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Managing pregnancy in women with sickle cell disease: a focus on physiopathology, risks, and multidisciplinary care

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Abstract

Sickle cell disease (SCD) is a significant global public health issue due to its prevalence and the associated acute and chronic complications. In high-income countries, the infant mortality rate has fallen to below 5%; this enables girls with SCD to reach adulthood and thus (potentially) become mothers. In this context, we address crucial aspects of the pathophysiology and management of pregnancy in women with SCD, since both the mother and the fetus face substantial risks. In France, there is now a shift toward the provision of multidisciplinary, personalized care by specifically trained professionals at hemoglobinopathy reference centers.

Keywords: Fetal complications, genetic counseling, hemoglobinopathy, maternal morbidity, multidisciplinary care, pregnancy management, sickle cell disease, transfusion therapy



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INTRODUCTION

Sickle cell disease (SCD) is an increasingly common comorbidity in pregnant women; this has resulted from the high incidence (between 300,000 and 400,000 newborns worldwide are affected every year) and a continuing increase in the survival rate (up to 95% after 18 years)^[1-3]. This disease is linked to a qualitative abnormality of the beta-chain of hemoglobin. It is inherited in an autosomal recessive manner, which means that an individual must inherit two copies of the defective gene (one from each parent) to develop the disease. Those who inherit only one copy are carriers of the gene and usually do not display any symptoms; this condition is known as sickle cell trait. Fetal and maternal morbidity and mortality rates in women with SCD (whatever the genotype, [Figure 1](#)) are known to be significantly related to the country's level of income^[4,5]. Although the gap between low-income countries and high-income countries is significant, the acquisition of expertise and the implementation of multidisciplinary specific programs dedicated to these pregnancies are effective in reducing maternal and fetal complications^[6-8].

However, the maternal mortality rate is still around six times higher in pregnant women with SCD than in their counterparts from the general population; unfortunately, maternal complication rates and pregnancy outcomes have not fallen in recent years^[4,9-11]. Many of these deaths are postpartum, and half are described as “avoidable” because (i) the deceased woman was not being cared for in a specialized center or (ii) the risks had been underestimated (e.g., in paucisymptomatic women before pregnancy)^[12]. Furthermore, socioeconomic and racial discrimination persists - particularly in high-income countries^[13]. In a recent study of 3,901 deliveries by women with SCD, Early *et al.* found that the maternal mortality rate was 26 times higher in the black group than in the control non-black group; the difference in race accounted for almost one-third of this increased risk^[14]. Furthermore, the lack of an international medical consensus on the management of pregnant women with SCD and barriers to the inclusion of these patients in clinical trials hinder the development of new treatments^[15].

At present, the management of pregnancy in women with SCD is based on optimal preparation before conception (a preconception consultation, with an assessment of the chronic disease and ongoing treatments, genetic counseling, the provision of information on the risks encountered during pregnancy, the prevention of complications, and preparation for childbirth) and postpartum follow-up (with an important discussion about contraception and a reduction in the likelihood of unintended pregnancies in this at-risk population)^[10]. Although a number of treatment options are available during pregnancy, transfusions (with proved positive effects on the fetus and mother) are no longer systematically recommended because of the significant risk of alloimmunization^[9,16,17].

The prevention of complications during pregnancy is based essentially on regular clinical, laboratory, and obstetric monitoring by a multidisciplinary team with expertise in SCD. The response to any infectious, vaso-occlusive, or obstetrical event must be rapid. Patient education is important: the patient must be aware of the signs and symptoms that should prompt a consultation with a physician.

MATERNAL AND FETAL RISKS

Pregnancy leads to more frequent complications of pregnancy and/or the disease - even in patients with initially mild disease or an SC or SB+ genotype (HbSC or HbSβ+)^[4,5,10,12,18].

Intended pregnancy

An intended pregnancy is the best way to avoid or reduce maternal and fetal risks for a pregnant woman with SCD. Genetic counseling is an integral part of preconception consultation. SCD is a monogenic autosomal recessive disorder. A fetus who receives a mutation from each parent will have SCD. Therefore,

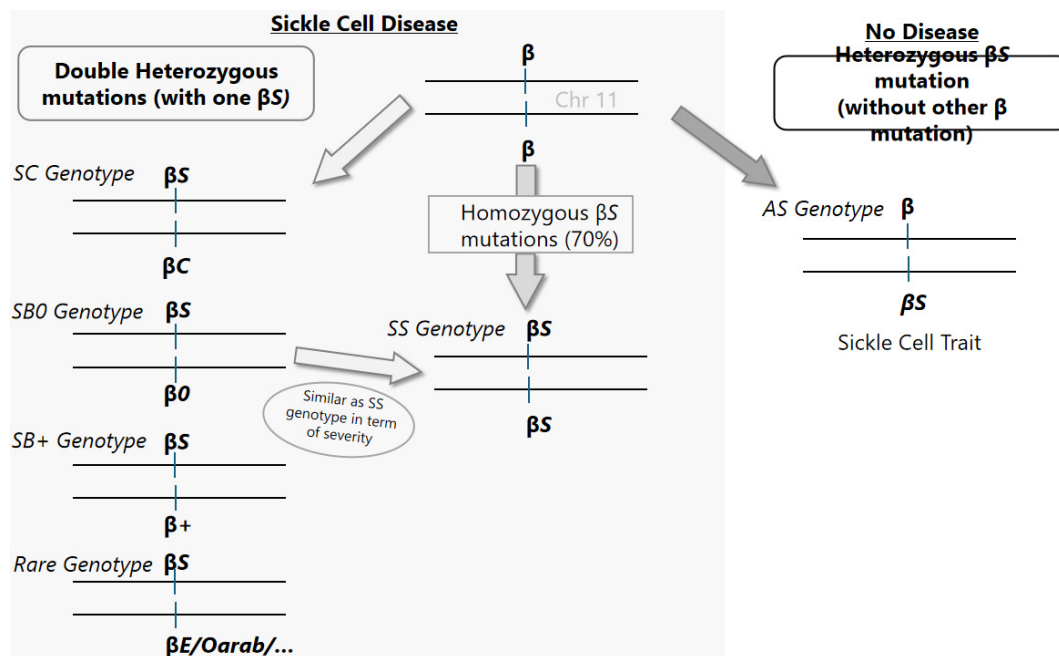


Figure 1. Representation of the different genotypes associated with sickle cell disease. Chr: chromosome.

the woman's partner should be encouraged to undergo screening for the sickle cell trait to estimate the risk of transmission to the offspring. In some countries, preimplantation diagnosis may be an option for at-risk couples to reduce the risk of transmitting the disease to their children. In vitro fertilization with preimplantation genetic testing is available, but few people are aware of these techniques. Some educational material about reproductive options exists^[19].

