

Review Articles

Ethical considerations in the prevention and management of genetic disorders with special emphasis on religious considerations

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ABSTRACT

Genetic diseases include not only single gene disorders, but multifactorial, somatic cell genetic disorders, mitochondrial and even chromosomal. One in 4 adults will suffer from a multifactorial or a somatic cell genetic disease. The common diseases in the community have a hereditary component namely diabetes mellitus, hypertension, ischemic heart diseases and many types of cancer. Even monogenic diseases which affect a small number of the newborns (2%-3%), have a greater impact on childhood diseases up to age 15 years. Therefore, it is imperative to scrutinize the available methods of prevention and management of genetic disorders, their ethical implications, and since east Mediterranean region is mainly occupied by Arabs and muslims, religious considerations become of paramount importance. Islam differs from many other religions in providing a complete code of life, which encompasses the secular with spiritual, the mundane with the celestial and hence forms the basis of the ethical, moral and even juridical attitudes and laws towards any problem or situation. Islamic teachings carry a great deal of instructions for health promotion and disease prevention including hereditary and genetic disorders. This review discusses how the Islamic teachings play an important role in the prevention and management of genetic disorders and the type of ethical implications involved in such management namely premarital medical examination, the question of consanguinity, the genetic counseling, the question of preimplantation diagnosis, the question of abortion and the offering of alternative ways of reproduction.

Keywords: Prevention, management of genetic diseases, ethical considerations, religious issues in genetics, Islam teachings.

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The majority of Asian and African countries population are Muslims by religion. The Arabian peninsula is the cradle of the Arabs, and Islam is their religion since it was established by prophet Mohammed, peace be upon him, in 622AD in Madina, the first city state. Within 10 years all the Arabs embraced Islam, and soon after the Islamic Empire was established which ruled over vast countries spreading from the western borders of china in the east to the Atlantic shores of Portugal, Spain and today's Maghrib and Mauritania, where Arabs and Arabic language prevailed. Islam differs from many other religions in providing a complete code of life. It encompasses the secular with the

spiritual, the mundane with the celestial, and hence forms the basis of the ethical, moral; and even juridical attitudes and laws towards any problem or situation. Man is the vicegerent of Allah (God) on earth. "Behold thy Lord said to angels: I will create a vicegerent on earth."¹ " He fashioned man in due proportion and breathed into him something of His spirit"² The progeny of Adam was also honored by Allah: "We honored the progeny of Adam, provided them with transport on land and sea, given them for sustenance things good and pure, and conferred on them special favors above a great part of our creation"³ Human life begins at the time of

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ensoulment, which is stated in the Hadith (Sayings of the prophet Mohammed, peace be upon him to be at 120th day from the moment of conception,⁴ which is equivalent to 134 days from the last menstrual period (LMP) used by obstetricians. Prior to that moment the embryo has sanctity, but not reaching that of a full human being.

Ibn Al Qayim who lived in the 8th century of Hijra (14th century AD) raised the following question in his book "Al Tibiah fi Ahkam Al Quran" "If it is asked: Does the embryo before ensoulment possess life? It is answered that it has the life of growth and nourishment like a plant. Once the soul enters the body then it has the sense of perception and volition, (which constitute the basis of human life)"⁵ Similarly Ibn Hajar Al Asqalani in his voluminous textbook "Fathu-lbari fi Sharh Saheehul Bukhari" argues that the liver is the first organ formed in the embryo as it is important for growth and nourishment. The formation of the brain, in his opinion, comes at a later stage when ensoulment is due.⁶ It is intriguing to find the great Islamic religious leaders link ensoulment to the formation and integration of the nervous system, whereby the centers of perception and volition are found. Recently professor Julius Koren presented a paper in Ottawa, Canada in a conference on "Ethics of organ transplantation" where he showed by studying multiple sections of different aborted fetuses that synapses in the brain do not propagate impulses except at the beginning of the 20th week of conception computed from LMP. (equivalent to 120 days from fertilization).⁷

