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ORIGINAL ARTICLE

AN OBSERVATIONAL STUDY ON THALASSAEMIA IN PREGNANCY AND ITS EFFECTS WITH A VIEW TO FIND MEASURES FOR REDUCTION OF ITS COMPLICATIONS AND IMPROVEMENT OF MATERNAL AND PERINATAL OUTCOME

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ABSTRACT: The thalassemia syndrome is the commonest genetic blood disorder, clinically divided into three broad groups: thalassemia major, intermedia and minor. Now-a-days, with adequate transfusion and chelation therapy, survival is prolonged into teens and early 20s and few successful pregnancies are possible. But, only a few studies are available on the effects of thalassemia in pregnancy. This study was conducted in the Department of G&O, NRS medical college, Kolkata with an objective to determine the frequencies of different types of thalassemia in pregnancy, its effects on pregnancy, find out measures to reduce the complications attributable to it during pregnancy, and to improve maternal and perinatal outcome.

INTRODUCTION: The thalassemia syndrome is the commonest genetic blood disorders, constituting a vast public health problem. The basic defect is reduced globin chain synthesis. Clinically, thalassemia syndrome is divided into 3 groups: thalassemia major, intermedia and minor. Patients of Thalassemia minor usually have no complaints except mild anemia during pregnancy without splenomegaly. Previously, a child born with homozygous β thalassemia would die in the first few years of life from anemia, congestive cardiac failure and intercurrent infection. But now a day, with adequate transfusion and chelation therapy, survival is prolonged into teens and early 20s and few successful pregnancies are possible. Thalassemia intermedia is a clinical designation, often used to characterize individuals who maintain their hemoglobin at 6- 9 gm. / dl without regular transfusion. Pregnant patients with thalassemia intermedia may present with moderate to severe anemia requiring transfusion to avoid heart failure. Without transfusion, fetal loss is up to 50% compared with normal fetal loss if Hb% is maintained more than 9 gm. % through transfusion. Interaction of thalassemia with other Hb variants like pregnancy with sickle cell β (0) thalassemia usually have history of abortion or stillbirth, on the other hand patients with sickle cell β (+) thalassemia, pregnancy is well tolerated except few complications during last two trimesters in the form of painful crisis before or just after delivery. Fetus of pregnant patients with Hb Bart's usually die in utero. Pregnant patients with HbH disease mainly present with anemia (Hb 4-6 gm. %) and some have miscarriages and some require transfusion. Thalassemia aggravates the hypercoagulable state of pregnancy requiring close monitoring during antepartum, intrapartum, and post-partum periods.

OBJECTIVES: The study was conducted with an objective to determine the frequencies of different types of thalassemia in pregnancy, its effects on pregnancy, find out measures to reduce the complications attributable to it during pregnancy, and to improve maternal and perinatal outcome.

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MATERIALS & METHODS: The study was conducted in the department of G&O, NRS medical college, Kolkata over 2 years. Those with mild anemia, mild jaundice with or without splenomegaly with low or normal Hb%, decreased MCV and MCH were investigated for thalassemia. Cut off value of MCV and MCH were taken as 80fl and 27pg respectively. Further investigation included hemoglobin electrophoresis on cellular acetate at alkaline Ph (8.2-8.6) which enabled the provisional identification of HbS, A, F, S/G/D, A_2 /C/E/O Arb, H, lepore and a other less common variants. In electrophoresis, if HbF > 2%, and a split HbA_2 band appears- it is useful in differentiating a chain from a β chain variant. Secondary screening also included an estimation of HbA_2 level. An increased HbA2 >3.7% with hypochromic microcytic red cell is virtually diagnostic of heterozygous β thalassemia. HbA_2 value of < 3.2 is usually considered normal, while those between 3.2 and 3.7 should be interpreted with care. Diagnostic work up included detailed history, clinical examination and laboratory tests. Laboratory tests included complete hemogram (Hb%, Hct, MCV, MCH, MCHC, total RBC count, platelet count RBC morphology, reticulocyte count), Coomb's test (selected cases), serum iron, TIBC, serum ferritin, LFT, routine examinations of urine, stool, bone marrow study (selected cases), chest x-ray, ECG, echocardiography(selected cases) and USG whole abdomen, including fetoplacental profile.

