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Review Article

Sickle Cell Disease and Pregnancy

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Abstract. Sickle cell disease (SCD) is the most common inherited hemoglobinopathy and is associated with increased risk of complications and early mortality. Nowadays, with improved health care facilities, antibiotic prophylaxis, vaccination, and availability of drugs like hydroxyurea, the life expectancy of SCD patients has improved. More women are reaching reproductive age group and are expressing their desire to reproduce. Though SCD adversely affects pregnancy, leading to increased incidence of maternal and perinatal complications like pre-eclampsia, preterm labor, IUGR, abortions etc., adequate care throughout pregnancy ensures a better outcome. Also, recent advancements in the fields of prenatal diagnosis and pre-implantation genetic diagnosis, help couples suffering from SCD to have a healthy baby. This paper focuses on the effects of SCD on pregnancy outcomes and effective management of complications during pregnancy, also comparing maternal and perinatal outcomes in studies conducted in different countries. The second part of the paper summarizes pregnancy management in SCD for better maternal and fetal outcomes.

Keywords: Sickle Cell Disease, Pregnancy.

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Introduction. Sickle cell disease (SCD) is the most common inherited hemoglobinopathy with approximately 300,000 neonates born globally every year, predominantly in countries like Nigeria, India and Democratic Republic of Congo.[1]

The term sickle cell disease includes different genotypes of homozygous HbS sickle cell anemia (SS) and the double heterozygote states of sickle hemoglobin C disease (SC), sickle beta plus thalassemia ($S\beta^+$Thal), sickle beta zero thalassemia ($S\beta^0$thal), sickle cell anemia with alpha thalassemia (SS αthal), and sickle cell anemia with high fetal hemoglobin (SS^+F).[2]

Strictly, sickle cell anemia (SCA) is caused by a homozygous mutation (hemoglobin S) and presents as chronic anemia accompanied by painful episodes. The main defect triggering these events is impaired microcirculation due to sickling of erythrocytes.

Until the 1970s, the management of patients with SCA was weak, and pregnancy was associated with high maternal and fetal mortality. Nowadays with newborn screening techniques and preventive measures such as vaccination and antibiotic prophylaxis since birth, overall disease outcomes and patient survival have improved and there is a significant reduction in maternal and neonatal mortality rates as well.[3] However, despite all advances, pregnancy in SCD is still associated with higher clinical and obstetric

complications compared to the general population.

The physiological adaptations that occur in the circulatory, hematologic, renal and pulmonary systems during pregnancy can overburden organs that already have chronic injuries secondary to SCD, increasing the rate of obstetric complications like eclampsia and pre-eclampsia, worsening of vasocclusive crises and acute chest syndromes. Though pregnancy in SCD carries a higher risk of maternal and fetal complications, it can be managed by ensuring adequate perinatal care.

This paper provides an overview of the literature on maternal, perinatal morbidities and their management in pregnancy with SCD, with a special focus on the public health implications of prenatal screening in low and middle-income countries (LMIC) of the South. Pre-existing anemia and malnutrition in pregnant women, highly prevalent in LMIC are important factors that might affect pregnancy outcomes and fetal growth.[2]

Material and Methods. This is a rapid review of various articles published on pregnancy and sickle cell disease in recent years. Articles were identified through a PubMed search, including studies of women with SCD with known maternal and/or perinatal outcomes, as well as any known characteristics of reproductive history. The paper begins by outlining the significance of the major issues affecting the pregnancy outcomes in women with SCD in the first half below. Next part focuses on effective management of SCD pregnancies.

Fertility in women with SCD. SCD patients have delayed physical as well as sexual development.[4] These are consequences of various factors like poor nutrition, repetitive infections, blood transfusions, painful crisis, and frequent hospital admissions.[5] The onset of menarche is delayed in women with SCD[4,6] and is strongly associated with the HbSS phenotype compared to the HbSC phenotype.[7] Women with SCD have unique risk factors that may affect their ability to conceive, including chronic inflammation, oxidative stress, transfusion-related hemochromatosis, and ovarian sickling, causing ischemia and reperfusion injury to the ovaries.

