Carrier Screening Program for β-Thalassaemia and Other Haemoglobinopathies in Married and Pregnant Indian Women: Experience of 19767 Cases at Block level Hospitals of Nadia District in West Bengal and a Guideline for Screening and Diagnosis.

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Abstract— To control birth of thalassaemia major children by identification of risk couples prenatal diagnosis has been recommended. To study the prevalence of β thalassaemia trait in pre-pregnancy and pregnancy in population screening for β thalassaemia has been conducted for a period of 10 years. Blood samples were tested for complete blood count and HPLC. We present our experience of married and antenatal thalassaemia screening in block level district hospitals of Nadia district of West Bengal in India. All antenatal women presenting in those hospitals over 10 years were counselled for beta thalassaemia and other haemoglobinopathy screening. If the married woman was detected heterozygous for thalassaemia/haemoglobinopathy, partner screening was advised. If the husband was also detected to be heterozygous, the risk couple was offered prenatal diagnosis. A total of 3831 married and 14211 antenatal women were counselled for beta thalassaemia and for other haemoglobinopathy, with compliance in all the cases. Beta Thalassaemia heterozygosity was detected in 500 (29.1%) cases, HbE traits in 712 (41,4%) and other haemoglobin variants in 506(29.5%). The economic burden to the society for treating thalassaemic patients is huge. The institution of prevention programs like carrier screening has proven cost-effective in populations with a high frequency of carriers. Screening of pregnant women early in pregnancy followed by prenatal diagnosis is acceptable and effective strategy for control of thalassaemia in developing countries like India.

Keywords- β Thalassemia trait, Pregnancy, Haemoglobinopathies.

I. INTRODUCTION

India is a country comprising 1.44 billion people, 17.78% of the global population **(1)** and the largest populated country of the world and has a huge diversity in its population structure due to difference in ethnic, religion, language and geography **(2).** Most of the communities of India prefer to marry within their community; the noncommunicable diseases (genetic diseases) show great prevalence in some of the communities, while these noncommunicable diseases are either absolutely absent or present in different forms in other communities.

According to the study report "India: Health of the Nation's States"- The India State-Level Disease Burden Initiative in 2017 by Indian Council of Medical Research (ICMR), it is estimated that the proportion of deaths due to Non-Communicable Diseases (NCDs) in India have increased from 37.9% in 1990 to 61.8% in 2016 **(3).**In 2019, the World Health Assembly extended the WHO Global action plan for the prevention and control of NCDs 2013–2020 to 2030 **(4).**

Thalassaemia and haemoglobinopathies are the most common inherited noncommunicable disorders in humans and they represent one of the major public health problems in many parts of the world including India **(5).**The increase in number is because of consanguineous marriage which has a deep-rooted norm among many people globally. Besides various clinical and psychological problems associated with thalassaemia, a lifelong treatment aspect makes it much more difficult for a person or family to sustain with thalassaemia or thalassaemia-affected children. It has been estimated that the prevalence of pathological hemoglobinopathies in India is 1.2 per 1000 live births **(6),** and births per year is being estimated at approximately 27.72 million **(1).** These figures would suggest the annual birth of 33,264 babies with a serious haemoglobin (Hb) disorder. In 1989, the World Health Organization (WHO) Working Group had released guidelines for the control of Hb disorders with an estimated value of 3.9% carrier frequency for β-thalassaemia (β-thal) in India, encompassing all types of β-thal trait **(7).** A WHO update on β-thal in India indicated a similar overall carrier frequency of 3.0– 4.0%, which, given the current national population, would translate to between 35.1 and 46.8 million carriers of the disorder nationwide **(8,9).**

Though the government has come up with a screening programme for thalassaemia, given the fact that it is optional, people tend to ignore it. Examples from Pakistan and Iran remind us to have a mandatory prenatal screening programme which is very much cost-effective. Besides the continuous effort of the government in initiating the screening programmes, the gap still exists in the control and prevention of thalassaemia. With a highly recommended notion, we suggest that it should be universal to have an antenatal screening programme to avert thalassaemia-related deaths**(10).**The objective of this study is to document the

prevalence of thalassaemia carriers among married and pregnant women in Nadia district of West Bengal, India. Globally, several anti-thalassaemia screening programs played a pivotal role in decreasing the incidence of beta-thalassaemia**(11).** However, in India, some collective efforts at the national level are needed regarding the prevention and management of β-thalassaemia. The current study was executed to find out the prevalence of thalassaemia minor among married and pregnant females.

