Prenatal Beta Thalassemia Screening in Babolsar, Iran 2006-2016

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Abstract: Objective: Thalassemia is one of the most common autosomal recessive genetic disorders in the world. Thus, prevention programs is a priority. Thalassemia screening at the time of marriage, since 1997 is one of the most successful steps to prevent new cases of thalassemia major, but now we are witnessing the spread of the disease. Methods: This study was a cross - sectional study conducted in two intervention stages which in the first study retrospectively through which to examine the underlying causes of thalassemia patients under 18 years (born in the years after 1997) and in the second stage analysis method of intervention that repeat screening thalassemia, along with tests before pregnancy or early pregnancy was performed. It held several meetings in the specialized committees of hospitals and health centers in the city do, each paired with anemia hypochromic microcytic (mcv <80 or MCH <27 or both) tend to pregnancy or are pregnant, counseling center thalassemia referred, which after necessary review, thalassemia carrier couples directly to the center for Genetics and suspected cases of other forms of thalassemia syndrome of the University of hematologists were introduced. Results: The first phase of the study is cross-sectional study on 25 cases of thalassemia patients under 18 years of age, 15 patients (60%) parents were couples before 1997, parents of 4 patients (16%) had a child with major thalassemia (s2), Parents of 10 patients (40%) couples have after 1997 (s1). Based on the above results, the second stage of the study, the 85-year intervention program entitled screening was conducted on 9750 pregnant women or before pregnancy, the results of the intervention program, identified 21 new beta thalassemia carrier couples, including couples 10 couples 10 couples couples before 1997 and after 1997 (without official marriage license, laboratory errors, and hemoglobinopathies), after identification of the 21 coaples beta, as soon as reference to the genetic center that was preventing the birth of four children with major thalassemia. Conclusion: The results of this intervention in the last 9 years (2006-2016), with timely identification, prevention of thalassemia that the birth of the fourth child of 25 children with thalassemia compared to the nine years before this project was (1997-2006) the method (before-after), can be realized value of these projects. Despite the prevalence of over 10% thalassemia minor and hemoglobinopathies such as sickle cell types and variations of it exist in this area, it is recommended that integrates screening in pre-pregnancy care or early pregnancy may program managers and decision makers in order to improve the quality of programs and improve care for carriers, to help minimize the incidence of the disease.
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1. Introduction

The most common hemoglobin disorders, single gene disorder Eastern Mediterranean region, which is associated with major health problems and treatment. Because these patients due to the high prevalence of chronic and clinical severity and the Eastern Mediterranean region imposes a heavy burden on public health. According to the WHO, more than 5.2% of individuals are carriers of hemoglobinopathies major health problem in 71% of the 229 countries considered to come 300-400 thousand births each year are born with defects, nose throat. More than 95% of these births occur in Asia, India and the Middle East. (1, 2, 3).

Hemoglobinopathies syndrome is the most common anemia, thalassemia is. Autosomal recessive single-gene disorders common beta (AR) is more common in Mediterranean and Middle East, Southeast Asia and the Far East extends from southwestern Europe and in large areas of Africa can be seen. (4 and 5) For the prevention of thalassemia in much of the Mediterranean and Cyprus and Sardinia, premarital screening and screening of all pregnant women ultimately population (Expanded Population Screening) were supported, despite the high prevalence of genes (16-20%) in this area, with a reduction of approximately "100% of thalassemia was 10 years. (6, 7) In our country, in the region of the Caspian Sea and the Persian Gulf and Oman Sea south of Khuzestan, Fars and Kerman is higher. The risk of birth of children with thalassemia in Iran, on average, one in 300 births is estimated that approximately "three times higher than the highest frequency in hereditary diseases, the incidence of Down syndrome

is one in a thousand. According to Iranian Blood Transfusion Organization, the number of 18 616 beta-thalassemia patients and 5% prevalence of Thalassemia gene in the country and the prevalence of more than 10% of the population carries the gene for beta thalassemia major and 2500 thalassemia major in Mazandaran province have been reported. Mazandaran province of over three million people and the proportion of patients with thalassemia major population is 112 per hundred thousand people. Mazandaran province accumulation of patients, more in the brook, and Babol, Babolsar and thalassemia prevalence of 265 per hundred thousand streams with the highest density of population in the country and Babolsar patients with 234 patients per hundred thousand people were in second place. (8-10)

