Section: Pathology

Original Research Article

EMERGING DETECTION OF HEMOGLOBIN E TRAIT DURING ANTENATAL HPLC SCREENING IN NORTH INDIA: DIAGNOSTIC AND EPIDEMIOLOGICAL IMPLICATIONS

Pooja Saini[1], Sunita[1], Lubna Khan[1], Mahendra Singh[1], Neelima Verma[1], Chayanika Kala[1], Pratima Verma[2], Aniruddh Jain[1]

[1]Department of Pathology, G.S.V.M. Medical College, Kanpur, Uttar Pradesh, India.
[2]Department of obstetrics and gynecology, G.S.V.M. Medical College, Kanpur, Uttar Pradesh, India.

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Corresponding Author:
Dr. Pooja Saini,
Email: dr.pooja2406@gmail.com

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ABSTRACT

Background: Hemoglobinopathies are a significant public health concern in India. Hemoglobin E (HbE), one of the most common structural hemoglobin variants, is classically prevalent in Northeast India and Southeast Asia. However, increasing migration and population intermixing have led to its detection in other regions of India. Identifying asymptomatic HbE trait carriers during antenatal screening is important because co-inheritance with β-thalassemia may result in severe HbE–β thalassemia in offspring. HbE co-elution in the HbA2 window on Bio-Rad D-10 can mimic elevated HbA2 levels. It requires careful chromatographic interpretation along with the clinic-hematological correlation. **Aim:** To evaluate the frequency and clinico-hematological profile of HbE trait detected during antenatal HPLC screening in a tertiary care centre in North India. **Materials and Methods:** A total of 2321 antenatal cases were screened, for hemoglobinopathies, over one-year. Complete blood count, peripheral blood smear examination, reticulocyte count and high-performance liquid chromatography (HPLC) analysis using Bio-Rad D-10 system were performed. Hemoglobin fractions were analyzed, and descriptive statistics were calculating using SPSS version 30. **Results:** Out of 2321 cases, 130 hemoglobinopathy cases were identified. HbE trait was detected in 20 cases (15.38%) of antenatal hemoglobinopathies. Hematologically, they exhibited mild microcytosis (MCV 78.22 ± 5.97 fL) and relatively preserved hemoglobin levels (9.44 ± 0.82 g/dL). HPLC demonstrated markedly elevated HbA_2 /E fraction (27.41 ± 6.51%) due to HbE co-elution in the HbA_2 window. **Conclusion:** Routine antenatal HPLC screening is highly effective in detecting silent HbE carriers, preventing the birth of children with severe compound heterozygous conditions like HbE-β thalassemia.

INTRODUCTION

Hereditary hemoglobinopathies represent a major public health challenge globally and in India, imposing a significant clinical and economic burden.[1,2,3] The Ministry of Health and Family Welfare guidelines strongly emphasize the critical need for universal antenatal screening to prevent the birth of children with severe hemoglobin disorders.[4] While β-thalassemia and sickle cell anemia are the most frequently observed hereditary hemoglobin disorders in the country, Hemoglobin E (HbE) is a highly significant variant.[5]

Hemoglobin E (HbE) results from a point mutation in the β-globin gene where glutamic acid is replaced by lysine at position 26 of the β-globin chain. This mutation also creates an alternative splice site in the β- globin mRNA, resulting in reduced synthesis of the βE chain. It is classically endemic in northeastern India (with prevalence rates up to 30-60%), Southeast Asia, and parts of eastern India.[6,7,8] However, recent studies have reported increasing detection of HbE in other regions of India,[9] specifically within North Indian states and Uttar Pradesh,[10,11] suggesting changing epidemiological patterns due to migration and population admixture. However, data on HbE prevalence in antenatal populations from North India remain limited, particularly in Uttar Pradesh.

Individuals carrying mild hemoglobin variants, such as HbE trait, usually do not manifest significant clinical symptoms and do not require specific

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treatment.[5,12] Its clinical significance lies in its interaction with other hemoglobinopathies, particularly β-thalassemia, resulting in compound heterozygous state (HbE–β-thalassemia), with significant clinical manifestations, ranging from mild anemia to severe transfusion-dependent states.[13,14]

The pathophysiology of HbE–β-thalassemia is complex. Ineffective erythropoiesis, apoptosis, and oxidative damage are central components of the disease with shortened red cell survival. The globin chain imbalance that results from the β-thalassemia mutations correlates with the severity of the disease. Lack of production of βE globin chains, unstable nature of Hb E and inadequate β globin gene due to β thalassemia mutations are responsible for thalassemic features.

