Volume 4, Issue 1, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

CONSANGUINITY AND GENETIC RISK FACTORS ASSOCIATED WITH CONGENITAL MALFORMATIONS IN A PAKISTANI BIRTH COHORT

Shabana Nazeer[1], Misbah Rehman[2], Dr. Ghulam Abbas Khan[3], Muhammad Sajid[4], Dr. Sajid Mahmood[*5], Dr. Mian Jahan Zaib Rasheed[6]

[1]*Human Genetics Department of Zoology, Faculty of Biology, Quaid-e-Azam University, Islamabad, Pakistan*
[2]*Sir Ganga Ram Hospital, Lahore, Pakistan*
[3]*Medical Officer, MNHC Daiwal Khushab, Health and Population Department,*
[4]*Department of Zoology, Government College University Faisalabad, Pakistan*
[*5]*Department of Zoology, Hazara University Mansehra, Pakistan*
[6]*Department of Botany, University of Sargodha, Sargodha, Pakistan*

[1]shabana87.qau@gmail.com, [2]misbahrehman9909@gmail.com, [3]drabbaskhan836@gmail.com, [4]ranasajidzoology@gmail.com, [*5]sajid_sbs12@hu.edu.pk, [6]jahanzaibrasheedgc@gmail.com

DOI: https://doi.org/10.5281/zenodo.18456535

Keywords
Consanguinity, congenital malformations, genetic risk, inbreeding coefficient, birth outcomes, first cousin marriages.

Article History
Received: 06 December 2025
Accepted: 16 January 2026
Published: 31 January 2026

Corresponding Author: *
Dr. Sajid Mahmood

Abstract

Parental consanguinity is common in South Asian populations and is regarded as a significant genetic risk factor for unfavourable pregnancy outcomes, including congenital abnormalities. However, information for the degree and pattern of risk in Pakistan is scarce and conflicting. A genetic epidemiology study was carried out at a tertiary care hospital in Islamabad on 1,889 mothers who gave birth to 1,967 babies. Parental marriage patterns were classed as consanguineous, distantly related, or non-related based on pedigree data. Congenital anomalies were detected through clinical examination and medical records, and they were classified using ICD-10 and OMIM guidelines. The relationship between consanguinity and congenital abnormalities was examined using chi-square analysis and odds ratios, and the inbreeding coefficient (F) was computed. The overall rate of consanguineous marriages was 52.9%, with 45.9% of all weddings occurring between first cousins. 54.6% of neonates with congenital abnormalities were born to consanguineous parents, versus 23.1% in non-related marriages. Although the connection between consanguinity and congenital abnormalities was not statistically significant (p = 0.0626), it did suggest a moderately higher risk (OR = 1.57). The total inbreeding coefficient for the studied population was 0.0315. Consanguineous union kids had a higher incidence of musculoskeletal, central nervous system, urogenital, and orofacial malformations. A prior history of congenital abnormalities was revealed as a substantial and significant risk factor (OR = 3.3, p = 0.0004). This study represents a high rate of consanguineous marriages, which increases the risk and burden of congenital abnormalities. While the association did not reach statistical significance, the observed trends and increasing probabilities highlight the genetic influence of close family marriages. These findings highlight the need of genetic counselling, public awareness, and the inclusion of genetic services into maternal and child healthcare systems in Pakistan.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Introduction

Congenital malformations are known to be a common cause of perinatal morbidity, childhood disability and premature mortality, and genetic factors are at the core of their etiology. Although the environmental exposures, maternal health, and nutritional status impact the fetal development, the inherited genetic variations continue to play a vital role in determining the likelihood of congenital anomalies, especially when consanguinity marriages are prevalent (Temaj et al., 2022; Bai et al., 2024). Knowledge of genetic epidemiology of congenital malformations is thus critical to effective prevention, counseling and planning of the way to give health to the people.

Consanguinity is a marriage between people who are related to each other by a single or more common ancestor, and in medical genetics, is considered to be a relationship between a second cousin or more. These unions predispose the deleterious recessive alleles to homozygosity, which in turn raises the risks of the autosomal recessive disorders and structural congenital anomalies (Bittles, 2023; Hamamy, 2019). The consanguinity rates, which constitute most consanguinity marriages all over the globe, are those of first cousin marriages where the increased number of marriages is 0.0625 (F) indicating a tangible influx of genetic relatedness between the parents and the children (Bittles and Black, 2010).

Consanguinity marriages are also practiced by over one billion people around the world, with the high prevalences being in South Asia, the Middle East, and North Africa (Bittles, 2022). Consanguinity is very well established within the sociocultural norms of Pakistan and is commonly preferred as socially, economically, and familiarly beneficial (Hussain and Bittles, 2018). The literature on consanguinity unions in Pakistan is reported to be between 40% and more than 60% with first-cousin unions being the major type (Shami et al., 2019; Afzal et al., 2025). It is critical that consanguinity has a genetic influence on reproductive outcomes in Pakistan because this country has a high prevalence rate.

