. Gestational age was determined by first-trimester ultrasound. Initial laboratory tests included complete blood count, reticulocyte count, urine analysis and culture, liver enzymes, screening for red cell auto- and allo-antibodies, repeated monthly to detect any sickle cell complications or alloimmunization. A second fetal ultrasound scan was performed during the second trimester, and two during the third trimester, to detect any IUGR. Induction of labor was recommended at 38 weeks. Folic acid supplementation was initiated before pregnancy or once diagnosis was made. HU was stopped 3 months before pregnancy or once the diagnosis was made. As it is the latest recommendation for prevention of preeclampsia, aspirin treatment after 12 weeks was started only in the most recent patients. Prophylactic red cell transfusion was planned by the hematologist in only a few patients, after 8 weeks of pregnancy, and was repeated every 3–4 weeks until delivery.

Table 1. Baseline characteristics of the study population.

Variables	Group 1 $N = 11$	Group 2 $N = 4$	Adjusted p-value	Group 3 $N = 2$	Adjusted p- value
Maternal age (year)	25.6 ± 3.8	29.3 ± 5.6	.465	32 ± 1.4	.192
BMI (Kg/m^2)	24.2 ± 4.3	22.8 ± 3.6	1.000	23.6 ± 2.1	1.000
Nulliparity	7 (63.6%)	1 (25%)	.555	2 (100%)	.915
Smoking	2 (18.2%)	0	1.000	0	1.000
Comorbidities	2 (18.2%)	0	1.000	0	1.000
Hb genotype			.600		1.000
SS	10 (90.9%)	3 (75%)		2 (100%)	
SC	1 (9.1%)	0		0	
Sβthal	0	1 (25%)		0	
Baseline Hb 1 month before pregnancy (g/dL)	9.1 ± 0.9	8 ± 1.2	.528	6.5 ± 1.3	.030
Allo-Ab before pregnancy	4 (36.4%)	0	.477	0	1.000
SCD complications before pregnancy					
None	1 (9.1%)	2 (50%)	.240	0	1.000
<3 VOC	3 (27.3%)	2 (50%)	1.000	1 (50%)	1.000
≥3 VOC	8 (72.7%)	0	.039	0	.156
Recurring ACS	2 (18.2%)	0	1.000	1 (50%)	.978
Stroke	0	0	–	1 (50%)	.045
MOF	0	0	–	1 (50%)	.045
Cholecystectomy	7 (63.6%)	3 (75%)	1.000	1 (50%)	1.000
Splenectomy	1 (9.1%)	1 (25%)	1.000	0	1.000

p-Values are obtained from multiple comparison post-hoc test: group 2 and 3 are compared to group 1.
Abbreviations: Ab: antibodies; ACS: acute chest syndrome; BMI: body mass index; Hb: hemoglobin; MOF: multi-organ failure; SCD: sickle cell disease; VOC: vaso-occlusive crisis.

According to the different treatments adopted the year before and during pregnancy, we divided our population into three groups. *Group 1* comprised patients with no treatment during pregnancy (only acute transfusion) but treated with HU before conception. *Group 2* consisted of patients without treatment before and during pregnancy (only acute transfusion). *Group 3* was made up of patients who received HU before pregnancy and were treated by chronic red cell transfusion while being pregnant.

For each patient, we recorded the following data: characteristics of the population (age, parity, ethnicity, body-mass index (BMI), smoking habits, comorbidities not related to SCD, Hb genotype, presence of allo/auto-antibodies, blood group, hemoglobin level and SCD complications before pregnancy), and prenatal and postpartum care of SCD pregnancy (number, reasons for and type of transfusion, and number of hospital admissions). Obstetrical complications were measured: unscheduled cesarean section, preterm delivery (defined as delivery < 37 weeks), pre-eclampsia (defined by systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg with 24-h proteinuria > 300 mg), eclampsia, HELLP syndrome (defined by platelet blood count <100,000/μl, elevated liver enzymes and hemolysis), gestational hypertension, IUGR (defined as estimated fetal weight <5th percentile), IUFD, placenta abruption and maternal mortality. Perinatal outcome included: low birth weight (defined as a birth weight < 2500 g), 5-min Apgar score, small for gestational age (SGA defined as a birthweight <10th percentile for gestational age), neonatal intensive care unit (NICU) admission and perinatal mortality. SCD-related complications: VOC (defined as otherwise unexplained a bone or joint painful episode), ACS (defined as the combination of fever, dyspnea and specific infiltration on a chest X-ray), severe anemia (defined as a decline by 2.0 g/dL or more in hemoglobin concentration below the patient's baseline value), pyelonephritis, pulmonary infection, urinary tract infection, stroke, cholecystitis and venous thromboembolism. Transfusion-related complications: allo- and auto-immunization (defined as *de novo* detection of red cell auto- and allo-antibodies during the current pregnancy, with or without symptoms), delayed hemolytic transfusion reaction (defined as abrupt onset of signs and symptoms of accelerated hemolysis evidenced by an unexplained fall in hemoglobin, elevated lactate dehydrogenase (LDH), elevated bilirubin above baseline and hemoglobinuria, all occurring between 4 and 10 days after transfusion, with development or intensification of symptoms suggestive of VOC and/or ACS, regardless of the detection of new antibodies), acute transfusion reactions, transfusion-related infections, and iron overload.