It should be noted that maternal complications (ovarian hyperstimulation, pain, and thromboembolic events) can occur during *in vitro* fertilization procedures.

When the SCD is unstable or when advanced organ damage is present, pregnancy should be postponed or strongly discouraged^[20,21]. An increasingly debated preconceptional issue is fertility preservation in women with SCD - especially after the age of 30 and for women taking hydroxyurea (HU)^[22-24]. Although the amount of literature data is growing quickly, there is no consensus on this topic.

Prenatal diagnosis

If each parent's status is known, a prenatal diagnosis can be considered. This can be performed via either chorionic villous sampling [before 14 weeks of gestation (WG)] or amniocentesis (after 16 WG). The level of risk (pregnancy loss, premature rupture of the membranes, intra-amniotic infection, *etc.*) associated with these procedures is currently considered to be low^[25]. Some women will refuse these procedures because of the perceived risks or because the results of the prenatal diagnosis will not affect the decision to pursue the pregnancy. A non-invasive technique that does not require knowledge of the father's status (single-gene non-invasive prenatal technique - sgNIPT) has been developed^[26]. This technique is not available in all centers due to the costs, material and expertise requirements; however, it should encourage and facilitate access to prenatal diagnosis, especially for women who would consider termination of pregnancy in case of a fetus with SCD. Depending on the term, the pregnancy may be terminated using surgical techniques (endo-uterine aspiration, dilation, and evacuation) or medical methods (induced vaginal expulsion).

Women who elect to carry a fetus with SCD to term may benefit from prenatal consultation with a pediatric hematologist and connections to support groups that include parents of children with SCD.

A comprehensive check-up

A comprehensive check-up should be carried out in the year preceding pregnancy, in order to assess the patient's baseline condition and anticipate any worsening in organ function. Most types of organ damage worsen during pregnancy; this includes SCD nephropathy (with the frequent elevation of proteinuria and, in some cases, associated preeclampsia (PE) and the accentuation of liver function impairments in patients with pre-existing liver disease^[27].

In cohort studies, SCD-related stroke is observed in 24 percent of patients before 45 years old^[28]. Except when bone marrow transplantation is available, a life-long transfusion program is recommended^[29]. Patients should be monitored regularly by expert physicians. In some high-risk situations (moderate-to-severe vascular stenosis, Moya-Moya syndrome, aneurysms, *etc.*), pregnancy may be strongly discouraged.

Osteonecrosis of the femoral head is very common in patients with SCD; in one study ($n = 1,785$), almost half of the patients with an HbSS genotype had developed this complication before the age of 35^[30]. Patients are usually screened for osteonecrosis during a routine consultation or if suggestive clinical signs are apparent. Pre-existing osteonecrosis often progresses during and after pregnancy.

Approximately 10% of people with SCD suffer from pulmonary arterial hypertension (PAH), and the proportion is higher among patients with an HbSS genotype^[31]. Screening is based on cardiac ultrasound (measurement of the systolic pulmonary artery pressure and the tricuspid regurgitation velocity), and diagnosis is based on right heart catheterization^[32]. PAH may worsen during and after pregnancy. Women with PAH must be monitored with cardiac ultrasound and must receive care and deliver in a specialized center.

Sickle cell retinopathy is also a frequent complication of severe forms of HbSC^[33]. A fundus examination and, if necessary, optical coherence tomography/tomography-angiography must be performed in the year before pregnancy. If needed, laser photocoagulation can be performed during pregnancy^[34].

Opioid-induced endocrinopathies (particularly adrenal insufficiency) are underdiagnosed and should be screened for in high-risk patients - ideally before pregnancy or, if not, during the first trimester^[35]. Appropriate hormone replacement therapy can be initiated, if necessary.

Maternal risks

Significant cardiovascular, pulmonary, and biochemical changes start early in pregnancy, at 6 WG. The mother's metabolism adapts to ensure adequate placental perfusion and support fetal growth and development^[36].

Systemic and pulmonary vascular resistances decrease, while cardiac output and blood volume increase by around 40%. The woman's baseline oxygen demand rises by up to 30%. Indeed, the chronic hypoxemia observed in SCD may reduce oxygen flow to the developing fetus, with a risk of fetal growth restriction and prematurity.

These physiological adaptations are crucial for meeting the metabolic demands of both the mother and the developing fetus. In women with SCD, however, these changes can present unique challenges and risks that

necessitate careful monitoring and management to safeguard the health of both the mother and child [Figure 2].

SCD-related risks

Pregnant women with the HbSS genotype appear to have a greater risk of adverse maternal and fetal/neonatal outcomes than women with the Hb S/C genotype^[4] [Figure 1].

Vaso-occlusive events

It is essential to tell patients that the risk of a vasoocclusive event (VOE) is higher during pregnancy, with potential impacts on maternal and fetal health. Women must know how to manage VOEs and should be referred to a specialized center if they require emergency hospital admission.

From the very first weeks of pregnancy onwards, the risk of VOEs increases significantly - especially for women with the SS genotype. A recent meta-analysis found that 7% of pregnant women with SCD (SS and SC genotypes) experience acute chest syndrome (ACS) or pneumonia during pregnancy^[37,38].

