Pattern of congenital malformations in consanguineous versus nonconsanguineous marriages in Kashan, Islamic Republic of Iran

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نموذج التشوُّهات الخِلْقية في زواج الأقارب بالمقارنة مع زواج الأباعد في كاشان، جمهورية إيران الإسلامية

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الخلاصة: توضّح هذه الدراسة أنماط ونماذج ومعدل انتشار التشوُّهات الخلقية بين نسل الأزواج الأقارب والأزواج الأباعد. وهي دراسة استباقية شملت 3529 مولوداً حياً خلال سنة، وكان من بينهم 109 مصابين بتشوُّهات خلقية (3.09 من كل ألف مولود حي). وكان معدل التشوُّهات الخلقية 2.0٪ بين المولودين من زواج الأباعد و7.0٪ بين المولودين من زواج الأقارب. أما أكثر التشوُّهات الخلقية شيوعاً فقد كانت التشوُّهات التناسلية البولية (32.1٪)، والعضلية الهيكلية (22.0٪)، والقلبية الوعائية (14.7٪). وقد مات 8.3٪ من بين مجمل المصابين بالتشوُّهات في الفترة الوليدية، وكان الذكور منهم أكثر اختطاراً للتشوُّهات. وكانت سوابق الإصابة بالتشوُّهات الخِلْقية أكثر شيوعاً في نسل الأزواج الأقارب منها في نسل الأزواج الأباعد.

ABSTRACT This study determined the types, patterns and prevalence of congenital malformation among the offspring of consanguineous and nonconsanguineous parents. In this prospective study of 3529 neonates delivered alive during a 1-year period, 109 had congenital malformations (3.09/1000 live births). The rate of congenital malformation was 2.0% among neonates from nonconsanguineous marriages and 7.0% from consanguineous marriages. The most common malformations were genitourinary (32.1%), musculoskeletal (22.0%) and cardiovascular (14.7%). Of the total malformed infants, 8.3% died within the neonatal period. Male infants were at greater risk for birth malformations. A history of congenital malformation was more common in siblings of consanguineous than nonconsanguineous marriages.

Profil des malformations congénitales dans les unions consanguines et non consanguines à Kachan en République islamique d'Iran

RÉSUMÉ Cette étude a déterminé les types, les profils et la prévalence des malformations congénitales chez les enfants nés de parents consanguins et non consanguins. Dans cette étude prospective, sur les 3529 nouveau-nés vivants à la naissance enregistrés sur une période de 1 an, 109 présentaient des malformations congénitales (3,09/1000 naissances vivantes). Le taux de malformations congénitales était de 2,0 % parmi les nouveau-nés issus de mariages non consanguins et de 7,0 % en ce qui concerne les mariages consanguins. Les malformations les plus fréquentes intéressaient les appareils urogénital (32,1 %) musculo-squelettique (22,0 %) et cardio-vasculaire (14,7 %). Sur l'ensemble des nourrissons porteurs de malformations, 8,3 % sont décédés dans la période néonatale. Le risque de malformations congénitales est apparu plus élevé chez les enfants de sexe masculin. L'existence d'une histoire de malformations congénitales au sein d'une même fratrie était associée plus fréquemment aux unions consanguines qu'aux mariages non consanguins.

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Introduction

Congenital malformations are a major cause of perinatal and neonatal death [*1*], both in developed and developing countries [*2*]. These malformations have multifactorial etiologies and 40% of cases are idiopathic [*3*], but there is an impression that they are more prevalent in populations with consanguineous marriages [*4*].

Epidemiologic surveys of congenital malformations in various part of the world and among different ethnic groups with widely varying marital habits, socioeconomic status and environment not only help in understanding the frequency of malformations in specific areas but also contribute to the general knowledge about the predisposing factors and different patterns of congenital malformations. There may be regional variations in the rate and pattern of congenital malformations or these could vary over time. Previous studies in the Islamic Republic of Iran were conducted in 1979 and 1986 [*5,6*]. To our knowledge there is no recent study in our country to explore the pattern and prevalence of congenital malformation. Therefore we carried out a pilot study with the goals of finding out the pattern and prevalence of congenital malformation and its relationship with consanguineous marriage in Kashan city, Isfahan Province, Islamic Republic of Iran, where the population is predominantly Muslim, with a relatively high rate of consanguineous marriages.

