Prevention in practice

Genetic disorders and congenital abnormalities: strategies for reducing the burden in the Region

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Introduction

Despite some encouraging recent initiatives, the control of genetic disorders and congenital abnormalities is generally not given the importance it deserves in countries of the Eastern Mediterranean Region (EMR). That these disorders are rare in the Region and are not amenable to control are serious misconceptions. This article aims to provide a brief outline of the epidemiology and magnitude of genetic disorders and congenital abnormalities in the EMR and examines feasible preventive strategies and intervention approaches that are appropriate to countries of the Region.

Epidemiological situation

Genetic disorders and congenital abnormalities occur in about 2%–5% of all live births, account for up to 30% of paediatric hospital admissions and cause about 50% of childhood deaths in industrialized countries [*1*]. Contrary to the generally held belief, the limited epidemiological data presently available from many countries in the EMR indicate that congenital and genetically determined disorders are at least as important in the Region as in more industrialized regions of the world. The magnitude of the problem of such disorders can be attributed to several factors including:

- the high rate of traditional consanguineous marriages, which increases the frequency of autosomal recessive disorders;
- a relatively high birth rate of infants with chromosomal disorders related to advanced maternal age such as Down syndrome and other trisomies;
- a relatively high birth rate of infants with malformations due to new dominant mutations related to advanced paternal age;
- the high frequency of haemoglobinopathies and glucose-6-phosphate dehydrogenase deficiency in many countries of the Region, possibly related to selective advantage against falciparum malaria and other as yet unknown factors;
- large family sizes, which may increase the number of affected children in families with autosomal recessive conditions;
- the lack of public health measures directed at the prevention of congenital and genetically determined disorders, the dearth of genetic services and inade-

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quate health care prior to and during pregnancy.

Genetic and congenital disorders are responsible for a considerable proportion of perinatal and neonatal mortality in many countries in the Region. Congenital malformations are now recognized as the leading cause of infant mortality in the United Arab Emirates (UAE) [2] and the second leading cause in Bahrain, Kuwait, Oman and Qatar [3–5]. Reports from Saudi Arabia indicate that about 25%–35% of perinatal deaths in two hospitals were attributed to congenital malformations [6,7]. In addition, the regional data available on the contribution of genetic and congenital factors to the etiology of disabilities suggest a large genetic component in mental handicap, blindness and deafness [8–12].

Chromosomal aberrations are among the most important causes of congenital malformation and mental handicap. The risk of having a child with Down syndrome increases with increased maternal age from 1 in 600 births for mothers under 30 years to 1 in 50 births for mothers over 40 years [13]. Available data for the EMR suggest that in some countries of the Region, 50% of Down syndrome children are born to mothers over 40 years [14]. The observed prevalence of Down syndrome among live births in the EMR has been reported to vary from 1.15 per 1000 in the UAE [15] to 2.5 per 1000 in Egypt [16].

Thalassaemias, sickle-cell anaemia and glucose-6-phosphate dehydrogenase (G6PD) deficiency are the commonest single gene disorders encountered in the Region. The epidemiology of these disorders shows marked intracountry as well as intercountry differences. The situation is further complicated by the marked molecular and clinical heterogeneity of thalassaemia and sickle-cell anaemia.

Sickle-cell disease has been reported to occur in 2.1% of neonates in Bahrain [17], 1.7% of women in southern Iraq [18] and 1.37% of neonates in Saudi Arabia [19]. Intracountry differences are evident in Saudi Arabia where carrier frequencies range between 2% and 27%, being highest in the eastern region and lowest in the central region [19–24].

The mild form of α-thalassaemia is common in the Arabian peninsula. A report from Oman suggests that 45% of the population are affected [25]. The reported figure from Bahrain is 24% [17], while in Saudi Arabia, it ranges from 2% to 50%, being highest in the eastern region [20–22]. β-thalassaemia exists in generally high but variable frequencies. The percentage of carriers ranges from 1% to 16% in the EMR [14].

