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Original Article

Pregnancy Outcome in Women with Sickle Cell Hemoglobinopathy and Normal Hemoglobin – A Case–Control Study

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Abstract

Introduction: Pregnancy in sickle cell disease (SCD) is associated with an increased risk of maternal and fetal morbidity and mortality.

Objective: The objective of this study was to study the maternal and perinatal outcome of pregnancy in women with SCD/trait.

Methods: This is a comparative study. Study group (subjects) consisted of 128 pregnant women with SCD/sickle cell trait who were attending the antenatal clinic or were admitted in obstetric wards and followed up until the 7th day after delivery. The control group consisted of 256 age and gravidity matched pregnant women who did not have SCD/trait recruited from the same hospital.

Results: Statistically significant complications during pregnancy included anemia, crisis, and preeclampsia. Incidence of preterm deliveries, cesarean section, adverse fetal outcome in terms of stillbirths intrauterine deaths early neonatal deaths, and low birth weight was not significantly higher in the study group than in the control group.

Conclusion: Incidence of preeclampsia (P = 0.0001) and congestive cardiac failure (P = 0.0001) was significantly high among the women with SCD.

Key words: Pregnancy outcome, Sickle cell disease, Sickle cell hemoglobinopathy, Sickle cell trait

INTRODUCTION

Pregnancy in women with sickle cell disease (SCD) is associated with increased adverse outcomes. Findings on the association between SCD and adverse pregnancy outcomes are conflicting, and the results do not address whether these associations are similar in both low- and high-income countries. World population report (1975) gives the incidence of anemia to be 100% among pregnant women in India.[1] Although it has declined over a period of time, it still persists at a higher level when compared to that in other countries. Sickle cell hemoglobinopathy and G6PD deficiency are additional factors that lead to or aggravate anemia during pregnancy. Both maternal and fetal risks are increased when women with SCD become pregnant. Sickle cell trait is also potentially dangerous in the presence of certain disease states, and in healthy persons under certain circumstances that lead to anoxia, dehydration, or physical stress. Advances in health care, technology, meticulous care, and coupled with close hematological consultation, have resulted in a major reduction in maternal mortality in women with SCD, but benefits to the fetus have been less striking. After preeclampsia, postpartum hemorrhage, and sickle cell anemia will surely attain an important position in maternal deaths in the next decade.[2]

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Aims and Objectives

This study was undertaken to assess the pregnancy outcome, complications related to pregnancy, mode of delivery, and perinatal outcome in women with SCD and trait and compare them with pregnancy outcome in non-SCD women.

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METHODS

This comparative study was carried out at a tertiary care hospital, at NKP Salve Institute of Medical Sciences, Nagpur, for 2 years from January 1, 2014, to December 31, 2015, after obtaining approval from the college ethical committee.

The study subjects were selected from the obstetric wards and antenatal clinics. Those antenatal women, who were diagnosed as having SCD or trait during antenatal visits or during routine health care or in the previous pregnancy or the early first trimester, were included in the study. Two controls were selected for each subject by matching age and gravidity of antenatal women.

A total of 42 women with SCD, 86 with sickle cell trait and 256 controls were recruited in their first trimester (i.e., first 12 weeks of pregnancy). Basic data, including socioeconomic status, caste, religion along with thorough obstetric history, any significant medical history and family history of SCD/trait, blood transfusions, and crisis, were recorded. Detailed clinical examination and blood and urine tests were carried out at the time of registration. These women were followed up in antenatal clinic and obstetric wards until 7th day after delivery for follow-up with regard to any complications, mode of delivery, and fetal outcome (age of gestation at birth, birth weight, and live birth/stillbirth) were analyzed and $P < 0.05$ was considered significant.

RESULTS

The mean hemoglobin level in the SS (homozygous sickling) group (7.425 ± 1.455 g/dL) was significantly lower as compared to that in the AS (heterozygous sickling) group (8.68 ± 1.0164 g/dL) and to that in the AA (nonsickling) group (9.243 ± 0.7112 g/dL). Furthermore, the mean hemoglobin level in the AS group was significantly lower than that in the AA group [Table 1].

As shown in Table 2, maternal complications were much more in women with SCD than women with normal hemoglobin. The risk of preterm labor was significantly associated with sickle cell trait, and the risk was twice in SCD as compared to thrice in sickle cell trait. Furthermore, the risk of congestive cardiac failure increases to 42 times that of preeclampsia increased 6 times and that of urinary tract infection twice in SCD as compared to normal subjects.

As shown in Table 3, LSCS may be a protective factor for AS patients as compared to normal subjects, their risk was significantly reduced (by 64%). On the other hand, though non-significant, the risk increased by 7% in SS patients.

As shown in Table 4, though non-significant, risk of intrauterine death and early neonatal death was 5 times higher and that of stillbirth 10 times high. Furthermore, a significant association was found with low birth weight (LBW) babies. The risk of LBW increases to 6 times in patients with SCD and twice that in sickle cell trait. Statistically significant number of babies with weight between 1501 g and 2000 g in SS and AS groups.

