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An economic review of the national screening policy to prevent thalassemia major in Iran

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This Paper is to describe the economic burden of thalassemia as a major health problem in thalassemia belt countries like Iran. Great emphasis is placed on prenatal diagnosis to prevent the disease, as the "economic" solution from a health care policy viewpoint. The alternative method of the current screening program in Iran is outlined and discussed especially with respect to the "cost-effectiveness" issue, along with some pitfalls of the general plan and the techniques under use. Further follow-up of program after such refinement is advised, and especially the provision of a working option of prenatal diagnosis to carrier couples is recommended.

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An economic review of the national screening policy to prevent thalassemia major in Iran

By

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Summary

The medical and economic burdens of thalassemia as a major health problem in thalassemia belt countries are introduced with great emphasis on prenatal diagnosis to prevent the disease as the "economic" solution from a health care policy viewpoint. The alternative method of screening to find carriers of the disease just before marriage and their referral to genetic counseling by the current program in Iran is outlined. As the results of this program compared with the results gained from comparable programs elsewhere look rather "unsatisfactory", the likely factors are mentioned based on findings in the literature and a model is presented to refine the pitfalls of the program looking at specific economic, methodological and also social issues that decrease compliance. The compliance issue is inquired into by interviews with some physicians, couples and families with affected children; some ethical considerations are shortly discussed and finally specific suggestions to improve the results of the program are made. It is concluded that while such a revision can improve the efficiency and credibility of the screening procedure and economize it, continuing follow-up is needed for problems that will be divulged especially in provision of a working option of prenatal diagnosis to carrier couples.

Keywords

Beta thalassemia, Health care policy, Health economics, Modeling analysis, Prenatal diagnosis, Screening tests, Therapeutic abortion.

Introduction

Background information

Thalassemia major is an inherited blood disorder passed on from parents to their children, causing an inability to produce adequate amount of Hemoglobin and leading to severe hemolytic anemia. Symptoms appear a few months after birth and without treatment death will ensue in early childhood. Treatment may extend the life into early adulthood but is very cumbersome and costly, mainly consisting of blood transfusions every 2-4 weeks and administering desferrioxamine (Desferal) by continuous infusion for 10-12 hours daily using a pump, to remove excess iron from the body. The treatment is so expensive that many children especially in poor countries receive inadequate dosages and die in childhood or adolescence. Even with adequate therapy, many children experience impairment of growth or sexual maturation [1]. Still optimal management of thalassemia major requires the development of specialized centers, and the care received over the lifetime of a patient becomes extremely costly. Prenatal diagnosis of thalassemia can be done for parents who are known carriers, so identified because of a previous affected child or a positive family genetic history. But the ideal option of preventing the birth of a first affected child requires community screening [2,3]. Therefore prenatal diagnosis of thalassemia relies on identification of couples at risk and in countries where the incidence of thalassemia is high, with a big burden of the disease to the population and economy, intensive preventive programs have been established and proved to be very successful [3]. Though beta thalassemia is the most common genetic abnormality causing health problems worldwide, it is not seen with the same frequency everywhere. It is prevalent in the so called thalassemia belt extending from along the Mediterranean sea through Turkey, Iran, India to south eastern Asia mainly Thailand and south of China. In Italy and Greece, the prevalence of the gene is from 5% to 15% and even 20% in some areas [4]. It is estimated that every year about 60,000 thalassemic babies are born all over the world. This disease is one of the prime examples where prevention has primary importance with obvious priority over treatment. There is no known cure but prevention is possible, practical, and successfully realized in some countries. In this respect, prenatal diagnosis has been the mainstay of all “control programs” designed so far. But it is not all that simple considering how the disease is transferred to the children. The parents of a thalassemic child are free of any disease symptoms but are carriers of the thalassemic genes; they have “thalassemia minor” or “thalassemia trait”. This trait commonly is only discovered as a mild anemia in routine blood tests that does not respond to iron supplementation if treated as “iron deficiency anemia”