There is a growing amount of evidence that consanguinity could be linked to the risk of congenital malformations, stillbirths, neonatal deaths, and inherited metabolic and neurological disorders (Hamamy et al., 2011; Sheridan et al., 2022). Population-based studies and systematic reviews have found a small yet significant increase in the risk of significant congenital anomalies in children born to consanguineous parents especially in the musculoskeletal, central nervous system, cardiovascular, and urogenital systems (Teeuw et al., 2011; Temaj et al., 2022). Nonetheless, the level of this association differs between studies and it depends on the genetic load in the background, the level of relatedness and the design of studies.

In developing nations, consanguinity-related genetic burden is usually worsened by inadequate genetic counseling services, lack of programs focused on premarital screening, and a poorly established congenital anomaly surveillance network (Zaki et al., 2025). Studies that are hospital-based are thus important in the production of base genetic epidemiological information especially in settings where there is no population-level registry (Luo et al., 2025). Although consanguinity is very common in Pakistan, very limited research has been conducted to quantitatively determine the relationship between consanguinity and congenital malformations based on standardized classifications and inbreeding coefficients.

Moreover, there is a complicated correlation between consanguinity and reproductive outcomes. At the same time as inbreeding amplifies the expression of the deleterious recessive alleles, long-term population ecologies can create some purging of very harmful genes, overcomplicating the estimation of risks (Hilliard, 2024; Bittles, 2023). It is due to this complexity that context-specific research studies that combine genetic, epidemiological, and reproductive data are required.

It is against this light that the current study was conducted to determine the relationship that existed between parental consanguinity and congenital malformations in consecutive births in a third-tier hospital in Islamabad. This study will

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

offer evidence-based information on genetic role of consanguinity in causing congenital malformations by evaluating marriage patterns, estimating the inbreeding coefficient and examining the system-wide distributions of congenital anomalies. The results will be used to facilitate the implementation of the specific genetic counseling, community awareness and policy level interventions to minimize the burden of preventable congenital disorders in Pakistan.

Materials and methods

Sampling site

The present research was centered on genetic epidemiology and incidence of congenital abnormalities in the Pakistan institute of medical sciences (PIMS) located in Islamabad. PIMS is a tertiary care hospital based in the heart of the Federal Capital, Islamabad, which was established in 1985. The hospital is sub-divided into a few sections namely Islamabad Hospital, Children Hospital, Maternal and Child Health Care Centre (MCH), Quaid-i-Azam Postgraduate Medical College (QPGMC) and College of Medical Technologies. Due to its high geographic position, it receives a significant inflow of patients in twin cities of Rawalpindi and Islamabad and other regions such as Bara Kahu, Ali Pur, Ari Syedan, Bani gala, Pind Bhagwal, Nilore, Talhaar, and Phulgiran. Also, a considerable portion of the patients in suburban districts, i.e. Chakwal, Murree, Wah Cantt, Gujjar Khan, Peshawar, Mardan, Nowshehra, etc. also come to PIMS.

Maternal and Child Health Care Centre (MCH) was set up through collaboration of Japanese government. The Centre has very sophisticated medical facilities that can address any type of emergency. Such facilities comprise of Diagnostic set up, Pathology Lab, Radiology, Blood Bank, CTG (Cardiotocography) machines, ultrasound and Emergency resuscitation.

To conduct the surveillance of CM among the neonates, the MCH General Wards such as Gynecology Ward, Prenatal Ward, Postnatal Ward and Nursery were visited. The most visited units were the Postnatal Ward and Nursery Unit 1 and 2 that were used to examine neonates. General Ward has a capacity of 90 beds; Labor Ward floor has capacity of 10 beds and the Private Ward has 35 beds capacity. The annual rate in MCH labor room has grown to over 5,000 in 2003 compared to 1,500 in 1994.

Consent Approval

My study proposal had been reviewed by the Review Committee of the Department of Animal Sciences at Quaid-i-Azam University (QAU) Islamabad prior to the formal beginning of the project. The research proposal was also evaluated by PIMS Ethical Review Committee. After these initial stages, the PIMS authorities (i.e. the Director and In Charge of General Ward and Nursery) approved the project to collect the data. The mother of each neonate/family head was also asked to give consent regarding filing the proformas.