The Islamic jurisprudence council of Mekkah Al Mukaramah (the Islamic World League) passed a Fatwa number 4 (Legal Resolution) in its 12th session held in 15-22 Rajab 1410H (10th-17th February 1990) which allowed abortion if the fetus is grossly malformed with untreatable severe condition proved by medical investigations and decided upon by a committee formed by competent trustworthy physicians, and provided that abortion is requested by the parents and the fetus is less than 120 days computed from moment of conception.⁸ This Fatwa was a landmark, as previous Fatwas only allowed abortion in the first 40 days of conception. At such a period it was almost impossible to ascertain any of the congenital or hereditary diseases. By extending the time of permissible abortion to 120 days computed from the moment of conception (namely 134 days from LMP), gives ample time to ascertain the diagnosis of severely affected embryo's and fetuses. Abortion is one of the reproductive options offered to manage and prevent genetic diseases, which will be discussed in this review.

The so called genetic diseases include not only single gene disorders, but a wide array of syndromes which include chromosomal, multifactorial, mitochondrial, and somatic cell genetic disorders.

Table 1 - Diagnosis of genetic disease.

Type	Diagnostic test
Chromosomal disorders	Chromosomal analysis
Single gene disorders	Pedigree analysis Clinical examination Biochemical analysis Deoxyribonucleic acid analysis
Multifactorial disorders	Clinical examination Biochemical analysis Deoxyribonucleic acid analysis Other investigations (imaging, functional, studies for example)
Mitochondrial disorders	Pedigree analysis Clinical examination, deoxyribonucleic analysis testing
Somatic cell genetic disorders	Histopathology Deoxyribonucleic analysis Chromosomal analysis

Table 2 - Incidence of genetic disease.

Type	N of subtypes	In 1000 live births
Chromosomal	>600	6
Single gene	-	-
Autosomal dominant	4458	20
Autosomal recessive	1730	2
X-linked recessive	412	2
Multifactorial		-
Major congenital malformations	>50	6
Chronic adult	>50	10+
Mitochondrial	59	Rare
Somatic cell genetic	>100	
N - number		

Table 1 shows how these disorders are diagnosed, and **Table 2** illustrates the incidence of each type per 1000 live births.

Islamic teachings concentrate on prevention of disease rather than cure. Islam encourages marriage and prohibits fornication and adultery. "O mankind reverence your Guardian-Lord, who created you from a single soul (person), created of like nature his mate, and from them twain scattered (like seeds) countless

Table 3 - Premarital medical exam.

Mandatory or optional
Infectious diseases and sexually transmitted diseases
Genetic diseases common in the community for example Thalassemia
If both are carriers and decide on marriage, the situation should be explained thoroughly but the decision is theirs

prophets and messengers of God (Allah) asked him to give them good and pure children (free from bad character and disease): Zakariya prayed to his Lord saying; "O my Lord grant me from thee a progeny that is pure."¹⁶ Similarly the faithfuls pray to God and say "Our Lord grant us wives and offspring who will be the comfort of our eyes."¹⁷ They can not be the comfort of their eyes unless they are healthy in body, mind, and of good character.

Table 4 - Recognized human teratogens.

Teratogen	Critical Period	Malformations
Rubella	Most affected if infection in first 6 weeks, very low risk > 16 weeks	Congenital heart disease (especially patent ductus arteriosus), cataracts, microcephaly, mental handicap, sensorineural deafness, retinopathy, later insulin dependant diabetes mellitus in 20%
Cytomegalovirus	3rd or 4th month	Mental handicap or microcephaly occurs in 5%-10% with congenital infection
Toxoplasmosis	12% risk at 6-17 weeks 60% risk at 17-28 weeks	Mental handicap, microcephaly, chorioretinitis
Alcohol	? first trimester	Mental handicap, microcephaly, congenital heart disease, renal anomaly, growth retardation, cleft palate, characteristic facies
Phenytoin	First trimester, about 10% affected	Hypoplasia of distal phalanges, short nose broad flat nasal bridge, ptosis, cleft lip and palate, mental handicap, later increased risk of malignancy, particulary neuroblastoma
Thalidomide	34-50 days from last menstrual period	Phocomelia, congenital heart disease, anal stenosis, atresia of external auditory meatus
Warfarin	Exposure at 6-9 weeks results in structural abnormalities in 30%, after 16 weeks mental handicap alone may be seen	Hypoplastic nose, upper airway difficulties, optic atrophy, stippled epiphyses, short distal phalanges, mental handicap
Chloroquine	-	Deafness, corneal opacities, chorioretinitis
Lithium	-	Congenital heart disease
Sodium Valproate	-	Neural tube defect (1%-2%), hypospadias, microstomia, small nose, long thin