High frequencies of G6PD deficiency have been reported in most countries of the Region, with the highest figures in the Arabian peninsula and the southern part of the Islamic Republic of Iran. Among males, prevalence figures for G6PD deficiency have been reported to be 26.4% in Bahrain [26], 17.9%–22.8% in the southern part of the Islamic Republic of Iran [27], 8.9%–12.4% in Iraq [28,29], 10% in Jordan [30], 27.3% in Oman [25] and 4.5%–22% in Saudi Arabia [31].

Consanguineous marriages, which are believed to increase the frequency of autosomal recessive conditions, are common in the EMR. The percentage of first cousin marriages among all marriages has been reported to be 11.4% in Egypt [32], 30% in rural areas in the Islamic Republic of Iran [33], 29.2% in Iraq [34], 32% in Jordan [35], 30.2% in Kuwait [36], 17.3% among Muslim Lebanese and 7.9% among Christian Lebanese [37], 37.1% in Pakistan [38], 31.4% in Saudi Arabia [39] and 30% in the UAE [15]. In Al-Ain, UAE, autosomal re-

cessive disorders have been reported to account for 80% of single gene disorders and 22% of congenital malformations among 16 419 births [*15*]. Recessively inherited disorders account for a substantial proportion of mental and physical handicap in other countries [*8,40,41*]. Similarly, children of consanguineous parents may be overrepresented in patients with severe mental retardation [*42,43*], blindness [*44*], hearing impairment and deaf–mutism [*45–47*].

Other autosomal recessive conditions include cystic fibrosis and phenylketonuria. Cystic fibrosis has been detected in 39 per 100 000 Jordanian neonates [*48*] and 23.6 per 100 000 Saudi neonates [*49*], while phenylketonuria has been detected in 11.6 per 100 000 neonates in the Islamic Republic of Iran [*50*]. A recent publication on genetic disorders among Arab populations lists 115 new genetic syndromes reported over the past two decades among Arabs [*51*]. Of these, 100 syndromes are autosomal recessive, 10 are autosomal dominant and five are possibly X-linked recessive or autosomal recessive.

Genetic factors also play a role in the cause of common multifactorial disorders. The importance of these common disorders is progressively increasing among Arab and other Eastern Mediterranean populations. Cardiovascular diseases are now the leading cause of death in many countries of the Region [*52*]. In Bahrain, Egypt, Iraq, Jordan, Kuwait and Qatar, the percentage of deaths attributable to diseases of the circulatory system ranges from 25% to 40%. Recent studies also indicate the high susceptibility of many Eastern Mediterranean populations to diabetes. Oman has been reported to have a diabetes prevalence of 9.8% among people of 20 years and above [*14*]. Recent reports from other Arab countries describe a similar trend [*53*].

Prevention

To initiate a nationwide intervention programme for the control of any health problem, there are two prerequisites. The first is evidence that the magnitude of the problem is significant, and the second is an indication that prevention is both feasible and cost–effective. In the case of genetic and congenital disorders, these requirements have been fulfilled as far as the EMR is concerned.

Analysis of the available epidemiological data clearly indicates that hereditary disorders and congenital malformations are rapidly becoming a major public health concern in the Region. The health care needs of most EMR populations necessitate that this problem be addressed promptly. Moreover, great advances have been made in our knowledge of genetic disorders, and the principle of equity in health care demands that the gap between medical progress and health care services should be narrowed whenever possible.

On the other hand, a major proportion of the disorders that are commonly encountered in the Region can be prevented by basic public health measures and activities focusing primarily on education and approaches in primary health care that are applicable in most countries. While basic genetic diagnostic facilities should be available in order to deal with all aspects of prevention and care, the establishment of such facilities, if they do not already exist, may not require the sophistication and high costs that many people think.

Action is therefore required to initiate activities to control genetic and congenital disorders in every country. The nature and sophistication of such activities will vary from one country to another, but national programmes should be established to provide basic services covering prevention,

health promotion and case management activities.