Study Design

It was a descriptive epidemiology research of newborns and still-born babies at maternity hospital within PIMS within 4 months, between October 2010 and January 2011. The descriptive study design is used to compare the differences between a population in terms of disease occurrences by assessing factors such as age, gender, caste and variations of environmental conditions. This type of a study design would be able to determine trends and patterns of the occurrence of a certain disorder in a certain geographical location as well as be able to determine the factors that are related. Nevertheless, it is not able to determine the causative agents. It consists of case reports, surveillance system, and cross-sectional study, and cluster investigations.

Questionnaire Designing

The data was collected through standard questionnaires that were formulated based on the light of the objectives of the study and included two parts (Annexure I, II). The first part of the variables to be recorded were the variables under Demography, maternal age, parental consanguinity and detailed pregnancy record including previous pregnancy detailed, birth

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

order, type of delivery, type of delivery, gestational age, history of CM in other offspring. The second section was on neonatal characters such as live or still-birth, sex, body length, birth weight, head circumference and APGAR (Activity, Pulse, Grimace, Appearance and Respiration) score, and existence of CM and type of it which were gathered through medical records.

Research Team

Data collection was done by forming a research team. It was composed of two human genetic laboratory researchers in the Department of Animal Sciences Quaid-i-Azam University, Islamabad, among which I was one. Also members of this team included on-duty staff at PIMS such as resident doctors and nurses.

Questionnaire Filling

Pediatricians checked and screened all newborns born in PIMS against congenital malformations. It entailed ultrasound in the ante-natal period, anomaly seen conspicuously at birth and anomaly found after birth with the help of ultrasound or X-ray. Congenital malformations among newborns were faculty of medical records that were pulled out and studied in detail. The questionnaire was done through a structured interview. The information was gathered and the questionnaires were completed through interviewing the delivering mother and analyzing the neonates. Part 1 of the questionnaire (Annexure I, II) was answered after interviewing the mother and then current pregnancy part was answered on the availability of record file. The questionnaire part 2 was to be completed following an examination of the neonate. The physical measurements were taken on the spot or taken out of the Discharge Slip of neonate and medical record.

Data of all pregnant ladies and their live-born neonates admitted in General Ward after delivery was included. Data of all the neonates in Nursery of General Ward was also recorded. Data from Private Ward was excluded due to the lack of cooperation from parents, medical and paramedical staff. The deliveries commencing on holidays (weekends, Eid, Muharram) were also not included in this study.

Dysmorphology Record and Clinical Ascertainment

In the case of anomalous condition in the neonates, the clinical features were noted down from the discharge slip of neonates or maternal file. In case of doubtful cases, the confirmation of diagnosis was done with the assistance of the on-duty medical officer. In the Nursery, the neonate file was discussed thoroughly with the doctors and all the detail of anomaly was carefully recorded.

Classification of Anomalies

Initial ascertainment of the anomaly was done by the gynecologist and neonatologist at the Child Ward. This information was recorded in the maternal file. Anomalies were named according to the scheme adopted by ICD-10 codes (International Classification of Diseases) and OMIM (Online Mendelian Inheritance in Man).

Data entry, storage and Statistical Analysis

Data from proforma was entered and stored in MS Excel (ver. 2007). Before any processing and analysis data were counter checked and its errors were removed. Data were analyzed through MS Excel 2007, GraphPad and SPSS. Data were summarized and analyzed using simple frequency tables, distribution matrices, Chi-square test, one way Analysis of variance (ANOVA) and odd ratio, in order to find out the significance of variables. Descriptive analysis was performed to calculate frequency distribution and percentages. The Chi-square test was used to compare differences between various data groups. The level of significance accepted at $p<0.05$. Relative risk of occurrence of malformation in neonates in relation to different maternal parameters and parental parameters was identified by odd ratio test (OR). Inbreeding coefficient (*F*) was calculated. To analyze the differences between different parameters and to access the pattern of change, data were represented graphically with the help of GraphPad.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Once the anomalies were classified their prevalence, proportion and confidence interval were calculated. Prevalence per 1,000 of anomaly was the calculation of the number of neonate with anomaly divided by total number of neonates and multiplied by 1,000 (Table 2.1). Proportion was calculated by dividing number of neonates with a specific anomaly by total number of neonates. In order to know the associations between different neonatal and parental parameters and to identify the significance level Chi-square test was performed. For the assessment of statistical significance 95% CI (confidence interval) was also calculated, which is the value of true prevalence ratio with confidence (Table2.1).