RESULTS: Average age of patients was 22 years (20-32yrs). Out of 31 patients, 8 (26.6%) were primigravida, 15 (48%) were 2nd gravida, & 8 (25.6%) were multigravida. Among 31 patients 4 (12.8%) had one 1st trimester miscarriage, 2 (6.4%) had prior more than one 1st trimester miscarriage. 4 patients (12.8%) received regular blood transfusion at an interval of 1-2 months, total > 15 units. 9 patients (28.8%) received irregular blood transfusion usually before delivery and in the post-partum period. 7 patients (22.4%) had family history of thalassemia. Out of 31, 17 (54.4%) had mild pallor, 4(12.8%) had moderate, and 10 (32%) had severe pallor. 12 (38.4%) had mild, 8 (25.6%) moderate, while 1 (3.2%) patient had severe jaundice.10 (32%) mothers had no jaundice. Out of 31, 3 (9.6%) had mild splenomegaly (length< 2 cm below costal margin), 2 (6.4%) had moderate splenomegaly (2 – 10 cm), 8 (25.6 %) had severe splenomegaly (>10 cm below costal margin), whereas 18 patients (57.6%) had no splenomegaly. Total RBC count of 31 patients ranged between 2.8 million/ml to 4.4 million / ml with an average of 3.2 million /ml. 3 patients (9.6%) had mild elevation of serum bilirubin (2 β thalassemia trait, 1 HbE trait). 13 patients (41.6%) had moderate elevation of bilirubin (12 E- β thalassemia, 1 sickle β thalassemia). 15 patients had normal bilirubin level (8 HbE trait, 7 β thalassemia trait). Out of 31, 6 patients had cardiomegaly on chest x-ray (5 E β-thalassemia, 1 β- thalassemia trait) whereas 25 patients had no abnormality (9 HbE traits, 9 β thalassemia trait, 7 E- β thalassemia). Out of 31 patients, 12 (38%) had ferritin level <1000 ng/ml, 10 (32%) patients had ferritin level between 1000- 2000 ng/ml, 4 (13%) had ferritin level > 2000ng/ml. 5 patients were unable to do ferritin level.

DISCUSSION: In two studies from Athens, Aessopos[1] (1999) and Daska lakis (1998) and their colleagues reported a total 31 pregnancies without severe complications. Kumar[2] and associates (1998) from Manipur, India described 32 women who had successful pregnancies. All of them stressed that underlying cardiomyopathy should be excluded and intensive surveillance is needed throughout pregnancy. Most of the patients were β-thalassemia major in their study. E hemoglobinopathy is more prevalent in this part of the country, so the patients in our study were

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mostly having E β thalassemia. In our study out of 31, 12 cases were E β thalassemia, 9 cases HbE trait, 9 cases were β thalassemia trait and 1 case was sickle β^+ thalassemia. Thalassemia minor patients presented only with mild anemia during pregnancy. White et al[3] (1985) and Landman, H[4]. (1988) found that these patients usually maintain Hb% around 10 gm. % and the lowest in 2nd trimester which is between 9-10 gm. %. In our study, thalassemia minor patients usually maintained Hb% >10 gm. % but 5 patients (27.5%) maintained Hb < 10 gm. % due to associated iron and folic acid deficiency (as indicated by serum ferritin). In their study, out of 31 patients, only 4 patients (12.8%) had mild IUGR, and 7 patients (22.4%) had moderate IUGR, but in the study of Sheiner E, Levy A; Yerushalmi R. Katz M[5], only 4.2% had IUGR. In our study, IUGR noted is much higher than other published data, may be due to associated malnutrition, built, other environmental and genetic influences over the pregnancy. In our study, 4 (12.8%) out of 31 patients had preterm delivery. But in the study of Sheiner E, Levy A; Yerushalmi R. Katz M[5], only 4- 6 % went into preterm labor. This higher rate of preterm labor in our study may be due to malnutrition, unhygienic condition and associated infections. In this study, thalassemia minor patients usually had mild pallor, and maintained Hb % between 8- 10 gm.% and MCV around 80 fl, but Gatto[6], Valentine and Neel[7] study (1942-48) showed MCV <75 fl. Anemia in thalassemia is usually microcytic and hypochromic. In this study, 10 patients (32%) had MCV > 80. Pregnancy itself causes some degree of macrocytosis; increase is usually around 4 fl. This may be the cause of increased MCV in these patients. However, in 1 patient (3.2%), MCV was > 100 fl probably due to associated folate deficiency.

