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Sickle Cell Disease in Pregnancy: Optimizing Care, Best Practice and Considerations in Lower-Resource Settings

Fardowso DW[1], Elioba JLR[2]*, Bwire I[1], Hodan IA[1], Mkojera J[1], Abubakar KA[1], Maryan AH[1], Okurut E[1]

[1]Department of Obstetrics and Gynecology, Kampala International University, Uganda

[2]Department of Obstetrics and Gynecology, Yei State Hospital, South Sudan

***Corresponding author:** John Luate Raimon Elioba, Department of Obstetrics and Gynecology, Yei State Hospital, South Sudan, Tel: +211923824619; Email: eliobajohnmd@gmail.com

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Abstract

SCD affects about 6.4 million people globally, with over 5 million in sub-Saharan Africa. Sickle cell disease in pregnancy poses significant challenges to both the fetus and the mother, Pregnancy in patients with sickle cell disease (SCD) has also been a challenge for both hematologists and obstetricians. Despite the improvement in care for the patient with SCD, it has been a challenge to manage pregnant women with sickle cell disease in a lower resource setting. This article focuses on the discussion of management options that can be contextualized in lower-resource countries including Uganda to reduce the challenges that health care professionals face in managing SCD in pregnancy. It highlights the key aspects of preconception, antenatal, intrapartum, and postpartum care of SCD in pregnancy. Our emphasis on the prevention and management of the complications based on the current literature, which are cost-effective.

Keywords: Sickle Cell Disease In Pregnancy; Vaso-Occlusive Crisis; Maternal Complications; Fetal Complications; Prenatal Care; Intrapartum Care; Postpartum Care; Kampala International University; Yei State Hospital

Abbreviations

SCD: sickle cell disease; HbS: hemoglobin S; NSTs: Non-stress tests; VOC: Vaso-occlusive crises; ACS: Acute Chest Syndrome; GA: General anesthesia; ACS: Acute chest syndrome.

Introduction

Sickle cell hemoglobinopathies encompass a range of inherited hemoglobin disorders, including sickle cell beta thalassemia, sickle cell trait, and sickle cell disease (SCD) [1]. Sickle cell disease, an autosomal recessive inherited illness affecting red blood cells, results from a genetic defect where valine replaces glutamic acid at the sixth position in the beta chain of hemoglobin on chromosome 11 [2]. This mutation, first described nearly a century ago, leads to the production of hemoglobin S (HbS), which is poorly soluble and polymerizes when deoxygenated. Symptoms of SCD include chronic anemia, painful episodes, acute chest syndrome, stroke, and increased susceptibility to bacterial infections [3].

Sickle cell disease poses significant challenges during pregnancy, both for the mother and the fetus. Pregnant women with SCD are at higher risk for complications such as pre-eclampsia, intrauterine growth restriction, preterm delivery, and increased maternal and fetal mortality [4].

The physiological changes of pregnancy can exacerbate the symptoms of SCD, leading to more frequent vaso-occlusive crises and severe anemia. Effective management of SCD during pregnancy requires a multidisciplinary approach, including regular monitoring, pain management, and timely interventions to address complications. Research in this area is crucial to developing evidence-based guidelines that ensure the safety and well-being of both mother and child [5].

Sickle Cell Disease (SCD) is a prevalent inherited condition, affecting approximately 6.4 million people globally. The highest numbers are in Sub-Saharan Africa (over 5 million), followed by India (more than 1 million), and smaller populations in North America, Latin America, the Middle East, and Europe [1]. In Uganda, around 20,000 babies are born with SCD each year, with significant childhood mortality due to SCD-related complications [6,7]. The prevalence of SCD among pregnant women in Uganda is estimated to be between 1-2%. Additionally, Uganda has a mean frequency of 20% for the sickle cell trait, contributing to the high incidence of SCD births [6].

Maternal Complications

Women with SCD face heightened risks of various complications during pregnancy. This includes Anemia due to chronic hemolysis, affecting 71.8% of cases [8]. Pregnancy increases the frequency of VOC, which are painful episodes caused by obstructed blood flow in small vessels [9]. Functional asplenia predisposes women to infections such as urinary tract infections and pneumonia [8]. The risk of preeclampsia is elevated, affecting 34.3% of pregnant women with SCD [10].

Fetal Complications

The fetus is equally at risk of complications due to maternal SCD. Intrauterine Growth Restriction (IUGR) can occur due to chronic placental insufficiency secondary to vaso-occlusion crisis that impairs fetal growth [5]. The risk of preterm birth is 2-3 times higher in pregnancies affected by SCD [11]. Low Birth Weight (LBW) is more common in mothers with HbSS genotypes, doubling the risk compared to those without SCD [12].