These patients are dependent on blood transfusions after multiple transfusions increase morbidity due to Iron overload and are deposited in vital organs and on disorders such as delayed growth and congestive heart failure and diabetes are vascular and liver and spleen. The survival of patients with thalassemia major by age 5 is 1%, up to age 10 is 7%, by age 20 is 32% and by age 30 decreased to 50%. The major problem in treating thalassemia patients, in addition to skyrocketing costs, favorable results were not irreparable harm mental health and social (emotional cost) for the families of patients and society. Due to the high cost of keeping these patients are experiencing great financial, the cost of treatment of thalassemia major in the amount of about $7,000 a year it is estimated that more than 90% is paid by the state. In other words, the number of patients included, the yearly amount of about 120 (about $ 800 USD) for direct treatment of patients spends a large share of the health budget of the country account for the importance of the subject remind us, and hence prevention programs in priority contract. The cost of prevention to treatment of 172.1 and the cost of prevention to the bone marrow transplant 112.1 (11-17)

No politics can not completely prevent the steady increase patient care costs, so prevention programs include community screening and counseling for couples at risk to begin to identify prospective long-term cost savings will be greater. Based on the transmission pattern is created by the marriage of two individuals who carry the thalassemia gene, the idea of preventing them, through screening, couples countries, including our country many years running and due to easy and low-cost (one dollar) and in availability of screening tests for the disease compared to the huge cost of treatment and care of patients ($ 7,000) and the amount of cost - benefit, implementation of prevention programs on it is very predictable. Prevention and control program of thalassemia prevention programs in the field of genetics is one of the most important and oldest health care system is executive policy since the beginning of 1376 in the form of integrated country programs to be carried out. Finally, according to reports published by the management of disease by the implementation of this program in the first eight years, the incidence has declined by nearly 80%, we have a birth of new cases in the country reached 1,200 in 1376 to 150 in 2014. Failure to implement prevention programs from birth thalassemia, with a prevalence of more than 10% gene beta in the north of the country expected annual 150 infants born with thalassemia major Mazandaran province was, that by using this program, the incidence of children with thalassemia in 1376 from 11 per hundred thousand are now (2014) to 1/1 percent reached thousands. (18-21)

Despite more than a decade of thalassemia control program has been implemented, are still cases of this disease. For more information about the study that challenges in prevention and control program of thalassemia major and solutions and appropriate intervention. In the first phase of this study, assess and identify existing challenges, by examining the underlying causes new cases of thalassemia in this city from the years 1997-2014 and secondly the intervention project entitled screening of pregnant women was conducted from September 2007, I try to take steps to prevent the birth of children with thalassemia major. An epidemiologic study and analyze the incidence and causes of integration re-thalassemia screening in early pregnancy care before can the program managers and decision-makers to improve the quality of programs and improve care for carriers, pan assist minimize the incidence of disease.

Analysis Method

For the incidence of new cases of thalassemia screening after execution, analysis and selection of appropriate intervention methods, this study was conducted in two phases (first phase: cross-sectional method - second step: analytical intervention). The "almost all people who have participated in this study were written consent.

First step: To investigate the cause of new cases of thalassemia major thalassemia prevention and control program after execution 1997-2015.

Prevention and control program of thalassemia in the country was established three important strategies: First Strategy (s1): Screening of all couples applying for marriage anemia, conducted before the official contract and obtaining a marriage license and special care couples were carrier based on national guidelines. The second strategy (S2): Take care of those parents' thalassemia major patients who are of childbearing age, in terms of family planning or appropriate references to genetic laboratories. The third strategy (3

S): Screening of all couples before 1376 (the first year of the program) in order to identify carrier couples, and couples who have not participated in the screening before marriage, including informal marriages. The methodology of this study, cross-sectional study that thalassemia patients referred to the cases of non-communicable health departments in hospitals and units of the required information was obtained. The information includes demographic data (birth and marriage parents, place...) was recorded due to lack of testing. The data classification, data analysis was performed. In this study the underlying causes of disease thalassemia disease based on three standard strategy in Thalassemia Disease Control and Prevention Act in 1376, were divided into three categories:

In the second stage comprising the steps of:

A) Coordinate public and private systems to refer couples with CBC and microcytic hypochromic anemia (MCV<80, MCH <27 thalassemia counseling center city (according to the algorithm (1)):

- During numerous meetings and committees diagonal iodates of Obstetricians and Gynecologists and child mortality, maternal child with laboratory and medical health centers and urban - rural, which is held every three months. In thalassemia screening program for pregnant women, and with Case - report of new cases of and prevention were invited. The identification and referral to pregnancy or pregnant women in which CBC routine tests pregnancy for pregnant women before 10 weeks in special laboratory thalassemia reference city be requested, (Test CBC (with Japan KX21h) the presence of anemia microcytosis (MCV<80, and 27> MCH) was studied that if the CBC impaired woman to call her husband CBC and CBC both cases where people showed microcytic anemia, thalassemia couples were referred to counseling center.

