A prospective study on prevalence of thalassemic gene disorder and hemoglobinopathies in pregnancy: Antenatal and intranatal outcome in a hospital-based population of Eastern India

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ABSTRACT

Background: Thalassemia syndromes are autosomal recessive disorders and the most commonly inherited hemoglobinopathies in the world. Among these, β-thalassemia is the most common type of thalassemia in Eastern India and in West Bengal. Thalassemic mothers are more predisposed to maternal complications such as hypertensive disorders, gestational diabetes mellitus (GDM), and adverse neonatal outcome in terms of low birth weight, prematurity, etc. This study was to assess the effect of thalassemia gene disorder and hemoglobinopathies (thal-hbpathy) on fetomaternal health. **Aims and Objectives:** This study was done to evaluate the effect of thal-hbpathy on fetomaternal health and to compare their antenatal, intranatal outcome with control unaffected mothers, and with anaemic non-thalassemic mothers. **Materials and Methods:** This is a prospective and observational study of 150 women who attended tertiary care hospital during 18 months, fulfilling pre-defined inclusion and exclusion criteria. All women were evaluated during antenatal and intranatal period. Observations were recorded and interpreted. **Results:** Among 150 participants, 80(53.3%) were having normal hemoglobin (Hb) level and normal hemoglobin high performance liquid chromatography(Hb-HPLC), 54(36.7%) had anemia (Hb <10.9g/dl) with normal Hb pattern on HPLC, and 16(10.66%) had thal-hbpathy. Hb-HPLC revealed β-thalassemia trait in 7.3%, E β-thalassemia trait in 0.7%, whereas HbE heterozygous 2.7% in our study population. Majority (15/16) of thal-hbpathy patients were anemic. Oligo-hydramnios was detected in 18.7% of thalassemic women as compared to anemic (3.7%) and normal group (3.7%), which were significant. Obstetric cholestasis (OC) 12.5%(2/16) and intrauterine growth restriction (IUGR) were observed in thal-hbpathy group antenatal patients which were statistically significant P<0.05. **Conclusion:** Overall prevalence of thalassemia was 10.7%. The important fetomaternal complications observed were prematurity, IUGR, OC, oligohydramnios, OC(PIH), and GDM.

Key words: Anemia; Thalassemia;Haemoglobinopathies; Intrauterine growth restriction;Obstetric cholestasis; Gestational diabetes mellitus; High performance liquid chromatography.

INTRODUCTION

Thalassemia is an autosomal recessive disorder which affects the hemoglobin synthesis process.The genes that encode for globin proteins are located on β- and α-globin gene clusters of chromosomes 11 and 16, respectively.[1] It is the most common single gene disorder in the world causing significant morbidity and mortality in India and abroad.[2]
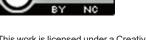
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Approximately 5% of the world population are carriers of hemoglobinopathies and about 2.9% are of thalassemia. Carriers are healthy individuals with mild anemia. Globally, there are 300,000–400,000 babies born each year with a Hb disorders.[1] Whereas Hb E has a substitution of lysine for glutamic acid at position 26 of the b-globin chain. This hemoglobin variant is particularly common in South-east Asia.[3] Combination of two hemoglobinopathy, that is, E – β thalassemia is common in Eastern India and in West Bengal. Thalassemia syndrome including β-thalassemia during pregnancy can present unique management challenges and requires close maternal and fetal surveillance.[2]

Identification of these disorders is immensely important epidemiologically and they can be detected by population screening.[4] Proper identification of hemoglobin variants during pregnancy can help in planning and timely intervention during pregnancy for optimization of fetomaternal outcome. As thalassemia disorder, that is, thalassemia major, E β-thalassemia is preventable condition, antenatal screening of hemoglobinopathies by high performance liquid chromatography (HPLC) should be made mandatory to decrease the disease burden. It can be easily implemented in target population by doing simple and cost-effective tests like HPLC.

Aims and objectives
The aim of the study was to compare pregnancy outcome among women with anemia having normal hemoglobin HPLC (Hb-HPLC) to those of thalassemic disease and non-thalassemic non-anemic mothers.

MATERIALS AND METHODS

The present study was prospective and observational study conducted in the Department of Obstetrics and Gynaecology at ESI-PGIMSR and ESIC Medical College, Joka, a tertiary care hospital in Kolkata. It was conducted over a period from January 2019 to June 2020. Ethical clearance was obtained from the Institutional Ethics Committee (date 04/01/2019 IEC No.412 (DEAN-JOKA)/IEC/2014-15/Vol 1). The study recruited 150 patients who attended antenatal clinic (ANC) satisfying inclusion and exclusion criteria

Sample size calculated according to standard formula:

$$4(P \times Q)/L^2$$

P=Prevalence - 4.61
Q=100-P-95.39
L=Error-3.5

Which comes out to be 143, so 150 women were recruited in the study.