(specially common in women). When both parents are carriers of the diseased gene, there is a 25% chance in each pregnancy resulting in a child with thalassemia major; 50% chance of a child who is a carrier; and a 25% chance of a healthy child with normal genes. Even if all instances where both partners are carriers were identified, the diagnosis of thalassemia major in the fetus would still be needed. Different techniques such as chorionic villus sampling (CVS) or amniocentesis have been used to get a sample for genetic analysis. Prenatal diagnosis of thalassemia major is made using molecular techniques to test such a sample but accurate characterization of the molecular abnormality depends upon a good knowledge of abnormal genetic forms or "thalassemia variants" in the community [5]. Prenatal diagnosis as the preventive strategy theoretically requires the termination of 25% of all cases of such pregnancies by abortion. Therefore therapeutic abortion is the final tool of prevention in standard control programs.

Thalassemia in Iran

Beta thalassemia is the most common hereditary disease in Iran. All patients with thalassemia major are registered by the regional health care centers. There are about 25,000 thalassemia major patients in Iran and the number of thalassemia carriers is estimated to be about three million. This figure is reproduced easily as beta thalassemia carrier frequency in Iran has been estimated 4-5% in screening studies performed overall, and the latest survey reported a population of 65,619,636 (July 2000) giving us an estimate of between 2,620,000 and 3,280,000 (mean 2,950,000) carriers. It is estimated that about 8,000 pregnancies are at risk each year. The prevalence of thalassemia major is not the same everywhere in Iran and depends on the geographical location with the highest incidence in regions near Caspian Sea and the Persian Gulf. The provinces of Mazandaran, Gilan, Hormozgan, Khuzestan, Kohkiluyeh-Boyerahmad, Fars, Bushehr, Sistan-Baluchestan, Kerman and Isfahan are the top 10 provinces most afflicted. In 1995-96, The Blood Transfusion Organization of Iran and Iran Thalassemic Patients Supporting Society supervised a project aiming at mass screening for beta thalassemia trait in high school students of Tehran. This project was organized as a national study in which 8300 students from 114 high schools in Tehran were tested in two months. It was based on the result of this study that the government decided to include β-thalassemia screening laboratory test in the compulsory package of medical tests on all couples prior to marriage [6]. The standard control program for thalassemia was not accepted in Iran where religious beliefs made it practically impossible to have legal therapeutic abortions. Instead there has been emphasis on identifying "both

carrier" fiancés and providing genetic counseling to change their minds, and not allowing them to marry anyway. This alternative method has been recommended in Iran even by those who were not ethically opposed to therapeutic abortion mostly for practical reasons, as there are still other issues such as access to fetal sampling techniques and laboratory diagnosis of the sample with their high expenses. The cost issue is especially important, as the insurance system will not cover expenses that are not in line with the government's general policies. Sending the samples to countries with high-tech facilities like UK for a laboratory diagnosis has been tried by a few couples but incomplete knowledge of the variety of the diseased genes in Iranian communities, the lengthy process for getting back the results and the high costs involved have all been limiting.

Screening for beta thalassemia trait

About 3% of the world population are carriers of a beta thalassemia mutation. Mass screening and genetic counseling programs have been carried out in many countries [7,8,9] but some factors undermine the effectiveness of antenatal screening for prevention of thalassemia. For example, many medical practitioners and the general public are still not aware of the screening procedures or do not comply; and so new patients are still being diagnosed in areas that the disease has been preventable locally by antenatal screening [10,11]. Defining a national health policy to mass screen for carriers could be a solution and forms the basis of thalassemia control programs. In an economic sense there is a trade-off between costs of diagnosis-prevention and treatment of undiagnosed cases. The system must consider the cost of acceptable care (near optimum) for all thalassemia cases, including those births that could have been avoided. The cost of care for other health care problems that are more common in thalassemics, the time lost by parents in caring for their children, and the disutility of having to deal with the emotional burden and heartache associated with this health problem should be considered too. In ideal circumstances the benefit:cost ratio is bigger than 1, which supports the notion of community-based screening but choosing a suitable economic tool for mass screening is an important step. The gold standard test for diagnosis of the carrier state is hemoglobin electrophoresis [12] but because of its high cost, it is not suitable for mass screening in developing countries with a big population like Iran. Most screening programs use an initial simple but sensitive test such as red cell MCV [13], or osmotic fragility test. Nestroft (Naked Eye Single Tube Red Cell Osmotic Fragility Test) has been shown to be a sensitive, cost effective, rapid and reliable screening test for detection of beta-thalassemia trait (the carrier state) in a population. The positive predictive value

