Original Article

Maternal and fetal outcome in pregnancy with HbE Hemoglobinopathy in high prevalence area of North Bengal at Tertiary Health Care Facility

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Introduction : This study is unique and first in the literature which compares feto-materanl outcome in HbE hemoglobinopathy mother with other anemic mother but without any hemoglobinopathy in the HbE high prevalence area of North Bengal as this group present in pregnancy as a special scenario.

Aims : Main objective of this study is to compare the feto-maternal outcome of pregnancy in HbE variant antenatal anemic women with respect to other antenatal anemic women with normal hemoglobin variant.

Methodology : It is a prospective cohort study. Anemic antenatal mothers are screened for HbE hemoglobinopathy by HPLC.They are grouped into Case group (HbE variants) and control group (anemic but with normal Hb variant).They are followed up till termination of pregnancy for detection of antenatal, intranatal, postnatal complication and neonatal or pregnancy outcome. Multiples variables are analyzed and compared with each group.

Results : The main outcome from this study is mean Hb concentration is significantly lower in HbE variant mothers than normal Hb variant antenatal anaemic mothers with more need for blood transfusion in postpartum period. Maternal hospital stay is also more in HbE variant mothers. Incidence of prematurity, fetal distress, and low APGAR score baby are high in HbE variant mothers. Neonatal respiratory distress syndrome and SNCU admissionare more in HbE variant mothers. Low birth weight baby is not significantly high in HbE variant mothers inspite of prematuirity.

Conclusion : In high prevalence area of HbE hemoglobinopathy adverse feto-maternal outcome is expected and regular antenatal check-up with monitoring for fetal growth and institutional delivery with good SNCU facility for newborn care is paramount for optimal feto-maternal outcome.

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Key words **: Anemia in pregnancy, Hemoglobinopathy HbE.**

Hemoglobinopathies are a diverse group of inherited disorders of hemoglobin production and function. They are the most common single-gene disorders that remain distributed in various frequencies throughout the world. In general, they can be classified broadly in two groups. One group is, disorder that result from structurally altered hemoglobin molecules (like sickle cell anemia) and another, that arises from numerical imbalance of otherwise normal globin chain synthesis (like β-thalassemia).

Cumulative gene frequency of haemoglobinopathy in India is 4.2%[1]. While the general incidence of thalassemia trait and sickle cell haemoglobinopathies in India varies between 3-17% and 1-44%[2] respectively because of consanguinity and caste and area endogamy, some communities show a very high

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Editor's Comment :

- **HbE hemoglobinopathyis associated with adverse feto-maternal outcome.**
- **Affected mother is more anaemic with more need for blood transfusion in postpartum period.**
- **Incidence of prematurity, fetal distress, and low APGAR score baby are high in HbE variant mothers.**
- **Neonatal respiratory distress syndrome and SNCU admissionare more in HbE variant mothers.**
- **Institutional delivery with good SNCU facility for newborn care is paramount for optimal feto-maternal outcome.**

incidence, making these diseases a major public health problem in our country[2,3].

HbE is the commonest abnormal hemoglobin variant in North-Eastern Region with prevalence of 7-50% and 1-2% in West Bengal[4]. Hemoglobin E disorder falls under the first category; structural defect in globin chain. It ($\alpha_2\beta_2^{26\ glulys}$) is a variant of hemoglobin, resulting from single β chain substitution of lysine for glutamic acid at position 26 codon of globin chain molecule[2]. Hemoglobin E is inherited. Hence there remains a chance of vertical penetration to her offspring.

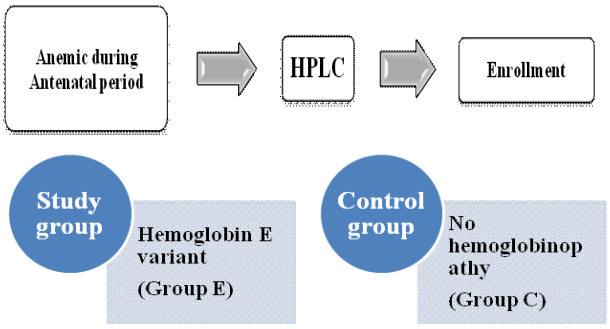
North Bengal comprises of four Sub-Himalayan districts of West Bengal is ethnically distinct not only from the rest of India but also from the rest of West Bengal. It is multi-ethnic and besides being inhabited by Bengalis, it is home to different population group like Rajbangsis, Marwaris and Hilly people like Nepalese, Bhutanese, Sherpa, Lepcha and many tribal populations like Santhals, Oraws and many others. In the plains of Darjeeling district, located in northern part of West Bengal, the Rajbangsis form a major chunk of the local inhabitants. The Rajbangsis are known to have a high prevalence of HbE mutation, though there is no published data till date. Subjects having HbE, either in homozygous or heterozygous state is otherwise normal but the probability of combining with β thalassemia trait can give rise to hemoglobin E-beta thalassemia. HbE-beta thalassemia can manifest as thalassemia minor, intermediate or even the grievous thalassemia major.