Methods

In this prospective hospital-based study all the babies born alive during a 1-year period (May 2001 to May 2002) in Shabihkhani maternity hospital were investigated. Kashan has a population of about 380 000 and 4000–4200 deliveries take place annually in this region. This teaching hospital has a rate of more than 3000 deliveries annually and both high-risk and normal obstetric cases are treated.

For each birth we recorded the following: gestational age, sex, maternal age and parity, type of delivery, perinatal care, obstetric history for any disease or medication during the recent pregnancy, consanguinity of parents and history of congenital malformations in the siblings. For genetic and racial homogenicity the study was confined to infants whose parents were Iranian nationality. Babies whose mothers had medical problems (e.g. diabetes) or a history of drug use in pregnancy were excluded.

All the neonates had a thorough physical examination at birth and in the first 24 hours of life by a paediatric resident and/or an attending paediatrician or neonatologist in the nursery to detect any congenital malformations and in doubtful cases the consultant neonatologist gave the final diagnosis. For further clarification, echocardiography, X-ray, cranial and abdominal ultrasonography, computed axial tomography and other relevant investigations were performed on all infants with congenital malformations. All the infants were followed up for a period of 2 months by a neonatologist. No autopsy examinations were performed on any infants who died.

To classify the malformations we used the *International classification of diseases, 9th revision, clinical modification (ICD-9-CM*). All major and minor abnormalities were recorded. A major congenital malformation was defined as any condition of prenatal origin which is potentially life-threatening or if not corrected would impair the child's development or well-being. Malformations were classed as minor when they affected non-vital organs, had little or no functional effect and did not cause distress in the neonatal period.

The data were analysed using Fisher's exact test and the chi-squared test.

Results

During the study period 3529 neonates (3471 singletons and 29 sets of twins) were investigated. Of these neonates, 109 (3.09%, 30.9/1000 live births) had congenital malformations. Some of the malformations, especially the cardiovascular ones, were discovered during the 2-month follow-up period and were included.

The rate of consanguineous marriage among the neonates was 21.8% (768/3529) and nonconsanguineous marriage was 78.2% (2761/3529).

Among the consanguineous group, 54 (7.0%) births had congenital anomalies, of which 39 (72.2%) were in first-cousin marriages and 15 (27.8%) were in second-cousin or more distant relatives. Congenital malformations in the nonconsanguineous group were 55 (2.0%). Therefore congenital malformations were 3.5 times more common in consanguineous versus nonconsanguineous marriages ($P < 0.0001$) (Table 1). Malformations in the consanguineous group were significantly more common in offspring of first-cousin marriages than second-cousin or more distant relative marriages ($P < 0.0001$). Out of 109 anomalies diagnosed 57.8% were classed as major and 42.2% minor, both of which were more common in the consanguineous group.

Table 2 shows the frequency of these malformations by anatomical system. The genitourinary system was the most commonly affected, involving 32.1% of the 109 malformations (9.92/1000 live births). Among this group the most frequent lesions were undescended testis, hypospadias and hydrocoele, representing 15.6%, 11.0% and 3.7% of the malformations respectively.

The musculoskeletal system defects came second in frequency in 22.0% (6.80/1000 live births). Metatarsus adductus (5.5%), congenital hip dislocation (4.6%) and club foot (2.8%) were the most prominent lesions.

There were 16 (14.7%) infants with congenital heart disease (4.53/1000 live births). The most common anomalies were ventricular septal defect, tetralogy of Fallot and endocardial cushion defect (4.7%, 1.9% and 1.8% respectively).

A total of 9 infants (8.3%) with congenital malformations died in the neonatal period: 2 out of 6 with central nervous system (CNS) defects, 1 out of 16 with cardiovascular system defects and 6 with multiple defects. The death rate was high-

Table 1 **Prevalence of congenital malformation among 3529 neonates from consanguineous and nonconsanguineous marriages**

Congenital malformataion	Consanguineous marriage (*n* = 768)						Non-consanguineous marriage (*n* = 2761)	
	First cousin (*n* = 477)		Second cousin or distant relative (*n* = 291)		Total			
	No.	%	No.	%	No.	%	No.	%
Major	29	6.1	11	3.8	40	5.2	23	0.8
Minor	10	2.1	4	1.4	14	1.8	32	1.2
Total	39	8.2	15	5.2	54	7.0	55	2.0*