and specificity of 85% to 100%, negative predictive value of 83% to 99% and sensitivity of around 95% have been reported for Nestroft [14,15]. Nestroft, as a single screening parameter is superior to any of the other "simple" tests, such as Mean Corpuscular Volume (MCV) and still is more cost effective [16]. As a result, Nestroft has emerged as the single most effective, inexpensive and easily reproducible test of population screening for beta-thalassemia trait. Nestroft in combination with MCV (with the cutoff at < 80 fl) has been proved 100% sensitive but this combination is not cost effective. The method used for screening in Iran is rather unclear and sometimes confusing as mostly just a complete blood count (CBC) is requested and many variables in the report are looked upon without having a specific measure or standard criteria. Still MCV seems to be the most important item looked into by informed physicians who judge the results of the tests. They also provide the "counseling" as a simple explanation of the inheritance mechanism and prognosis of thalassemia major. So expenses of genetic counseling are kept to a minimum, as a doctor's visit fee, especially in small cities where genetics sub-specialists are not easily available.

Materials and methods

Searches were done on available electronic databases such as "Medline", electronic information available at international or domestic thalassemia support organizations, Iranian national databases, collections of university periodicals and theses, research projects, presentations and reports of seminars and governmental reports with the following queries: "screening" and "thalassemia", "Iran" and "thalassemia", "economics" and "thalassemia". The retrieved results were first sorted out by examining the abstracts and the full texts of papers related to the topic were studied. Unfortunately, the number of Iranian papers cited in international databases was only a handful so the available domestic sources of information were scrutinized with regard to comparable studies, the size of samples and design of study so that figures could be extracted from the most reliable ones available at the national level. The different approaches to prevention of thalassemia became evident at this early stage, then the resultant data and statistics of the different programs were examined more closely to get the programs' results. Also interviews were performed to study different social, ethical, and medical perspectives of the "Iranian control program" as they proved to be important in defining its compliance level and technical credibility. Finally a refined model with due consideration of the pitfalls, technical improvements and cost-effectiveness concerns was reached at by using modeling techniques of economic evaluation. Modeling as an analytical method describes

the essential events that occur over time, in the form of simple decision analysis trees. It simplifies reality to a level that shows the essential consequences of different options for decision-making and has recently been used frequently in health economics, providing a "best estimate" that is more relevant to daily practice in comparison with randomized clinical trials.

Results

Thalassemia control program in Iran

Fars province, located in southeast Iran, holds 5% of the population of Iran but nearly 10% of its thalassemic patients. In 1997-98 a study was performed to evaluate the situation of thalassemia in Fars. A program to prevent thalassemia major was started a decade ago when estimates stated that there was a 7% rate of beta thalassemia carriage in that province. To evaluate the prevalence of beta thalassemia minor, all males in their final year of high school were selected; 24,485 boys were examined. The frequency of beta thalassemia minor was estimated at 6.88% in the whole province [17]; There were a total of 2,193 thalassemia major patients consisting of 1,263 (57.6%) boys and 930 (42.4%) girls and the frequency of thalassemia major was 7.2 in 10,000 population. Mean age of the patients was 10.1 years with a SD of 6.6 years. A large part of the decrease in prevalence of thalassemia major was in the under-10-year-old population and less significant after adjustment for population age distribution. The decrease was concluded to be in fact the result of the birth control program, rather than the program for the prevention of beta thalassemia. Studying the reasons for the relative failure of the program and setting up new strategies were recommended as the program having started a decade ago proved only moderately successful. In other studies it was claimed that annual number of children born with congenital disorders in Iran had fallen by 38% and potential births of children with thalassaemia major had fallen from over 1,200 to about 860 per year while the population increased overall. On the other hand, recent evidence shows that Iran has actually reduced its population growth to 1.2 percent, a rate only slightly higher than that of the United States. Iran's population growth rate dropped from an all-time high of 3.2 percent in 1986 to just 1.2 percent in 2001, one of the fastest drops ever recorded. The results of the former study explain much of the success claimed in the latter studies. Also the claimed decrease is not such a success when compared to some endemic areas in the Mediterranean, where long-established control programs have achieved 80-100% prevention of newly affected births [18].

