The natural history and the national pre-marital screening program in Saudi Arabia

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ABSTRACT

The genetic disorders are chronic in nature and, therefore, require continuous support and health care. Consequently, the genetic diseases cause formidable economic and psychosocial burdens on the family with negative reflection on the community at large. The genetic diseases are a heterogeneous group that result in varieties of chronic health ailment as a result of defects in the genetic material. The congenital malformations and some genetic defects may result from exposure to radiation, pharmaceutical drugs, the exposure of the mother during pregnancy to certain infectious diseases, such as rubella, toxoplasma or viruses. It may also result as a side effect of chronic diseases, including diabetes, hypertension or varieties of environmental factors, or both. The other group of genetic diseases are transmitted from parents to the offspring through a specific pattern of inheritance exemplified by recessive genetic disorders. This group includes the sickle cell gene, the thalassemias, the hemophilias, inborn errors of metabolism and red cell enzymopathies. The main etiological factors of genetic diseases and congenital malformations are 1) Genetic defects which are transmitted to offspring through carriers of affected parents. 2) Mutations in the genetic materials due to spontaneous mutations, exposure of the mother during pregnancy to infectious diseases, such as rubella and toxoplasma, receiving certain teratogenic drugs during pregnancy, exposure of the mother to ionizing radiation during pregnancy such as x-ray and chronic diseases of the mother, such as diabetes mellitus. 3) Others such as difficult labor or injury to the baby, during or after labor. This paper reviews the natural history of common blood genetic disorders and the means of prevention and control, focusing on pre-marital screening as a means of prevention.

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The gene for sickle cell disease was first discovered in the Eastern Province of the Kingdom of Saudi Arabia (KSA) in 1963. Consequently, a series of investigations has, uncovered, beside the sickle cell gene, the presence of thalassemias and red cell enzymopathies.[1-23] Over the past 2 decades, epidemiological field studies led to the establishment of blood genetic diseases map and frequency and distribution, **Figure 1**. The high frequency of the blood genetic disorders was evident in the previously malaria-endemic regions. Thereafter, clinical and laboratory investigations have revealed a wealth of information and enrich our knowledge on various aspects of blood disorders in the KSA.[24-30] As a result, it became evident that there is a necessity to establish a Natural Working Group (NWG) to coordinate various activities and services. This group, a voluntary body, was established in 1990 and a National Committee at the Ministry of Health was established in 1994. Both incorporated expertise working in relevant fields and both worked closely to standardize services and

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establish centers and/or day care clinics, or both in various parts of the country. The NWG incorporates members from various disciplines including physicians, nurses, laboratory specialists, social worker, family members of affected individuals and advocates from the community. The coordinators and deputy coordinate were chosen from various parts of the country. To plan and implement the suggestions and views of the NWG, a National Committee was appointed by the Minister of Health. The national coordinator is the chairman of the National committee for blood genetic disorders at the Ministry of Health with membership from other health institutions.

The National Working Group. The main tasks of the national working group include the following: 1. To assess and update the frequency and distribution of Saudi population of genetic disorders in the Kingdom of Saudi Arabia, 2. To improve management and care for patients suffering from genetic disorders, 3. To improve awareness and educational program of relevance, 4. To implement the national control and prevention strategies, 5. To be involved in continuing education and training. 6. To conduct research and assessment of prevention and care programs, 7. To be involved in local, national, regional and international peer links and interactions.

The National Committee. Evaluation and follow up, necessitate the establishment of a National Committee to coordinate the activity and hold a yearly meeting to discuss new advancement in the field, reflect on the achievement of the last year and foresee the projected plan for the following year. The major objectives of national committee for genetic disorders are 1) Assessment of epidemiological situation. 2) Formulation and evaluation of prevention and care policies related to genetic diseases. 3) Planning a national program for control and prevention of genetic diseases. 4) Devising and adopting a mechanism for coordination and quality control. 5) Assessing and revision of the plan of work as necessary.

The World Health Organization Collaborating Center. The WHO Collaborating Center (WHOcc) was established in 1992, where Department of Biochemistry was designated as the "Collaborating Center for hemoglobinopathies, thalassemias and enzymopathies with specific tasks to be carried out at National and Regional Levels. The main tasks of WHO collaborating center include: 1) To develop further approaches for improvement of the delivery of control services for the genetic disorders to community. 2) To assess and improve the community knowledge and attitude towards the control of hereditary genetic diseases. 3) To assist in training for the population in the fields of investigations, diagnosis and care. 4) To develop and improve diagnostic methods and care for hereditary diseases. 5) To investigate clinical aspects and molecular pathology of genetic diseases. 6) To participate in the implementation of inter and intra-country meeting recommendations and regional programs on prevention and control of the hereditary diseases. To conduct research in genetic services and ethical aspects in the relation to the Islamic believes and traditions.