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II. MATERIALS AND METHODS

Participants were married women of block level district hospitals of Nadia district of West Bengal in India who divided into two groups (group I: married women group II: pregnant women / antenatal cases). These divisions were done to maximize the chances of reaching the roots of the disease for the purpose of immediate prevention. The most emphasis was given on group II, because if we get the information about their thalassaemia status, then their husbands would be screened and they can decide accordingly and eventually prevent the birth of β-thal major (β-TM) children and she could opt for prenatal diagnosis (PND) to find out the thalassaemia status of the fetus. If the fetus is found to carry β-TM, then she could always opt for medical termination of pregnancy, providing it is within the stipulated period of gestation according to the existing act of Medical Council of India. Emphasis was also given to group I (married women) because if the woman knows the thalassaemia carrier status of herself and her husband, and if both are found to be carriers, then also they could opt for prenatal diagnosis (PND) to find out the thalassaemia status of the fetus. Initially, the level of awareness in people of West Bengal was not great, so that there were not enough participants in the screening programs. But now state governments of India are taking initiatives and passed compulsory testing of blood for Haemoglobinopathies as the frequency of traits (both beta and HbE along with some other Hb variants) are increasing day-by-day.

Sometimes we also found that thalassaemia disease or even carrier status is a social stigma to the people. As our goal is to address the maximum number of carriers in the screening programs, and to prevent the further births of thalassaemic children, group II (pregnant women) were an easy target population to reach the maximum number of carriers likely to give birth to thalassaemic children. For a state like West Bengal, where there is great diversity of cultures, heritage, religion and socioeconomic structures and also there is consanguineous marriages, it is very difficult to address people from every class of the society by a single strategy. That is why different strategies were implemented in different situations to maximize the chance of addressing the affected and carriers.

Written consent for evaluation of thalassaemia and other haemoglobinopathy status was obtained from all participants as per guidelines of the institutional ethics committee. Peripheral blood samples were collected from every participant, in vials containing 5 mM EDTA. The handling of all human blood samples was carried out in accordance with the guidelines established by the Local Ethics Committee.

Basically, three levels were employed for screening the population. The initial screening was done by Hb and complete blood count (CBC) in an Automated Haematology Analyser (Cell Counter: Acculab CBC 360 neo 530; Acculab Biomedical Pvt Ltd, Mumbai, India and ABX Micros ES 60: Horiba Medical, Montpellier Cedex 4, France) using the manufacturer's protocol. The participants were evaluated for Hb, mean corpuscular volume (MCV), mean corpuscular Hb (MCH), mean corpuscular Hb concentration (MCHC), red blood cell distribution width (RDW) and haematocrit or packed cell volume (PCV). The complete and final screening was done through Hb variant analysis by high performance liquid chromatography (HPLC). Haemoglobin variants (Hb A, Hb F and Hb A2/E) were estimated by HPLC (VARIANT II; Bio-Rad Laboratories, Hercules, CA, USA) using the manufacturer's protocol. The screening was done following standard WHO guidelines for interpreting HPLC and CBC data.

III. RESULTS

A total of 19,767females, married girls of age <18 years (n=3831) and pregnant women (n=15936),were tested for their thalassaemia and other haemoglobinopathy status by the Ranaghat Thalassaemia Detection Centre (an Auxiliary unit of STCPWB), Ranaghat, Nadia, West Bengal; the samples were collected from different district hospitals of Nadia district of West Bengal; the results of these screening programs are summarized in **Table 1& Table 2.** Overall carrier frequency in married girls (age <18 years) was 10.88% **(Table 1)**and in pregnant females was 10.78%**(Table 2)**from the data of this Nadia district.