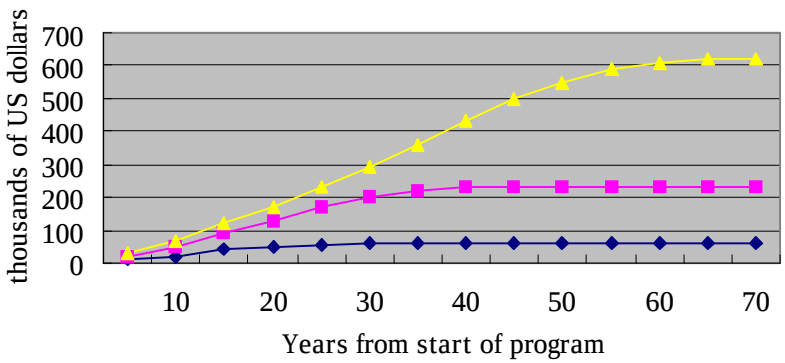
Discussion

Economic aspects of thalassemia

The economic burden of thalassemia is determined by the birth prevalence of affected infants, their survival, availability, costs and effectiveness of treatment, social support and the extent to which affected individuals are accepted and integrated into society. The need for care and its costs at any given point in time depend on the number of living patients in the population. The availability of better health services leads to a cumulative increase in the number of patients needing care and also a higher annual cost per patient because cost of care usually rises as treatment options improve. Children with thalassaemia major are easy to diagnose; regular blood transfusion is available in most countries, is life saving and gives excellent short-term quality of life. However, in the absence of therapy to remove excess iron, it leads to death from iron overload at an early age. Therefore iron chelation therapy is needed to ensure long-term survival ***(figure 1)***.

There are many costs associated with thalassemic patients: blood transfusions, medicines and other essential treatments, hospital care and home visits. Thalassemic patients receive red blood cell transfusions every two to three weeks, amounting to as much as 52 pints of blood a year. Fifty to sixty percent of all donated blood in Iran is transfused to thalassemic patients. Each bag of donated blood costs at least 25 dollars for Blood Transfusion Organization in Iran. Desferrioxamine is imported and is currently about 3 US dollars per vial of 500 mg. A 12-year old, 30 kg patient on regular blood transfusion will require three vials daily throughout his life time. By including the cost of consumables like disposable syringe, scalp-vein needle, etc. the expenditure for Desferal therapy works out to 280 US dollars a month. The infusion pump is also imported and costs 400 dollars.

Figure 1. Cumulative annual treatment costs with birth of a thallasemic patient per year



The lowest curve represents "no chelation therapy", the middle curve "sub-optimal therapy", the most common situation in Iran, and the curve on top represents "optimal chelation therapy". The cost of regular blood transfusion without chelation therapy is relatively low and as patients live for a few years only, the cumulative cost becomes fixed at some point. The cumulative costs (and patients' survival) rise with chelation therapy, and long-term patient survival will be the highest with optimal (the most costly) treatment.

Many of the costs to the patients are covered by different plans financed from public budgets in Iran but still most thalassaemics cannot afford the high cost of optimum treatment and usually die before they reach 20 years of age. The treatment of thalassemic patients costs a huge amount that the national health budget is forced to pay.

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In Iran the average birth prevalence of thalassaemia major is 0.74 per 1000, and the proportion of patients expected to survive at least into their late teens has risen from practically none thirty years ago to over 90% today. Over 23,000 patients are currently under care, representing a forward commitment of around $220 million per year for at least the next thirty years.

In the absence of prevention, annual treatment costs could rise to over $700 million per year. The estimated annual and 10 year projected costs for treating thalassaemia, and the estimated annual cost of prevention in Iran have been compared in some studies notably those by WHO ***(table 1)***.