Pregnancy does not contraindicate the use of appropriate analgesics by women with SCD when needed. We recommend the creation of a personalized pain management plan for VOEs, either as soon as a woman learns she is pregnant or even earlier for patients with severe disease. This ensures that women receive prompt, effective relief if they need to be admitted to a hospital other than their regular healthcare facility. Consultation with pain specialists can be beneficial for managing these complex cases, which are sometimes complicated by opioid use disorders^[39,40]. Intensification of the treatment by transfusion or blood exchange (manual or automated) can be considered for severe cases. Respiratory physiotherapy with a spirometer is usually prescribed during the hospital stay and should be performed once or twice a day at home thereafter. The greater risk of a thromboembolic event during a VOE must not be forgotten, with the systematic, prophylactic prescription of anticoagulants throughout the hospital stay.

Stroke and cerebral vasculopathy

Pregnancy is a high-risk situation for women with SCD in general and for those with known pre-existing cerebrovascular disease in particular. Indeed, the risk of cerebrovascular events is 22 times higher for women with SCD than for controls^[14].

Prophylactic treatment with aspirin in this population can be considered and should be prescribed by a neurologist with expertise in the management of cerebrovascular disease in SCD. There is no consensus on the mode of delivery for women with stable, moderate stenosis or micro-aneurisms; all such cases must be discussed with expert physicians.

Thrombotic and embolic events

Pregnancy is a hypercoagulable state, with high levels of procoagulant factors (VII, VIII, IX, X, and XII), elevated fibrinogen, and a four-fold greater risk of phlebitis and pulmonary embolism^[41,42].

Pregnant women with SCD often display a hypercoagulable state - especially during VOEs. The risk of venous thromboembolism (VTE) in this population is 1.5 to 5 times greater than in the general

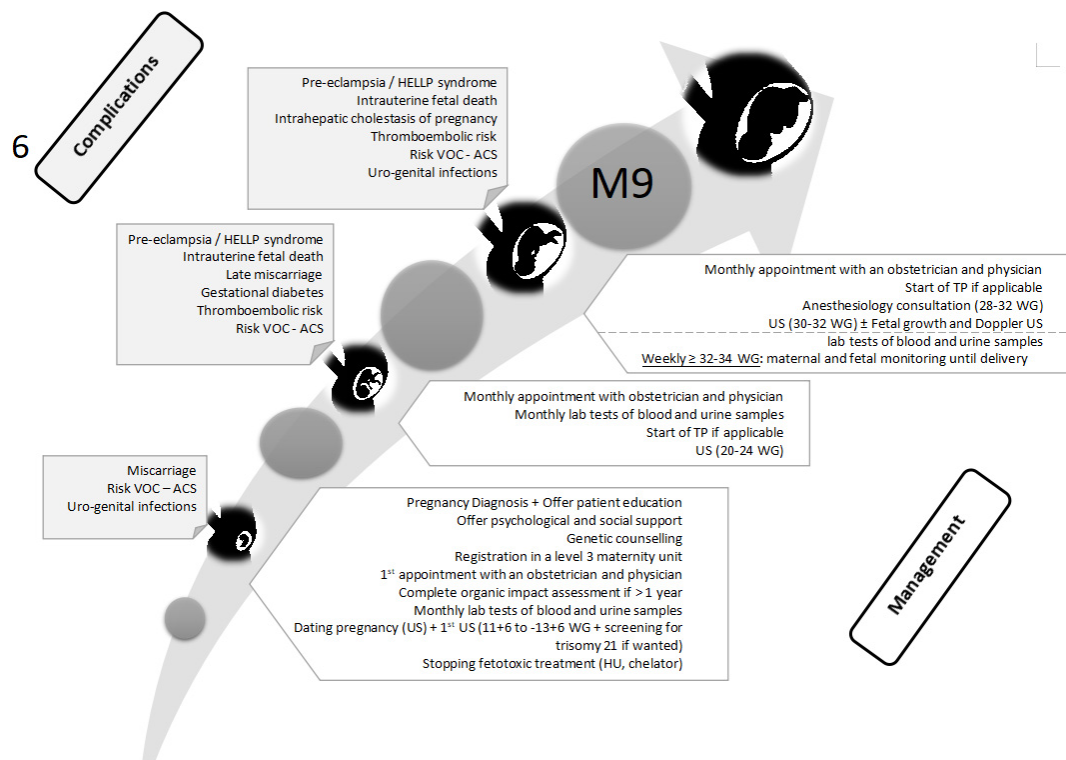


Figure 2. Summary of the medical and obstetric management of pregnant women with SCD and complications during the pregnancy. ACS: Acute chest syndrome; HELLP: hemolysis; HU: hydroxyurea; M: month; TP: transfusion program; US: ultrasound; VOC: vaso-occlusive crisis; WG: weeks of gestation.

population^[43]. An analysis of National Medicaid Data (2006-2018) in the USA evidenced venous thromboembolism in 11.3% of 6,388 pregnant women with SCD^[44]. Age, HbSS genotype, hypertension, and history of VTE were identified as independent risk factors for pregnancy-related VTE, although these findings need to be confirmed. In another retrospective study of a large cohort of 1,193 non-pregnant patients, the likelihood of VTE was independently linked to HbSS or HbSβ0 status, a lower percentage of fetal hemoglobin, treatment with HU, higher white blood cell counts, a higher hemoglobin level, and impaired kidney function^[45]. Splenectomized patients (including patients with SCD) have an increased risk of VTE^[46].

Hence, screening for other risk factors for thromboembolism is essential when deciding whether to initiate curative or curative anticoagulation treatment. However, there is a need for a new specific thromboembolism score in this population^[47].

Increased risk of infections

Due to functional asplenia, infections by encapsulated bacteria (e.g., *Haemophilus*, *Pneumococcus*, and *Meningococcus* species) are more frequent among people with SCD; hence, vaccination against these pathogens is essential. The UK's Royal College of Obstetricians and Gynaecologists recommends systematic antibiotic (penicillin) prophylaxis during pregnancy, although the putative benefits are subject to debate^[48]. The elevated risk of urinary tract infections in pregnant women with SCD is well documented^[4].

