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Research Article

# Multidisciplinary Approach for the Management of Sickle Cell Disease during Pregnancy

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## Abstract

**Objectives**: While several decades ago women with SCD were discouraged from becoming pregnant, today most should be supported if they choose to pursue a pregnancy. However, this situation remains at risk. This retrospective study aimed to identify risk factors for adverse outcomes in pregnancies of women with SCD and to test a multidisciplinary approach for the comprehensive management of these pregnancies. **Methods:** The present study analyzed 147 records of pregnancies in 63 women with SCD (including SS, SC, $S\beta^{0,}$ and $S\beta^{+}$ genotypes) who were treated between 2005 and 2023, in our institution. **Results:** Of 130 accepted pregnancies, 101 (78%) resulted in living neonates. Spontaneous abortion was observed in 16% and abortion for medical reasons in 5%. Mother's genotype, prior SCD complications and gestational age were predictors for delivery of living newborns. Eighty-five pregnancies (65%) encountered 92 adverse maternal events, while 35 maternal complications were reported during the postpartum. No maternal death was observed. Among 103 newborns, 76% were full-term and 24% were pre-term, 59% were caesareans and 42% natural births were observed. Intrauterine growth retardation was the major fetal event (10%). Early neonatal death concerned only one newborn. One infant died on day 16 from severe sepsis. Fewer voluntary abortions and miscarriages were documented during the multidisciplinary approach period compared to the prior period. **Conclusion:** SCD during pregnancy remains a high-risk situation that can lead to many maternal and fetal complications. Effective management during pregnancy should include preconception planning, genetic counseling, education, and collaborative care in reference centers. It is crucial that hematologists, obstetricians, and pediatricians closely monitor these pregnancies.

**Keywords:** Pregnancy; sickle cell disease; prognosis; adverse birth outcomes; maternal complication.

## Introduction

Pregnancy in women with sickle cell disease (SCD) is considered of high risk with increased rates of severe complications and maternal mortality [1-4]. SCD is an autosomal recessive hemoglobinopathy marked by structurally abnormal hemoglobin (HbS). The disorder involves a point mutation corresponding to a single DNA base change with substitution of valine for glutamic acid at the sixth position on β globin chain. Patients with homozygous hemoglobin (SS) often present with severe symptoms, while those with a heterozygous mutant allele (SA) demonstrate minimal clinical symptoms. The combination of hemoglobin S with another type of β subunit gene mutation, such as hemoglobin C or β thalassemia (β-thal), forms a compound heterozygous hemoglobinopathy (SC, $S\beta^+$or $S\beta^0$). With the exception of the compound $S\beta^0$, the heterozygous genotypes are usually less clinically severe than hemoglobin SS [5].The structurally abnormal HbS leads to chronic hemolytic anemia and to a variety of severe clinical manifestations, such as vaso-occlusive crisis (VOC) and acute chest syndrome (ACS). Pregnancy in SCD patients is considered at risk for both the mother and the fetus. Exacerbation of SCD signs, especially anemia, may be a major mediator associated with the risk for severe maternal morbidity and other adverse pregnancy outcomes, and with adverse fetal outcomes including prematurity and fetal death [6-8].

In high-income countries treatment advances have enabled women to embrace motherhood [9]. However, there is still a lack of knowledge in women with SCD regarding their management, and fetal and maternal outcomes. The purpose of the present study was to describe pregnancy outcomes and to assess risk factors associated with adverse events in women with SCD during the intra-partum and post-partum periods, and to validate a multidisciplinary approach for the management all along their pregnancy.

## Patients and methods

### Patient population

In a retrospective study from June 2005 to August 2023, a total of 63women, aged 18 to 40 years, with SCD in any stage of the disease were followed for at least one pregnancy in one of the maternity wards of the Hospices Civils de Lyon. Overall those 63 women led to 147 pregnancies. After mid-2014, 100 pregnancies from this cohort study were included in a specific program (HEMAGO) involving a cooperative support between hematologists, obstetricians, and pediatricians (Figure 1), and were followed at the maternity ward of the Croix-Rousse Hospital, a tertiary centre for pregnant women with SCD affiliated with the Lyon University Hospital Centre. During their visits to the prenatal clinic, women were included in the study based on their positive SCD status, established by Hb electrophoresis and confirmed by genetic analysis when required. A thorough history was taken with special emphasis on the obstetric history and significant past history of underlying disease. The records of all patients were reviewed, and data associated with pregnancy, delivery, and neonate were collected retrospectively.

Medical records were analyzed and compared between pre-HEMAGO and HEMAGO periods, and with those from 31 prior pregnancies involving 18 women of the studied cohort while previously followed in centers located abroad (mainly in Africa) or in another French center (mainly in French overseas islands) (Figure 1). The study was approved by the Hospices Civils de Lyon Review Board. The study adhered to the principles of the Declaration of Helsinki. A non-opposition informed consent was waived by the Institution due to the use of de-identified data.

### Measurement and classification of the variables

Pre-pregnancy demographic data, clinical data and laboratory parameters were collected from medical records, including SCD genotype, SCD complications (VOC, ACS, organopathies), age, body mass index (BMI), Hb level, mean corpuscular volume (MCV), platelet count, polymorphonuclear (PMN) count, hemoglobin fetal (HbF) percentage, delay from last acute SCD complication to pregnancy, hydroxyurea (HU) use, simple or exchange red blood cell (RBC) transfusion program, number of prior pregnancies. BMI was calculated as weight (Kg)/size$^2$ ($m^2$) and categorized as underweight (<18.5), normal weight (18.5-25), overweight (>25-30), and obesity (>30). Moderate anemia was defined as Hb level less than 100 g/L, and severe anemia as Hb level less than 70 g/L. Adverse maternal events analyzed during pregnancy were SCD complications, gestational hypertension, pre-eclampsia/eclampsia, infection, hemostasis disorder, placental abruption, pre-term premature rupture of membranes, pre-term delivery, peri-partum infection, post-partum hemorrhage. Adverse fetal events included intra-uterine growth restriction, intra-uterine fetal demise. For twin and triplet pregnancies, adverse fetal events were considered present if either infant met criteria. Sex and genotype of the newborns, birth weight, and gestational week at birth were also reported.

