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2. THE PREVENTION OF THALASSAEMIA REVISITED BY THALASSAEMIA INTERNATIONAL FEDERATION A HISTORICAL AND ETHICAL PERSPECTIVE

AUTHORS: Angastiniotis M., & Eleftheriou A.

INTRODUCTION

The Thalassaemia International Federation (TIF) adopts and advocates the position of the World Health Organisation (WHO) that a genetic control programme should be an intrinsic part of national healthcare systems, encompassing the components of prevention, clinical management and social care.

TIF, in this chapter, revisits the thalassaemia prevention programmes, strategies, policies which exist in a selection of its member countries. It discusses their effectiveness and whether any changes in policy or public attitudes to thalassaemia prevention have occurred through the years, in view of the significant improvements in patient outcomes, public health (including prevention of communicable diseases) and healthcare systems.

An effort will be made to answer the questions:

- Have a) the improved prognosis (mainly due to the increasing use of oral chelating agents), b) the improvement of iron load monitoring [15], c) the provision of multidisciplinary care, and d) the recent availability of new innovative therapeutic and curative products [16] influenced public health decision-makers and/or the attitude of the public at large with respect to prevention of thalassaemia?
- Are public awareness, screening, genetic counselling and prenatal diagnosis still recognised and considered essential components of an effective prevention programme?
- Are these principles, and the essential elements of national coordination and funding, which aim at the reduction of birth incidence, still regarded as the main pillars of an effective prevention programme and is the possibility of an increasing birth incidence in countries where optimal care is available a real one?

Haemoglobin disorders are a group of hereditary anaemias which, without lifelong optimum care, are fatal, often in early childhood. In high prevalence regions of the world, they constitute a serious medical and public health problem. In a zone ranging from the Mediterranean basin to China, as well as Africa, these conditions are prevalent in the indigenous populations. However, migrations over the years have introduced them to many parts of the world, especially to western countries [1]. Patients receive varying levels of care, according to national policies and priorities. Optimal care is defined as the application of clinical and laboratory approaches that are validated at a given period of time and have proven outcomes, and which may change as new practices are adopted.

Over the years, advances in clinical care of thalassaemia have changed the prospect for survival and quality of life [2,3]. The accumulation of experience and knowledge, particularly in the Southern Mediterranean countries over the last 2-3 decades, have led to the publication, initially by the WHO (in 1993) and later by TIF and others, of guidelines for both management (latest edition in 2021) [4] and prevention [5] of thalassaemia. Guidelines for the prevention of thalassaemia are based on elements identified in the 1970s as applied mainly by the countries of the Southern Mediterranean. These were supported by the WHO and its expert medical groups that were established in the 1980s and which led to the resolution on prevention published by WHO [6, 7]. Prevention programmes were initiated at a time when basic treatment was being increasingly adopted in the

early 1970s and concerns about resources such as availability of blood for transfusion were predominant in the planning of services. The value of effective prevention programmes has been significantly appreciated in these countries since they have allowed, mainly through the reallocation of resources, the survival and quality of life of patients to improve. In developing countries, however, where more than 75% of the patient population is born and lives, optimum care cannot be, and is not, provided. Therefore, improving the effectiveness of prevention programmes constitutes the most important element that would contribute to great improvements, given that only a very small percentage of patients (TIF estimates this is less than 10% of the global patient community) in these countries has access to what is today referred to as optimal care.

HISTORICAL ASPECTS AND GENERAL PRINCIPLES

Steps towards better management historically date back to the 1960s when blood transfusion became increasingly used [8], and iron chelation was recognised as an essential component of treatment [9]. Over the ensuing years these basic modalities of care have been optimised, and new oral iron chelating agents have been introduced. Increased survival led to the recognition of multi-organ damage due to transfusional iron overload and toxicity, and the need for a multi-disciplinary approach to clinical management. In addition, psychosocial aspects were recognised, and community support was introduced. This escalating complexity of patient care required increasing resources and demands on healthcare systems. Reducing birth incidence as a means of reducing the public health impact and persuading health authorities to provide optimal care to patients as a means of ultimately saving resources, became imperative. The lack of precise epidemiological data in many countries has not allowed the development of appropriate health policies and actions.

The importance of comprehensive control programmes was recognized as early as the 1950s when Silvestroni and Bianco in Italy, recommended to the High Commission for Hygiene and Health in 1955 the provision of free medical care for patients and the establishment of large-scale screening and preventive counselling programmes [10]. Lack of public and healthcare professional awareness was a limiting factor, along with the fact that only counselling for "at-risk" carrier couples was available at the time. However, the dreadful clinical picture experienced in these early years, the uncertain prognosis and the projection of an ever-increasing number of new cases as life expectancy was improving with better care, led health authorities and medical specialists to adopt and implement a programme for the prevention of newly affected births in some high prevalence countries. This gave "at-risk" couples the option of avoiding an affected birth.