As is the case for all splenectomized patients, patients with SCD should be aware of the signs and symptoms that should prompt consultation and should always have a supply of amoxicillin at home for the early initiation of treatment.

Pregnancy-related risks

Miscarriage

There are very few literature data on the estimated risk of early miscarriage (pregnancy loss < 14 WG) in pregnant women with SCD. However, Serjeant *et al.* found a higher risk of miscarriage in an SCD population than in non-SCD counterparts (36% vs. 10%, respectively)^[49].

Notably, Kroner *et al.* found that women taking HU appear to have a higher risk of miscarriage when taking the medication during the conception period and during pregnancy^[50]. Discontinuation of HU (as soon as the woman becomes aware of the pregnancy) is not associated with a significant risk of miscarriage. However, great care must be taken when interpreting the results, as the data were based on self-reported surveys, which may be subject to great memory bias.

Retained pregnancy loss of pregnancy can be managed with endo-uterine aspiration under general anesthesia to minimize pain and VOs. If an autopsy is needed, medically induced vaginal expulsion under epidural anesthesia is advisable.

Preeclampsia

PE is defined by systolic/diastolic blood pressure values > 140/90 mmHg, new-onset or progressing proteinuria, and adverse outcomes/complications after 20 WG. It affects 3% to 8% of pregnant women in the general population and two to three times more pregnant women with SCD^[5,51]. There are probably several etiologies and disease mechanisms, although the results of many studies indicate that the placenta has a central role.

Complications of PE can occur at any time after the diagnosis and include hemolysis, elevated liver enzymes, low platelets syndrome (which is sometimes difficult to diagnose, given the high prevalence of thrombocythemia in SCD), eclampsia (seizures), and intrauterine growth restriction (IUGR).

At present, the only treatment for this pregnancy-specific disease is delivery of the neonate and the placenta. Management of PE takes account of the gestational age at onset, fetal growth, and the need to control high blood pressure. This necessitates close clinical and laboratory monitoring of the maternal-fetal couple to determine the optimal timing for delivery, minimizing the risk to both the mother and the child.

If PE occurs at the end of pregnancy, the decision to deliver the fetus is an easy one; moderate prematurity is acceptable and avoids late-onset PE. Cases of severe PE or early PE (< 32-34 WG) might require an injection of corticosteroids to mature the baby's lungs in anticipation of delivery in the following 2 to 3 weeks. However, recent studies have shown that corticosteroid treatment increases the risk of a VOE in patients with SCD^[52,53]. This risk has been demonstrated in pregnant women with SCD, and so the treatment of PE must be balanced against the risk of VOs during pregnancy^[54]. If necessary (and after discussion between the pediatrician, the attending physician, and the obstetrician), prophylactic transfusion or exchange can be performed prior to the corticosteroid injection.

There is no evidence suggesting that women with SCD have elevated incidences of gestational diabetes or intrahepatic cholestasis.

Cesarean section

Cesarean sections appear to be slightly more frequent in women with SCD than in the general population (36% vs. 30%, respectively, according to the 2015 meta-analysis by Boafor *et al.*)^[4,5]. This difference might be due to the pregnancy-related complications in SCD (e.g., PE and its complications) and thus more frequent emergency procedures. In turn, the higher incidence of cesarean section leads to more postpartum complications, including infections (endometritis and sepsis), thrombosis, and postpartum hemorrhage^[13].

Fetal and neonatal risks

Prematurity, fetal growth restriction

Prematurity, Fetal growth restriction (FGR) affects 8% to 10% of pregnancies worldwide. It is characterized by a significant difference between the ultrasound biometric parameters of the fetus and the value corresponding to its gestational age. Normal fetal growth is genetically defined, but influenced by numerous other factors, including the mother, fetus and/or placenta. Individuals born after IUGR face cardiovascular and renal diseases, metabolic disorders like type 2 diabetes, and chronic lung disease^[55-57].

During pregnancy, the woman's basal oxygen requirement increases so that the fetus and the maternal organs are perfused normally. Maternal-to-placenta blood flow accounts for up to 25% of cardiac output and is essential for maintaining the increased oxygen supply. A condition with chronic hypoxemia (like SCD) can reduce the oxygen flow to the developing fetus and can lead to FGR or IUGR and, therefore, prematurity. Indeed, small for gestational age (birth weight < 10th percentile) is two to three times more frequent in women with SCD than in the general population^[4,5]. Furthermore, the premature birth rate is around 2.4 times higher in women with SCD than in the general population. There are no indications on whether this prematurity is spontaneous or induced; however, one can hypothesize that in view of the higher frequency of maternal complications, inductions account for a large proportion of premature deliveries. The physician must not react too hastily to a VOE; indeed, a VOE in a pregnant woman can be striking and intense, and it is often tempting to induce the delivery and relieve the woman's suffering. Obviously, once the term of 36 WG is reached, the neonate will not experience major harm. Before 36 WG, however, an intense course of treatment with an appropriate analgesic will enable the pregnancy to continue.

Stillbirths and neonatal death

Given the higher rates of prematurity and IUGR among pregnant women with SCD, it is not surprising to observe that the frequency of stillbirth (or *in utero* fetal death) or neonatal death is also higher (by about four times) in major meta-analyses^[4,5]. However, there are few data on the gestational age at the onset of IUFD and the pregnancy's status (the presence of IUGR, PE, *etc.*), so the link between these conditions and the disease mechanism remain to be characterized.

Neonatal opioid withdrawal syndrome

When the mother-to-be has used opioids, there is a non-negligible risk of withdrawal syndrome for the neonate - especially when these medications were taken a few days before delivery. Withdrawal syndrome is characterized by sleeping problems, diarrhea, vomiting, sneezing, weight loss, irritability, and sometimes convulsions. Pediatricians should be informed of the opioid dose, the gestational age at which the woman received opioids, and the last time she took them. This syndrome necessitates admission to an intensive care

unit, and pregnant women with SCD should be informed of this risk.

