ORIGINAL ARTICLE

# Fetomaternal Outcomes among Patients with Sickle Cell Disease: A Retrospective Study

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## Abstract

**Introduction:** We are presenting a study on pregnancy with sickle cell disease (SCD), which is the most common genetic disorder with high mortality and morbidity with varying severity. It is an increasing global health problem.

**Materials and methods:** The cases were retrieved and a case–control study was done at GMERS Medical College and Hospital over a duration of 3 years from November 2019 to September 2022. General characteristics of 32 pregnancies and their fetomaternal complications were studied. A descriptive statistical analysis of the above-mentioned data was performed, and percentages were calculated.

**Results:** Among 32 cases, 62.5% of cases were multigravida. Anemia (moderate and severe anemia) was the most common complication (71.87%). Hemolytic crisis was seen in 18.75%, and painful crises were seen in 6.25% cases, 9.37% of cases had acute chest syndrome. Complications such as urinary tract infection (UTI) were seen in 6.25%, preeclampsia in 34.37%, 56.25% had preterm deliveries, and history of miscarriage and stillbirth was seen in 34.37%. Intrauterine growth restriction (IUGR) was seen in 9.37%, neonatal death – 3.12%, low birth weight – 62.5%, fetal distress – 12.50%, and intrauterine fetal death (IUFD) – 6.25%. Maternal mortality was seen in 12.50% cases.

**Discussion:** Because of physiological adaptations along with sickle cell crisis, maternal and fetal complications are more in SCD patients.

**Conclusion:** The study will help understand the outcomes of pregnancy in SCD patients and will help for a better approach in treating these patients.

**Keywords:** Heterozygous, Homozygous, Pulmonary hypertension, Vaso-occlusion.

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## Introduction

Sickle cell disease is a genetically inherited group of conditions with an abnormal hemoglobin (HbS) due to its genetic alteration. Sickle cell disease comprises homozygous – HbSS or heterozygous – HbSß thal, HbSC, HbSD Punjab, and HbSE – genotypes. Homozygous SCD (HbSS) is the most severe form of SCD. In Gujarat, in the tribal belts of Chhotaudepur, Panchmahal, Dahod, Godhra, Narmada, SCD is common and our center receives many referrals from there. Pregnancy in women with SCD and its complications are included in this study. India ranks second when it comes to SCD burden globally. The highest prevalence of SCD is in India among all south Asian countries, where over 20 million people live with SCD.[1] India holds for 14.5% of total SCD newborns. About 1–2 million tribals have sickle cell trait and approximately 80,000 have SCD in Gujarat.[2] Sickle cell disease results from polymerization of sickle hemoglobin in a low-oxygen state, which leads to fragile and rigid sickle-shaped red blood cells. This causes hemolytic anemia due to easy breakage of cells, and also these sickle-shaped cells cannot flow through smaller blood vessels easily and cause blockage or vaso-occlusion in vessels, which in turn can lead to acute painful crisis. Acute chest syndrome (ACS), stroke, retinal disease, avascular necrosis, leg ulcer, cholelithiasis, pulmonary hypertension (PH), and renal dysfunction are other complications of SCD.

This is why perinatal care is of utmost importance. Sickle cell disease is associated with a higher risk of morbidity and mortality in pregnancy.[3] There is a need for additional studies on the fetomaternal outcomes of SCD as there are limited data available. Whatever data are available with us have potential impact on modern obstetrics care.[4] Women with SCD coming for routine care should be discussed about genetic screening, conception, pregnancy, and pregnancy-related complications due to her condition. Nonsickle causes of renal dysfunction should be excluded preconceptionally in women with abnormal renal functions. Also these females are prone to develop ventricular diastolic dysfunction, PH and early cardiac death, should be investigated for the same. Screening and initial evaluation of PH are done with the help of noninvasive Doppler echocardiography. There is an increased risk of PH and mortality with a raised tricuspid regurgitant jet velocity (TRV).[5] All pregnant and breastfeeding mothers should be advised to take folate and vitamin D supplementation.[6]

Annual vaccination of influenza and pneumococcal vaccine should be reviewed as a part of antenatal care. Teratogenic medications like ACE inhibitors, ARBs, and hydroxyurea should be stopped.[7] Iron chelators are not recommended. In patients

