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Chronic disease program in Iran: Thalassemia control program

Ghobad Moradi[1], Ebrahim Ghaderi[1]

1 Assistant Proffesor, Kurdistan Research Center for Social Determinants of Health (KRCSDH), Kurdistan University of Medical Sciences, Sanandaj, Iran

Health Care System

Abstract

BACKGROUND: β-thalassemias (beta-thalassemia) is the most common genetic disorder; it is an inherited globinopathy which is transmitted to people due to a mutation in genes that create globin chain. In Iran, the disease gene is more common in the northern and southern regions. It is estimated that more than 60 mutations of the disease exist in different geographical areas of Iran. Iran has begun to adopt strategies to control the β-thalassemia for two decades; the most important of which is the screening of couples when they want to get marry. The present study aimed to review the thalassemia control program in Iran, the history of the disease, and the disease control strategies.

METHODS: This review was conducted according to hand and electronic resources. Books, guidelines and document that exist in thalassemia control program were reviewed in the Iranian Ministry of Health, World Health Organization resources, PubMed, Google Scholar, SID (scientific information database), Magiran and, Iranmedex.

RESULTS: Thalassemia program was appropriately structured and has been achieved successes. Reduction the numbers of new cases of β-thalassemia were notably. In some areas, thalassemia program has some defects and the program faced some cultural barriers.

CONCLUSION: Due to the improvements in the social and economic situation of the people, it seems necessary to focus on prenatal diagnosis (PND) and pre-implantation genetic diagnosis (PNG) technique strategies and provide their necessary facilities.

KEYWORDS: Thalassemia, Surveillance, Epidemiology, Program, Iran

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Introduction

Thalassemia is the most common genetic disorder in humans which is an inherited globinopathy. It is estimated that about 4% to 7% of the world population i.e. 300 million are carriers of the gene. It is transmitted to the people due to mutation of genes that create α or β globulin chains. It is an autosomal recessive disorder leading to reduced production or non-production of β globin chains. B-globin is identified by a structural gene that is located on the short arm of chromosome 11. More than 95% of all β-thalassemia mutations in the world are point mutation in β-type globin gene and only a small percentage are gene-deleted. Nowadays, more than 200 mutations that affect β-globin gene have been identified that cause β-thalassemia phenotype. A small number of mutations, i.e. four mutations are responsible for the illness of 90% of patients.[1-3]

If both β-gene chains are defective, the individual will be affected by major or severe thalassemia and anemia. β-thalassemia, which is the most common form of disease, has three types; mild (minor thalassemia or carrier); average (intermediate thalassemia); and severe (major Thalassemia).[4] Because of anemia and increased erythropoietin, hematogenesis happens outside the bone marrow and liver and spleen may become enlarged. Extensive expansion of

Corresponding Author:
Ebrahim Ghaderi
Email: ebrahimghaderi@yahoo.com

bone marrow impairs growth, change the face, and long bones and spinal column may suffer from pathological fractures. The disease may also cause hemolytic anemia, splenomegaly, leg ulcers, liver dysfunction, diabetes, zinc deficiency, metabolic disorders and heart failure.[5,6]

In addition to the above mentioned physical problems, endocrine disorders are among the other complications of this disease. Hypogonadism is caused due to pituitary sensitivity to hypoxia; secondary amenorrhea, spermatogenous cell abnormalities, short stature, osteoporosis, osteopenia, hepatocellular carcinoma, and hepatitis C are the other complications [3,7,8]. The disease can be diagnosed in childhood based on the symptoms of severe anemia, hypochrome, and microcytic hemoglobin. Disease can be treated either via frequent blood transfusions or using iron-chelating drugs; both methods impose high costs on patients and society.[3]

Thalasemia is an important health issue in high burden area because it could be prevented and its treatment has expensive cost.[9,10] Based on thalassemia situation in Iran and without appropriate strategic for control of this diseases, it can have heavy burden in the country. Therefore, we have reviewed and discussed thalassemia program in Iran. The present study aimed to review the thalassemia program in Iran health system and existing studies about the thalassemia in Iran, the history of disease, and disease control strategies were reviewed.