Pregnancy results were divided between spontaneous abortion [early (before 12 weeks) and late (between 12 and 22 weeks)], induced abortion (for maternal or fetal medical reasons), live birth, and types of stillbirth (death after 28 weeks). Pre-term labor was defined as onset of labor before 37 completed weeks of gestation, full-term from 37 to 42 weeks, and post-term >42 weeks. Pregnancy-induced hypertension was defined as blood pressure more than 140/90 mmHg on two occasions six hours

apart. Pre-eclampsia included the same factors, but combined with proteinuria > 0.3 g/24h. Premature rupture of membranes was defined as the loss of amniotic fluid before 37 weeks. Intra-uterine fetal demise was defined by a spontaneous fetal cardiac arrest after 14 weeks in pre-partum period. Early neonatal death was defined as neonatal death within seven days of birth. Low birth weight was defined as weight <2.5 Kg and severe low birth rate was defined as weight <1.5 Kg. The post-partum period was defined as the first 6 weeks after the index delivery hospitalization. The complications were not mutually exclusive. Pregnancies could have more than one complication reported.

### HEMAGO program

From mid-2014, deliveries of women with SCD were done in a hospital equipped with all facilities for efficiently managing high-risk pregnancies. Pregnancy were planned when possible and closely monitored by a multidisciplinary team involving obstetricians and hematologists. HU was stopped as soon as pregnancy was suspected or confirmed. Preventive blood transfusion was not systematic, but was recommended in patients with a pre-existing transfusion program prior to pregnancy, severe pre-existing organ damage, severe obstetric history, and severe or repeated crises during follow-up. At each visit, women were assessed for blood pressure and urine analysis. Women at high risk for pre-eclampsia were taken low-dose aspirin. During the first and second trimesters, patients were monitored for placenta previa, placental abruption, and pre-term labor. They were prescribed multivitamins and folate supplements without iron in frequently transfused patients. Between 24 and 28 weeks, monthly ultrasound was done to assess fetal growth. From 32 weeks to 34 weeks, biophysical profile testing was done every week and between 28 and 30 for assessing umbilical artery flow and the ratio between systolic and diastolic for prediction of intrauterine growth retardation (IUGR). Systemic administration of corticosteroids for fetal lung maturation was not recommended due to the risk of maternal VOC. Although more frequent, due to maternal complications, cesarean section (CS) was not systematic, in the absence of maternal contra-indications. It was advisable not to exceed the term of 38 weeks of amenorrhea. Post-partum follow-up in hospitalization systematically lasted 5 days. Breastfeeding was initiated as soon as possible after birth after evaluating the risk of delaying the re-introduction of HU therapy.

## Statistical analyses

All evaluation parameters were subjected to a descriptive analysis. The quantitative variable evaluation parameters were described using position parameters (mean or median) and dispersion [standard deviation (SD)]. The qualitative variable evaluation parameters are shown in the form of number and frequency for each modality. Continuous variables were compared by ANOVA, Welch's ANOVA, or Kruskal-Wallis tests, according to data distribution. Differences among categorical variables were compared by the $\chi^2$ test or Ficher's exact test accordingly. The stepwise logistic regression model was used to explore the risk factors for adverse maternal and fetal outcomes. Estimated hazard ratios (HRs) are reported as relative risks (RR) with 95% confidence intervals (CI). The statistical significance cut-off was set at a p-value < 0.05. All computations were run using the BMDP statistical Software (BMDP Statistical Software, Los Angeles, CA).

## Results

### Demographic and characteristics

Seventeen pregnancies ended before week 16 via voluntary abortions. Analyses included therefore 130 pregnancies in 63 women (median age at the time of pregnancy: 29 years), with 40, 40, 25, 13, 7, 4 and one of the women contributing to their first, second, third, fourth, fifth, sixth and seventh pregnancies respectively. Eighteen women (28%) have already experienced pregnancy between June 2006 and September 2022, before consulting at our Institution. The number and outcome of pregnancies before and during the study is shown in Figure 1 and Figure 2. During the study, pregnancies involved twins and triplets in three and one cases, respectively. There were 103 births of living neonates including 2 from twin pregnancies. The women's characteristics are displayed in Table 1. HbSS, HbSC, HbS/$\beta^0$-thaland HbS/$\beta^+$-thal were present in 66 (51%), 51 (39%), 7 (5%) and 6 (5%) pregnancies, respectively. Regarding the clinical and biological parameters in women at the beginning of pregnancy, the mean level (± SD) of Hb was 93 ± 15 g/L, the mean level of MCV was 82.1 ± 13 fL, the mean level of platelets was 362 ± 180 G/L, and the mean level of PMN was 5.9 ± 3.9 G/L. Among 122 pregnancies in which prior history of SCD complications was documented, 118 (96%) were preceded by VOC, 35 (29%) by ACS, and 51 (42%) occurred in a context of chronic organopathy. The median time from last SCD event to pregnancy was 12.7 months (range: 0.52 to 287.8 months). Sixteen pregnancies occurred after a prior participation to simple or exchange RBC transfusion program. Forty pregnancies reported a prior HU use, and were potentially exposed to HU, as HU was not generally stopped at least 15 days before conception.