Statistical analysis was performed using SPSS 25 statistical software (IBM SPSS statistics). Continuous variables were expressed as mean ± 1 standard deviation, while categorical variables were expressed as numbers (frequency), unless indicated otherwise. We used the Pearson' chi-squared test to compare the proportions of multinomial categorical variables between the 3 groups. Shapiro-Wilk test was performed to check the normal distribution of continuous

Table 2. Antepartum and postpartum outcome of SCD pregnancies.

Variables	Group 1 $N=11$	Group 2 $N=4$	Adjusted p-value	Group 3 $N=2$	Adjusted p-value
Hospital admission for SCD complications	10 (90.9%)	3 (75%)	1.000	0	.015
Number of hospital admission					
1–2	5 (45.5%)	2 (50%)	–	0	–
≥3	5 (45.5%)	1 (25%)	–	0	–
Number of transfusion			.696		.756
1	1 (9.1%)	2 (50%)		0	
2–3	5 (45.5%)	2 (50%)		0	
≥4	4 (40%)	0		2 (100%)	
Reason for transfusion					
SCD complication	9 (81.8%)	3 (75%)	1.000	0	.063
Perioperative/ Peripartum	6 (54.5%)	2 (50%)	1.000	0	.465
Prophylactic program	–	–	–	–	–
Type of transfusion					
Simple	10 (90.9%)	4 (100%)	1.000	2 (100%)	1.000
Exchange	3 (27.3%)	1 (25%)	1.000	1 (50%)	1.000
VOC	10 (90.9%)	3 (75%)	1.000	0	.015
ACS	4 (36.4%)	2 (50%)	1.000	0	.915
Severe anemia	8 (72.7%)	1 (25%)	.285	0	.156
Pyelonephritis	2 (18.2%)	0	1.000	0	1.000
UTI	3 (27.3%)	0	.729	0	1.000
Pulmonary infection	2 (18.2%)	1 (25%)	1.000	0	1.000
VTE	0	1 (25%)	.258	0	–

p-Values are obtained from multiple comparison post-hoc test: group 2 and 3 are compared to group 1.
Abbreviations: ACS: acute chest syndrome; SCD: sickle cell disease; UTI: urinary tract infection; VOC: vaso-occlusive crisis; VTE: venous thromboembolism.

variables, such as maternal age, BMI, and baseline Hb levels. One way ANOVA test was used to compare the means of continuous variables between the 3 groups. Thereafter, we performed a post-hoc Bonferroni test to obtain the adjusted p-values for the comparison of group 2 and 3 with group 1. An adjusted p-value below .05 was considered statistically significant.

Results

Among 43,274 deliveries, we found 17 pregnancies with SCD. The prevalence of SCD in our population was 3.93/10,000 pregnancies. Fifteen received no treatment (only acute transfusion) during pregnancy and among them, eleven were receiving HU treatment at least 3 months before pregnancy (*Group 1*) and four were not treated before pregnancy (*Group 2*); two patients started a chronic red cell transfusion program during pregnancy and were on HU treatment before (*Group 3*). One woman had two deliveries, each considered as a separate case. Among the 12 patients who were on HU, only one patient stopped HU and conceived 2 months after, whereas the remaining 11 patients stopped it during the 1st trimester. The small number of sickle cell pregnancies found was in accordance with the prevalence of the disease in pregnancy and with literature reports, where the analysis is always multicenter.