The national working group, the national committee and WHO center complement each others in variety of ways (**Figure 2**).

The National Prevention Programme. The Recessive Disorders (RD), particularly Blood Genetic Disorders, give rise to chronic health problems, psychosocial and economical burdens and pose a major challenge due to the following factors: 1. High frequency and distribution in different parts of the KSA. 2. The chronic nature of these diseases and the absences of safe and definitive cure. 3. Negative effects on the affected individual, the family and the community at large. These findings have led to the introduction of the National Preventive Programme, where intervention can be carried out at various levels **(Figure 3)**. Interventions at the level of newborn screening and school children screening are long term strategies and expected to be introduced in due course. The prenatal diagnosis and abortion of the affected fetus are faced with serious ethical and societal values restrictions rendering this method impractical.[31,32] In this regards, the Moslem World League-Islamic council issued a Fatwa that states; "If the fetus reached 120 days counted from moment of conception, abortion is not allowed except when it is proved by report from a committee formed of competent trustworthy physicians that continuance of the pregnancy has a confirmed risk to the mother's life then it is allowed to about whether the fetus is malformed or no to drive away larger harm (hurt, damage or detriment)."

"Before 120 days of pregnancy counted from moment of conception it is proved and confirmed by a report from a committee formed of competent trustworthy physicians and on the basis of medical and laboratory findings that the fetus is grossly malformed with untreatable severe condition and if he stays and is born on time his life will be vicious and painful for him and for his family, then it is allowed to abort it on the basis of the patients requisition."

The option of pre-implementation genetic diagnosis (PGD), in conjunction with in-vitro fertilization (IVF), is of limited application, due to the high cost and technical limitations making it only available in a limited scope. Early diagnosis of the high risk group and carrier detection, including pre-marital screening seems to be the only strategy that can be adopted at a large scale.

Aspects of Health and Progeny. The "right" of bringing up of the offspring and preservation of the

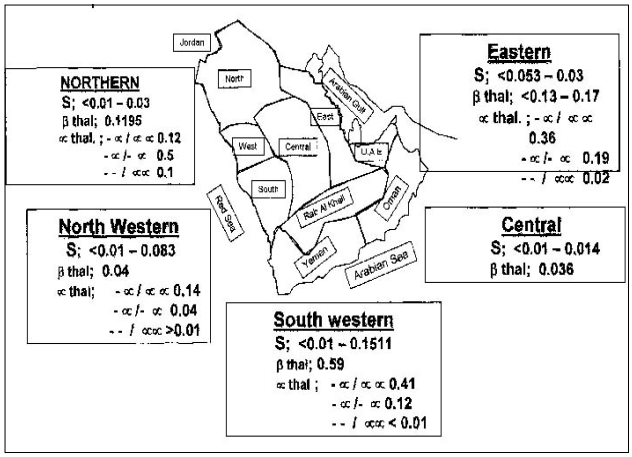

Figure 1 - Frequency of sickle cell anemia, β - and α - thalassemias (thal) in different regions of the Kingdom of Saudi Arabia. S - sickle cell anemia.

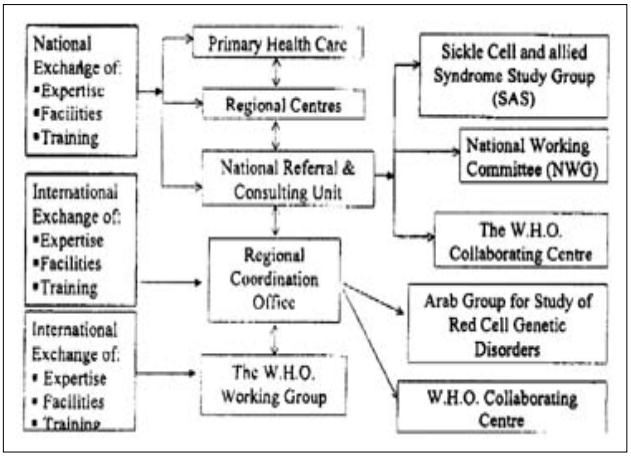

Figure 2 - Network for Blood Genetic Disorders, national, regional and international links. WHO - World Health Organization