The first attempts at large scale and national prevention were adopted by some Italian provinces, Greece and Cyprus from the 1970s [11,12, 13,14]. These have served as models for other high prevalence countries, to formulate their own programmes. Later, prenatal diagnosis was introduced and became an additional choice for couples [15].

Support for these programmes also came from the WHO, which formed a Working Group in the 1980s.

In one of the WHO working group first meetings it was stated:

"A genetic control programme is an integral strategy combining the best possible patient care with prevention through carrier screening, genetic counselling and the availability of prenatal diagnosis" [14].

Further to this, according to WHO Executive Board decision (EB118.R1) in May 2006, Member States are urged to "design, implement, and reinforce in a systematic and effective manner, comprehensive national, integrated programmes for prevention and management of thalassaemia, including information and screening. Such programmes being tailored to specific socioeconomic and cultural contexts aimed at reducing incidence, morbidity and mortality".

These prevention programmes were developed in accordance with fundamental principles of genetic counselling [17,18] i.e. the autonomy of the individual or couple, the right to complete information, and strict confidentiality. Following these principles, couples were enabled to make 'informed choices' concerning marriage and reproduction, according to the information provided by the professional(s) offering counselling.

For all the above reasons, voluntary avoidance of new births affected by thalassaemia has been gradually encompassed in several national thalassaemia policies.

In this Chapter, a survey of practices in various countries and an investigation to identify any changes that have occurred through the years, in policy or public attitudes to thalassaemia prevention given the improvement in patient outcomes seen in recent years, is undertaken. The possibility of an increase in birth incidence of affected births due to the free choice of parents in countries where optimal care is available has already been experienced in a few countries. Indeed, currently, because of the implementation of complex but comprehensive clinical management, which now includes early detection and effective management of complications, patients are surviving into the 7th decade [19, 20, 21]. These good outcomes hold true however, in high income settings but are variably achieved in several middle- and low-income countries. The need to control birth incidence by offering a prevention programme is still, for these reasons, necessary in countries in which premature death of patients is the prominent clinical outcome.

PREVENTION PROGRAMMES

The free and informed choice of "at-risk" couples is the guiding principle of any programme of control presented to an "at-risk" population, including the provision of adequate and accurate information. Community awareness, and the quality of genetic counselling also have a significant impact on parental choices. All "at-risk" couples are presented with the same choices in premarital and preconception screening and need the appropriate counselling in order to proceed to their own 'informed' decisions (Table 1). These are significant elements affecting the choice of partner, marriage and in creating a family. Therefore, planning a service requires that these considerations are effectively addressed, in nationally coordinated, supported and funded strategies.

Table 1. Choices available for couples who are at-risk

Risk identified	Choices
Before marriage or pregnancy	1. To avoid marrying another carrier 2. To separate from a relationship that puts their future children at-risk 3. To marry their chosen partner, with knowledge of the risk involved
After marriage or cohabitation	1. To proceed with a pregnancy, accepting the risk of possibly bearing an affected child 2. To avoid having children (e.g., choosing adoption) 3. To undergo prenatal diagnosis, choosing to either accept an affected child or interrupt the pregnancy 4. To use pre-implantation genetic diagnosis as an alternative to prenatal diagnosis, and so avoid pregnancy interruption
When already pregnant	1. To undergo prenatal diagnosis (if in early pregnancy) 2. To accept any outcome with no further action 3. To interrupt the current pregnancy with no further action

In cases where prevention policies for thalassaemia have been implemented, those which have demonstrated success and effectiveness include mainly the following key components:

- National strategy on prevention which suggests government approval, control and
- support
- Public awareness programme
- Screening programme to identify carriers
- Genetic counselling services
- Prenatal diagnosis as a choice for at-risk couples
- Preimplantation genetic diagnosis
- New emerging technologies (such as non-invasive prenatal diagnosis)

The difficult choices faced by "at-risk" couples, make the quality of information and counselling expertise provided of the utmost importance and this, unfortunately, falls below expectation in many settings [22]. Cultural differences across the world have resulted in a variety of practices, which must be taken into account [23] and understood when practical policies are to be decided, and ethical considerations are discussed. Consanguineous marriage is common in most countries of the Middle East, where the β-thalassaemia carrier rate is also high. Interruption of pregnancy has a variable acceptance across many cultures and individual couples may even differ among themselves. The acceptance of pre-implantation genetic diagnosis (PGD) over prenatal diagnosis and the possible interruption of pregnancy, for example, in many settings has had limited utilisation due to cost and complexity. If non-invasive pre-natal diagnosis becomes feasible it may also have a poor uptake across the world because of the continuing need for pregnancy interruption. All these factors suggest the conclusion: a single policy on prevention cannot be universally accepted in view of the diversity of cultures, services offered and the patient clinical outcomes that are experienced in various settings.