Management Strategies

Prenatal Care

The challenge in the antenatal period of Sickle Cell Disease (SCD) is the prevention of general and SCD-specific complications. Preventing SCD-specific complications requires multidisciplinary care, with the involvement of obstetricians, hematologists, and midwives interested in SCD [5]. Early antenatal and regular visits allow for the identification of potential complications and the establishment of a personalized care plan. Women with SCD require a multidisciplinary approach to care, involving obstetricians, hematologists, and other specialists as needed [5].

At the first antenatal visit, women must be evaluated using routine blood investigations and urine analysis during pregnancy. Mothers should be made aware of frequent and regular antenatal visits. Mothers are advised to avoid precipitating factors resulting in sickle cell crisis as much as possible, such as exposure to high temperatures, low fluid intake, and excessive work. At each visit, the woman is assessed for blood pressure, and urine analysis should be done to rule out pre- eclampsia, and urinary tract infection (UTI), as patients with SCD are more prone to these [1].

If the woman has not been seen preconceptually, she should be offered partner testing. If the partner is a carrier, appropriate counseling should be offered as early as possible in pregnancy, ideally by 10 weeks of gestation, to allow the option of first-trimester diagnosis and termination if that is the woman's choice [13]. Cell-free fetal DNA (cffDNA) after 10 weeks' gestation in the maternal circulation, is a source of fetal genetic material that offers an alternative to sampling chorionic villi (usually done at 10-12 weeks) or amniocentesis (usually done between 14-20 weeks gestation) for prenatal diagnosis.

Women should be offered a viability scan at 7-9 weeks of gestation, then a routine first-trimester scan (11–14 weeks of gestation), and a detailed anomaly scan at 20 weeks of gestation [13]. Serial fetal biometry scans (growth scans) every four weeks starting between 24-28 weeks of gestation5. Regular ultrasound scans are necessary to monitor fetal growth and detect any signs of fetal growth restriction. Doppler studies may also be used to assess placental function and fetal well-being. Non-stress tests (NSTs) and biophysical profiles (BPPs) are often employed in the third trimester to monitor fetal health [14].

Vitamin D deficiency is common in pregnancy. RCOG recommends that repletion of vitamin D at 1000 to 2000 international units daily seems safe in pregnancy [13]. Iron supplementation should be given only if there is laboratory evidence of iron deficiency, and daily antibiotic prophylaxis with penicillin is recommended during pregnancy. Patients with SCD are hyposplenic and are at risk of infection, particularly from encapsulated bacteria such as Neisseria meningitides, Streptococcus pneumonia, and Haemophilus influenza [13].

Women with SCD should be considered for low-dose aspirin 75-150 mg once daily from 12 weeks of gestation to reduce

the risk of developing preeclampsia [5,13]. Recent evidence suggests that aspirin may increase the risk of postpartum hemorrhage, so it should be stopped at 36 weeks. Women with SCD should be advised to receive prophylactic thromboprophylaxis with low-molecular-weight heparin during antenatal hospital admissions [13].

Women with SCD should be considered for prophylactic low-weight heparin (LMWH) from 28 weeks of pregnancy until six weeks postpartum, and if women have additional risk factors, prophylaxis should start earlier in pregnancy [15]. Danaparoid can be used as it offers additional benefits compared to traditional agents including ease of administration and costs, it should also be considered for women intolerant of heparin compounds in conjunction with a consultant haematologist [13]. The challenge with new oral anticoagulants (NOACs) is limited access in low-resource settings.

Blood transfusions are often used in the management of SCD in pregnancy to reduce the risk of complications such as severe anemia, acute chest syndrome, and stroke. Transfusion therapy may be administered prophylactically or in response to specific complications. However, it requires careful monitoring due to the risks of alloimmunization and iron overload [16].

The World Health Organization analgesic ladder is recommended starting with paracetamol for mild pain. NSAIDs can be used for mild to moderate pain between 12 and 28 weeks of gestation. Weak opioids such as dihydrocodeine can be used for moderate pain, and stronger opiates such as morphine can be used for severe pain. Pethidine should be avoided because of the risk of toxicity and Pethidine-associated seizures in patients with SCD [13].

