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ORIGINAL ARTICLE

Carrier Screening for β Thalassemia in Pregnant Indian Women: Experience at a Single Center in Madhya Pradesh

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Abstract To study the prevalence of β thalassemia trait in pregnancy in urban population screening for β thalassemia in pregnant women at a single center in Indore (MP) has been conducted for a period of 2 year. Blood samples were tested for complete blood count and hemoglobin electrophoresis. During the 2 year period a total of 1,006 women were screened; 28 women who carried abnormal pattern were detected. The mean gestational age for screening was 13 ± 4 weeks. The prevalence of carriers was 2.78 %. As much as 99 % of pregnant women undergoing screening were willing for prenatal diagnosis if required. The economic burden to the society for treating thalassemic patients is huge. The institution of prevention programs like carrier screening has proven costeffective 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 thalassemia in developing countries like India.

Keywords β Thalassemia trait · Pregnancy · Hemoglobinopathies

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Introduction

Thalassemia syndromes are the commonest genetic disorders of blood and constitute a vast public health problem in many parts of the world. The highest prevalence of thalassemia is in Mediterranean, Central Africa, and South East Asia. Beta thalassemia is the most common single gene disorder in our country India. The incidence of thalassemia is very high, with over 30 million people carrying the defective gene. Carrier frequency varies from 3 to 17 % in different populations [1]. Over 9,000 thalassemic children are born every year and the treatment is very expensive [2]. Hence the burden induced on the society is tremendous. The most effective approach to reduce the burden of the society and reduce the disease incidence is implementation of a carrier screening program, offering genetic counselling, prenatal diagnosis, and selective termination of affected fetuses. India is located on the thalassemic belt and there is a high prevalence of β thalassemia minor women which is reported to be very variable. India does not have a national thalassemia control program yet. The goal of this research was to study the prevalence of β thalassemia minor pregnant women in India. We present the data of screening for thalassemia and other hemoglobinopathy at a single center.

Materials and Methods

Present study was conducted at Disha Fertility and Surgical center, Indore from June 2007 to May 2009. Counseling sessions were planned. A questionnaire was developed and pretested. Language and sequence of the questions were changed to improve the feasibility of the study. All pregnant women along with their spouse were offered

counseling for thalassemia. Counseling was done regarding method for screening thalassemia, reason for performing test, including social aspects, various tests available for prenatal diagnosis. Various medical and ethical issues involved with this were also discussed. A nondirective approach was used when presenting women with various options. Ethical committee approval was taken.

Verbal consent was taken from all regarding use of screening and further implications. Hemoglobin, red cell indices were measured by a cell counter and hemoglobin fractionation was carried out by high performance liquid chromatography (HPLC). Modular HPLC system with basic configuration includes a pump, manual injector, variable length detector, and data system was used. Details about previous pregnancies and family history of thalassemia were enquired. All the women were examined for anemia, hepatosplenomegaly, and other signs of thalassemia. Individuals who were positive were investigated further for diagnosis of β thalassemia and other abnormal hemoglobin. If woman was found to have thalassemia trait, husband's blood sample was taken for HPLC. Then the couple was subjected to genetic counseling. Couples at risk were counseled about thalassemia disease and given the option of prenatal diagnosis and possibilities were explained. Maternal medical records were reviewed for several demographic and clinical variables. Women were contacted by phone for any missing information. In cases with HbA2 $>$ 3.5 %, or with variant hemoglobin, mutation screen was done by amplification refractory mutation system polymerase chain reaction (ARMS-PCR). The fetal sampling was done via chorion villus sampling (CVS) transcervically under local anesthesia and ultrasonic guidance after written informed consent. During pregnancy, women had regular antenatal visits where hemoglobin levels were assessed and ultrasonographic evaluation of fetal growth every 4 weeks starting at 26–28 weeks.