The thalassaemia patient journey in each setting is a factor that influences public responses to prevention. To date, limited information exists on the quality of care across the world, and even less on patient outcomes, including both morbidity and mortality, especially in developing countries. This requires the establishment of national patient registries [24], which in fact very few countries keep (for more information see Chapter on Registries).

The adoption of programmes aimed at the reduction of birth incidence cannot be an isolated policy. It must, at the same time address the unmet needs of patients, who now, with good quality care, have the chance to return any investment in their care by becoming productive members of society. When considering the reduction of new affected births as a policy, the element of autonomy of the couple is vital and is based on 'informed choice', which depends on accurate unbiased information [25]. The extent to which this is adhered to cannot be quantified when looking at an overview of national policies. The objective of such policies is not always clearly stated by health planners but ultimately, they offer the chance for reduction of affected births. How this is achieved, the contribution of carrier screening, the acceptability of pregnancy interruption and other measures, will vary from country to country and from culture to culture. The efficacy of the prevention programmes is most often evaluated by the reduction of affected births. However, control of a disease is ultimately a reduction in suffering, so the improvement of the lives of affected patients and family outcomes must be the ultimate goals.

Patient care leaves much to be desired in most of the world (for more information see other relevant Chapters). Moreover, new therapies are emerging, which due to cost, are anticipated to only reach a minority of patients in the developing world. Moreover, universal health coverage has yet to reach most of the global population. Collectively, these facts demonstrate a picture of inequity in care. Hence, policies for the reduction of affected births cannot be considered an outdated philosophy.

Each society initiating a genetic prevention programme must consider the above arguments and include its own ethical considerations. In Vietnam for example one ethicist considered the need to differentiate genetic screening from the moral objections commonly associated with eugenics on the basis of the primary motive for screening (avoidance of suffering) and the preservation of voluntary choice. He concluded that beta thalassemia screening in Vietnam would hold up the ethical principle of nonmaleficence and also preserve and enhance reproductive choice [26]. In other societies voluntary choice is at risk by strong counselling against 'unsafe marriage' [27]. Such considerations cannot be ignored by any society.

PUBLIC AWARENESS

One aspect that is a major factor in any public health policy is the adequate preparation of the public through an effective education and awareness raising policy [28]. The real impact of this is difficult to adequately assess, since there may be policies and actions in place, but whether they reach the public effectively can only be assessed through research using questionnaires.

In Qatar a survey of 476 of university students (mostly female) found that only 100 had heard of the premarital screening programme. Only 178 participants were willing to cancel marriages, given incompatible results. In Qatar, mandatory premarital screening was initiated in 2009 [29]. Likewise in Bangladesh over two-thirds (67%) of college students had never heard of thalassaemia even though most of the respondents (88%) showed a positive attitude towards 'premarital' screening to prevent thalassaemia [30]. The same ignorance was found following interviews with parents of thalassaemic children in which nearly all respondents (97%) had not heard about the term 'thalassemia' before the disease was diagnosed in their children; all (100%) were unscreened for carrier status prior to marriage [31]. The importance of a health education program on thalassemia prevention and control was demonstrated in Phnom Penh, Cambodia, where knowledge and attitude towards prevention and control of severe thalassaemias as well as the intention to undergo screening, was significantly improved compared to those who did not benefit from an education programme [32]. It is important to increase community understanding of thalassaemia and its prevention, and an important target group are the young who are approaching marriageable age. In Indonesia unaffected youth aged 15-24 years, were found to have poor knowledge (62.1%) of thalassaemia, through a relevant questionnaire. Many (82.6%) believed they were not carrying thalassaemia trait despite the fact that most (95.7%) had never been tested [33]. Another important consideration is the presence of migrants who may be unaware or have little knowledge of thalassaemia. This was demonstrated in Thailand where migrants from neighbouring countries (Myanmar and Cambodia) had extremely poor thalassaemia awareness (4.1%) compared to Thai subjects (79.6%), concluding that the knowledge gap in migrants needs urgent attention and sociocultural and structural barriers merit further attention when designing thalassaemia screening [33].

An additional problem is the inadequacy/ineffectiveness of screening programmes in many LMICs resulting in a high prevalence of undiagnosed haemoglobinopathy carriers among pregnant women attending antenatal clinics. Among 2107 pregnant women at 11 ± 3 weeks of gestation registering for antenatal care (ANC) at four government hospitals in Pune city, India, the prevalence of undiagnosed haemoglobinopathy carriers was 6.3% (3.3% β-thalassaemia, 1.7% AS and HbE carriers was 1.4%). The beta thalassaemia carriers belonged to the underprivileged social groups and part of the reason is that in light of the magnitude of nutritional anaemia among pregnant women in India, haemoglobinopathies are underprioritized as issues of public health concern [35].

