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Thalassemia Trait as a Cause of Anaemia in ANC Patients

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Abstract:-

Introduction-Anaemia is commonest haematological disorder that can occur in pregnancy. Thalassemia syndromes are commonly found genetic disorders of the blood. Beta thalassemia is considered as most common single gene disorder in our country. Detection of thalassemia is increasing nowadays. If a female with trait marries a person of similar trait, baby can develop thalassemia major which is lethal. Failure to differentiate iron deficiency anemia from thalassemia may lead to iron load which is hazardous to patient. So we conducted this study to know the proportion of thalassemia trait in our institution so we can add it to our routine ANC profile. Materials and Methods: A prospective cross-sectional study was conducted from October 2017-October 2019 after due permission from ethical committee. A total of 82 anemic ANC patients till 18 weeks of pregnancy were studied. After detailed history, CBC, HPLC method was done in patients with hemoglobin <11gm. Spouse of positive beta thalassemia patients were further tested for similar trait by HPLC method. Results- Incidence of Beta thalassemia in our study was 20.4%. HbA2 was higher in positive patient group than in negative patient group. There was statistically no significant difference in HbA and HbF levels, whereas Hb, RBCS, MCV, MCH,MCHC showed no significant difference. This indicates possibility of coexistence of iron deficiency anaemia with beta thalassemia trait. So elevated HbA2 level (> or = 3.5%) is an established screening test for beta thalassemia trait.

Keywords- Thalassemia trait, anemia, HPLC

I. INTRODUCTION

➢ *ANEMIA*

Anemia is the commonest hematological disorder that may occur in pregnancy. Hemoglobin level below 11g/dL at any time during pregnancy is considered anemia. [(1)]Anemia either directly or indirectly takes part in about 20% of maternal deaths.

Increased prevalence of anemia in pregnancy can occur because of following reasons[(1)]

- Increased demands of iron
- Diminished intake of iron
- Diminished absorption
- Disturbed metabolism
- Pre-pregnant health status

➢ *THALASSEMIA*

The thalassemia syndromes are the commonly found genetic disorders of the blood. The basic defect is a reduced rate of globin chain synthesis so red cells being formed are with an inadequate hemoglobin content. [(2)] Thalassemia is divided in two groups alpha and beta thalassemia.

Alpha Thalassemia: Alpha peptide chain production is controlled by four genes, located on chromosome 16 (two on each copy). Depending upon the degree of deficient alpha peptide chain synthesis,4 Clinical types of syndromes have been identified.

Beta Thalassemia:
2 beta peptide chains production is directed by two genes, one on each copy chromosome 11.
Beta Thalassemia major: When mutation affect both the genes, there is red cell destruction as there is no beta chain production.
Beta Thalassemia minor (Beta thalassemia trait): When there is mutation of 1 gene, beta peptide chain production is reduced by half .

Beta thalassemia is considered as most common single gene disorder in our country. India is located on the thalassemic belt and there is a high prevalence of β thalassemia minor in women which is reported to be very variable,varying from 1.48% to 3.64% in different states of the country.[(3)]More than 9,000 thalassemic children are born every year and the treatment is very expensive.[(4)]

The most important approach to reduce the burden of the society and reduce the beta thalassemia incidence is employment of a carrier screening program, offering genetic counselling, prenatal diagnosis, and selective termination of affected fetuses.

As thalassemia usually presents with a microcytic hypochromic anemia, it needs to be differentiated from iron deficiency anemia. Various parameters are available to screen beta thalassemia which include peripheral blood smear examination, red cell osmotic fragility test, free red cell porphyrins and red cell indices, which can then be confirmed by HPLC method and mutational analysis.

Diagnosis of thalassemia is done by the identification of an abnormal hemoglobin variant or elevated levels of HbA2 (≥3.5%) for beta thalassemia carriers and identification of H bodies for alpha thalassemia carriers. [5-9] High-performance liquid chromatography (HPLC) is the most effective method for detection and quantitative estimation of hemoglobin variants. [5-9]

II. AIM & OBJECTIVES

1.To detect the thalassemia trait as cause of anemia in pregnancy
2.To test spouse if patient is having thalassemia trait.
3.To advise genetic counselling in positive couples.
4.To study the effect on obstetric career.