B) In the center of thalassemia advice: couples counseling and referral centers to cooperate by written consent is obtained. For couples with microcytic anemia hemoglobin electrophoresis (Mindra devices made in Japan) and ferritin by Elisa kits using Biosystem). In cases where the testing, beta-thalassemia carrier couples identified, prenatal diagnostic test for CVS, were referred to the genetic center thalassemia. (Couples hypochromic and microcytic anemia with natural HgbA2 as suspected and iron deficiency anemia the next steps were referred to specialists, hematologists. C) pre-birth diagnostic tests and study centers hemoglobinopathies Genetic diagnosis before birth to the baby's parents, in fact, is to determine how the inheritance of genes. For this purpose, place and type of genes and mutations in each of the couples and then their inheritance practices cvs status of the fetus can be determined. Obviously if faulty gene transfer by both parents, with children suffering birth abortion can be prevented. This experimental stages: extraction of blood samples and DNA (proteinase Boiling method SDS-K, salting) of different methods of PCR and sequencing (DNA sequency) and digestion (RFLP) was performed and determined the mutation people method called rapid molecular methods of ARMS (Ampilification refractory mutation system). PCR is a method for detecting mutations that point for you and in cases where both CBC showed microcytic hypochromic anemia thalassemia couples referred to counseling center.

Findings:

The study consists of two phases: the first phase: examining the causes of 25 Beta thalassemia, Thalassemia screening in couples with the city of Babolsar in 1997-2015 years and the second stage of the study involved analysis of October 85 the city implemented that during this period or before pregnancy were studied 9750 pregnant mother.

- First, based on the information recorded in the patients' medical records were collected. A total of 25 patients with thalassemia major are under 17 years of age average age of 12.7 years 8-18Sal ratio of male to female M/F = 1.7, 65% of patients were from rural areas categorized patients according to the start time of screening before marriage (1376): 60% of patients, parents, couples and parents before 1997. 40% of patients after the 1376 couples.

- Parents of 15 patients (60%) of couples were before 1997. Contains:

- 11 couples (44%) of couples were married before 76 and screening Budo were not aware of their minor

- Parents of 4 patients (16%) had a child with thalassemia major (S2) without pre-birth testing, risk pregnancy, prenatal diagnosis accepted without testing again "were thalassemic birth control

- Parents of 10 patients (40%) were 76 couples after. contains:

-6 Couples (16%) as the Lab-thalassemia minor couples were identified and pre-marriage counseling, but due to financial difficulties and negligence, did not set out to test prenatal diagnosis.

-2 Thalassemia patients (8%) are the twin sons because of laboratory errors, the tests said their parents were born healthy.

-2 Thalassemia patients (8%) when one parent is a carrier of cell cycle anemia because CBC indices in cell cycle anemia, thalassemia in the Border line is not recognizable.

- 1 pair (4%) after 76 couples without screening (S3) with the permission of their informal marriage.

Table 1- causes new cases of thalassemia in newborns, in Babolsar City, 1997-2014

Causes new cases of thalassemia	Type of strategy	Percent
Married before the screening program	S3	44
Dereference couples from marriage register (informal contract)	S3	4
Special laboratory error thalassemia	S1	8
HgbS hemoglobinopathies	S1	8
Socio-cultural poverty	S1 and S2	16
Lack of care	S1 and S2	20
Total	S1, S2 and S3	100

