PREVENTION AND CONTROL OF THALASSEMIA IN RAMATHIBODI HOSPITAL, THAILAND

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Abstract. Eight thousand seven hundred and thirty-six pregnant women were screened for thalassemia and hemoglobinopathies by mean corpuscular volume less than 80 femtolitres (fl). Three thousand six hundred and seventy women (42%) were MCV less than 80 fl. In this group there were 2,390 women (70%) who had positive Hb typing by high performance liquid chromatography (HPLC) such as β-thalassemia major, β-thalassemia hemoglobin E disease, β-thalassemia trait, heterozygous and homozygous hemoglobin E, α-thalassemia-1 trait and hemoglobin H disease and 77% of their partners came and had hemoglobin typing done. Seventy-five couples at risk for having severely affected thalassemia fetuses were detected from this screening program. Prenatal diagnosis was performed in 58 couples (77.3%). Eight affected fetuses were detected. All pregnancies with affected fetuses except one with β-thalassemia/HbE were terminated. There were 3 fetal losses (6%) as the result of prenatal diagnosis procedure.

INTRODUCTION

The thalassemia syndromes are inherited disorders of hemoglobin production characterized by a reduction in globin chain synthesis leading to an imbalance of the globin chains production. This single gene group of diseases is a major public health problem in many parts of the world. In Thailand, about 500,000 Thai people are affected, 40% of the population are carriers and 50,000 couples are at risk for having an affected child each year (Tanphaichitr, 1999). Three major public health problems of thalassemia are homozygous β-thalassemia, β-thalassemia/HbE disease and Hb Bart's hydrops fetalis. The present curative management of severe thalassemia is stem cells (cord blood, bone marrow) transplantation which is high cost and only a small number of patients can afford it. Although Hb Bart's hydrops fetalis is not a serious public health problem, the morbidity to the pregnant women is greater and more serious than normal pregnancy.

Although thalassemia is a common hematological disease most of clinicians ignore this national health problem. This severe disease can be reduced and made more accessible by public education, detecting in the context of known family history and screening in premarital or preconceptional couples. From the obstetrician's point of view, prevention and control in pregnant women is one of the best ways to reduce the birth of severe thalassemia infants. Three major aspects of prevention and control are carrier detection, genetic counseling and prenatal diagnosis. Our first year strategy in prevention and control of thalassemia is reported.

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MATERIALS AND METHODS

All pregnant women who came to antenatal clinic at Ramathibodi Hospital had an automated complete blood count done. Pregnant women who had a mean corpuscular volume (MCV) less than 80 fl proceeded to have hemoglobin typing done by high performance liquid chromatography (HPLC). When the result of the hemoglobin typing was positive, the patient was asked to bring her husband to have hemoglobin typing done. Once the tests of the couples showed them to be at risk for having severely affected child, intensive counseling was given with emphasis on a chance of having an affected child such as Hb Bart's hydrops fetalis, homozygous β-thalassemia and β-thalassemia/HbE disease with the options for prenatal diagnosis.

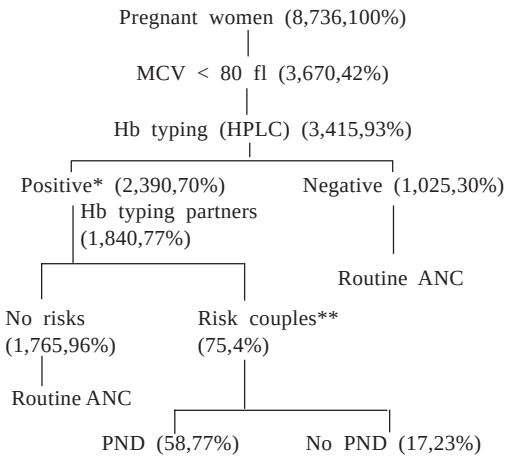
In the group with a chance of having a Hb Bart's fetus, the couples could choose to have prenatal diagnosis by an invasive procedure either chorionic villus sampling (CVS) for gestational age between 10-14 weeks, cordocentesis for gestational age between 18-22 weeks or serial ultra-

sonography every 4 weeks from 18 weeks until 36 weeks, if they preferred the non-invasive methods.