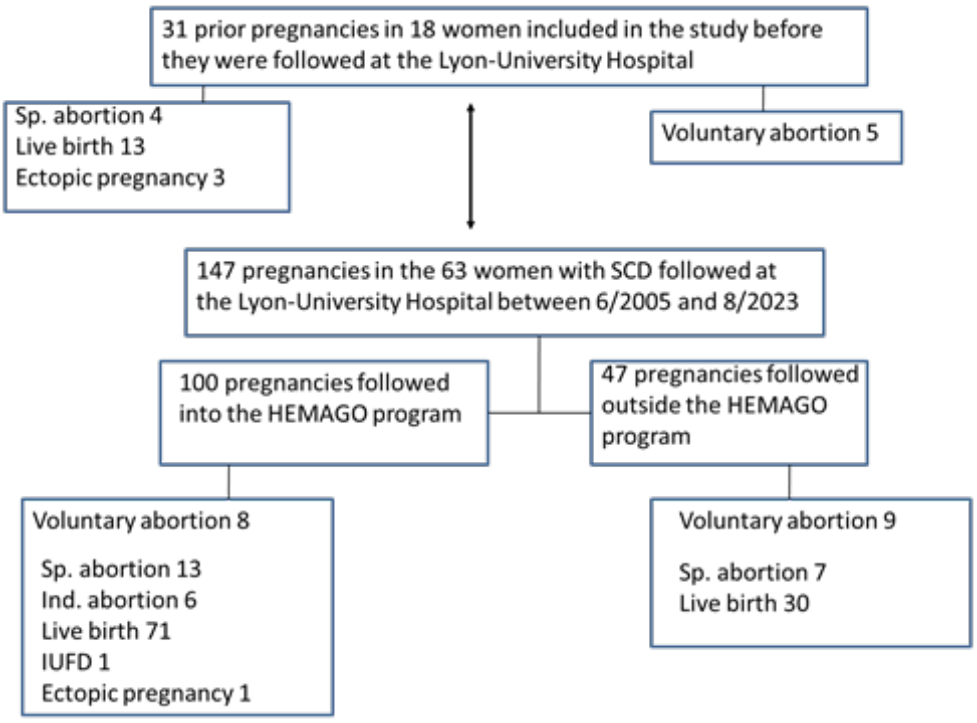



**Figure 1:** Flow diagram of the study

Abbreviations: Ind. abortion, induced abortion (abortion for medical reasons excluding ectopic pregnancy); IUFD, intrauterine fetal death; Sp. abortion, spontaneous abortion (including early and late miscarriages).

### Outcome and predictors for delivery of living newborns

Overall, 101 pregnancies (78%) resulted in living neonates. Spontaneous abortion was observed in 16% of pregnancies and abortion for medical reasons, excluding ectopic pregnancy, was performed in 5% of pregnancies. In the univariate analysis, adverse predictors for delivery of living newborns included SC women's genotype ($p = 0.03$), prior history of ACS ($p = 0.04$), and gestational age at birth < 37 weeks ($p = 0.01$). A multivariate logistic regression analysis was conducted using the enter method, considering the significant factors from the univariate analysis. However, none of the above factors remained as the independent predictors in the multivariate analysis.

### Maternal outcome predictors

Eighty-five pregnancies (65%) encountered 92 registered adverse maternal events, as defined above. There was no maternal mortality. Thirty-nine maternal complications were reported during post-partum among pregnancies that have led to living neonates. Table 1 depicts the prevalence of maternal complications during the intra-partum and post-partum period. Prior history of chronic organopathy was statistically associated with a higher risk of maternal complication during pregnancy ($p = 0.01$), while a prior history of ACS was not. In terms of maternal complications during pregnancy, there was no statistical difference between first pregnancies and later pregnancies. It was also the case with respect of genotype. Maternal complications during pregnancy were not associated with a higher risk of fetal complications or maternal post-partum complications. The only significant adverse factor associated with post-partum maternal complications was SS mother's genotype ($p = 0.01$). In a multivariate analysis, entering mother's genotype (SS versus SC), BMI (overweight/obesity versus underweight/normal weight), SCD antecedents (VOC/ACS/organopathy versus VOC only), mother's age, gestational age (< 37 versus ≥ 37 weeks), and first pregnancy versus further pregnancies in the model, only SS genotype [RR: 10.5; 95% CI: 1.01–122.8; $p = 0.02$] and overweight/obesity [RR: 8.7; 95% CI: 1.01–90; $p = 0.03$] were shown of unfavorable prognostic value for maternal events.

| Characteristics | Pregnancies included in HEMAGO (n = 92) | Pregnancies not included in HEMAGO (n = 38) | Overall (n = 130) |
|---|---|---|---|
| **When discovering pregnancy** | | | |
| Genotype | | | |
| SS | 45 (49%) | 21 (55%) | 66 (51%) |
| SC | 41 (45%) | 10 (26%) | 51 (39%) |
| $S\beta^0$-thal | 3 (3%) | 4 (10%) | 7 (5%) |
| $S\beta^+$-thal | 3 (3%) | 3 (8%) | 6 (5%) |
| Age (years) | | | |
| Mean ± SD | 30 ± 5 | 27 ± 4 | 29 ± 5 |
| Median | 29 | 26 | 29 |
| Range | 20 – 40 | 18 – 36 | 18 – 40 |
| Hb level (g/L) | | | |
| Mean ± SD | 94 ± 15 | 95 ± 14 | 94 ± 15 |
| Severe anemia | 5 (5%) | 1 (3%) | 6 (5%) |
| Moderate anemia | 48 (52%) | 11 (29%) | 59 (45%) |
| BMI* | | | |
| Underweight | 7 (8%) | 3 (16%) | 10 (10%) |
| Normal weight | 47 (57%) | 12 (63%) | 59 (58%) |
| Overweight | 7 (8%) | 1 (5%) | 8 (8%) |
| Obesity | 22 (27%) | 3 (16%) | 25 (24%) |
| Treatment** | | | |
| HU | 34 (37%) | 6 (21%) | 40 (33%) |
| Transfusions | 12 (13%) | 4 (14%) | 16 (13%) |
| **During pregnancy** | | | |
| Multiple gestation | 1 | 3 | 4 |
| Pregnancy results | | | |
| Sp. abortion | 13[I](14%) | 8[II](21%) | 21(16%) |
| Ind. abortion | 6 (7%) | 0 | 6 (5%) |
| Live birth | 71 (77%) | 30 (79%) | 101 (78%) |
| IUFD | 1 | 0 | 1 |
| Ectopic pregnancy | 1 | 0 | 1 |
| Gestational week*** | | | |
| Pre-term | 16 (23%) | 8 (27%) | 24 (24%) |
| Normal | 55 (77%) | 22 (73%) | 77 (76%) |
| Post-term | 0 | 0 | 0 |
| Delivery method*** | | | |
| Natural | 29 (41%) | 13 (43%) | 42 (42%) |
| Elective CS | 16 (23%) | 6 (20%) | 22 (22%) |
| Emergency CS | 26 (36%) | 11 (37%) | 37 (37%) |

| | | | |
|---|---|---|---|
| Adverse events | 74 | 18 | 92 |
| SCD crisis | 23 | 3 | 26 |
| Hypertension | 2 | 4 | 6 |
| Infection | 15 | 2 | 17 |
| Pre-/Eclampsia | 6 | 2 | 8 |
| Diabetes | 2 | 0 | 2 |
| PROM | 4 | 2 | 6 |
| Severe anemia | 3 | 0 | 3 |
| Thrombocypenia | 2 | 2 | 4 |
| Thrombosis | 2 | 0 | 2 |
| Isolated proteinuria | 2 | 1 | 3 |
| Hematoma | 1 | 0 | 1 |
| Cholestasis | 1 | 1 | 2 |
| Hervet strapping | 4 | 0 | 4 |
| Chorioamnionitis | 1 | 0 | 1 |
| Placenta previa | 1 | 0 | 1 |
| Hemorrhage | 1 | 1 | 2 |
| Other | 4 | 0 | 4 |
| **Post-partum** | | | |
| | | | 39 |
| Adverse events*** | 31 | 8 | 3 |
| SCD crisis | 2 | 1 | 18 |
| Hemorrhage | 12 | 6**** | 3 |
| Abscess | 2 | 1 | 2 |
| Thrombosis | 2 | 0 | 3 |
| Severe anemia | 3 | 0 | 4 |
| Hematoma | 4 | 0 | 3 |
| Scar disunion | 3 | 0 | 1 |
| Cardiac arrhythmia | 1 | 0 | 1 |
| Hellp syndrome[III] | 1 | 0 | 1 |
| Other | 1 | 0 | |