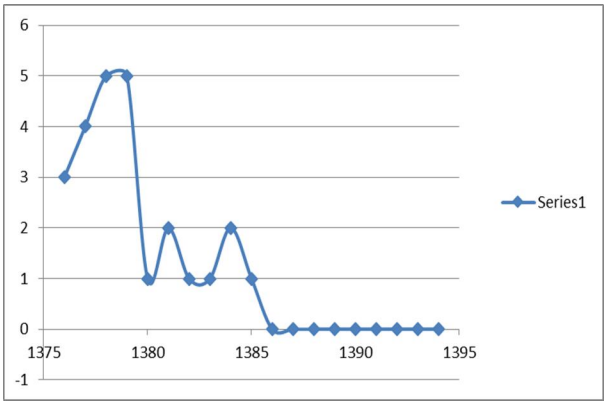

Figure 1- Trend of thalassemia in the city of Babolsar 1997-2015

Second step: from October 2006(1385) to prevent new cases of thalassemia screening program for pregnant women was conducted in the city. Run this program in addition to the fact that national strategies overlaps with all the challenges of this program also provides fixes.

At this stage, the analytical study intervention has been performed from October 2006 till 2016 (1385 till 1394) in this city (the algorithm) that during this period or before pregnancy were studied 10,200 pregnant mother. 268 couples who suffer from anemia hypochromic and microcytic (MCV < 80 and MCH < 27of the personnel - care centers in rural and urban and the number of women trained by the experts, were referred to counseling center thalassemia Babolsar. In thalassemia counseling center with performing specific tests including CBC and serum ferritin and hemoglobin electrophoresis for couples, Beta-thalassemia cases were separated from other types of thalassemia carrier couples identified in this study, 21 pre-birth diagnosis for cvs testing and genetic centers were referred immediately to determine the mutation.

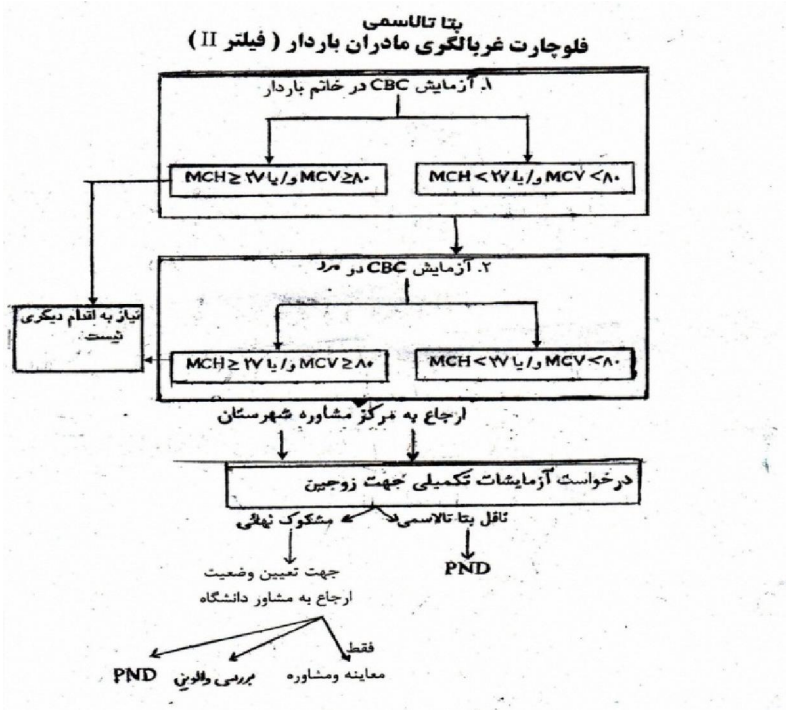

Figure 2- Beta thalassemia screening algorithm pregnant women

In the second stage, performed during screening, 21 beta-thalassemia carrier couples identified.

- 10 couples (50%) of couples before 1376 (couples before the screening program)
- 11 couples (55%) of couples after 1997
- 7 couples (52%) without a license and without participating in the screening of marriage to married (Challenge 1)
- 4 couples (16%) were not identified because of laboratory errors hemoglobin marriage (Challenge 2)

Of this number, 21 couples new identified 15 couples in early pregnancy were identified when genetics cvs and DNAanalysis was performed and the occurrence of four children with thalassemia major when a fetus) SB (thalassemia heterozygotes compound) that by doing therapeutic abortion, was prevention. The 21 couples were carrier under the control of the health care system that a number of carrier couples were then informed of their carriers, the method of tubal ligation after the birth, as a permanent method of family planning chose. 250 couples who hypochromic and microcytic anemia and iron deficiency anemia with HgbA2 natural suspected hematologists were referred to specialists for further action needed only five mutation detection and prenatal diagnosis was stage one and two.