Therefore, detecting asymptomatic HbE carriers in the reproductive age group is critical. High-performance liquid chromatography (HPLC) has become an indispensable tool for identifying and quantifying hemoglobin variants with high accuracy and reproducibility.

The present study was undertaken to assess the prevalence of HbE trait among pregnant women in Kanpur and to evaluate its implications for antenatal screening in North India.

MATERIALS AND METHODS

This hospital-based prospective observational study was carried out at the Department of Pathology of tertiary care centre in Uttar Pradesh of North-India, over a one-year period from February 2025 to January 2026 after obtaining approval from the Institutional Ethics Committee.

The study population consisted of antenatal women attending the Department of Obstetrics and Gynecology during the study period who underwent universal screening for hemoglobinopathies. The blood samples were evaluated in Department of Pathology.

Inclusion criteria comprised all antenatal women undergoing routine hemoglobinopathy screening during the study period. Patients requiring blood transfusion were screened only after a minimum interval of 12 weeks post-transfusion to avoid interference with HPLC interpretation. Participation in the study required informed consent from all patients.

Exclusion criteria included previously diagnosed cases of hemoglobinopathies.

A total of 2321 consecutive antenatal women were screened for hemoglobinopathies. Venous blood samples were collected in EDTA vials. Complete Blood Count (CBC) was performed using an automated six-part hematology analyzer to record hemoglobin, red blood cell (RBC) count, and RBC indices. Peripheral blood smears (PBS) were stained with Leishman stain for morphological evaluation. Reticulocyte counts were determined manually after supravital staining with new methylene blue. HPLC analysis was conducted using the Bio-Rad D-10 Variant system (HbA_2 /F program). Blood samples were obtained and haemolysate was prepared by using lysis buffer. Each sample required approximately 6.5 min for HPLC analysis. The instrument was calibrated using HbA2/F calibrator, which provides assigned values expressed as area percentage and retention time for both HbA2 and HbF and it is analyzed at the beginning of each analytical run.

In this system HbE and Hb Lepore elute in the HbA2 window and if the sample contains greater than 16.5% fetal hemoglobin (HbF), it may elute in the LA1c/ CHb window. Diagnoses were established after analysing chromatographic findings and correlating with the clinical presentation, RBC indices, peripheral blood smear findings and reticulocyte counts. Sickling test was also done to validate the finding of HbS on HPLC.

β-thalassemia trait is identified by mildly elevated HbA_2 levels ranging from 4–9% and HbF levels usually ranging from 1–3%. The MCV and MCH are reduced, while the RBC counts are relatively elevated. RDW is normal to mildly increased in most cases. Peripheral blood smear examination showed microcytic hypochromic red blood cells with target cells.

HbE trait is identified by a prominent peak in the A_2 /E window ranging from 20–35%, as HbE co-elutes with HbA_2 on the Bio-Rad D-10 HPLC system. HbA remains the predominant hemoglobin fraction, while HbF levels must be within normal limits. In contrast to β-thalassemia trait, where HbA_2 levels are usually below 9%, the markedly elevated A_2 /E window peak favors the diagnosis of HbE trait. RBC indices are normal to mildly reduced, particularly MCV and MCH values. Peripheral blood smear examination shows predominantly normocytic normochromic red blood cells, with mild microcytosis and hypochromia in some cases. Most of the patients with HbE trait are clinically asymptomatic.

Hb Lepore trait shows elevated HbA_2 levels in the range of 10-18%, which are higher than those typically observed in β-thalassemia trait but lower than the A_2 /E window peaks usually seen in HbE trait. Hb Lepore elutes in the A_2 window similar to HbE; however, mildly elevated HbF levels in range of 3-7% are also observed, favoring Hb Lepore trait over HbE trait. The MCV and MCH are reduced, and peripheral blood smear examination shows microcytic hypochromic red blood cells.

Hereditary persistence of fetal hemoglobin (HPFH) is clinically asymptomatic, with elevated HbF ranging from 15 to 30% on HPLC. δ-β thalassemia trait also shows elevated HbF in range of 5-20% on HPLC. HPFH is distinguished from δ-β thalassemia trait by comparing RBC indices and peripheral blood smears. In HPFH, the RBC indices are within normal limits and peripheral blood smear examination shows normocytic normochromic red

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blood cells. Whereas, MCV and MCH values are reduced, and microcytic hypochromic red blood cells are on peripheral blood smear of δ-β thalassemia trait.