Statistical expressions used in the analysis

$$\text{Percentage} = \frac{\text{No. of neonates with a specific anomaly}}{\text{No. of total anomalies}} \times 100$$

$$\text{Prevalence} = \frac{\text{No. of neonates with a specific anomaly}}{\text{No. of total neonates}} \times 1000$$

$$\text{Proportion} = \frac{\text{No. of neonates with a specific anomaly}}{\text{No. of total anomalies}}$$

$$95\ \%\ CI = p \pm 1.96\sqrt{\frac{p(1-p)}{N}}$$

(Where p = proportion, N = total number of neonates
CI = Confidence Interval)

Table 1: The following online databases were surveyed during the course of this project:

Databases	Description	URL
NCBI, PubMed	National Centre for Biotechnology Information	www.ncbi.nlm.nih.gov/ www.ncbi.nlm.nih.gov/pmc/
OMIM	Online Mendelian Inheritance in Man	www.ncbi.nlm.nih.gov/omim/
London Dysmorphology Database	London Dysmorphology Database	www.lmdatabases.com
CARIS	Congenital Anomaly Register & Information	www.wales.nhs.uk
ICD	International Classification of Diseases	www.who.int/classifications/icd/en
EUROCAT	European surveillance of Congenital Anomalies	www.eurocat-network.eu/

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Pak Medi Net | Pakistan Medical Journals repository | www.pakmedinet.com/

Results

Maternal and demographic risk factors of CM.

CM is being linked to numerous demographic factors as well as maternal factors. Of importance as predictor of congenital malformations were maternal age, education, ethnicity, origin, family structure, consanguinity, number of prior birth defects, and number of prior pregnancy loss. Table 2 has provided some of these factors with their association and risk with CM being checked with Chi-square and Odd ratio (OR) test. Overall, 52 percent of the women who were enrolled in my data fell within the age range of 25-35 years, 43.7 percent of the women fell under the first fall category of the age range, which is below the age of 25 years, and only 4.1 percent women were above the age of 35 years. Highest cases of deformed newborn babies were among mothers who were aged 25-35 years. Chi-square test demonstrated non-significant result (p=0.424), however, the age group 1 st (<25) and 2 nd (25-35) had statistically significant OR.

In regard to marriage pattern, 52% of all 1,889 females had cousin /close (Consanguinity group) and 12.1% belonged to distantly related (DR) group and 34.9% women had non-related marriages. There was missing of about 1 percent data about to marriage type of the neonatal parents. Consignuity and congenital malformation statistically were not found to have significant results (p=0.0626). The moderately strong effect of consanguinity on OR was found, however (1.57).

Distribution of the anomalies, in regard to maternal education, was also investigated. Approximately 55% mothers were those with at second level and above education. There were 108 anomalies (5.71) that were experienced in the course of study. The percentage of aberrations established was 3.03 per cent of the 108 aberrations were recorded in the neonates who had the mothers who were of the high literacy group, 1.37 per cent aberrations in the neonatal mothers who had the illiterate mothers and the rest 1.37 per cent who had the primary mother of the neonate. The outcome was statistically insignificant (p=0.77).

The incidence of CM in the babies of women with primigravida and second and multigravida mothers was not showing any significant association (p=0.157) even though the primigravida and multigravida had significant OR (1.7 and 1.6) respectively. Among 108 women, who gave birth to children with CM 39 (36.1%) 108 women were primigravida, 18 second pregnancy, and 48 multigravida. The most typical population in data was multigravida (44%). Past birth defect and past pregnancy loss were being taken into consideration as risk factor of congenital malformations. In this research an association between past birth defect and CM was very significant (p=0.0004), thus was regarded as significant risk factor of CM with OR (3.3) as well.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Table 2: Risk factors for congenital malformations in neonates with respect to different parameters

Variables*	Normal alive neonates*	Neonates with CM*	Dead/ Abortion	Total sample	OR
Maternal age (year)					
<25	762	38	36	836	1.8
25-35	897	54	43	994	2.2
>35	72	2	5	79	1.0 reference
Total	1731	94	84	1909	
				χ^2 = 1.712 , d.f. 2 ; p=0.424 (Non-Significant)	
Consanguinity**					
Yes	877	59	51	987	1.57
No	584	25	42	651	1.0 reference
Total	1461	84	93	1638	
				χ^2 =3.468 , d.f. 1 ; p= 0.0626 (Non-Significant)	
Mother Education					
None	387	24	28	439	1.1
Primary	369	24	18	411	1.2
> Secondary	961	53	35	1049	1.0 Reference
Total	1717	105	81	1899	
				χ^2 = 0.4996 , d.f.2 ; p= 0.7789 (Non-Significant)	
Gravida					
1	566	39	23	628	1.7
2	447	18	25	490	1.0 Reference
≥3	750	48	35	833	1.6
Total	1770	101	80	1951	
				χ^2 =3.695 , d.f.2 ; p= 0.1577 (Non-Significant)	
Previous birth defect					
Yes	54	10	2	66	3.3
No	1709	95	81	1885	1.0 Reference
Total	1763	105	83	1951	
				χ^2 =12.50 , d.f.1 ; p= 0.0004 (Highly Significant)	
Previous pregnancy status					
Abortion/dead	249	16	21	286	1.1
Alive	1514	89	62	1665	1.0 Reference
Total	1763	105	83	1951	
			χ^2 =0.1011, d.f.1 p=0.7505 (Non-significant)		

