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Antenatal screening for hemoglobinopathies with HPLC and their fetomaternal outcome

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Abstract---Introduction: Hemoglobinopathies are diverse group of inherited disorders of hemoglobin production and function. They represent the most common single-gene disorders that are found in humans and are distributed in various frequencies throughout the world. Pregnancy in women with sickle cell disease can increase the risk of maternal and perinatal mortality. HPLC offers the advantages over the routine Hemoglobin electrophoresis as it can more accurately identify and quantitate abnormal hemoglobin. HPLC forms an accurate, rapid and reproducible tool for early detection and management of thalassemia and abnormal hemoglobin variants. Material and Methods: This is an observational study was undertaken in the Department of Obstetrics & Gynaecology and Department of Hematology of S.C.B Medical College, Cuttack. During this period those pregnant women, who attended gynaecology OPD of SCB medical college, Cuttack were investigated during various months of gestations. All pregnant women were counselled and offered screening for hemoglobinopathies after informed and written consent. Results: Among the antenatal women with hemoglobinopathy, 90.91% were anemic, 09.09% were not anemic. Among the normal group 71.06% were anemic, 28.94% were not anemic. So, there was more prevalence of anaemia among hemoglobinopathy than normal subjects which was statistically

significant. ($p=0.004$). Among the antenatal women with hemoglobinopathy, 92.86% with sickle cell disorder were anemic and 93.75% So out of total women with hemoglobinopathy 93.18% were anemic. In our study 4.55% of hemoglobinopathy cases came for first antenatal check-up before 12 weeks, 18.18% between 12-28 weeks, and 77.27% after 28 weeks. Among the normal group 9.03% came for first antenatal check-up before 12 weeks, 25.00% between 12-28 weeks, and 65.97 % after 28 weeks. Conclusion: Different types of hemoglobinopathies are prevalent in Odisha. Though it was thought earlier that hemoglobinopathies were more common in western Odisha, but due to population migration the incidence has increased in central and coastal Odisha. As pregnancy is greatly affected by hemoglobinopathy. The maternal morbidities like pre-eclampsia, preterm labour, Urinary tract infection, asymptomatic bacteriuria, antepartum hemorrhage and neonatal morbidities like low birth weight, FGR, SNCU admission rate, neonatal mortality increase in women with hemoglobinopathy.

Keywords---Fetomaternal Outcome, Antenatal screening, Hemoglobinopathies.

Introduction

Hemoglobinopathies are diverse group of inherited disorders of hemoglobin production and function. They represent the most common single-gene disorders that are found in humans and are distributed in various frequencies throughout the world.¹ These Inherited disorders of haemoglobin fall into two main groups the structural hemoglobin variants that result from single amino-acid substitutions in the alpha or beta chains, and the thalassemia that is characterized by the imbalance in the production of hemoglobin chains.³

According to the WHO, approximately 5% of the world's populations are carrier of inherited hemoglobin disorders. Over 9 million carriers become pregnant and that over 332,000 affected conceptions or births occur annually worldwide, the majority in low- and middle-income countries.⁴ These disorders have occurred frequently in tropical regions in the past; however, they are now encountered in most countries as a result of population migration.⁵

Incidence of thalassemia trait and sickle cell disorder varies between 3-17% and 1-44%, respectively in India.⁶ Some communities have a very high incidence because of consanguinity and caste and area endogamy making the disease a major public health problem in India. The heterogeneous population of Odisha also harbors almost all major hemoglobinopathies.⁷

The complications of sickle cell anemia result either from anemia (e.g., fatigue, shortness of breath) or from obstruction of blood flow by sickle-shaped red blood cells (e.g., pain and ischemic organ damage).⁸⁻¹⁰ There is paucity of clinical manifestation when HbS co-exists with normal adult hemoglobin (HbA). Sickle cell trait is generally considered as benign carrier state with rare complications.¹¹

With advances in hematological management, women with hemoglobinopathy enjoy an increased life expectancy and quality of life. It is increasingly common for these women to reach childbearing age and to attempt pregnancy. Pregnancy brings about a number of physiological changes in pregnancy and may exacerbate the underlying diseases (i.e., hemoglobin disorders) and increase the risk of obstetric complications.¹² Physiological increase in blood volume leads to mild dilutional anemia, but women with hemoglobin disorder may experience a significant decrease in hemoglobin level. Hypoxia secondary to anemia might account for the adverse maternal and perinatal outcomes for pregnant women with inherited hemoglobin diseases.¹³