Another important reason for infertility is hypogonadotrophic hypogonadism due to deposition of iron in the hypothalamo-pituitary axis because of multiple blood transfusions and iron overload. A single-center study in Egypt demonstrated that adolescents with SCD and excessive iron stores have significantly lower levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and estrogen when compared to those without excessive iron stores.[8]

Like all other organs, intravascular occlusion due to sickling of RBCs can occur in ovaries too, leading to infarction, ovarian dysgenesis, and primary ovarian insufficiency.[9] Also, NSAIDs which are very widely used for VOCs in SCD, have been shown to inhibit ovulation in mammalian species, likely due to inhibition of cyclooxygenase 2 (COX-2), thereby reducing prostaglandin synthesis. The result is impairment in ovulation, fertilization, and implantation.[10]

Pregnancy in SCD. Pregnancy in sickle cell disease can be complicated as both prospective mother and neonate are at increased risk of adverse outcomes. The physiological changes of pregnancy like increased metabolic demand, increased blood viscosity and hyper-coagulability gets aggravated in SCD patients leading to increased incidence of complications like a vaso-occlusive crisis, acute chest syndrome, osteonecrosis, hepatic necrosis, leg ulcers, and thromboembolic events. Vaso-occlusion also occurs in placenta leading to villous fibrosis, necrosis, and infarction, thereby causing impaired uteroplacental circulation, which leads to chronic fetal hypoxia and adverse fetal outcomes.[11,12]

Early reports on the outcome of pregnancy in women with sickle cell anemia, depicted an almost universal adverse outcome for mother and child, but with improvements in medical care, especially the introduction of preconception care, the outcome has dramatically improved. This improvement in feto-maternal outcome is poorly reflected in sub-Saharan Africa where the prevalence and complications of sickle cell disease in pregnancy is highest in the world, and a maternal mortality rate of 0.38 - 1.29/100,000 births and perinatal mortality rate of 1.21 - 2.50/100,000 births are still being reported.[13] This has been attributed to modest medical and antenatal care facilities, and scarce so, or non-existence of preconception care facilities in most communities in sub-Saharan Africa.

Obstetric and non- obstetric complications. Pregnancy in SCD is associated with increased risk of obstetric complications like pre-eclampsia and eclampsia, so, their incidence is significantly higher in SCD patients as compared to the general population.[14]

The risk of gestational diabetes is also found to be high, though not statistically significant.[15] Micro-vascular damage and decreased uteroplacental circulation in these mothers leads to an exaggerated risk of spontaneous abortions and stillbirths. Other factors contributing to adverse fetal outcomes include poor general health of the mother and drug abuse like tobacco, alcohol and narcotics.[16]

Pregnancy exacerbates the pre-existing anemia in SCD women, leading to a higher incidence of severe anemia and increased requirement of blood transfusions. There is a higher rate of cesarean deliveries in SCD patients, though this disease is not

an indication in itself.[12]

Further, the incidence of sickle cell disease-related complications like VOCs, ACS is increased during pregnancy. Defective splenic functions in SCD due to auto-splenectomy, superimposed with the immune-compromised state of pregnancy leads to increased risk of infections like pneumonia, pyelonephritis, UTIs, postpartum infections, etc. Pregnancy, by involving a hypercoagulable state, predisposes SCD women to thromboembolic complications like deep vein thrombosis and cerebral venous thrombosis.

Hence, due to a number of obstetric and non-obstetric complications, maternal mortality is significantly higher in SCD women compared to the general population. Though better health care facilities and increased awareness in developed countries have reduced maternal mortality, the situation is still the same in developing countries. **Table 1**, below, summarizes the factors associated with maternal outcomes in women with SCD.

Perinatal morbidities. Hypoxia and anemia seen in patients with sickle cell disease are important factors that affect fetal growth. Anemia in the mother causes impaired placental perfusion and thereby reduces the nutritional substrate transport and oxygen delivery to the fetus. All this is associated with an increased incidence of IUGR in SCD pregnancy. In low-income countries, other factors like maternal malnutrition, multiple pregnancies, and reduced health care facilities also play a crucial role in adverse perinatal outcomes.[2]

Incidence of preterm deliveries is high in SCD pregnancy, the exact mechanism is still unclear, but increased production of prostaglandin has been implicated.[2] Other reasons for it are anemia, urinary tract infections, abruption placenta, placenta previa and toxemia of pregnancy, which are more commonly seen in pregnant women SCD.[2]

Table 2 below summarizes the factors associated with adverse perinatal outcomes in women with SCD, as reflected in the review.

There is also an increased incidence of other neonatal complications like HIE, RDS, and jaundice in neonates born to SCD mothers[18,27] leading to increased neonatal admissions. Five-minute APGAR score was compared in an Indian study, it was found that 50% of neonates born to SCD mothers had 5 min APGAR score < 7.[28]

Table 1. Maternal outcomes in SCD.