Tables 1 and 2 summarize the characteristics of the population and the prenatal and postpartum care, respectively. All patients came from Middle West Africa. Seven (63.6%), 1 (25%), and 2 (100%) patients in group 1, 2, and 3 respectively were nullipara. The vast majority of the patients had the HbSS genotype (one patient in group 1 was HbSC and one patient in group 2 was HbSβ^0-thal). Four women in group 1 were already alloimmunized before pregnancy. No women had a rare blood group (generally defined by the lack of a high frequency antigen or an infrequent combination of clinically relevant antigens) or auto-antibodies.

No patient had non-SCD-related comorbidities, except for one woman in group 1 who suffered from systemic lupus erythematosus. Most of the patients had already had cholecystectomy before pregnancy. Compared to group 2 and 3, group 1 contained higher proportion of patients who were severely affected with at least 3 painful crises during the 12 months before conception (72.7% versus 0%, $p=.039$, versus 0%, $p=.156$) (Table 1).

There was no significant difference in the number of hospital admission and acute transfusion for SCD complications between group 1 and group 2. In contrast, no patients in group 3 required hospital admission or acute transfusion for SCD complications ($p=.015$ and $p=.063$; respectively) (Table 2).

Group 2 was composed of women mildly affected, with no sickle cell complication during the year before pregnancy in most cases. Conversely, the women of group 3 were characterized by MOF or previous stroke, and a low baseline Hb level 1 month before pregnancy.

No SCD-related complications during pregnancy were found in group 3. Conversely, all patients of groups 1 and 2 developed SCD-related complications, particularly in terms of VOC, severe anemia and ACS.

Table 3. Appearance of SCD-related complications according to the pregnancy's trimesters.

Complications	Period	Group 1 $N = 11$	Group 2 $N = 4$	Group 3 $N = 2$
VOC	T1	5 (45.5%)	0	0
	T2	5 (45.5%)	0	0
	T3	7 (63.3%)	1 (25%)	0
	PP	0	2 (50%)	0
ACS	T1	0	0	0
	T2	3 (27.3%)	0	0
	T3	2 (18.2%)	1 (25%)	0
	PP	0	1 (25%)	0
Severe anemia	T1	1 (9.1%)	0	0
	T2	4 (36.4%)	0	0
	T3	4 (36.4%)	0	0
	PP	1 (9.1%)	1 (25%)	0
Pyelonephritis	T1	0	0	0
	T2	1 (9.1%)	0	0
	T3	1 (9.1%)	0	0
	PP	0	0	0
UTI	T1	3 (27.3%)	0	0
	T2	1 (9.1%)	0	0
	T3	0	0	0
	PP	0	0	0
Pulmonary infection	T1	0	0	0
	T2	1 (9.1%)	0	0
	T3	1 (9.1%)	0	0
	PP	0	1 (25%)	0
VTE	T1	0	0	0
	T2	0	0	0
	T3	0	0	0
	PP	0	1 (25%)	0

Abbreviations: ACS: acute chest syndrome; PP: postpartum; T1: first trimester; T2: second trimester; T3: third trimester; UTI: urinary tract infection; VOC: vaso-occlusive crisis: VTE: venous thromboembolism.

The most frequent complication in both groups was VOC (90.9% in group 1 versus 75% in group 2, $p = 1.000$) (Table 2). In addition, complications were noted only during the third trimester and early postpartum in group 2 patients, but throughout pregnancy in group 1 patients (Table 3). No transfusion complications were observed among the three groups.

There was no statistically significant difference in the obstetrical and perinatal outcomes between the 3 groups. However, the prevalence of IUGR, LBW, emergency CS, APGAR < 7 at 5 min, and RDS were higher in group 1. The only obstetrical complications found in group 3 were preeclampsia and preterm birth, observed in the same patient in whom prematurity was preeclampsia-induced. No complications were found in group 2 (Table 4).

Discussion

We report the outcomes in a small series of pregnant women with SCD, according to the different treatment regimens adopted before (HU or chronic red cell transfusion or no treatment) and during pregnancy (chronic red cell transfusion or no treatment) and showed that it is important to treat SCD during pregnancy.

Sickle cell pregnancy is life-threatening for both mother and fetus, as is clear from the literature, and its management is still an unresolved problem. Several studies, systematic reviews and meta-analyses show that sickle cell pregnancies have been linked to higher rates of *obstetrical complications* [2,4–6,16,17], adverse *perinatal outcomes* [17–20] and *SCD-related complications* [2,13,21–23]. Moreover, the higher number of SCD complications during pregnancy increases the rate of transfusion and consequently blood consumption, the risk of allo/auto-immunization, and the incidence of delayed hemolytic transfusion reaction (the most feared transfusion-related complication) [24,25].