Table 2- couples were carrier of thalassemia screening program for pregnant women

Detected carrier couples	The number of carrier couples were detected	Percent
Couples before 1997 (S3)	10	50
Informal license (s3)	7	25
Laboratory errors (S1)	1	5
HgbS (S1)	2	10
HgbE	1	5
Total	21	100

Table 3- Profile and demographic variables and 20 couples were carrier of thalassemia screening program for pregnant women

Variables	Age or Percent
The average age of mothers (21-42 years)	30 years
Address: City Village	 27.8% 78.2%
Level of education: High school Diploma Higher than diploma	 90% 5% 5%
Ethnicity: Persian Non-persian	Persian language Non-Persian language
Years of marriage Before 1997 After 1997	 50% 50%
Informed couple from being Minor Informed Non-informed	 30% 70%
Pregnancy status During pregnancy Before pregnancy	 73.2% 28%

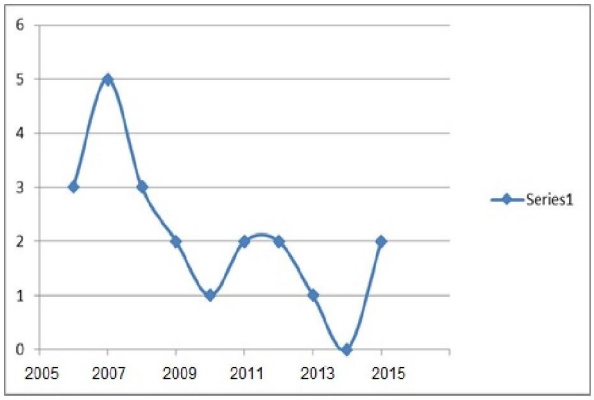

Figure 3- carrier couples identified new trends in maternal screening

Discussion:

Now, nearly two decades after the start of thalassemia prevention programs going on in our country. Reload results and the success of this program can be weaknesses and allowing the completion of thalassemia prevention programs help. Although the number of children with thalassemia major in recent years compared to 76 years significantly decreased, in 1997, birth of thalassemia in Mazandaran province and 11 per 100 thousand births in 1390 to 1.1 per 100 thousand births reached. But the incidence of new cases has not reached zero.

Table 4- Comparison of different regions associated with the incidence of new cases of thalassemia since 1997

Variables	Isfahan city	Cities of Isfahan Province	Fars Province	Babolsar city
Years of study	1997-2002	1997-2006	1997-2007	1997-2012
prevalence of carriers (Carrier.OF)	5%	5%	7%	10-15%
number of thalassemia patients	54	96	312	25
S1	36%	35.5%	29.8%	36%
S3	64%	49%	53.2%	48%
S2	-	15.6%	17%	16%
Total	100%	100%	100%	100%

In a study of the incidence of new cases of thalassemia Ali Reza Moafi in the city in spite of the couples had a screening program in 1999-2002, similarly, a recent study showed that about 20% of laboratory errors that are the reasons HgbS asymptomatic carriers of cholera CBC Border line is these areas (22) (Challenge 1).

Sickel test to test the south of the country in the region and added that the study program with the knowledge that thalassemia patients in this region SB0 (cycle -Tal) seen in the Border line- CBC hemoglobin electrophoresis or column in question HgbA2 were among 18 couples were carrier, two couples who were carriers of HgbS and minor product was a therapeutic abortion was pregnant.

In this research the Dr. M. Zynalyan and Dr. Ashraf Samavati, titled incidence of new cases of thalassemia after the control program to prevent the end of 2007 in the towns affiliated to Isfahan patient SBO is not recognized, 10% of couples S3 after 1376 frequently without screening were approved issue in this study, there have also been mentioned that one-third (3.1) S3 couples were couples without official authorization (23). (Challenge 2)

In the study of Dr. Mehr noush Kousariyan at a medical center thalassemia Sari M Kosaryan from 1992-2002 years have done, new diseases in the vast majority of families are not aware of their minor (S3), who, unlike results the area where the couples before almost "equal and their this research study is not stated, but what was common to see groups S1 for testing before birth due to negligence. (24).

In another study in Fars province by the doctor Mehdi Bagheri in the years 1997-2002 was conducted in the predisposing causes thalassemia major, patients in this study on the strategic plan is triple the same country, but marriage is no mention of informal and HgbS and informal marriages (25) 'according to a separate report from the Center for Disease Control, During the period between 1997-2004 (4.7% of cases) was due to laboratory errors.

