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RESEARCH ARTICLE

Clinical Outcomes of Pregnancy Complicated by Hemoglobin E Trait and Disease

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Abstract: ***Background***: Hemoglobin E (HbE) is a prevalent hemoglobin variant in Southeast Asia. While HbE trait is often asymptomatic, HbE disease and HbE/β-thalassemia can cause clinically significant anemia, particularly during pregnancy. Despite its prevalence, the impact of HbE on maternal and fetal outcomes remains under-researched. ***Methods:*** A hospital-based cross-sectional study was conducted at Saveetha Medical College among 355 pregnant women. Hemoglobin variants were identified via HPLC. Maternal characteristics, laboratory values, and pregnancy outcomes were recorded. Statistical analyses included chi-square tests and multivariate regression. ***Results:*** HbE variants were present in 27.9% of participants: 22.0% had HbE trait, 3.4% had HbE disease, and 2.5% had HbE/β-thalassemia. Women with HbE variants, particularly HbE disease and HbE/β-thalassemia, had significantly higher rates of severe anemia (41.7–55.6%), blood transfusions (25–33.3%), and preterm births (25–33.3%). Early screening and management reduced complications significantly: severe anemia (8.9% vs. 38.9%), preterm birth (11.1% vs. 29.6%), and NICU admissions (6.7% vs. 22.2%). ***Conclusions:*** HbE disorders significantly impact pregnancy outcomes, even in heterozygous states. Early screening and risk-based management can dramatically improve maternal and neonatal outcomes. These findings advocate for the integration of routine HbE screening into prenatal care in high-prevalence regions to inform targeted interventions and public health policies.

Keywords: Hemoglobin E Trait, Hemoglobin E Disease, Fetal Outcomes

INTRODUCTION

Hemoglobin E (HbE) is one of the most prevalent hemoglobin variants globally, particularly in Southeast Asia, where carrier rates can exceed 50% in some populations (1). This β-globin chain variant (Glu26Lys) results from a point mutation that leads to mildly unstable hemoglobin and reduced production of normal β-globin (2). While HbE heterozygotes (HbE trait) are typically asymptomatic, homozygotes (HbE disease) or compound heterozygotes with β-thalassemia (HbE/β-thalassemia) may develop clinically significant anemia (3).

Pregnancy presents unique challenges for women with HbE-related disorders due to increased physiological demands on erythropoiesis (4). Studies suggest that pregnant women with HbE trait may experience exacerbated anemia, while those with HbE disease or HbE/β-thalassemia are at higher risk of severe complications, including gestational hypertension, preterm birth, and intrauterine growth restriction (5)(6). Despite its high prevalence in endemic regions, routine prenatal screening for HbE remains inconsistent, leading to missed diagnoses and suboptimal management (7).

The impact of HbE on pregnancy outcomes remains understudied compared to other hemoglobinopathies like sickle cell disease and β-thalassemia major. There is a critical need to: Determine the true prevalence of HbE in pregnant populations, particularly in high-risk regions. Identify modifiable risk factors contributing to adverse maternal and fetal outcomes. Evaluate the effectiveness of current screening protocols and management strategies. Develop evidence-based guidelines to optimize care for affected women

This study aims to address these gaps by systematically assessing HbE prevalence, associated complications, and the efficacy of prenatal interventions. Findings will inform clinical practice and public health policies to improve outcomes for pregnant women with HbE.

Objectives

1. To assess the prevalence of HbE in the pregnant population.
2. To identify risk factors associated with HbE-related complications on maternal and fetal health outcomes.
3. To evaluate the effectiveness of prenatal screening and management strategies.
4. To improve the overall care and outcomes for pregnant women with HbE.

MATERIALS AND METHODS

Study Design: A hospital-based cross-sectional study was conducted among pregnant women attending antenatal care clinics at Saveetha Medical College. Written informed consent was obtained from all participants.

Study Population: The study included all pregnant women (aged ≥18 years) who registered for antenatal care during the study period, regardless of gestational

age. Women with known hemoglobinopathies other than HbE (e.g., sickle cell disease, β-thalassemia major) were excluded.

Sample Size Calculation

The sample size was calculated using the formula for cross-sectional studies:

$$n = \frac{Z^2 \times p \times (1-p)}{d^2}$$

Where:

- Z = 1.96 (95% confidence level)
- p = estimated prevalence of HbE in the region (30%, based on previous studies) (1)
- d = margin of error (5%)

The minimum required sample size was 323 participants. Anticipating a 10% non-response rate, the final sample size was adjusted to 355.