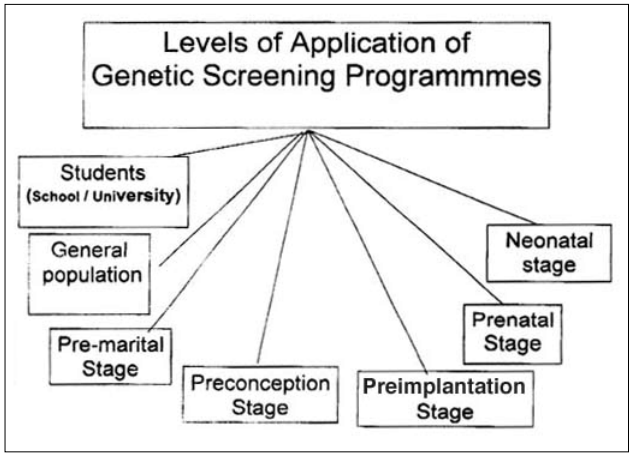

Figure 3 - Intervention of the prevention programme.

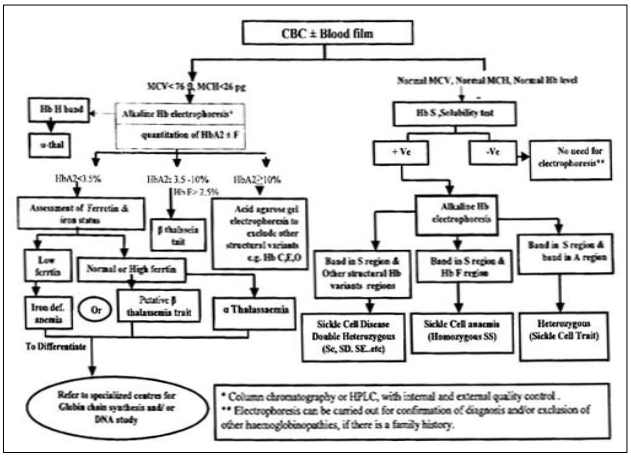

Figure 4 - Flowchart for detection of sickle cell disorders and thalassemias. CBC - complete blood count, Hb - hemoglobin, α-thal - α-thalassemias, MCH - mean corpuscular hemoglobin, MCV - mean corpuscular volume, F - Ferretin, HbA2 - hemoglobin alpha 2, HPLC - high power liquid chromatography.

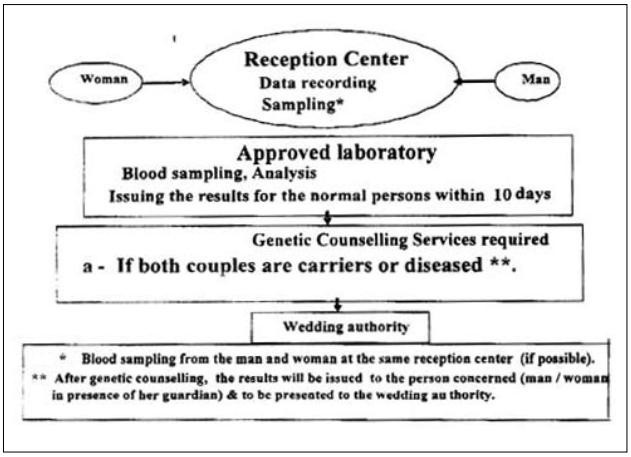

Figure 5 - Flowchart of the approved pre-marital screening program in the Kingdom of Saudi Arabia.

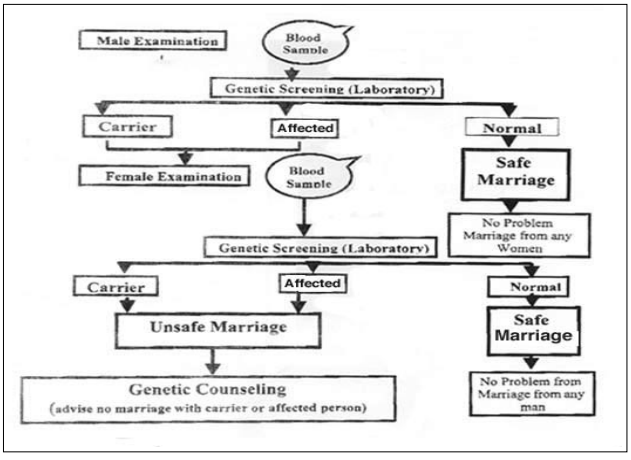

Figure 6 - Flowchart for genetic counselling linked to pre-marital screening.