For example, in Oman [36] 36% of married participants in a survey who reported that they did not volunteer for a premarital test, gave ignorance as the reason, while another 13% did not know where to go for a test; among other reasons, 6% stated there was lack of knowledge of the partner's status before marriage. Most, believed that a premarital test is necessary, but 30% were not in favour of taking it even though 50% agreed that the test should be made compulsory. The situation in Oman is mirrored in other countries. In Malaysia [37], in 70% of families in which a child with thalassaemia was born, neither parent was aware of their carrier status until their child's diagnosis, while in other cases they did not receive accurate information or support for prenatal diagnosis and option for pregnancy interruption. Of the 38 parents interviewed, 20 (52.6%) indicated that they would terminate an affected pregnancy. Notably, 52.2% of Muslims supported termination. Likewise, in Saudi Arabia [38], of 920 students, 445 (48%) had never heard of thalassaemia and despite the mandatory premarital testing for thalassaemia, only 50% of married students stated having heard of the disease.

This lack of awareness constitutes a lack of communication and ineffectiveness of the policies adopted (or not effectively implemented) to reach the wider society and are witnessed across the world. In many cultures a fear of stigmatisation (often underplayed as a factor) plays a large part in the decision to be screened; the reason may be a perceived compromise of being a good choice in the marriage 'market'. This issue is ignored in health education campaigns and will take much time, even years, to overcome in some societies [39, 40].

Lack of population awareness, cultural and religious factors, the element of stigmatisation and marriage practices all differ widely across the world and greatly influence the acceptance of genetic prevention. A dialogue with the public has been an essential component of programmes, such as the one practiced in Cyprus and other countries [41]. In prevention programmes it is important to understand why the participating population does not always share the expectations of those running the programme. One objective of health authorities is to reduce marriages between carriers though premarital screening and directive counselling which may not be acceptable to all. In a study in Iran [42], qualitative interviews were used to investigate why such couples married even after counselling; the result indicated that inadequate or inaccurate information was given to some, but strong emotional attachment between couples, taking the test at the wrong time, family interference and family insistence on marriage, having seen cases with no problems, and specific thoughts and beliefs are other important reasons for marriage among couples with thalassemia minor in Iran. A similar study from the Jazan province of Saudi Arabia [43], revealed that more than half of the at risk couples rejected the premarital counselling advice because they believed that their marriage was their unavoidable destiny, about 30% of the attendees reported that disease complications were not well explained during the counselling, and 18.2% proceeded with the marriage because they thought the risk of transmitting the disease to their children was small and 5.2% proceeded with their marriage because they believed their children's lives would not be affected by the disease. In Oman, another country of the Arab peninsula, the premarital screening and counselling program was introduced in 1999; of 159 participants in the screening programme, the response to positive results, showed that 23% cancelled their engagement, while 13.8% continued with marriage for either emotional or family reasons. On the other hand, 18.9% were undecided as an initial response to positive results. Cancelling a relationship is difficult even in cultures where marriages are arranged and often consanguineous [44]. Similarly in Yemen approximately half of respondents (50.79%-56.61%) tend to go ahead for marriage in case of positive results for inherited and infectious diseases respectively [45].

COUNSELLING

Information to the public must be supplemented by individually informing the "at-risk" couple in a session, or even better in a series of counselling sessions. To offer as many 'choices' as possible, carrier detection should occur before conception; the timing of screening is thus of great importance [46]. In areas where thalassaemia is of low prevalence, reaching out to the "at-risk" population is difficult and screening in early pregnancy has been adopted. This however limits the choices of parents to either accept an affected child or proceed to prenatal diagnosis and thereafter to possible interruption of an affected pregnancy. The difficulties of conveying correct, reliable, updated and understandable information to couples was recognised early and not only in the case of haemoglobinopathy prevention [47].

One important question is the quality of counselling and who, with what qualification and/or prior training, offers the service. Rowley et al. [22] investigated the effects on programme efficiency, comparing if the counselling was offered by primary providers and tertiary providers. They used indicators such as (i) the proportion of β-thalassaemia births after counselling, (ii) the knowledge of both partners "at-risk" after counselling and (iii) whether the individual counselled brought his/her partner to be tested. The two groups differed only in the case of bringing the partner to be tested. The similarity in effectiveness however may be because the study was preceded by a training session, so that the primary group were made familiar with a 'counselling protocol'. In the real world, haemoglobinopathy counselling is not offered by professional tertiary, trained professionals. Especially in large, high-risk populations, such counsellors are scarce and usually concerned with rare hereditary conditions while haemoglobin disorders are left to clinic doctors, nurses and laboratory personnel who know the condition, but however are not trained in counselling. In some cultures, directive counselling is the norm.

