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Lihadh Al-Gazali, Hanan Hamamy and Shaikha Al-Arrayad

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# Practice

## Genetic disorders in the Arab world

Lihadh Al-Gazali, Hanan Hamamy, Shaikha Al-Arrayad

Available evidence suggests that congenital and genetic disorders are responsible for a major proportion of infant mortality, morbidity, and handicap in Arab countries.<sup>1-3</sup> The population of the region is characterised by large family size, high maternal and paternal age, and a high level of inbreeding with consanguinity rates in the range of 25-60%.<sup>1 2 4 w1</sup> Certain disorders are common throughout the Arab world, including haemoglobinopathies, glucose-6-phosphate dehydrogenase deficiency, different congenital malformations caused by recessive genes, and several metabolic disorders.<sup>1 2</sup> Other recessive disorders cluster in certain groups and subpopulations.<sup>1 2 5</sup> Genetic services vary in extent and coverage in different Arab countries, but mostly they remain patchy, selective, and inadequate.<sup>2 5 6</sup>

We present the magnitude of the problem and the currently available genetic services in Arab countries, together with recommendations for developing strategies for prevention. In view of the good coverage of primary healthcare systems in most Arab countries, community genetic services that include screening programmes could be strengthened by the efficient training of primary healthcare personnel.<sup>2</sup>

### Why are genetic disorders common in the Arab world?

Available data suggest that genetic and congenital disorders are more common in Arab countries than in industrialised countries; recessively inherited disorders account for a substantial proportion of physical and mental handicap.<sup>1-3 6</sup> Several factors may contribute to the high prevalence of genetically determined disorders:

- High consanguinity rates—25-60% of all marriages are consanguineous, and the rate of first cousin marriages is high (figs 1 and 2; table A on [bmj.com](http://bmj.com)).<sup>4 w1</sup> In addition, isolated subpopulations with a high level of inbreeding exist. Furthermore, in many parts of the Arab world the society is still tribal.<sup>5 6 w1</sup> This has made the epidemiology of genetic disorders complicated, as many families and tribal groups are descended from a limited number of ancestors and some conditions are confined to specific villages, families, and tribal groups, leading to an unusual burden of genetic diseases in these communities (table B on [bmj.com](http://bmj.com)).<sup>1 2 5</sup>
- The high prevalence of haemoglobinopathies, glucose-6-phosphate dehydrogenase deficiency, autosomal recessive syndromes, and several metabolic disorders (fig A and table C on [bmj.com](http://bmj.com)).<sup>1 2 5</sup>

### Summary points

The population in Arab countries is characterised by large family size, high maternal and paternal age, and a high level of inbreeding

Genetic disorders are common in Arab countries and account for a substantial proportion of physical and mental handicap

Generally, no public health measures are directed at the prevention of congenital and genetic disorders, which is also restricted by cultural and legal limitations

Some countries have started cost effective prevention programmes for certain common genetic disorders, such as premarital carrier screening for haemoglobinopathies

Strategies for the prevention of genetic disorders in this region should include integration of community genetics into the primary healthcare system, education, and strengthening the existing specialised genetic service

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- The rate of children with Down's syndrome in some Arab countries exceeds the 1.2-1.7 per 1000 typical for industrialised countries. This may be related to the relatively high proportion of births to older mothers in the region (up to 50% of children with Down's syndrome in the region are estimated to be born to mothers aged 40 or over).<sup>1 2 7 w3</sup>
- The lack of public health measures directed at the prevention of congenital and genetic disorders, with inadequate health care before and during pregnancy, particularly in low income countries<sup>3</sup>
- Services for the prevention and control of genetic disorders are restricted by certain cultural, legal, and religious limitations, such as the cultural fear of families with genetic diseases being stigmatised within their community and the legal restrictions on selective termination of pregnancy of an affected fetus.<sup>1 2 5 6</sup>



Extra tables, boxes, figures, and references w1-w12 are on [bmj.com](http://bmj.com)

**Sources**

We collected information for this report from published literature through a Medline search, from experts working in medical genetics and providing genetic services, and from personal archives of references taken from locally published medical journals in Arab countries. The main documents that we used extensively as references include the World Health Organization Eastern Mediterranean Regional Office publication *Community Control of Genetic and Congenital Disorders*<sup>2</sup> and the *Oxford Monographs on Medical Genetics on Genetic Disorders among Arab Populations*.<sup>1</sup>