Table 1 - Common blood genetic diseases which can be screened by pre-marital examination.

Disorders	Main medical features/complications	Disorders
Sickle cell anemia	Chronic anemia Acute pain crisis Skeletal deformities and other organ complications	Routine (general) diagnostic test - CBC, RBCs indices and Hb solubility test Hb electrophoresis (Alkaline/Acidic), Isoelectric-focusing Confirming molecular test
Thalassemia	Chronic anemia Skeletal deformities and other organ complications Blood transfusion requirements	Routine (general) diagnostic test - CBC, RBCs indices Hb A_2 and F determination α/β ratio Confirmatory molecular test
G6PD deficiency	Acute anemia due to exposure to oxidant beans, drugs and chemicals	Determination of G6PD activity and phenotype or both
Hemophilia	Increased bleeding time than usual	Estimation of factor 8,9 activity Bleeding and coagulation time

CBC - complete blood count, RBCs - red blood cells
Hb - hemoglobin, G6PD - glucose-6-phosphate dehydrogenase

Table 2 - Serious infectious diseases which can be screened by pre-marital examination.

Diseases	Main medical features/complications	Main diagnostic investigation
Syphilis	Genital inflammation Abortion of fetal death	TPHA VDRL
AIDS	Immune deficiency Liability to bacterial and viral infection	Virus detection by polymerase chain reaction Detection of antibodies Confirmatory molecular test
Hepatitis B and C virus infections	Liver function disturbance and liability to develop hepatocellular carcinoma	HB S Ag and HCV Ab Virus detection by polymerase chain reaction
German measles	Abortion and congenital malformation	Rubella IgM

TPHA - treponema pallidum hemagglutination, VDRL - venereal disease research laboratory, HBsAg - hepatitis B surface antigen, AIDS - acquired immune deficiency syndrome
HCV Ab - hepatitis C virus antibodies, IgM - immunoglobulin M

health and mind of the progeny (Althorrhea), the building unit of the family and community are advocated by "Islamic Shareah.". The "Shareah" has ensured the purposes of the habitat of Earth as "the Will of Allah," through varieties of guidelines, including appropriate marriage and the selection of the equitable, in order to produce and care for the offspring. Fourteen centuries ago, the Prophet Peace be upon him has indicated that the genetic factors plays an important role as it is quoted in the Hadith "select for your progeny and marry to the equitable and marry them"[33] This is also indicated in the story of the "Bedwin" from " Beni Fezarah" who came to the Prophet (PBUH) complaining that his wife has given birth to a black boy. The Prophet (PBUH) asked him: "Do you have camels"? The man answered "Yes". The Prophet (PBUH) said : "what is their color?" The man answered "Red" The Prophet (PBUH) asked him: "Is there anyone of different color? The man answered : "Yes". The Prophet (PBUH) asked him: "Why you think is that?" The man answered: "This may be due to "Erq's,[33] indicating that the "Black Camel" may resemble one of his ancestors. The Prophet (PBUH) said: " That is the case with your child". This story clearly indicates that the line of inheritance was known long ago, before the era of Genetics and that this case is a recessive condition, where the factor does not appear in all generations. The Islam has in fact take care of the 5 necessities of the appropriate life that appear in the Magasid Al-Shareah" (Purposes of Shareah) such as preservation of the Religion, the Mind, the Progeny, the Wealth and Self. These "necessities" includes the preservation of health and mind of progeny that is indicated by the Hadiths of the Prophet (PBUH): The Strong "Momin" is loved by Allah more than the weak, and there is Good in All.[35] "In addition, as the marriage is considered religious, ethical and societal requirements and its ties need to be established on solid ground, the Prophet (PBUH) said to a man who proposes to a woman ": look at her, there is something in the "Alansar's eyes," indicating that one has to ensure that the partner in the marriage is healthy and free of defects. Taken all of the above into consideration, we can comprehend that Islam has dictated that the proper ground is to be prepared for the offspring in order to be healthy in his body and mind. As we are witnessing a remarkable advancement in medical sciences and the new technologies, where it became feasible to carry out early diagnosis and early intervention, these procedures have to benefit safety and the health of the "progeny".

