RESEARCH ARTICLE

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Epidemiological Investigation of a Twenty-Year Major β-Thalassemia Surveillance in Kerman, Iran

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Background & Aims of the Study: Since beta-thalassemia is the most commonly inherited disease in Iran, its preventive and controlling programs are considered vitally important in the healthcare system. This study was conducted to investigate the incidence rate and epidemiology of major beta-thalassemia (MBT) over the last twenty years in Kerman, Iran.

Materials and Methods: This cross-sectional study, as a kind of health system research, carried was out on all patients with beta-thalassemia (born from March 1998 to March 2018) registered in Kerman Health Center. The data, extracted from the national records of genetic diseases, were analyzed in SPSS software (version 16) using Fisher's exact test.

Results: Based on the results of the present study, the incidence rate of MBT was calculated at 0.99 cases per 10,000 live births. According to this result, 29 subjects with MBT were born from 1998 to 2018. The most important cause of thalassemia was determined as non-identification of thalassemia minor in carrier couples and their lack of awareness about their complication (62%). The other cause was the non-cooperation of screened carrier couples in attending prenatal diagnosis (20.7%). It was revealed that in 23 MBT cases, the parents were relatives (79.3%). The diagnosis of 62% of patients had been made before they turned one year.

Conclusion: It is recommended that the following measures been adopted to avoid MBT incidence: strengthening the care team, cooperating with gynecologists in identifying pregnant women suspected of having thalassemia minor in the first weeks of pregnancy and referring them to genetic counseling centers for condition determination, educating families and changing carrier couples attitudes toward abortion, monitoring and improving screening laboratories, and implementing public education programs for specific groups.

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Background

Beta-thalassemia (BT) is a kind of hereditary anemia in which the synthesis of the β-hemoglobin chain is impaired. This disease is more prevalent in regions endemic for falciparum malaria as well as in those where consanguineous marriages are common. It is more prevalent in the Mediterranean, North and Central Africa, Middle East, South and Southeast Asia, and South America (1, 2). Beta-thalassemia has been classified into three main groups, namely thalassemia minor (i.e., carrier), intermediate, and major. According to the reports, there are 80-90 million carriers of BT in the world (2).

In general, beta-thalassemia is inherited in an autosomal recessive pattern. In case that two carries of beta-thalassemia get married, there is a 25% probability to develop major beta-thalassemia (MBT) in each pregnancy (3, 4). More than 60,000 new cases of MBT are born worldwide in a year, mostly in developing countries or in countries with inadequate healthcare (2, 5). Annually, more than 18,000 patients die due to this disease (6). The patients with MBT and their families are faced with serious medical, social, and economic problems. In addition, taking care of these patients imposes a considerable financial burden for the healthcare system (3, 7, 8), since it is associated with physical complications, serious problems, and early mortality. Unless MBT is diagnosed before birth, it will later (typically between 6 and 24 months of age) be presented with symptoms, such as anemia, splenomegaly, and bone changes. Other clinical manifestations include fever, diarrhea, and growth disorders (2, 9). If these patients, requiring regular blood transfusion, do not receive treatment, they will die in their early years of life.

Frequent blood transfusion causes accumulation of iron in the heart, pancreas, liver, and other organs of such patients leading to heart and liver failure, endocrine gland disorders, and diabetes (1, 4, 10). As a result, to help decrease the iron burden, it is necessary that these patients receive iron chelation therapy, as well as typical examinations and periodic follow-ups for examining their heart, liver, and spleen (10, 11). The permanent treatment for this disease is bone marrow transplantation, which can only be accomplished under special clinical conditions, such as sharing compatible human leukocyte antigens (5, 12). Various measures are currently implemented in Iran to prevent thalassemia major, among which pre-marriage couple screening, genetic counseling, and prenatal diagnostic (PND) screening programs can be mentioned (12, 13).