Result

In this 2 year duration 1,320 women of age group 22–43 years were registered for antenatal care. Total pregnant women who accepted screening test were 1,006 (76.21 %) while 314 (23.79 %) refused. Uptake rate was high. Reporting early acceptability was significantly associated with a higher education level. Common cause for no acceptance was cost for the test and further invasive test if test reports positive. During the study period out of 1,006 women who underwent screening were found to be having β thalassemia trait and seven had other hemoglobin variants. Population comprises 2.78 % of women with β thalassemia trait and 0.69 % with other minor hemoglobin variants. Screening of partner of these 28 women was offered. Acceptance was 100 %. In 27 out of then it was found normal. One couple was found to have β thalassemia trait. So CVS was done to exclude thalassemia major. Pregnancy was continued as the result of CVS showed thalassemia trait. The β thalassemia minor group showed prominent microcytosis (MCV 66.9 $\pm$ 2.6 fl) but only mild anemia (Hb 11.41 $\pm$ 12.9 g/l). Out of 1,006 pregnant women during the period of 1 year, 57.6 % women's hemoglobin was $>$11 gm%. 36.88 % women had mild anemia (Hb 10–11 gm%), 4.17 % moderate anemia (Hb 7–10 gm%), 1.79 % severe anemia (Hb $<$ 7 gm%). With selective screening out of 206 women with moderate and severe anemia, 7.76 % women found to have abnormal hemoglobin pattern. In universal screening of women with mild anemia and no anemia only 1.5 % women were having hemoglobinopathy.

Discussion

Hemoglobin disorders present a significant health problem. The basic defect is reduced rate of globin chain synthesis, red cells being formed with inadequate content of hemoglobin. Thalassemia is classified according to globin chain that is deficient. Two major forms involve impaired production or stability of either α or β peptide chains, causing α thalassemia or of β chains causing β thalassemia.

In β thalassemia minor hemoglobin A2 (composed of two α and two δ chains) is more than 3.5 %. Hemoglobin F is usually more than 2 %. Anemia is mild and red cells are hypochromic and microcytic. There is usually pregnancy induced augmentation of erythropoiesis. There is no specific therapy for β thalassemia minor during pregnancy. Prophylactic iron and folic acid supplementation are given.

Women who are carrier for β thalassemia minor appear perfectly healthy, other than a mild anemia. Clinicians often mistake the small red blood cells of the women with β thalassemia minor as a sign of iron-deficiency anemia and incorrectly prescribe iron supplements that have no affect on the anemia. However, where two carriers decide a family there is one in four chances that their child could inherit β thalassemia major, one in four of a child being normal and one in two chance of the child also being a carrier.

A simple blood test often employed is called Hemoglobin Electrophoresis will tell about the carrier or a trait of thalassemia minor. Hemoglobinopathies are the only genetic disease where it is possible to detect carriers using hematological findings rather than DNA analysis. However, hematological diagnosis is sometimes presumptive, and in these cases, DNA analysis becomes necessary. Complete screening is based on the detection of red cell

indices, HbA2, HbF, and hemoglobin variant values. In particular, HbA2 determination plays a key role in screening programs for β-thalassemia because a small increase in this fraction is one of the most important markers of β thalassemia heterozygous carriers [3]. Heterozygous β thalassemia is usually silent at the clinical level. His phenotype is characterized by microcytosis and hypochromia with increased hemoglobin A2 value. Therefore, HbA2 determination plays a key role in screening programs for hemoglobinopathy. Cases with co existent nutritional deficiencies may have borderline A2 levels, masking an underlying hemoglobinopathy. However, in the present none of the women have borderline A2 levels.

It has been estimated that there are 45 million carriers of β thalassemia in India and about 15,000 infants with homozygous β thalassemia are born every year which constitutes about 10 % of the total thalassemics born in the world [4]

The state of β thalassemia could be alarming as consanguinity is high and the literacy rate is low. A thalassemia prevention program is the need of the hour in India. The approach to deal with the thalassemic problem is to prevent and control births of the new cases. This requires an accurate identification of couple at high risk to have a thalassemic child. Emphasis is given on selective screening for β thalassemia minor in pregnant women who belong to ethnic population having high prevalence for thalassemia. In the present study β thalassemia minor was diagnosed among all types of caste, so no inference could be made as per selective screening among particular caste. Therefore a policy of universal screening was decided.

In this study, we initiated awareness and screening as well as a genetic counseling program mainly in the districts of Indore (MP)

Colah et al. [5] reported that antenatal screening is acceptable in India; however, awareness generation is still a primary requisite.