STUDY	ABORTION/ STILLBIRTH (%/ n)	MATERNAL DEATH (%/ n)	PAINFUL CRISIS (%/ n)	ACUTE CHEST SYNDROME (%/ n)	SEVERE ANAEMIA (%/ n)	JAUNDICE (%/ n)	INFECTIONS (%/ n)	PRE-ECLAMPSIA (%/ n)	LSCS (%/ n)
Daigavane et al, 2013[17] (India)	10%/ 8	0	30%/ 18	10%/ 6	23.3%/ 14	10%/ 6	NA	3%/ 8	26%/ 16
Natu et al, 2014[18] (India)	24%/ 6	NA	NA	NA	64%/ 50	40%/ 10	12%/ 3	56%/ 14	NA
Sonwane S et al, 2005[19] (India)	11.1%/ 3	4%/ 1	40%/ 10	NA	24 %/ 6	4%/ 1	8%/ 2	20 %/ 5	64%/ 16
Desai et al, 2014[20] (India)	9.9%/ 13	NA	47.3%/ 62	NA	22.1%/29	NA	NA	6.1%/ 8	17.6%/ 23
Boafor et al, 2015[14]	8.1%/ 131	3.02%/ 46	NA	NA	NA	NA	25.7%/ 690	10.3%/ 229	35.5%/ 1354
Gaddikeri et al, 2017[21] (India)	33.3%/ 4	8.3%/ 4	58.3%/ 31	NA	33.3%/ 4	25%/ 14	41.6%/ 22	33.3 %/ 4	25%/ 14
Thame et al, 2007[22] (West Indies)	10%/ 13	NA	34%/ 62	18%/ 15	NA	NA	6%/ 8	6%/ 8	29%/ 33
Acharya N et al, 2013[23] (India)	NA	NA	25%/ 1	NA	75%/ 3	NA	25%/ 1	25%/ 1	100%/ 4
Muganyizi et al, 2013[24] (Tanzania)	25.5%/ 38	11.4%/ 17	NA	NA	16%/ 24	NA	11.8%/ 18	24%/ 36	26.8%/ 40
Elenga N et al., 2016[25] (French Guiana)	11%/ 3	0	19%/ 5	4%/ 1	NA	NA	30%/ 8	11%/ 3	37%/ 10

Table 2. Perinatal outcomes in SCD.

STUDY	PREMATURITY (%/ n)	LBW (%/ n)	IUGR (%/ n)	STILLBIRTH (%/ n)	NEONATAL DEATH (%/ n)	5MIN APGAR <7 (%/ n)
Daigavane et al, 2013[17] (India)	16.6%/ 10	53.3%/ 32	3.3%/ 2	10%/ 8	6.6%/ 4	NA
Natu et al, 2014[18] (India)	20%/ 5	NA	33.3%/ 6	4%/ 1	4%/ 1	NA
Sonwane S et al, 2005[19] (India)	72%/ 18	77.7%/ 19	NA	11.1%/ 3	3.7%/ 1	NA
Desai et al, 2014[20] (India)	45%/ 59	NA	2.8%/ 3	9.9%/ 13	NA	NA
Boafor et al, 2015[14]	21%/ 437	16.5%/ 322	12.2%/ 290	8.1%/ 131	2.5%/ 24	NA
Gaddikeri A et al, 2017[21] (India)	25%/ 14	84.6%/ 21	50%/ 27	8.3%/ 4	8.3%/ 4	NA
Ashish K et al, 2008[27] (India)	56%/14	56%/ 14	NA	8%/ 2	8%/ 2	NA
Acharya N et al, 2013[23] (India)	50%/ 2	100%/ 4	NA	25%/ 1	NA	50%/ 2
Muganyizi et al, 2013[24] (Tanzania)	27.5%/ 41	33.5%/ 50	NA	25.5%/ 38	NA	34.2%/ 51
Elenga N et al., 2016[25] (French Guiana)	41%/11	NA	19%/ 5	3.7%/ 1	0	NA
Serjeant et al, 2004[26] (Jamaica)	44.2%/ 19	44.7%/ 20	NA	7.1%/ 6	1	6.7%/ 3

Management of Adverse Events in Pregnancy with SCD. Six major adverse events need planning with effective management for better maternal and neonatal outcomes, as described below:

1. *Painful crisis* – pregnant women presenting with vaso-occlusive crises should be hospitalized, adequate bed rest and fluid intake should be ensured. For pain relief, paracetamol and other NSAIDs should be given. If pain is not relieved narcotic analgesics may be used. However, meperidine should be avoided because of associated toxicity and risk of convulsions.[29]
2. *Acute chest syndrome (ACS)* – Pregnant women with SCD presenting with complaints of severe cough and chest pain should be evaluated for ACS. Pulmonary infiltrates on chest x-ray, leukocytosis, blood, and sputum cultures is done to ascertain infectious complications. Treatment includes appropriate antibiotics, oxygen support, hydration, analgesics and if required blood transfusion.[29]
3. *Pulmonary Embolism* – women presenting with chest pain and respiratory distress with normal chest x-ray should be suspected to have pulmonary embolism. Treatment should be started with LMWH awaiting the confirmation of the diagnosis. It is to be noted that elevated D-dimer will not confirm the diagnosis as it can rise in other conditions like ACS and acute painful episodes.[29]
4. *Strokes* – Infarctive and hemorrhagic strokes should be suspected in any female presenting with acute neurological impairment. Treatment of choice is emergency exchange transfusion. Thrombolysis is not helpful to treat stroke in SCD.[29]
5. *Hematological Complication* – Anemia is the most common complication of pregnancy. Blood loss, bone marrow suppression by parvovirus infection and nutritional deficiencies are the causes.[2] Prophylactic red blood cell transfusion is done in some centers as it is believed that the risk of complications like stroke, ACS, sequestration is decreased. However, RCOG guidelines (Royal College of Obstetrician and Gynecologists) do not recommend the same. Transfusions are only indicated when Hb<7gm/dl because such low hemoglobin leads to decreased fetal oxygenation and abnormal fetal outcomes.[29] HELLP syndrome can develop in up to 10% of women with pre-eclampsia. It can be managed conservatively or by urgent delivery depending on gestational age.
6. *Infections* – The major sites of infection are the urinary tract and the respiratory system. Less often, puerperal endometritis, hepatitis, transient bacteremia, osteomyelitis, and HIV have been encountered. During infection, fever and acidosis lead to increased sickling and worsening anemia. Appropriate antibiotics should be started at the earliest to avoid further complications. Acute cholecystitis can also occur during pregnancy and

presents with fever, chills, and right upper quadrant pain. Such attacks may simulate sickle hepatopathy, hepatitis or hepatic sequestration. Liver function tests and ultrasound assessment will help in diagnosis. Antibiotics and symptomatic management, followed by elective cholecystectomy, is advised in the postpartum period.[2]

Prenatal Diagnosis. Prenatal diagnosis remains an important option for couples at- risk of having a child with SCD. With increasing awareness in the community, more couples are opting for prenatal diagnosis.[30] First-trimester prenatal diagnosis by chorionic villus sampling at 10 to 12 weeks of gestation and DNA analysis is the method of choice.[31] Often couples at risk are identified late in the second trimester, and they can still be offered amniocentesis at 14-15 weeks gestation and DNA analysis or fetal blood sampling by cordocentesis at 18 to 19 weeks gestation and HPLC analysis of the fetal blood to look for the percentage of adult and sickle hemoglobin present.[31]

Celocentesis for aspiration of celomic fluid at 7-9 weeks gestation allows earlier prenatal diagnosis for monogenic disorders like beta-thalassemia and sickle cell anemia. However, there is a problem of maternal cell contamination. It has been recently shown that this can be overcome through Embryo-fetal erythroid precursors selection using anti CD 71 Microbeads or by direct micromanipulator pick up of the cells selected based on their morphology.[32]

Preimplantation genetic diagnosis (PGD) is not a replacement for prenatal diagnosis but another option particularly for couples who would like to have a healthy baby but who do not wish to terminate an affected pregnancy as is most often done after prenatal diagnosis as it involves the selective transfer of unaffected embryos following in-vitro fertilization (IVF). This approach is also valid for couples with an unsuccessful reproductive history who are opting for undergoing assisted reproduction. However, there can be technical problems of allele drop out and contamination leading to misdiagnosis.[33]

Pregnancy Management in SCD.

Pre-conceptual care. All women with SCD in reproductive age should be provided with relevant information on how SCD affects pregnancy and what measures should be taken for better maternal and fetal outcomes. It is during this period that she should be made aware of the importance of partner screening and the options for prenatal screening.

A complete medical and social history of the mother should be obtained, including her vaccination status, current medications, any other co-morbid condition, and any drug abuse. Vaccination against all encapsulated organism, including Neisseria meningitides, Streptococcus pneumonia, and Haemophilus influenza should be updated. In addition, Hepatitis B and Influenza vaccine should be given. Folic acid (5 mg) should be given once daily both preconception and throughout pregnancy. Iron is recommended if there is evidence of iron deficiency, but most of the women have iron overload. Most of the women are on hydroxyurea. It is recommended that drugs like hydroxyurea, ACE (angiotensin-converting enzyme) inhibitors, and iron chelators should be discontinued at least 3 months before conception due to the risk of teratogenic side effects.[34] Screening for complications like pulmonary hypertension by 2D echocardiography, retinal screening for proliferative retinopathy, iron overload, renal and liver function studies to rule out sickle nephropathy and hepatic involvement should be done yearly.[2]