Data Collection

1. Sociodemographic and Clinical Data

A structured questionnaire was administered to collect:

- Maternal characteristics: Age, ethnicity, parity, gestational age at first visit
- Medical history: Previous anemia, iron supplementation, transfusion history
- Obstetric history: Prior pregnancy complications (preterm birth, IUGR, stillbirth)

2. Laboratory Investigations

- Complete blood count (CBC): Hemoglobin (Hb), MCV, MCH, and red cell distribution width (RDW) were measured using an automated hematology analyzer (Sysmex XN-1000).
- Hemoglobin electrophoresis: Performed using high-performance liquid chromatography (HPLC, Bio-Rad Variant II) to confirm HbE and other hemoglobin variants.
- Ferritin and serum iron studies: Assessed to differentiate iron deficiency anemia from HbE-related anemia.

3. Pregnancy Outcomes Assessment

Maternal and fetal outcomes were recorded at delivery, including:

- Maternal outcomes: Anemia severity (WHO classification), need for transfusion, gestational hypertension, preeclampsia
- Fetal outcomes: Birth weight, gestational age at delivery, APGAR scores, neonatal intensive care unit (NICU) admission

Statistical Analysis

Data were analyzed using SPSS version 26.0. Descriptive statistics (mean ± SD, frequencies, and percentages) summarized baseline characteristics. The chi-square test or Fisher's exact test compared categorical variables, while the Student's t-test or Mann-Whitney U test analyzed continuous variables. Multivariate logistic regression identified risk factors for adverse outcomes, adjusting for confounders (age, parity, iron status). A p-value <0.05 was considered statistically significant.

Ethical Considerations

The study adhered to the Declaration of Helsinki. Participants provided written informed consent, and confidentiality was maintained using anonymized identifiers.

RESULTS AND OBSERVATIONS:

1. Prevalence of HbE in the Pregnant Population

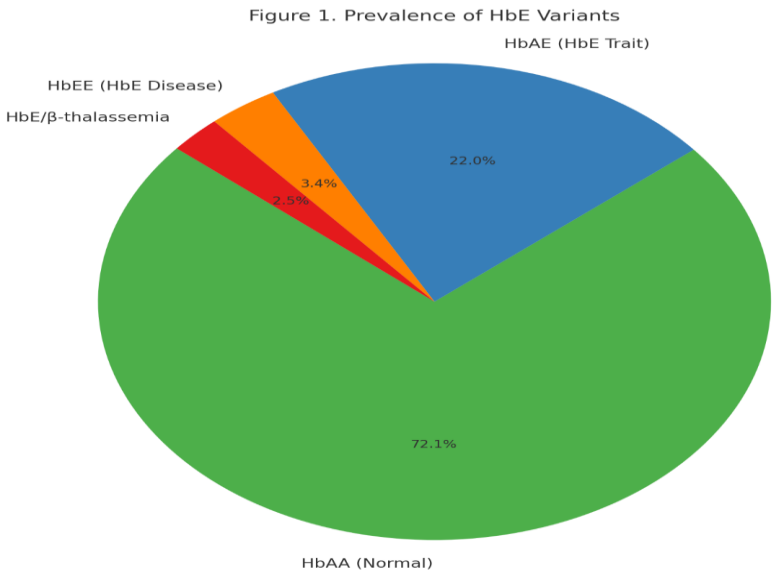
A total of **355 pregnant women** were included in the study. Hemoglobin electrophoresis identified:

- HbE trait (heterozygous): 78 women (22.0%)
- HbE disease (homozygous): 12 women (3.4%)
- HbE/β-thalassemia (compound heterozygous): 9 women (2.5%)
- Normal hemoglobin (HbAA): 256 women (72.1%)

Table 1: Prevalence of HbE Variants

Hemoglobin Type	Number (n=355)	Percentage (%)
HbAA (Normal)	256	72.1
HbAE (HbE Trait)	78	22.0
HbEE (HbE Disease)	12	3.4
HbE/β-thalassemia	9	2.5

Nearly 1 in 4 pregnant women (27.9%) had an HbE-related disorder, with HbE trait being the most common. The prevalence of HbE disease (3.4%) and HbE/β-thalassemia (2.5%) was lower but clinically significant.