Obstetricians in these regions often face the pregnancies complicated by severe anemia, irrespective of any haemoglobinopathies. Moreover, being a zone highly prevalent with HBE, antenatal anemic women in scheduled visit occasionally revealed HBE trait or disease when advised for routine Hb electrophoresis. These causes confusion among the clinicians, as there is not enough data till date to estimate the severity and treatment of these anemic antenatal women with hemoglobin E. The purpose of this study lays on this context.

Thus, the main objective of this study is to compare the feto-maternal outcome of pregnancy in HbE variant antenatal anemic women with respect to other antenatal anemic women with normal hemoglobin variant.

Methodology :

It is a prospective cohort study done at Gynecology & Obstetric Department of North Bengal Medical College and Hospital during 1year period from June 2013- May 2014. All antenatal mothers are screened for Hb% and if they found to have anemia depending on cutoff value of Hb% 10gm/dl; they are selected in the cohort and advised for HPLC study. It is simple, rapid, sensitive, reliable method for detection of Hb variant. After that they are grouped into Case group (group E) include HbE variants and control group(group C) include anemic but normal Hb variant.After enrolment into specific group they are follow up till termination of pregnancy for detection of antenatal, intranatal, postnatal complication, mode of delivery and neonatal or pregnancy outcome. Multiples variables are analyzed and compared with each group.



Inclusion criteria for case:

a) Exclusive HbE variants

b) With other haemoglobinopathy in combined with HbE variant

Exclusion criteria for case:

a) Anemic women with unkown HbE status

b) Lost to follow up

c) Presence of other haemoglobinopathy without HbE variants

d) Expected date of delivery after study period

e) Critically ill moribund patient due to other chronic cause like chronic renal disease, heart disease, uncontrolled DM

Based on feasibility in North Bengal Medical College and Hospital we consider following statistical test values confidence level 95%, relative precision 20%, anticipated proportion of pregnancy complicated by anaemia with normal Hb variant 70%. Minimum sample size based on this is approximately 67 in each group [sample size determination in health study; SK Lwanga; Epidemiological and Statistical methodology; WHO table 8d]. In this study we finally taken 70 candidates in each group considering expected dropout.

Primary outcome of the study is to determine and compare antenatal, intranatal and postnatal complications in anaemic antenatal women with HbE variants versus anaemic women without haemoglobinopathies and to compare neonatal

outcome of women with HbE variants and women without hemoglobinopathy.

After completion of meticulous follow up all the characteristics are placed in master charts separately for HbE variant mother (group E) and normal Hb variant mothers (group C). Data was then entered in SPSS 16 for analysis (SPSS Inc, Chicago, IL, USA). Statistically significant is consider when P value is <0.05.

Results

Total number of cases in each group is 70. Majority of pregnancy is in 20-26 years women and almost equal in both groups that is 74.24% & 72.85% in group E and group C respectively. The age distribution in both the groups is comparable. More incidence of HbE variant is seen in high socio-economics status group. On the contrary, anemic but normal Hb variant mothers are in relatively lower socioeconomic status group as in those group of women incidences of nutritional anemia is relatively high.

Most of the mothers is primigravida (68.57% and 68.28% in HbE variants and normal Hb variant respectively). This is likely because of social factor that in 1st pregnancy most of the mothers attended in hospital than in subsequent pregnancy. Along with the fact that primigravida mothers more commonly referred to this tertiary hospital from peripheral hospital than multigravida mothers.

Mean Hb% in HbE variant mother was 8.20 gm% with standard deviation 1 and in anaemic normal Hb variant mother 8.64 gm% with standard deviation 0.7. This difference is statistically significant (P 0.002). Among the women with HbE variants most are HbE trait (AE) [58.57%]. No case of combination of HbE variants with sickle cell disease (SE) found. Only one case (1.42%) of HbE-β thalassemia found. Rest 40% is HbE disease (EE). Finding of study by Ong. HC *et al*[5] on Malayasian aborigine shows relative prevalence of different variants as follows: 71.2% with HbE trait abnormality, 17.6% with Hb E homozygous disease, and 11.2% with HbE-β thalassemia disease. The high frequency homozygous HbE (EE) in our study is probably due to area endogamy and poor premarital and pre-conceptional counseling.