men and women."⁹ In another aya (verse) of the holy Quran it orders unmarried men and women to get married. "Marry those among you who are single".¹⁰ The prophet Mohammed, peace be upon him said: "Marriage is my way, those who shun my way are not from me (namely my people)".¹¹ He also said: "Marry and procreate for I will be proud of you (on the day of judgment), among all nations".¹² He said: "If someone wants to marry and he is of good character and religion, make it easy for him to marry. If you don't, then corruption will spread".¹³ He advised Muslims to choose for their daughters, husbands with good character and free from physical and social illnesses. Similarly he warned not to marry a girl only for her beauty when her character is blemished.¹⁴ He also said: "Choose for your offspring the suitable woman for hereditary plays a role".¹⁵ The

Premarital examination to avoid genetic diseases will be a welcome, especially in a community where the rate of consanguineous marriage is high. **Table 3** gives the pertinent features of premarital medical exam.

The control and prevention of congenital and genetic diseases implies control of teratogens. **Table 4** gives examples of well known teratogens that could be avoided. Rubella is virtually eliminated in many countries by vaccinating school children girls at premarital age. Syphilis and other STD (sexually transmitted diseases) will not appear if all sexual desires are channeled through marriage as Islamic teachings implies. Fornication, adultery, and sodomy are all harshly punished in Islamic legal code, and religiously they are considered of the greatest sins, that each Muslim should avoid. Alcohol is the most

frequent chemical substance causing mental retardation and congenital anomaly. Islam totally prohibits imbibing alcoholic beverages. Similarly smoking causes abortion, congenital anomalies and small for date babies. It is prohibited in Islamic teachings and many fatwas have reiterated its prohibition. Any substance that is going to be harmful to the baby (namely teratogen) should be avoided as the prophet Mohammed, peace be upon him said: "Do no harm".¹⁸ There are simple measures which reduce congenital diseases namely adding folic acid to the diet such as bread proved to reduce the incidence of serious congenital diseases viz.: anencephaly, spina bifida and syringomyelocele (open neural tube). Similarly iodized salt helps to prevent the occurrence of cretinism and hypothyroidisms in the newborns. **Table 5** shows the risks related to genetic diseases in general population, while **Table 6** shows the risks of consanguinity. The highest risks are from first degree marriage viz.: Parent child and sib to sib where they share half the genetic pool. All cultures and religions consider such a relation as a taboo. However it is well known that the Pharoes and the old Persians allowed marriage between brothers and sisters. In the old testament (book of Genesis) it is claimed that Abraham married his half sister Sarah,¹⁹ while Lot had sex with his two daughters and both of them became pregnant of that incest and delivered Moab and Benammi.²⁰ Islamic teachings refute such claims and consider the messengers of God as the purest persons on earth, and will never do such horrendous acts.

First cousin marriage carry an increase of 3%-5% of genetic diseases where they share 1/8 of the gene pool, while in second cousin marriage they will share 1/64 of the gene pool. An average of 30% first cousin marriage in the community would increase the birth prevalence of all autosomal recessive disorder between 5 and 10 times. This will double the congenital malformations detected at birth from 2.5 to 5% of all live births.²¹ The gene of autosomal recessive disease in the community may increase exponentially namely 15 to 30 times in first cousin marriages.²¹ The inborn errors of metabolism which are mostly recessive and therefore directly increased by consanguinity, show an unprecedented surge in Riyadh, where the figures from King Faisal Hospital show an alarming high incidence, which seems to be directly related to the high consanguinity in Saudi Arabia.^{22,23} Twenty percent to 25% of all marriages are first cousins, another 20%-25% are second cousin marriages and 15%-20% are family related, a total of 60%-65% of consanguinity marriages.²⁴

However, when the autosomal recessive gene in the community is very common namely Thalassemia, sickle cell anemia and glucose 6 phosphate dehydrogenase deficiency where the incidence in Hafoof and Qatif (Eastern province of Saudi Arabia)

Table 5 - General population risks.