Materials and Methods

This review was conducted according to hand and electronic resource. Hand research was done in books, guidelines and document that exist in thalassemia control program in Iranian Ministry of Health (MOH). We interviewed with experts in thalassemic office in several provinces for finding all documents about thalassemia program in Iran. These documents were reviewed for history, epidemiology and trend of the program by two researchers. Electronic search was done in the World Health Organization (WHO) internet site, MOH internet site, PubMed, Google Scholar, SID (scientific information database), Magiran and Iranmedex. We used thalassemia, epidemiology, program and Iran as keywords for searching. Abstract of papers were reviewed and full text of appropriate paper were studied accordingly.

Results

Distribution of thalassemia in the world

The disease occurs worldwide and in all races. It is estimated approximately 1.5% of the world population are carriers of β-thalassemia and at least 60000 new cases are born annually.[3] The disease has higher outbreak rate among the Mediterranean, i.e. Italy, Greece, Cyprus and Sicily Island, and also some parts of North and West Africa, the Middle East i.e. Iran, Turkey, Syria, and parts of east and south-east Asia, i.e. India and Pakistan; these countries and regions are commonly known as the thalassemia belt.[3,9] The disease is spread over south-west Europe to the Far East and it is seen in large areas of central Africa. Such a form of distribution is due to the spread of malaria which has been endemic to these regions for centuries; malaria parasite is unwilling to the red blood cells of thalassemia patients, therefore they are resistant against malaria.[11]

Distribution of thalassemia in Iran

In Iran, about 20,000 thalassemia patients have been registered until 2003. The disease has been spread all over the country, but it is more prevalent in the outlying parts of the Caspian Sea (Gillan, Mazandaran and Golestan), bordering parts of the Persian Gulf and Oman Sea (Bushehr, Hormozgan and Sistan-o-Baluchestan), and Khuzestan, Fars and South of Kerman provinces. In these areas, approximately 10% of the populations are β-thalassemia carriers while in other parts of the country, 3% to 8% are the carriers of the gene.[11,12]

In Iran, there are about 2 to 3 million carriers.[13] The national program for control of thalassemia was started in Iran in 1996 and since then the emergence of new cases has reduced and number of thalassemia major patients was 13,000 to 14,000

people.[14,15] It is estimated 1,000 thalassemia major patients are born in Iran annually. Recent studies have shown that β-thalassemia mutations in Iran are different and heterogenic and there are more than 60 different mutations in different geographical regions of the country.[16-19]

Due to the high proportion of consanguineous marriages and its impact on gene pool, the rate of severe forms of the disease has been increased. The proportion of consanguineous marriages in Iran is 38%, from which 27.9% are the consanguineous marriages between cousins. Consequently, it is very important to screen and identify rare mutations in our population.[12,20]

Because of the positive effects of thalassemia major prevention program, the number of newborns with β-thalassemia has been decreased. Since the initiation of the program, 2819 couples underwent prenatal diagnosis (PND) in genetic laboratory network of Iran. Age analysis of patients with severe symptoms of thalassemia has shown significant decrease of the number of thalassemia major cases.[14]

Thalassemia control strategies in the world

In areas in which thalassemia is common, different strategies for thalassemia control are recommended. These strategies include:

- *Identifying carriers:* carriers can be detected since the birth. In some countries, in which thalassemia is very prevalent, thalassemia is detected at the time of marriage or prior to pregnancy. Sometimes this is done in school age or in a similar period. The simultaneous administration of such tests and actions to raise awareness can reduce the incidence of thalassemia.
- *Genetic counseling:* before and after marriage and prior to pregnancy.
- *Population screening:* in specific populations and places where the disease is common.
- *Prenatal diagnosis:* Experience shows that the use of aforementioned interventions may not result in successful prevention. Therefore, PND is considered as one of the most important thalassemia control strategies all over the world.[2,21]