Pregnancy in women with sickle cell disease can increase the risk of maternal and perinatal mortality. Kobak and colleagues published the first report outlining the effects of sickle cell disease on pregnancy in 1941.¹⁴

Advances in SCD management and obstetric and perinatal care allow a significant improvement in the pregnancy outcome for women with sickle cell disease. Both maternal and perinatal mortality among pregnant women with sickle cell disease have been dramatically dropping since 1972,¹⁵ but these women are at increased risk of pregnancy-related complications.^{16,4} Women with sickle cell trait or thalassemia trait can tolerate pregnancy well with few complications and women with HbH disease or α -thalassemia intermedia are able to have a successful pregnancy.

HPLC offers the advantages over the routine Hemoglobin electrophoresis as it can more accurately identify and quantify abnormal hemoglobin. HPLC forms an accurate, rapid and reproducible tool for early detection and management of thalassemia and abnormal hemoglobin variants. This is of utmost importance as there is a high incidence of beta thalassemia trait in the Indian subcontinent.¹⁶

Material and Methods

This is an observational study that was undertaken in the Department of Obstetrics & Gynaecology and Department of Hematology of S.C.B Medical College, Cuttack.

During this period those pregnant women, who attended gynaecology OPD of SCB medical college, Cuttack were investigated during various months of gestations. All pregnant women were counselled and offered screening for hemoglobinopathies after informed and written consent.

Inclusion Criteria

All antenatal mothers attending OPD and labour room irrespective of their gestational age.

Exclusion Criteria

- Those patients who refused to deliver in the institute.
- Those patients who refused to give informed written consent.
- Those patients having history of blood transfusion within one month.

Method

The study group was picked up from the women attending ANC OPD and labour room. 476 antenatal cases were taken in the study group taking into the account the inclusion and exclusion criteria. Clinical evidence of anaemia and hemolytic facies were looked for and complete blood count was done, along with LFT and Iron profile. HPLC was done for all the cases. All the cases were followed till delivery and 6 weeks of postpartum period.

About 5 ml. intravenous blood samples were collected after obtaining the informed consent using EDTA as anticoagulant by disposable syringes and needles from each antenatal woman free of at least one month's blood transfusion. Hematological indices like, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell width was measured.

The sickling test was performed by using freshly prepared 2% sodium metabisulphite solution as reducing agent and the sealed smear incubated for about 2 hours and 12 hours and examined for detection of sickled RBC. About 2ml of intravenous blood sample was collected in EDTA vial and Chromatography was performed in BIORAD variant II HPLC analyzer.

Statistical Analysis

All data were recorded and tabulated for comparative study and presented in the form of tables and charts. The outcomes were compared with the control group and statistically analyzed. *P* value was calculated by chi-square test.

Results

Table -1: Age distribution of antenatal women

Age group	Hemoglobinopathy		Control		Total		Chi square and <i>p</i> value
	Number	%	Number	%	Number	%	
<25	24	54.55	241	55.79	265	55.67	$\chi^2 = 1.414$ df = 2 <i>p</i> = 0.493
25-29	15	34.09	118	27.31	133	27.94	
>30	05	11.36	73	16.90	78	16.39	
Total	44	100	432	100	476	100	

The table 1 show that, among the antenatal women with hemoglobinopathy, 54.55% were below 25 years of age, 34.09% were between 25-29 years of age and 11.36% were above 30 years of age. Among the normal antenatal women 55.79% were below 25 years of age, 27.31% cases were between 25-29 years of age and 16.90% were above 30 years of age. So, there was no significant age difference among the hemoglobinopathy and normal antenatal women and both the groups could be comparable.

Table – 2: Proportion of anaemia among Antenatal women

Antenatal women	Hemoglobinopathy		Control		Total		Chi square df and <i>p</i> value
	Number	%	Number	%	Number	%	
Anemic	40	90.91	307	71.06	347	72.90	$\chi^2 = 7.959$ df = 1 $p = 0.004$
Normal	04	09.09	125	28.94	129	27.10	
Total	44	100	432	100	476	100	

The Table 2 show that, among the antenatal women with hemoglobinopathy, 90.91% were anemic, 09.09% were not anemic. Among the normal group 71.06% were anemic, 28.94% were not anemic. So, there was more prevalence of anaemia among hemoglobinopathy than normal subjects which was statistically significant. ($p=0.004$).