III. MATERIALS AND METHODS

The study was subjected for approval to 'Ethical committee of MGM University. Written and informed consents for the present study was taken from all the subjects.
Study design: A prospective cross-sectional study
Study period: 2 years, October 2017- October 2019
Study place: Department of OBGY MGM Medical college and Hospital, Aurangabad.
Sample size number- 82

➢ *Methods*

Complete blood count was done and hematological parameters were recorded. Detailed history to ascertain the ethnic origin, consanguinity, any history of blood transfusion, iron therapy in past and previous pregnancies was obtained.

HPLC method was done in patients whose hemoglobin was <11gm.
Spouse of positive beta thalassemia patients were further tested for similar trait by HPLC method.
Couples at risk were further advised for genetic counselling and prenatal diagnosis.
Patients who attended the antenatal clinics in late second trimester and third trimester or those did not consent were excluded.

Inclusion criteria:
Antenatal patients with <18 weeks of pregnancy with anemia.

Exclusion criteria for cases:
Anemia associated with other known causes.

➢ *Statistical Analysis*

The collected data was entered in MS EXCEL sheet. All the analysis was done by using the windows based SPPS statistical package (version 24.0, spssinc: Chicago, il USA and p values <0.05 was taken as the levels of significance.) the qualitative data was represented in form of frequencies and percentages. The quantitative data was represented in form of mean,standard deviation, and 95% CI.

IV. OBSERVATIONS AND RESULTS

Total No. of patient tested	82
Thalassemia trait positive patient	17
Thalassemia trait negative patient	65
Thalassemia major patients	0

Table no.1: Observation of the study

In our study total 82 anaemic ANC patients till 18 weeks gestation were screened for thalassemia trait. 17 patients were positive for thalassemia trait and 65 patients were negative for that trait. The incidence of beta-thalassemia was 20.4% in my study.

➢ *RESULTS*

Religion	Patients with Thalassemia Positive (n=17)		Patients with Thalassemia Negative (n=65)		Fisher Exact Test	p-value
	Number	Percentage (%)	Number	Percentage (%)	3.965	0.141 NS
Hindu	15	88.24	54	83.08		
Muslim	01	5.88	11	16.92		
Sindhi	01	5.88	00	0.00		

Table 2.Distribution of patients according to religion

In both the groups majority i.e. 88.24% and83.08% respectively were Hindus.In my study there was only 1 Sindhi patient who tested to be positive indicating the possibility of high prevalence of beta thalassemia trait in this community.

Table 3 Distribution of patients according to age group

Age groups (years)	Patients with thalassemia positive		Patients with thalassemia negative		t-value	p-value
	Number	Percentage (%)	Number	Percentage (%)	1.10	0.282NS
18-23	07	41.18	34	52.31		
24-29	08	47.06	23	35.38		
30-35	02	11.76	08	12.31		

Majority of patients diagnosed with Beta thalassemia were in the age group 24-29 years

Table 4. Distribution of patients according to Gravidity

Gravida of Antenatal Mother	Patients with Thalassemia Positive (n=17)		Patients with Thalassemia Negative (n=65)		χ^2 -Value	p-value
	Number	Percentage (%)	Number	Percentage (%)	10.409	0.001 HS
Primigravida	03	17.65	40	61.54		
Muiltigravida	14	82.35	25	38.46		

In our study 82.35% of positive patients of beta thalassemia trait were multigravida whereas 61.54% negative for beta thalassemia trait were primigravida.It could signify that the positive patients may not have been screened in their previous pregnancies and so must have been detected in next pregnancy.

Table 5.Distribution of patients according to blood transfusion in past and previous pregnancies

History of blood transfusion	Patients with Thalassemia Positive (n=17)		Patients with Thalassemia Negative (n=65)		χ^2 -Value	p-value
	Number	Percentage (%)	Number	Percentage (%)	10.309	0.001HS
Yes	07	41.18	06	9.23		
No	10	58.82	59	90.77		

41.18% among positive patients had history of blood transfusion. This could indicate that positive cases must not have responded to iron therapy as that was not the root cause and so needed blood transfusion.