Major beta-thalassemia is the most commonly inherited disease in Iran. Although the prevalence of BT carriers in Iran has been evaluated at 4%, in northern and southern regions of the country (i.e., close to the Caspian Sea and the Persian Gulf, respectively), this rate increases to around 10%. It is also estimated that there are currently 18,000 patients with BT in Iran (3, 5, 13). The incidence of this disease is estimated to be 1 case per every 10,000 live births (5). In Iran, more than 90% of the patients' treatment cost is covered by the government allocating a considerable portion of the country's healthcare budget to this domain (8).

Iranian national program for the prevention of MBT has been piloted in several towns since 1991. The major policy of this program developed with the aim of reducing the incidence of MBT in 1996 and launched a year later, is based on preventing carrier marriages. In this regard, a network of genetic diagnostic laboratories was established to conduct genetic and PND testing since 1999. As a result, the rate of MBT incidences has decreased to 80% cases throughout the country so far, with 1,000 cases per year to less than 200 ones (5). However, in spite of the implementation of controlling and preventive programs, new cases of MBT have been reported in some regions of Iran, including Sistan and Baluchestan,

Khuzestan, Hormozgan, and Kerman (5).

One of the reasons for the high incidence of genetic diseases, especially diseases with autosomal recessive inheritance paradigm, is the high frequency of consanguineous marriages in that region. In a study performed in Kerman, the rate of couples in consanguineous marriage participating in premarital counseling programs was 34.4% (14), indicating the high frequency of this type of marriage in this part of the country.

Kerman province, located in the southeast of Iran, is one of the regions in which thalassemia is highly prevalent (3, 15). The rate of thalassemia incidence varies across this province, with the highest prevalence in the southern area (15). One of the reasons for high thalassemia observation in Kerman can be related to the migration of thalassemia carrier couples from the other high prevalence provinces having common borders with this province. The identification causes leading to MBT can help in planning and decision-making regarding the incidence reduction of this disease. This study was conducted from 1998-2018 to determine the incidence rate of MBT and identify the factors associated with its incidence in Kerman despite the implementation of controlling strategies.

Materials & Methods

This cross-sectional study, as a kind of health system research, was carried out on all patients with beta-thalassemia (born from March 1998 to March 2018) registered in Kerman Health Center. A hematologist diagnosed this disease in patients.

The necessary data were extracted from the National Form for the Investigation of Genetic Disease Incidence. This form included patients' demographic information, such as gender, date of birth, care status, date of beginning the treatment, status of other blood siblings, as well parents' information, including the year of marriage, any familial relationship, education level, occupation, premarital screening, history of parental genetic care, and cause of disease incidence.

This form had been completed by one of the employees at Kerman Health Center based on the information obtained from the patient's family, genetic reports, household healthcare file, and blood transfusion center records. Subsequently, it had been confirmed by the genetic program officer of Kerman Province Health Centers. The number of live births was obtained from the district Registration Office Website and used for calculating the incidence rate (16).

The inclusion criterion was Iranian patients with confirmed MBT whose information had been recorded at Kerman Health Center and had a medical record at the Blood Transfusion Center as well. On the other hand, the cases referred to blood transfusion centers of Kerman were excluded from the study. Moreover, the subjects whose parents had not been under the coverage of the Kerman Province Health Center, however, had used genetic consultation services at Kerman were not entered into the research. The collected data were analyzed in Microsoft Excel software (version 2010) and SPSS software (version 16.0) using Fisher's exact test. This study was approved by the Ethics Committee of Kerman University of Medical Sciences (Ethics Approval Number: IR.KMU.REC. 1398.239).

Care process

All couples classified as either definite thalassemia carriers or as high-risk/suspicious couples, based on the results of screening tests, were introduced to a healthcare team. These couples received care and follow-ups from the beginning of their marriage, until the establishment of fertility conditions. Initially, they were referred to the genetic diagnosis laboratory to determine the type of their genetic mutation. Afterward, chorionic villus sampling (CVS) was conducted from weeks 10-14 of

each pregnancy to inform the parents of the possibility of affected fetus and provide them with advice for abortion. If parents agreed to carry out the abortion, they were referred to the Forensic Medicine Center to confirm the diagnosis and receive permission for an abortion. The couples were then admitted to a hospital to perform an abortion (5).