Table -3: Proportion of Anaemia among hemoglobinopathy cases

Antenatal women	Sickle cell Disorders		Thalassemia Disorders		Total		Chi square df and <i>p</i> value
	Number	%	Number	%	Number	%	
Anemic	26	92.86	15	93.75	41	93.18	$\chi^2=0.031$ df = 1 $p=0.860$
Normal	2	7.14	1	6.25	3	6.82	
Total	28	100	16	100	44	100	

The table 3 shows, among the antenatal women with hemoglobinopathy, 92.86% with sickle cell disorder were anemic and 93.75% So out of total women with hemoglobinopathy 93.18% were anemic.

Table – 4: Hematological profile and HPLC Result

Hemoglobinopathy	No of cases	Hb	RBC count	MCV	MCH	HbA	HbA2	HbF	%
Sickle cell trait	17	9.1±3.5	5.46±1.6	74±1.8	22±3.5	40.4±8.4	3.1±0.5	1.6±0.5	38.64
Sickle cell disease	07	6.1±2.8	2.8±1.4	68±8.5	25.2±2.9	20.5±10.5	2.5±1.5	21.6±3.5	15.9
S β Thal	04	7.2±2.4	2.9±1.1	70±4.5	22.5±3.8	24.6±2.8	6.5±1.8	13.7±1.5	9.1
β Thal Trait	15	9.5±2.1	4.6±1.5	68±10	19.6±2.2	89±2.5	4.8±0.6	1.3±1.4	34.09
HbE β Thal	01	7.8±1.8	3.8±1.6	65±5.4	23±2.8	3.5±2.5	29.5±2.2	16.4±2.5	2.27

MCV between carriers (62.08fl) and normal cases (79.7fl) was statistically significant. MCV is the key indicator for diagnosis and screening. MCH among hemoglobinopathies was lower than in normal cases (25.6pg) in most variants and significantly lower in α Thalassemia trait (21.35pg). RDW was normal in spite of low MCV and MCH in most carriers of α Thalassemia trait.

Table – 5: Distribution of antenatal women by Gestational Age at Booking

Gestational Age	Hemoglobinopathy		Normal		Total		Chi square df and <i>p</i> value
	Number	%	Number	%	Number	%	
<12	2	4.55	39	9.03	41	8.61	x ² = 2.454 df = 2 <i>p</i> = 0.293
12-28	08	18.18	108	25.00	116	24.37	
>28	34	77.27	285	65.97	319	67.02	
Total	44	100	432	100	476	100	

The table 5 show that, 4.55% of hemoglobinopathy cases came for first antenatal check-up before 12 weeks, 18.18% between 12-28 weeks, and 77.27% after 28 weeks. Among the normal group 9.03% came for first antenatal check-up before 12 weeks, 25.00% between 12-28 weeks, and 65.97% after 28 weeks. So, there was no statistical difference in gestational age at first antenatal visit between normal and hemoglobinopathy subjects.

Table – 6: Comparison of Different Maternal Complications

Maternal Complications		Hemoglobinopathy		Normal		Total		Chi square, df, <i>P</i> value
		Number	%	Number	%	Number	%	
Preterm labour	Yes	23	52.27	43	9.95	66	13.87	x ² = 47.630 df = 1 <i>p</i> = 0.0001
	No	21	47.73	389	90.05	410	86.13	
	Total	44	100	432	100	476	100	
Preeclampsia	Yes	12	27.27	84	19.44	96	20.17	x ² = 1.519 df = 1 <i>p</i> = 0.217
	No	32	72.73	348	80.56	380	79.83	
	Total	44	100	432	100	476	100	
Oligohydramnios	Yes	10	22.73	12	2.78	22	4.62	x ² = 36.051 df = 1 <i>p</i> = 0.0001
	No	34	77.27	420	97.22	454	95.38	
	Total	44	100	432	100	476	100	
Antepartum Hemorrhage	Yes	08	18.18	19	4.40	27	5.67	x ² = 14.179 df = 1 <i>p</i> = 0.0016
	No	36	81.82	413	95.60	449	94.33	
	Total	44	100	432	100	476	100	
Sepsis	No Sepsis	28	63.64	354	81.94	382	80.25	x ² = 19.07 df = 4 <i>p</i> = 0.0075
	Asymptomatic bacteriuria	06	13.64	20	4.63	26	5.46	
	Puerperal Sepsis	03	6.82	36	8.33	39	8.19	
	UTI	05	11.36	20	4.63	25	2.26	
	Pneumonia	02	4.54	02	0.46	04	0.84	
	Total	44	100	432	100	476	100	
Postpartum Hemorrhage	Yes	05	11.36	31	7.78	36	7.56	x ² = 1.001 df = 1 <i>p</i> = 0.316
	No	39	88.64	401	92.82	440	92.44	
	Total	44	100	432	100	476	100	