Table 6.Distribution of patients according to History of Receiving Iron in past and previous pregnancies

History of Receiving Iron	Patients with Thalassemia Positive (n=17)		Patients with Thalassemia Negative (n=65)		χ^2 -Value	p-value
	Numbe r	Percentag e (%)	Numbe r	Percentag e (%)	1.736	0.227NS
Yes	07	41.18	16	24.62		
No	10	58.82	49	75.38		

In my study 41.18% of beta Thalassemia trait positive patients had history of receiving iron therapy in past or previous pregnancy whereas 75.38% of negative patient group had no history of receiving iron therapy in the past.This could indicate that 41.18% patients received iron therapy assuming it to be iron deficiency anemia and this would have been fatal for Thalassemia patients. So again antenatal screening for thalassemia is very important.

Table 7. Distribution of patients according to Family history of haemoglobinopathy

Family History	Patients with Thalassemia Positive (n=17)		Patients with Thalassemia Negative (n=65)		χ^2 -Value	p-value
	Number	Percentage (%)	Number	Percentage (%)	43.04	0.0000 HS
Positive	06	35.29	01	1.54		
Negative	11	64.71	64	98.46		

In this study we found that 35.29% of beta thalassemia positive patients had family history of hemoglobinopathy. Significant Association of family history in thalassemia trait transmission was found. It signifies that, all patients having positive family history should be screened for haemoglobinopathies at earliest.

Table 8 Distribution of patients according to Consanguinity

Consanguinity	Patients with Thalassemia Positive (n=17)		Patients with Thalassemia Negative (n=65)		χ^2 -Value	p-value
	Number	Percentage (%)	Number	Percentage (%)	1.517	0.218NS
Yes	03	17.65	05	7.69		
No	14	82.35	60	92.31		

In my study it was observed that there was no statistically significant difference of consanguinity between positive and negative case groups. It was observed that 17.65% thalassemia trait patient had consanguineous marriage among the positive cases group. This could indicate the practice of consanguineous marriages, is an accepted socio- culture phenomenon which may have an effect on the transmission of thalassemia.

Table 9. Distribution of patients according to Hemoglobin level

Haemoglobi n Level	Patients with Thalassemia Positive (n=17)		Patients with Thalassemia Negative (n=65)		χ^2 -Value	p-value
	Number	Percentage (%)	Number	Percentage (%)	8.595	0.014 S
> 7gm	01	5.88	08	12.31		
7.1gm-9gm	01	5.88	25	38.46		
9.1gm-10gm	15	88.24	32	49.23		

In oIn In our study 88.29% beta thalassemia positive patients had mild anemia as compared to negative patient group where 48.23% had mild anemia and 38.46% had moderate anemia. So we can pick up patients having mild anemia to investigate. This could indicate that during early pregnancy maternal hemoglobin level in beta thalassemia positive patients may fall to some extent but severe anemia may not occur.

Table 10. Comparison of HPLC results according to Red Cell Indices

Red Cell Indices	HPLC Results		t-Value	p-Value
	Positive Mean±SD	Negative Mean±SD		
HB(gm%)	9.16±1.17	8.61±1.28	1.619	0.109 NS
RBC Count	4.43±0.60	4.05±0.51	2.633	0.010 S
MCV(fl)	64.40±11.19	68.42±9.88	1.451	0.151 NS
MCH(pg)	20.87±2.17	21.13±4.15	0.249	0.804 NS
MCHC(d)	29.94±2.07	29.34±3.07	0.759	0.450 NS
HbA	83.21±22.71	95.79±4.68	4.2039	0.0001HS
HbA2	4.24±1.29	2.37±0.85	7.1928	0.0001HS
HbF	3.58±6.76	0.39±0.25	3.8629	0.0002HS

In our study HbA2 was higher in positive patient group than in negative patient group. There was statistically significant difference in HbA and HbF levels, whereas Hb, RBCS, MCV, MCH, MCHC showed no significant difference. This indicates the possibility of co-existence of Iron deficiency anemia with beta thalassemia trait. Which could mean that iron deficiency could be interfering with results.

Hence elevated Hba2 level (> or = 3.5%) is an established screening test for beta thalassemia trait.