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with the first-trimester pregnancy-associated plasma protein A (PAPP-A) values of <0.5 multiple of the median, more frequent scans are considered after 20 weeks of gestational age to rule out IUGR.[8] Women who underwent prophylactic transfusions have less number of adverse outcomes like pain crises, pneumonia, preterm delivery, and perinatal death as compared with women who did not receive a prophylactic transfusion. Additional studies are needed to understand the benefits of prophylactic transfusions in management of SCD in pregnancy.[9] Chronic organ injuries, which are caused by SCD, are overburdened by the physiological adaptations that occur in the hematologic, pulmonary and renal systems during pregnancy, leading to increasing rate of obstetric complications such as ACS, worsening of vaso-occlusive crisis, and preeclampsia/eclampsia. In recent times, there has been a debate to redefine hypertensive disorders of pregnancy in women with SCD because as compared with general population, these patients have lower blood pressures at steady state.[10] This is the reason why pregnant women with SCD having normal-range blood pressure values may have higher blood pressures compared with their pre-pregnancy values. Therefore, in the SCD population, early signs of preeclampsia may be missed. In pregnant women with SCD, persistently high blood pressure of >130/80 mm Hg, treatment with an antihypertensive should be considered.[11]

Possible reasons for higher incidence of acute painful crisis in pregnancy with SCD include psychological and physical stress. For example, nausea and vomiting during early pregnancy lead to dehydration, the procoagulant state in pregnancy contributes to vaso-occlusive disease, and also, SCD is a condition with high risk of infections such as influenza and urinary tract infection (UTI), which can lead to sickle crisis. Pain management is one of the important tools in treatment. Weak opioids, paracetamol, oral fluids, and rest are treatment options for mild pain and are managed in the community.[12] Oxycodone, diamorphine, and morphine can be used for severe pain. Pethidine causes risk of toxicity and pethidine-associated seizures in patients with SCD, as better avoided. Diagnosis of acute chest syndrome is made by respiratory symptoms and/or fever and a new pulmonary infiltrate on X-ray chest. Basic treatment includes prompt pain relief, treatment of bacterial or viral infection, and incentive spirometry. Sickle cell disease is also responsible for both infarctive and hemorrhagic acute strokes. Some women with SCD present with acute anemia, and this may be attributable to B19 parvovirus infection, which causes a red blood cell maturation arrest and an aplastic crisis identified by a reticulocytopenia. Prophylactic low-molecular-weight heparin (LMWH) from 28 weeks of pregnancy until 6 weeks postpartum should be considered in women with SCD. Prophylaxis should be considered from the beginning of pregnancy in women with additional risk factors.[13] Delivery of the baby should be considered between 38 and 40 weeks of gestation in pregnant women with SCD who have a normally growing baby, and if there are no other contraindications, vaginal birth after a previous cesarean (VBAC) can be offered.

Adequate hydration and warmth are important during labor and analgesia. Depot-medroxyprogesterone acetate (DMPA) and levonorgestrel–intrauterine system (LNG–IUS) are preferred as contraception of choice.[13]

## Materials and Methods

This study consists of a retrospective study of pregnant women admitted with SCD at GMERS Hospital, Gotri, between November 2019 and September 2022, with the confidentiality of these patients being preserved. Statistical analysis was done with the help of data recorded and compiled on an Excel spreadsheet. GMERS hospital, Gotri, is a tertiary center in Vadodara, Gujarat, which receives a number of local sickle obstetric referrals. The cases were identified based on their Hb electrophoresis and high-performance liquid chromatography (HPLC) reports. The study comprised 32 pregnancies (singleton) in women with SCD: homozygous sickle cell disease (SS) 30 and sickle ß thalassemia ($Sb^+$) 2. Patients with heterozygous sickle cell trait are not included in the present study. The information collected from hospital records were – the woman's age at delivery, hemoglobinopathy, hemoglobin concentration, gestational age at delivery, data regarding the outcome of pregnancy (miscarriage, stillbirth, IUFD, live birth, and NICU admission, neonatal death), mode of delivery, and birthweight. Obstetrics complications such as preeclampsia, eclampsia, postpartum hemorrhage, IUGR, fetal distress, gestational diabetes, history of miscarriage/stillbirth, sickle cell-related complications (acute chest syndrome, hemolytic, vaso-occlusive, painful and aplastic crisis, UTI, and pulmonary complications) and maternal death were noted. The approval for this study was obtained from the Ethics Committee of the hospital. Gestational age was calculated from the last menstrual period or ultrasound dating (prematurity before 37 weeks of gestation). Stillbirth or IUFD was considered at or after 28 weeks of gestation. Neonatal death is defined as the death of a live-born baby within 28 days. Preeclampsia refers to blood pressure >140/90 mm Hg after the 20th week of gestation, with or without severe features associated with it. The incidence of low birth weight (LBW) was considered as <2500 gm. All obstetrics admissions with SCD were managed by the joint obstetric, anesthesiology and medicine departments. Women who attended the antenatal clinic elsewhere or were delivered elsewhere and later admitted with complications to this institute were also included.