MANAGEMENT AND FOLLOW-UP DURING PREGNANCY AND THE POSTPARTUM PERIOD

From the moment the woman is known to be pregnant to the time of delivery, personalized, close monitoring of both the mother-to-be and the fetus should be carried out jointly by the woman's usual physician and an obstetrician with experience in managing patients with SCD [Figure 1]. The follow-up should be conducted at a hospital equipped with a maternity clinic and a neonatal intensive care unit.

These check-ups should be monthly during the first and second trimesters of pregnancy and more frequent during the third trimester (twice a week at the maternity clinic until 34 WG and then once a week until delivery). The monitoring must take account of any history of complications during a previous pregnancy and any intercurrent events (such as proteinuria, hypertension, and IUGR) that will require more frequent screening.

All check-ups should include clinical examinations and laboratory tests. In order to detect PE, early-onset VOs, infections or fever, the women's blood pressure, urine protein/creatinine ratio, urine culture results, and pain levels should be documented at each consultation. A positive urine culture should trigger treatment, even when no symptoms of a urinary tract infection are present. These check-ups should be completed with a comprehensive panel of laboratory tests: hemoglobin, reticulocytes, lactate dehydrogenase, liver enzymes, and an electrolyte panel.

From 22 WG onwards, the fetus should undergo monthly ultrasound screening for IUGR and umbilical artery Doppler velocity abnormalities. At the end of the third trimester, fetal heart monitoring is added to the list of check-ups; the timing and frequency depend on the fetus's growth.

Patient education

The implementation of a patient education program during pregnancy is crucial for preventing or mitigating complications related to SCD and pregnancy. Individual consultations and group workshops are both effective methods. In France, a variety of tools and templates for individual sessions have been developed and might be of value elsewhere if disseminated more broadly^[45,58].

Studies have shown that education and counseling significantly improve pregnancy outcomes for women with chronic conditions like SCD. Greater awareness and understanding of potential complications are associated with greater adherence to recommended care plans and, thus, better maternal and fetal health outcomes^[59-61].

At our center, we organize an annual group workshop for women with SCD who are pregnant (or planning to become pregnant) and their partners, with a focus on pregnancy, childbirth, and breastfeeding. The workshop's objectives are to alleviate fears and biases, improve the caregiver-patient relationship, and enhance adherence to monitoring protocols during pregnancy. The sessions are designed to provide comprehensive information and support that will help women with SCD and their partners to navigate the challenges of pregnancy with confidence. Excellent counseling tools for pregnant women with SCD are available (e.g., <https://www.cdcfoundation.org/blog/world-sickle-cell-day-promoting-wellness-pregnant-people-sickle-cell>).

Furthermore, the integration of educational programs with multidisciplinary care (provided by obstetricians, hematologists, and pain management specialists) can further improve outcomes. This collaborative approach ensures that all aspects of the patient's health are addressed and provides a holistic support system.

Treatments

The woman's initial consultation is necessarily time-consuming because it includes an exhaustive assessment of the patient's medical history. The course of the pregnancy should be discussed with the mother-to-be and, ideally, her partner. The need for reassurance must be balanced against the need to provide information on potential maternal-fetal risks.

The most frequently prescribed drugs during pregnancy are described in [Table 1](#).

Drugs

Folic acid (vitamin B9) (B03BB01)

Folic acid treatment must be continued to avoid neural tube defects (during the first trimester) and folate deficiency in the context of chronic hemolytic anemia (throughout pregnancy)^[62,63]. There is little published evidence on the optimal dose level before and after pregnancy, although 5mg per day is the most frequently recommended dose for pregnant women with SCD^[48,64].

Aspirin (acetylsalicylic acid) (B01AC06)

In the absence of contraindications, the introduction of low-dose aspirin (120-160 mg/day) is advisable for pregnant women with SCD. Although the value of primary prevention in this population is still subject to debate, it is deemed to reduce the incidence of PE before 37 WG in high-risk women (i.e., those with a history of vascular disease such as PE or IUGR in a previous pregnancy) in non-SCD populations^[65]. No major complications have been reported (e.g., excessive bleeding or fetal malformation) for low-dose aspirin treatment. Considering the high risk of vascular disease in women with SCD, the initiation of low-dose aspirin during pregnancy is common but has not been validated scientifically. The benefit of primary prevention in women with SCD has not been evaluated, although a randomized trial is ongoing (NCT05253781). However, when a woman with SCD has a personal medical history of PE or IUGR, aspirin treatment should be initiated without any hesitation.

Aspirin should be initiated before placentation is complete (i.e., between 16 and 18 WG), taken every evening, and discontinued around 36 WG or earlier, depending on the risk of prematurity or the need for discontinuation before delivery.

For women with a prenatal indication of aspirin due to their medical condition (specific cardiovascular or neurovascular indications), their treatment should not be discontinued, as low-dose aspirin generally does not contraindicate epidural anesthesia and induce postpartum hemorrhage.

Thromboprophylaxis

Due to the absence of robust data, prophylactic or curative anticoagulation is not recommended systematically for pregnant women with SCD. Given the greater risk of thrombosis in these women, prophylactic anticoagulation with low-molecular-weight heparin and the use of support stockings are