In addition to these strategies, there are some other important measures to be taken:

- Public training
- identifying target groups and covering them with important programs and measures to control the disease
- improving the methods of detecting carriers
- appropriate consultation
- Providing molecular diagnosis
- Diagnosis of mild disease phenotypes
- Increasing access to PND
- Facilitating the process of embryonic samples
- Increasing access to DNA analysis
- Promoting prevention programs, and
- Allocation of resources for disease control.[21]

A history of thalassemia control in Iran

Thalassemia program pilot was initiated in Iran in 1991 and pilot program was implemented in some districts. In that time, the main strategy of the program was to screen the couples prior to their marriage and to suggest separation of carriers and marrying a non-carrier. This strategy was carried out based on the following figure (Figure 1). In order to develop the program and since many carrier couples insisted on being married and were interested to have child, in 1997, it was suggested to promote prenatal diagnosis.[22].

The second strategy was established in 2001. Based on this strategy, patients' families were identified and consultation services were provided for them. If they had not have healthy children, they were referred to prenatal diagnosis centers to have healthy children; consequently, genetic testing and prenatal care were developed in Iran. This has led to a dramatic reduction in new cases of β-thalassemia major. In addition, since all the partners were referring to laboratories, it became possible to investigate and control the incidence of the disease via a strong system. Figure 2 represents the strategy.

The third strategy was started in provinces with high prevalence rates in 2005. Accordingly, the couples who had married prior to 1997 and