Pre-eclampsia occurred in 27.27% of women with hemoglobinopathy in comparison to 19.44% of normal antenatal women. The difference was not statistically significant. Oligohydramnios found in 22.73% of women with hemoglobinopathy in comparison to only 2.78% of normal antenatal women. The difference was statistically significant (*p* < 0.0001). Antepartum hemorrhage found in 18.18% of women with hemoglobinopathy in comparison to 4.40% of normal antenatal women. The

difference was statistically significant ($p=0.00016$). Postpartum hemorrhage occurred in 11.36% of women with hemoglobinopathy in comparison to 7.78% of normal antenatal women. The difference was not statistically significant. The table 6 show that the incidence of different type of sepsis like asymptomatic bacteriuria, Puerperal Sepsis, UTI, pneumonia among antenatal women with hemoglobinopathy was 13.64%, 6.82%, 11.36%, 4.54% respectively, in comparison to normal antenatal women in whom incidence was 4.63%, 8.33%, 4.63%, 0.46% respectively. The differences were statistically significant ($p<0.05$).

Table – 7: Comparative Incidence of different type of sepsis Sickle cell and Thalassemia Disorders

Sepsis	Sickle cell Disorders		Thalassemia Disorders		Total		Chi square df and p value
	Number	%	Number	%	Number	%	
No Sepsis	16	57.14	12	75.00	28	63.64	$\chi^2=2.267$ df = 4 $p = 0.686$
Asymptomatic Bacteriuria	05	17.86	01	06.25	06	13.64	
Puerperal Sepsis	02	07.14	01	06.25	03	06.82	
UTI	04	14.29	01	06.25	05	11.36	
Pneumonia	01	03.57	01	06.25	02	04.54	
Total	28	100	16	100	44	100	

The table 7 show that, the incidence of different type of sepsis like asymptomatic bacteriuria, Puerperal Sepsis, UTI, pneumonia among the cases with sickle cell disorder was 17.86%, 7.14%, 14.29%, 3.57% respectively, in comparison to cases with thalassemia in whom incidence was 6.25%, 6.25%, 6.25%, 6.25% respectively. So, the occurrence of different types of sepsis was similar among thalassemia and sickle cell cases.

Table 8: Comparison of Different Perinatal Outcomes

Perinatal Outcomes		Hemoglobinopathy		Normal		Total		Chi Square df and p value
		Number	%	Number	%	Number	%	
FGR	Yes	18	40.91	41	09.49	59	12.39	$\chi^2=36.301$ df = 1 $p=0.00001$
	No	26	59.09	391	90.51	417	87.61	
	Total	44	100	432	100	476	100	
Still Birth	Yes	02	04.55	12	02.78	14	02.94	$\chi^2=0.437$ df = 1 $p=0.508$
	No	42	95.45	420	97.22	462	97.06	
	Total	44	100	432	100	476	100	
SNCU Admission	Yes	14	31.82	43	09.95	57	11.97	$\chi^2=18.110$ df = 1 $p=0.00002$
	No	30	68.18	389	90.05	419	88.03	
	Total	44	100	432	100	476	100	
Neonatal Death	Yes	04	09.09	07	01.62	11	02.31	$\chi^2= 9.872$ df = 1 $p=0.0016$
	No	40	90.91	425	98.38	465	97.69	
	Total	44	100	432	100	476	100	

The table 8 show that, the incidence of FGR was 40.91% among the women with hemoglobinopathy whereas the incidence was 9.49% among the normal control group, which was statistically significant ($p < 0.0001$). The incidence of still birth was 4.55% among the women with hemoglobinopathy whereas the incidence was 2.78% among the normal group, which was not statistically significant. The incidence of SNCU admission of babies was 31.82 % among the women with hemoglobinopathy whereas the incidence was 9.95% among the normal control group, which was statistically significant ($p < 0.001$). The incidence of neonatal death was 9.09% among the women with hemoglobinopathy whereas the incidence was 1.62% among the normal control group, which was statistically significant ($p < 0.05$).