Results

The mean ages of fathers and mothers at the patient's birth were 31.4±7.9 and 28.4±7.4 years, respectively. Moreover, the mean age of the patients was 11.3±5.9 years. The parents of 23 cases (79.3%) were relatives. The diagnosis and treatment of 62% of patients were accomplished before they reached one year old. Considering the parents' occupation, most fathers (41.4%) and mothers (89.7%) were workers and housewives, respectively. Furthermore, the education level of most fathers (55.2%) and mothers (48.3%) was under diploma. Other demographic characteristics are presented in Table 1. It was found out in the current study that the thalassemia incidence rate was 0.99 per 10,000 live births. Table 2 summarizes the frequency and incidence rates by year.

In spite of the implementation of controlling and preventive programs, 29 patients (i.e., 12 boys and 17 girls) were born with thalassemia since 14 and 15 couples had gotten married before and after the commencement of the screening program, respectively (i.e., before 1997). The trend of beta-thalassemia major incidence is depicted in Figure 1.

According to the findings presented in Table 3, the main factors affecting MBT incidence were non-identification of thalassemia carrier couples (62%) and non-cooperation of carrier couples in PND (20.7%).

No significant relation was observed between the education of the father (P=0.91) or mother (P=0.55) and the factors affecting MBT incidence. Moreover, the level of father's

Table 1) Demographic characteristics of children with major beta-thalassemia in Kerman

Variables		Frequency (Percentage)
Father's education	Academic	2 (6.9)
	Diploma	7 (24.1)
	High school	9 (31)
	Elementary	7 (24.1)
	Illiterate	4 (13.8)
Mother's education	Academic	2 (6.9)
	Diploma	12 (41.4)
	High school	7 (24.1)
	Elementary	7 (24.1)
	Illiterate	1 (3.4)
Father's occupation	Civil servant	5 (17.2)
	Worker	12 (41.4)
	Self-employed	9 (31)
	Retired	1 (3.4)
	Unemployed	2 (6.9)
Mother's occupation	Housewife	26 (89.7)
	Employed	3 (10.3)
Region	Urban	17 (58.6)
	Rural	12 (41.4)

Table 2) Annual frequency and incidence rate of major beta-thalassemia among every 10,000 live births in Kerman from 1998-2018

Date	Number of live births	Number of patients	Incidence in 10,000 births
1998	10616	3	2.82
1999	10527	1	0.94
2000	10847	1	0.92
2001	10468	0	0
2002	11301	1	0.88
2003	11004	1	0.90
2004	11662	0	0
2005	12551	4	3.18
2006	12620	2	1.58
2007	13660	1	0.73
2008	13718	4	2.91
2009	14340	1	0.69
2010	14145	1	0.70
2011	14571	0	0
2012	15004	1	0.66
2013	15571	0	0
2014	16739	3	1.79
2015	17691	2	1.13
2016	18467	2	1.08
2017	18285	0	0
2018	16584	1	0.60
Total	290371	29	0.99