**Abbreviations: APOs, adverse pregnancy outcomes; BMI, body mass index; CS, cesarean section; Hb, hemoglobin; HU, hydroxyurea; Ind. abortion (abortion for medical reasons excluding ectopic pregnancy), induced abortion; IUFD, intrauterine fetal death; NA, not available; PROM, Premature rupture of membranes; SD, standard deviation; Sp. abortion, spontaneous abortion (including early and late miscarriages); y, years.**

*** Available in 102 pregnancies; ** available in 120 pregnancies; ***only concerning pregnancies leading to delivery of a living newborn; **** of which one cerebral hemorrhage; [I] including 11 early and 2 late miscarriages; [II] including 7 early and one late miscarriages; [III]Hellp syndrome was a variant of pre-eclampsia characterized by features of hemolysis, elevated liver enzymes and low platelets.**

**Table 1:** Main characteristics of the 130 pregnancies in the 63 women with SCD followed in our institution between June 2005 and August 2023.

### Fetal outcome predictors

Antenatal fetal adverse events were observed in 25 pregnancies leading to living neonates. Twenty-three events were reported in 19 newborns during the post-partum period. Fetal complications during the intra-partum and post-partum period were presented in Table 2. IUGR was the major fetal event (10% of living newborns) documented during pregnancy. Early neonatal death concerned only one newborn from a multiple gestation on day 6. One neonate died on day 16 from severe sepsis. Overall 10 neonates (53%) who presented complications during the post-partum period had already presented at least one fetal event during pregnancy. A previous adverse fetal event did not show any influence on subsequent pregnancies.

| Characteristics | Neonates from pregnancies included in HEMAGO (n = 72) | Neonates from pregnancies not included in HEMAGO (n = 31) | Overall (n = 103) |
|---|---|---|---|
| **Birth weight*** | | | |
| Severely low | 6 (8%) | 3 (10%) | 9 (9%) |
| Low | 15 (21%) | 7 (22%) | 22 (21%) |
| Normal | 51 (71%) | 21 (68%) | 72 (70%) |
| Median (Kg) | 2.78 | 2.77 | 2.77 |
| (Range) | (0.71 – 4.21) | (0.61 – 3.77) | (0.61 – 4.21) |
| **Sex** | | | |
| Male | 33 (46%) | 18 (58%) | 51 (50%) |
| Female | 39 (54%) | 13 (42%) | 52 (50%) |
| **Genotype** | | | |
| SS/SC/Sβ-thal | 7 (10%) | 5 (16%) | 12 (12%) |
| Sickle trait | 65 (90%) | 26 (84%) | 91 (88%) |
| **Adverse events during pregnancy** | | | |
| IUGR** | 4 | 6 | 10 |
| Polyhydramnios | 1 | 0 | 1 |
| Anemia*** | 1 | 0 | 1 |
| Chorioamniotite | 1 | 0 | 1 |
| Fetal distress | 4 | 1 | 5 |
| Macrosomia | 1 | 2 | 3 |
| Seat presentation | 2 | 1 | 3 |
| Abnormal heart rate | 0 | 1 | 1 |
| **Adverse events post-partum** | | | |
| Septicemia**** | 0 | 1 | 1 |
| Early neonatal death***** | 0 | 1 | 1 |
| Anemia | 3 | 2 | 5 |
| Jaundice | 7 | 3 | 10 |
| Pulmonary distress | 2 | 1 | 3 |
| Pneumonia | 1 | 0 | 1 |
| Hypoglycemia | 1 | 0 | 1 |
| HIV infection | 0 | 1 | 1 |

*** Low birth weight was defined as weight <2.5 Kg and severe low birth rate was defined as weight <1.5 Kg;**Intrauterine growth retardation; ***Anemia requiring in utero transfusion; ****One neonate died from sepsis on day 16; ***** One twin died on day 6.**

**Table 2:** Characteristics of the Living Newborns

### Comparison between SS, SC, and Sβ-thal genotypes

Among the 130 analyzed pregnancies, 66(51%) concerned women with SS genotype, 51 (39%) women with SC genotype, and 13 (10%) women with Sβ-thal genotype (7 $S\beta^0$ and 6 $S\beta^+$). Women age at pregnancy, first and subsequent pregnancies, maternal and fetal adverse events during pregnancy did not differ significantly between pregnancies occurring in women with SS and those with SC genotype. Antecedents of ACS and chronic organopathy were higher in women with SS genotype (41% versus 12%, $p = 0.001$; and 52% versus 32%, $p = 0.03$, respectively). More pregnancies followed HU therapy or RBC transfusion program when occurring in women with SS genotype (54% versus 8%, $p < 0.001$; and 27% versus 0%, $p < 0.001$, respectively). Pregnancies from women with overweight or obesity were more frequent in the SC genotype group (57% versus 17%, $p < 0.001$). Delivery of a living neonate occurred in 55 pregnancies (83%) in women with SS genotype versus 34 (67%) in women with SC genotype ($p = 0.03$), while spontaneous abortions were more frequent in women with SC genotype (22% versus 12%, $p = 0.1$). Delivery method involved CS in 73% of pregnancies in women with SS genotype versus 47% in those with SC genotype ($p = 0.01$). Maternal post-partum complications were more frequent in women with SS genotype (43% versus 22%, $p = 0.03$).