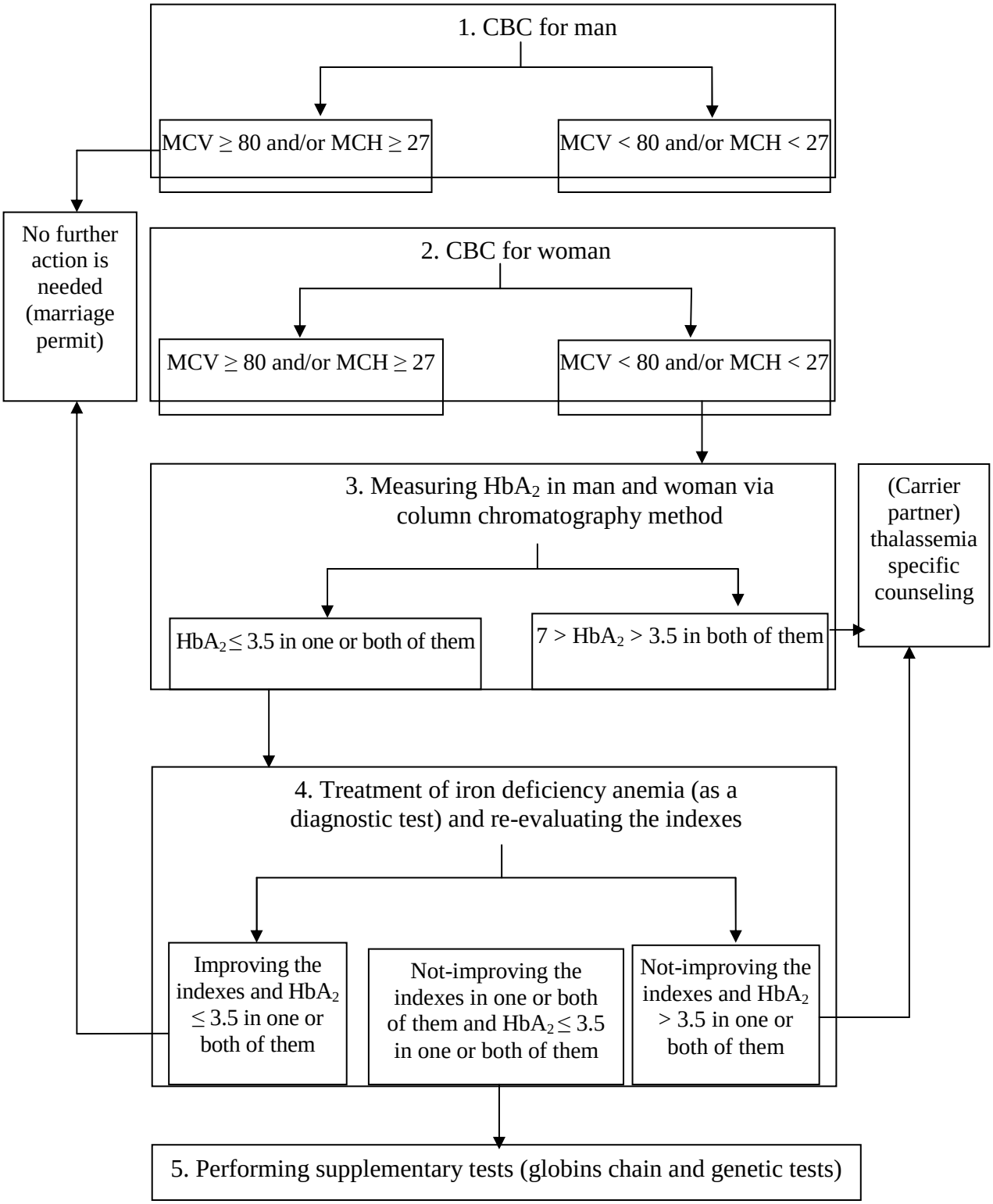

Figure 1. National algorithm of the steps of thalassemia tests (to detect β-thalassemia carrier couples)
CBC: Complete blood count; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; HbA_2: Hemoglobin, alpha $_2$.

