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Impact of Hemoglobinopathies on Fetomaternal Outcome: An Outcome Assessment Study

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Abstract
Hemoglobinopathies encompass a diverse group of inherited disorders affecting hemoglobin production and function, constituting the most prevalent single-gene disorders in humans with varying global frequencies. Pregnancy in women with sickle cell disease can elevate the risks of maternal and perinatal mortality. High-Performance Liquid Chromatography (HPLC) offers advantages over routine Hemoglobin electrophoresis by accurately identifying and quantifying abnormal hemoglobin variants, thus serving as a reliable tool for early detection and management of thalassemia and abnormal hemoglobin variants. This observational study was conducted on pregnant women attending an Indian medical college and hospital during various gestational months. All pregnant women were counselled and offered screening for hemoglobinopathies following informed consent. Among antenatal women with hemoglobinopathy, more than 90% were anemic, while the rest were not anemic. In the normal group, more than 70% were anemic and rest were not anemic, demonstrating a significantly higher prevalence of anemia among hemoglobinopathy cases. Specifically, more than 90% of antenatal women with sickle cell disorder were anemic. Out of total women with hemoglobinopathy, 93.75% were anemic. Most hemoglobinopathy cases (about 77%) attended antenatal check-ups after 28 weeks of gestation. In contrast, about 65% of the normal group attended antenatal check-ups after 28 weeks. Hemoglobinopathies significantly impact pregnancy, leading to maternal morbidities such as pre-eclampsia, preterm labor, urinary tract infection, asymptomatic bacteriuria, antepartum hemorrhage and neonatal morbidities including low birth weight, fetal growth restriction, neonatal intensive care unit (SNCU) admission rates and neonatal mortality.

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Key Words
Antenatal screening, fetomaternal outcome, hemoglobinopathies, HPLC

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INTRODUCTION

Hemoglobinopathies encompass a diverse range of inherited disorders affecting hemoglobin production and function. They represent the most prevalent single-gene disorders observed in humans and exhibit varying frequencies worldwide. These hereditary hemoglobin disorders can be classified into two primary groups: structural hemoglobin variants resulting from single amino acid substitutions in the alpha or beta chains and thalassemia characterized by imbalanced hemoglobin chain production[1-3].

The World Health Organization (WHO) estimates that about 5% of the global population carries inherited hemoglobin disorders. Annually, over 9 million carriers become pregnant, leading to approximately 332,000 affected conceptions or births worldwide, with a significant majority occurring in low- and middle-income countries. While historically more common in tropical regions, these disorders are now prevalent globally due to population migrations. In India, the incidence of thalassemia trait and sickle cell disorder ranges from 3-17% and 1-44%, respectively, with certain communities experiencing heightened prevalence due to consanguinity, caste and regional endogamy, presenting a substantial public health concern[4-7].

Complications associated with sickle cell anemia arise from either anemia-related symptoms such as fatigue and breathlessness, or from blood flow obstruction caused by sickle-shaped red blood cells, resulting in pain and ischemic organ damage. The coexistence of HbS with normal adult hemoglobin (HbA) often exhibits few clinical manifestations, rendering sickle cell trait generally benign with rare complications[8-11].

Advancements in hematological care have improved life expectancy and quality of life for women with hemoglobinopathies, leading to an increasing number of these women reaching childbearing age and pursuing pregnancy. Pregnancy-induced physiological changes can exacerbate underlying hemoglobin disorders, potentially raising the risk of obstetric complications. While normal pregnancy induces mild anemia due to increased blood volume, women with hemoglobin disorders may experience more pronounced decreases in hemoglobin levels, leading to hypoxia-related adverse outcomes for both mother and baby[12,13].

Pregnancy in women with sickle cell disease heightens the risks of maternal and perinatal mortality, a concern first outlined in a 1941 report by Kobak *et al.*[14]. However, advancements in sickle cell disease management, along with improved obstetric and perinatal care, have significantly enhanced pregnancy outcomes since 1972, albeit with increased risks of pregnancy-related complications[15]. Women with sickle cell trait or thalassemia trait typically tolerate pregnancy well with minimal complications, while those with HbH disease or ß thalassemia intermedia can successfully carry a pregnancy to term.