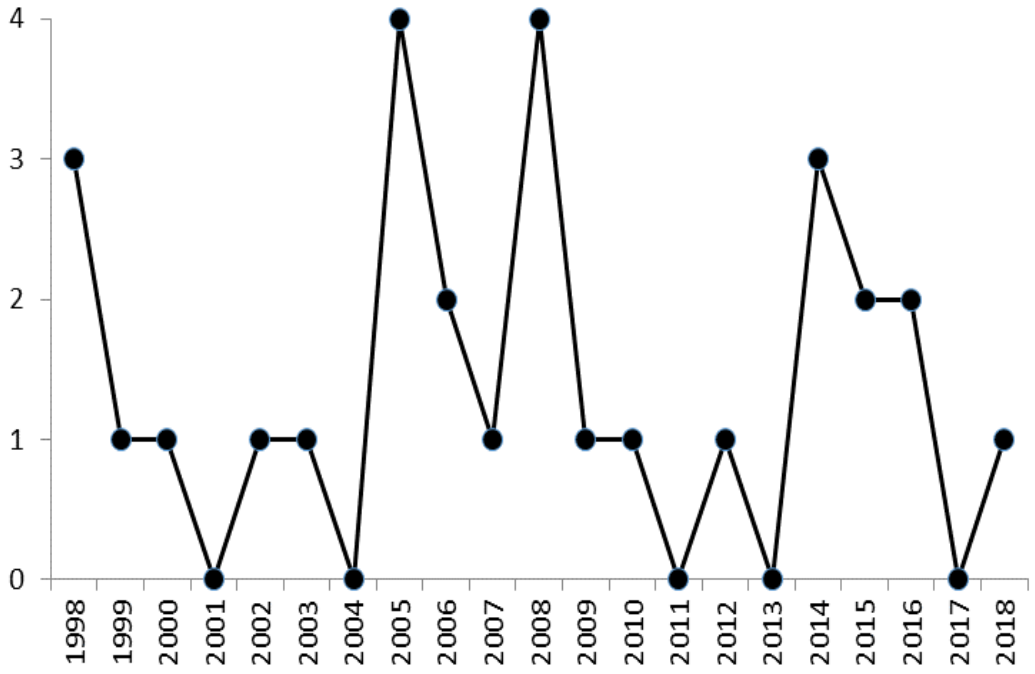

Figure 1) Trend of major beta-thalassemia incidence from 1998-2018 in Kerman

Table 3) Factors affecting major beta-thalassemia incidence from 1998-2018 in Kerman

	Affecting factors	Frequency (Percentage)
Identification process	Mistakes in screening test	2 (6.9)
	Failure to identify couples gotten married before the screening program	11 (37.9)
	Failure to identify couples with a previous thalassemia child	3 (10.3)
	Lack of a screening certificate before marriage	3 (10.3)
Genetic care process	Did not do the PND test for lack of financial affordability, family non-cooperation, previous history of abortion and fear of re-abortion of the fetus, history of aborting an affected fetus and fear of sampling, or preventive religious beliefs	6 (20.7)
	not aborting the affected fetus because of difficulty in the administrative and executive process of abortion	1 (3.4)
Genetic diagnosis process	Non-identical fetal and parental mutations	3 (10.3)
	Total	29

Table 4) Age of diagnosis and treatment of children with major beta thalassemia

Age of diagnosis and treatment initiation	Before 6 months	From 7-12 months	From 13-18 months	From 19-24 months	After 24 months	Unknown
Frequency (Percentage)	10 (34.48)	8 (27.58)	4 (13.79)	2 (6.89)	4 (13.79)	1 (3.44)

(P=0.99) or mother's education (P=0.42) revealed no significant relationship with the age of treatment onset. Similarly, the occupation of the father (P=0.19) or mother (P=0.99) showed no significant relationship with the cause of MBT. The same relationship was found out regarding the relationship between the mother's occupation (P=0.90) and the age of initiating the treatment.

However, a significant relation was observed between the father's occupation and the age of initiating treatment (P=0.007). Accordingly, 11%, 80%, 83% of fathers who were respectively self-employed, civil servants, and workers started the diagnosis and treatment before the patients turn one year old. Finally, no significant relationship existed among the age of initiating treatment (P=0.79) or the factors affecting disease incidence (P=0.42) and the place of residence. According to the results presented in Table 4, 34.48% of the patients were diagnosed and treated under 6 months.

Discussion

This study was conducted to investigate the incidence rate of MBT and identify the factors associated with its incidence in Kerman Health Center. The population of the study consisted of all subjects referring to this center from 1998-2018. In this study, the incidence rate was calculated at 0.99 per 10,000 live births. Although the incidence rate of new MBT cases has decreased considerably after the commencement of the preventive and controlling programs (17-19), it has not still reached zero (5).

Currently, the incidence of MBT is estimated at 1 per 10,000 live births in Iran. The expected incidence of this disease without the implementation of preventive programs is an average of 1 per 1,000 live births per year (5). This value was reported to be 4.5 per 10,000 live births in Kerman from 1997-2013, with the highest prevalence in the southern

area of this province (5). Therefore, it is recommended that similar studies be conducted to identify the causes of MBT incidence and provide effective strategies for preventive measures.