In this study, thalassemia minor patients usually had no splenomegaly. Whipple and Bradford[8] (1936) found no splenomegaly in thalassemia minor patients. In β thalassemia minor, normally iron overload is not seen; however in some cases increased iron absorption from gut leading to hemosiderosis have been reported. In this study, ferritin level of β thalassemia minor is usually maintained < 1000ng/ dl and bilirubin is within normal range that correlates with the published data by Sheiner E, Levy A, Yerushalmi R. Katz M[5] on 2004(January). In this study, course of pregnancy in patients with thalassemia minor including perinatal outcome is favorable, only 3% had PPH, and 12-13% had preterm delivery, but this is similar to the non-thalassemic patients. Similar results are seen in the study by Sheiner E, Katz M[5], 2004. Here we found that the rate of caesarean section is similar to that of non thalassemic pregnant patients whereas Sheiner E, Levy A, Yerushalmi R Katz M[5] 2004 showed that thalassemia minor patients were more likely to have caesarean section than nom thalassemic parturient (16.9% vs. 12.2% respectively). But later it was found that thalassemia minor was not found as an independent risk factor for caesarean delivery. In our study, thalassemia minor patients maintained HbF level between 0.7-7% and that corresponds to published data (Wintrobe[9] & Damashek[10], 1940 - HbF maintained between 1-5%). Patients with E β thalassemia usually present with moderate to severe anemia with splenomegaly (moderate to severe). In this study, they maintained their Hb % between 6-8 gm. %. We found that 40% patients required either antenatal, intranatal or post natal blood transfusion. In a multicentric trial by six north-eastern medical institutes in US it was shown that 32% patients required regular and 40 % patients needed irregular transfusion. This disparity may be due to the fact that our study contained less number of patients and differences in the socio-economic status, built, environmental factor and availability of blood for transfusion. In our study, patients receiving regular blood transfusion maintained ferritin level >1500 ng/ dl and those who received irregular transfusion maintained their ferritin level > 1000ng/dl. But the multicentric study mentioned earlier showed mean peak ferritin level was 2743

ng/dl and 70% had ferritin level > 1000 ng/dl. We found that MCV in our subjects were 70fl. In large Italian study, Mazza et al[11], 1976 found the MCV was < 83 fl in 75% of patients. In our study, Eβ thalassemia patients usually had moderate to severe splenomegaly in 10 (32%) cases, and had raised bilirubin level in 11 (35%) cases, preterm deliveries in 6(22%) cases, and PPH in 7 (22%) cases. In our study, Eβ thalassemia patients had moderate to severe IUGR in 6 (20%) cases which is comparable (21%) with the multicentric study in United States. Mode of delivery is not dependent upon these clinical and biochemical parameter of thalassemia as is evident from both our study and that multicentric study. In this study, we had only 1 patient of sickle β^+ thalassemia who maintained Hb % level 9.2gm%, MCV >80 fl, HbF 23.9% and ferritin level of 732 ng/dl. She was mild anemic, with mild splenomegaly. She required blood transfusion in antenatal and intranatal periods. She had preterm labor, without PPH. She delivered a baby with moderate IUGR and had no crisis during labor or puerperium. In a study from Jamaica, Serjeant et al[12], 1973 found significant higher incidence of abortion and stillbirth in sickle β^0 thalassemia patients. Also they found painful crisis, before or just after delivery, severe PPH, eclampsia and convulsion secondary to subarachnoid hemorrhage.

CONCLUSION: From this study, we found that thalassemia trait and intermedia patients were fertile and conceived without aid. Pregnancy was uncomplicated in cases of thalassemia trait, and most of them did not require transfusion. E β thalassemia behaves like thalassemia intermedia. And successful pregnancy outcome is possible even with a baseline Hb% of 6-7gm/dl and pregnancy is not complicated with cardiac decompensation in spite of this low Hb value. Incidence of IUGR and preterm delivery is not increased when compared with non-thalassemia pregnancies.

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Hb%	Level	<7 gm.%	7-10 gm.%	>10gm%
	No. of patients	10 (32%)	12(38.4%)	9 (28.8%)
MCV	Level	<60 fl	60-80 fl	>80 fl
	No. of patients	3 (9.6%)	18(57.65%)	10 (32%)

Table 1. Hemogram (% of total number)

Range of haemoglobin of these patients was 5.2 gm. % - 11 gm. %, with an average of 8.6gm%. 10 patients had Hb% < 7gm%, 12 had 7-10 gm. %, and 9 had > 10 gm. %. MCV ranged between 50.8 to 101.4 fl. 3 had < 60fl, 18 patients had 60-80fl, and 10 had >80fl.