The situation in the early days of screening in Cyprus (1980), in an analysis of the causes of 55 children born with thalassaemia despite an ongoing screening campaign, indicated that parents were not advised to go for testing (49%), or neglected to be screened (13%), or were given wrong advice (13%, usually by an obstetrician), or presented late in pregnancy (16%); 9% were screening laboratory errors [48]. This is still the situation in many high prevalence countries across the world, where poor counselling, due to inexperience and/or lack of training is added to the challenges.

In a recent publication (2018), there were only 7,000 professional and qualified genetic counsellors globally, and of these only 350 were in the high prevalence countries (mainly in Asia); these countries include a 1.6 billion population with countless genetic conditions and with annual anticipated thalassaemia and sickle cell disease births of around 25,000 and 20,000 respectively [49]. The possibility of having professional counsellors for haemoglobinopathy prevention is, therefore, very small.

Counselling services that are based on internationally accepted principles are the reliable source of in-depth information for the "at-risk" couples and lead to real informed choices. The global lack of trained counsellors is a major obstacle to the provision of quality counselling, albeit this does not mean that genetic counsellors should always be employed. The professionals (doctors, nurses), social workers and others who do counsel in real life should be trained before being permitted to assist people in understanding the implications of their risk for genetic diseases and presenting them with choices.

CULTURAL INFLUENCES

Most Islamic countries, particularly in the Middle East, practice mandatory premarital screening. This is, to a great extent, due to the fact that pregnancy interruption is not allowed by civil law in some countries, even though according to religious law, expressed in various theological opinions (fatwas), termination is acceptable up to the first 100-120 days of pregnancy [50]. Premarital screening, for these reasons, is conducted with the aim of limiting marriages between carriers. Marriage restriction in these countries is not, however, supported by the social norms, which include customary cousin (consanguineous) and arranged marriages. However, mandatory premarital screening has been said to promote community awareness of haemoglobinopathies, which may in the long-term increase the efficacy of the programme [51]. Nonetheless, even where premarital screening is mandatory, marriage cancellation may be not acceptable to most [52] and counselling cannot easily overcome social and cultural influences [53]. Researchers in Saudi Arabia, having established that a proportion of the at-risk couples married in spite of 'incompatible' results, suggest strengthening of counselling, reinforced to ensure that the healthiest practices are adopted and include interventions to address the consanguineous marriage practice [54]. Anecdotally, some centres in KSA report marriage cancellation are getting more acceptable; in Medina for example 90% of carriers avoid marriage to other carriers and 0 SCD births have been recorded; in Riyadh the same experience is reported (virtual meeting with centres November 2022).

Consanguineous marriage is associated with a higher risk of having offspring with an autosomal recessive condition, if this is present in the family. The prevalence of congenital anomalies in the offspring of first cousin marriages (where they occur) is estimated to be 1.7 – 2.8% higher than the general population risk [55]. If evidence-based recommendations are to be the basis of community and individual counselling, then the social factors behind these traditions must also be considered, and the benefits weighed against the risks. Culturally sensitive advice in genetic prevention is imperative and the contribution of other academic disciplines, such as sociology and anthropology, as well as legal and religious input, help provide a more tailored approach to communication between the medical specialists and the general population.

In some countries where consanguineous marriage is common, the possibility of cascade screening for biological relatives of patients with beta-Thalassaemia is being explored. One such programme is included in the Punjab thalassaemia prevention in Pakistan. At this stage there is low uptake of cascade screening, a 'decision support intervention for relatives' has been developed to assist counselling families [56, 57]. Family screening has also been proposed in Indonesia. In a study from West Java, it was demonstrated that 42.7% of thalassemia carriers were identified from 8 extended families of the case index, much more than in the control group, which identified 10.6% thalassemia carriers from 12 extended families without a history of thalassemia. This demonstrates the efficiency of cascade or extended family screening [58].

Particular sensitivity to cultural responses to prevention programmes is also important in countries with large immigrant communities. In the UK for example, cultural, social, and (to a lesser extent) religious factors were found to mitigate against the advantages of early screening, particularly within faith communities. Social stigma emerged as key to this process. In England thalassemia commonly affects people of Cypriot, Indian, Pakistani, Bangladeshi, and Chinese origin; in the UK, 80% of babies born with thalassemia have parents of Indian, Pakistani, or Bangladeshi ancestry. A study using mainly interviews and qualitative and mixed method analysis, helped to explain the ambivalence, and sometimes contradictions, demonstrating the complexity of views and experiences, the range of impacts associated with genetic screening, and the outward ripple effect of screening information to the extended family and wider community. The findings suggest that cultural and social sensitivity is important if the unintended harms of screening, particularly the social/psychological burden of value conflict—are to be adequately addressed and minimized [59]

Health planners should also be aware of cultural change over time. One example is Cyprus, where premarital screening has been the choice of the services, the public and the Church, which wanted to limit the interruption of affected pregnancies by pursuing the timely detection of carrier couples. In the 21st century, civil weddings are increasing, and many couples cohabit and marry after the first, or even second, pregnancy, and these are significant cultural changes for Cyprus. So, there are new social issues which may make premarital testing less effective as a measure, and pre-conception screening the focus of public education. Likewise, in the Middle East, cousin marriage is decreasing with recent urbanisation [60, 61, 62].