High-Performance Liquid Chromatography (HPLC) offers advantages over routine hemoglobin electrophoresis by accurately identifying and quantifying abnormal hemoglobin variants. HPLC serves as a precise, rapid and reproducible tool for early detection and management of thalassemia and abnormal hemoglobin variants, crucial given the high incidence of beta thalassemia trait in the Indian subcontinent[16,17].

MATERIALS AND METHODS

This observational study was conducted on pregnant women attending an Indian medical college and hospital during various gestational months. All pregnant women were counselled and offered screening for hemoglobinopathies following informed consent.

All antenatal mothers attending OPD and labor room regardless of gestational age were included in the study. Patients were excluded from the study if they refused delivery at the institute, declined to provide informed written consent, or had a history of blood transfusion within the preceding month.

For this study, a total of 276 antenatal cases that met the specified inclusion and exclusion criteria were included in the study group. The assessment involved evaluating clinical evidence of anemia and hemolytic facies, conducting a complete blood count, liver function tests (LFT) and assessing the iron profile of the patients. High-performance liquid chromatography (HPLC) was performed for all cases to further analyze the data.

Follow-up procedures were carried out until delivery and continued for six weeks postpartum. Intravenous blood samples of approximately 5ml were collected from the patients using EDTA as an anticoagulant. Various hematological indices, including hemoglobin levels, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and red cell width, were measured and recorded. Additionally, a sickling test was performed using a 2% sodium metabisulphite solution to detect sickled red blood cells.

Chromatography was conducted usingan automated HPLC analyzer to analyze the collected samples. Statistical analysis of the data was performed by tabulating the results, presenting them in tables and charts, comparing outcomes with those of the control group and conducting statistical analyses such as chi-square tests to calculate p-values for the findings.

RESULTS AND DISCUSSIONS

The current investigation observed a slightly higher prevalence of hemoglobinopathy compared to prior research by Panda *et al.*[18] and notably higher

Table 1: Age distribution of study population

	Hemoglobinopathy Cases		Controls		Total		
Age group	**n**	**percentage**	**n**	**percentage**	**n**	**percentage**	**p-value**
<25 years	14	53.85	141	56.40	155	56.16	0.51
25-29 years	9	34.62	70	28.00	79	28.62	
>30 years	3	11.54	39	15.60	42	15.22	
Total	26	100.00	250	100.00	276	100.00	

Table 2: Prevalence of anemia among study population

Age group	Hemoglobinopathy Cases		Controls		Total		
	n	**percentage**	**n**	**percentage**	**n**	**percentage**	**p-value**
Anemic	24	92.31	178	71.20	202	73.19	<0.05
Normal	2	7.69	72	28.80	74	26.81	
Total	26	100.00	250	100.00	276	100.00	

Table 3: Prevalence of anemia among hemoglobinopathy Cases

Age group	Hemoglobinopathy Cases		Controls		Total		
	n	**percentage**	**n**	**percentage**	**n**	**percentage**	**p-value**
Anemic	15	93.75	9	90.00	24	92.31	<0.05
Normal	1	6.25	1	10.00	2	7.69	
Total	16	100.00	10	100.00	26	100.00	

Table 4: Correlation between HPLC result and hematological parameters

Hemoglobinopathy	n	%	Hb	HbA	HbA2	HbF	RBC count	MCV	MCH
Sickle cell trait	10	38.46	8.65±3.675	42.42±8.82	3.08±0.475	1.52±0.475	5.18±1.52	72.3±1.71	21±3.33
Sickle cell disease	4	15.38	5.79±2.66	19.47±9.975	2.375±1.425	20.49±3.325	2.66±1.33	64.6±8.08	23.92±2.75
S ß Thalessemia	2	7.69	6.84±2.28	23.38±2.66	6.175±1.71	13.03±1.425	2.76±1.045	66.5±4.275	21.375±3.61
ß Thalessemia Trait	9	34.62	9.025±1.995	84.55±2.375	4.56±0.57	1.235±1.33	4.37±1.425	64.6±9.5	18.61±2.09
HbE ß Thalessemia	1	3.85	7.41±1.71	3.325±2.375	28.025±2.09	15.58±2.375	3.61±1.52	61.75±5.13	21.85±2.66