The national pre-marital screening program, as means of prevention. The detection of carrier of a recessive disorder is considered a safe, simple, practical and widely accepted procedure as a means

of prevention of these diseases. Therefore, the National Committee and other departments of Ministry of Health have put forward a recommendation to adopt a Pre-marital Screening for the common blood genetic disorders and some serious infectious diseases.

The approved program of pre-marital screening. A Royal decree was passed on (4/1/1423; 81/3/2002 AD.). 1. Arrange for health awareness program through the media explaining the benefits of medical pre-marital screening and the serious effects of infectious and genetic disorders over a period of 3 years. 2. Preparation and habitation of laboratories making available equipments and carry out training in all the regions in order to facilitate the pre-marital screening concerning diseases determined by Ministry of Health including infectious and genetic diseases. 3. Make available the pre-marital screening to those Saudis who wish to benefit from it and maintain the confidentiality of information during retrieval and filing, 4. Coordinate with the Ministry of Justice to ensure that the "Ma'zoon" explains the benefits of pre-marital screening

The decree stipulated that those concerned observe confidentiality and coordinate with the Ministry of Justice to have the packing of the "Mazoon," explaining the usefulness of the program. The next 2 years have shown that an increasing number of members of the community accepted and benefited from the program. A second" Royal decree passed on 7/11/1424 (30/12/2003 AD), making it a mandatory for all those who plan to marry, men and woman, to take a Pre-marital screening test.

The "Royal Decree" no 3 issued at 7/11/1424 stated that "For screening of genetic diseases, the pre-marital examination to be issued before wedding. The results of examination to be explained to the concerned but not to prevent marriage.

The Ministry of Health has put forward a program to test for sickle cell gene and the thalassemias **(Figure 4)**, taking into consideration that the carriers has to benefit from non-directive genetic counseling. A certificate to be issued to the couple who will complete the procedure. The wedding (Aqd Al-Geran) will then be governed by the wish of those concerned regardless of the screening results **(Figures 5 & 6)**.

Objectives of the "national pre-marital screening" program. Considering religious, ethical, psychosocial and economical aspects, the main objectives of the pre-marital screening can be summarized as follows: 1. Limitations of the frequency and distribution of blood genetic disorders and minimizing the burden on the individual, family and the community. 2. Limitation of burden of having newly affected children. 3. Raise the awareness and knowledge of the community regarding the pattern of inheritance and genetic disorders and appropriate method of selection of the equitable. 4. Help families avoiding psychosocial problem that result from the presence of the affected child in the family. 5. Minimizing the economical burden on the family and health care providers. 6. Limiting negative complication that result from an affected child in the family and affected children in the community.

Pre-marital screening - other aspects of relevance. The pre-marital screening could be of wider nature and include larger spectrum of health /genetic screening, including general checkup, clinical, radiological and laboratory investigations. These medical screening are of relevance, where those related to fertility and genetic disorders carry preventive measures. These procedures will be of benefit for early recognition and prevention of disease complications and allow early intervention as appropriate. The main basic data and examination of relevance to pre-marital screening are 1. Basic data, name, age, sex, file no, address, for example, 2. Personal history, 3. General medical history, 4. Past history for chronic diseases, 5. Family history for chronic diseases, 6. Family pedigree, 7. Complete medical examination.

The pre-marital screening could also include the Blood group and the Rhesus (Rh) factors, where it is important to discover the incompatibility. If the wife has Rh-ve, while her husband has the Rh+ve, then precaution is to be taken to prevent the formation of Anti D in the wife's blood, as it may cause abortion. The program may also include some serious infectious diseases, particularly those who may be transmitted to the mother, and consequently to the fetus. Of relevance are acquired immune deficiency syndrome (AIDS), hepatitis and other diseases for which medical treatments are costly or inefficient. On the other hand, treatment of the infection with Syphilis in curative and vaccination of girls against Rubella is an effective measure in order to prevent the progeny from rubella-related malformation. **(Tables 1 & 2)**.

In conclusion, the national history of the blood genetic disorders in KSA, indicates clear relevance to the Malaria endemicity, where sickle cell, the thalassemias and red cell enzymopathies genes are frequent in the endemic regions. However, the development in the travel and communication systems as well as the need for movement from region to another, has led to the spread of the defective gene(s) in different parts of the country. Hence, the need for a national program for prevention and control. For several years, experiences, care and prevention efforts have accumulated and finally culminated in the Royal Decree introducing pre-marital screening, as means of prevention from the most common genetic

diseases. Only future objective assessment will judge the wisdom of the introduction of the program.

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