Table 1. Treatment during the pregnancy

	Set up - used	Indication	Contraindication	Dose used
Analgesics (except non-steroidal anti-inflammatory drugs)	Throughout pregnancy	Pain	NA	NA
Low-dose aspirin	Start < 16-18 WG End ≤ 36 WG	Reduction of PE, history of vascular disease such as PE or IUGR in prior pregnancy	Allergy, bleeding during the first trimester	120-160mg/day, in the evening
Erythropoietin	Throughout pregnancy	Severe hemolytic forms or ineffective response to HU alone Chronic renal failure	NA	> 200 U/kg
Folic acid	3 months prior to conception and throughout pregnancy	Prevention of fetal neural tube defects at the first trimester / Anemia throughout pregnancy	NA	5 mg/day
Hydroxyurea	Stop from 3 to 6 months before the intended pregnancy (recommended)	DHTR or transfusion contraindications	Using during pregnancy can be considered if the benefit/risk ratio is favorable Multidisciplinary discussion	Usual dose
Iron chelators	NA	NA	Contraindicated during pregnancy	NA
Iron supplementation	Throughout pregnancy	Iron deficiency affecting erythropoiesis	Hyperviscosity risk	Oral supplementation: dosage adapted to the depth of deficiency
Oxygen therapy	Throughout pregnancy	NA	Not yet validated	NA
Low-molecular-weight heparin	Throughout pregnancy	During hospitalization and postpartum: during 6 weeks after cesarean section and during 4 weeks after vaginal delivery	Not always recommended	Prophylactic dose
Transfusion program	Throughout pregnancy	Acute / severe complications of SCD Pre-existing TP before the pregnancy Transition from HU Multiple pregnancy	DHTR Complex alloimmunization Rare group	Based on clinical target (every 3 to 6 weeks)
Vaccines	2nd and 3d trimester	Booster for whooping cough Annual COVID-19, influenza and RSV vaccines Other necessary boosters	Live vaccines	NA

DHTR: Delayed hemolytic transfusion reaction, HU: hydroxyurea, IUGR: intrauterine growth restriction, Kg: kilogram; mg: milligram; NA: not applicable; PE: pulmonary embolism; RSV: respiratory syncytial virus; SCD: sickle cell disease; TP: transfusion program; WG: weeks of gestation.

recommended during the hospital stay and after delivery^[48]. The treatment's exact duration after delivery depends on the delivery mode (6 weeks after a cesarean section and 4 weeks after vaginal delivery) but is subject to debate; it may be careful to extend treatment until 2 months post partum^[44].

Iron supplementation

Iron supplementation is rarely recommended in pregnant women with SCD. The most severely ill patients (particularly those who have received transfusions) have significant iron stores or secondary iron overload. In the case of iron deficiency affecting the reticulocyte count or total hemoglobin levels (more frequent in patients in a pre-pregnancy phlebotomy program), iron supplementation may be introduced with caution in order to avoid the hyperviscosity induced by rapid erythroid regeneration. Nonetheless, it is important to consider the benefit/risk ratio of iron supplementation because recent studies have evidenced the negative impact of maternal iron deficiency on the fetus in general, and particularly on brain development^[66].

Vitamin D (cholecalciferol) (A11CC)

Due to ethnic factors, vitamin D deficiency is more common in women with SCD^[67]. However, the guidelines on vitamin D supplementation for women with SCD are the same for their counterparts in the general population.

Hydroxyurea (L01XX05)

Fetal toxicity is the major concern for HU treatment because teratogenicity has been observed in animals (partially ossified cranial bones, absence of the eye socket, hydrocephaly, *etc.*). However, the data on patients with SCD - even those exposed during the first trimester - are reassuring^[50,68]. It is advisable to discontinue HU treatment 3 to 6 months before the intended pregnancy. In practice, some practitioners discontinue HU once pregnancy is confirmed - particularly in women with severe SCD. The risk-benefit ratio is an important variable, and all cases must be discussed with expert physicians. Due to persistent uncertainties about the fetotoxicity of HU, it is currently recommended to start an exchange transfusion program in patients treated with HU before pregnancy.

Erythropoietin (B03XA01)

Erythropoietin is not an approved treatment for SCD but is sometimes used (in combination with HU) in severe hemolytic forms or when HU alone is ineffective^[69]. This treatment is also prescribed in people with chronic renal failure. The doses used (> 200 U/kg) are higher than those approved in CKD^[70]. The treatment can be continued throughout pregnancy or initiated only when a particular clinical situation (such as severe anemia < 7 g/dL or the appearance of a contraindication to transfusion) arises.

Newly approved drug treatments for SCD [crizanlizumab (L04AA47), voxelotor, and L-glutamine (A12BA03)]

Given the lack of safety data in pregnant women, these novel therapeutics must be discontinued before or upon pregnancy^[71]. These drugs might be toxic for the fetus (miscarriages in animals have been reported with crizanlizumab) or even teratogenic. In the event of prenatal exposure, the fetus must be rapidly and regularly screened for abnormalities or growth restriction.

Analgesics

All analgesics other than non-steroidal anti-inflammatories (withdrawn from 24 WG onwards because of fetal and neonatal toxicity) can and should be administered as needed during pregnancy. The pediatrician in charge of the newborn should be informed about prolonged or recent administration of opioids so that the potential management of withdrawal syndrome can be anticipated.

Iron chelators (deferioxamine (V03AC01), deferasirox (V03AC04), and deferiprone(V03AC02))

According to their respective summaries of product characteristics, all iron chelators are contraindicated during pregnancy. Deferoxamine has not been shown to be teratogenic or toxic to the fetus, except when maternal concentrations are high. However, there are no robust data on deferoxamine in pregnant women with SCD. Some case reports in pregnant women with thalassemia have not demonstrated adverse fetal

outcomes when deferoxamine was administered during the second and third trimesters^[72,73]. There are no literature reports of harmful consequences of early (first-trimester) fetal exposure to deferasirox or deferiprone^[74].

Therefore, these drugs should only be prescribed during pregnancy when the potential benefits to the mother clearly outweigh the potential risks to the fetus.

Vaccines

Apart from live vaccines, no vaccines are contraindicated in pregnant women with SCD; on the contrary, primary and booster vaccinations during pregnancy are as strongly recommended as they are in the general pregnant population. Due to functional asplenia, women with SCD must be vaccinated against encapsulated germs. As in the general population, a whooping cough vaccine booster for the mother is recommended so that the fetus is protected^[75,76]. Vaccinations against coronavirus disease 2019 and influenza are possible and recommended in pregnant women with SCD, who are particularly at risk of severe viral diseases and the associated obstetric and fetal complications^[76,77]. Severe COVID-19 was observed in unvaccinated pregnant women with SCD especially in SC-genotype^[78].