AVAILABILITY AND IMPACT OF PRENATAL DIAGNOSIS

Prenatal diagnosis leading to interruption of pregnancy is viewed with particular distaste, not only on religious grounds, but also by couples "at-risk" and families, whatever their cultural background [18]. Factors that made the interruption of pregnancy acceptable in some settings included the spectre of premature death of the child, the complexity, expense and risks of treatment, and the painful experience of a previous affected child. Modell et al. [63] showed that prenatal diagnosis was introduced on the basis of the collective informed choices of couples "at-risk". In Cyprus, avoiding marriage to another carrier was rejected by 90% of the population as a means of prevention of thalassaemia, while prenatal diagnosis was immediately accepted [11]. A large majority accepted prenatal diagnosis also in Sardinia [64, 65] and Greece [12]. The effect of prenatal testing and interruption of affected pregnancies has been a basic factor in reducing affected birth incidence in the Mediterranean countries and others, such as Iran, where all aspects of prevention (including prenatal diagnosis) are implemented leading to an over 80% reduction in birth incidence [66] This is not always acceptable in other cultures, but it is noted that without this choice, avoiding carrier marriages may also not be acceptable. Prenatal diagnosis is available in several Islamic countries, but access seems to be limited; this includes Iraq (Kurdish), and Pakistan (Punjab) even though many couples face family opposition (20%) when they had to opt for termination [67]. Even though access is limited prenatal diagnosis is offered in Bangladesh with 232 cases reported [68]. In Guangzhou (Guangdong province of China), 1880 at risk couples were detected by screening and were offered prenatal diagnosis at 10–13 weeks' gestation based on informed consent; of these 345 couples terminated the affected pregnancy indicating acceptability of this choice in this part of China [69]. Similar acceptability was reported by the Center for Prenatal Diagnosis of Fujian Provincial Maternal and Children's Hospital (Fuzhou, China), with couples at risk for both HbH disease and β-thalassaemia. Prenatal examinations included including chorionic villus samples, amniotic fluid samples (the majority) and umbilical cord blood samples. In Fuijan province, premarital, pregestational, and prenatal screening of thalassemia together with intensification of health education of thalassemia-related knowledge has been conducted in highly prevalent areas across the province, aiming to reduce the prevalence of thalassemia in newborns [70]. In India also prenatal diagnosis is acceptable and in the National Institute of Immunohaematology, Mumbai, over 30 years, 3478 couples (first trimester: 2475; second trimester: 1003) from all over India were offered PND, and 801 foetuses (23.0%) were affected and all except three couples opted for termination of these pregnancies [71]. Prenatal diagnosis is practiced in several centres in India [72].

A study from Thailand confirmed that acceptance of PND in Thai pregnant women was not always associated with pregnancy termination. Multiple factors influenced the decision to terminate, but not their religious affiliation. Such factors include the outcomes of the disease in the child's life and the attitudes of significant members of the family [73].

In addition, preimplantation genetic testing (PGT) is available in several centres in China [74]. In China the feasibility of Non-invasive prenatal testing for thalassemia after carrier screening is now being investigated. It is acceptable for high-risk couples reluctant to undergo an invasive procedure, requiring only a simple blood draw from the pregnant woman; where NIPT detects an affected foetus or detects only one pathogenic allele (6 cases), invasive prenatal diagnosis is recommended. In one study, NIPT dramatically reduced the number of invasive prenatal diagnosis required by approximately 69.5% [75, 76].

CURRENT TRENDS

These complex steps and difficult choices have led couples to question the need to avoid the birth of affected children, particularly with improved patient prognosis. This trend is currently limited but visible. Taking the example of Cyprus, where since the 1980s the birth of thalassaemia patients was reduced to 0-2 per year from an expected number of 50-70; in recent years up to 8 new cases per year have been seen (Fig.1 data from the Cyprus thalassaemia registry).