In the present study, the major factors affecting MBT incidence were non-identification of thalassemia carrier couples married before the screening program, and non-awareness about their complication. Some of these couples had one or more healthy children, and the mothers had undergone complete blood count (CBC) tests in their recent or previous pregnancies. Accordingly, their microcytosis was not measured, and/or their spouses were not subjected to any CBC test. In a study performed by Zeynalian et al. in Isfahan, 49% of MBT cases belonged to the couples who had never been screened, while 91.5% of them had got married before the national screening program commenced (8). In another study conducted by Ghorbani Aliabadi in Jiroft, Iran, 23.1% of couples had not undergone premarital screening tests (20). Similarly, the findings of a study carried out in Zahedan, Iran, revealed that 70.2% of couples became aware of being a thalassemia carrier after they had given birth to their first thalassemia major child (21).

It was expected that the disease incidence would decrease since the national guidelines emphasized screening couples getting married before 1997 in high prevalence provinces especially Kerman (8). On the one hand, these mothers have lost their fertility with aging becoming unable to give birth to more children (22). However, considering the dramatic reduction in the rate of fertility in Iran, the population policies and changed from 2012 (23) encouraging families to increase childbirth. Regarding this, the probability of thalassemia incidence would increase since there are still uncooperative unscreened couples giving birth to new children.

In the present study, two of the couples were unaware of their complication because of mistakes in the screening test and three couples did not undergo premarital tests to become aware of their condition. One of these cases was among the survivors of Bam earthquake who stated that because of the chaotic conditions after the earthquake, the Notary Public's office registered their wedding without receiving a certificate of thalassemia screening. In a study conducted in Isfahan, 11.8% of major thalassemia incidences were the result of mistakes in the screening tests. This finding was in line with that of the present study revealing that these mistakes had occurred at the baseline or early years of implementing the pilot program. Over time, the laboratory screening system enhanced decreasing the screening test mistakes as a result (8). In a study carried out in Zahedan, 2.2% of carrier couples had been diagnosed healthy because of laboratory errors (21). In another study performed in Jiroft, 10% of the studied couples reported that they were not aware of their complication in spite of undergoing the premarital screening test (20).

In this study, three couples had given birth to thalassemia children before the implementation of the screening program. They even bore another thalassemia child due to a lack of identification by the healthcare team and not receiving education in the early years of the implementation of preventive and controlling programs. The abortion of fetus in one of these cases was not possible since they referred to pregnancy care and had the PND test late. It is noteworthy that, in Iran, permission for abortion is issued only until the 20th week of pregnancy (24).

In studies performed in Zahedan (21) and Isfahan, it was revealed that respectively 25% and 15.6% of the families with a thalassemia child had already experienced the birth of a thalassemia child. The most important reason (60%) was cited to be poor healthcare (8). In a study conducted in Jiroft, 41.8% of patients had a thalassemia sibling (20).

Seven couples had been diagnosed as carriers during premarital screening and

received counseling by the genetic consultation center and healthcare team in Kerman. Although these couples were fully aware of the risk of thalassemia, refused to refer to genetic diagnosis laboratories for the following reasons: financial problems, family non-cooperation, and religious beliefs. However, since all insurance organizations are committed to paying 100% of the governmental tariff related to the genetic tests of insured thalassemia carrier couples, it seems that the high cost of these tests is no longer a leading cause of thalassemia incidence in insured carriers (8).

In another case, since the parents had to undergo abortion procedures of their first child in the 6th week of pregnancy, they were reluctant to abort their recent child; therefore, they refused to undergo fetal blood sampling. Moreover, the pregnant women did not cooperate to have PND tests in their recent pregnancy because whether they had a bad experience of CVS in their previous pregnancy, they did not believe their next child would develop the disease, or religious issues were preventing them. It was reported that in Jiroft, only 20.9% of the cases had undergone PND tests during pregnancy (20). Therefore, it is recommended that the most time of consultation sessions, rather than providing information and raising awareness, should be dedicated to changing couples' attitudes towards the PND test and abortion.