Discussion

In the present study, 476 antenatal women were screened, 44 women found to have five different types of hemoglobinopathy. The Prevalence of hemoglobinopathy was 9.24% which was slightly higher than the previous study (8%) at Berhampur, Odisha by panda et al¹⁸ 2009 and is quite higher in comparison to general population (3-5%). The reason being Population of Odisha belong to the zone of high hemoglobinopathy incidence. Many such patients are receiving better health care for which their life expectancy has increased and they are aspiring for pregnancy. Better facilities for diagnosis, for which this disease can be known easily.

The age group of antenatal women with hemoglobinopathies varied from 19-35 years in the present studies, which is in accordance with the reports of different studies.¹⁹ In this study 54.55% were below 25 years of age, 34.09% were between 25-29 years of age and 11.36% were above 30 years of age. The age distribution was similar in several studies²⁰ for women with different types of anaemia (SCD, SCT, thalassemia) and no anaemia. The age difference between the women with hemoglobinopathies and normal antenatal women was not statistically significant.

In the present study anaemia was more common among the antenatal women with hemoglobinopathy than normal pregnant women (90.91% vs 71.06) which was statistically significant. ($p = 0.004$).

The high incidence of anaemia could be due to additive effect of hemoglobinopathies as these conditions per se can produce anaemia. Thus Pregnancy with anaemia should be screened for hemoglobinopathy routinely while investigating for anemia. Hemoglobinopathy may contribute partly for the overall high incidence of anaemia in pregnancy in our country. Most of these conditions (carriers) are usually asymptomatic and need investigations by proper equipment (Automated capillary zone electrophoresis or HPLC for diagnosis).

In the present study the incidence of different type of sepsis like asymptomatic bacteriuria, Puerperal Sepsis, UTI, pneumonia among antenatal women with hemoglobinopathy was 13.64%, 6.82%, 11.36%, 4.54% respectively, in comparison to normal antenatal women in whom incidence was 4.63%, 8.33%, 4.63%, 0.46% respectively. All cases of pneumonia in hemoglobinopathy cases are due to COVID -19. The differences were statistically significant ($p < 0.0007$) and in accordance with previous studies. The prevalence was similar in sickle cell and

thalassemia disorder. Sepsis rate was more common might be due to auto splenectomy in SCD.

Afolabi et al²¹ and Serjeant et al²² reported that postpartum hemorrhage does not seem to be more common in women with SCD. In our study postpartum hemorrhage occurred in 11.36% of women with hemoglobinopathy in comparison to 7.18% of normal antenatal women. The difference was not statistically significant. So postpartum hemorrhage was not more common in hemoglobinopathy women than normal women.

Villers et al²³ and Al Jama et al²⁴ reported that intrauterine growth restriction and low birth weight was significantly associated with SCD. Nassar and colleagues reported that intrauterine growth restriction has complicated more than half of the pregnancies with B- thalassemia intermedia.

In the present study the incidence of FGR and LBW baby was 39.39% and 54.55% among the women with hemoglobinopathy whereas the incidence was 7.54% and 17.10% among the normal control group respectively, which were statistically significant ($p < 0.0001$) and 45% FGR occurred in sickle cell disorder in comparison to 30.77% in thalassemia disorder. The findings were in accordance with the previous studies. The cause of FGR and LBW babies may be due to uteroplacental insufficiency and anaemia leading to hypoxia.

Blattner et al²⁵ found no increase in the risk of stillbirth in women with SCT when compared with those with normal hemoglobin.

In the present study the incidence of still birth was 4.55% among the women with hemoglobinopathy whereas the incidence was 2.78% among the normal control group. The difference was not statistically significant and supports the previous studies. Daigavane M et al⁴ also found no significant difference among SCD and normal pregnant women.

Conclusion

Different types of hemoglobinopathies are prevalent in Odisha. Though it was thought earlier that hemoglobinopathies were more common in western Odisha, but due to population migration the incidence has increased in central and coastal Odisha. More number of pregnant women with asymptomatic carrier state of different hemoglobinopathies attends S.C.B Medical College for antenatal check-up as it is a tertiary care premier institution of Odisha. As pregnancy is greatly affected by hemoglobinopathy. The maternal morbidities like pre-eclampsia, preterm labour, Urinary tract infection, asymptomatic bacteriuria, antepartum hemorrhage and neonatal morbidities like low birth weight, FGR, SNCU admission rate, neonatal mortality increase in women with hemoglobinopathy.

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