## Results

Most cases were multigravida (62.5%). Mean age at admission was 24.84 years (range 19–40 years), and mean gestation age at admission was 35.28 weeks (range 28–39 weeks). About 21 cases were referred from tribal belts. About 27 patients (84.37%) were from lower socioeconomic status. About 24 cases (75%) required blood transfusions. The characteristics are outlined in Table 1. The maternal obstetric complications are outlined in Table 2. Obstetrics complications were present in 22 (68.75%) pregnancies, 11 cases (34.37%) were of preeclampsia, 18 cases

**Table 1:** Characteristics of the deliveries

| | |
|---|---|
| Number of admissions | 32 |
| Mean age (years) | 24.84 |
| Mean gestational age (week) | 35.28 |
| Multigravida (%) | 20 (62.5%) |
| Referred patients (%) | 21 (65.62%) |
| Lower socioeconomic class (%) | 27 (84.37%) |
| Blood transfusion (%) | 24 (75%) |
| Transfusion reactions | 0 |
| SCD-related complications (%) | 16 (50%) |
| Obstetric complications (%) | 22 (68.75%) |

**Table 2:** Maternal obstetric complications during pregnancy

| | |
|---|---|
| Obstetric complications (%) | 22 (68.75%) |
| Previous miscarriage | 3 (9.37%) |
| Previous stillbirth | 8 (25%) |
| Preterm labor | 18 (56.25%) |
| Preeclampsia/Eclampsia | 11 (34.37%) |
| Postpartum hemorrhage | 1 (3.12%) |

**Table 3:** SCD-related maternal complications during pregnancy

| | |
|---|---|
| SCD-related complications (%) | 16 (50%) |
| Severe vaso-occlusive crises | 1 (3.12%) |
| Acute chest syndrome | 3 (9.37%) |
| Urinary tract infection | 2 (6.25%) |
| Impaired cardiac function | 0% |
| Cerebral infract | 1 (3.12%) |
| Hemolytic crisis | 6 (18.75%) |
| Painful crisis | 2 (6.25%) |
| Severe anemia | 6 (18.75%) |
| Maternal death | 4 (12.50%) |

**Table 4:** Mode of delivery

| | | |
|---|---|---|
| Normal delivery (62.5%) | Induced | 4 (12.50%) |
| | Spontaneous | 14 (43.75%) |
| Instrument delivery (%) | 02 vacuums (6.25%) | |
| Cesarean section (%) | 14 (43.75%) | |

(56.25%) delivered before 37 completed weeks of gestation, 3 cases (9.37%) had a history of miscarriage, and 8 cases (25%) had a history of stillbirth in previous pregnancy.

Sickle crises requiring admissions were 16 (50%) out of 32 pregnancies. Sickle cell disease-related complications are mentioned in Table 3. Episodes of crises: hemolytic crisis (6 cases – 18.75%) was common during pregnancy. There were no cases of aplastic crisis. Acute chest syndrome was seen in 3 (9.37%). Painful crisis was seen in 2 cases (6.25%), UTI was seen in 2 cases (6.25%), and 1 case (3.12%) of severe vaso-occlusive crisis was seen. About 4 (12.50%) maternal deaths were reported. No case was reported with impaired cardiac function. Pregnancies were complicated by severe anemia (<7 g%) in 6 (18.75%).

In total, 20 out of 32 women underwent vaginal delivery (62.5%), out of which 2 (6.25%) were vacuum-assisted deliveries. About 14 (43.75%) were delivered by emergency cesarean section (Table 4). Fetal distress was the most common indication for cesarean sections.

Perinatal outcomes are outlined in Table 5. Average birth weight was 2192 gm. Twenty cases (62.5%) of low birth weight, 8 babies (25.80%) required NICU admission, 3 cases (9.37%) of IUGR, and 3 perinatal mortalities (9.37) were reported.

**Table 5:** Perinatal outcomes

| | |
|---|---|
| Average weight (gm) | 2192 |
| Low birth weight (%) | 20 (62.50) |
| Intrauterine growth restriction (%) | 3 (9.37) |
| Fetal distress (%) | 4 (12.50) |
| Still birth/IUFD (%) | 2 (6.25) |
| NICU admissions (%) | 8 (25) |
| Neonatal death (%) | 1 (3.12) |