- *Following Observations Were Noticed In Positive Cases Of Thalassemia Trait*

1. 13 spouses of positive beta thalassemia trait women were ready for genetic counselling.
2. Out of these 4 were tested positive for beta thalassemia trait.
3. All 4 were advised genetic counselling followed by prenatal diagnosis.
4. Out of these only 2 couples underwent prenatal diagnosis
5. Both fetuses were positive for beta thalassemia major.
6. Termination was advised to couples with fetus B thalassemia major positive.
7. 11 patients delivered and 2 patients underwent termination and 1 patient had spontaneous abortion.
8. 14 Patients were multigravida and 3 patients were primigravida.
9. 5 patients had history of abortion; all were spontaneous abortion.

V. DISCUSSION

In our study total 82 anemic ANC patients till 18 weeks gestation were screened for thalassemia and 20.7% patients were found to be positive for thalassemia trait. This could indicate that thalassemia trait is very common in anaemia and could be one of the major causes of anemia in pregnancy.

Dipal S Bhukhanvala et al (2012) in a similar study found that overall prevalence of beta-thalassemia trait was 3.38% among 3009 antenatal patients.[10]Gupta V et al (2015) conducted a similar study to screen antenatal thalassemia in pregnant women visiting a hospital in Jodhpur, Rajasthan, India.1500 women were screened for thalassemia and the prevalence rate was 5.9%.[11]A study conducted by Dipanshu Sur et al (2016) found the incidence of beta thalassemia trait in 1279 pregnant females was 3.1%.[12]

Our study could be showing high incidence of beta thalassemia which may be because of small study sample size or our institution being tertiary care centre.

In our study in both the groups majority i.e. 88.24% and 83.08% respectively were Hindus. There was only 1 Sindhi patient who tested to be positive indicating thepossibility of high prevalence of beta thalassemia trait in this community, but we could not get enough data as only one patient of this community had come.

Praveen Kulkarni et al 2010 found in their study that majority of patients (70.5%) were Hindus by religion.[13]Asha Baxi et al 2010 in a similar study found that beta thalassemia minor was diagnosed among all types of caste(Brahmin, Sindhi),so no inference could be made as per selective screening among ethnic risk caste and advised for universal screening.[14]DMohantyetal(2005)inasimilarstudyfoundthatmajorityofpatients78.2%were Hindus.[15]

In our study 82.35% of positive patients of beta thalassemia trait were multigravida whereas 61.54% negative for beta thalassemia trait were primigravida. It could signify that the positive patients may not have been screened in their previous pregnancies so there is a need to add in the ANCprofile.In a similar study conducted by Praveen Kulkarni et al (2010) it was observed that 50% of the pregnant women with the beta thalassemia trait were primigravida.[13]

In our study patients negative for Thalassemia trait had no history of blood transfusion, whereas 41.18% among positive patient group had history of blood transfusion. This could indicate that out of the positive cases for Thalassemia trait must not have responded to iron therapy and so needed blood transfusion which was not the case in negative case group. In a similar study conducted by Nessar et al found that 3(0.66%) patients had history of blood transfusion in past and previous pregnancy and 2 patients required blood transfusion for the first time duringpregnancy.[7]In my study patients with positive history of blood transfusion is more could be because of small sample size.

In our study 41.18% of beta thalassemia trait positive patients had history of receiving iron therapy in past or previous pregnancy whereas75.38% of negative patients group had no history of receiving iron therapy in the past. This could indicate that 41.18% patients received iron therapy assuming it to be iron deficiency anemia which could be fatal for thalassemia patients. Similar findings were noted in a study conducted by Sheetal Arora et al (2017), that failure to exclude iron deficiency anaemia in a patient with Thalassemia syndrome may lead to continuation of iron therapy for a prolonged period, resulting in iron overload or secondary hematochromatosis. So Hb electrophoresis should be done in anemia.[16]In a similar study conducted by Parfrey PS et al (1981) Iron overload was observed in beta thalassemia minor.[17]A similar study was conducted by Shukla S. et al to know the prevalence of beta thalassemia and other hemoglobinopathies by using HPLC method. They included patients of microcytic hypochromic

anemia with history of receiving iron therapy.[18]In a similar study conducted by J.M. White et al observed that (contrary to common practice)betathalassemiapatientshouldbegivenironsupplementsduringpregnancy as they found iron deficiency in patients who received iron therapy for more than 16 weeks.[19]

In our study 35.29% of positive patients had family history of B thalassemia and sickle cell anemia. So, all patients having positive history should be screenedforhaemoglobinopathiesasearliestasthereisstrongassociationwithfamily history of hemoglobinopathies in transmission of thalassemia. Asha Baxi et al 2010 In her study details about previous pregnancies and family history of thalassemia. Noted that carrier frequency varies from 3-17% in different population.[14]