Consanguinity profile of neonate's parents

The prime explanatory variable as regards to congenital malformations was parental consanguinity. There were three broad types of marriages which consisted of close marriages, distantly related marriages and none related marriages. These three groups of marriage further had sub-categories. Close marriages comprised of first-cousin (1C), first-cousin-once-removed (11/2C), and double-first-cousin (2-1C). Related marriage, second cousin (2C), second cousin once removed (2-1/2C), bradari marriage exist in the first and second category respectively, and the third category had non-related marriages (Table 3).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

I also used the approach adopted by the rest of the investigator (Al-awadi et al., 1985; Saugstad, 1977) by considering the marriage to be consanguinity when the relationship between the married individuals was less than the second cousins. Table 3.3.2 indicates different types of marriages. Marriage record of the 1,865 subjects was available out of total data. Approximately 1% of data was not provided on to marriage type since the subjects did not reveal their relations. The consanguinity between the parents of the neonate were 45.9 percent (n=858) first-cousin and 6.38 percent (119) first-cousin-once-removed and 0.54 percent (n=10) double first cousin. The second cousin marriages of marriage groups were among the distantly related marriage group, with 6.81% and bradari with 5.36%. The non-related marriages or non consanguinity marriages comprised of 34.9 percent (n = 621) marriages.

I also investigated the percentage of the type of marriage by the place of residence (Table 4). The general percentage of consanguineous marriage was 52.2. The rate was highest in Punjab 50.8% (n = 469) and then Federal Capital Islamabad 22.5% (n = 208) and finally KPK and AJK 16.9% (n = 156). The reason behind highest rate of consanguinity in Punjab is the fact that in my data set the second most representative group was Punjab following Federal Capital.

Inbreeding coefficient (F) was also determined based on the marriage record on the total data and the individual province. Calculation did not cover the proportion of second-cousin and second-cousin-once-removed marriage type since they were not considered in the calculation of consanguinity/close marriage group. The total approximation of inbreeding coefficient (F) of data was 0.0315 (Table 3). It was found that F was highest in Federal area (0.0353), then AJK (0.330), and KPK (0.0326), whereas F was lowest in Punjab (0.0295). The degree of inbreeding coefficient (F) of any population is based on the percentage percentage of the various subsets of consanguinity marriages. Thus, the close marriages (50.8) in Punjab were highest compared to other provinces yet the coefficient of inbreeding was low. This coefficient of inbreeding was higher in federal area since the first cousin marriage was higher 52% in this region as compared to Punjab where the first cousin marriage was 42%.

Table 3: Detailed distribution of marital unions

Marriage type	No.	%age
Close marriages	**987**	**52.92**
First cousin	858	45.98
Double first cousin	10	0.54
First cousin once-removed	119	6.38
Distantly related marriages	**227**	**12.17**
second cousin, sec cousin-once removed	127	6.81
Distantly related marriages	100	5.36
Non-related marriages	**651**	**34.94**
Total	**1,865**	
Inbreeding co-efficient (*F*)	0.0315	

Table 4: Distribution of three major type of marital unions and inbreeding coefficient

	Marriage pattern				
Province	Total	Close marriages	Distantly related	Non-related	inbreeding coefficient (*F*)
AJK	141	77	16	48	0.0330
Federal	348	208	33	107	0.0353
KPK	281	156	36	89	0.0326

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Punjab	947	469	115	363	0.0295
Sindh	21	13	4	4	0.0357
Total	1738	923	204	611	0.0315

I also compared the subject's consanguinity with parental consanguinity (Table 5). It was observed that the closely related parents preferred the closely related spouses for their offspring (59.6%). In distantly related parents, 70.0% subject observed close marriages/cousin marriages, 4.8% distantly related and 25.1% were non-related. The subjects having non-related parents have observed close marriages, distantly related marriages and non-related marriages in the percentage of 43.0, 13.5, 43.55, respectively (Table 6).