Oxygen therapy (V03AN01)

Due to the pathophysiology of SCD and the proven role of hypoxia as a trigger for VOE, oxygen therapy might help to reduce the incidence of maternal-fetal complications^[79]. Although a prospective, multicenter clinical trial is ongoing (NCT02813850), oxygen therapy has not yet been validated in this setting.

Transfusion programs

Top-up transfusion and manual or automated exchange are applicable and safe during pregnancy^[80,81]. The choice of technique depends on the availability in the hospital, the patient's hemoglobin level, the target HbS level, and the quality of peripheral venous access.

The benefits and risks of prophylactic transfusion programs during pregnancy have been investigated in several studies and meta-analyses^[9,16,27]. Transfusion appears to be associated with a lower incidence of adverse maternal (VOC and ACS) and pregnancy outcomes. However, given that (i) 30% of pregnancies in women with SCD are uncomplicated and (ii) transfusion in women with SCD is associated with an elevated risk of alloimmunization and a delayed hemolytic reaction, systematic prophylactic transfusion is not strictly recommended^[16,82]. The USA, UK, and French guidelines now favor the non-routine implementation of transfusion programs with the continuation of transfusion programs in women regularly transfused before pregnancy, and a switch of HU to transfusion programs during pregnancy, which applies to the vast majority of patients with SBo or SS genotypes^[48,64,83].

The TAPS-2 Phase II clinical trial was designed to address this issue. However, the recently published results did not provide answers to the various outstanding questions and highlighted the difficulty of conducting a clinical trial in pregnant women with SCD. Among 88 eligible women (194 were screened), 35 were included and randomized (18 in the intervention group, i.e., systematic transfusion, and 17 in the control group). The key points were that only 11 of the 18 patients in the intervention group received at least three transfusions, while almost all patients in the control group (16 out of 17) required at least one transfusion. Unsurprisingly, given the small numbers of included patients and the low transfusion rate in

both groups, there were no statistically significant intergroup differences in prenatal or postnatal maternal or infant outcomes. TAPS-2 was in line with an earlier study by Koshy *et al.*, which randomized 72 pregnant patients with SCD (100% SS genotype) into two groups: half in the prophylactic transfusion group and half received red cell transfusions only for medical or obstetric emergencies^[84]. That study demonstrated a reduction in painful crises and complications of the disease, without differences in other medical or obstetric complications, and an increased risk of alloimmunization in the prophylactic transfusion group. The high rate of transfusion in the non-prophylactic arm (70% received at least one transfusion) highlights the necessity of this therapy in many cases in hbSS patients but limits the ability to draw definitive conclusions about the strategy of strict prophylactic transfusion strategies. Furthermore, the benefit is less clear-cut for other genotypes, and the high frequency of red blood cell alloimmunization during pregnancy should encourage physicians to exercise caution.

Malinowski *et al.* retrospectively tested a risk prediction model on a single-center cohort of 131 patients (199 pregnancies) in Canada. The model was applied during the first trimester of pregnancy to assess whether there was an elevated maternal and/or fetal risk. By taking account of standard clinical and laboratory variables (a low first-trimester hemoglobin level, a VOE requiring admission in the year before pregnancy, multiple transfusions before pregnancy, and HbSS and HbS β 0 genotypes), the researchers showed that this score was useful for deciding whether or not to implement a transfusion program or to intensify fetal surveillance or delivery planning^[82].

Recently, Habibi *et al.* reinforced a case-by-case approach to transfusion management in pregnant women with SCD, based on each individual's medical and transfusion history as recommended by the USA and UK guidelines^[85]. This approach could be used in a prospective study to explore the incidence of alloimmunization or delayed hemolytic reactions and to document fetal and maternal morbidity and mortality rates in these settings, rather than to assess the benefit per se of transfusion.

The consensus indications on transfusions are detailed in our recent viewpoint article^[86]. Given the lack of improvement in maternal and fetal morbidities over the last decade, and the demonstrated positive impact of transfusions on maternal and fetal health in significant studies where no alternatives were available, the indications for transfusion may evolve or even increase in high-income countries where transfusion safety and the use of appropriately matched red blood cells (with extended phenotyping) are feasible^[87]. Our recent practices are illustrated in [Figure 3](#).

Timing and mode of delivery

As with pregnancy follow-up, the timing and mode of delivery should be decided following consultation between the referring physician and the obstetrician. The decision is based on the women's medical and obstetric data and the presence of any intercurrent complications arising during pregnancy.

Ideally, delivery is organized in advance. There is no international consensus on the timing. However, considering the high risk of late pregnancy complications, delivery at 38-39 WG appears to be reasonable if no new medical or obstetrical events are ongoing. The presence of severe chronic complications of SCD (e.g., Moya-Moya, a history of episodes of acute chest syndromes, kidney failure, *etc.*) may suggest that delivery at around 37 WG is more appropriate. Obstetrical indications for early delivery (IUGR, PE, *etc.*) must also be taken into account.

There are no medical reasons for the systematic recommendation of cesarean section in women with SCD - especially since this technique is associated with more frequent complications, such as infection, postpartum

