ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 05 | May - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

STUDY OF CARDIAC DYSFUNCTIONS IN PREGNANT WOMEN WITH SICKLE CELL ANEMIA - A COMPARATIVE PROSPECTIVE COHORT STUDY

Obstetrics & Gynaecology

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ABSTRACT

Background: Sickle cell disease (SCD) is a haemoglobinopathy (haemolysis of red blood cells) typically inherited in an autosomal recessive pattern and results in repeated vaso-occlusive crises that severely affect multiple organs.1 The most common type of SCD is sickle cell anaemia (SCA). In female patients, the underlying anaemia, non-inflammatory vasculopathy and multi-organ dysfunction, including cardiomyopathy and pulmonary arterial hypertension (PAH), complicate pregnancy and delivery, contributing to high morbidity and mortality for both mother and fetus. **Methods:** A comparative prospective cohort study conducted in the year of 2021 (12 months) among 165 Pregnant women with sickle cell anemia as case group, 165 Pregnant women without sickle cell anemia as control group, was carried out in patients attending ANC Out patient department, Emergency ward, in Department of Obstetrics and Gynaecology, in a tertiary care hospital. **Results:** In our study, Prevalence of cardiac dysfunction was more in pregnant women with sickle cell disease compared to control group. There was significant difference between case and control group in terms of prevalence of cardiac dysfunction. We found that cardiac dysfunction was more prevalent in Homozygous(SS) pattern patients compared to Heterozygous (AS) pattern patients. Pulmonary arterial hypertension was main complication of sickle cell anemia. Prevalence of pulmonary arterial hypertension and tricuspid regurgitation was statistically significant between homozygous and heterozygous pattern patients, More prevalence was seen in homozygous(SS) pattern patients. Prevalence of other cardiac dysfunction is high in homozygous pattern patients compared to heterozygous pattern. Echocardiography using the latest sophisticated ultrasound techniques is a useful and irreplaceable non-invasive technique to study the changes in cardiac structure and function in Sickle cell disease patients. Pulmonary Hypertension is an increasingly recognized complication of Sickle cell disease, directly affecting survival. Thus, prompt diagnosis using echocardiography is essential. **Conclusion:** Pulmonary Hypertension is an increasingly recognized complication of Sickle cell disease, directly affecting survival. Thus, prompt diagnosis using echocardiography is essential. Treatment strategies that include transfusions, exchange transfusions which reduces both haemolysis and sickling, and novel agents that target the biology of vasculopathy may prevent the heart complications of SCD patients in the near future, leading to an increased survival for our SCD patients.

KEYWORDS

Sickle cell disease, Heterozygous and homozygous pattern, Pulmonary arterial hypertension, Cardiomyopathy

INTRODUCTION

Sickle cell disease (SCD) is a haemoglobinopathy (haemolysis of red blood cells) typically inherited in an autosomal recessive pattern and results in repeated vaso-occlusive crises that severely affect multiple organs.[1] The most common type of SCD is sickle cell anaemia (SCA). In female patients, the underlying anaemia, noninflammatory vasculopathy and multi-organ dysfunction, including cardiomyopathy and pulmonary arterial hypertension (PAH), complicate pregnancy and delivery, contributing to high morbidity and mortality for both mother and fetus. Pregnancy-related physiological changes increase the clinical risk in SCD women. These patients are at greater risk of gestational hypertension and preeclampsia, eclampsia, abruption, antepartum bleeding, preterm labour and fetal growth restriction. Consequently, close medical care and treatment is essential in such patients.[2]

Pregnancy was contraindicated for SCD patients in the past, but recent advances in the diagnosis and treatment of disease complications during pregnancy have been associated with more favourable outcomes and an increase in the number of women proceeding with pregnancy.[3]

PAH is a main cause of death in SCD patients, having a prevalence of 20–40% and a high 2-year mortality rate. Therefore, all SCD patients, especially pregnant women, should be screened regularly with transthoracic Doppler echocardiography to estimate pulmonary artery pressures and cardiac output.[7] Heart failure caused by PAH should also be considered in pregnant patients.[3] PAH is directly associated with chronic haemolytic anaemia. Haemolysis and the consequent release of haemoglobin from RBCs increases the consumption of nitric oxide (NO) and the released arginase reduces the production of NO. Nitric oxide is a potent vasodilator and a critical regulator of vascular homeostasis. Its reduction is thus associated with vasoconstriction and proliferative vasculopathy that results in PAH.[7,8] Moreover, recurrent episodes of acute chest syndrome that typically occur in 40% of patients and cause restrictive chronic lung disease, are another possible cause of PAH. PAH may remain undetected until the disease is advanced.[9]