In our study it was observed that there was no statistically significant difference in consanguinity between positive and negative case groups. It was observed that 17.65% thalassemia trait patient had consanguineous marriage among the positive cases group. This could indicate the practice of consanguineous marriages, is an acceptedsocio-culturalphenomenonwhichmayhaveaneffectonthetransmissionof thalassemia.Parveen Kulkarni et al (2010) conducted a similar study in which They observed that 6.8% of the carrier pregnant women were born out of 2nd degree consanguineous marriages.[13]

In our study 88.29% beta thalassemia positive patients had mild anaemia as compared to negative patient group where 48.23% or had mild anaemia and 38.46% had moderate anaemia. This could indicate that during early pregnancy maternal haemoglobin level in beta thalassemia positive patients may fall to some extent but severe anaemia does not occur.Similar findings were noted in a study conducted by Dr. Trisha Das et al (2015) in which they concluded that positive thalassemia trait had mild anemia in early pregnancy.[20]The difference of mean Hb% are statistically significant in both the groups throughout the pregnancy and the differences increased as pregnancy advances.Similar findings were seen in the study conducted by Praveen Kulkarni et al 2010 where majority i.e 55.5% pregnant women with beta thalassemia trait had a haemoglobin concentration <10gm%, with a mean Hb of 10.06+1.00gm%.[13]

In our study HbA2was higher in positive patient group than in negative patient group. There was statistically significant difference in HbA and HbF levels in both groups, whereas Hb, RBCS, MCV, MCH, MCHC showed no significant difference. This indicates the possibility of co-existence of Iron deficiency anemia with beta thalassemia trait. Hence elevated HbA2 level (> or = 3.5%) is an established screening test for beta thalassemia trait, which could mean that iron deficiency could be interfering with results. In a similar study conducted by Surbhi Bajaj et al, (2015) it was concluded that HPLC analysis is of the blood is the gold standard for diagnosis of beta thalassemia trait.[21]A study by Asha Baxi et al (2012) stated similar findings that HbA2 determination plays a key role in screening programs for beta thalassemia then red cell indices.[14]InastudyconductedbyQadiretal2017itwasobservedthatmeanhaemoglobinlevel was as 9.43±0.40 g/dl and mean HbA2 was 4.26±0.5,which showed HbA2 served as a good predictor for screening of beta thalassemiatrait.[22]In a study conducted by Sheetal Arora et al 2017, it was observed that HPLC method were performed to improve the detection of beta thalassemia trait with or without iron deficiency[16]

VI. CONCLUSIONS

- The incidence of beta thalassemia trait was 20.4% in my study.
- The majority of patients of beta thalassemia trait 88.24% were Hindus. Among all enrolled cases There was only 1 Sindhi patient which came for screening and was found to be positive for beta thalassemia trait indicating the possibility of high prevalence of beta thalassemia in this community.
- 82.35% of beta thalassemia trait patients in positive case group population were multigravida.
- In our study 41.18% of beta thalassemia trait patients in positive cases group had history of blood transfusion in past and previous pregnancies.
- In our study 41.18% of beta thalassemia trait patients in positive cases group had history of receiving iron therapy in past and previous pregnancies.
- In our study there was significant association of family history in transmission of beta thalassemia trait.
- In our study there was significant association of consanguinity with beta thalassemia trait positive patients.
- In our study majority 88.29% of beta thalassemia trait patients in positive cases group had mild anemia.
- Statistically significant association between increasing of HbA2 level and positive patients group was observed in our study. This study indicates the possibility of co-existence of Iron deficiency anemia with beta thalassemia trait. Which could mean that iron deficiency could be interfering with results.
- In our study, out of 17 positive women only 76.47% of husbands could be tested, due to their failure to turn up for testing due to lack of awareness and inability to understand the importance of screening of both partners.
- In our study 4 spouses were positive for beta thalassemia trait, out of which 2 underwent prenatal diagnosis and both fetuses were positive for beta thalassemia major.
- Termination was advised to couples with fetus beta thalassemia major positive.

- 11 patients delivered and 2 patients underwent termination and 1 patient had spontaneous abortion.

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