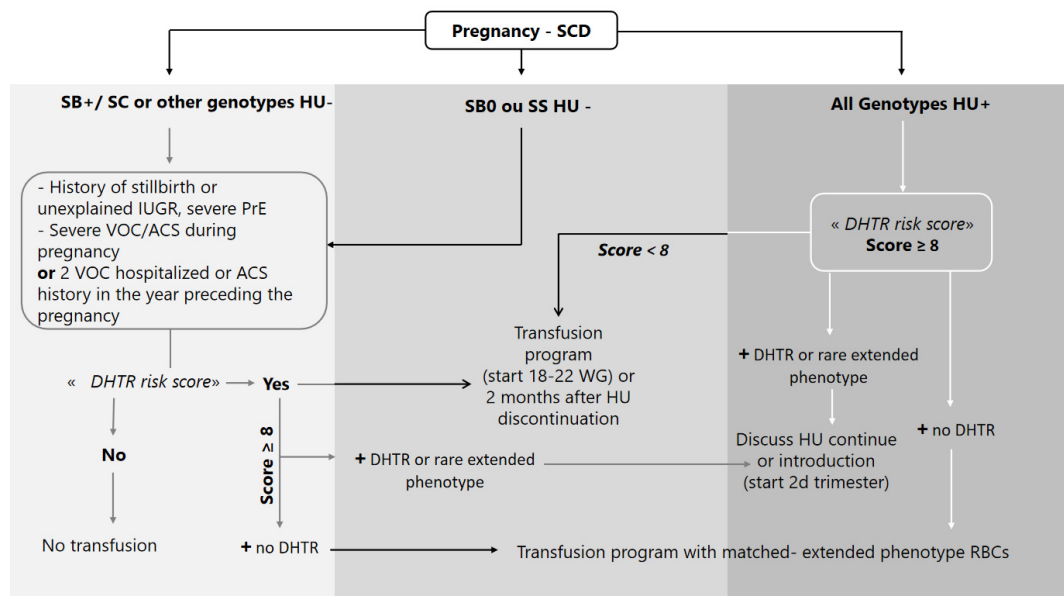


Figure 3. Management of pregnant patients with sickle cell disease based on a modified DHTR risk score. The modified risk score for DHTR combines the risk score of Narbey *et al.*^[90] with the risk of alloimmunization in patients who have received fewer than 20 units of RBCs, as described by Floch *et al.*^[91]. Notably, the risk of DHTR was underestimated for patients with a history of DHTR in the study by Narbey *et al.*^[81,90]. ACS: Acute chest syndrome; DHTR: delayed hemolytic transfusion reaction; HU: hydroxyurea; IUGR: intrauterine growth restriction; PrE: preeclampsia; RBC: red blood cells; SCD: sickle cell disease; VOC: vaso-occlusive crisis; WG: weeks of gestation.

hemorrhage, and deep venous thrombosis. However, there are contraindications for vaginal delivery: severe cerebral vasculopathy (such as Moya-Moya) and untreated severe sickle retinopathy (ischemic or neovessels), due to the risk of hemorrhage during the delivery thrust. Hip replacement or avascular necrosis of the femoral head are potential obstacles to vaginal delivery due to the positioning required during the pushing stage. Before a planned vaginal delivery, different birthing positions can be trialed to ensure that they do not cause pain or risk hip dislocation.

Labor is induced in line with local protocols, although it must be borne in mind that active pain management must be initiated early. That is why epidural anesthesia is strongly recommended to avoid acute pain and the onset of a VOE. Hydration, warming, and oxygen therapy are also recommended for reducing the risk of VOE during labor and the postpartum period. There are no contraindications to obstetrical maneuvers (such as episiotomy or instrumental delivery), if required. This end-of-pregnancy care strategy can be difficult to implement in low-income countries, due to cultural factors or the lack of medical resources for pregnancy monitoring.

Postpartum care

Special attention must be paid to the postpartum period. Indeed, major complications still occur during this period; for example, 20% to 25% of new mothers with SCD experience a VOE in the postpartum period^[48].

Hydration, oxygen therapy, and pain management must be maintained, and thrombosis prevention [using antithrombotic support stockings and prophylactic low-molecular-weight heparin (LMWH) injections] should be initiated - especially after a cesarean section^[48].

The hospital stay is often longer for pregnant women with SCD than for healthy women. Close monitoring of fever, pain, or any sign of thrombosis is essential during this period, and women should be warned clearly of the high risk of postpartum VTE and the symptoms that should prompt them to seek emergency care after leaving the maternity hospital.

To improve reproductive health in women with SCD and to avoid closely spaced or unintended pregnancies, contraception should be planned earlier^[88]. Contraception should be discussed with the woman and prescribed subject to the standard contraindications - especially a history of VTE. Estrogens should be avoided to minimize the likelihood of hypercoagulation in this at-risk population.

Breastfeeding is permitted and indeed encouraged for women with SCD, provided that preventive measures (hydration and warmth) are continued throughout the breastfeeding period. Analgesic use should be tailored to the mother's needs, as many medications are considered compatible with breastfeeding. However, analgesics can often be discontinued earlier than in the general population to enable the resumption of certain treatments (e.g., HU and opioids) [Table 1]. Nevertheless, breastfeeding is currently contraindicated for women with sickle cell anemia who are receiving HU, despite limited pharmacokinetic data on the drug's excretion in breast milk. In a study of 16 women, Ware *et al.* reported a relative infant dosage of 3.4%, which is below the recommended 5%-10% safety threshold but depended on the mother's dose intake and the time elapsed between ingestion and breastfeeding^[89]. The HELPFUL study (NCT04093986) is ongoing and might shed light on options for breastfeeding and potential risks for the newborn.

In our center, we offer a specialist consultation for women who wish to breastfeed after reinitiating HU, with emphasis on the minimum time interval between HU intake and breastfeeding. A breast pump can also be prescribed, and laboratory monitoring of the baby is recommended. We recommend avoiding the reinitiation of HU during breastfeeding for premature infants or when breastfeeding is particularly frequent.

CONCLUSION

In view of the persistent maternal-fetal risks, the treatment of pregnant women with SCD requires multidisciplinary expertise and must be carried out in maternity units offering a high standard of care. It is currently difficult to "export" this type of care to low-income countries, where the vast majority of patients live. Medical education and training must be tailored to the resources available in these settings. There is a need for expert consensus on the role of HU during pregnancy in women with severe SCD, when transfusion is not feasible or safe. High-income countries should set up clinical trials of innovative treatments for patients in low-income countries, with the dual aim of clarifying transfusion indications and assessing the safety (or potential risks) of HU treatment for both mothers and their unborn children.

DECLARATIONS

Authors' contributions

Studied the literature, analyzed the data, wrote the manuscript, designed the figures and tables, and responded to the reviewers' comments: Joseph L, Driessen M

Designed the figures and tables: Manceau S

Availability of data and materials

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Joseph L GBT, addmedica, Novartis, and Vertex. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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