*P < *0.0001; non-consanguineous marriage versus total consanguineous marriage.*

Table 2 **Pattern of congenital malformations among 109 neonates by anatomical system**

Type of congenital malformation	No. of cases (*n* = 109)	%	Rate/1000 live births (*N* = 3529)
Genitourinary	35	32.1	9.92
Undescended testis	17	15.6	4.82
Hypospadias	12	11.0	3.40
Hydrocoele	4	3.7	1.13
Renal agenesis	1	0.9	0.28
Adrenogenital syndrome	1	0.9	0.28
Musculoskeletal	24	22.0	6.80
Metatarsus adductus	6	5.5	1.70
Congenital dislocation of hip	5	4.6	1.42
Club foot	3	2.8	0.85
Limb deformity	3	2.8	0.85
Polydactyly	2	1.8	0.57
Syndactyly	2	1.8	0.57
Spinal deformity	1	0.9	0.28
Absent digits	1	0.9	0.28
Hemihypertrophy	1	0.9	0.28
Cardiovascular	16	14.7	4.53
VSD	5	4.7	1.42
Tetralogy of Fallot	2	1.9	0.57
VSD + double outlet right ventricle + PS	1	0.9	0.28
Hypoplastic left heart syndrome	1	0.9	0.28
VSD + patent ductus arteriosus	1	0.9	0.28
Supravalvar PS	1	0.9	0.28
Single ventricle + L-transposition of great vessels + PH	1	0.9	0.28
ASD + tricuspid atresia + PS + dextrocardia	1	0.9	0.28
Total anomalous pulmonary venous return + ASD	1	0.9	0.28
Endocardial cushion defect + PH	2	1.8	0.57
Gastrointestinal	7	6.4	1.98
Cleft lip/palate	3	2.8	0.85
Imperforated anus	2	1.8	0.57
Tracheoesophageal fistula	1	0.9	0.28
Diaphragmatic hernia	1	0.9	0.28
Central nervous system	6	5.5	1.70
Anencephaly	2	1.8	0.57
Myelomeningocoele	2	1.9	0.57
Myelomeningocoele + hydrocephalus	1	0.9	0.28
Cortical atrophy	1	0.9	0.28

Table 2 **Pattern of congenital malformations among 109 neonates by anatomical system** *(concluded)*

Type of congenital malformation	No. of cases (*n* = 109)	%	Rate/1000 live births (*N* = 3529)
Eye and ear	5	4.6	1.42
Periauricular skin tag	3	2.8	0.85
Glaucoma	1	0.9	0.28
Malformed external ear	1	0.9	0.28
Chromosomal (Down syndrome)	2	1.8	0.57
Cutaneous (Epidermolysis bullosa)	1	0.9	0.28
Multiple	13	12.0	3.60

n = *total number of newborns with congential malformations.*
N = *total number of live births examined.*
VSD = ventricular septal defect; PS = pulmonary stenosis; PH = pulmonary hypertension; ASD = atrial septal defect.

est (6/13, 46.2%) in infants with multiple malformations.

Miscarriages and stillbirths in previous pregnancies were 1.5 and 2.3 times more common in consanguineous than nonconsanguineous groups respectively.

Of the 109 congenital malformations 74 cases (67.9%) were male and 35 (32.1%) female (ratio 2.1:1). These included 2 infants with ambiguous genitalia who were proven by chromosomal study to be 1 male and 1 female. Regarding birth weights there were no significant differences between offspring of consanguineous versus nonconsanguineous marriages. The mean birth weight in the consanguineous group was 3370 g (SD 463) and 3211 g (SD 469) in the nonconsanguineous group.

A total of 5 cases (9.3%) with congenital malformations in the consanguineous group had a history of affected siblings (2 of which had the same anomaly and the other 3 a different kind) ($P < 0.0035$) (Table 3). There was no history of malformations in siblings of affected neonates in the nonconsanguineous group. Only 7 siblings of 2706 nonconsanguineous marriages who themselves did not have any malformation had a history of congenital anomalies.

Discussion

Although this study was a hospital-based survey, the majority of deliveries in Kashan take place in this hospital and the data can be taken as a good reflection of the congenital malformations in the area. The prevalence of different congenital malformations in neonates varies from one country to another, which might be due to racial and environmental factors or differences in survey methods.