Heterozygous HbD Punjab trait is identified by a significant peak in the D-window at a retention time of 3.8 ± 0.1 minutes, located just before the S-window, with HbA remaining the predominant hemoglobin fraction. Sickle cell trait is identified by a peak in the S-window, with HbA levels exceeding HbS levels. Sickling test was positive in these cases.

Compound HbE–β-thalassemia is identified by a markedly elevated peak in the A_2 /E window due to co-elution of HbE, along with significantly elevated HbF levels and reduced HbA fraction. Hemoglobin levels are moderately to severely reduced, and these patients can have wide clinical manifestations ranging from mild, asymptomatic anemia to severe, transfusion dependent cases.

RESULTS

Among the 2321 screened cases, 130 cases of hereditary hemoglobinopathies with abnormal Hb were identified during the study period. Preliminary identification of Hb variants was based primarily on retention time windows and area percentages on HPLC; however, clinical presentation, RBC indices, peripheral blood smear findings, and reticulocyte counts were also correlated to arrive at a definitive diagnosis.

Table 1 depicts that out of all the antenatal hemoglobinopathy cases, HbE trait was diagnosed in 20 cases (15.38%), making it the second most common hemoglobinopathy after 93 cases of β-thalassemia trait (71.53%). The third most common hemoglobinopathy was 8 cases (6.15%) of Heterozygous HbD Punjab trait. Additionally, 2 cases (1.53%) of compound HbE-β-thalassemia were also identified.

One asymptomatic antenatal female showed elevated HbF levels of 18.2% on HPLC. There was no history of blood transfusion, no clinical symptoms, and RBC indices were within normal limits. Peripheral blood smear examination showed normocytic normochromic red blood cells. In view of these findings, a diagnosis of heterozygous hereditary persistence of fetal hemoglobin (HPFH) was considered.

Another asymptomatic antenatal female showed elevated HbA_2 levels of 10.4%. HbA remained the predominant hemoglobin fraction. However, mildly elevated HbF levels (3.2%) were also observed, favoring Hb Lepore trait over HbE trait. The MCV and MCH were reduced, while the RBC count and RDW were relatively elevated. Peripheral blood smear examination showed microcytic hypochromic red blood cells. Based on the combined hematological and chromatographic findings, a diagnosis of Hb Lepore trait was made.

One antenatal female showed elevated HbF levels with normal HbA_2 levels on HPLC, along with reduced MCV and MCH values, elevated RBC count, and microcytic hypochromic red blood cells on peripheral smear examination. These findings were suggestive of δ-β thalassemia trait.

Table 1: Frequency Distribution of HbE Trait and other Hemoglobinopathies Detected by HPLC in the Antenatal Population

Diagnosis	Number of Cases	Percentage (%)
β-thalassemia trait	93	71.53%
HbE trait	20	15.38%
HPFH	1	0.76%
Hb Lepore trait	1	0.76%
δ-β thalassemia trait	1	0.76%
Heterozygous HbD Punjab trait	8	6.15%
Sickle cell trait (HBAS)	4	3.07%
Compound HBE–β-thalassemia	2	1.53%
Total	**130**	**100%**

Most carriers of mild hemoglobinopathies, particularly β-thalassemia trait, HbE trait, HPFH, and δ-β thalassemia trait, were clinically asymptomatic at the time of screening. In contrast, patients with compound HbE–β-thalassemia showed more significant clinical manifestations ranging from mild pallor and fatigue to severe progressive pallor

Table 2 shows that the hematological parameters tabulated as mean ± SD, while values for single-case hemoglobinopathies are presented as absolute values. HbE trait cases reflected relatively mild abnormalities compared to other hemoglobinopathies. The hemoglobin value was maintained at a mean of 9.44 ± 0.82 g/dL, while it was significantly lower for the two compound HbE-β-thalassemia cases at 7.0 and 6.4g/dL. MCV for HbE trait cases was 78.22 ± 5.97 fL, indicating milder red cell size reduction and MCH was 25.36 ± 0.92 pg. Whereas, both MCV and MCH were further lower for the compound HbE-β-thalassemia cases.

