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The Frequency of Consanguineous Marriages and Their Effects on Offsprings in Tabriz City.

Rahmani SA*, Aboualsoltani F**, Pourbarghi M^ε, Dolatkah H[±], Mirza Aghazade A^β.

* Assistant Professor of Medical Genetics, **General Practitioner, ^ε Student of Medicine, [±] Pediatrician, Taleghani Hospital, ^β Assistant Professor of Biostatistics, Tabriz University of Medical Sciences, Tabriz, Iran.

Correspondence: Dr. Rahmani, Department of Biochemistry and Medical Genetics, School of Medicine, Tabriz University of Medical sciences. Telephone and Fax: 0411-5570671, Email: rahmaniseyedali@yahoo.com

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Abstract:

Background: Too much diversity and an ever increasing number of genetic disorders appear as a big challenge in the coming future. One of the main sources of genetic disorders is the consanguineous marriages which are, unfortunately, very common in our society.

Objectives: In order to prepare ourselves to accept the challenges regarding congenital malformations due to consanguineous marriages, the first step is to get complete information of their prevalence and their risk factors.

Methods: The study was made during 2003-2007 in the city of Tabriz, Iran. We selected 6000 families and data was obtained via a questionnaire comprised of information including marital ages, number of pregnancies, type of delivery, ratio of consanguineous and non consanguineous marriages, jobs of parents, and effects on child malformations.

Results: Consanguineous marriages of all types were related with increased congenital malformations (with ratio 43/1000 for consanguineous marriages and for non consanguineous marriages 28/1000). Mother age less than 18 and more than 35 particularly was accompanied with increased malformations while education of mother came out to be inversely related to congenital malformation.

Conclusion: Increased stillbirths, consanguineous marriage and malformations, especially of musculoskeletal system, require new planning on a national level to control and inform people of the consequences of consanguineous marriages.

Keywords: Consanguineous marriage, congenital malformation, Trisomy 21, genetic disease.

Introduction:

Congenital malformations are the malformations that are present at birth and may or may not have a genetic basis. Some are very clear and present at birth (e.g. Amelia) while others show themselves later in life (e.g. different metabolic diseases and enzyme related disorders such as phenylketonuria). These have a genetic basis while some others like congenital Rubella syndrome do not. On the other hand, both kinds can result in defects called multifactorial disorders (e.g. congenital heart disease). A single disorder seen in some members of the family (more than one) is called familial disorder. Familial disorders may or may not be hereditary e.g. congenital hypothyroidism due to low iodine in the environment.⁽¹⁾

Various causes of congenital malformations can be divided into 3 categories: unknown, genetic, and environmental. The cause of a majority of human malformations is unknown. A significant proportion of congenital malformations of unknown cause are likely to have an important genetic component. Malformations with an increased recurrent risk, such as cleft lip and palate, anencephaly, spina bifida, certain congenital heart diseases, pyloric stenosis, hypospadias, inguinal hernia, talipes equinovarus, and congenital dislocation of the hip, fit in the category of multifactorial disease as well as in the category of polygenic inherited disease. The multifactorial/threshold hypothesis postulates the modulation of a continuum of genetic characteristics by intrinsic and extrinsic (environmental) factors.

Spontaneous errors during development may account for some of the malformations that occur without apparent abnormalities of the genome or environmental influence. Occurring errors of development may indicate that we are far away from our goal of eliminating birth defects because a significant percentage of birth defects are attributable to the statistical probability of errors in the developmental process, similar to the concept of spontaneous mutation. It is estimated that the majority of all conceptions are lost before term, many within the first 3 weeks of development. The World Health Organization estimated that 15% of all clinically recognizable pregnancies end in a spontaneous abortion, 50% to 60% of which are attributable to chromosomal abnormalities. Finally, 3 to 6% of offspring are malformed, which represents the background risk for human maldevelopment.⁽²⁾ The chance that both parents are carriers of a mutant allele at the same locus is increased substantially if the parents are related and each of them have inherited the mutant allele from a single common ancestor, a situation called consanguinity.⁽³⁾

First cousin marriages are the most common reason for couples seeking genetic advice; these are legal in many western countries, but may be the subject of religious or social restrictions. In many Asian communities they are actively encouraged.⁽⁴⁾