Inclusion criteria
The following criteria were included in the study:

Pregnant women
a) Attending antenatal OPD irrespective of age and parity.
b) Anemia (Hb% ≤10.9g/dL).
c) History(h/o) of ≥1child born with thalassemia or hbpathies.
d) Family h/o of thalassemia or hbpathies.
e) Diagnosed cases thalassemia.

Exclusion criteria
The following criteria were excluded from the study:

a) Pregnant women with other established medical disorders like renal disease, cardiac disease, diabetes, hypertensive disorder, asthma, or any chronic medical condition before pregnancy.
b) Previous history of recurrent pregnancy loss, bad obstetric history, coagulopathy, and sepsis.
c) Women not willing toprovide written and informed consent.
d) Women with recent history of blood transfusion.

Study procedure
a) Strict protocol for inclusion and exclusion criteria was followed before recruitment of patients. Detailed history and examination including detailed general examination were done for every participant.
b) Study participants were subjected to complete hemogram, HPLC including serum ferritin and routine antenatal investigations.
c) Once selected for recruitment, proper counseling regarding diagnosis of thalassemia gene disorder and hemoglobinopathies was done and allocated in appropriate groups.
d) All patients in allocated groups were followed up in obstetrics department till delivery to monitor antenatal andintrapartum complications as well as maternal and perinatal outcome.
e) In all these three groups, pregnancy outcome was compared.

Data collection and interpretation
HPLC reporting for pregnant mothers is done after observing CBC, HbF, HbA, HbA2/E, MCV, MCH, MCHC, RDW values, and serum ferritin along with routine antenatal investigations.

Statistical analysis
Data were entered in Microsoft Excel Sheet; statistical analysis was done using SPSS software version 20. Data were summarized by routine descriptive statistics by

calculating percentages, mean with SD, median, and range. The statistical analysis with these three determining groups will be done using P<0.05 with 95% confidence interval.

RESULTS

The study was conducted on 150 pregnant women. The following results were obtained after analyzing the data (Table 1).

In this study, participants were divided in three groups:
- Group 1–Anemia –hemoglobin ≤10.9g/dL (Hb-HPLC) normal pattern.
- Group 2– Thalassemia gene disorder and hemoglobinopathies (thal-hbpathies).
- Group3– Normal – hemoglobin ≥11g/dL, Hb-HPLC is normal pattern.

Proportion of patients with anemia (36%) was significantly higher than that of the patients with thal-hbpathies (10.7%) (Z=4.50;P<0.0001), 53.3% patients had Hb≥11g/dL and HPLC normal.

Sixteen (10.7%) women had thal-hbpathies and out of them, 11(7.3%) were β-thalassemia trait. Anemia was present in 15 of these thal-pathies mothers. One patient having HbE heterozygous maintained normal hemoglobin throughout pregnancy and was undetected earlier before pregnancy. (Table 2).

Mean ferritin level was 19.2 ng/mL in anemia patients and in thalassemia patients, it was 47.3 ng/mL. P<0.000 is statistically significant. Mean ferritin was 64.3 ng/mL among normal hemoglobin group (Table 3).

The incidence of GDM inthal-hbpathies group is 12.5%, whereas it was noted in 6.2% in normal group,

Table 1: Distribution of the mothers according to Hb and Hb-HPLC

Diagnosis	Number	%
Anemia (Hb ≤10.9g/dL, HPLC normal)	54	36
Thalassemic gene disorder	16	10.7
Normal (Hb ≥11g/dL and HPLC normal)	80	53.3
Total	150	100

HPLC: High performance liquid chromatography

Table 2: Thal-hbpathies condition of the mothers as per HPLC findings

Thalassemia condition	Number	%(n=16)	%(n=150)
β-thalassemia trait	11	68.7	7.3
E β-thalassemia trait	1	6.3	0.7
HbE Heterozygous	4	25	2.7
Total	16	100	10.7

5.6% in anemic group. About 18.7% thal-hbpathies had oligohydramnios, whereas it was 3.7% in anemic and normal group each. Pregnancy hypertension was more or less equally distributed in all three groups with 6.2%, 5.6%, and 5% in thal-hbpathies, anemic, and normal group, respectively. About 12.5% thal-hbpathies women had obstetric cholestasis (OC), whereas it was 5.6%and 1.2% in anemic and normal groups, respectively.IUGR was found in 12.5% of thal-hbpathies group. It was 3.7% and 8.7% in anemic and normal group, respectively.