Mean gestational age 37.28 with standard deviation 2.22 in study groups and 37.96 with standard deviation 2.23 in control groups. Total number of preterm deliveries was 24.61% in HbE variant & 13.43% in normal Hb variant respectively (P 0.04) (Table 1). In the study by Luewan S *et al*[6] there is three fold increased rate of preterm birth but in the study by Ong HC *et al*[5] there is no such increase rate of preterm birth is noticed. Table 1 also shows comparison of different modes of delivery and onset of labour process between two groups; the difference between them are not statistically significant.

Table 1

	Group E		Group C		P value
Mean Gestational age at delivery	37.28 wks with SD 2.2		37.96 wks with SD2.3		0.04
Gestation at time of delivery					
Preterm delivery	16	24.61%	9	13.43%	0.04
Term delivery (37-40wks)	42	67.74%	52	78.78%	
Postdated (>40wks)	4	6.45%	5	7.57%	
Mode of delivery					
Vaginal delivery	32	49.23%	42	62.68%	0.28
Forceps delivery	11	16.92%	8	11.94%	
LSCS	22	33.84%	17	25.37%	
Onset of labour					
Spontaneous labour	41	63.07%	50	74.62%	0.25
Induction of labour	17	25.15%	14	20.89%	

Antenatal complications like Preeclampsia, Heart failure, Antepartum haemarrhage, prelabour and/or preterm rupture of membrane, oligohydramnios, intrauterine growth restriction, gestational diabetes mellitus, urinary tract infection is not increase significantly in HbE variant mother in compared to normal Hb variant (Table 2). Study by Ong HC[5] revealed no increased in preeclampsia in HbE variant patients in compared to normal variant. So this study, to some extent support this event.

Study by Luewan S et al[6] heralded that increased incidence of IUGR in HbE variant mothers which is contradicted by this study. In the study by Ong HC[5] mean birth weight was significantly lower inspite of no increaserd prematuirity, this might be due to intra-uterine growth restriction, but it was not clearly mentioned in their study.

Incidence of fetaldistress was significantly high in HbE variant (27.58%) than normal Hb variant mothers (12.5%). [P 0.01] The probable explanation for this is cumulative effect of increased incidence of prematuirity,

Table 2

Antenatal complication	Group E (n= 65)		Group C (n=67)		P value
	Number	%	Number	%	
Preeclampsia	14	21.53	8	11.94	0.14
Heart failure	3	4.28	2	2.85	0.65
APH	5	7.69	2	2.98	0.23
PPROM	5	7.69	4	5.97	0.69
IUGR	5	7.69	3	4.48	0.43
Oligohydramnios	11	16.92	11	16.42	0.93
GDM	1	1.53	0	0	0.27
UTI	5	7.14%	3	4.28%	0.46

induction of labour and maternal complication like PIH, PROM, dysfunctional labour, abruptio placente in HbE variant mothers.

Although, percentage of dysfunctional labour (17.24%) is more in study group than control group (15.6%) but not statistically significance. Incidence of Abruptio placente, PPH, subinvolution, retained placenta is slightly high in HbE variant mothers that is 3.44%, 20%, 4.61%, 1.53% respectively compared to normal Hb variant mothers 1.56%,10.44%, 2,98%, 2.98% respectively; although the differences are not at statistically significant. Incidence of sepsis in HbE variant (2.85%) is higher than normal Hb variant (1.42%) mothers (P 0.56).Only 2(3.22%) cases had lactational problem after live birth in HbE mothers.

Total cases of blood transfusion in HbE group is 21(30%) which is significantly higher (P 0.07) than normal Hb variant anemic pregnant women (12 cases, 17.12%). Most of the transfusion re quired in post-partum period. No cases of reaction occurred in HbE variant mothers and there is also no major transfusion reaction. Mean duration of hospital stay is 5.18 day with standard deviation 3 in HbE variant mothers and in normal Hb variant mothers it is 4.3 days with standard deviation 3 (P 0.05).