Consanguinity without known genetic disease in the family appears to cause an increase in mortality and malformation rate which is extremely marked in the children of incestuous mating, but which is of little significance when the relation-

ship is more distant than that of first cousins. First cousin marriages, the most common counseling problem, seem to have an added risk of about 3 percent, so that a total risk of 5 percent for abnormality or death in early childhood, about double the general population risk, is a reasonable though approximate guide. It is possible, but not certain, that the risk is less for populations with a long tradition of cousin marriage; it is only recently that genetic disorders are being fully recognized and accurately diagnosed in these populations. By contrast, some immigrant groups of Asian origin in the UK show an unusually high frequency of recessively inherited disorders, some extremely rare. This may well reflect increased consanguinity due to isolation and restriction of marriage partners.⁽⁴⁾ We performed this research in order to obtain the frequency of consanguineous marriages in our society and evaluate the consequences of such marriages related to congenital malformations in offspring and propose appropriate procedures for awaking people of the futurity.

Methods:

This study was a type of social cross sectional investigation that was done during 2003-2007 in the city of Tabriz in Iran. An ethical approval form was prepared for the research.

The studies in other countries showed that some congenital malformations have a low incidence rate. Simple epidemiological studies in our country (Iran) also have been the proof performed of this. For involving all malformations it was

necessary for the volume of the sample to be selected in a way that by considering P-value=0.002, confidential results could be gained.

Since prevalence of Congenital Heart Diseases is approximately 1/125 to 1/250 and prevalence of Neural Tube Defects (NTDs) is 1/100 to 1/1500 and prevalence of cleft lip (without cleft plate disorders) is 1/250 to 1/600, the sample volume was calculated by following formula

$$N = \frac{Z^2 pq}{d^2}$$

$$N = \frac{(1/96)^2 * 0.002 * 0.998}{(0.0002)^2} = 1917 \approx 2000$$

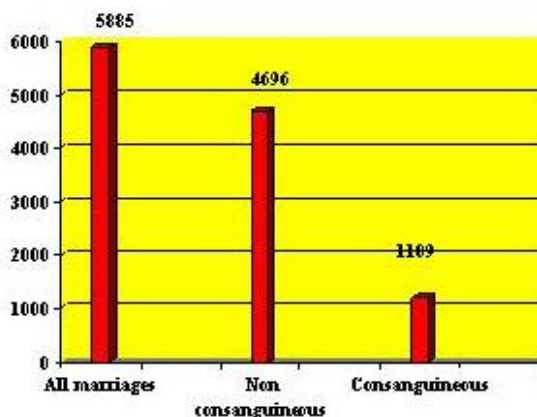
If the average number of the children for each woman under study is considered to be two, for investigating the existence of diseases in these children, 100 families have to be interviewed. If the prevalence of consanguineous marriages is considered approximately 20%, for accessing 1000 families with consanguineous marriages, 5000 families have to be interviewed. By considering all the aspects and for the results to be valuable and attributable to a whole community, also considering at least a 2 year period for spouses to have a baby, the statistics experts advised that 6000 families be interviewed in this research.

Samples were collected by random cluster sampling method and by consulting national census data published in 1993; according to which 287,050 families with a total of 1,211,216 lived in Tabriz.

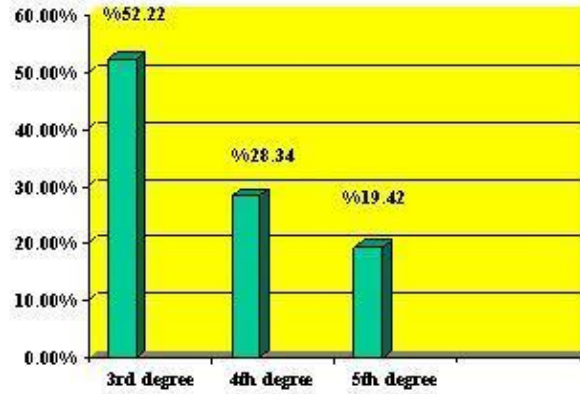
Results:

In this study average age for first marriage was 19.5 ± 0.05 years for women and 26 ± 5 years for men. At the time of study, average age for women and men was 35.5 ± 8.4 and 43.4 ± 9.2 years respectively. As for pregnancy experience, 14.5% of women under 20, 73.9% of women between 21-30 years and 11.6% of women above 35 had experienced pregnancy. Average number of pregnancies was 3.12 and average number of children per parents was 2.55. Out of 15301 alive born, 7980 were males and 7321 were females, with a female to male ratio of 1/1.09. Out of 5885 mothers studied, 1425 mothers were totally illiterate while, 1595 had primary school education, 1040 middle school education, 1452 higher secondary school education and 370 mothers were university graduates. Out of 5695 fathers enrolled in the study, 908 had primary school education, 1706 had middle school education, 120 were high school educated, 1179 were higher secondary school educated and 776 were university graduates. Of the

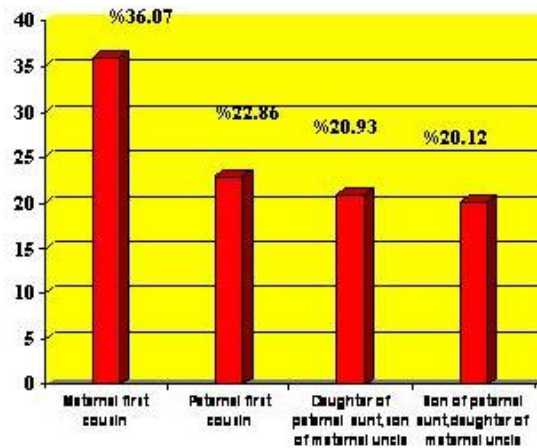
mothers, 723 (12.28%) of them were working outside the home, 439 (7.45%) worked outside and at home, and 4723 (80.25%) of them were housewives. Average period between marriage and first pregnancy was 14.14 months. 4696 (79.8%) of marriages were non consanguineous and 1189 (20.12%) were of consanguineous type (Graph 1). Out of consanguineous marriages (1189 total), 621 (52.22%) marriages were between third degree relatives, 337 (28.34%) between fourth degree relatives, and 231 (19.42%) between fifth degree relatives (Graph 2). The most common of these consanguineous marriages were third degree maternal first cousins with a rate of 224 (36.07%) out of total 621 marriages (Graph 3).



Graph 1: Rate of different types of marriages



Graph 2. Percent of different types of consanguineous marriages



Graph 3. Percent of different types of 3rd degree

Number of mothers with single abortion was 1030 (17.5%) while 559 (9.49%) experienced repeated abortions (at least two abortions). There was no significant correlation between abortions and marriage types. Average neonatal mortality rate was 0.017 in non-consanguineous marriages and 0.21 in consanguineous marriages.

Out of 5885 mothers, 1294 of them had relative parents while 4591 had non-relative parents and the rate of infertility

in the former was 643 (24%) and 311 (14%) for the later.

In nonconsanguineous marriages, 110 (4.2%) of mothers had experienced single stillbirth and 50 (1.1%) of them had experienced more than one (at least two) stillbirths. In consanguineous marriages, 43 (4.3%) of mothers had experienced single stillbirth and 33 (1.8%) of them had two cases of stillbirths. There was a significant statistical correlation ($p < 0.05$) between the age of mother at the time of

delivery and congenital defects in offspring (Chi-Square= 7.89, d.f=2).

Congenital malformations were 1.7 times higher in children of mothers with 35 years old or above compared to children of mothers between 18-35 years old. Rates of Down Syndrome (Trisomy 21) was 10 times higher in mothers 35 years old or above than mothers between 18-35 years old, and was 2.1 times higher in mothers between 15-18 years old (Chi-Square= 19.7999, d.f=4).

A significant correlation was seen between the type of marriage and congenital malformations; so that in cases of non-consanguineous marriages, the congenital malformation rate was 28/1000. For consanguineous marriages (third degree to 5th degree) it was 43/1000. Although malformations usually were seen on the all body organs, skeletal system (bones and joints) malformations were the most common (Table 1)

Table 1: Prevalence of different congenital malformations

Organ	Risk of malformation
Bones and joints	0.0083
Central nervous system	0.008
Urogenital malformations	0.0038
Alimentary tract	0.0012
Cardiovascular	0.005
Visual	0.0008
Acoustic	0.0003
Other	0.0006
Sum	0.028

There was a reverse correlation between mother education and congenital malformations (Chi-Square= 7.74, d.f=2) however, no significant correlation was found between father age and congenital malformations. Where the jobs of parents is concerned, no relation was observed between occupation and congenital malformations in offspring (Chi-Square= 0.602, d.f=2) ($p>0.025$).