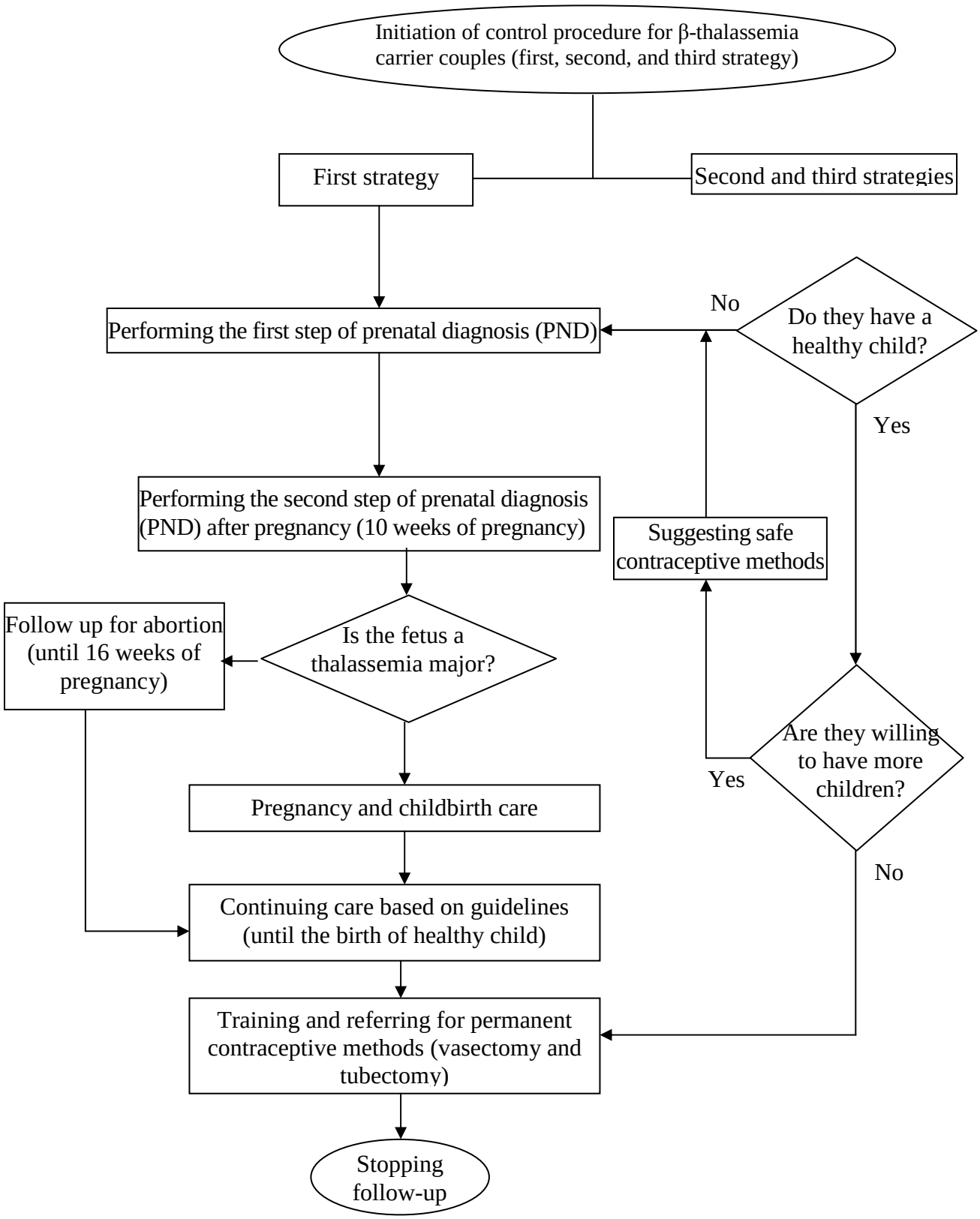

Figure 2. Controlling β-thalassemia carrier couples

had children/healthy children were tested to determine if they are carriers; the carriers were counseled to prevent the birth of children with thalassemia major (Figure 3).

Genetic counseling and genetic diagnostic laboratory network was established in 2008 and was incorporated in the network system. The main tasks of the network were to counsel people and refer them for genetic testing and prenatal diagnosis of thalassemia. Each genetic counseling team was consisted of a physician and an expert. Teams were trained in real and virtual classes. The network was responsible for counseling couples who were both carriers. After counseling, if couples insisted on marriage, they would be referred to prenatal diagnosis centers and epidemiologic control departments in nearby health centers.[11,23]

Preventing the birth of children with thalassemia major in Iran health system

Currently, prevention of the birth of children with thalassemia major in Iran health system is performed through the following options:

- *First option:* motivating carrier couples to cancel their marriage;

Only couples who are both thalassemia carriers (minor) will have children with thalassemia major, so the easiest way to prevent the birth of children with thalassemia major is to motivate them not to marry each other. It was the basis of the first strategy of thalassemia major prevention at the beginning of the program.

- *Second option:* Avoiding thalassemia couples from having children;

The second option to prevent the birth of thalassemia major children included avoiding thalassemia couples from having children and motivating them to adopt a child if they were eager to have children. This was the basis for further development of thalassemia program in later phases.