Intrapartum Care

Sickle Cell Disease (SCD) poses significant challenges during labor, requiring vigilant monitoring and management. The physiological stress of labor can exacerbate SCD complications, such as vaso-occlusive crises (VOC) and acute chest syndrome (ACS), necessitating continuous maternal and fetal monitoring. For the mother, monitoring should include regular assessments of oxygen saturation, hydration status, and pain levels, with the aim of detecting and managing complications early [9]. Continuous fetal monitoring through cardiotocography (CTG) is essential due to the heightened risk of fetal distress, often related to maternal hypoxia and anemia [5]. Delivery of females with Sickle Cell Disease (SCD) should be done in a hospital equipped with all facilities for efficiently managing high-risk pregnancies. Adequate hydration and oxygen saturation should be maintained, and enough warmth should be provided [1].

Studies support vaginal delivery as the recommended mode of delivery, with the need for a cesarean section based on obstetric indications [5]. The timing of delivery for women with SCD in pregnancy is generally recommended between 37 to 39 weeks, with the exact timing decided on an individual basis. Delivery closer to 37 weeks may be appropriate for individuals with high-risk genotypes or those with known SCD complications or comorbidities such as frequent vaso-occlusive episodes or hypertension. The reasoning is based on the high risk of placentally-mediated complications such as growth restriction, oligohydramnios [5].

Cesarean delivery is more common in women with SCD, often due to complications such as pre- eclampsia, intrauterine growth restriction (IUGR), and fetal distress [17]. The decision to perform a cesarean should be based on a careful assessment of the risks and benefits, taking into account the mother's and fetus's health status [9].

SCD poses significant challenges during labor, requiring vigilant monitoring and management. The physiological stress of labor can exacerbate SCD complications, such as vaso- occlusive crises (VOC) and acute chest syndrome (ACS), necessitating continuous maternal and fetal monitoring. For the mother, monitoring should include regular assessments of oxygen saturation, hydration status, and pain levels, with the aim of detecting and managing complications early [9]. Continuous fetal monitoring through cardiotocography (CTG) is essential due to the heightened risk of fetal distress, often related to maternal hypoxia and anemia [5]. In low-resource settings where electronic fetal monitoring is not accessible, intermittent auscultation using a fetoscope or fetal Doppler can be used effectively every 15-30 minutes in active labor and every 5-15 minutes in the second stage [18]. CTG is recommended for monitoring fetal distress, and cross-matched blood should be kept available at the delivery time [1].

Effective pain management is crucial during labor for women with SCD to prevent the onset of VOC, which can be triggered by inadequate pain control. Epidural analgesia is often recommended as it provides effective pain relief and reduces the likelihood of a crisis. Epidural analgesia is safe and effective [5]. General anesthesia (GA) increases the risk for Acute Chest Syndrome (ACS) [19]. Opioid analgesics may also be used, though they require careful monitoring due to the risk of respiratory depression. Complementary non-pharmacological strategies, such as relaxation techniques and proper positioning, are also beneficial in managing pain [16]. The World Health Organization analgesic ladder is recommended starting with paracetamol for mild pain. NSAIDs can be used for mild to moderate pain between 12 and 28 weeks of gestation. Weak opioids such as dihydrocodeine can be used for moderate pain, and stronger opiates such

as morphine can be used for severe pain. Pethidine should be avoided because of the risk of toxicity and Pethidine-associated seizures in patients with SCD [13]. Vaso-occlusive crises (VOC) are the most common intrapartum complications in women with SCD, characterized by severe pain due to the obstruction of blood vessels by sickled erythrocytes [16]. Management includes aggressive hydration, oxygen therapy, pain control, and, in some cases, blood transfusions to reduce the severity of the crisis [17]. Acute chest syndrome (ACS) is another life-threatening complication during labor, presenting with symptoms such as chest pain, fever, and hypoxia [9]. Immediate intervention is required, including oxygen therapy, broad-spectrum antibiotics, and, in severe cases, exchange transfusion to reduce the sickling of red blood cells [20].

Twenty-four hours prior to delivery, prophylactic low molecular weight heparin (LMWH) should be discontinued and then initiated again after 12 hours of delivery [1]. Fondaparinux and Danaparoid should be reserved for women intolerant of heparin compounds in conjunction with a consultant haematologist [13].

Postpartum Care

The postpartum period is particularly challenging for women with Sickle Cell Disease (SCD), as they are at heightened risk for complications such as vaso-occlusive crises (VOC) and thromboembolism. Immediate postpartum care should focus on the prevention and management of these complications through careful monitoring and targeted interventions. Ensuring adequate hydration and oxygenation is essential to prevent VOC and other complications [17]. Breastfeeding is not contraindicated in women with SCD [18].