Table 1. *The estimated costs of treatment and prevention of thalassaemia in Iran (thousands of US dollars; from WHO documents)*

The number of annual births of thalassaemia major	Annual cost of optimal treatment (no prevention)		Annual cost of prevention		The ratio of annual cost of treatment to prevention	
	Yr 1 (1 birth cohort)	Yr 10 (10 birth cohorts)	Year1	Year10	Year1	Year 10
1251	12,387	123,874	7,730	7,730	1.6	16.0

Spending on preventive measures is much more cost effective than its treatment in Iran. As annual prevention costs are effectively constant but annual treatment costs rise year-on-year, the cost-effectiveness of prevention increases with every year that it is in place.

The 10-year projection figures imply actually that it is impossible for Iran to provide optimal treatment for all patients who may be born, and that effective prevention is a necessary condition for those already living to be treated adequately.

Health policy aspects of thalassemia control program in Iran

National programs of community information, carrier screening and counseling, and availability of prenatal diagnosis have greatly reduced the birth prevalence of thalassaemia major in all countries where they have been established. In Iran a national prevention program has been under development, and the national patient register has showed evidence of a reduction in affected births though it has not been enough. There are a few problems in the health policy aspect of the control program. Due to religious restrictions on abortion, the routine prevention of the birth of thalassaemic children by prenatal diagnosis has not been "practically" possible in Iran. Legally speaking, there is a religious general regulation (called Hokm) that prohibits any kind of abortion after the 4th month of pregnancy but permits instances before that time only when the mother's life is endangered, provided the necessary and lengthy procedure (taking to a council committee) is performed to

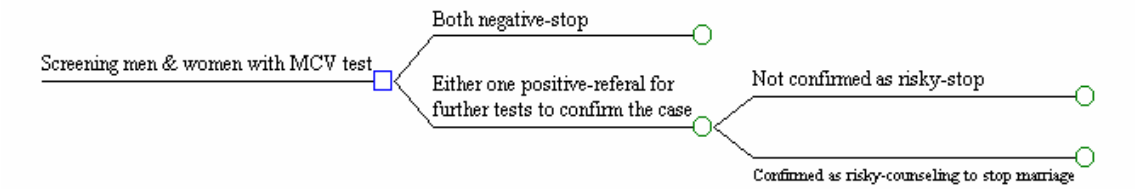
document it. After the specialists raised a question to the current religious leader (called Faghih) specifically for thalassemia major, they got a permit for abortion only in cases of thalessemia major before the 4th month of pregnancy. This permit seems rather enough but technically may not be that easy as the physicians try to be more conservative issuing a "definitive" opinion, and obviously it takes time as getting the result of the test itself is a lengthy matter; Therefore chances of success for the legal option has become so remote that recently in a daily newspaper a few specialists warned and criticized the "legal void" that makes families resort to illegal abortions for thalassemic babies. This sort of problem is not unique to Iran. In a study in UK, only a minority of couples of Hindu, Sikh and Pakistani origin accepted fetal diagnosis and termination of pregnancy within the second trimester and alternative methods of control were recommended whenever that attitude prevailed [19]. The health policy adopted in Iran is trying to use an alternative means to prevent the birth of thalassaemic children, by avoiding from marriage of two carriers together [20]. In a large, three year long study on 100,000 cases in Isfahan, after identification of carriers and genetic counseling provided to them, the average of high risk couples deciding not to marry was 90% and no new cases of thalassemia were detected in the children of the screened population. It was concluded that when both members of the couple were trait-positive their preferred choice was "not to marry", rather than to marry and use other methods or no method to prevent the birth of a thalassemic child. Cultural and religious ideas seemed to have a role in these decisions and the establishment and use of a genetic counseling center seemed to help prevent most of new thalassaemia cases by stopping risky couples from marriage [20]. But other studies need to be done to confirm such a result. Ten percent of the risky couples that insisted on getting married were reported trying to register the marriage in another area outside Isfahan. The study did not follow them nor included their offspring in its results. Results of the four year long premarital screening program aiming at reducing the incidence of thalassemia major in the city of Denizli of Turkey are interesting [5]. The couples at risk were counseled and offered prenatal diagnosis and termination of pregnancy in case of an affected fetus.