Table 1. Screening results of Married Girl cases in Nadia district of West Bengal (n=3831)

Normal	<18 yrs	Carrier	<18 yrs	Patient	<18 yrs
3408 (88.95%)	57 (1.48%)	417 (10.88%)	6 (0.15%)	6 (0.15%)	1 (0.02%)

Table 2. Screening results of Pregnant mother cases in Nadia district of West Bengal (n=15936) [Normal = 14211]

Total No	HbA0	HbA2	HbF	HbE	HbD	HbS	Hb	MCV	MCH	RDW
Carrier 1718 (10.78%)	74.65± 1.94	6.30± 3.67	1.11± 0.19	20.98 ± 12.15	15.3± 21.67	36.07± 1.31	10.25 ± 0.30	78.85± 3.28	25.50± 1.11	13.05± 1.80
Patient 07 (0.04%)	58.39± 47.38	63.2± 52.28	2.63± 2.91	-	-	8.96±1. 30	68.9± 16.55	25.13± 5.30	12.46± 2.23	63.2± 52.28

The most important focus of any screening program in Eastern part of India are the heterozygotes or carriers and the asymptomatic or less symptomatic β-TI, β-thal minor and HbE patients. Thus, we studied these data in more detail; HbE were found to be the most frequent allele in this district, comprising about 41.44% (n=712), as this district is adjacent to Bangladesh, where HbE haemoglobinopathy prevails. The distribution of different disease alleles [HbE, β-thal, HbD-Punjab (HBB: c.364 G4C),HbS (HBB: c.20A4T)] and other variants in this district of West Bengal is given in **Table 3**. In 1718 heterozygous/carriers, β-thal trait was found in 29.10% (n=500) cases and HbE trait was seen in 41.44%cases. 27 (1.57%) cases carried sickle cell trait and 23(1.34%) cases carried HbD-Punjab trait in 1718 heterozygotes. As HbE (41.44%) and the β-thal (29.10%) alleles comprise about 70.54% heterozygotes, so the prevalence of HbEE and HbE-β-thal should be higher in this Nadia district of West Bengal population, if proper prenatal diagnostic services not available.

The study revealed that severity of anaemia was observed among carriers of first trimester pregnant women,Hb level observed <7 g/dl in 0.79% (126/15936), <8 g/dl in 1.86% (297/15936), <9 g/dl in 6.06% (964/15936) and <10 g/dl in 25.09% (3998/15936) **(Table 4),** whereasnot among the normal ones **(Table 5).**

Table 3. Distribution of Carriers among Pregnant mothers in Nadia district of West Bengal (n=1718)

Type of Thal	No. of carrier	% (Out of 1718)
HbE	712	41.44
Beta	500	29.10
HPFH	8	0.46
Delta/Beta	3	0.17
HbD	23	1.34
HbS	27	1.57
Lepore	2	0.11
Other	443	25.78
Total	**1718**	

Table 4. Severity of anaemia in pregnant females in Nadia District

Haemoglobin g/dl	No. of females	% Percentage
<7	126	0.79
7-8	297	1.86
8-9	964	6.06
9-10	3998	25.09
10-11	5251	32.95
>=11	5300	33.25
Total	**15936**	**100**

Table 5. Blood parameters of Normal Pregnant mothers in Nadia district of West Bengal (n=14211)

Total Nos.	HbA0	HbA2	HbF	Hb	MCV	MCH	RDW
14211 (0.89%)	87.27± 15.27	3.12± 0.82	0.52± 0.42	11.02± 2.31	87.71± 18.03	28.07± 5.28	11.89± 2.99

Distribution of carriers and patients were studied by age group. About 0.80% (128/1718) of the pregnant women were below 18 years of age with a carrier detection rate of 17.96% (23/128), the highest carrier detection rate, followed by 13.22% (105/794)in the 18-21 years age group and >30 years age group and the lowest carrier detection rate was 10% (427/4266) in those of 21-25 years group **(Table 6).**The distribution of normal, carrier and patients among antenatal mothers were depicted in **Figures 1-5.**

Table 6 : Distribution of Normal, Carrier and Patients in age-wise Antenatal mothers [<18yrs and >18yrs](n=15936)