DISCUSSION

SCD is an important hereditary hemoglobinopathy, a disease characterized by the production of defective hemoglobin S (HbS).[1] Sickle cell Hb is produced by substitution of Valine by glutamic acid at position six of the β chain of the normal Hb. Gene mutation – when homozygous, the individual has sickle cell anemia (Hb SS); when heterozygous, the individual has sickle cell trait (Hb AS).[2] The abnormal HbS tends to polymerize on deoxygenation, and red blood cell containing HbS becomes less pliable and consequently deform into the sickle shape. SCD is a multisystem disorder, and the risk of sickle cell anemia during pregnancy includes an increase in preeclampsia, preterm birth and small-for-gestational-age infants, chronic hemolysis, postpartum hemorrhage, repeated infections, and growth retardation in addition to an acute life-threatening complication called crisis. Pain from ischemic necrosis of bone marrow or other organs usually becomes more frequent. Pulmonary

Table 1: Hemoglobin levels in GM/DL in SS/AS/AA groups

Hb (%)	SS (*n*=42)	Percentage	AS (*n*=86)	Percentage	AA (*n*=256)	Percentage
8.1–10 g	6	14.28	22	25.58	206	80.46
6.1–8 g	30	71.42	47	54.65	44	17.18
<6 g	6	14.28	17	19.76	6	2.34

Hb	Comparisons					
	SS versus AA			AS versus AA		
	OR	95% CI	*P*	OR	95% CI	*P*
≤8 g% versus>8 g	24.72	9.49–74.68	0.001	11.99	6.52–22.30	0.001

AS versus AA OR=11.98, 95% CI 6.52–22.30, *P*=0.0001. SS versus AA (Hb>8 vs. ≤8) OR=24.72, 95% CI 9.49–74.68, *P*=0.0001 (risk of SCD is almost 25 times more among subjects with Hb≤8 g% as compared to those with>8 g%. Hb: Hemoglobin

Table 2: The maternal complications during pregnancy and postpartum in SS, AS, and AA group

Variables	Complications risk comparisons					
	SS versus AA			AS versus AA		
	OR	95% CI	*P*	OR	95% CI	*P*
Hemoglobin						
Hb ≤8 g%	24.72	9.49–74.68	0.001	11.99	6.52–22.30	0.001
Hb >8 g%						
Miscarriage						
Yes	1.82	0.41–8.20	0.3066	0.84	0.20–2.79	0.7689
No						
Preterm labor						
Yes	2.14	0.48–7.52	0.1975	3.3	1.29–8.37	0.0036
No						
Congestive cardiac failure						
Yes	42.5	4.84–1961.6	0.0001	6.07	0.31–359.5	0.0959
No						
ARDS						
Yes	0	NA	0.0005	0	NA	NA
No						
UTI						
Yes	1.82	0.41–6.20	0.3066	2.8	1.13–6.83	0.0102
No						
Preeclampsia/eclampsia						
Yes	6.11	2.74–13.34	0.0001	1.45	0.65–3.09	0.302
No						
PPH/DIC						
Yes	3.39	0.7–10.46	0.0155	0.48	0.05–2.25	0.3389
No						
Pulmonary embolism						
Yes	0	NA	0.0005	0	NA	NA
No						
AVN femur						
Yes	0	NA	0.0134	0	NA	NA
No						
Maternal death						
Yes	0	NA	0.0005	0	NA	NA
No						
Crisis						
Yes	0	NA	0.0001	0	NA	0.0144
No						

Table 3: The mode of delivery in SS, AS, and AA group. Mode of delivery (excluding miscarriages)

Normal	SS versus AA			AS versus AA		
Yes	0.81	0.38–1.81	0.5737	83.96	35.88–200.0	0.0001
No						
Instrumental						
Yes	2.63	0.24–16.76	0.2406	0.66	0.12–2.44	0.5139
No						
LSCS						
Yes	1.07	0.46–2.34	0.8601	0.36	0.16–0.73	0.0028
No						

complications are also common. Risks of maternal mortality are increased. Fetal wastage is also common and more than one-third of pregnancies in a woman with sickle cell syndrome terminate in abortion, stillbirth, or early neonatal death.[3] LBW babies were born to SS mothers due to premature deliveries and fetal growth retardation.[4] Perinatal mortality is also very high.[4]

Among the complications during pregnancy, crisis was more significantly associated with the SS group as compared to that in the AS group (*P* value of SS-0.001; AS-0.014). Crisis as a complication during pregnancy is reported to be 48.6% by Dare *et al*.,[3] 56% by El-Shafei *et al*.,[4] 28% by Chhabra *et al*.,[5] 88% Leborgne-Samuel *et al*.,[6] and 41.4% by Odum *et al*.[7]

Table 4: Perinatal outcome in SS, AS, and AA group (As there were four miscarriages, the data are different)