Several programs, with the aim of preventing homozygous β thalassemia, based on carrier screening and counseling of couples at marriage; preconception or early pregnancy, are operating in several at-risk populations in Mediterranean areas [6, 7].

Until gene therapy becomes a reality, the only approaches to the control of hemoglobinopathies are prevention and avoidance. Cao et al. [8] reported reduction of the birth rate of thalassaemia major from 1:250 live births to 1:4,000 in Turkey after execution of comprehensive genetic preventive programme based on voluntary screening and non-directive counseling. ACOG recommends screening for β thalassemia in couples of Mediterranean society. [9]

While conducting this study our experience was that most of the couples readily agreed for screening and this test can be included as essential test. The most feasible option in our view is to screen the mother periconceptionally or antenatally in early pregnancy preferably in the first trimester. The parents are often receptive and would usually agree to get any tests done for the well being of their baby. Limitations in this study were that pregnant women present for antenatal care at varied gestational age and uniformity for screening at specific gestational age could not be maintained. Also, late booking decreases the importance of screening test. In present study as our main aim was to find out prevalence of thalassemia trait, we offered test to all pregnant women who came for antenatal care irrespective of their gestational age. Ideal methodology for screening thalassemia is by performing test ideally preconceptionally or early in pregnancy (before 8 weeks). If the mother is found to be a carrier, her husband can be tested for carrier status and if he is also a carrier, prenatal diagnosis can be offered after proper genetic counseling.

Obstetric emphasis is on prenatal diagnosis. Prenatal diagnosis of β thalassemia using CVS can be carried out at 9–11 weeks. Amniocentesis can be carried out in 14–18 weeks of pregnancy; fetal blood testing can be done in 18–20 weeks of pregnancy. Techniques include site specific restriction endonuclease analysis, PCR, and oligonucleotide probes. CVS and fetal blood sampling have a reported miscarriage rate of 1 in 100 tests and amniocentesis 1 in 200. Preimplantation blastomere biopsy can also be done. Preimplantation genetics can now be offered to assure the placement of unaffected embryos in utero.

These patients do not have impaired fertility or pregnancy outcome. Because of higher rates of IUGR and oligohydramnios, ultrasound surveillance of fetal weight should be done for early detection of IUGR [10, 11]

Countries like Pakistan, Iran, Saudi Arabia, and Lebanon which initially practiced only premarital screening to disallow marriage where both partners were carriers have now reinterpreted religion to include prenatal diagnosis and abortion till a particular gestation [12].

The Iran National Thalassemia Prevention Program, a combination of extended family and mandatory premarital screening reduced the birth rate of a thalassemic child by 30 % between 1997 and 2004 [13].

Carrier screening by premarital screening followed by prenatal diagnosis and medical termination of pregnancy is acceptable to our communities. This approach is safe without significant marital, social, maternal, and fetal adverse events. Screening program can be made successful in India by increasing awareness not only among population but also among health care professionals so that they can offer screening test on correct time and can improve detection rates (Tables 1, 2, and 3).

Table 1 Anemia in patients with hemoglobinopathy

Hemoglobin (gm/dl)	No. of patients (%)	No. of patients with hemoglobinopathy
<7	18 (1.79)	1
7–9	42 (4.17)	2
9–10	146 (14.51)	13
10–11	225 (22.37)	7
≥11	575 (57.16)	5
Total	1,006	28

Table 2 Distribution of patients with β thalassemia trait according to caste

Caste	No. of patients
Sindhi	5
Gujrati	5
Marwari	4
Kunbi	1
Punjabi	6
Bhilal (sc)	1
Brahmin	6

Table 3 Distribution of patients according to type of hemoglobinopathies

Hemoglobinopathy	No. of patients
β thalassemia trait	28
Thal trait Hb E	1
Hb D Punjab	3
Hb J	1
Hb Q India	1
Sickle cell trait	1

Conclusion

Universal screening is better in diagnosing woman with hemoglobinopathies. Carrier screening for thalassemia should be offered to all pregnant women attending antenatal clinic. Ideally, this screening should be done preconceptionally or as early as possible in the pregnancy. Implementation of a simple carrier screening in pregnancy is practicable in India.

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