### Comparison between the pre-HEMAGO and the HEMAGO periods

Nine (19%) versus 8 (8%) pregnancies ($p = 0.04$) ended before week 16 via voluntary abortions during the pre-HEMAGO and the HEMAGO periods, respectively. Thirty pregnancies (79%) ended in the delivery of a living neonate during the pre-HEMAGO period and 71 (77%) during the HEMAGO period. Maternal complications during pregnancy were seen in 58% during the first period versus 68% during the second period, with a higher rate of SCD complications during the HEMAGO period (25% versus 8%, $p = 0.03$). The proportion of pregnancies starting after HU treatment or transfusion program, the gestation duration, and the delivery method used did not differ significantly among the two periods. Spontaneous miscarriages were observed in 14% of pregnancies for the HEMAGO period versus 21% for the pre-HEMAGO period. Six abortions for medical reasons, excluding ectopic pregnancy, were realized during the HEMAGO period.

## Discussion

Despite major advances in obstetric care and treatment of SCD, women with SCD continue to have increased risk for pregnancy complications compared with pregnant women from the general population [10]. Complications during pregnancy and the post-natal period can be disease-related and/or pregnancy related. The physiological changes during pregnancy may favor SCD symptoms leading to an increased risk of adverse events for mothers and neonates [11,12]. A higher prevalence of abortion, pre-eclampsia/eclampsia, high blood pressure, cardiomyopathy, and post-partum hemorrhage was also reported [11,13]. Deliveries were also more likely to develop vein thrombosis and bacterial infections, and to require cesarean methods [12]. In addition, newborns develop more complications. Fetal deaths, pre-term births, low birth weights, and fetal distresses were more frequently observed than in women without hemoglobinopathy [14,15].

In our study, mother's SS genotype was associated with increased risks. This can explain that prior history of chronic SCD organopathy was significantly associated with maternal side effects during pregnancy. This confirmed that multi-organ failure associated with SCD showed higher risks in previous studies when compared with the general population [16]. The higher prevalence of thrombosis has been previously attributed to the hypercoagulable state of women with SCD [17], and to the high rate of blood transfusions among women with SCD [18]. Infectious complications are likely due to predisposition of SCD patients to encapsulated bacterial infections via the reduced humoral immune response secondary to functional or surgical asplenism [19]. Hypertension and eclampsia/pre-eclampsia were frequently observed in our series during pregnancy, and these occurrences were already largely documented [3, 20-24]. A lower prostacyclin-to-thromboxane ratio in women with SCD has been previously reported, potentially suggesting a greater proclivity to vasoconstriction [25]. Consecutively, a monitoring of blood pressure and urinalysis has been generally recommended at least monthly [26]. During pregnancy, anemia is linked to dilution via increased plasma levels. However, no data demonstrated that baseline anemia was majored in women with SCD [7]. Nevertheless, severe anemia was more frequently observed in pregnant women with SCD [27], requiring a systematic optimization of hemoglobin level before pregnancy while reviewing and updating immunization status.

Mother's genotype influences prognosis during pregnancy. In a large meta-analysis including 21 studies, pregnancies in women with SS genotype were at higher risk of maternal mortality, pre-eclampsia, stillbirth, and pre-term delivery, compared with women without SCD [2]. Although considered of better prognosis than SS genotype, a high rate of maternal and fetal complications was demonstrated in women with SC genotype [23]. In our series, pregnancies in women with SS genotype also appeared at higher risk as compared with pregnancies in women with SC genotype. Indeed, the incidence of severe SCD antecedents before pregnancy was higher, requiring more frequently recourse to HU therapy and transfusion/exchange program. However, more pregnancies led to delivery of a living newborn. Although no clear explanation could be given, it could be hypothesized a stricter survey of women with SS genotype during pregnancy and a quicker decision to go to CS as delivery method. Our population of women with SC genotype

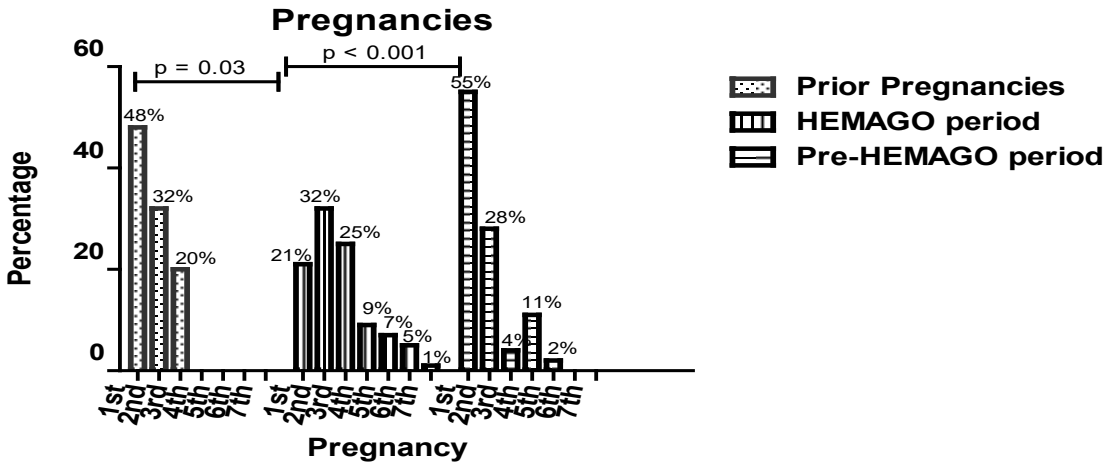
had also a significant higher BMI that could influence the risks for certain diseases and, although not significant, higher the rate of spontaneous abortions.

The absence of SCD treatment during pregnancy was shown to increase maternal and perinatal morbidity. Chronic transfusions were recommended to women with prior stoke or multi-organ failure or already under transfusion program [28]. Use of HU has not been recommended during pregnancy because of its potential risk of miscarriage and concerns about teratogenic effects [29, 30]. However, the existing knowledge on HU exposure during pregnancy remains limited and incomplete, as that of recently approved disease-modifying therapies [31]. Theoretically, HU therapy should be discontinued at least 3 months before conception and until after breastfeeding. This was not the case in our series, in which HU was only stopped as soon as pregnancy was confirmed. However, we did not demonstrate any overt teratogenicity potentially attributable to HU, confirming prior larger studies [32, 33]. HU was even recommended for severely affected patients during the second and third trimesters [34]. Prior HU use was more common in pregnancies with adverse maternal events, suggesting it may be a marker of severity, rather than an independent risk factor for adverse maternal events.