Age	Groups	Normal	Carrier	Carrier (%)	Patient	Total
<18yrs	I	105	23	17.96	0	128
18-21yrs	II	689	105	13.22	0	794
21-25yrs	III	3835	427	10.00	4	4266
25-30yrs	IV	5763	665	10.34	1	6429
>30yrs	V	3819	498	11.53	2	4319
Total (n)		**14211**	**1718**		**7**	**15936**

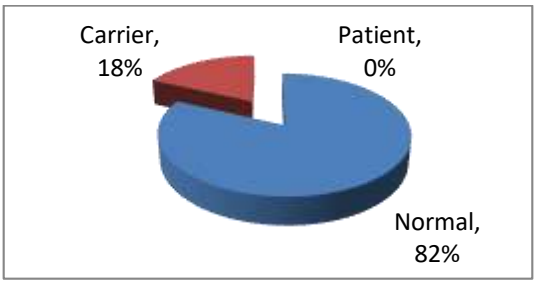

Fig 1.

Group-I (n=128) <18yrs

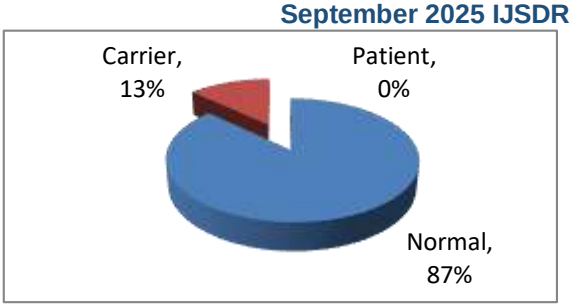

Fig.2

Group-II (n=794) 18-21yrs

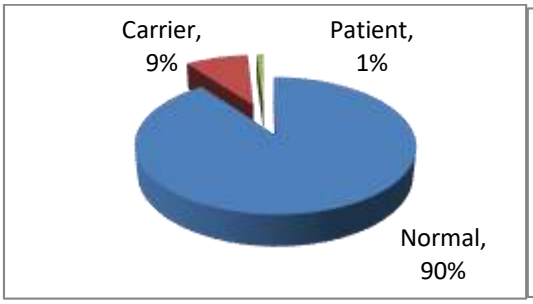

Fig 3

Group-III (n=4266) 21-25yrs

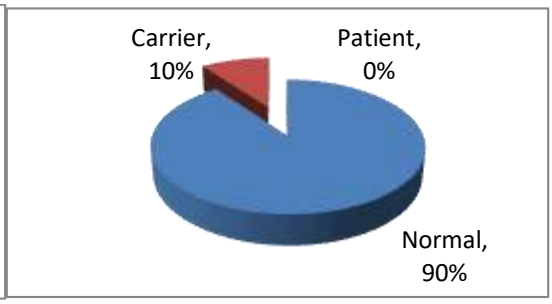

Fig 4

Group-IV (n=6428) 25-30yrs

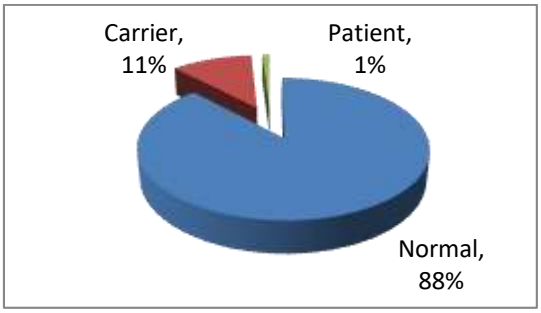

Fig 5

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Group-V (n=4319) >30yrs

IV. DISCUSSION

Thalassaemia carriers among married and pregnant women were detected across the Nadia district, West Bengal, India, in significant proportions.

Our study showed that the Beta thalassaemia carrier (trait) rate was 29.10%, and the Haemoglobin E carrier rate was 41.44%.Several studies have indicated that the outcome for thalassaemia carriers during pregnancy may be uneventful, but some have noted problematic outcomes such as severe gestational anaemia or pregnancy-induced hypertension**(12,13).** These findings underscored the importance of preventing the transmission of the carrier trait. Proper counselling should be given to individuals of premarital age and both married couples and antenatal mothers.All pregnant women shouldbe encouraged to undergo thalassaemia testing to identify their status, allowing for appropriate management.