Of 5885 females enrolled in the study 4914 (83.5%) considered consanguineous marriages as unfavorable and 971 (16.5%) contemplated them favorable. From those who disapproved consanguineous marriages, 4619 (94%) of them related it with increased rate of congenital malformations and those who approved such marriages preferred them because of more acquaintance of spouse

before marriage and also because of low expectations of partners and families.

Discussion:

The coefficient of inbreeding (F) is the probability that a homozygote has received both alleles at a locus from the same ancestral source; it is also the proportion of loci at which a person is homozygous or identical by descent.

In Table (2) the coefficients of inbreeding for consanguineous marriages have been shown.

If a person is inbred through more than one line of descent, the separate coefficients are summed to find his or her total coefficient of inbreeding.⁽³⁾

Table 2: Coefficients of inbreeding for the offspring of a number of consanguineous mating.

Type	Degree of Relationship	Population of Genes in Common	Coefficient of Inbreeding of Child
MZ twins	—	1	—
Parent-child	1st	½	¼
Brother-sister (including dizygotic twins)	1st	½	¼
Brother-half sister	2nd	¼	1/8
Uncle-niece or aunt-nephew	2nd	¼	1/8
Half uncle- niece	3rd	1/8	1/16
First cousins	3rd	1/8	1/16
Double first cousins	2nd	¼	1/8
Half first cousins	4th	1/16	1/32
First cousins once removed	4th	1/16	1/32
Second cousins	5th	1/32	1/64

In our study, no significant correlation was observed between mother activity (employed or housewives) with congenital malformations. Thus in our community, type of activity and environment did not act as risk factor. However, in the study performed by Brandt and Neilsen in 1990, mother's jobs were related to congenital malformations where movie making jobs seemed to be the most affective cause for congenital malformations.⁽⁵⁾ Similarly, in another case control study, a striking correlation was seen between neural tube defects (NTDs) in the first trimester and mother being in contact with organic solvents at home or outside.⁽⁶⁾

Influence of father's profession on anencephaly was studied by Suarez and Breuder in 1990 in Texas, United States. They showed that children whose fathers were in contact with organic solvents had 1.55 times more risk of congenital malformations.⁽⁷⁾ But in our study, after grouping fathers according to their different occupations, no statistical correlation was seen between types of jobs and congeni-

tal malformations in their children (Chi-Square=0.602 d. f=2) ($P>0.025$).

Similarly, occupation of consanguine parents had no important consequences on their children's malformations. In our study, congenital malformations were significantly higher in children of mothers with 35 years old or above compared to children of mothers between 18-35 years old. For example the known Down syndrome (Trisomy 21) was 10 times higher in mothers 35 years old or above compared to mothers between 18-35 years old, and was 1-2 times higher compared to mothers between 15-18 years old. These findings are compatible with other references.

Results indicate a direct correlation between the age of mothers and congenital malformations, particularly for pregnancies after 35 years old, accompanied by a high prevalence of congenital malformations⁽⁸⁾, which is the main risk factor for Down syndrome.^(9,10) Further, a mother's age below 18 years old involved a risk of increased congenital malformations, especially numerical chromosomal abnormalities.⁽¹¹⁾

Congenital defects rate came out to be 28 in every 1000 births in the world with an average of 25 in 1000 births, but it differs from place to place because of different social customs in marriages, nutritional habits, hygienic conditions and genetic potentials.^(7,8,9) Bone and joints malformations were the most prevalent malformations in this study, while in authenticated references, central nervous system malformations were seen as the most common (Table 3).^(7,8) This requires new research and more investigations for planning and finding ways to decrease musculoskeletal malformation in Tabriz city.

Table 3: Prevalence of congenital malformations in authenticated references

Organ	Risk of malformation
Central nervous system	0.007
Cardiovascular	0.004
Kidney and urinary tract	0.0015
Limbs	0.0035
Other	0.0035
Sum	0.025

In our study neural tube defects rate was a little less than reported elsewhere. This increased rate in other countries may be related to alcoholic consumption in mothers which is not consumed in our country.