Table 5: Subject and parental consanguinity

	Subject marriages		**Parental marriages**	
Marriage type	No.	%age	No.	%age
Close marriages	987	52.9	677	38.4
Distantly related	227	12.2	357	20.2
Non-related	651	34.9	731	41.4
Total	**1865**		**1765**	

Table 6: Comparison of subject and parental consanguinity

			Parental Marriage			
Marriage detail of subject	Close marriages		Distantly related		Non-related	
	No.	%age	No.	%age	No	%age
Close marriages (n=987; 52.9%)	399	59.6	245	70.0	309	43.0
Distantly related (n=227: 12.2%)	94	14.0	17	4.8	97	13.5
Non-related (n=651; 34.9%)	177	26.4	88	25.1	313	43.5

Neonatal birth status (alive, normal, dead, and anomalous) according to gender has been presented with marriage type in Table 7, Fig.1 shows the distribution of anomalies with respect to marriage type. It was observed that in anomalous male, female and total anomalous neonates the percentage was high in close/consanguineous marriage group compared to non-related marriage group. However, when close marriage and distantly related marriage groups were compared for anomalies distribution, percentage was high for distantly related marriage group.

Table 7: Neonatal outcome (percentage) and marriage pattern

Neonatal outcome	**Close marriages**			**Distantly related**			**Non related**		
Gender	M	F	Total	M	F	Total	M	F	Total
Normal alive single neonates	42.76	43.77	**86.52**	46.52	36.52	**83.04**	46.79	41.44	**88.23**
Neonates with CM (Alive/dead)	3.44	2.53	**5.86**	3.48	4.35	**7.83**	2.29	1.53	**3.82**
Dead /abortion excluding	2.74	1.32	**4.05**	1.30	4.35	**5.65**	3.36	2.14	**5.50**

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

CM dead								
Twins/trip/quad	3.75	**3.75**	1.74	1.74	**3.48**	0.61	1.68	**2.29**

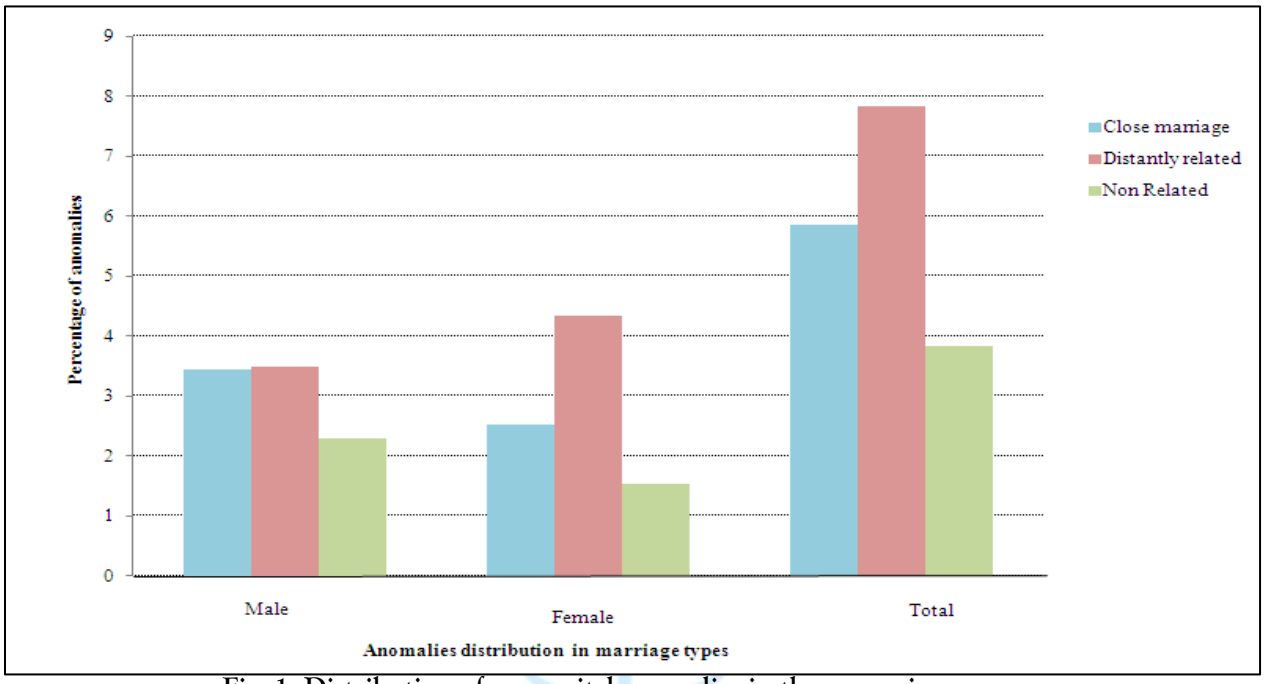


Fig. 1: Distribution of congenital anomalies in three marriage groups

I also analyzed the physical parameters of neonates (alive, normal, singleton) in relation to marriage type. Mean of birth weight, body length, OFC, and APGAR score of male, female and total neonates were compared between three marriage types. This comparison was done by single factor analysis of variance (ANOVA). The result is statistically non-significant for each of this parameter except mean APGAR score at 1 minute which significantly varied between three marriage type. There was no difference in mean birth weight of neonates born to parents of consanguineous group and non-consanguineous group. Similarly mean of other neonatal parameters (body length, OFC and APGAR score at 5 minute) remained same in all marriage types (Table 8).