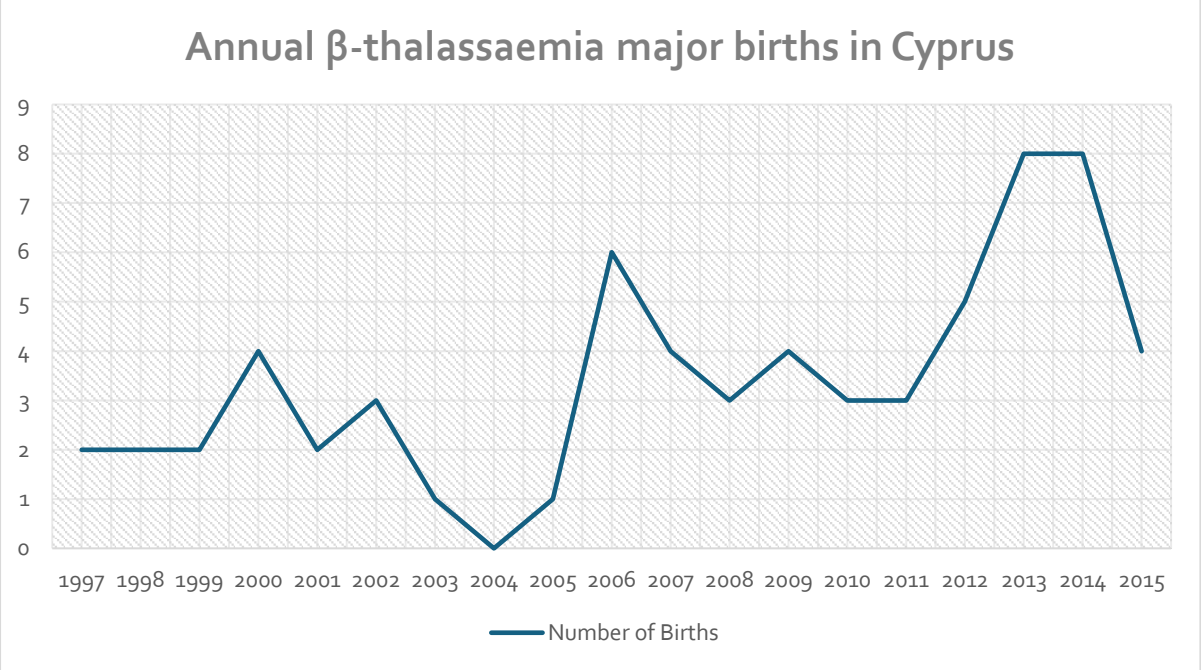

Figure 1. Annual births of babies with β-thalassaemia major in Cyprus. (Source: Cyprus Thalassaemia Registry)

When asked by journalists, one Cypriot couple responded that a child with thalassaemia can live to old age, so 'we have chosen to have our baby'. This confidence in outcomes has also been experienced in Italy; in Sicily, the residual cases 'were because of a conscious choice by expectant parents in relation to improved life expectancy as well as improved quality of life of the affected patients [77]. Other reasons for residual births exist of course, for example, the influx of migrant groups with cultural differences with perhaps a lack of appropriate and sufficient knowledge on the disease compared to the indigenous population, poor communication and counselling and laboratory errors [78]. In many countries' ignorance, poor communication and poor laboratory standards are expected to be the more prominent reasons.

CONCLUSIONS

Almost 50 years ago programmes were initiated in high prevalence countries, mainly in the Mediterranean basin, aiming to limit new affected births. These countries had in mind the need to reallocate resources to more effectively address the increasing needs for lifelong management of patients. Over the years, these needs have been largely satisfied in these countries, and this is reflected in the results related to patient outcomes. These may indeed not have been achieved if the thalassaemia birth incidence remained unchecked.

Populations "at-risk" have made choices based on awareness programmes and the poor clinical picture, including early mortality of affected children and the difficulties faced by the families. Social determinants, such as having to still find paid blood donors or replacement donations (which remains the case in many countries) and to provide medications beyond the capacity of the family income were, and still are in many countries, important factors in the acknowledging the necessity of thalassaemia prevention programmes.

Over the years, this situation has begun to change, but only in some very limited parts of the world where patient outcomes have indeed shown dramatic improvements. In many of the high prevalence countries of the world, however, conditions related to significantly improved patient outcomes have not substantially changed.

As long as the burden of care for thalassaemia patients manifests as out-of-pocket expenses for families and is not supported by healthcare systems, inequalities and poor outcomes will continue to shape the global landscape of these conditions.

The impact on the whole family in countries where universal health coverage is not effective, must not be underestimated. In a social study from a developing country [79] 42% of the surveyed families pay their own health expenses and nearly 80% are in debt. Such information on the plight of families is indeed the daily experience in the work of TIF. This is without considering other psychosocial effects, including isolation and stigmatisation. The socioeconomic consequences of chronic illnesses must always be at the forefront when health planning is being considered.