Strategies and feasible approaches

While the overall objective of a national programme is the prevention of genetic and congenital disorders in the community, the strategies adopted to achieve this objective should be carefully selected to match the unique demographic, cultural and religious characteristics of the population and should take into consideration the priorities set and the resources available. In all countries, irrespective of the resources available, certain public health measures capable of reducing the burden of genetic and congenital disorders can be feasibly implemented without major resource implications. These primary prevention measures, which should be integrated into primary health care, include the following:

- reducing genetic disorders related to advanced parental age, such as Down syndrome and autosomal dominant conditions due to new mutations, as part of the family planning services;
- reducing the occurrence of congenital abnormalities such as neural tube defects, and avoiding the sequelae of micronutrient deficiencies such as mental retardation due to iodine deficiency by promoting healthy nutrition for women;
- preventing congenital rubella syndrome by immunizing against rubella infection;
- reducing mortality and chronic handicap due to rhesus haemolytic disease through routine prenatal screening:
- reducing congenital abnormalities and stillbirths by better control of maternal diabetes prior to and during pregnancy;
- reducing the risk of miscarriage, congenital abnormality and fetal growth retardation through avoidance of smoking and alcohol intake during pregnancy;
- avoiding congenital abnormalities caused by certain infections such as syphilis by prevention, early detection and prompt treatment;
- reducing the occurrence of hereditary disorders in high-risk families through genetic counselling;
- providing information on the implications and availability of carrier testing for common disorders such as the haemoglobinopathies and G6PD deficiency.

Secondary prevention entails either the prevention of the birth of affected babies through prenatal diagnosis and selective abortion, or prevention of the full expression of the condition by proper early management aimed at minimizing the clinical features of the disease. In many countries of the Region, however, selective abortion is generally unacceptable and secondary prevention will, in this case, refer to efforts to minimize the adverse clinical manifestations of these disorders through early detection and proper management.

To initiate interventions for the control of genetic and congenital disorders at the national level, the establishment of a vertical programme for genetics is not necessary. The strategies and public health approaches previously mentioned can be incorporated into the existing health care system. Integration into reproductive health programmes is probably the most appropriate way to achieve this objective. A multitude of prevention approaches can be feasibly integrated, at the primary health care level, within the reproductive health programmes already operating in the country, such as the maternal and child health care clinics and family planning clinics. Although some additional training and re-

sources will be required, the potential benefit is considerable in terms of reduction of suffering as well as reduction of the health and economic burden related to the care of patients with genetic and congenital disorders.

The interventions that need to be integrated can be applied: a) before and during pregnancy and b) after delivery for the neonate.

Before and during pregnancy

Preconception information and services for family planning can help reduce the number of high-risk pregnancies related to increased parental age. Advice should be given to couples to complete their intended family size preferably before the age of 35 years for women.

The incidence of chromosomal disorders and spontaneous abortion rises rapidly with maternal age after the age of 35 years [*13*]. Disorders due to new dominant mutations increase with advanced paternal age. Families should be informed of these risks. When family planning is generally available and couples are aware of the genetic risks associated with advanced parental age, they tend to curtail reproduction once they have reached the desired number of children. This leads to a selective fall in births to older parents. In western Europe, for example, the percentage of children born to women over 35 years fell from more than 20% to about 6% between 1950 and 1975 [*54*].

Miscarriage is strongly associated with maternal age: after the age of 40 years, over one-third of recognized pregnancies miscarry [*14*]. Miscarriage is a common cause of maternal morbidity, with associated blood loss and risk of anaemia and folate deficiency. In addition, between the ages of 40 and 47 years, the risk in each pregnancy of a liveborn child with a serious chromosomal disorder rises from 1.5% to 8%. A relatively large proportion of children in the Region are reported to be born to older mothers (16%–19% to mothers over 35 years, 3%–7% to mothers over 40 years) [*14*].

It is also worth noting that a reduction in the proportion of older fathers reduces the rate at which new mutations enter the population, and this initiates a gradual long-term decrease in the frequency of inherited disease. Family planning, when widely available, is used preferentially by older couples and can reduce the prevalence of genetic problems related to parental age.

In the presence of a hereditary disorder in the family, taking a good family history will help to detect high-risk couples who can then be offered genetic counselling and referral to specialized centres if indicated.

When the couple are informed of the possibility that they are at an increased risk of having a genetically abnormal child, they can choose to plan conceptions according to medical advice and can make use of the genetic services available. Since primary prevention of genetic disorders depends largely on preconception information, screening and counselling, there is a strong case for including these approaches in primary health care services. Basic training and education of primary health care workers in the field of genetic counselling, detection and referral of high-risk families can be integrated in their training courses.