Live birth						
Yes	0.14	0.03–0.55	0.0002	0.67	0.14–4.24	0.5744
No						
IUD						
Yes	4.97	0.69–30.47	0.0246	1.45	0.13–10.32	0.6696
No						
Stillbirth						
Yes	10.29	1.12–125.29	0.0022	1.48	0.25–28.77	0.7481
No						
Early neonatal death						
Yes	4.63	0.91–20.51	0.013	0.98	0.09–5.64	0.9838
No						
Low birth weight						
<2500 g	6.12	2.74–13.53	0.0001	2,24	1.15–4.82	0.0082
≥2500 g						
Birth weight						
<1500 g						
Yes	2.5	0.75–7.26	0.0649	0.73	0.17–2.36	0.5846
No						
1501–2000 g						
Yes	12.4	4.21–37.47	0.0001	5.03	1.80–14.66	0.0002
No						
2001–2500 g						
Yes	0.6	0.01–4.43	0.627	1.84	0.53–5.80	0.2434
No						
>2500 g						
Yes	0.19	0.09–40.33	0.0001	0.44	0.23–0.86	0.0077
No						

Preeclampsia was more in the SS group as compared to that in the AA group (42.85% vs. 15.11%, $P = 0.0001$). Preeclampsia among women with SCD was observed to be 2.4% by Idrisa *et al*.,[8] 16.2% by Dare *et al*.,[3] and 12.62% by Deshmukh *et al*.[9]

The risk of hemoglobin level <8 g/dL was significantly more, i.e., is 25 times more in the SS group ($P = 0.001$) and 12 times in the AS group (0.001) as compared to AA group.

The incidence of preterm labor was twice in SCD when compared to the control group. In women with SCD, preterm deliveries are reported to be 21.6% by Dare *et al*.,[3] 20% by Chhabra *et al*.,[5] 23% by Howard *et al*.,[10] and 21% by Leborgne-Samuel *et al*.[6]

Majority of cesarean sections in all the three groups were due to fetal distress, followed by CPD in our study, cesarean section was required in 12 of 38 (31.57%) in the SS group, 11 of 82 (13.41%) in the AS group, and 73 of 242 (30.16%) in the AA group. The cesarean section rate is reported to be 14.6% by Idrisa *et al*.,[8] 29.7% by Dare *et al*.,[3] 12% by El-Shafei *et al*.,[4] 66.66% by Howard *et al*.,[10] 48% by Leborgne-Samuel *et al*.,[6] and 43.2% by Odum *et al*.[7]

Dare *et al*.[3] reported that among the 29.7% cesarean sections, indications for cesarean section were CPD in 45.5%, fetal distress associated with intrauterine growth restriction in 18.1%, and transverse lie, severe preeclampsia with failed induction of labor and placenta previa in 9% each. Indications reported by El-Shafei *et al*.[4] were fetal distress in 67%, CPD in 10%, previous cesarean section in 10%, and miscellaneous in 13% (overall incidence 12%).

When compared to the control group, there was a higher risk of adverse fetal outcomes. Seven *et al*.[11] reported that there was no significant difference in pregnancy outcome among SCD and the control group in terms of perinatal mortality.

There were two maternal deaths in our study among the SS group (4.76% $P = 0.0005$) due to the consequences of severe anemia, following crisis and one had acute respiratory distress syndrome. There was no maternal death among the AS group and control (AA) group.

Thus, the risk of congestive cardiac failure is alarmingly high, i.e., 42 times more risk in ($P = 0.0001$) women with SCD. A high incidence of LBW babies was due to fetal hypoxia throughout the pregnancy caused by anemia and fetoplacental insufficiency.

Specialized antenatal care provided by a multidisciplinary team and should include (according to RCOG)[12]

- Folic acid administration 5 mg once daily preconceptionally and throughout the pregnancy
- Medical review by hematologist and screening of end-organ damage
- Avoid precipitating factors for crisis such as dehydration, exposure to extreme temperatures
- Thromboprophylaxis by LMW heparin and aspirin prophylaxis as recommended by RCOG and NICE guidelines
- Blood pressure and urine analysis at each visit
- Fetal growth monitoring by regular scans at every 4 weeks
- Top-up transfusion indicated for women with acute anemia, i.e., Hb under 6 g/dl or a fall of over 2 g/dl
- Exchange transfusion for acute chest syndrome is indicated with early recognition and antibiotic administration being the key for management
- Painful crisis the most frequent complication of SCD should be managed by strict monitoring of vitals, analgesia in form of opioids, and thromboprophylaxis
- Post-delivery care and vigilance for the prevention of complications.

Education and counseling of women with SCD and their partners contemplating pregnancy and during pregnancy

are needed alongside a comprehensive screening of SCD. Guidelines are needed for all health-care professionals. For a multidisciplinary approach, referral centers should be well equipped with supplies of blood, ventilators, ability to screen, and treat complications with all intensive care facilities.

CONCLUSION

Incidence of preeclampsia ($P = 0.0001$) and congestive cardiac failure ($P = 0.0001$) was significantly high among women with SCD.

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