In the present study the prevalence of congenital malformation (30.9/1000) is consistent with reports from Atlanta, United States (31/1000 live births) [*7*] and Giza, Egypt (31.6/1000) [*8*], close to results from a hospital in Tehran, Islamic Republic of Iran (35/1000) [*5*] and Al-Hasa, Saudi Arabia (33.4/1000) [*9*] and higher than other studies in Spain (20.23/1000) [*10*] and India (27.2/1000) [*11*] but lower than the 3.8% and 4.7% reported from Copenhagen, Den-

Table 3 **History of congenital malformation in siblings of neonates from consanguineous and nonconsanguineous marriages**

Congenital malformation in newborn	History of malformation in sibling			Total
	Positive		Negative	
	Same type No.	Different type No.	No.	No.
Consanguineous marriage				
Positive	2	3	49	54
Negative	11	0	703	714
Total	16	0	752	768
Nonconsanguineous marriage				
Positive	0	0	55	55
Negative	7	0	2699	2706
Total	7	0	2754	2761

mark [*12*] and British Colombia, Canada [*4*] respectively.

In our study the frequency of congenital malformations was 7.0% in offspring of consanguineous marriages, which was higher than the study from southern Islamic Republic of Iran (4.0%) but in offspring of nonconsanguineous parents was close to this study (2.0% versus 1.7%) [*6*]. Abdulrazzaq et al. found consanguinity was an important factor in the causation of specific illnesses in offspring such as malignancies, congenital abnormalities, mental retardation and physical handicap [*13*].

In the present study, among 54 congenital malformations in the consanguineous group, 72.2% were in first cousins and 27.8% in second cousins or more distant relatives. In Al-Jama's study [*14*] 33.2% of malformed infants were in the consanguineous group, 74% were from first-cousin and 26% were from second-cousin or more distant relatives marriages. These are similar to our findings.

In our study the genitourinary tract, musculoskeletal and cardiovascular systems were the most commonly affected sites, in descending order of frequency. Other surveys revealed different results. Studies from eastern Saudi Arabia showed the most affected systems were the CNS, musculoskeletal [*3*] and renal [*14*]. Other studies from Saudi Arabia [*3*], the United Arab Emirates [*15*] and Hungary [*16*] showed the alimentary tract, CNS and cardiovascular were the most affected systems. The cardiovascular, musculoskeletal and CNS malformations were most common in a study from Saudi Arabia [*17*]. There may be a genetic predisposition to certain malformations. Moreover, the lower incidence of some defects in our study may be due to geographic differences, under-diagnosis or the small sample size.

Birth defect mortality in our study was close to a study from Libya [*18*] (8.3% versus 7.5%) but lower than Egypt (14.7%) [*8*]. The highest death rate in patients with mul-

tiple malformations confirmed that these anomalies were incompatible with life.

Our study showed higher rates of miscarriage and stillbirth in previous pregnancies in the consanguineous marriage group. In 2 studies in the Gulf region there were no significant differences in rates of abortion, stillbirth and neonatal death between consanguineous and nonconsanguineous marriages [*13,19*]. In Jordan [*20*] and Turkey [*21*] studies mentioning abortion did not show any significant difference between consanguineous and nonconsanguineous groups but there was a higher rate of stillbirths and infant mortality in the consanguineous group.

Although in some studies sex was not found to be associated with congenital malformations [*8,14,22*], in our study congenital malformations were more common in the male sex (male to female ratio 2.1:1), which concurs with the findings of Lary and Paulozzi [*23*] and Riley et al. [*24*].

We found no significant difference in birth weight among the infants from consanguineous versus nonconsanguineous marriages. Our finding is compatible with the study in Saudi Arabia which revealed a lower mean birth weight of the offspring of consanguineous couples that was not statistically significant [*25*] and no association was found between parental consanguinity and prematurity or low birth weight in a study of Arab women in Jerusalem [*26*]. Another study showed the mean birth weight of the offspring was significantly lower and the variance in birth weight was slightly larger for first-cousin marriages than nonconsanguineous marriages [*27*].

Our study showed that a history of congenital anomalies, whether the same or a different condition, was more common in siblings of consanguineous versus nonconsanguineous marriages. In a study from Egypt 8.42% of malformed infants had a history of affected relatives of the same or different condition [*8*].

According to our study we recommend that all neonates, especially offspring of consanguineous marriages, should be thoroughly examined and investigated for congenital malformations. Premarital counselling, especially on the subject of parental consanguinity, is advised.

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