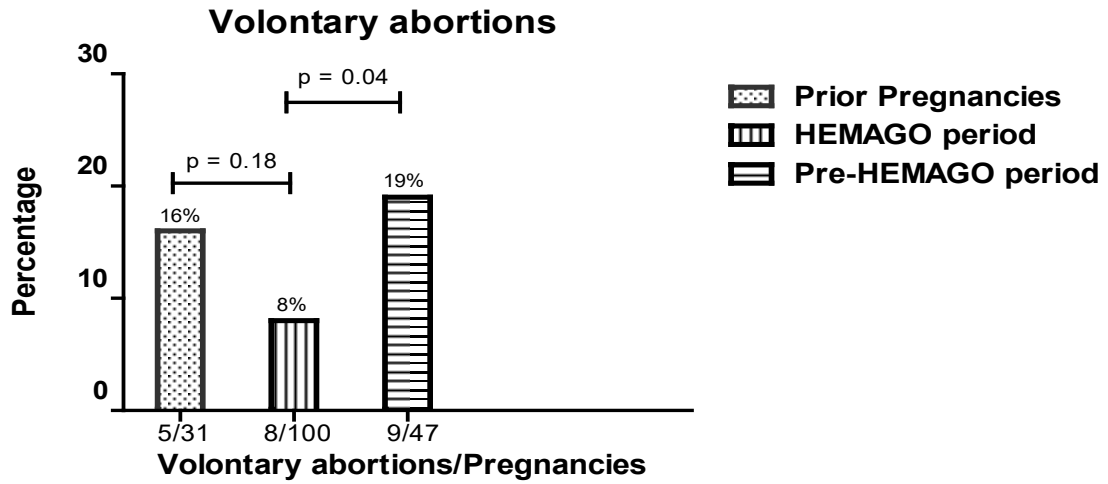
There is no consensus on the overall approach to managing pregnant women with SCD. Genetic counseling should be offered before conception or early in pregnancy. A careful monitoring during pregnancy and a multidisciplinary management approach can prevent potential adverse outcome. Our HEMAGO program has been developed in this setting in accordance with recent international expert opinions [26,35], which recommend performing at least monthly multidisciplinary follow-up, administering prophylactic aspirin for pre-eclampsia prevention between gestational weeks 12 and 36, initiating prophylactic transfusion therapy in certain severe cases, or choosing automated RBC exchange in case of iron overload or severe ACS. Primary results from our program showed less voluntary and spontaneous abortions and more induced abortions for medical reasons than during the pre-HEMAGO period, and significant improvements comparatively to prior pregnancies followed in other centers (Figure 2). This tends to confirm the contribution of a multidisciplinary team in a tertiary center for the management of pregnancy in women with SCD. Contrasting with most of the experts from the international Delphi panel who recommended awaiting spontaneous labor up to 40 weeks of gestation in the absence of maternal and/or fetal complications, we recommended systematically delivery at 38 weeks. The contribution of our HEMAGO program remains, however, currently limited, but results remain somewhat preliminary. Our study was subject to several limitations. First, it is likely that some data could not be documented and were omitted from the analyses. This is especially the case for voluntary and spontaneous abortions for the period preceding women's follow-up in our institution. Furthermore, our study was based on a retrospective analysis. Some data regarding prior history of SCD complications and maternal and fetal complications during pregnancy could not be retrieved as they were not documented. The implication of these limitations is that the prevalence of complications for certain subgroups may be underestimated.

Most individuals with SCD live in low-resource settings and should be educated regarding their reproductive health, which could be affected by SCD complications, such as poor nutrition, iron overload following prior blood transfusion, recurrent VOC and infections. Maternal and fetal adverse outcomes are significantly lower in developed high-income countries than in low-income ones [2]. This mostly concerns the risk of miscarriage as confirmed, in our study, between pregnancies occurring during the HEMAGO period and pregnancies occurring before follow-up in our institution. Achieving optimal results mainly depends on providing adequate care in an experienced health care facility with expertise, involving a multidisciplinary approach, from preconception planning to the post-natal management.

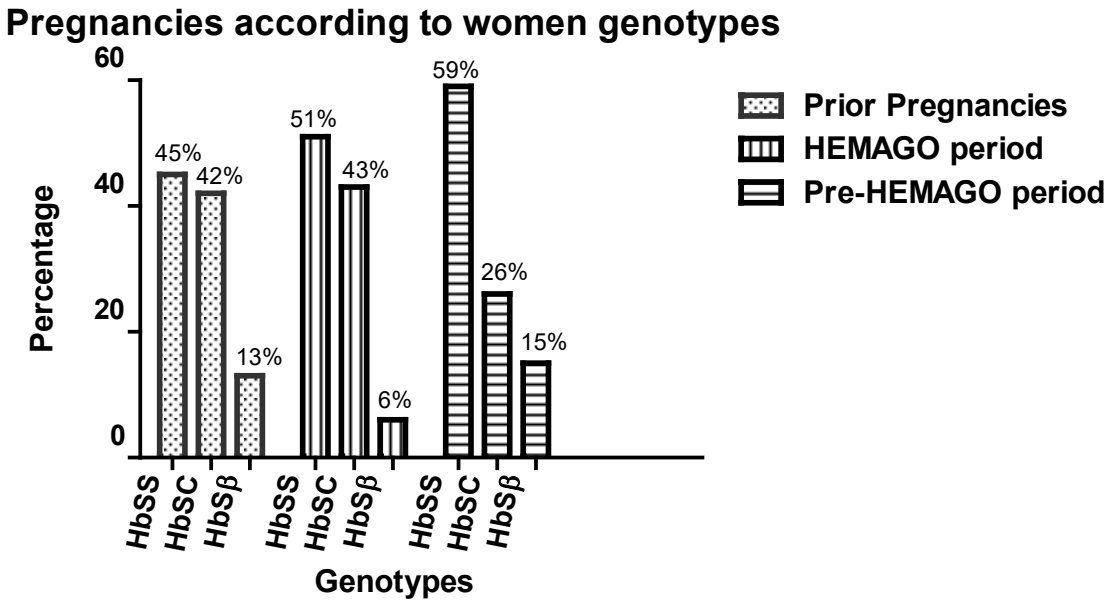
(A)


Pregnancies
p = 0.03
p < 0.001
48%
32%
20%
21%
32%
25%
9%
7%
5%
1%
55%
28%
4%
11%
2%
Percentage
Pregnancy
Prior Pregnancies
HEMAGO period
Pre-HEMAGO period