	Thalassemia minor		E-β Thalassemia	Sickle β^+ Thalassemia
	β Thal trait	Hb E trait		
Hb (gm. %)				
<7	0	1 (3.2%)	9 (38%)	0
7-10	7 (22%)	2 (6.4%)	2(6.4%)	1(3.2%)
>10	2 (6.4%)	7 (22.4%)	0	0
MCV (fl)				
<60	0	0	3 (9.6%)	0
60-80	7 (22.4%)	4 (13%)	7 (22.4%)	0
<80	2 (6.4%)	5 (16%)	1(3.2%)	1 (3.2%)

Table 2: Hemogram (%of total number)

	Thalassemia minor		E- β thalassemia	Sickle β^+ thalassemia
	β thal trait	HbE trait		
Hb % <8 gm.%	0	1 (3.2%)	10 (32%)	0
Splenomegaly >6 cm	0	0	9 (29%)	0
Hb F	1.1- 6.7 (28.8%)	0.7- 1.3 (28.8%)	6- 43 (35.2%)	23.9 (3.2%)
Transfusion requirement	0	1 (3.2%)	11 (35%)	1 (3.2%)

Table 3: Clinico-biochemical profile (%of total number)

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Out of 31, 9 patients (28.8%) had β thalassemia trait, 9 (28.8%) were HbE trait, 12 (38.4%) were E- β thalassemia, 1 (3.2%) was sickle (β^+) thalassemia. Amongst 31 patients, range of HbF was 0.7% to 43%. Patient with β thalassemia trait had HbE between 1.1% and 6.7%. Those with HbE trait had HbF 0.7% - 1.3%. Patients with E-β thalassemia had 6% - 43%, whereas, patients with sickle β^+ thalassemia had HbF 23.9%.

		β-Thalassemia trait	HbE trait	E- β Thalassemia	Sickle β^+ Thalassemia
Fetal loss		3 (9.6%)	2 (6.4%)	1 (3.2%)	1 (3.2%)
IUGR					
	Mild	2 (6.4%)	2 (6.4%)	5 (16%)	0
	Moderate	3 (9.6%)	4 (12.8%)	4 (12.8%)	1 (3.2%)
	Severe	0	0	3 (9.6%)	0
Preterm birth		1(3.2%)	3 (9.6%)	6 (19.2%)	1(3.2%)
PPH		0	1(3.2%)	8 (25.6%)	0
Postdated pregnancy		2 (6.4%)	0	0	0
Stillborn		0	0	2 (6.4%)	0

Table 4: Pregnancy outcome

Out of 31 patients, 9(28.8%) had mild IUGR. 12 (38.4%) patients among 31 had moderate IUGR. 3 (9.6%) had severe IUGR, all belonged to E- β thalassemia group. 7 (22.4%) patients had no IUGR.18 among 31 patients delivered at term. Out of 18 patients, 7(38.5%) were HbE trait, 6 (33%) were β thalassemia trait, and rest 5 (27.5%) were E β thalassemia. 11 (35.2%) had preterm delivery. Among them, 3 (27.9 %) were HbE trait, 1 (9.1%) was β thalassemia trait, and 6 (54.9%) had E β Thalassemia, 1 had sickle β thalassaemia.2 patient had postdated pregnancy, both were β thalassemia trait. PPH occurred in 9 (28.8%) patients- 8 (88.8%) amongst them were E β thalassemia, 1 (11.1%) was HbE trait.

Patients	Hb %(gm.)	Transfusion (unit)	Ferritin (ng/ml)	Type of thalassemia	IUGR	Associated features
1	6.4	2	2100	E β Thal	Severe	Malnutrition+ multiparity
2	6.4	2	1080	E β Thal	Severe	Malnutrition
3	5.8	13	1820	E β Thal	Severe	Malnutrition
4	8.2	3	1350	Hb E Trait	Moderate	Malnutrition
5	9.8	No	320	Hb E Trait	Moderate	No
6	9.8	No	250	β Thal trait	Moderate	No
7	9.2	2	752	Sickle β^+ thal	Moderate	No
8	6.9	8	2132	E β Thal	Moderate	Malnutrition
9	9.8	No	356	β Thal trait	Moderate	No
10	5.7	6	825	E β Thal	Moderate	Malnutrition+ short stature

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11	9.8	No	526	Hb E Trait	Moderate	No
12	10.2	No	494	Hb E Trait	Moderate	No
13	9.8	No	232	β Thal trait	Moderate	No
14	6.8	4	1650	E β Thal	Moderate	Malnutrition
15	8.4	2	-	E β Thal	Moderate	No

Table 5: IUGR (moderate to severe)

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