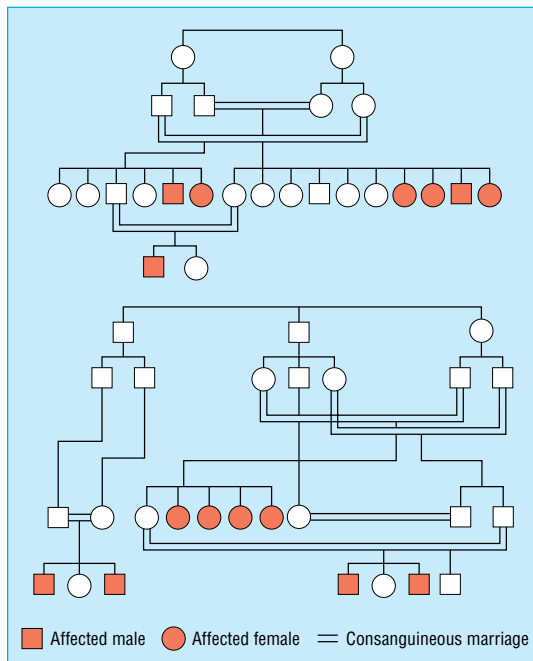
**Genetic prevention programmes**

Despite the difficulties that exist, several Arab countries have initiated cost effective prevention programmes for certain common genetic disorders.

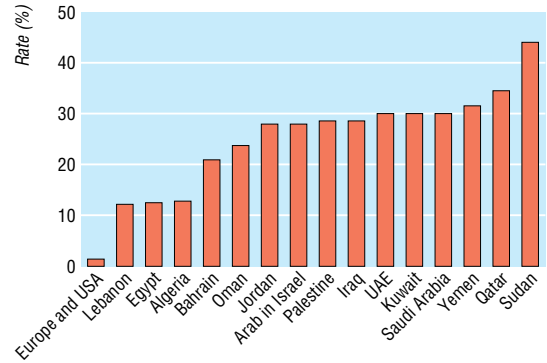
**Premarital carrier screening**

A screening programme for genetic carriers is a systematic attempt to identify and counsel as many people at genetic risk in a population as possible, whether or not they have a family history of a genetic disorder. Several countries in the Arab region have introduced premarital screening for haemoglobinopathies. In Saudi Arabia, a Royal decree was passed in 2003 for a mandatory premarital screening test followed by non-directive genetic counselling for haemoglobinopathies; the decision to marry is then left to the couple. Prenatal diagnosis and termination of pregnancy are not offered to carrier couples, even though a 1990 ruling (Fatwa) allows termination of pregnancy in the first 120 days after conception if the fetus is shown beyond doubt to be affected with a severe malformation that is not amenable to treatment.<sup>w4</sup> Similar programmes exist in other Arab countries such as Bahrain, the United Arab Emirates, Tunisia, and Jordan (box A on [bmj.com](http://bmj.com)).<sup>5 6 8 w5</sup>

However, experience shows that if options are not made available to carrier couples such programmes



**Fig 1** Two Arab pedigrees showing high level of consanguinity, large family size, and several affected children in different sibships



**Fig 2** Average rates of marriages between first cousins among Arabs. UAE=United Arab Emirates

will not be effective in reducing the burden of genetic diseases, as many carrier couples go ahead with their planned marriage.<sup>2</sup> Arab countries should take note of the comprehensive primary care based programme for thalassaemia screening and genetic counselling that was started in 1996 in Iran (a Muslim country where termination of pregnancy was not legal). The programme identifies carrier couples before marriage and offers counselling, thus providing them with the opportunity to separate. However, an audit in 1999 showed that couples were still opting to marry rather than separate and that they requested prenatal diagnosis and selective termination of pregnancy.<sup>9</sup> Amendment of the law in 2001 to allow the option of selective termination of pregnancy up to 15 weeks' gestation for thalassaemia resulted in a 70% reduction in the annual birth rate of affected infants.<sup>9</sup>

**Family oriented approach to prevention**

When a gene for a recessive disorder is present in a family, the diagnosis of the disease in a child serves as a marker of the extended family that is at increased genetic risk. In communities where a high level of consanguinity exists and large families are common, family oriented screening offers an alternative to population screening for identifying current and future couples at risk of producing affected children.<sup>2 10</sup> This approach is particularly suitable to populations with a high level of consanguinity and clustering of rare genetic diseases in certain tribes or families. It produces a high yield of information on carriers and couples at risk, family members understand the condition because they have had contact with an affected child, and usually one gene variant is present in a given family or tribe, simplifying and reducing the cost of DNA based diagnosis.<sup>2 10</sup> This approach was tested in Pakistan in 15 large consanguineous families with  $\beta$  thalassaemia and was found to be feasible. The programme was successful because carriers had the option of prenatal diagnosis and selective termination of pregnancy, which is legal in Pakistan. A similar approach was implemented in the Arab Negav Bedouin community, where the genetic data on carrier status for genetic disorders common in this community were incorporated into the decision making process of arranged marriages, giving carriers the option to choose a non-carrier partner.<sup>w6 w7</sup>