Thalassaemia carrier status in pregnant women is a multidisciplinary problem. It not only affects the health of the pregnant mother but also poses a risk of transmission to the baby. The prevalence of thalassaemia carriers is very much high in the Nadia district. Maternal complications and deaths may be occurred due to thalassaemia carrier status. Approximately 66.74% (10,636/15,936) ofpregnant women were found anaemic (haemoglobin <11 g/dl).

There were severe anaemia (Hb <7 g/dl) also noted among 126 pregnant women in this district. To reduce pregnancy-related complications, it is crucial to screen for thalassaemia early in pregnancy and provide genetic counselling to the parents. Additionally, serum iron ferritin levels should be estimated before administering iron tablets to enhance haemoglobin levels.Raising awareness among higher secondary students about thalassemia will be helpful in reducing carrier transmission.Further studies on thalassaemia in pregnancy may contribute to preventing carrier transmission and reducing maternal complications in the future.

Results were also analyzed to establish which of the variables (MCV and MCH) were more suitable for screening and to determine suitable cut-off points for measuring the Hb A2/E percentage. The MCH was superior to the MCV (as it varies greatly in different haemoglobinopathy conditions) for thalassaemia screening as it was a more stable measurement. As in this population, the HbE traits and HbEE patients are very common, so here the MCV values cannot help to exclude traits/carriers even in case of some patients, since in so many cases the MCV values are more than normal. An MCH level of <27.0 pg can be taken as a suitable cut-off point for screening **(14).** Pregnant women presenting at any antenatal clinic with an MCH level of

<27.0 pg should be investigated further to confirm or exclude a diagnosis of thalassaemia trait. The investigative recommendations, which were followed strongly includes the following: all pregnant women were tested for β-thal trait and also for other Hb variants (HbE and HbS for the Eastern Indian population), even though the MCV and MCH levels were more than 75.0 fL and more than 27.0 pg. When the MCH value was <25.0 pg, selected pregnant women were tested for β-thalassemia (β-thal), especially when the person concerned appeared to be ‘‘normal’’ after being screened for β-thal trait and HbE or HbS. Again, in our opinion, the RDW Index is also one of the best index as it provides a sensitivity and specificity between 90.0–100.0% to distinguish iron deficiency anaemia from thalassaemia.

The screening policy should be with a complete blood count (CBC) and HPLC. Consent for testing must be obtained and recorded. Testing of the women should ideally be completed before 10 weeks and the whole process including testing of the baby's biological father, if applicable, should be completed within the first 12 weeks of pregnancy; even women presenting for the first time late in pregnancy should be offered testing because the results will be relevant both to this and future pregnancies and will enable genetic advice about future pregnancies to be given.

If a significant Hb variant is identified it should be confirmed by a suitable method, preferably by DNA analysis. If no relevant variant haemoglobin is identified, Hb A_2 percentage should be assessed, when appropriate. This is essential if the mean cell haemoglobin **(**MCH**)** is <27 pg. An Hb A_2 level of ≥3.5% in the presence of a MCH <27 pg indicates heterozygosity for β thalassaemia. An Hb A_2 of >4% with a normal MCH should be assessed further as it may indicate a milder β thalassaemia carrier state that would warrant testing of the baby's biological father. It is recognised that in some mild or atypical β^+ mutations, the Hb A_2 levels may fall below 3.5%.In addition, co-existing delta thalassaemia may reduce the Hb A_2 into the normal range and mask a beta thalassaemia trait.

In the context of an MCH <27 pg, an isolated raised HbF of ≥5% identifies possibleheterozygosity for δβ thalassaemia and testing of the baby's biological father is required. In the presence of a normal MCH, HPFH should be considered when the Hb F is ≥10%.