Despite these advances in understanding, SCD in pregnancy is challenging for obstetricians and hematologists. Indeed, there are specific recommendations for the management of SCD in the general population, whereas during pregnancy there is a lack of formal evidence to guide clinical practice. Currently, the only two treatments recognized as disease-modifying are not recommended during pregnancy.

The role of *prophylactic chronic red cell transfusion* is still controversial. Although in the most recent meta-analyses [14,26] and in several studies [13,27–32], chronic transfusion seems to decrease maternal and perinatal morbidity and mortality, and to reduce the incidence of VOC, other studies show that it decreases acute painful episodes during pregnancy but does not influence fetal or maternal outcome [33–35]. Moreover, a large retrospective study in France compared women without SCD with 128 singleton SCD pregnancies in which prophylactic transfusion was used, and no benefits were observed [36]. In addition, most of these studies were retrospective, are now quite dated, involved populations with different standards of living, used different approaches to transfusion and had different obstetric follow-up (Table 5). For all these reasons, even if its use seems promising, there is still insufficient evidence to recommend chronic red cell transfusion in pregnancy.

As for HU treatment, the recommendation is to stop it almost 3 months before pregnancy and restart it after the end of breastfeeding [9,10], because HU is teratogenic in animal models and there are no adequate and well-controlled studies in pregnant women [11]. Despite this, we thought it would be reasonable to start considering HU treatment in pregnancy also. Firstly, because it is currently the only FDA-approved drug (FDA category D) for the treatment of SCD and its use could be essential to improve sickle cell pregnancy outcomes. In fact, the FDA defines its category D as follows: "*There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing*

Table 4. Pregnancy outcomes of SCD patients.

Variables	Group 1 $N = 11$	Group 2 $N = 4$	Adjusted p-value	Group 3 $N = 2$	Adjusted p-value
PTB	4 (36.4%)	0	.477	1 (50%)	1.000
PreE/HELLP	3 (27.3%)	0	.729	1 (50%)	1.000
IUGR	3 (27.3%)	0	.729	0	1.000
Emergency CS	5 (45.5%)	0	.297	0	.672
LBW	4 (36.4%)	0	.477	0	.915
APGAR $<$ 7 at 5 min	2 (18.2%)	0	1.000	0	1.000
NICU admission	4 (36.4%)	2 (50%)	1.000	0	.915
RDS	2 (18.2%)	0	1.000	0	1.000
Prematurity	4 (36.4%)	0	.477	1 (50%)	1.000

p-Values are obtained from multiple comparison post-hoc test: group 2 and 3 are compared to group 1.
Abbreviations: CS: cesarean delivery; HELLP: hemolysis, elevated liver enzymes, low platelets; IUGR: intra-uterine growth restriction; LBW: low birth weight; Min: minutes; NICU: neonatal intensive care unit; PreE: pre-eclampsia; PTB: preterm birth; RDS: respiratory distress syndrome.

Table 5. Summary of study design and recommendations, regarding the role of prophylactic transfusion in pregnancy [15].

First author, year	Study design	Number of the study population (Prophylactic/symptomatic)	Recommendation of prophylactic transfusion
Morrison, 1976 [27]	RC	65 (36/29)	Yes
Cunningham, 1983 [28]	RC	108 (54/54)	Yes
Koshy, 1988 [33]	RCT	72 (36/36)	No
Morrison, 1991 [29]	RC	131 (103/28)	Yes
Koshy, 1991 [35]	RC	111* (36/75)	No
El-Shafei, 1995 [34]	RC + PC	571 (244/327)	No
Gilli, 2007 [31]	RC	31 (14/17)	Yes
Asma, 2015 [30]	RC	37 (24/13)	Yes
Benites, 2016 [32]	RC	24 (10/14)	Yes

*Includes 72 patients from the Koshy 1988 cohort.
Abbreviations: PC: prospective cohort; RC: retrospective cohort; RCT: randomized controlled study.

experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks" [37]. Secondly, a chemical teratogenic in laboratory animals is not necessarily also teratogenic in humans [38]. In addition, HU has been demonstrated to be a potent teratogen in a wide variety of animal models, including mice, hamsters, cats, miniature swine, dogs, and monkeys, but at a dose higher than the usual human dose on a mg/m^2 basis: over 150 mg/kg/day [39]. Thirdly, several case reports showed no teratogenic effect in humans when the treatment was taken during the first trimester or throughout pregnancy [40–46].