The couples at risk for having a homozygous β-thalassemia or β-thalassemia/HbE disease child were offered chorionic villus sampling or cordocentesis according to gestational age. Every couple who chose prenatal diagnosis would have DNA analysis done for detecting the mutation point of the β-thalassemia gene. In cases of known point of mutation either CVS or cordocentesis was offered while unknown point of mutation, only cordocentesis was suggested. In cases of having a previous affected child, their children were brought to have DNA analysis done as well. The couples who refused prenatal diagnosis were asked to bring the child back for hemoglobin typing at the age of 6 months to 1 year.

All the couples at risk were followed up in the thalassemia clinic (special clinic for looking after all risk couples before and after prenatal diagnosis). The couples who were found to have a severely affected child were counseled for the option to either continue or terminate pregnancy.

The data of the program for prevention and control of severe thalassemia was collected from March 1997 to June 1998 and the line of management in screening, counseling and prenatal diagnosis is shown in Fig 1.



* result of positive Hb typing
- β-thal major, b-thal / HbE disease
- β-thal trait
- heterozygous and homozygous HbE
- α-1trait, HbH disease

**risk for :
- β-thal major, β-thal/HbE disease
- Hb Bart's hydrops fetalis

Fig 1–Algorithm for thalassemia screening, counseling and management of risk couples.

RESULTS

From March 1997 to June 1998, 8,736 pregnant women attended antenatal clinic. Three-thousand six hundred and seventy women (42%) had MCV less than 80 fl. Among this group, 93% had hemoglobin typing done and a positive result was found in approximately 70%. In the positive result women, 77% of their husbands came and had hemoglobin typing done. Finally, we detected 75 at-risk couples who had a chance of having severely affected child from the total of 3,670 pregnant women in whom MCV < 80 fl.

Of at-risk couples, 57 were new cases with no family history of thalassemia. Eighteen couples had previous severe thalassemia children; 9 were β-thalassemia/HbE disease, 1 was homozygous β-thalassemia and 8 were Hb Bart's hydrops fetalis. There were 37 couples at risk for Hb Bart's fetus, 38 couples at risk for β-thalassemia. Fifty-eight couples (77%) accepted prenatal diagnosis. No cases who had previous thalassemic children denied prenatal diagnosis and all of them came to antenatal clinic as early as possible. Seventeen couples who refused prenatal diagnosis after genetic counseling were new cases and all were at risk for β-thalassemia HbE disease (Table 1).

There were 8 affected fetuses, 5 cases were Hb Bart's fetus and 3 cases were β-thalassemia HbE disease. No Hb Bart's fetus was born in the serial ultrasound group. All affected fetuses were terminated except one β-thalassemia/HbE fetus where the couples decided to carry on with pregnancy and the cord blood result after birth confirmed to be a diseased fetus. Unfortunately, there were 3 fetal losses from 50 couples who underwent invasive tests (cordocentesis). One developed chorioamnionitis and other two aborted within 7 days after fetal blood sampling and all were normal fetuses.

DISCUSSION

Thalassemia is the most common inherited hematological disorder in Southeast Asia, especially in Thailand. Two common types, homozy-

Table 1
Results of prenatal diagnosis.

PND	Primip	Multip		Total
		No previous thalassemia	Previous thalassemia	
Risks of Hb Bart's				
CVS or cordocentesis	15(2)	6	8(3)	29
Ultrasound	7	1	0	8
Risks for β/β of β/E				
CVS or cordocentesis	9(2)	2	10(1)	21
Non-accepted	7	10	0	17

( ) : number of thalassemic fetuses diagnosed.

gous β-thalassemia and β-thalassemia/HbE disease, occurred in about 5,000 new cases born every year (Tanphaichitr, 1999). All these thalassemic patients are a burden to the parents and represent the major public health problems. Although Hb Bart's fetuses are not major public health problems, maternal morbidity due to severe preeclampsia and postpartum hemorrhage are increased in association with this Hb Bart's fetus (O-prasertawat *et al,* 1990). Therefore, it is necessary to have a program for prevention and control of all these severe diseases.

Firstly, a screening program has been set up for the detection of the heterozygous couples. Many methods were introduced for this purpose, for example erythrocyte osmotic fragility test (EOFT), red blood cell indices, hemoglobin electrophoresis, etc. In this study, red blood cell indices particularly mean corpuscular volume (MCV) was use to screen thalassemic carriers since all pregnant women in this hospital have automated complete blood count done as a routine booking requirement so it is convenient to use this for mass screening in our institution. The cut off point is less than 80 fl which is normally used in the screening program (Gehlbach and Morgenstern, 1988; Yeo *et al,* 1994; ACOG, 1996). From our study, we found that 42% of all pregnant women had MCV less than 80 fl which correlated to the report of the whole nation that approximately 40% of the population are carriers (Tanphaichitr, 1999). Although MCV less than 80 fl could be the result of iron deficiency anemia or illnesses such as chronic renal failure and lead poisoning, almost all our pregnant women were healthy with hemoglobins well above 10 g%. According to Flatz's study, healthy Thai people rarely suffer for iron deficiency anemia (Flatz and Flatz, 1980).