Effective postpartum pain management is critical to prevent the onset of VOC. Multimodal analgesia, which includes the use of non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and regional anesthesia (e.g., epidural), can be employed to manage pain effectively [20]. However, the choice of analgesics must consider the patient's breastfeeding status. Opioids, while effective, should be used cautiously due to the risk of neonatal respiratory depression. Alternative options such as NSAIDs or acetaminophen are generally safer for use during breastfeeding [17].

Regular monitoring for signs of infection and ACS is crucial [21]. Clinicians should remain vigilant postnatally as the risk of sickle cell crisis remains increased, with 21–25% of women experiencing a crisis post-delivery, particularly following general anesthesia5. Women with SCD are particularly vulnerable to postpartum hemorrhage due to anemia and potential coagulopathies [17]. Regular monitoring of hemoglobin levels, coagulation profiles, and signs of infection is also crucial.

Following vaginal delivery, anticoagulant therapy with warfarin or heparin may be restarted 6 hours later, usually with no problems. Following cesarean delivery, full anticoagulation is withheld, but the optimal duration is unclear. The American College of Obstetricians and Gynecologists, 2018 recommends resuming UFH or LMWH 6 to 12 hours after cesarean delivery.

Breastfeeding is generally encouraged for women with SCD, as the benefits of breastfeeding often outweigh potential risks. However, certain medications used in the management of SCD, particularly opioids and other pain medications, may require careful consideration and monitoring [21]. Non-opioid analgesics are preferred during breastfeeding, but if opioids are necessary, infants should be closely monitored for any signs of sedation or respiratory depression [9]. Neonates and young infants are at risk from the adverse effects of opioids. Codeine should not be given during breastfeeding. Dihydrocodeine and tramadol and other opioids can be used but should be at the lowest effective dose, for the shortest duration [5].

Long-term follow-up care is essential for women with SCD in the postpartum period to monitor for chronic complications and maintain overall health. Regular assessments for anemia, infection, and VOC are crucial, along with preventive measures such as vaccinations and screenings for chronic conditions like pulmonary hypertension and renal dysfunction [20,22].

Mental health support should also be integrated into follow-up care, as women with SCD are at increased risk for postpartum depression and anxiety [5]. Additionally, counseling on the risks associated with subsequent pregnancies and the importance of preconception planning should be provided [9].

Postpartum contraception is crucial for women with SCD to prevent unintended pregnancy. Women with SCD face challenges in choosing appropriate contraceptive methods due to the disease's impact on vascular and thrombotic risk. Non-hormonal methods such as barrier methods and copper IUCD are safe as they do not increase the risk of thrombosis.

Among hormonal contraceptives, progestogen-containing contraceptives such as the progesterone-only pill, injectable contraceptives, and the levonorgestrel intrauterine system are safe and effective in SCD. Estrogen-containing contraceptives should be used as second-line agents. Permanent methods are suitable options for couples who have completed their families. Combined hormonal contraceptives increase the risk of thromboembolism and should be used with caution.

Challenges in Managing Sickle Cell Disease (SCD) in Low-Resource Settings

Although SCD is the most prevalent genetic disease in Africa, contributing to serious health and socioeconomic impacts, it remains largely neglected in the region. SCD often results in multiple organ failure and premature death, primarily affecting children under five years, adolescents, and pregnant women [18]. A study in Sierra Leone found that 1 in 20 critically ill obstetric patients referred to an obstetric HDU in a limited resource setting had a code for SCD [22].

SCD imposes a significant financial burden on families. Low-income countries frequently lack adequate healthcare infrastructure, including access to specialized SCD clinics, diagnostic tools, and medications [23]. A 2022 study in Brazil estimated the annual cost attributed to SCD at approximately 414 million USD, with 290 million USD related to indirect costs and 123 million USD to direct costs [22].

Hydroxyurea and blood transfusions are the main disease-modifying treatments for SCD, but Hydroxyurea is not recommended during pregnancy. Hematopoietic stem cell transplantation (HSCT) is the only curative option, though not advised for pregnant women. Promising early results from gene therapy trials may offer future alternatives [24].

Management approaches for these morbidities are more advanced in developed countries, however, the differences in settings and resource limitations in developing countries pose significant challenges that impact management options [25]. Genetic screening and curing the disease once diagnosed are particularly challenging, nevertheless, high maternal and perinatal morbidity and mortality can be reduced by devising strategies to implement healthcare cost-effectively using available resources [15].

Conclusion

Managing SCD in pregnancy requires a multidisciplinary approach and the development of context-specific guidelines to improve maternal and fetal outcomes. Addressing systemic barriers and inequities in healthcare access is crucial for reducing the burden of SCD in low-resource settings.

Competing Interest

The Author declares no competing interest

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