In a similar study on the second phase of the study was to evaluate the cost-effectiveness of antenatal screening thalassemia in Hong Kong since 1999 to 2005 was performed using retrospective study and 14% of couples at risk for thalassemia in the fetus or who do EB0 PND23% (18 embryos) had fetuses that abortion was treated with total costs is calculated directly or indirectly. Pre-birth screening HK $ 10 million a quarter (25%) the cost of care and treatment 18 diagnosed with major (40million HK $) effectiveness of pre-birth screening program for thalassemia is common in areas where effective. About the cost effectiveness of beta-thalassemia screening program before birth reports of several researchers English (1995) and Quebec and the Occupied Palestinian Territories was published in 2000. But there is no such reports of because embryos homozygous in the womb or early neonatal death and the need for long-term care do not care costs (the cost of care Maternal complications such as preeclampsia, pregnancy-induced psychological effects of fetal hydrops) (26) A recent study identified four major fetal therapeutic abortion conceptual framework, if non-recognition treatment and care costs $ 28,000, which was equivalent to 756 million riyals thalassemia 4 cases per year and 40-year lifespan equivalent to more than 30 billion was saved.

In China, a study entitled reviews before birth beta in the South China Dongzhi Li and Can Liao, Jian Li Xingmei Xie conduct that has the 545 fetuses at risk of testing before birth method DNA HPLC, analysis was carried out 24% of fetuses with that abortions were treated (27).

In a prospective study called beta thalassemia prevention of prenatal diagnosis by screening in Sardinia that during the three years of 100 cases per year (one in every 250 live births) decreased to less than 5 cases per year. (Notably, these results are only obtained 11 percent of the population of the island Page people who control is the solution.) (28)

Examination of that as a screening hemoglobinopathies in neonates, by Grover, S Newman, D Wethers state of New York was 2% carrier couples anemia, sickle cell frequently Recognizing before birth, 75% of fetuses with that abortions were treated. (29) As in the given one of the challenges are asymptomatic carriers of thalassemia control program is HgbS (11% identify carriers (HgbS

not yet official action to control the hemoglobinopathies.

According to the survey results of intervention in six years, 20 couples beta when 13 diagnosis before birth, birth 4 major Drsalhay 93-85 Pyshgyry that compared the incidence of 13 cases of thalassemia in the eight years before mentioned (Salhay 85-1377) method (before- after) the value of the plan can be realized, "that's terms (cost- benefit) is also part of the costs hidden cost as emotional cost)) that stresses the patient and his family is emotional stress is save this screening.

With this project, the care system more intelligent and stronger, and prevents negligence couples (couples S1 or S2 or S3) and in case of financial difficulty in fulfilling PND couples with correspondence from the center of the genetics and insurance, was used. During the years 1997-2006 sort of factors that are causing new thalassemia cases were preventable. Run this program not only coherent national strategies covered all but the challenges catcher national program in this area is high and the October 2006 case of thalassemia major has been reported in the city.

With the passage of time tends to pregnancy and fertility of high-risk couples is reduced to 1997. As well as with the advancement of technology and updated latest laboratory equipment and training of personnel, equipment and personnel errors is declining. But what seems risky to the increasing couples with or without awareness that the marriage did not participate in the screening and are not recognized (s3 after 76 years) as long as this trend continues for the pair to identify important filter screening of pregnant women and prevention of thalassemia birth will be. Therefore, it is suggested:

- Integration of care before Azbardary screening or early pregnancy may program managers and decision makers in order to improve the quality of care improvement program vectors, pan minimize the incidence of the disease to help.

- The establishment and implementation of the electronic health record household formation for easy access to medical information carriers or patients and their families by authorities and operators of thalassemia prevention and control program.

- In order to complete thalassemia prevention program, has become the cause of thalassemia prevention program and other hemoglobinopathies.

- Equipping laboratories marriage ways to identify such centers hemoglobinopathies (sickle method and apparatus for hemoglobin testing and HPLC.

- Do need to regulate the informal and non-permanent screening before marriage and if not doing so, legal action with those involved in it.

- To raise awareness, the implementation of population-wide screening (population screening) after the presentation of the general population education programs (similar to the successful implementation of this screening Cyprus) not only screening before marriage.

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