## Discussion

The study summarizes fetomaternal outcomes in patients admitted with SCD during the period from November 2019 to September 2022. The hospital receives a number of patients from eastern hilly tracts of Gujarat and the maximum patients from Chhotaudepur. The total number of patients admitted in GMERS Gotri during this study period was 4220 out of which patients diagnosed with SCD were 32, which makes the prevalence of sickle cell disease – 0.73%. All pregnancies were singleton. Several published reports suggest that twin pregnancy with SCD is associated with poor outcomes.[14] Out of 32 patients, only 1 patient was booked with the hospital and received proper antenatal care, including thromboprophylaxis and blood transfusions, and was timely managed when she presented with acute chest syndrome and painful crisis, also investigated for any existing renal dysfunction and PH. The remaining 31 patients were unbooked and admitted for labor pains or associated complications. About 64.51% of cases were referred. Six patients were delivered outside and referred here for further management of sickle cell-related complications and blood transfusions. The cases with missed diagnoses of SCD have declined over the years due to improved lab facilities. Maternal mortality can be reduced by 90% in women with SCD by multidisciplinary care approach. This was demonstrated by a previously done before–after study model.[15] The mean age of admitted patients was 24.84 years, similar to the study done in Kerala, where the reported mean age was 25.83.[16] Anemia is the most common complication associated with SCD in this study. A total of 90.62% cases had anemia, out of which, 18.75% had severe, 53.12% had moderate, and 18.75% had mild anemia. A study done in Burla, Odisha, had all cases presenting with anemia.[17] Here, 75% of cases received a blood transfusion. About 46.87% of cases received multiple transfusions. Similar studies done in India reported higher transfusion rates of 66.6% and 52.7%.[3,18] The impact of aspirin therapy and prophylactic transfusion has not been properly studied in different trials. These gaps in information should be fulfilled by well-designed studies. Another study addresses that red blood cell exchange for obstetrics' SCD patients can be feasible and safe, and can reduce the visits to the hospital due to avascular necrosis and vaso-occlusive crises like SCD-related complications.[19] Nocturnal oxygen supplementation also shows decreased need for red cell transfusions as per recent research reports.[20]

About 68.75% patients were admitted for obstetrics-related complications. The commonest complication in this study was preterm delivery with 56.25% of patients. Desai et al. reported 45% preterm delivery in their study.[3] About 34.37% cases were complicated by preeclampsia. The exact cause of preeclampsia in SCD patients is unknown. This may be because of placental infarction, endothelial dysfunction/damage, or inflammation. None of the patients from this study was HIV-positive. One study suggests that existing HIV infection in women with SCD increases rates of severe preeclampsia.[21] Sickle cell disease-related maternal complications were present in 50% of cases, which in turn contributed to maternal mortality. Maximum cases were

of hemolytic crisis (18.75%) corresponding to a study done by Kavitha et al., which also reported maximum cases of hemolytic crisis.[22] About 9.37% cases had acute chest syndrome. Nwafor et al. documented 12.24% mothers complicated by acute chest syndrome.[23]

There is a strong association between SCD and maternal pulmonary complications according to one meta-analysis.[24] To reduce the associated maternal morbidity and mortality in these patients, risk factors associated with pulmonary complications should be identified and treated preconceptionally.[24] One case of maternal mortality had cerebral infarction. Similarly, the study by Haseeb had 6.6% cases of thromboembolism and 2.6% had a stroke.[25] One patient suffered from a severe case of vaso-occlusive crisis. Nkwabong reports 10% vaso-occlusive crisis complications.[26] At least one episode of VOC during pregnancy is experienced by approximately 55% of pregnant patients with SCD.[27] The study included two cases of painful crises. A combination of local or regional blocks, patient-controlled intravenous or epidural analgesia, nurse-controlled analgesia, and oral and intravenous drugs are recommended for pain crisis, as a multimodal management option.[28] Urinary tract infection is said to be the commonest infection in SCD. The present study had 6.45% of UTI. Kavitha et al. reported 47.05% cases of UTI.[22] The present study reported 4 (12.50%) maternal deaths, of which 2 cases were diagnosed with hemolytic crisis, 1 with cerebral infract, and the remaining one had atonic PPH. Girish et al. reported 5% maternal mortality.[18]

Fetal concerns in SCD are consequences of uteroplacental insufficiency, alloimmunization, and opioid exposure. The average birth weight was 2192 gm. About 62.5% babies were LBW. The majority of studies have reported similar higher rates of LBW.[3,16,17,22,26,29]

Kavitha et al. reported 50% cases with IUGR, which is in contrast to this study, where only 6.45% cases were reported to have IUGR.[22] Perinatal mortality documented was 9.67%, which is also lower as compared with other studies.[17,26]

Another complication seen in newborns of SCD-affected mothers is neonatal aspiration syndrome (NAS). When mothers have been exposed to opioids, newborns are at risk of NAS. Lower rates of NAS have been noted with intermittent opioid exposure.[30] In recent COVID times, our hospital has not come across a single case of SCD infected with COVID-19. There is a known adverse impact of both sickle cell disease (SCD) and COVID-19 on pregnancy.[31]

## Conclusion

There is definitely a higher risk of fetal and maternal complications in mothers with SCD, there for antenatal booking at a multidisciplinary hospital from the first trimester itself and awareness regarding genetic counseling for SCD is a must in the prevalent area to reduce the SCD burden on maternal mortality and morbidity.

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