Table 8: Physical parameters of neonates and parental marriage types

Neonate's parameter	Parental marriage		
	Close marriages	Distantly related marriages	Non-related marriages
Mean Weight(kg)			
M	2.88±0.5 ^{ns}	2.90±0.6^{ns}	2.90±0.5^{ns}
F	2.79±0.57^{ns}	2.78±0.58^{ns}	2.84±0.59^{ns}
Total	2.83±0.5^{ns}	2.90±0.6^{ns}	2.90±0.6^{ns}
Mean Length (cm)			
M	49.70±2.9	49.60±2.8	49.90±2.8
F	49.40±2.85	48.80±2.91	49.50±2.67
Total	49.60±2.9^{ns}	49.30±2.8^{ns}	49.70±2.7^{ns}

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Mean OFC (cm)			
M	33.60±1.4	33.80±1.50	33.70±1.4
F	33.40±2.18	33.50±1.89	33.60±1.30
Total	33.60±1.8^{ns}	33.70±1.7^{ns}	33.60±1.3^{ns}
APGAR score at 1 mint			
M	6.80±1.4***	6.90±1.3	7.20±1
F	7.00±1.1**	6.56±1.5	6.80±1.3
Total	6.90±1.3	6.70±1.4**	7.00±1
APGAR score at 5 mint			
M	8.40±1.1	8.40±1	8.50±0.7
F	8.40±0.78	8.40±1	8.30±1
Total	8.40±1^{ns}	8.40±1^{ns}	8.50±0.9^{ns}

ns = Non-significance *** Highly significant difference of APGAR score at 1 mint in male neonates between close marriages and non-related marriages. ** Significant difference of APGAR score at 1 mint in female neonates between close marriages and distantly related marriages ** Significant difference of APGAR score at 1 mint in total neonates between distantly related and non-related marriages

Table 9 illustrates the still births/neonatal death (reproductive loss) associated with marriage pattern. Of the total 5.59% mortalities 2.80% attributed to close marriages, 2.14% were in non-related and in distantly related marriages 0.66% mortalities occurred. Although incidence of mortalities were high in consanguineous group (2.80%, 2.14%) the difference did not attain the significance (p=0.846).

About 17.03% neonates were classified as low birth weight LBW (<2500g) out of the total 1,967 neonates. Although the offspring of consanguineous marriages have been found to have lower birth weight than those of non-consanguineous marriages, there were slightly high percentage of LBW neonates in consanguineous group (9.35%) compared to non-consanguineous (5.69%), but no major difference in distribution of LBW neonates by consanguineous status (p=0.790) (Table 10, Fig. 2).

Table 9: Distribution of deceased and alive neonates in relation to parental marriage type

Marriage type	Deceased*	Alive Normal singleton	Total
Close marriages	55	854	905
Diatantly related marriages	13	191	203
Non related marriages	42	577	619
Total	**110**	**1,622**	**1,732**

χ^2 = 0.334, d.f. 2; p=0.846 (Non-Significant)nt), * including all dead neonates, abortions and miscarriages.