Women with anemia group had an increase incidence of hypothyroidism and polyhydramnios, that is, 14.8% and 1.8%, respectively, whereas in normal group, it was 11.2% and 1.2%. None of thal-hbpathies group had these complications (Table 4).

One (6.3%) woman in thal-hbpathies group required antenatal blood transfusion, which was statistically significant (P=0.011) (Table 5).

Corrected Chi-square (χ^2) test showed that there was significant association between caesarean delivery in thal-hbpathies group (P<0.0001) (Table 6).

DISCUSSION

Pregnancy with thalassemia is considered high risk for both mothers and fetus. Favorable outcomes can be obtained by continuous pre-conceptional, antenatal, and postpartum assessment. Pre-marriage counseling and prenatal screening of partners of thalassemic women should be done to decrease the thalassemic burden of the society. Prenatal diagnostic tests like CVS/NIPT should be done when both husband and wife are affected by thalassemia to decrease the number of babies born with thalassemia. Advances in chelation therapy along with regular transfusion have introduced a new era for thalassemic population.[5]

Our study highlighted the pregnancy complications of thal-hbpathies and comparison was done with the normal and anemic women. Very few studies were done in Eastern India to determine such outcomes in three groups mentioned earlier.

On analysis of the thal-hbpathies group (Table 2), we found 10.7% had thal-hbpathies, out of which 7.3% were β-thal trait, 0.7% were E β-thal trait, and 2.7% were HbE heterozygous. Similar observations were made by Mondal et al.,[2] who reported the prevalence of thal-hbpathies in 12.17% out of which β-thal trait was the most common abnormality (4.60%), followed by HbE trait (3.02%), β-thalassemia major/intermedia (1.66%),and E β-thal (1.16%) cases. Dolai et al.,[6] found β-thal trait in 10.38%,

Table 3: Distribution of mean ferritin (ng/ml) in groups

	Number	Mean	SD	Minimum	Maximum	Median	P value
Ferritin (ng/ml)							
Anemia	54	19.2	9.4	4.7	53	19	<0.0001
Thal-hbpathies	16	47.3	31.0	12.4	218.5	46	
Normal	80	64.3	17.4	5	100	60	

Table 4: Individual antenatal complications in present pregnancy distributed in three groups

Complication	Anemia (n=54) (%)	Thal-hbpathies (n=16) (%)	Normal (n=80) (%)	Total (n=150)(%)
GDM	3 (5.6)	2 (12.5)	5 (6.2)	10 (6.7)
Oligohydramnios	2 (3.7)	3 (18.7)	3 (3.7)	8 (5.3)
Pregnancy hypertension	3 (5.6)	1 (6.2)	4 (5)	8 (5.3)
Obstetric cholestasis	3 (5.6)	2 (12.5)	1 (1.2)	6 (4)
IUGR	2 (3.7)	2 (12.5)	7 (8.7)	11 (7.3)
Hypothyroidism	8 (14.8)	0	9 (11.2)	17 (11.3)
polyhydramnios	1 (1.8)	0	1 (1.2)	2 (1.3)

χ^2-5.07, P=0.75, not significant

Table 5: Antenatal blood transfusion in three groups

History of antenatal blood transfusion	Anemia	Thal-hbpathies	Normal	Total
Yes	0	1	0	1
No	54	15	80	149
Total	54	16	80	150

χ^2=9.06; P=0.011

Table 6: Mode of delivery and the patients of the three groups

Mode of delivery	Anemia	Thal-hbpathies	Normal	Total
Lower segment caesarean section	32	11	12	55
Normal vaginal delivery	21	5	63	89
Forceps	1	0	5	6
Total	54	16	80	150

χ^2=33.29; P<0.0001, significant

Hb E trait in 4.30%, sickle cell trait in 1.12%, borderline Hb A2 value 0.73%, low Hb A2 0.68%, and Hb D trait 0.37% which were almost similar to findings of our study. Three year retrospective study by Kasparek et al.,[7] on pregnant women in Switzerland, β-thalassemia trait was the most common hemoglobinopathy. In contrary to the findings of our study Berwal et al.,[8] and Chakrabarti et al.,[9] reported, E β-thal trait incidence ranges from 38.7–54%, followed by β-thal trait 12–29% on pregnant women in West Bengal.