Patients with SCD have a unique form of cardiomyopathy with restrictive physiology and is characterized by diastolic dysfunction, left atrial dilation, and normal systolic function. This combination results in mild, secondary, pulmonary venous hypertension and elevated Tricuspid Regurgitant Velocity (TRV). Sudden death is common in other forms of restrictive cardiomyopathy. These finding of this unique restrictive cardiomyopathy may explain the increased mortality rates. and sudden death seen in patients with SCD with mildly elevated TRV.In Pregnancy, physiological changes increase the above mentioned clinical risks in SCD women.

AIM

Sickle cell anemia in pregnancy is associated with multiple cardiac dysfunctions as mentioned above so aim of our study is to evaluate the cardiac dysfunctions early in the pregnancy by 2D echocardiography in order to reduce cardiac complications.

OBJECTIVES

Objectives of the study were : to compare the cardiac dysfunctions associated with sickle cell anemia in pregnancy vs matched pregnant women without sickle cell anemia.

Other objectives were:

1) To determine the prevalence of cardiac dysfunction associated with sickle cell anemia in pregnancy.
2) To determine the number of patients requiring intensive care due to cardiac dysfunctions associated with sickle cell anemia in pregnancy.
3) To emphasize the role of routine 2D Echocardiography in pregnant women with Sickle cell anemia.
4) To emphasize the role of intensive intrapartum cardiac monitoring in pregnant women with sickle cell anemia.

METHODS

This is a comparative prospective cohort study conducted in the year of 2021 (12 months) among 165 Pregnant women with sickle cell anemia as case group, 165 Pregnant women without sickle cell anemia as control group, was carried out in patients attending ANC Out patient department, Emergency ward, in Department of Obstetrics and Gynaecology, Government medical college, Nagpur. Protocol writing and permission from ethics committee was obtained.

Inclusion Criteria

Patient willing to participate in study and providing the consent for the study. Pregnant woman with sickle cell disease (HbSS, Heterozygous, or HbSC diagnosed by hemoglobin electrophoresis)

Exclusion Criteria

Pregnant women with Congenital Heart Disease , Rheumatic heart disease , Evidence of pre existing cardio vascular disease, Cardiac failure due to some other cause , Chronic hypertension , Diabetes mellitus , Other hemolytic anemias and patients not willing for study.

METHODOLOGY

This was a comparative prospective cohort study .The study was commenced after obtaining approval from ethics committee. The study was performed on patients admitted in the Department of Obstetrics and Gynaecology in Government Medical College and Hospital Nagpur. Both case and control groups are matched with respect to demographic variables.

Case group includes pregnant women with sickle cell disease. Control group includes pregnant women without sickle cell disease. Patients fulfilling inclusion criteria were studied. Informed consent was taken. Sickle cell disease was confirmed by Hb electrophoresis. These patients were subjected to detailed clinical examination. All important investigations like Electrocardiogram and 2D Echocardiography were performed. Inclusion and Exclusion criterias were assessed. Both groups were subjected to investigations and cardiac dysfunctions were noted. Cardiac dysfunctions in both the groups were compared. Also maternal, fetal outcomes and number of patients requiring Intensive care unit management were noted.

RESULTS

Statistical Analysis

Data was coded and analysed with the statistical software, SPSS version 19.0

Descriptive statistics included summary measures like Mean, Standard Deviation for quantitative variables like Age and Birth Weight. Frequency and percentages will be derived to summarize qualitative variables like Booking Status, Residence, cardiac dysfunctions. All the information will be shown in tables and relevant charts.

Decision Rule: "P value <0.05 was considered significant". I.e. if here we had considered 95% confidence interval with 5% level of significance and we rejected our Null hypothesis if the P value < 0.05 otherwise we accepted.

Null hypothesis Ho: There is no significant difference between two groups.

Table No 1 : Distribution Of Case Group According To Sickle Cell Pattern.

Sickle cell pattern	No. of Cases	Percentage
SS	57	34.55
AS	108	65.45

Table No 2: Distribution Of Case Group According To Condition Of Patients (cases) At The Time Of Admission.