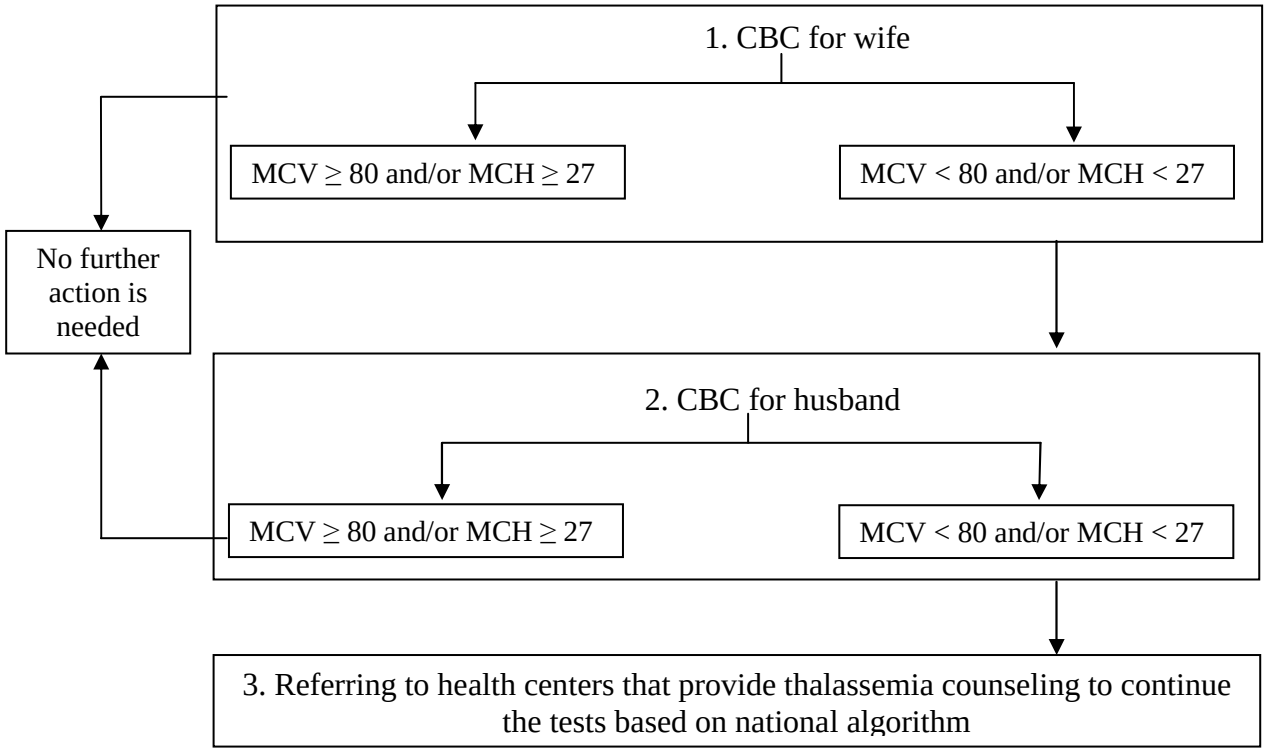

Figure 3. Detecting thalassemia major couples who married prior to 1997 (for regions with high prevalence rates)

CBC: Complete blood count; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; HbA_2

• *Third option:* prenatal diagnosis (PND);

PND and determining how genes are inherited from parents to embryos is the third option to prevent the birth of children with thalassemia major. The type of genes, their position, mutation type, and the inheritance status of the fetus from each couple should be determined. If defective genes are from both parents, the fetus will be a thalassemia major type and abortion will be the only alternative to prevent the birth of a thalassemia major child. This was the basis of the third strategy. Accordingly, in case of diagnosis of thalassemia major in the fetus, parents will be referred to coroners to receive permission for legal abortion. After authorization by gynecologists abortion is performed in a hospital. Legal limit for abortion is up to 16 weeks of pregnancy. Genetic tests and diagnostic procedures for prenatal diagnosis (PND) are as follows:

First: In order to identify the gene and its mutation type, couple and sometimes some other family members are invited to do blood test.

Second: After about 10 weeks of pregnancy, fetal tissue samples are prepared and the status of gene transfer is tested from parents to fetus.[24]

The main objective is to assess the abnormalities at birth or chromosomal diseases (such as Down syndrome) or other genetic diseases. In many countries, if fetus is affected by diseases or if parents are not willing to have the baby, families are allowed to terminate pregnancy and do abortion.