Total live birth was 62(88.57%) and 66(94.28%) in HbE variant and normal Hb variant respectively (P 0.23). Incidence of abortion (7.14% vs 4.28%; P 0.46) and IUFD (2.85% vs 1.42%; P 0.55) was not significantly increased in HbE variant mother than control group. Also, in the study by Frischer H *et al*[7] pregnancy wastage is not increased among HbE mothers.

Among live birth babies; Mean APGAR score of HbE variant mothers at 1st is 5.51 (SD 1.6) and & at 5th min 8.64 (SD 1.8). This different in both groups is statistically significant (P 0.04). More newborn found to be mild to severely depressed in HbE variant mothers than normal Hb variant mothers (Table 3). Possible explanation for this difference may be due to more incidence of fetal distress, resulting in premature birth and low birth weight baby.In a prospective study by B Mahamuda *et al*[8] in Bangladesh mentioned significant increased incidence of lower gestational age baby with low APGAR score at 1st and 5th min depending of severity of anaemia. Another study by Nisha Shah *et al*[9] found significant high incidence of prematurity in anaemic mothers than normal mothers.

Mean birth weight is 2.623kg with standard deviation 0.6 in HbE variant mothers. It is 2.721kg with standard deviation 0.5 in normal Hb variant mothers. Mean bitrh weight is calculated in each groups excluding abortion but including still birth and IUFD. Maximum percentage of birth weight are in >2.5-3.5kg that is 61.23% & 77.27% in HbE and normal Hb variant mothers. But birth weight 1.5-2.5kg more frequent in HbE variant mothers than normal Hb variant mothers, 32.26% &16.67% respectively. But this difference is not statistically significant.

SNCU admission of newborns in HbE mothers is statistically significant (41.9% vs 24.2%; P=0.01).Regarding neonatal complication, only respiratory distress syndrome is significantly high in HbE variants mothers than normal Hb variant mothers. Other complications like jaundice, sepsis, meconium aspiration syndrome, necrotising enterocolitis & hypoglycemia are more in HbE variant mothers but not statistically significant (Table 4). Slightly increase percentage of perinatal death in HbE variant mother but it is not statistically significant (9.2% vs 5.9%; P= 0.48). This is likely due to advanced neonatal management in SNCU despite high frequency of neonatal morbidity in HbE variant mothers. The high incidence of neonatal morbidity likely due to increased frequency of preterm birth, fetal distress, low birth weight baby.

Conclusion

This study compares feto-materanl outcome in HbE hemoglobinopathy mother with other anemic mother but without any hemoglobinopathy in the HbE high prevalence area of North Bengal as this group present in pregnancy as a special scenario.

The main outcome from this study is mean Hb concentration is significantly lower in HbE variant

Table 3

Mean APGAR score	Group E (n=62)	Group C (n=66)	P value
1st min	5.51 (SD=1.6)	5.93 (SD=1.2)	0.04
5th min	8.64 (SD=1.8)	9.13 (SD=1.4)	0.04

Table 4

Complication	Group E (n=62)		Group C(n=66)		P value
	number	%	number	%	
Jaundice	16	25.81	11	16.67	0.21
Sepsis	10	16.13	7	10.61	0.35
Respiratory distress	8	12.90	2	3.03	0.03
Meconeum aspiration syndrome	3	4.84	1	1.52	0.28
Necrotizing enterocolitis	1	1.61	1	1.52	0.96
Hypoglycemia	1	1.61	0	0	0.29
SNCU admission	26	41.9	14	21.2	0.01
Perinatal death	6	9.23	4	5.96	0.48

mothers than normal Hb variant antenatal anaemic mothers with significantly more need for blood transfusion in postpartum period for HbEvariant mothers. Maternal hospital stay more in HbE variant mothers than normal variant mothers for pregnancy event. Incidence of prematurity, fetal distress, and low APGAR score baby are significantly high in HbE variant mothers than normal Hb variant mothers.Neonatal respiratory distress syndrome, SNCU admission are more in HbE variant mothers.Low birth weight baby is not significantly high in HbE variant mothers inspite of prematuirity.

In high prevalence area of HbE hemoglobinopathy adverse feto-maternal outcome is expected and regular antenatal check-up with monitoring for fetal growth and institutional delivery with good SNCU facility for newborn care is paramount for optimalfeto-maternal outcome.

Limitations: This study is a prospective cohort study with comparison between to groups of anemic mothers where one group in anemic due to HbE hemoglobinopathy and other group is anemic due to other causes. But the different causes of anemia in control group of mothers is not addressed, so that group is heterogenous. In this study, outcome of normal mothers without anemia is not compared with HbE mothers with anemia.

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