The World Health Organization Eastern Mediterranean Regional Office publication *Community control of genetic and congenital disorders* [*14*] provides an outline of the basic requirements to strengthen the capabilities of primary health care workers in preventing genetic diseases. These include.

- training in taking and recording a basic genetic family history, taking account of

the complexities of large families with multiple consanguineous marriages;

- guidelines on detecting possible genetic risks (e.g. history of previous stillbirth, neonatal death, congenital malformation, multiple abortion or hereditary blood disorder in the family);
- guidelines on lines of referral and clear information on specialist services available;
- training in the basic ethical principles and techniques of genetic counselling.

Prevention and management of sexually transmitted diseases. Some sexually transmitted diseases such as syphilis are teratogenic and their prevention and early treatment can prevent congenital malformations in the baby.

Immunizing against rubella. The possibility of rubella infection should be brought to the knowledge of women before conception. It may be desirable to test for immunity to rubella prior to pregnancy and to offer immunization to those who are seronegative.

Screening for rhesus haemolytic disease. It is essential to confirm that screening for rhesus blood group and antibodies is a routine component of pregnancy care and that adequate supplies of anti-D immunoglobulin are available.

Treatment of existing conditions. Women with insulin-dependent diabetes mellitus have about a 6% risk of having a seriously malformed child in each pregnancy. They can greatly reduce the risk by meticulous glycaemic control which must be started before pregnancy because major malformations are determined very early during embryonic development.

Advice regarding nutrition and iron/folate supplementation. Throughout the reproductive years, and particularly preconception, there is strong evidence that an optimal diet reduces the frequency of unsuccessful pregnancy outcomes and severe congenital malformations. Supplementing women's diet with vitamins, including folate, prior to and in the first months after conception reduces the risk of fetal neural tube defect and also of some other congenital malformations [*55,56*]. When fertility is high, as in most countries of the Region, it is not easy to identify a preconception period and it may be preferable to supplement women's diet throughout their reproductive span. Because of the high prevalence of iron deficiency anaemia and iodine deficiency, supplementation with iodine and iron may be considered. Iodization of salt has already been introduced in many EMR countries and food fortification with iron and folic acid is being seriously considered by some.

Information regarding the deleterious effects on the developing embryo of smoking, alcohol intake, unsupervised medication, exposure to X-rays and certain mutagens at the workplace should be made available to women prior to pregnancy.

Information on the availability and implications of carrier testing for specific genetic disorders common in the society, such as haemoglobin disorders and G6PD deficiency, should be provided to families at risk.

After delivery for the neonate

Neonatal screening programmes for some genetic disorders, where early diagnosis and management could ameliorate the clinical picture, are being implemented in several countries. These may include neonatal screening for phenylketonuria and other inborn errors of metabolism, for sickle-cell anaemia and G6PD deficiency and for congenital hypothyroidism. Midwives or nurses can take heel-prick blood samples and the drops of blood can be collected on to

filter paper which is then posted to a neonatal screening laboratory. These programmes require specialized laboratory services, which already exist in many countries.

Training programmes for midwives can be conducted to facilitate the diagnosis of congenital abnormalities and prompt referral of affected neonates to appropriate centres.

Conclusions

The considerable challenge posed by genetic disorders and congenital abnormalities calls for the development of prevention programmes through the establishment of community genetics services. The strategies proposed in this article do not necessarily require sophisticated technical facilities but are primarily based on strengthening training of health professionals and public education. However, the molecular revolution that has characterized the past two decades has introduced into medical practice many procedures that help in the diagnosis and prevention of genetic diseases, and it is important for countries of the Region to take account of these developments. Such technology can be introduced gradually into national prevention programmes.

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Hereditary disorders alone represent a major health problem in the majority of countries of the Region due to the high number of consanguineous marriages and high rate of consanguinity (16.5% to 55%). Haemoglobinopathies, e.g. thalassaemia, sickle cell disorders and glucose-6-phosphate dehydrogenase deficiency, are common in Bahrain, Cyprus, Islamic Republic of Iran, Lebanon and Saudi Arabia. Cystic fibrosis has been reported in Islamic Republic of Iran, Jordan and Saudi Arabia.

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