Condition	Risk
Spontaneous miscarriage	1 in 6
Perinatal death	1 in 30-100
Neonatal death	1 in 150
Cot death	1 in 500
Major congenital malformation	1 in 33
Serious mental or physical handicap	1 in 50
Adult cancer	1 in 4

Table 6 - Risk of consanguinity shared genes in relatives.

Relatives	Risk
Parent-child, sibling to sibling	1/2 risk 50%
Uncle-niece, aunt-nephew	1/4 risk 5%-10%
First cousins	1/8 risk 3%-5%
2nd cousins	1/64 risk low

Table 7 - Control and prevention of the hereditary disorders.

Screening: Population, family for carriers and affected persons
Premarital carrier detection (common in the community)
Genetic counseling
Newborn screening for common and treatable conditions
Education programs for the community
Management strategies
Genetic registries
Avoidance of teratogens and mutagens during pregnancy
Prenatal Diagnosis - Abortion

and Jizan (South West province of Saudi Arabia), involves 20%-25% of the whole population, the carriers of the trait are one in 4, or one in 5 in the whole community, any marriage will have a high risk of marrying another carrier of the trait.²⁵⁻²⁹

Table 7 lists the most important points in control and prevention of hereditary disorders. Screening of all newborns for common and rare diseases can establish early diagnosis and proper management.