	Symptomatic (15)		Asymtomatic (150)		p-value
	No. of Cases	%	No. of Cases	%	
SS	15	100	42	28	<0.0001,Highly Significant.
AS	0	0	108	72	

Among 165 cases, 108 patients (65.45%) were Heterozygous(AS) and 57(34.55%) patients belonged to Homozygous(SS) pattern. In our study, prevalence of heterozygous pattern is more compared to homozygous pattern.

Among 165 patients, 15 patients were symptomatic. All symptomatic patients belong Homozygous(SS) pattern. All heterozygous(AS) patients(108) were asymptomatic. There is significant difference between heterozygous and homozygous patients in terms of condition of patients at the time of admission.

In our study, Prevalence of cardiac dysfunction is more in pregnant women with sickle cell disease compared to control group. Among 165 case group, 41 patients were presented with cardiac dysfunction. Among control group, 4 patients were presented with cardiac dysfunction. There is significant difference between case and control group in terms of prevalence of cardiac dysfunction(Table 3).

We found that cardiac dysfunction is more prevalent in Homozygous (SS) patients compared to Heterozygous (AS) patients. Among 57 homozygous patients, 28(49.12%) patients had cardiac dysfunction whereas among 108 heterozygous patients, 13(12.04%) patients had cardiac dysfunction. There is significant difference between Homozygous and heterozygous patients in terms of prevalence of cardiac dysfunction(Table 4).

Pulmonary arterial hypertension is main complication of sickle cell anemia.

In our study, we found that 41 patients of case group had cardiac dysfunction. Among them 17(41.46%) patients presented with pulmonary arterial hypertension, 28(68.29%) patients presented with tricuspid regurgitation,

4(10.6%) patients presented with left atrial and ventricular dysfunction, 2 (4.88%) patients with cardiomyopathy and one(2.6%) with type 1 bundle branch block with concentric left ventricular hypertrophy. Among control group , 4 patients had cardiac dysfunction. All 4 patients had tricuspid regurgitation (100%). Prevalence of cardiac dysfunction in case group is high compared to control group but difference was not statistically significant in terms of types of cardiac dysfunction between case and control group(Table 5). Prevalence of pulmonary arterial hypertension and tricuspid regurgitation was statistically significant between homozygous and heterozygous patients, More prevalence was seen in homozygous(SS) patients. Prevalence of other cardiac dysfunction is high in homozygous pattern patients compared to heterozygous , but difference was not statistically significant(Table 6).

Table No.3 Association Of Cardiac Dysfunction Between Case And Control Group.

Cardiac Dysfunction	Cases		Control		p-value
	No. of Cases	%	No. of Cases	%	
YES	41	24.85	4	2.42	<0.0001,Highly Significant
NO	124	75.15	161	97.58	

Table No.4 : Association Of Cardiac Dysfunction With Sickle Cell Pattern(Heterozygous And Homozygous Pattern).

Sickle cell pattern	No. of Cases	cardiac dysfunction				p-value
		YES		NO		
		No. of Cases	%	No. of Cases	%	
SS	57	28	49.12	29	50.88	<0.0001,Highly Significant.
SA	108	13	12.04	95	87.96	

Table No. 5 : Distribution Of Study Population Based On Types Of Cardiac Dysfunction Between Case And Control Groups.

cardiac dysfunction	No. of Cases					p-value
		Cases (N=41)		Control (N=4)		
		No. of Cases	%	No. of Cases	%	
PAH (Pulmonary arterial hypertension)	17	17	41.46	0	--	0.286,Not Significant
TR(Tricuspid regurgitation)	32	28	68.29	4	100	0.308,Not significant
Left ventricular and left atrial dysfunction	4	4	9.76	0	--	1.000,Not significant

Type 1 bundle branch block with concentric LVH(Left ventricular hypertrophy)	1	1	2.44	0	--	1.000,Not significant
Peripartum cardiomyopathy	2	2	4.88	0	--	1.000,Not significant

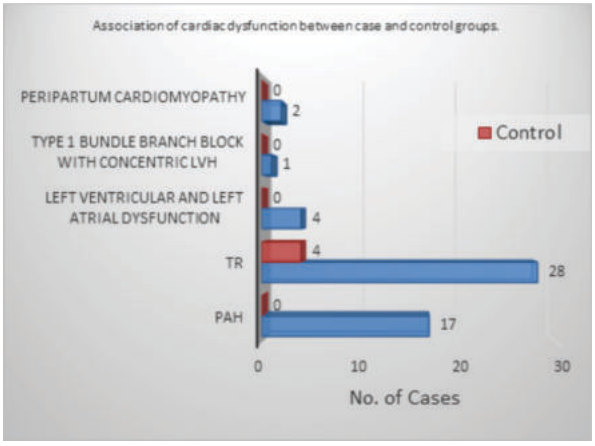

Table No. 6 :distribution Of Types Of Cardiac Dysfunctions With Sickle Cell Pattern (Homozygous And Heterozygous Pattern).