Given the lack of recommendations to treat SCD in pregnancy and the myriad complications arising from its non-treatment, also considering the description of our population and the literature data, our aim is to propose a protocol to treat the disease during pregnancy by means of chronic red cell transfusion and HU. The main limitation of this study was the small number of its population and like any retrospective study, potential bias exist. However, this is the first study that describe the sickle cell pregnancy outcomes while considering also the patient's SCD history and the treatment adopted before pregnancy. Although difficult to conduct, the ideal study design should prospectively randomize pregnant patients with sickle-cell disease into 3 arms: no treatment, HU, or blood transfusion.

In our description, chronic transfusion seems to be protective against SCD complications and to reduce hospital admissions and the number of acute transfusions. No SCD complications and no hospital admissions or acute transfusions were observed in group 3 during pregnancy and postpartum. Moreover, no allo/auto-immunization and no transfusion-related complications were observed in any group. This is probably due to the selection of phenotype-matched RBCs when the patient was previously immunized or in presence of autoantibodies and the selection of Rh/Kell-matched red cells when not immunized and to the small size of the population. In contrast, chronic transfusion does not seem to prevent preeclampsia, which, despite aspirin therapy, was the only obstetrical complication observed in group 3, together with preterm birth (due to preeclampsia induction), probably because in this case the transfusion program was started too late (after 10 weeks). According to the hypothesis proposed by a recent review, to have an impact on preeclampsia, given its pathophysiology, prophylactic chronic transfusion should be initiated in the first month of pregnancy in order to avoid abnormal placental formation [15]. On the other hand, leaving a sickle cell pregnancy without a chronic treatment seemed to increase SCD complications, even if one woman was mildly affected and without treatment before pregnancy. All the patients of group

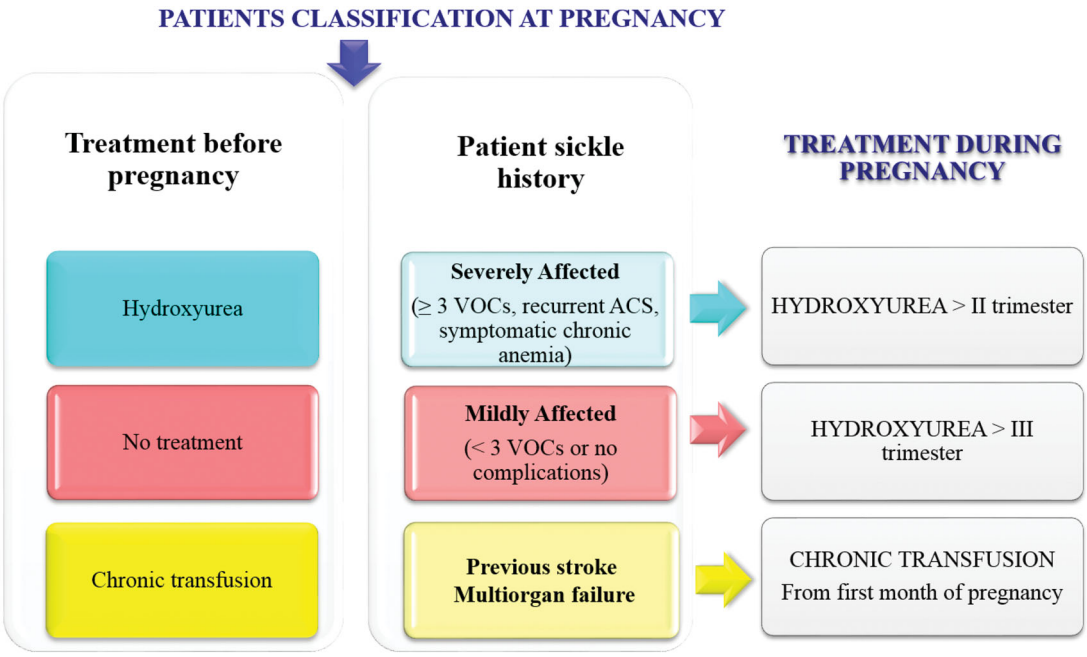

Figure 2. Protocol proposed to treat sickle cell disease in pregnancy. VOCs: vaso-occlusive crisis; ACS: acute chest syndrome.