In cases where the family does not wish to do an abortion, prenatal diagnosis helps the treatment team and the family to become ready to deal effectively with birth of an infant who will have the disease. The other goal of prenatal diagnosis is to ensure parents who are concerned about their fetus. This is especially true in families who already had children with the disease. In Iran, in the case of early diagnosis of some diseases and following some legal observations, it is possible to do abortion. Prenatal diagnosis of thalassemia in Iran has become available since 1993. However, it was officially started in 1996, when abortion therapy was introduced.[11,22]

Discussion

Thalassemia program is appropriately structured and has been achieved successes especially in reduction in β-thalassemia major in Iran but in some areas thalassemia program has some defects and the program faced some cultural barrier.[10,22,25] The age of the patients has elevated because of good management of the diseases so we should note this situation in the surveillance program. Given the conditions in Iran, it may become necessary to use new methods of prenatal diagnosis. One of the other genetic approaches for prenatal diagnosis which is called PND is used to detect chromosomal abnormalities of the fetus before birth. However, when abnormalities in the fetus are detected, it is very difficult for the couple to make a decision for doing the abortion and it may lead to physical and psychological complications for them. Using [re-implantation genetic diagnosis (PGD) can avoid such problems.

A new method has been developed to replace PND which can decrease its problems[2]. Pre-implantation genetic diagnosis technique (PGD) is even one of the methods to determine of fetal sex as well by DNA analysis. This procedure can be done at approximately 15-18 weeks of gestation by amniocentesis, or at approximately 10-12 weeks of gestation by chorionic villus sampling (CVS).[26] The main purpose of using PGD is to prevent the transmission of genetic diseases from carrier parents to their children.

Some PGD applications are as follows; for patients who underwent IVF (In vitro fertilization) or microinjection surgery more than 3 times, but the surgeries did not result in pregnancy; when women are over 35 years of age; in case of structural anomalies such as trans-location (displacement of chromosome fragments) found in couples' cerotype test; in case of multiple abortions when there is not any other reason for abortion; diagnosis of sex-linked diseases such as hemophilia which is particularly more prevalent in boys than girls; monogenic diseases such as

thalassemia, which may occur in the newborn. PGD can be used to separate a cell from a developing embryo and perform genetic experiments on it, and then the embryos that are free of genetic abnormalities are transferred to the womb, and expect a healthy baby without the need for abortion which was necessary in the older methods.[27] This approach not only is more ethical but also will reduce psychological complications of couples. Furthermore, this method would be very helpful for people with religious attitudes who may not accept abortion.[28]

Conflict of Interests

Authors have no conflict of interests.