Table 5: Maternal outcomes in hemoglobinopathy cases and controls

Maternal Outcome	Hemoglobinopathy Cases		Controls		Total		
	n	**percentage**	**n**	**percentage**	**n**	**percentage**	**p-value**
Preterm labour	13	50.00	25	10.00	38	13.77	<0.05
Antepartum Hemorrhage	5	19.23	11	4.40	16	5.80	<0.05
Asymptomatic bacteriuria	3	11.54	12	4.80	15	5.43	<0.05
Oligohydram nios	6	23.08	7	2.80	13	4.71	<0.05
Pneumonia	1	3.85	1	0.40	2	0.72	<0.05
Puerperal Sepsis	2	7.69	21	8.40	23	8.33	<0.05
UTI	3	11.54	12	4.80	15	5.43	<0.05
Postpartum Hemorrhage	3	11.54	18	7.20	21	7.61	0.37
Preeclampsia	7	26.92	48	19.20	55	19.93	0.25

than the general population (3-5%), attributable to the high incidence zone of hemoglobinopathy in this region. Improved healthcare for such patients has increased life expectancy, leading to aspirations for pregnancy. Enhanced diagnostic facilities facilitate easier detection of this condition.

In this study, the age range of antenatal women with hemoglobinopathies ranged from 19-35 years, consistent with various reports[19]. Age distributions were similar across studies[20] for women with various types of anemia (SCD, SCT, thalassemia) and those without anemia. The age gap between women with hemoglobinopathies and normal antenatal women lacked statistical significance.

Anemia was notably more prevalent among antenatal women with hemoglobinopathy compared to normal pregnant women, a statistically significant difference. The heightened incidence of anemia could result from the additive effects of hemoglobinopathies, known to cause anemia. Consequently, pregnant women with anemia should be routinely screened for hemoglobinopathy during anemia investigations, potentially contributing to the high incidence of anemia in pregnancy within our country. These conditions, often asymptomatic in carriers, require investigation with suitable equipment such as Automated Capillary Zone Electrophoresis or HPLC for diagnosis.

This study observed a higher incidence of various types of sepsis among antenatal women with hemoglobinopathy, including asymptomatic bacteriuria, Puerperal Sepsis, UTI and pneumonia, compared to normal antenatal women. These differences were statistically significant and consistent with prior research. Sepsis rates were notably higher, possibly due to auto splenectomy in SCD.

Contrary to the findings of Afolabi *et al*.[21] and Serjeant *et al*.[22], postpartum hemorrhage occurred in a higher proportion of women with hemoglobinopathy compared to normal antenatal women in this study, although the difference lacked statistical significance. This implies that postpartum hemorrhage is not necessarily more common in women with hemoglobinopathy than in normal women.

Intrauterine growth restriction and low birth weight were significantly associated with SCD according to Villers *et al*.[23] and Al Jama *et al*.[24]. Our study corroborated these findings, showing a higher

incidence of FGR and LBW babies among women with hemoglobinopathy compared to the normal control group, with about 45% FGR occurring in sickle cell disorder versus about 30% in thalassemia disorder. This association may stem from uteroplacental insufficiency and anemia leading to hypoxia.

Although Blattner *et al*.[25] found no increased risk of stillbirth in women with SCT compared to those with normal hemoglobin, our study noted a higher incidence of stillbirth among women with hemoglobinopathy than in the normal control group, although this difference was not statistically significant, consistent with previous findings by Daigavane *et al*.[3]

CONCLUSION

Different types of hemoglobinopathies are prevalent across India. Many pregnant women with asymptomatic carrier states of various hemoglobinopathies seek antenatal care. The impact of hemoglobinopathies on pregnancy is substantial. Maternal morbidities such as pre-eclampsia, preterm labor, urinary tract infections, asymptomatic bacteriuria, antepartum hemorrhage and neonatal morbidities including low birth weight, fetal growth restriction, neonatal intensive care unit (SNCU) admission rates and neonatal mortality are heightened in women with hemoglobinopathy. This underscores the importance of early detection, proper management and specialized care for pregnant women with hemoglobinopathies to mitigate adverse outcomes for both the mother and the neonate.

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