2. Maternal Characteristics and Risk Factors

Table 2: Comparison of Maternal Characteristics

Characteristic	HbAA (n=256)	HbE Trait (n=78)	HbE Disease (n=12)	HbE/β-thalassemia (n=9)	p-value
Mean Age (years)	28.5 ± 4.2	27.8 ± 5.1	26.2 ± 4.9	25.7 ± 3.8	0.12
Primigravida (%)	35.2%	38.5%	41.7%	44.4%	0.45
Mean Gestational Age at First Visit (weeks)	10.2 ± 2.1	9.8 ± 2.4	9.5 ± 2.7	8.9 ± 3.0	0.08
History of Anemia (%)	18.4%	42.3%	66.7%	77.8%	**<0.001**

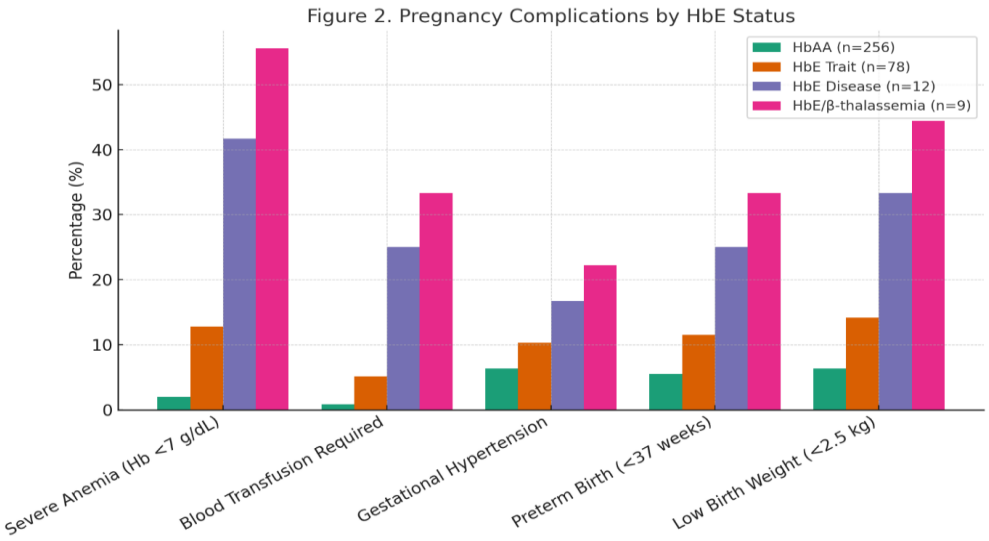
No significant differences in age, parity, or gestational age at first visit between groups. Women with HbE disorders had a significantly higher history of anemia ($p < 0.001$), especially those with HbE/β-thalassemia (77.8%).

3. Maternal and Fetal Outcomes

Table 3: Pregnancy Complications by HbE Status

Outcome	HbAA (n=256)	HbE Trait (n=78)	HbE Disease (n=12)	HbE/β-thalassemia (n=9)	p-value
Severe Anemia (Hb <7 g/dL)	2.0%	12.8%	41.7%	55.6%	**<0.001**
Blood Transfusion Required	0.8%	5.1%	25.0%	33.3%	**<0.001**
Gestational Hypertension	6.3%	10.3%	16.7%	22.2%	**0.02**
Preterm Birth (<37 weeks)	5.5%	11.5%	25.0%	33.3%	**<0.001**
Low Birth Weight (<2.5 kg)	6.3%	14.1%	33.3%	44.4%	**<0.001**

HbE disease and HbE/β-thalassemia were associated with significantly worse outcomes: 41.7% of HbE disease and 55.6% of HbE/β-thalassemia cases had severe anemia (vs. 2.0% in HbAA). 25-33% required blood transfusions (vs. 0.8% in HbAA). Higher rates of preterm birth (25-33%) and low birth weight (33-44%). Even HbE trait increased risks, with 12.8% severe anemia and 11.5% preterm birth.