In the present study, 79.3% of the couples had consanguineous marriages, 57.1% of which were between close relatives. Consanguineous marriages can cause rare genetic diseases especially in those with an autosomal recessive inheritance paradigm.

The results of studies conducted by Zeynalian and Mirimoghadam revealed that 67.7 and 77% of patients with thalassemia were respectively the offspring of consanguineous marriage (8, 21). Furthermore, in a study carried out by Ghorbani Aliabadi, it was found that 65.9% of the couples had a familial relationship (20).

In the present study, a couple, whose premarital tests were indicative of having a thalassemia major fetus, agreed to abort the fetus in a subsequent consultation session. However, they refused to abort the fetus since the administrative course of abortion was long and tedious. In another case, although three couples had premarital screening tests and were reported to be healthy, they bore a child with MBT. After performing CBC and hemoglobin A2 electrophoresis tests, as well as determining the type of genetic mutation, it was revealed that out of the two mutations found in the patients, one had been inherited from the mother, while the other mutation was not found in the father.

In this study, 62% of patients diagnosed having thalassemia before 12 months of age, were treated immediately. In a study performed by Ghorbani Aliabadi in Jiroft, 51.6% of patients were detected within 6-8 months of age (20). In case that couples are not aware of their conditions as carriers, the diagnosis procedure will be delayed increasing the mortality rate and disease complications. It also may lead to the birth of another child with thalassemia in the family (25). Therefore, the healthcare staff should be trained to consider the timely identification of such patients vitally important.

Conclusion

Since the most important cause of MBT incidence was determined as the healthcare system’s non-identification of the thalassemia carrier couples, it is recommended that this sector adopt appropriate measures to avoid this issue. Among such measures can be strengthening the healthcare team, cooperating with gynecologists and obstetricians in identifying suspicious pregnant women in their early weeks of pregnancy and referring them to genetic consultation centers, as well as a routine screening of couples and pregnant

women without a history of screening in healthcare centers. Periodic monitoring of screening laboratories should be conducted to assure the accuracy of their tests.

It is also recommended to adopt the following measures: confronting and resolving the abortion dilemma, offering education to the families of pregnant women receiving health care to attract their cooperation, changing carrier couples' attitude to abortion through influential local people, and implementing public education programs among target groups. Moreover, it is suggested that carrier couples receive psychological counseling in healthcare centers from the early weeks of pregnancy.

Footnotes

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis 2010;5:11. PMID: 20492708
2. Origa R. β-Thalassemia. Gene Med 2017;19(6):609-19. PMID: 27811859
3. Khodaei GH, Farbod N, Zarif B, Nateghi S, Saeidi M. Frequency of thalassemia in Iran and Khorasan Razavi. Int J Pediatr 2013;1(1):45-50. Link
4. Helmi N, Bashir M, Shireen A, Ahmed IM. Thalassemia review: features, dental considerations and management. Electron Physician 2017;9(3):4003-8. PMID: 28461877
5. Khorasani G, Kosaryan M, Vahidshahi K, Shakeri S, Nasehi MM. Results of the national program for prevention of β-thalassemia major in the Iranian Province of Mazandaran. Hemoglobin 2008;32(3): 263-71. PMID: 18473242
6. Hassanzadeh J, Mirahmadizadeh A, Karimi M, Veisani Y, Rezaeian S. Trends in 5-, 10-, 20-, and 30-year survival rates of beta-thalassemia patients in Southern Iran, 1995-2016: a retrospective cohort study. J Public Health Res 2017;6(3):153-7. PMID: 29291192
7. Esmaeilzadeh F, Azarkeivan A, Emamgholipour S, Akbari Sari A, Yaseri M, Ahmadi B, et al. Economic burden of thalassemia major in Iran, 2015. J Res Health Sci 2016;16(3):111-5. PMID: 27840337
8. Zeinalian M, Samavat A, Fadayee Nobari R, Azin SA. Incidence rate of major beta-thalassemia and study of its causes after prevention and control program of thalassemia in Isfahan province. Sci J Iran Blood Transfus Organ 2009;6(4):238-47. (In Persian) Link
9. Amirabadi F, Saravani S, Miri-Aliabad G, Khorashadi-Zadeh M. The association between dental health status and oral health-related quality of life of children diagnosed with β-thalassemia major in Zahedan city, Iran. Int J Pediatr 2019;7(2):8985-91. Link
10. Cappellini MD, Bejaoui M, Agaoglu L, Canatan D, Capra M, Cohen A, et al. Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up. Blood 2011;118(4):884-93. PMID: 21628399
11. Saliba AN, Harb AR, Taher AT. Iron chelation therapy in transfusion-dependent thalassemia patients: current strategies and future directions. J Blood Med 2015;6:197-209. PMID: 26124688
12. Sabloff M, Chandy M, Wang Z, Logan BR, Ghavamzadeh A, Li CK, et al. HLA-matched sibling bone marrow transplantation for β-thalassemia major. Blood 2011;117(5):1745-50. PMID: 21119108
13. Akhlaghpoor S. Chorionic villus sampling for beta-thalassemia: the first report of experience in Iran. Prenat Diagn 2006;26(12):1131-6. PMID: 17009347
14. Rezabeigi Davarani E, Khanjani N, Iranpour A, Mohseni M, Najar Mansoori S. Educational needs of couples attending in pre-marriage counseling classes in health center of Kerman. J Health Based Res 2016;2:69-80. (In Persian) Link
15. Saleh-Gohari N, Bazrafshani M. Distribution of β-globin gene mutations in thalassemia minor population of Kerman Province, Iran. Iran J Public Health 2010;39(2):69-76. PMID: 23113009