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Table 2: Comparison of hematological parameters across different hemoglobinopathies, with data expressed as mean ± SD

Diagnosis	n	HB (g/dL)	RBC COUNT (x10^12/L)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW%	Retic Count %
β-thalassemia trait	93	9.61 ± 1.12	5.52 ± 0.7	67.84 ± 12.23	23.75 ± 3.68	34.61 ± 3.15	15.13 ± 1.02	1.06 ± 0.24
HbE trait	20	9.44 ± 0.82	5.78 ± 0.56	78.22 ± 5.97	25.36 ± 0.92	34.2 ± 1.02	15.18 ± 1.19	0.96 ± 0.34
HPFH	1	9.8	4.92	86	29	33	13.5	1.2
Hb Lepore	1	8.8	5.56	64	21	32	17.13	1.5
δ-β thalassemia trait	1	10.1	5.42	68	23	31	15.16	1.5
Heterozygous HbD Punjab trait	8	10.23 ± 1.24	5.12 ± 0.66	65.8 ± 5.8	23.27 ± 0.6	32.60 ± 0.85	17.13 ± 0.32	2.37 ± 0.25
Sickle cell trait (HbAS)	4	10.6 ± 1.31	4.87 ± 0.58	77.9 ± 1.27	25.75 ± 1.84	33.05 ± 0.35	16.32 ± 0.71	1.5 ± 0.34
Compound HbE-β thalassemia	Case 1	7.0	3.15	69.5	22.4	32.2	37.8	1.8
	Case 2	6.4	3.42	62.5	21.1	31.8	42.7	2.6

Note: Absolute values are given for hemoglobinopathies with 1 to 2 cases, as n=1 and n=2 preclude SD calculation

Peripheral blood smear examination of HbE trait patients demonstrated mixed red cell morphology. Predominant normocytosis was observed, alongside microcytosis with hypochromia in 8 cases (40%). Target cells were present in 6 (30%) cases, while markers of severe dyserythropoiesis (basophilic stippling, nucleated RBCs) were entirely absent. Both cases of compound HbE-β-thalassemia showed microcytosis and hypochromia, with one case also displaying nucleated RBCs.

Table 3 demonstrates the distinct hemoglobin fraction patterns that allowed for the definitive diagnosis of various hemoglobinopathies on HPLC (as Mean ± SD and absolute values for single-case hemoglobinopathies). Patients with HbE trait demonstrated a reduced HbA fraction (62.32 ± 6.60%). A key diagnostic finding was the markedly elevated peak in the A_2 /E window due to co-elution of HbE and HbA2, measuring 27.41 ± 6.51%. HbF levels remained low at 0.91 ± 0.35%. In contrast, the two cases of compound HbE–β thalassemia showed higher HbA2/E fraction of 35.72% and 39.64%, alongside HbF fraction of 20.31% and 27.87%.

Table 3: Distribution of hemoglobin fractions (HbA, HbA_2 /E, HbF, HbS and HbD Punjab) across different hemoglobinopathies as determined by High-Performance Liquid Chromatography (HPLC) expressed as mean ± SD

Diagnosis	n	HbA (%)	HbA2/E(%)	HbF (%)	HbS (%)	HbD Punjab (%)
β-thalassemia trait	93	82.99 ± 1.97	5.04 ± 0.56	1.15 ± 1.44	0.00 ± 0.00	0.00 ± 0.00
HbE trait	20	62.32 ± 6.60	27.41 ± 6.51	0.91 ± 0.35	0.00 ± 0.00	0.00 ± 0.00
HPFH	1	78.74	3.82	18.23	0.00	0.00
Hb Lepore trait	1	80.13	10.41	3.24	0.00	0.00
δ-β thalassemia trait	1	80.36	2.32	8.61	0.00	0.00
Heterozygous HbD P unjab trait	8	55.80 ± 6.11	2.20 ± 0.10	0.07 ± 0.12	0.00 ± 0.00	33.57 ± 6.81
Sickle cell trait HbAS	4	65.75 ± 9.97	4.30 ± 0.14	0.70 ± 0.14	21.10 ± 10.75	0.00 ± 0.00
Compound HbE-β thalassemia	Case 1	41.87	35.72	20.31	0.00	0.00
	Case 2	25.12	39.64	27.87	0.00	0.00

Note: Absolute values are given for hemoglobinopathies with 1 to 2 cases, as n=1 and n=2 preclude SD calculation

Figure 1 is a representative HPLC chromatogram illustrating an elevated HbA_2 fraction with predominant HbA_0 and HbF in normal range- a profile diagnostic of β-thalassemia trait. While HbF is typically normal in these cases, mild elevations may occasionally be observed.