### Neonatal screening programmes

Clinical screening of newborn infants involves systematic examination with a checklist of all births, whether alive or stillbirths, by an experienced paediatrician to detect any abnormalities.<sup>2</sup> The United Arab Emirates and Oman have established national or hospital based registries for congenital abnormalities. Some of these registries report to the International Clearing House for Birth Defects.<sup>w8</sup>

Biochemical neonatal screening programmes in the region have started as research projects that have provided valuable information on the incidence of haemoglobin disorders, glucose-6-phosphate dehydrogenase deficiency, congenital hypothyroidism, phenylketonuria, and cystic fibrosis.<sup>2</sup> National screening programmes for phenylketonuria (started in the United Arab Emirates in 1995) and for congenital hypothyroidism (started in Saudi Arabia in 1985 and the United Arab Emirates in 1998) have been successful.<sup>5 11 w9</sup> Jordan started a similar programme in certain areas in 2006, with the intention of expanding it nationally. Screening of newborns for phenylketonuria in Gaza, started in 1994, covers only the government clinics, although two third of all newborns are delivered in United Nation Relief and Work Agency clinics where no phenylketonuria screening is offered.<sup>w10</sup> The Emirate of Abu Dhabi introduced screening for sickle cell disease with high performance liquid chromatography in 2002.<sup>3</sup> Plans exist to make this a national programme across the United Arab Emirates.

Strong evidence exists to show that metabolic diseases constitute a significant cause of neonatal and infant death among Arabs.<sup>1 2</sup> Therefore, screening programmes using the Guthrie system would be valuable in the prevention and early treatment of these disorders. Saudi Arabia has an active selective newborn screening programme for inherited metabolic diseases that reaches 10-20% of newborns. Screening is based on dried blood spot samples and tandem mass spectrometry. The Saudi experience indicates that approximately 50% of diseases identified by this method are manageable.<sup>11</sup> However, in many cases treatment does not prevent the considerable morbidity. Economic cost should also be taken into account.

### Antenatal screening for chromosome abnormalities and congenital malformations

In some industrialised countries, pregnant women have non-invasive screening for Down's syndrome and other congenital anomalies through the assessment of maternal serum markers and ultrasonography at around 11 weeks post-conception. This is followed by invasive prenatal diagnosis if the test is positive, giving the couple the option of selective termination of pregnancy of an affected fetus. As termination is not legal in many Arab countries, the value of introducing prenatal screening programmes is questionable. A better method of prevention would be the general availability of preconception information and family planning for older mothers, which would be expected to lead to a reduction of around 50% in the frequency of new cases of Down's syndrome.<sup>2</sup>

Ultrasound scanning is routinely done for pregnant women during their first antenatal visit in most Arab countries. The scan is usually done without any pretest information being given to the couple

### A patient's perspective

When I married my cousin, I thought about genetic diseases and the probabilities of my children having those diseases. I knew that three sisters who were distantly related to me had some problems, which I thought could have happened by chance or because their mother was old when she had them.

My first pregnancy was normal until the sixth month, when I was told that my baby had water in his brain. It was hard not to know what exactly was wrong with the baby. The waiting was over when my baby was born on 29 August 2002. I found that he had many congenital abnormalities. In the beginning, the doctors did not know what the actual problem was. I later found out that another branch of my family had two children with similar problems, which made me realise that my child, the three sisters, and the two other children all have the same condition. The geneticist explained to us that it is inherited and I have 25% risk of having another affected child. I agreed to do genetic studies to find the gene, because I was concerned about the next pregnancy. My second child was normal, and that was a blessing from God.

The gene was located in my family, and the geneticist told us that in the next pregnancy the baby can be tested and terminated if found to be affected, but I would have to go abroad for that. When I became pregnant with my third child, I decided not to go for the test because as Muslims we consider life itself as a test. When God gives me a child with a problem, it is like he is testing me to see how I accept, help, teach, and be patient with this child. I am sure that in every creation in this world there is a wisdom that is known only by God. I am six months pregnant now, and ultrasound has shown that the baby is affected.

Female patient, *United Arab Emirates*

about the possibility of finding an abnormality and with no explanation of the consequences. If the results suggest an abnormality, the woman is referred for a detailed anomaly scan, and further invasive techniques, such as amniocentesis, might be needed. The couple will then have to face the major decision of selective termination of a fetus affected by severe genetic or congenital disorder (see patient's story). In most Arab countries, except Tunisia,<sup>w5</sup> selective termination of pregnancy is not legally available. This often leads to ethical dilemmas.<sup>2 5</sup> It is therefore important to clarify the role of ultrasonography for fetal anomalies in obstetric services in this region.<sup>2 5</sup>