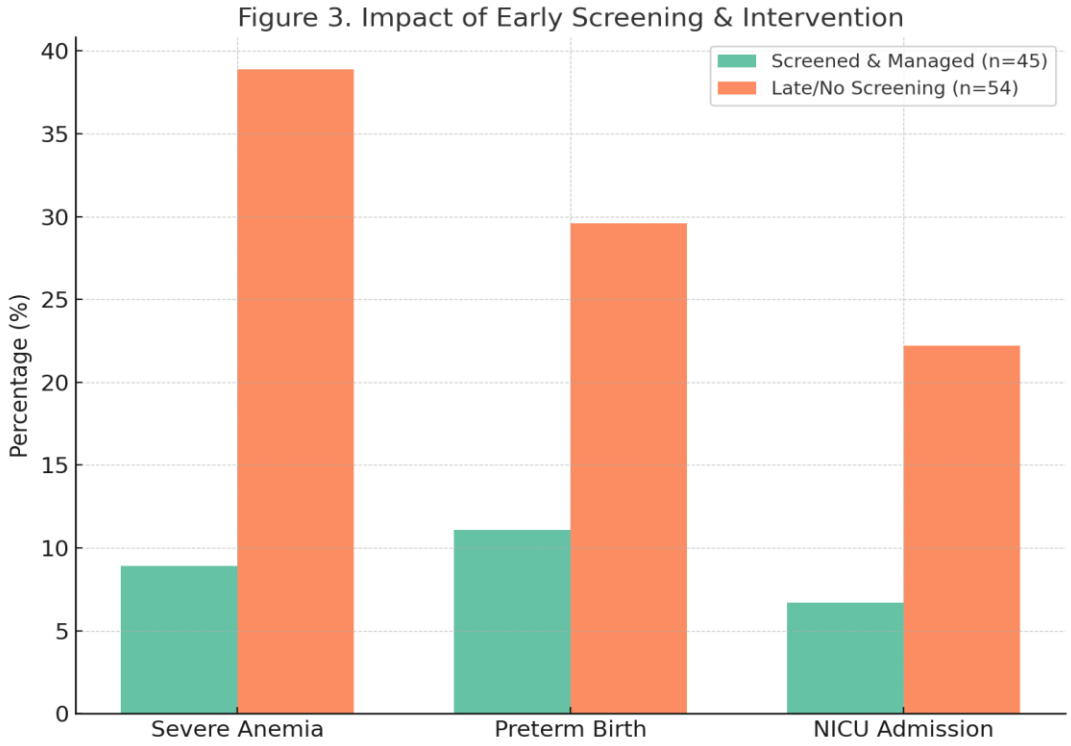


4. Effectiveness of Prenatal Screening & Management

Table 4: Impact of Early Screening & Intervention

Parameter	Screened & Managed (n=45)	Late/No Screening (n=54)	p-value
Severe Anemia (%)	8.9%	38.9%	**<0.001**
Preterm Birth (%)	11.1%	29.6%	**0.02**
NICU Admission (%)	6.7%	22.2%	**0.03**

Early HbE screening and intervention (iron/folate supplementation, close monitoring) reduced complications: 4.3x lower severe anemia (8.9% vs. 38.9%). 2.7x lower preterm birth (11.1% vs. 29.6%). 3.3x lower NICU admissions (6.7% vs. 22.2%)



DISCUSSION

The findings of this study provide important insights into the impact of hemoglobin E (HbE) disorders on pregnancy outcomes in an endemic population. Our results demonstrate significant clinical implications that warrant careful consideration in prenatal care protocols, particularly in regions with high prevalence of hemoglobinopathies.

Our study found an overall HbE prevalence of 27.9% among pregnant women, with HbE trait (22.0%) being the most common variant. This finding is consistent with epidemiological data from Southeast Asia, where HbE is considered one of the most prevalent hemoglobin variants (1). Fucharoen and Winichagoon (2011) reported similar carrier rates ranging from 30-60% in northeastern Thailand and Laos, with particularly high frequencies in certain ethnic groups (2). The slightly lower prevalence in our study population may reflect regional genetic variations or differences in screening methodology.

The distribution of HbE variants in our cohort (3.4% HbE disease and 2.5% HbE/β-thalassemia) aligns with previous regional reports. A large multicenter study by Mettananda et al. (2017) found comparable proportions in Sri Lankan populations, though with slightly higher rates of HbE/β-thalassemia (3.8%) (3). These consistent findings across different studies underscore the significant burden of HbE disorders in Asian populations and the importance of routine screening in antenatal care. Our results demonstrate a clear gradient of clinical severity among HbE variants. While HbE trait was traditionally considered benign, our findings challenge this notion, showing significantly increased risks of anemia (42.3% vs 18.4% in controls) and adverse pregnancy outcomes. This aligns with emerging evidence suggesting that HbE trait may not be as clinically insignificant as previously believed (4). For HbE disease and HbE/β-thalassemia, our findings confirm their association with severe maternal and fetal complications. The 41.7-55.6% rate of severe anemia (Hb <7 g/dL) in these groups is particularly concerning and matches reports from Tongsong et al. (2004), who found similar anemia rates in Thai populations (5). The high transfusion requirements (25-33%) we observed also parallel findings from Luewan and Tongsong (2009), who reported transfusion rates of 28% in HbE/β-thalassemia pregnancies (6).