cardiac dysfunction	No. of Cases	cardiac dysfunction				p-value
		SS (N=57)		AS (N=108)		
		No. of Cases	%	No. of Cases	%	
PAH	17	15	26.32	2	1.85	<0.0001,Highly Significant
TR	28	18	31.58	10	9.26	0.001,Highly Significant
Left ventricular and left atrial dysfunction	4	3	5.26	1	0.93	0.119,Not Significant
Type 1 bundle branch block with concentric LVH	1	1	1.75	0	--	0.345,Not Significant
Peripartum cardiomyopathy	2	2	3.51	0	--	0.118,Not Significant

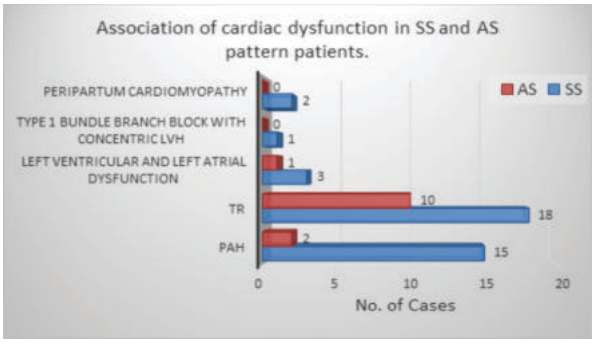

Table No.7: Distribution Showing Number Of Patients Requiring Icu Admission Due To Cardiac Dysfunction Associated With Sickle Cell Anemia In Pregnancy.

ICU admission	No. of Cases	Cases	Control	p-value
YES	18	18(10.91)	0	<0.0001,Highly Significant
NO	147	147(89.09)	165(100)	

11% of cases required ICU management with intrapartum cardiac monitoring due to cardiac dysfunction which is statistically significant.

Table No.8 : Distribution Showing Number Of Patients Requiring Intensive Cardiac Monitoring.

Intensive cardiac monitoring	No. of Cases	Cases	Control	p-value
YES	18	18(10.91)	0	<0.0001,Highly Significant
NO	147	147(89.09)	165(100)	

11% of cases required ICU management with intrapartum cardiac monitoring which is statistically significant.

DISCUSSION

A comparative prospective study performed in tertiary care centre in pregnant women having sickle cell disease attending antenatal clinics in department of Obstetrics and Gynaecology with study population of 165 women in the age group of 15 to 45 years having sickle cell disease, willing to participate in the study and ready to follow the instructions, were included in the study. Total 165 women were included in each group, group A included 165 pregnant women with sickle cell disease (Heterozygous/Homozygous) and Group B included 165 pregnant women without sickle cell disease. We have analysed the results of our studies and compared with a prospective study – cardiac dysfunctions in heterozygous(AS) and homozygous (SS) pattern women with other studies.

It was found in this study that complication rate is higher in the Homozygous (HbSS) pregnant women compared to Heterozygous (HbSA) women. Pulmonary arterial hypertension is main complication of sickle cell anemia.

Cardiac Dysfunctions In Our Study Is Compared With Other Studies.

- In our study, 41.46% of patients with cardiac dysfunctions presented with Pulmonary arterial hypertension .

Prevalence of pulmonary arterial hypertension is compared with following studies.

- William H Marshall, Stephen Gee conducted study at The Ohio state University Wexner Med Centre, Columbus found 6-11% prevalence of PAH in their study.[12]
- Study conducted by Minoodokht Bavarsad Karimi, Iran university of medical sciences, Tehran , Iran , found 20-40% prevalence of pulmonary arterial hypertension .[13]
- Study conducted by Kevin G Lazo, Department of Medicine, Long Island Jewish Medical Center, USA, found prevalence of pulmonary hypertension in sickle cell disease adults ranges from 6-11%.[11]
- Study conducted by Amit R Patel, MD, Assistant professor medicine, section of cardiology, Department of Medicine

Chicago, found 30-40% prevalence of PAH.[10]