16. National Organization for Civil Registration. Available at: URL: https://www.sabteahval.ir; 2019. Link
17. Khorasani G, Kosaryan M, Vahidshahi K, Shakeri S, Nasehi MM. Results of the national program for prevention of β-thalassemia major in the Iranian Province of Mazandaran. Hemoglobin 2008;32(3): 263-71. PMID: 18473242
18. Miri M, Tabrizi Namini M, Hadipour Dehshal M, Sadeghian Varnosfaderani F, Ahmadvand A, Yousefi Darestani S, et al. Thalassemia in Iran in last twenty years: the carrier rates and the births trend. Iran J Blood Cancer 2013;6(1):11-7. Link
19. Hashemieh M, Naghadeh HT, Namini MT, Neamatzadeh H, Dehshal MH. The Iran thalassemia prevention program: success or failure? Iran J Ped Hematol Oncol 2015;5(3):161-6. PMID: 26705456
20. Ghorbani Aliabadi E, Mirrashidi FS, Kiani A, Shahrokhi Sardoo E. Investigating the causes of Beta Thalassemia after start of prevention program in Jiroft city during 2001-2015. J Jiroft Univ Med Sci 2019; 6(1):168-77. Link
21. Miri ME, Fadaiy RM, Izadie S. Lack of knowledge of being minor thalassemi is the main cause of major thalassemia incidence in Zahedan, the South-East of Iran. Hakim Res J 2011;14:174-9. (In Persian) Link
22. Moafi AR, Rahgozar S, Hourfar H, Shirani B. Evaluation of the causes of new cases of major thalassemia after screening for minor thalassemia in Isfahan. J Isfahan Med Sch 2004;22(73):11-4. (In Persian) Link
23. Zare Z, Saffari E, Tabar RK. Fertility motivations and their relation with attitude towards Government incentives for childbearing in women of reproductive age. J Mazandaran Univ Med Sci 2018;28(162):104-14. Link
24. Badieian Mosavi N, Hejazi SA, Sadeghipour F, Fotovat A, Hoseini M. Examination of fetal indications in 548 cases of abortion therapy permissions issued by forensic medicine center of Razavi Khorasan, Iran, in 2015. Iran J Obstet Gynecol Infertil 2018;21(5):6-13. Link
25. Hassanzadeh J, Mirahmadizadeh A, Karimi M, Rezaeian S. Delay in diagnosis of hemoglobulinopathies (thalassemia, sickle cell anemia): a need for management of thalassemia programs. Iran J Pediatr 2017;27(2):e6740. Link