References

1. Miri-Moghaddam E, Naroienajad M, Eshghi P, Zeinali S, Savadkohi F. Molecular basis and prenatal diagnosis of beta-thalassemia among Balouch population in Iran. J Mazandaran Univ Med Sci 2005; 15(48): 111-5. [In Persian].
2. Thein SL. Dominant beta thalassaemia: molecular basis and pathophysiology. Br J Haematol 1992; 80(3): 273-7.
3. Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis 2010; 5: 11.
4. Weatherall DJ, Clegg JB, Higgs DR, Wood WG. The hemoglobinopathies. In: Scriver CR, Editor. The metabolic & molecular bases of inherited disease. 8th ed. Philadelphia, PA: McGraw-Hill; 2001. p. 14571-636.
5. Aessopos A, Farmakis D, Deftereos S, Tsironi M, Tassiopoulos S, Moyssakis I, et al. Thalassemia heart disease: a comparative evaluation of thalassemia major and thalassemia intermedia. Chest 2005; 127(5): 1523-30.
6. Shamshirsaz AA, Bekheirnia MR, Kamgar M, Pourzahedgilani N, Bouzari N, Habibzadeh M, et al. Metabolic and endocrinologic complications in beta-thalassemia major: a multicenter study in Tehran. BMC Endocr Disord 2003; 3(1): 4.
7. De S, V. Growth and puberty and its management in thalassaemia. Horm Res 2002; 58(Suppl 1): 72-9.
8. Borgna-Pignatti C, Cappellini MD, de Stefano P, Del Vecchio GC, Forni GL, Gamberini MR, et al. Survival and complications in thalassemia. Ann N Y Acad Sci 2005; 1054: 40-7.
9. Weatherall DJ. Thalassemia as a global health problem: recent progress toward its control in the developing countries. Ann N Y Acad Sci 2010; 1202: 17-23.
10. Miri-Moghaddam E, Naderi M, Izadi S, Mashhadi MA. Causes of New Cases of Major Thalassemia in Sistan and Balouchistan Province in South-East of Iran. Iranian Journal of Public Health 2012; 41(11): 67-71. [In Persian].
11. Health deputy, disease control center. Comprehensive guideline and training material for national program of prevention of beta-thalassemia major. Tehran, Iran: Seda Publishing Center; 2004. [In Persian].
12. Habibzadeh F, Yadollahie M, Merat A, Haghshenas M. Thalassemia in Iran; an Overview. Arc Iranian Med 1998; 1: 27-33. [In Persian].
13. Nozari G, Rahbar S, Golshaiyzan A, Rahmanzadeh S. Molecular analyses of beta-thalassemia in Iran. Hemoglobin 1995; 19(6): 425-31.
14. Abolghasemi H, Amid A, Zeinali S, Radfar MH, Eshghi P, Rahiminejad MS, et al. Thalassemia in Iran: epidemiology, prevention, and management. J Pediatr Hematol Oncol 2007; 29(4): 233-8.
15. Akhlaghpoor S. Chorionic villus sampling for beta-thalassemia: the first report of experience in Iran. Prenat Diagn 2006; 26(12): 1131-6.
16. Fakher R, Keikhaei B, Aberumand M. Prenatal Diagnosis (PND) of β -Thalassemia in the Khuzestan Province, Iran. Journal of Clinical and Diagnostic Research 2007; 1(6): 454-9.
17. Derakhshandeh-Peykar P, Akhavan-Niaki H, Tamaddoni A, Ghawidel-Parsa S, Naieni KH, Rahmani M, et al. Distribution of beta-thalassemia mutations in the northern provinces of Iran. Hemoglobin 2007; 31(3): 351-6.
18. Haghi M, Pouladi N, Hosseinpour Feizi M, Hosseinpour Feizi A. B-Thalassemia in Iran. JSSU 2010; 18(2): 127-33. [In Persian].
19. Najmabadi H, Ghamari A, Sahebjam F, Kariminejad R, Hadavi V, Khatibi T, et al. Fourteen-year experience of prenatal diagnosis of thalassemia in Iran. Community Genet 2006; 9(2): 93-7.
20. Merat A, Haghshenas M, Pour ZM, Plonczynski MW, Harrell AN, Coleman MB, et al. Beta-thalassemia in southwestern Iran. Hemoglobin 1993; 17(5): 427-37.
21. Cao A. Carrier screening and genetic counselling in beta-thalassemia. Int J Hematol 2002; 76 (Suppl 2): 105-13.
22. Samavat A, Modell B. Iranian national thalassaemia screening programme. BMJ 2004; 329(7475): 1134-7.
23. Ministry of Health and Medical Education. Non-communicable disease data and statistics in Iran [Online]. [cited 2005]; Available from: URL: www.irannamaye.ir/article/view/1093291 [In Persian].
24. Kuliev A, Rechitsky S, Verlinsky O, Ivakhnenko V, Evsikov S, Wolf G, et al. Preimplantation diagnosis of thalassemias. J Assist Reprod Genet 1998; 15(5): 219-25.
25. Dehshal MH, Ahmadvand A, Darestani SY, Manshadi M, Abolghasemi H. Secular trends in the national and provincial births of new thalassemia cases in Iran from 2001 to 2006. Hemoglobin 2013; 37(2): 124-37.

26. Cao A, Galanello R. Beta-thalassemia. Genet Med 2010; 12(2): 61-76.
27. Qureshi N, Foote D, Walters MC, Singer ST, Quirolo K, Vichinsky EP. Outcomes of preimplantation genetic diagnosis therapy in treatment of beta-thalassemia: A retrospective analysis. Ann N Y Acad Sci 2005; 1054: 500-3.
28. Ahmed S, Green JM, Hewison J. Attitudes towards prenatal diagnosis and termination of pregnancy for thalassaemia in pregnant Pakistani women in the North of England. Prenat Diagn 2006; 26(3): 248-57.