- In our study, 9.76% of patients with cardiac dysfunctions presented with left atrial and left ventricular dysfunction and cardiomyopathy in 4.88%. While Omar Niss, Charles T Quinn, Adom Lane, conducted study of cardiomyopathy with restrictive physiology in sickle cell disease at Division of hematology, Cincinnati Children's Hospital Medical Centre, Cincinnati, Ohio, found 8-14% prevalence in their study.[14]

- In our study, 2.44% of patients with cardiac dysfunctions presented with type 1 bundle branch block with concentric LVH. Liem et al[15], conducted study on dysrhythmia in SCD patients. They found 38% prevalence of QT prolongation in sickle cell disease patients.[15]

- Maisel et al[16] studied 30 SCD patients with 24 hour electro-cardiographic monitoring during acute crisis and found significant arrhythmias in 80% of patients with over half the patients having ventricular arrhythmias. A subgroup of these patients underwent gated nuclear studies and there was a trend towards more arrhythmias in patients with ventricular dysfunction. Further evaluation of electrocardiographic findings and arrhythmias is needed in order to identify SCD patients at higher risk for sudden cardiac death.[16]

In our study, we did not find any case of arrhythmia patients.

As our institute is tertiary care centre, located in central part of India where prevalence of SCD is more(40%), we observed increased incidence of cardiac dysfunction in SCD pregnant women compared to

other studies.

In our study, we found one maternal death due to stroke secondary to severe pulmonary hypertension. Margaret S Villers , Margaret G Jamison, Laura M De Castro, Andra H James et al[17] conducted Study of Morbidity associated with sickle cell disease in Pregnancy. There were 17,952 deliveries (0.1% of the total) to women with SCD. There were 10 deaths (72.4 per 100,000 deliveries). Cerebral vein thrombosis, pneumonia, pyelonephritis, deep venous thrombosis, transfusion, postpartum infection, sepsis, and systemic inflammatory response syndrome were much more common among women with SCD. They were more likely to undergo cesarean delivery, to experience pregnancy-related complications (such as gestational hypertension/preeclampsia, eclampsia, abruption, antepartum bleeding, preterm labor, and fetal growth restriction), and to have cardiomyopathy or pulmonary hypertension at the time of delivery. Thus they concluded that women with sickle cell disease are at greater risk for morbidity in pregnancy than previously estimated.

Despite the increased complication rates reported among HbSS pregnant women compared to their HbAA counterpart as reported in this study, the overall maternal and early perinatal outcomes were comparable. Despite the increased risk of complications in Homozygous pregnant women reported generally in most studies, Sun PM et al[18] in a study also found no significant difference in perinatal outcome of Homozygous(HbSS) compared to HbAA individual and there was no maternal death reported in the study.[18] However, it is important to be vigilant at all times while managing Homozygous pregnant women as complications can arise at anytime. Preconception care[19] should be emphasized for this category of women (Homozygous pregnant women) and multidisciplinary approach and prompt intervention are highly recommended to minimize perinatal and maternal deaths.

CONCLUSION

We conclude that SCD patients have several problems with their heart function and heart vessels. The combination of moderate-to-severe anaemia and the resultant volume load produces increased cardiac output at rest. Left ventricular mass is increased secondary to compensatory hypertrophy that occurs in response to ventricular dilation, and the severity of dilation correlates with increasing degree of anaemia. Myocardial contractility seems to be negatively affected although the data are conflicting. These differences may be due to genetic variations or polymorphisms. Diastolic dysfunction presents at an early age, even among individuals with low NYHA classes. Echocardiography using the latest sophisticated ultrasound techniques is a useful and irreplaceable non-invasive technique to study the changes in cardiac structure and function in Sickle cell disease patients.

Finally, Pulmonary Hypertension is an increasingly recognized complication of Sickle cell disease, directly affecting survival. Thus, prompt diagnosis using echocardiography is essential. Treatment strategies that include transfusions, exchange transfusions which reduces both haemolysis and sickling, and novel agents that target the biology of vasculopathy may prevent the heart complications of SCD patients in the near future, leading to an increased survival for our SCD patients.

Comprehensive care may promote awareness of Sickle Cell Disease among affected women to present early for booking, assessment and management of symptoms.

It is hoped that the results of this study will contribute to the existing knowledge about Sickle Cell Anaemia in pregnancy and help to strengthen the monitoring, management and follow up of this group of patients.

Acknowledgments

Authors would like to thank participants to share their perceptions. They would also like to thank the staff of department of obstetrics and gynaecology to extend their support in conducting the study.

Conflict Of Interest

There is no conflict of interest in this study.

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