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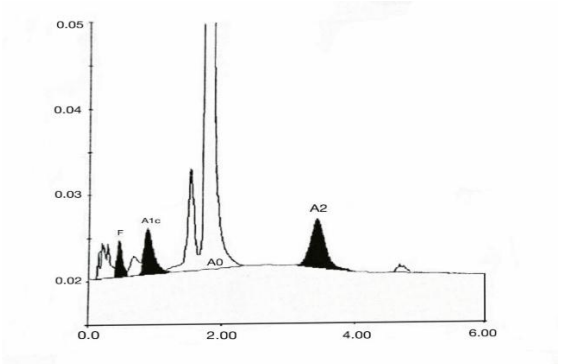

Figure 1: HPLC chromatogram showing elevated HbA_2 fraction (6.2%), with predominant HbA_0 (82.3%), and HbF in normal range (1.2%), consistent with β-thalassemia trait

Figure 2 is a representative HPLC chromatogram showing a large peak in the A_2 /E window with preserved HbA_0 fraction, consistent with HbE trait. HbE co-elutes with HbA_2 in the same window, but they still have different retention times.

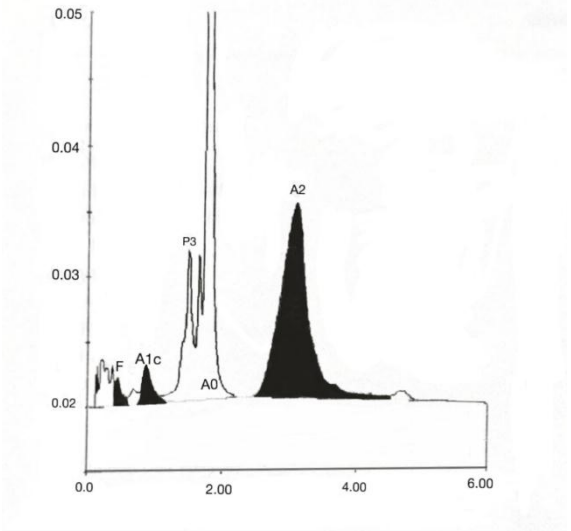

Figure 1: HPLC chromatogram showing a large peak (34.8%) in the A_2 /E window with preserved HbA_0 (52.7%) fraction, consistent with HbE trait

Figure 3 is a representative HPLC chromatogram showing reduced HbA_0 with markedly elevated HbF and increased HbE fraction, consistent with compound HbE-β thalassemia.

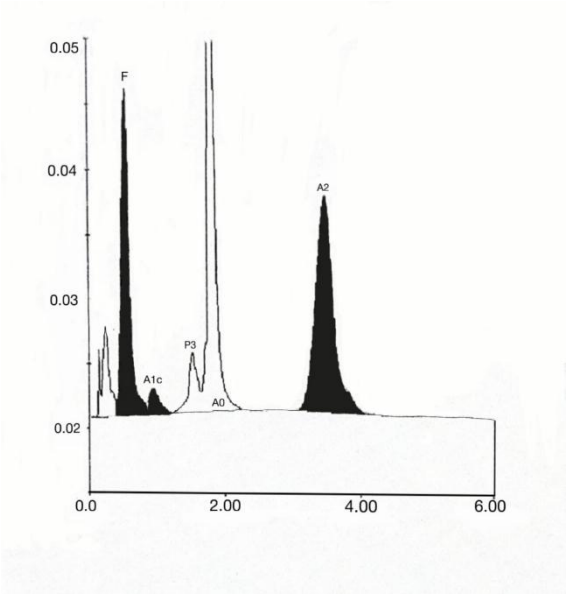

Figure 3: HPLC chromatogram showing reduced HbA_0 (41.8%) with markedly elevated HbF (20.3%) and increased HbE fraction suggested by a large peak in A_2 /E window (35.7%), consistent with compound HbE–β thalassemia

DISCUSSION

HbE trait emerged as the second most common hemoglobinopathy detected during antenatal screening in our cohort, with a notable prevalence of 15.38% among antenatal women in North-India, a region where HbE is traditionally considered uncommon. HbE is classically prevalent in northeastern India; however, increasing detection in other regions may be attributed to migration, inter-regional marriages, and population admixture. This finding suggests a shift in the epidemiological distribution of hemoglobin variants in North India.