1 and almost all of group 2 developed SCD complications, particularly in terms of CVO, ACS and severe anemia. Moreover SCD complications in group 2 appeared only in the third trimester and early postpartum, the most critical period according to the literature data [3]. In addition, leaving a SCD pregnancy without a chronic treatment when the woman was severely affected and on HU treatment before pregnancy (group 1) led not only to more SCD complications, but also to increased acute transfusions, hospital admissions, non-elective cesarean sections and obstetrical and perinatal complications. Compared to groups 2 and 3, more obstetrical and perinatal complications were observed in group 1, especially in terms of preterm birth, IUGR, preeclampsia, low birth weight and NICU admissions. Given our results and the literature data mentioned before, we propose to treat all SCD pregnancies by a management that differs according to the severity of the disease and the treatment adopted before pregnancy (Figure 2). Despite the potential risk of teratogenicity, we still consider HU treatment for these patients. In our series, 11 out of the 12 the patients treated with HU before pregnancy stopped the treatment almost 5 weeks after conception, and no teratogenic effects were observed.

We offer HU treatment at the end of the first trimester to all woman severely affected before pregnancy (>3 VOCs over the previous 12 months, recurrent ACS, or pain that interferes with daily activities) or already on HU treatment. In mildly affected patients, with no treatment before pregnancy, we start HU treatment at the beginning of the third trimester, in order to cover the most critical period for SCD complications. Continuing chronic transfusion should be reserved for all patients already on a transfusion program before becoming pregnant or for patients with previous stroke or MOF (as in two patients of group 2). This is because prophylactic transfusion beyond these indications is tempered by concerns over acute and delayed transfusion reactions, alloimmunization, transfusion-related infections, and iron overload [47]. These complications were not observed in our study, probably because of the small study population. To confirm the importance of the transfusion risks and HU interruption, in terms of the protocol proposed, we report a case where we restarted HU treatment. This was a case of an African woman with the HbSS genotype, with no MOF or previous stroke, treated before pregnancy with HU, which was stopped at conception. HU interruption caused worsening of SCD, leading from the first trimester to several hospital admissions for VOC. At 21 weeks, VOC was complicated by hemolytic crisis and required admission to the intensive care unit and the transfusion of 11 red blood cells units in 6 days. Despite therapy, 14 days after transfusion of the first blood unit, the hemoglobin level fell to 4.4 g/dL. Because of suspected delayed hemolytic transfusion reaction, we decided to avoid transfusion and to treat with intravenous immunoglobulin for 5 days. Once the patient was stabilized, we decided to restart HU treatment, with the result that there have been no more VOCs, transfusions or hospital admissions until delivery and postpartum.

Our analysis shows the importance of treating SCD during pregnancy. It seems that when the patient is severely affected before conception, the pregnancy and perinatal outcomes are worse. We have shown that not treating a sickle cell pregnancy exposes both mother and fetus to a very high risk of morbidity and mortality, even if one woman was mildly affected and not treated before pregnancy. These complications are more numerous when a woman is severely affected before conception, because stopping HU treatment increases not only the SCD complications, but also the obstetrical and perinatal complications, hospital admissions, the number of acute transfusions and the rate of non-elective cesarean section. While chronic transfusion seems to protect against SCD complications, if started from the first month of pregnancy it could also be protective against all obstetrical complications, including preeclampsia.

Conclusions

In conclusion, we advocate all sickle cell pregnancies to be treated. Each woman with SCD should be considered on an individual basis and therapy will depend on the treatment adopted before, but also on the patient's history. The treatment choice is between the only two treatments recognized as disease-modifying outside pregnancy. Chronic transfusion should not be discontinued in pregnancy and reserved for cases of proven benefit (previous stroke or women already in a transfusion program or with MOF), in order to avoid important transfusion complications. HU treatment should be reserved for severely and mildly affected patients (with or without HU treatment before pregnancy), respectively from the second and third trimesters of pregnancy. Because HU decreases HbS sickling, it may improve the outcome of sickle cell pregnancy, without any teratogenic risk if started after the first trimester. We should stress that sickle cell pregnancies always need multidisciplinary management and that the protocol proposed is not a substitute for the role of the hematologist, but it can guide both the gynecologist and the hematologist in their clinical practice in order to improve pregnancy outcomes. Additional prospective clinical studies are needed to show the outcomes of the systematic treatment proposed.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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