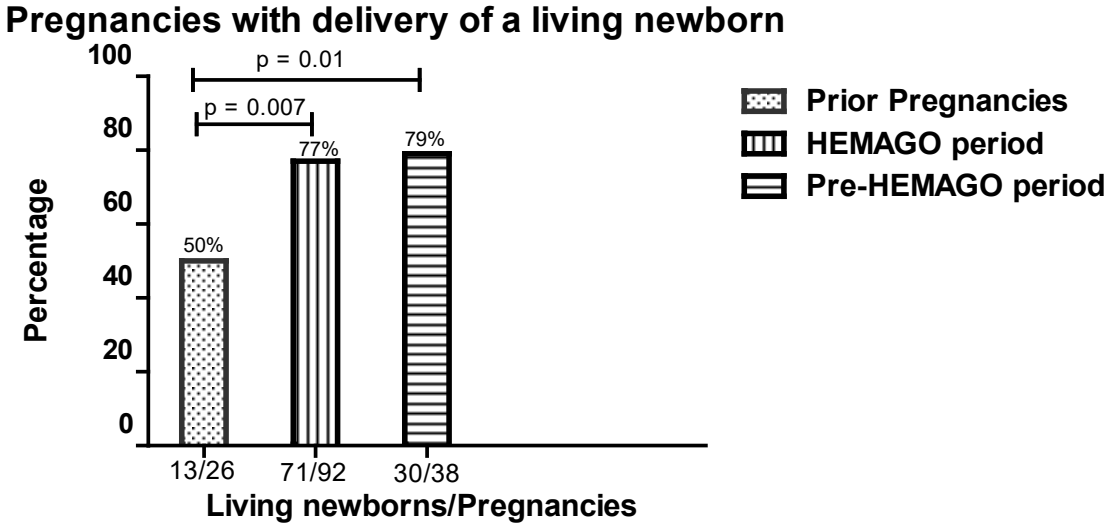
(B)


Volontary abortions
p = 0.04
p = 0.18
16%
8%
19%
Percentage
5/31
8/100
9/47
Volontary abortions/Pregnancies
Prior Pregnancies
HEMAGO period
Pre-HEMAGO period

(C)


Pregnancies according to women genotypes
Percentage
60
40
20
0
45%
42%
13%
51%
43%
6%
59%
26%
15%
HbSS
HbSC
HbSβ
HbSS
HbSC
HbSβ
HbSS
HbSC
HbSβ
Genotypes
Prior Pregnancies
HEMAGO period
Pre-HEMAGO period

(D)


Pregnancies with delivery of a living newborn
Percentage
100
80
60
40
20
0
p = 0.01
p = 0.007
50%
77%
79%
13/26
71/92
30/38
Living newborns/Pregnancies
Prior Pregnancies
HEMAGO period
Pre-HEMAGO period

(E)

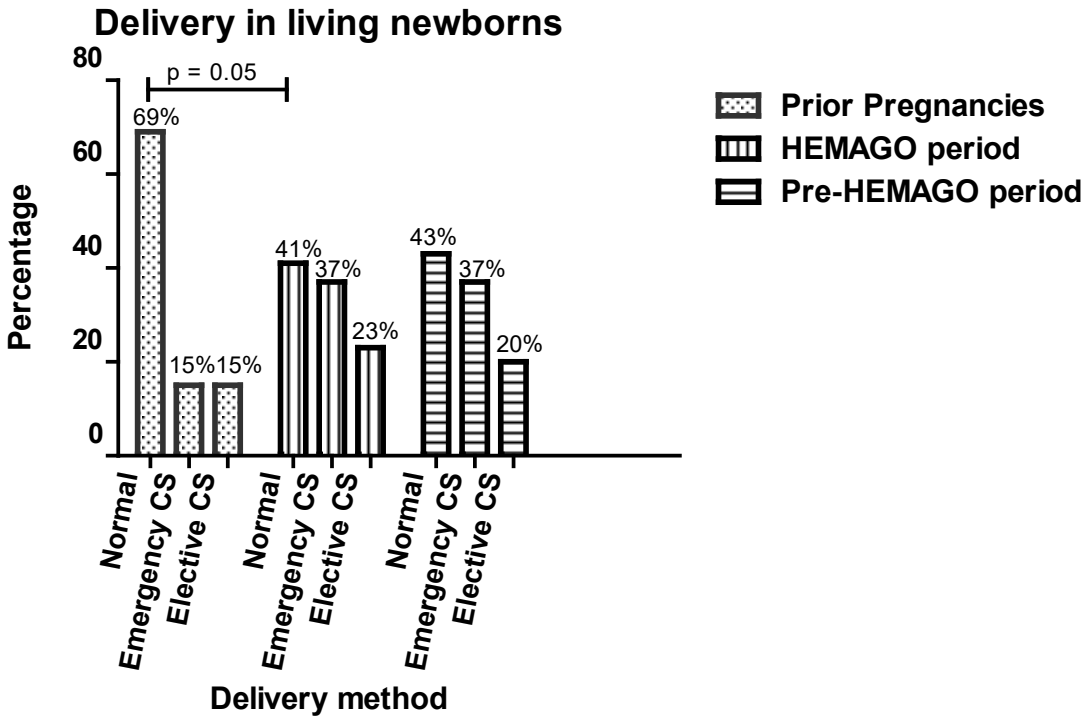



**Figure 2:** Comparison of pregnancies in the 63 women included in the study, occurring before and during the study.

(HEMAGO and pre-HEMAGO periods): (A) First and further pregnancies; (B) voluntary abortions; (C) All pregnancies according to women genotype; (D) pregnancies with delivery of a living newborn; (E) delivery methods in living newborns

**Data availability**

The data used to support the findings of this study are available from the corresponding author upon reasonable requests.

**Conflicts of interest**

The authors declare that there is no conflict of interest regarding the publication of this article.

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**Author's contributions**

MM took care of patients, acquired and interpreted the data, and drafted the manuscript; RB provided technical support; EC took care of patients; AF and FR took care of patients and critically reviewed the manuscript; GC took care of patients, acquired and statistically analyzed the data, interpreted the data and wrote the manuscript. All authors gave final approval before submission.