All pregnant women with MCV less than 80 fl had hemoglobin typing done by high performance liquid chromatography (HPLC) method which is now the common accepted method for the detection of abnormal hemoglobin. (ACOG, 1996; The Thalassemia Working Party of the BCSH General Hematology Task Force, 1994; Maiavacca *et al,* 1992). In the HPLC group the results were positive in 70%. All partners of this positive group were asked to come and had blood tests for hemoglobin typing but only 77% were screened with full information given. Out of 1,840 couples, 75 couples (4%) were at risk for having a severely affected child. These risk couples were counseled in detail during private interview and informations were given with particular emphasis on option for prenatal diagnosis. When PND was accepted, pre PND procedure was again discussed, including the possible complications of this invasive procedure, the failure to obtain sufficient fetal material for the analysis and the risk of misdiagnosis. The option for therapeutic abortion was also offered for couples having a severely affected fetus. After genetic counseling, 58 couples underwent prenatal diagnosis. In the group of risk for Hb Bart's fetus, 29 couples chose invasive procedures and 8 couples chose ultrasonographic scanning. Five Hb Bart's fetuses were detected from the invasive procedure and all were terminated. Many studies reported the advantages of early ultrasonic evaluation of risk couples for Hb Bart's fetus, and by using the criteria suggested there was no Hb Bart's fetus detected (Lan *et al,* 1997; Ghosh *et al,* 1987; Ko *et al,* 1999). In the near future, ultrasound scan-

ning in early pregnancy in this specific group may be the appropriate way in reducing the invasive procedures with unnecessary pregnancy loss.

In the group with risk for homozygous β-thalassemia and β-thalassemia HbE disease, only 21 out of 38 couples (55%) chose prenatal diagnosis which, unfortunately, was the only invasive procedures available for them. We detected 3 affected fetuses and one couple decided to carry on with pregnancy considering the various degrees of severity of the β-thalassemia HbE disease. Interestingly, seventeen couples (45%) in this group refused prenatal diagnosis and all of them were new cases with no history of affected child in the family or in the relatives. There were many factors that influenced the decision of these couples : 1) multiparity with one or more normal children, 2) fear of abortion in couples with previous history of abortion, 3) religion and unwilling to have therapeutic abortion in spite of severely affected fetus, 4) relatively expensive procedure. To reduce this non-compliance of prenatal diagnosis, the best approach is by education via the media and trying to convince them to accept the safety of the PND procedure. The cost of procedure can be made flexible by either reducing the cost or even free of charge in some cases. Above all, obstetricians, pediatricians and general practitioners should be familiar with this common disease (Beris *et al*, 1995).

From our screening program, 57 new risk couples (76%) were detected. These couples had no history of having a severely affected fetus and such couples can be detected only from the prospective screening program. From the obstetrician's point of view, a screening program should be the national policy in prevention and control of thalassemia. The program should be easily accessible at reasonable cost for obtaining the national policy aim to reduce 10% of thalassemic infants born by the year 2000.

There were 18 cases of previous thalassemic children in our series. Understandibly, all requested prenatal diagnosis, particularly the invasive procedure. The reason for chosing this procedure was the desire to know the early result of their pregnancies. If the result was positive the method for termination is easier and with less psychologic trauma which is more acceptable to these couples.

In fifty cases with intervention, there were one chorioamnionitis and two spontaneous abortions. Six percent of fetal losses in this study are within the range of other studies (Coa and Rosatelli, 1993; Fucharoen *et al*, 1991; Anandakumar *et al*, 1993). All fetal losses were from cordocentesis and unfortunately came from families with no previous thalassemic history and moreover all were normal fetuses. This serious complication needs to be greatly reduced to become acceptable to at risk couples deciding for prenatal diagnosis, especially, in the risk group of β-thalassemia. Nowadays, many methods such as fetal cell sorting in maternal blood and pre-implantation cell detection have been trying to reduce the complications of the invasive procedure. If such methods are succeeded, hopefully, PND will be more accepted and more new cases will be detected.

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