HbE trait is clinically silent as seen in our study and is unlikely to be diagnosed without targeted laboratory screening. Its importance lies in its potential to form compound heterozygous states such as HbE–β-thalassemia, which can present with significant morbidity.[15]

Hematologically, the HbE trait presented with a mild microcytic profile (MCV 78.22 ± 5.97 fL) and relatively normal hemoglobin levels. This profile is consistent with other Indian and South Asian cohorts noting that milder hemoglobinopathies present merely with microcytosis and hypochromia, which can often be misdiagnosed as routine iron deficiency anemia of pregnancy without HPLC confirmation.[16,17]

The diagnostic hallmark of HbE on the Bio-Rad D-10 HPLC system is its co-elution with HbA_2 .[14] In our study, HbE trait patients showed an apparent HbA_2 fraction of 27.41 ± 6.51%. This apparent HbA_2 elevation represents a combined HbA_2 + HbE peak, rather than an isolated HbA_2 elevation, a characteristic analytical feature of HPLC.[18] Misinterpretation of this window can lead to

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diagnostic errors; hence, values exceeding 10% in the A_2 window strongly suggest the presence of HbE.[18,19] Interpretation of elevated peaks in the A_2 window requires careful differentiation between HbE trait, Hb Lepore trait, and β-thalassemia trait. In our study, markedly elevated A_2 /E peaks (>20%) favored HbE trait, whereas HbA_2 levels in β-thalassemia trait remained below 9%. Mildly elevated HbF levels further supported Hb Lepore trait in appropriate cases. These observations highlight the importance of careful interpretation of retention time, peak percentage, RBC indices, peripheral smear findings, and HbF levels while evaluating abnormal peaks in the A_2 window to avoid diagnostic errors. Similar points were highlighted in a previous study that highlighted HbE syndromes as an emerging diagnostic challenge in North India and emphasized the importance of careful interpretation of HPLC findings in regions where HbE is not traditionally prevalent.[20]

The detection of HbE in Uttar Pradesh underscores that the variant is no longer restricted to Northeast India. This finding is consistent with emerging reports from North India.[10,11] The clinical significance of detecting the HbE trait lies not in treating the carrier, but in genetic counselling.[21] Co-inheritance of HbE with β-thalassemia produces compound HbE-β-thalassemia. Two such cases were identified in this study demonstrating marked anemia (Hb 7.55 ± 1.05 g/dL). Compound HbE-β-thalassemia can also present with significant morbidity, mimicking β-thalassemia major.[22] Our findings support inclusion of HbE in national antenatal screening protocols, which currently focus predominantly on β-thalassemia. Identifying HbE carriers during early pregnancy allows for timely partner screening and prenatal diagnosis to prevent such severe outcomes.

While HbE was a primary focus due to its emerging prevalence, our screening also identified the Heterozygous HbD Punjab trait in 8 cases (6.15%) of the hemoglobinopathy cases. Although the overall prevalence in the total screened antenatal population was 0.34%, its position as the third most common variant in our cohort is significant. HbD Punjab is classically characteristic of North-Western Indian populations, where regional prevalence is traditionally estimated around 2.0%.[23] Its notable frequency within our Kanpur cohort further underscores the complex genetic admixture and shifting epidemiology across Uttar Pradesh. Similar to the HbE trait, the HbD Punjab trait is clinically silent but holds severe reproductive implications; co-inheritance with β-thalassemia or HbS can lead to clinically significant chronic hemolytic conditions.[24] This reinforces the necessity of comprehensive, broad-spectrum HPLC screening during antenatal care rather than targeted screening alone.

Limitations of the Study

This study was conducted at a single centre, which may limit the generalizability of the findings to other regions with different population characteristics. The sample size, although adequate for common hemoglobinopathies, was relatively small for rare variants, restricting detailed analysis of these conditions.

Diagnosis was based on HPLC, which may limit precise characterization of uncommon or borderline cases. Furthermore, other rare variants such as Hb D-Iran can also co-elute in this window on the Bio-Rad D-10 system. Definitive differentiation between HbE and Hb D-Iran requires alternative techniques like capillary electrophoresis or molecular analysis, which were not employed in this study.[25]

CONCLUSION

HbE is classically prevalent in northeastern India, but HbE trait has emerged as the second most common hemoglobinopathy detected during antenatal screening in our cohort. The HbE trait is a largely asymptomatic condition characterized by mild hematological variations and a distinct HPLC pattern where the variant co-elutes in the HbA_2 window. Its importance lies in its potential to form compound heterozygous states such as HbE–β-thalassemia, which can present with significant morbidity. However, because HbE trait lacks outward clinical signs, it often goes unnoticed until a child is born with severe compound HbE-β-thalassemia. This study from a tertiary center in North-India strongly supports the need for universal HPLC-based antenatal screening programs to identify silent carriers, and empower couples with informed reproductive choices.

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