## References

1. Alayed N, Kezouh A, Oddy L, Abenhaim HA (2014) Sickle cell disease and pregnancy outcomes: a population-based study on 8.8 million births. J Perinat Med 42: 487-492.
2. Oteng-Ntim E, Meeks D, Seed PT, Louise Webster , Jo Howard, et al. (2015) Adverse maternal and perinatal outcomes in pregnant women with sickle cell disease: systematic review and meta-analysis. Blood 125: 3316-3325.
3. Kuo K, Caughey AB (2016) Contemporary outcomes of sickle cell disease in pregnancy. Am J Obstet Gynecol 215: 505. E1-5.
4. Early ML, Eke AC, Gemmill A (2023) Comparisons of severe maternal mortality and other adverse pregnancy outcomes in pregnant people with sickle cell disease vs anemia. JAMA Network Open 6: e2254545.
5. Piel FB, Steinberg MH, Rees DC (2017) Sickle cell disease. N Engl J Med 2017; 376: 1561-1573.
6. Rust OA, Perry KG Jr (1995) Pregnancy complicated by sickle hemoglobinopathy. Clin Obstet Gynecol 38: 472-484.
7. Hassell K (2005) Pregnancy and sickle cell disease. Hematol Oncol Clin N Am 19: 903-916.
8. Elenga N, Adeline A, Balcaen J, Tania Vaz , Mélanie Calvez, et al. (2016) Pregnancy in sickle cell disease is a very high-risk situation: an observational study. Obstet Gynecol Int 2016: 9069054.
9. Joseph L, Driessen M. A (2024) comprehensive view of pregnancy in patients with sickle cell disease in high-income countries: the need for robust data and further decline in morbidity and mortality. Lancet Haematol 11: e75-e84.
10. Early ML, Eke AC, Gemmill A (2023) Severe maternal morbidity and mortality in sickle cell disease in the National Inpatient Sample, 2021-2018. JAMA Network Open 6: e2254552.
11. Barfield WD, Barradas DT, Manning SE (2010) Sickle cell disease and pregnancy outcomes: women of African descent. Am J Prev Med 38: S542-S549.
12. Villers MS, Jamison MG, De Castro LM (2008) Morbidity associated with sickle cell disease in pregnancy. Am J Obst Gyn 199: 125.
13. Smith-Whitley K (2019) Complications in pregnant women with sickle cell disease. Hematology (ASH Education Program) 359- 366.
14. Nkwabong E, Ngoundjou Dongmo P, Tayou C (2022) Outcome of pregnancies among women with sickle cell disease. J Matern Fetal Neonatal Med 35: 1108- 1112.
15. Kavitha B, Hota BH (2017) Sickle cell disease complicating pregnancy: a retrospective study. J NTR Univ Health Sci 6: 242-246.
16. Boulet SL, Okoroh EM, Azonobi I (2013) Sickle cell disease in pregnancy: maternal complications in a Medicaid-enrolled population. Matern Child Health J 17: 200-207.
17. Ataga KI, Key NS (2007) Hypercoagulability in sickle cell disease: new approaches to an old problem. Hematology (ASH Education Program) 91-96.
18. Rogers MA, Levine DA, Blumberg N (2012) Triggers of hospitalization for venous thromboembolism. Circulation 125: 2092-2099.
19. Lopez Revuelta K, Ricard Andres MP (2011) Kidney abnormalities in sickle cell disease. Nefrologia 31: 591-601.
20. Lari NF, DeBaun MR, Oppong SA (2017) The emerging challenge of optimal blood pressure management and hypertensive syndromes in pregnant women with sickle cell disease: a review. Expert Rev Hematol 10: 987-994.
21. Sousa VT, Ballas SK, Leite JM (2022) Maternal and perinatal outcomes in pregnant women with sickle cell disease: an update. Hematol Transfus Cell Ther 44: 369-373.
22. Boafor TK, Olayemi E, Galadanci N (2016) Pregnancy outcomes in women with sickle-cell disease in low and high income countries: a systematic review and meta-analysis. BJOG 123: 691-698.
23. Oteng-Ntim E, Ayensah B, Knight M, Howard J (2015) Pregnancy outcome in patients with sickle cell disease in the UK – a national cohort study comparing sickle cell anaemia (HbSS) with HbSC disease. Br J Haematol 169: 129-137.
24. O'Hara C, Singer DE, Niebuhr DW (2020) The risk of pregnancy related hypertension disorder associated with sickle cell trait in US service women. Mil Med 185: e183-e190.
25. Nagel RL, Daar S, Romero JR (1998) HbS-Oman heterozygote: a new dominant sickle syndrome. Blood 92: 4375-4382.
26. Sharma D, Kozanoglu I, Ataga KI (2024) Managing sickle cell disease and related complications in pregnancy: results of an international Delphi panel. Blood Adv 8: 1018-1029.
27. Al Harthi SSS, Arulappan J, Al Yazeedi B (2024) Adverse pregnancy, fetal and neonatal outcomes in women with sickle cell disease in a Middle Eastern country. Women's Health 20: 1-12.
28. Malinowski AK, Shehata N, D'Souza R (2015) Prophylactic transfusion for pregnant women with sickle cell disease: a systematic review and meta-analysis. Blood 126: 2424-2435.
29. Diav-Citrin O, Hunnissett L, Sher GD, Koren G (1999) Hydroxyurea use during pregnancy: a case report in sickle cell disease and review of the literature. Am J Hematol 60: 148-150.
30. Kroner BL, Hankins JS, Pugh N (2022) Pregnancy outcomes with hydroxyurea use in women with sickle cell disease. Am J Hematol 97: 603-612.
31. Migotsky M, Beestrum M, Badawy SM (2022) Recent advances in sickle-cell disease therapies: a review of voxelotor, crizanlizumab, and L-glutamine. Pharmacy (Basel) 10: 123.
32. Habibi A, Cannas G, Bartolucci P (2023) Outcomes of pregnancy in sickle cell disease patients: results from the prospective ESCORT-HU cohort study. Biomedicines11: 597.
33. Ballas SK, McCarthy WF, Guo N (2009) Exposure to hydroxyurea and pregnancy outcomes in patients with sickle cell anemia. J Natl Med Assoc 101: 1046-1051.
34. Montironi R, Cupaiolo R, Kadji C (2022) Management of sickle cell disease during pregnancy: experience in a third-level hospital and future recommendations. J Matern Fetal Neonatal Med 35: 2345-2354.
35. James AH, Strouse JJ (2024) How I treat sickle cell disease in pregnancy. Blood 143: 769-776.