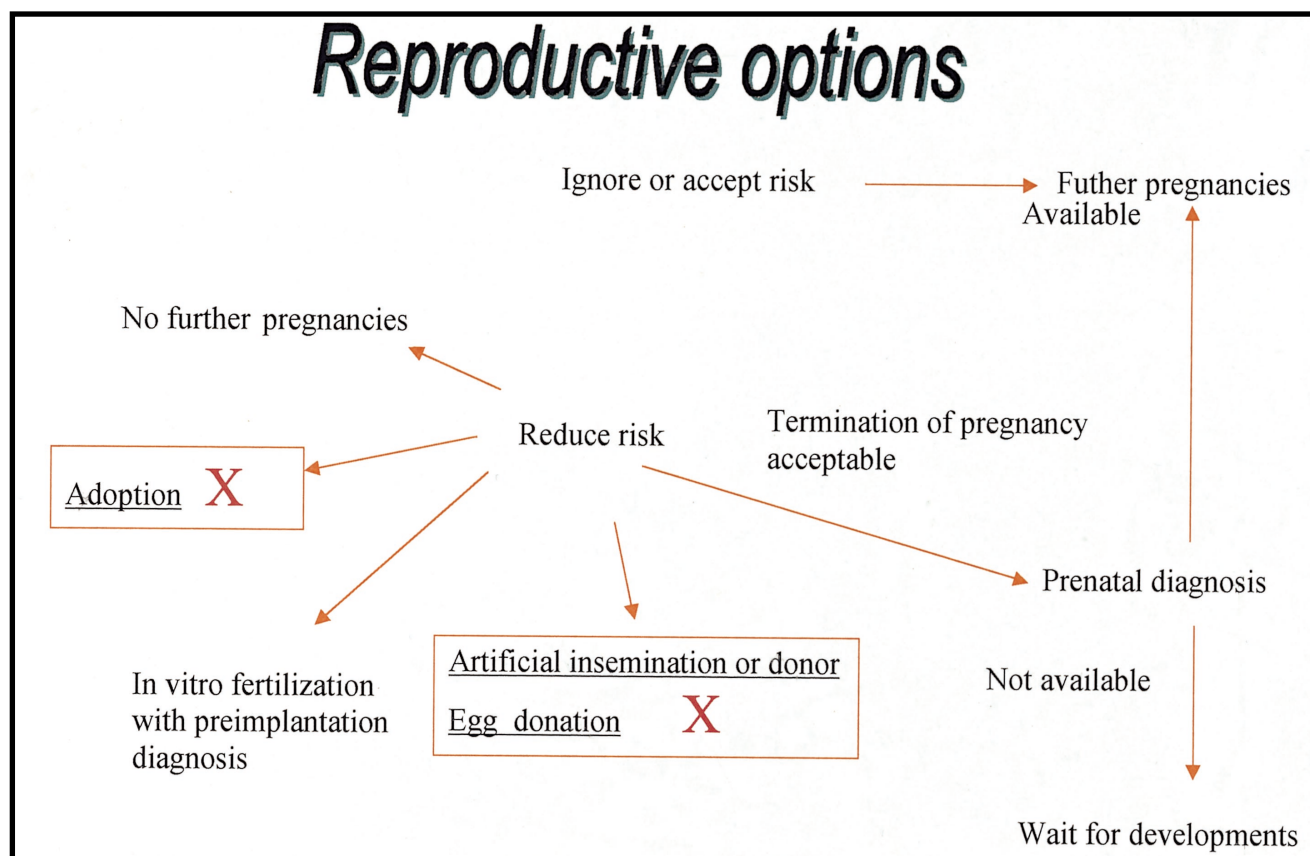


Figure 1 - Reproductive options.

Simple tests for phenyl ketonuria, homocystinuria, galactosemia and many others can avert calamity in those affected diets free from phenyl alanine or methionine or gotaclose are available and if the newly born is given such a diet, he will grow normally. He will need the diet for few years only and then can revert to normal diet. During adulthood, the pregnant lady suffering from phenyl ketonuria should stick to phenylalanine free diet all through her pregnancy to avoid any harm to her baby.

Premarital carrier detection is important especially in communities where consanguinity is very high. If the fiancé and fiancée are found carrying the same autosomal recessive gene, then genetic counseling should be provided, and all the pertinent facts and risks to the progeny explained. If they insist on marriage, the decision is theirs, but reproductive alternatives should be discussed with them. **Figure 1** shows the different reproductive options. If the couple accept the risk of pregnancy the alternatives will be: 1. Preimplantation diagnosis, where in vitro fertilization is carried out. The zygotes are grown to 8 cell stage (morulla stage), where a cell is removed examined for aneuploidy (abnormal number of chromosomes) and deoxyribonucleic acid (DNA) testing for the culprit gene. If proved negative, the

morulla/blastula is implanted. If it is positive then it is discarded and another morulla/blastula tested. The beauty of this method is that it avoids abortion. However, it is not yet available except in few centers in the world. The success rate of pregnancy and take home baby of all in vitro fertilization (IVF) projects, is low (15%). There seems to be no short term risks by removing a cell from the growing morulla/blastula, but nobody can ascertain the future and long term risks. 2. Adoption: is not allowed in Islam, though caring for orphan or children of unknown parents is encouraged and considered as a charity and a great act of worship. However the lineage of the child should be kept to his biological parents. 3. Artificial insemination by a donor, or egg donation: are all out of bounds in Islamic law. Procreation in Islamic law is limited to husband and wife, during the existence of matrimonial bondage. If divorce or death of a spouse occurs no procreation will be allowed. 4. Prenatal Diagnoses: This will involve blood testing of the mother for alpha fetoproteins, gonadotrophins and more recently for fetal cells. Chorion villous sampling (CVS) is carried out in the 7th to 8th week of pregnancy and if the fetus is proved suffering from serious congenital anomaly then abortion is offered. If CVS was not available,

then ultrasound study, amniocentesis and blood sampling from the fetus will confirm the diagnosis. If the congenital anomaly is very serious, abortion could be carried, provided it is carried out prior to the 120 days from conception.

In conclusion, Islamic teachings offer a great deal in the prevention and control of genetic diseases to Islamic communities, which form the majority of the population in many Asian and African countries. It is important to educate to people the dangers of consanguinity, which is very common in the area. Premarital examination should be encouraged which may detect the trait in those intending to get married. Proper counseling should be provided, the dangers explained and the options discussed. Prenatal diagnosis and the option of abortion for serious devastating diseases (prior to 120 days from conception) will reduce the incidence of such diseases. Neonatal screening can avert havoc by simple measures namely specific diets, or certain operative measures. Avoiding teratogens and provision of folate and iodine in the diet will help in reducing congenital diseases.

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