In our country, visual and acoustic malformations are more common compared to developed and non Muslim countries likely due to high rates of consanguineous marriages in our country. 80% of congenital blindness and 70% of congenital deafness follow autosomal recessive hereditary patterns which express themselves in homozygous conditions resulted by consanguineous marriages.^(12, 13) Congenital blindness and deafness are malformations that do not affect life span too much, but impact the

quality of the person's life. The studies in different countries showed that the main risk factor for increases in these malformations was consanguineous marriage.^(14, 15, 16, 17) In a study in the north of India, it was found that the IQ of children in consanguineous marriages was significantly lower than the children in a control group that their parents were not consanguine. A study in 1993 in Glasgow of 205 blind kids has shown that 44% of them were due to consanguineous marriages.⁽¹⁸⁾ Also, an investigation in 1991 in Russia on 2848 blind individuals revealed that 1108 of them were due to consanguineous marriages. In 1991 in America, from 1000 blind children, 42% were children from consanguineous marriages.⁽¹⁹⁾

In 1996 in Shahid Moradi school of Tabriz, out of 94 blind students 51 (54%) were the consequences of consanguineous marriages.⁽²⁰⁾ There were 122 congenitally blind participants in our study and 32 of them had consanguine parents. Considering 20.2% of the mothers had consanguineous marriages, if we didn't consider consanguineous marriages as the risk factor for increase of blindness we would expect 24 blind children; yet this number has increased to 38 blind children because of the effects of defective and recessive genes in consanguineous marriages. On the whole, 25 in 1000 of the children who were born from non consanguine parents had congenital malformations whereas this rate was 43 in 1000 for children whose parents were consanguine. In this study there was no significant correlation between the father education and congenital malformations in offspring ($P>0.30$), but it was not the

same for mothers education and congenital malformation rate ($P < 0.05$).

The malformation ratio in the children of uneducated or elementary educated mothers to the children of the mothers who had secondary school education was 1.1 to 1. This ratio was 1.7 to 1 for mothers with university education. By correlating mother's education, mother's age and type of marriage the following formulas were achieved:

Congenital malformation = 1 + mother education + type of marriage

Congenital malformation = 1 + mother education + mother age

Above relations showed that age, education of the mothers and marriage type had independent effects on congenital malformations.

The incidence of malformations in males and females was the same but type of malformations was different ($P < 0.005$)

Skeletal and joint malformations such as club foot and congenital dislocation of hip bone, were more common in female children than males (1.3 to 0.8) while urogenital malformation were seen more in males than females. The urogenital malformations not appearing in female children at the time of birth might be the cause of such difference which needs more research by urologists.

Simultaneous studying of type of marriage showed the following formula:

Congenital malformation = 1 + type of marriage + age

The above model showed that type of marriage and age had no counter effects on congenital malformations. But studying the type of malformations show that neonates of mothers above 35 years old at the time of delivery and with consanguineous marriage were in high risk of

congenital malformations compared to those neonates whose mothers had the ages between 18 to 35 years old and their parents were non consanguine. The records of mothers deliveries showed that although the congenital malformations rate increased with each pregnancy (being 2.5% in first, 2.8% in second, 3% in third and 3.6% in fourth pregnancy and so on), these differences were not statistically significant. The positive history of abortions had significant correlation with congenital malformations ($P < 0.05$), since mothers with no abortion, one abortion and more than one in the past had 2.7%, 3.7% and 4.8% of children with congenital malformations respectively.

Also, the mothers whose parents were non consanguine had less stillbirth cases compared to mothers whose parents were consanguine. Average stillbirth rate was 0.071 0.035 in the former and 0.12 0.045 in the later. We have no standards for comparing the later group with international statistics, but the rate of stillbirths in the former is compatible with the international statistics. It seems that factors like acquaintance of spouses, less economical problems, and interference of grandparents in consanguineous marriages and on the other hand, cultural differences, prevalence of perversity, especially possibility of drug addiction in the young in non Consanguineous marriages were the most important factors bringing tendency towards consanguineous marriages.

However, the cooperation of the government and related official institutes for solving the economical problems of the young, warning the young and their families about the risks of consanguine-

ous marriages, providing genetic counseling and required facilities, congenital disease screening projects, preventing consanguineous marriages seriously, and preparing educational information programs can be effective steps in preventing the consequences of consanguineous marriages.

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