In the absence of a variant Hb and β or δβ thalassaemia heterozygosity, α thalassaemia carrier states should be considered if the MCH is <27 pg. This should be considered regardless of iron status as there is insufficient time in the antenatal setting to reassess indices after iron treatment. If the MCH is <25 pg, the individual should be assessed for the possibility of α^0 thalassaemia heterozygosity in the light of his or her family origin.

It should be noted that a diagnosis of β thalassaemia or Hb E heterozygosity does not exclude co-existing α^0 thalassaemia heterozygosity and, in ethnic groups with a significant prevalence of the latter, DNA analysis is indicated when relevant to reproductive choice. For example, if one partner has β thalassaemia or Hb E heterozygosity and the other possible α^0 thalassaemia heterozygosity, both partners should be offered testing for α^0 thalassaemia.

Severe iron deficiency anaemia (haemoglobin concentration < 8 g/dl) can reduce the Hb A_2 level slightly (by up to 0.5%). Outside of pregnancy, anaemia should be treated and the haemoglobin analysis repeated when the patient is iron deficient. In pregnant women, there is no justification for delaying the investigation for haemoglobinopathies whilst treating iron deficiency presumptively, as this will delay the process of identifying at-risk carrier couples, who could be offered a prompt prenatal diagnosis. It may be appropriate to simultaneously investigate pregnant women for iron deficiency, for example using serum ferritin, but this is not specifically part of haemoglobinopathy screening.

V. RECOMMENDATIONS

- A diagnosis of β thalassaemia heterozygosity should be made on the basis of the MCH and the haemoglobin A_2 percentage.
- A diagnosis of δβ thalassaemia heterozygosity should be made on the basis of the MCH and the haemoglobin F percentage.
- A diagnosis of α^0 thalassaemia heterozygosity should be suspected on the basis of the MCH and a normal or low haemoglobin A_2 in an individual of appropriate family origin and should be confirmed by DNA analysis of the mother and, when the same diagnosis is suspected in the biological father, by DNA analysis also in the father.
- The possibility of co-existing α^0 thalassaemia heterozygosity should be assessed, on the basis of family origin, in mothers with β thalassaemia or Hb E heterozygosity and, when the diagnosis would be relevant to reproductive choice, DNA analysis should follow.
- The possibility of misdiagnosis may occur as severe iron deficiency anaemia (Hb < 8 g/dl) can reduce the Hb A_2 level slightly (by up to 0.5%). Serum ferritin test is recommended in those cases, though this is not specifically part of haemoglobinopathy screening.

VI .CONCLUSION

Thalassaemia carriers among pregnant women may complicate the pregnancy. Thalassemia carriers are predominant in Nadia district of West Bengal; India. Early screening and awareness generation among the people may reduce the carrier in future. Further study in-depth is required to manage the pregnant women having thalassaemia carriers.Genetic counselling and extensive family screening must be executed to decrease the birth rate of thalassaemia-affected children. At the same time, awareness among parents and physicians regarding antenatal screening should be expanded in order to reduce the Blood transfusion incidence. A coherent preventive plan must be implemented at the national level to eliminate this life-threatening inherited disorder.

As some unknown Hb variants have also been reported **(14),** which can affect the surety of success in PND. Frequency of all these factors may vary considerably in different districts. There is a need to establish a systematic screening program, which should be proposed at different times in life that would help investigators to avoid misdiagnosis and to improve screening for heterozygotes and some β-TI cases in a cost-effective way.

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VIII. DISCLOSURE STATEMENT

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

IX. CONFLICT OF INTEREST

The authors declare no conflict of interest.

X. DECLARATION OF INTEREST

The authors acknowledge the Ranaghat Thalassaemia Detection Centre,run by National Health Care charitable Trust (an Auxiliary unit of STCPWB),situated at T. B. Hospital, Srinathpur Ranaghat, Nadia, West Bengal, India, for their initial financial and infrastructural support and also the Institute of Genetic Engineering (IGE), Kolkata, West Bengal, India and SAG Foundation, Kolkata, West Bengal, for their academic, scientific and infrastructural support for some part of the project. The authors acknowledge the Dept of Health, Govt. of West Bengal, West Bengal, India. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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