In our study on analysis of mean ferritin level (Table 3), it was 58.1 μg/L in thal- hbpathies group and 64.3 μg/L for normal hemoglobin group. However, mean ferritin was reported by Chakrabarti et al.,[9] that was 19.2 μg/L for anemic pts with normal HPLC levels.In contrary to our findings, Berwal et al.,[8] observed the mean ferritin level 185.40±49.26 μg/L at the time of booking and 194.13±48.80 μg/L at the time of delivery. In Swiss study done by Kasparek et al.,[7] the median of ferritin level was 41 μg/L (4–623 μg/L).

In our study, we found oligohydramnios (18.7%) was the commonest obstetrical complication followed by GDM, cholestasis of pregnancy, and IUGR, 12.5% each in thal-hbpathies group of women (Table 4). But these findings were not statistically significant when compared to anemia and normal group. In a study by Berwal et al.,[8] observed that 26% women developed pregnancy hypertension, followed by IUGR (16%) and GDM (8%). About 46% of the patients had preterm labor. The study done in Thailand by Hanprasertpong et al.,[10] reported similar fetomaternal complications. However, they found significant risk of pre-eclampsia (RR-1.73, CI = 1.01–3.00) in their study. In a retrospective and case–control study done in Switzerland, significant increase in maternal complications, that is, abortion, GDM, urinary tract infection, intrahepatic cholestasis, and abnormal placentation was reported by by Kasparek et al.[7] In Iranian case–control study by Amooee et al.,[11] found significant correlation of oligohydramnios with β-thalassemia minor as compared to healthy control (10.8% vs. 5.4%, P=0.001), whereas no significant difference was found with pregnancy hypertension and gestational diabetes mellitus (GDM) and polyhydramnios. In our study, also oligohydramnios was the most common pregnancy complication in thal-hbpathies group.

Regarding blood transfusion (Table 5), only 1(6.3%) patient in thal-hbpathies group had history of antenatal blood transfusion, which was significantly higher than other two groups (χ^2=9.06; P=0.01, S-significant). In contrary to our study, Berwal et al.,[8] reported higher number of blood transfusion (mean=6.84±5.39) in thal-hbpathies group. That may be due to lower mean hemoglobin and high prevalence of HbE β-thalassemia and β-thalassemia homozygous in their study population.

About mode of delivery (Table 6) in our study, proportions of LSCS were significantly higher among the patients with thal-hbpathies (68.8%) followed by anemia (59.3%) as compared to normal group (15%) (Z=6.57; P<0.0001). However, by observing indications of LSCS, it is concluded that LSCS was not due to anemia or thal-hbpathies per se but due to coexisting adverse antenatal or intranatal complications. Amooee et al.,[11] also found that cesarean delivery was significantly higher in thal-hbpathies group compare to normal pregnant group (38.3% vs. 26.5%; P=0.001), which is similar to our study. Berwal et al.,[8] observed that maximum study population with thal-hbpathies group had vaginal delivery, only 14% had cesarean delivery, which was contrary to our study findings where caesarean deliveries are more in thal-hbpathies group, though the indications were almost similar. The study done by Ruangvutilert et al.,[12] there was no significant difference in cesarean rates between thal-hbpathies group and normal group. There were no differences regarding delivery mode and in rate of cesarean sections (49.4% vs. 43.6%; P=0.227, RR=1.26, 95% CI=0.86–1.85) in a retrospective Swiss study done by Kasparek et al.[7]

Limitations of the study
The study had limited sample size and shorted duration of study. The uneven distribution of patients in the anemic and thalassemia hemoglobinopathy groups, statistical data could not be compared with precision. The study could not get scope for prenatal diagnosis of major thal-hbpathies as male partners of study populations were normal. The study did not analyze the diet, nutritional awareness, and other etiological factors responsible for anemic pregnant mothers, so as to prevent one of the silent factors for maternal and perinatal mortality and morbidity in our country.

CONCLUSION

Thal-hbpathies including β-thalassemia trait and HbE carrier are more prevalent in Eastern India. It needs strict implementation of outpatient screening among antenatal pregnant mothers. This will decrease the disease burden in offspring born with thalassemia major and other hemoglobinopathies. Thereby it will indirectly reduce the need for multiple blood transfusions, chelation therapy and associated financial burden to the society. The study also observed the importance of early diagnosis of anemic states and its early correction in the pregnancy to achieve the favorable fetomaternal outcome. The important maternal complications observed were oligohydramnios, GDM, OC, IUGR, and pregnancy hypertension. Although no significant findings were observed, larger studies are required to draw meaningful conclusion.

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