### Pre-implantation genetic diagnosis

Pre-implantation genetic diagnosis is welcomed in Arab countries, as it does not involve the decision to terminate the pregnancy. A recent study from United Arab Emirates found that most people favour this mode of prevention.<sup>12</sup> The procedure is, however, still in its early stages, with many limitations. Pre-implantation genetic diagnosis involves assisted reproductive technology. It is a complex, time consuming, and expensive procedure that is available only at a small number of centres and for a limited number of genetic conditions. It is available in Saudi Arabia, where several single gene disorders can be diagnosed.<sup>11 w11</sup> Various numerical chromosome aberrations such as trisomies 21, 13, and 18 and sex chromosome abnormalities are being diagnosed in Jordan by use of the fluorescent in situ hybridisation technique after in vitro fertilisation in a few private obstetric hospitals.<sup>6</sup> Pre-implantation genetic diagnosis for common disorders such as  $\beta$  thalassaemia could be included in future prevention programmes.

### Role of education in preventing genetic disorders

Medical genetics education assumes particular importance in the region because of the high frequency of

**Box 1: Premarital advice about consanguinity at the primary healthcare level<sup>2</sup>**

- Detailed family history should be taken to spot any genetic disease
- The couple should be asked about any known inherited disease in the family, history of birth defects, impairment of hearing or vision, learning difficulties, any unexplained neonatal or infant deaths, and failure to thrive among infants
- If a genetic disorder is suspected in the family, the couple should be referred to a specialised genetic counselling clinic
- If no known inherited disorder exists in the family, first cousins intending to marry are informed of the doubling of the risk for birth defects<sup>15</sup>

genetic disorders and the generally low genetic literacy. Inadequate numbers of specialised personnel experienced in medical genetics are available, genetics is not emphasised in medical curriculums, and effective teaching methods and integration between medical genetics and other related clinical specialties are lacking.<sup>2</sup> In most Arab countries, health services are delivered by a network of primary healthcare centres where workers are not adequately trained to deal with common genetic disorders. They need to acquire the necessary skills in first level counselling to provide premarital and preconception counselling and counselling before newborn and carrier screening (box 1). Genetic counselling for people or families at high risk or those with unfavourable test results is provided by the few specialists in the field.

The World Health Organization Eastern Mediterranean Regional Office publication *Community Control of Genetic and Congenital Disorders*<sup>2</sup> provides an outline of the basic requirements to strengthen the capabilities of primary healthcare workers in preventing genetic diseases (box B on [bmj.com](http://bmj.com)). Recognising the need for genetic services (fig B on [bmj.com](http://bmj.com)), Jordan is developing a national strategy for the prevention of genetic diseases, which includes provision of community genetics training and education courses for primary healthcare physicians and nurses.<sup>6</sup> Bahrain has started a programme for the dissemination of information through primary healthcare physicians.<sup>8</sup> The service has been standardised, and premarital counselling has become widely available through all health centres. At one time,

**Box 2: Strategies for the prevention and control of genetic and congenital disorders in the Arab world<sup>2</sup>**

- Integration of community genetic services into primary healthcare systems, such as the integration of preconception counselling and screening into the existing reproductive health programmes in the country; this requires education and training of primary health workers
- Education of the public through updating high school curriculums and mass media educational campaigns that are scientifically based and appropriately delivered with respect to local cultural and religious beliefs
- Strengthening human resources by updating medical and nursing college curriculums related to the practice of human genetics, with more emphasis on practical guidelines for how to approach common genetic and congenital disorders
- Initiation of population screening programmes and national birth registries
- Introducing new technology and strengthening of existing genetic service
- Defining the ethical, legal, religious, and cultural factors in formulating genetic services, such as specific guidelines for prenatal genetic diagnosis and termination of a fetus affected by a genetic or congenital disease

**Role of GPs outside the Arab world**

General practitioners looking after Arab families outside the Arab world should always inquire about the presence and degree of consanguinity. They should be familiar with its risk of increasing genetic disorders (box 2) and be able to detect genetic risk in such families by asking about a family history of learning difficulties, anaemia, malformations, and handicapping disorders. They should also be able to provide counselling information about risk and screening for disorders known to be common in these communities, such as thalassaemia, sickle cell disease, and glucose-6-phosphate dehydrogenase deficiency.

structured courses in provision of community genetic services were supplied to family doctors in Egypt.<sup>12</sup>

One of the most important aspects of prevention programmes for genetic disorders is to have a well informed and educated population. Saudi Arabia, the United Arab Emirates, and Bahrain have introduced genetics information, particularly on haemoglobinopathies, to the public through health workers and primary healthcare centres and through the media, but no studies have measured the effect of such programmes.

**Conclusion**

The effect of genetic and congenital disorders in Arab countries is high. Genetic services are inadequate and do not cover all the population. Preventive strategies, summarised in box 2, should be adopted at a national level, with development of regional and international collaboration and with technical support from WHO.

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