This study along many others indicates that premarital screening in the context of offering therapeutic abortion is a very useful tool for detecting carrier couples and an effective way of controlling thalassemia major. It also shows that only a small proportion of cases are likely to face the final decision to terminate pregnancy or not. It was also shown long ago that prevention programs based on carrier screening and genetic counseling in the absence of prenatal diagnosis produced no consistent effect on the birth rate of thalassemia major [21]. Didn't Iran opt a solution that had been tried before and failed?

Conclusions

Pitfalls of the current thalassemia control program in Iran

Using a simple decision tree as a scheme of the current program:



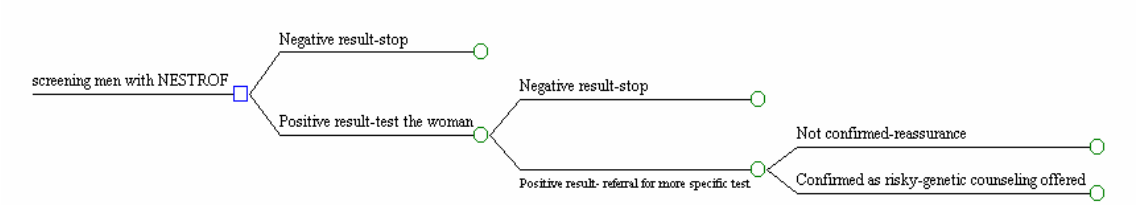
The following pitfalls can be listed:

1. There is no need to screen both men and women applying for marriage. In the standard package of pre-marriage tests in Iran, men would provide a sample of blood to be tested by VDRL, and a sample of urine for addiction. Women were only asked to provide urine samples before the current program was started. Adding a thalassemia screen test to this package for only men has many advantages over screening men and women both. The costs are lower for many reasons of which some are obvious like performing half the number of tests in the first stage and not drawing a blood sample from women as before. Also there will be less referral to doctors for confusion over positive results when only one couple is a carrier, and less psychological trauma of "hereditary disease stigma" especially for women as we will discuss how false positive results are so common in them. More standardization of the screening tool and its criteria including specific cutoff points of MCV, with some collaboration between the marriage registration offices requesting the screen, laboratories performing the test, and physicians judging on borderline cases is necessary at this point.

2. Still relying mostly on microcytosis revealed on MCV for thalassemia minor screening has lead to a large number of false positive results especially as the number of iron deficient women in Iran is very high. Sources in the ministry of health have reported a 17 percent rate of iron deficiency anemia (34 percent rate of iron deficiency) in women of childbearing age in Iran (project report to the World Bank, 2000). Iron deficiency is the most common cause of acquired microcytosis worldwide and especially prevalent in developing countries like Iran. This source of confusion could be largely avoided if the first screen is done on men or another also cheaper

and more accurate test called Nestroft is used as the screening test.

3. Prohibiting couples from marriage has a big disadvantage of endangering the compliance rate and also adds to the size of the "stigma" of being labeled as a carrier. It seems that providing the genetic counseling and asking the couple to consider the ultimate risk, the necessary procedures to help prevent the birth of a thalassemic child and the involved costs and risks (including death of healthy fetuses because of sampling procedure) is enough and practically more efficient in this respect. The proposed decision tree is as follows:



4. In long-term, a suitable screening test can be included in the health check package of schools and the necessary information provided along with the results so that it may help as a matter to be considered before choosing a partner for marriage. The currant policy of denying the permit to marry just as the couple prepares for the ceremony does not provide the necessary compliance rate and also in not ethical in essence.

5. The currant thalassemia control program has ignored a prevention policy for already married couples who may or may not have affected children before. The considerable number of families with more than one affected child observed in some Iranian studies serves as a good proof. Provision of a working option of prenatal diagnosis and therapeutic abortion for at least this group of couples seems necessary at this stage. Concerning the laboratory diagnosis requirements concerns, Iranian scientists have been able to detect up to 85% of the cases overall till now, ranging from 70 - 90 % for different geographic and ethnic origins [22]. More successful prenatal diagnosis in the Iranian population requires more work to be done in identification of the mutant genes.

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