Ante-natal care. The first prenatal visit should be a comprehensive assessment. Routine blood investigations like complete blood count, HIV, HBs Ag, HCV should be done along with urine examination. Mother should be explained the importance of a regular antenatal visit; it is recommended to visit obstetrician every other week during the first two trimesters.[35] Blood pressure and urinalysis should be performed at each consultation, and midstream urine for culture performed monthly as these women are prone to pre-eclampsia and increased risk of urinary tract infections.[2]

Mothers should be explained to avoid precipitating factors of sickle cell crises such as exposure to extreme temperatures, dehydration, and overexertion. Also, repeated vomiting can cause dehydration and precipitate crisis. Hence, she should seek medical advice at the earliest.

Women who are at increased risk of pre-eclampsia are advised to take low-dose aspirin 75 mg from 12 weeks of gestation unless they have aspirin sensitivity.[36]

Early studies recommended prophylactic transfusion during pregnancy as there was a decrease in maternal morbidity and perinatal mortality among transfused women, but these are not recommended due to risks of alloimmunization, iron overload, transfusion reactions and infections.[37] Also, recent studies demonstrated that prophylactic transfusion decreased the incidence of maternal, painful crises but did not influence fetal or maternal outcome.[38,39] Transfusion is indicated in case of severe anemia, and exchange transfusion is recommended in case of stroke and acute chest syndrome.

Intrapartum care. Delivery of SCD mother should be conducted in a center equipped with all health care facilities to manage high risk pregnancies. Pregnant women with SCD who have a normally growing fetus should be offered elective birth through induction of

labor at 38 to 40 weeks of gestation, as SCD by itself is not a contraindication to attempt vaginal delivery or vaginal birth after cesarean section. If there is any indication or impending complications, cesarean delivery should be considered. Women should be kept warm and given adequate fluid during labor. Pain can be managed with adequate use of analgesics. Epidural anesthesia is particularly useful in this regard, and efforts should be made to shorten the duration of labor as well. Continuous intrapartum electronic fetal heart rate monitoring is recommended owing to the increased risk of fetal distress. Blood should be cross-matched and kept ready at the time of delivery.

Post-partum care. In the postpartum period, it is crucial to assess the degree of anemia aggravated by blood loss during labor and delivery, and replacement instituted when indicated. Hydration and oxygenation should be maintained, and early mobilization encouraged. Crises should be managed as for non-pregnant women. NSAIDs are routinely administered in the postpartum period and can be used during breastfeeding. Breastfeeding should be encouraged, as in women without SCD. Thromboprophylaxis in the form of low-molecular-weight heparin is recommended for seven days following a vaginal delivery or a period of 6 weeks following cesarean section. Antithrombotic stockings are also recommended. Screening of newborn for sickle hemoglobin is recommended. Mother should be advised regarding contraception, 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. Barrier methods are as safe and effective in women with SCD as in the general population.[36]

Hydroxyurea and Pregnancy. Hydroxyurea has emerged as a wonder drug for SCD patients, thereby reducing morbidities like VOCs, acute chest syndrome, and also decreasing the requirement of blood transfusion. Hydroxyurea is classified as an S-phase anti-neoplastic agent (pregnancy category D). It has been shown to be potentially teratogenic due to its ability to initiate damage to genetic material (i.e. DNA).[40] Toxicities of hydroxyurea have been reported, including cytopenias, rash[41] and the potential for teratogenicity was demonstrated in pregnant mammalian models using high doses of hydroxyurea[42,43,44] although such reports are lacking in humans. It is recommended that hydroxyurea should be discontinued at least three months before conception to avoid the risk of teratogenicity.[36]

There has always been an ethical dilemma about whether all couples at risk of having a child with sickle cell disease require prenatal diagnosis as many affected babies may have a milder clinical presentation.[45] It has been suggested that evaluating genetic modifiers may help.[46] However, the fact remains that it is impossible to predict the severity of the disease. The decision to terminate or continue an affected pregnancy should be taken by the couple and not be the counselor.

Conclusions. Since the literature on perinatal outcomes in SCD is limited, and the potential impact of additional improvements in modern obstetric care and treatment for SCD is significant, there is a substantial need for additional studies of pregnancy-associated complications and outcomes for women with SCD. This review aims to assess the studies which have assessed the prevalence of maternal complications during the intrapartum and postpartum periods for women with SCD. The review also highlights the effective management of pregnancy and its complications in women with SCD to ensure successful maternal and neonatal outcomes.

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