Offering people in these countries the possibility to choose and even prevent the birth of affected children, therefore remains perhaps a less painful alternative to experiencing multiple medical complications and early death. For such countries, limiting new annual affected births remains a policy, which may be regarded as justified. The concept of eugenics, often cited as criticism of prevention of any genetic disease, cannot be sustained when the overall picture of severe and lifelong suffering is understood. When Galton first used this term [80], he had in mind the 'the improvement of the inborn qualities or stock of the human population'. In medical genetics, the aim of hereditary disease prevention programmes is to offer and contribute to improvements in the lives of patients and their families [81].

In countries where the patient outcomes indicate the possibility of a long and good quality of life, the perspective on prevention has changed or has begun to change. Couples are now seeing adult patients, often professionals, and are asking why should their child not have the same fate? People are aware of new therapies, which may either cure or seriously reduce the need for blood transfusions and all the consequences that follow this dependency. Is the choice of 'prevention' still relevant in such settings? However, the added value of prevention cannot be ignored when weighed by policymakers in respect to ensuring the provision of quality care to existing patients and the competition for medical, public health and infrastructure resources, that the steadily and exponentially increasing numbers of affected children will entail, in the absence of prevention. Indeed, the increase in patient numbers goes hand-in-hand with increasing costs for treatment, that even in the developed high Human Development Index (HDI) countries of the world may not be sustainable. Therefore, risk information and genetic counselling must still be available for people to make fully informed choices.

Public awareness policies, and their continual amendments to reflect societal perceptions, norms and other impacting factors (e.g. migration of populations) should continue to be pursued by national, regional and international professional, medical, scientific (e.g. haematology associations) organisations as well as health bodies (e.g. WHO) and patient support groups (e.g. TIF) in an effort to safeguard the welfare of patients across all countries, including importantly those where no policies are currently implemented and/or suboptimal services exist. In these cases, awareness can help in advocacy and motivational actions.

It must be remembered that social changes will affect the application of prevention programmes. One example are the changing marriage patterns in some societies; there is divorce between marriage and reproduction, since couples may have children and marry later or not at all. The demise of church weddings and the increase in civil weddings in a country like Cyprus may affect screening since it was the Church that mandated premarital screening and not civil authorities.

People at risk for genetic diseases like thalassaemia, in whichever healthcare environment they may live, will always be faced with challenges and painful choices in their reproductive lives, and the effort of every government to provide all available tools to support their decisions must continue. Their support by healthcare professionals and patient organisations at the national, regional and international levels, in addition to relevant official health bodies (mainly the WHO) is imperative to ensure informed decisions are made [78]

In summary those responsible for developing national prevention programmes must consider the following:

- Who to screen and when: schools, premarital, antenatal, family (consanguinity): these depend on population structure and immigrant/ethnic groups, gene frequencies, and cultural considerations.
- Genetic counselling – trained doctors/nurses/laboratory scientists are the most likely counsellors in the absence of qualified genetic counsellors. In multicultural societies the linguistic and cultural barriers must be met. Offering choices considering culture and prognosis which are changing in all societies.
- Prenatal diagnosis and termination of pregnancy are free choices but so is marriage cancellation. The autonomy of couples and individuals must be respected.
- IVF/PGT are expensive choices which need to be financially supported by the programme. The limitations of these techniques must be explained in counselling.
- Neonatal screening is suitable for sickle cell and other variants but less accurate in the detection of beta thalassaemia. Early diagnosis will help sickle cell disorders more than other syndromes.

NEW APPROACHES

Point of care devices: to detect thalassaemia carriers which allow for cheap screening. Such devices are now marketed for both sickle cell [83, 84] and thalassaemia [85] and are suitable for areas where laboratory and other services are generally limited.

Next Generation Sequencing NGS: This is expected to be useful in multi-ethnic societies/populations in which a wide range of mutations and combinations complicate screening, with extreme heterogeneity of haemoglobinopathies. In classical phenotypic screening there are weaknesses in carrier testing since carriers who have normal or borderline red cell indices and/or HbA2 levels may be missed. [86, 87]. This high-throughput DNA sequencing technology reduces price, time, workflow complexity, and error rate and is being increasingly adopted in population wide screening.

Non-invasive prenatal diagnosis: a non-invasive test for haemoglobin disorders using fetal DNA in the maternal plasma, has the potential of avoiding invasive prenatal procedures and so reducing danger to the foetus. This technology has limitations and is not yet routinely used even though the use of NGS has the potential to improve diagnostic accuracy [88]

Treating the foetus: from intrauterine transfusion to gene therapy. The use of intrauterine blood transfusion is particularly useful in the management of Hemoglobin Bart's hydrops fetalis syndrome; raising the total Hb in the affected foetus has the potential of stopping progression of heart failure in the foetus along with all its consequences to the pregnancy. Surviving foetuses will be transfusion dependent patients along with the accompanying complications [89]. Future approaches such as in –utero HSCT and genetic therapies may improve the outlook for this syndrome.

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