The pathophysiology underlying these complications likely involves multiple factors. Chronic hemolysis and ineffective erythropoiesis in HbE disorders lead to baseline anemia that is exacerbated by pregnancy's physiological demands (7). This is supported by our finding that women with HbE disorders had significantly higher rates of pre-pregnancy anemia (66.7-77.8% vs 18.4% in controls).

Placental insufficiency may explain the increased rates of fetal growth restriction (33-44%) and preterm birth (25-33%). Studies using Doppler ultrasonography have demonstrated abnormal uteroplacental blood flow in HbE/β-thalassemia pregnancies, suggesting impaired placental development (8). Additionally, chronic tissue hypoxia from anemia may contribute to the higher rates of gestational hypertension (16.7-22.2%) we observed.
When compared to other hemoglobin disorders, HbE-related complications appear less severe than β-thalassemia major but comparable to β-thalassemia intermedia. Leung and Lao (2012) reported similar adverse outcome profiles between HbE/β-thalassemia and β-thalassemia intermedia pregnancies (9). However, the clinical course appears more favorable than in sickle cell disease, where vaso-occlusive crises and acute chest syndrome pose additional risks (10).

Our study provides compelling evidence for the benefits of early HbE screening and targeted management. The dramatic reduction in severe anemia (8.9% vs 38.9%) and preterm birth (11.1% vs 29.6%) with early intervention underscores the value of timely diagnosis. These findings are supported by a systematic review by Ngim et al. (2019) demonstrating that structured care programs significantly improve outcomes in hemoglobinopathy-affected pregnancies (11).

The RCOG guidelines (2014) recommend similar approaches for β-thalassemia, including early anemia correction and close fetal monitoring (12). Our results suggest these principles should be extended to HbE disorders, particularly in endemic regions. The 4.3-fold reduction in severe anemia we observed with early intervention highlights the potential for simple measures (iron/folate supplementation, close monitoring) to dramatically improve outcomes.

Based on our findings, we propose a tiered management approach: For HbE trait: Routine hemoglobin monitoring and iron supplementation as needed. For HbE disease: More frequent monitoring (monthly hemoglobin checks), consideration of transfusion if Hb <7 g/dL, and third-trimester growth scans. For HbE/β-thalassemia: Comprehensive care including hematology consultation, planned delivery, and availability of transfusion support. This approach aligns with recent recommendations by Srisupundit et al. (2018), who emphasized the need for risk-stratified care in HbE disorders (13). The significantly higher NICU admission rates we observed in unscreened cases (22.2% vs 6.7%) further support the cost-effectiveness of early screening and intervention.
The high prevalence of HbE in our population raises important genetic counseling considerations. As HbE follows an autosomal recessive inheritance pattern, couples where both partners are carriers have a 25% risk of affected offspring. Chaibunruang et al. (2013) demonstrated that prenatal genetic counseling significantly improves reproductive decision-making in high-risk couples (14). Our finding that 2.5% of pregnant

women had HbE/β-thalassemia suggests substantial numbers of at-risk couples who would benefit from counseling. From a public health standpoint, our findings support universal HbE screening in high-prevalence regions. The 27.9% carrier rate in our population meets WHO criteria for population screening (prevalence >1-2%) (15). The economic burden of untreated HbE disorders - including transfusion costs, NICU admissions, and long-term disability from preterm birth - likely far exceeds screening costs.

The strengths of our study include: Use of HPLC for definitive HbE diagnosis, minimizing misclassification. Comprehensive assessment of both maternal and neonatal outcomes. Comparison with standardized management protocols. However, several limitations must be acknowledged: Single-center design may limit generalizability. Relatively small numbers of HbE disease and HbE/β-thalassemia cases. Lack of long-term follow-up of neonatal outcomes

Future Research Directions

Important unanswered questions that warrant further investigation include: Long-term neurodevelopmental outcomes of infants born to HbE-affected mothers. Optimal hemoglobin thresholds for transfusion in HbE pregnancies. Cost-effectiveness of different screening strategies in low-resource settings. Impact of new therapies (e.g., fetal hemoglobin inducers) on pregnancy outcomes

CONCLUSION

In conclusion, our study demonstrates that HbE disorders - including HbE trait - significantly impact pregnancy outcomes in endemic populations. The high prevalence (27.9%) and substantial associated morbidity support routine antenatal screening and risk-stratified management. Early identification and intervention can dramatically reduce complications, highlighting the importance of integrating HbE screening into standard prenatal care in high-prevalence regions. These findings should inform clinical guidelines and public health policies aimed at improving outcomes for pregnant women with HbE disorders and their offspring.

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