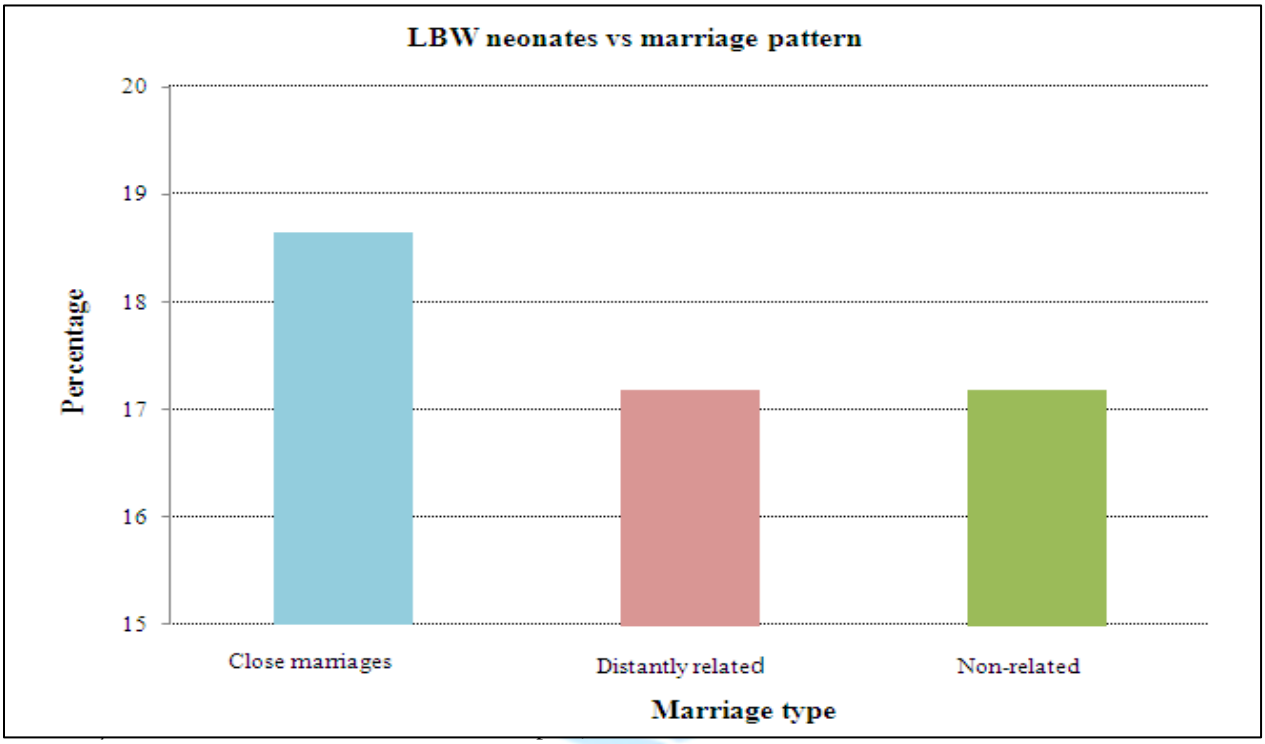
Table 10: Distribution of LBW neonates in relation to parental marriage type

		LBW neonates w.t < 2.5kg			
Marriage type	**Total deliveries**	**M**	**F**	**Total**	**OR**
Close marriages	987	81	103	**184**	1.08
Diatantly related marriages	227	21	18	**39**	1
Non-related marriages	652	54	58	**112**	1.0 Reference
Total	**1,866**	**156**	**179**	**335**	

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

χ^2 = 0.470, d.f. 2; p=0.790 (Non-Significant)



respectively (χ^2 = 17.58, d.f.16, p=0.3491). The difference between the incidence of major congenital malformation in babies of close marriage parents and that of non-related parents was close to significant (χ^2 = 14.86, d.f. 8, p=0.0619). No statistically significant difference was found in the incidence of major malformations between close marriage and distantly related parents (χ^2 = 4.943, d.f. 7, p=0.667).

Of the 59 (54.6%) anomalies resulting from consanguineous marriages 12.96% were found to be of musculoskeletal system, 12.04% of nervous system, 10.19% of urogenital system, 4.63% of cardiac system, 5.56% orofacial, 4.63% digestive marriages and non-related marriages. It was observed that musculoskeletal anomalies (24.07%) were most common of the total anomalies and it was more frequent among close marriage type compared to non-related parents (12.96%, 5.56%). Likewise, of the nervous system anomalies (22.2%), 12.0 % were contributed by parents of close marriage group with non-related group had 7.41% of these anomalies. Congenital anomalies of urogenital, orofacial and digestive system were the common birth defect associated with consanguinity in percentages of 10.09, 5.56, 4.63 compared with non-consanguineous group having percentages 0.93, 0.00, 0.00, respectively.

Table 11: Frequency of various anomalies in relation to parental marriage pattern

Congenital malformation	Total		Close marriages		Distantly related		Non-related	
	n	%	N	%	N	%	N	%
Musculoskeletal system anomalies	26	24.07	14	12.96	3	2.78	6	5.56
Nervous system anomalies	24	22.22	13	12.04	3	2.78	8	7.41
Urogenital system	16	14.81	11	10.19	4	3.70	1	0.93

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

anomalies							
Cardiovascular system anomalies	13	12.04	5	4.63	3	2.78	4	3.70
Syndromic anomalies	11	10.19	3	2.78	3	2.78	4	3.70
Orofacial anomalies	8	7.41	6	5.56	1	0.93		0.00
Digestive system anomalies	7	6.48	5	4.63	1	0.93		0.00
Respiratory system anomalies	1	0.93	0	0.00		0.00	1	0.93
Others	2	1.85	2	1.85		0.00	0	0.00
Total	108		59	54.63	18	16.67	25	23.15

Close marriage, Distantly related and Non-related marriage (χ^2 = 17.58, d.f.16 ; p=0.349 (ns)

Close marriage vs. Distantly related marriage (χ^2 = 4.943, d.f.7; p=0.667 (ns)

Close marriage vs. Non-related marriage (χ^2 = 14.86, d.f.8, p=0.062 (ns)

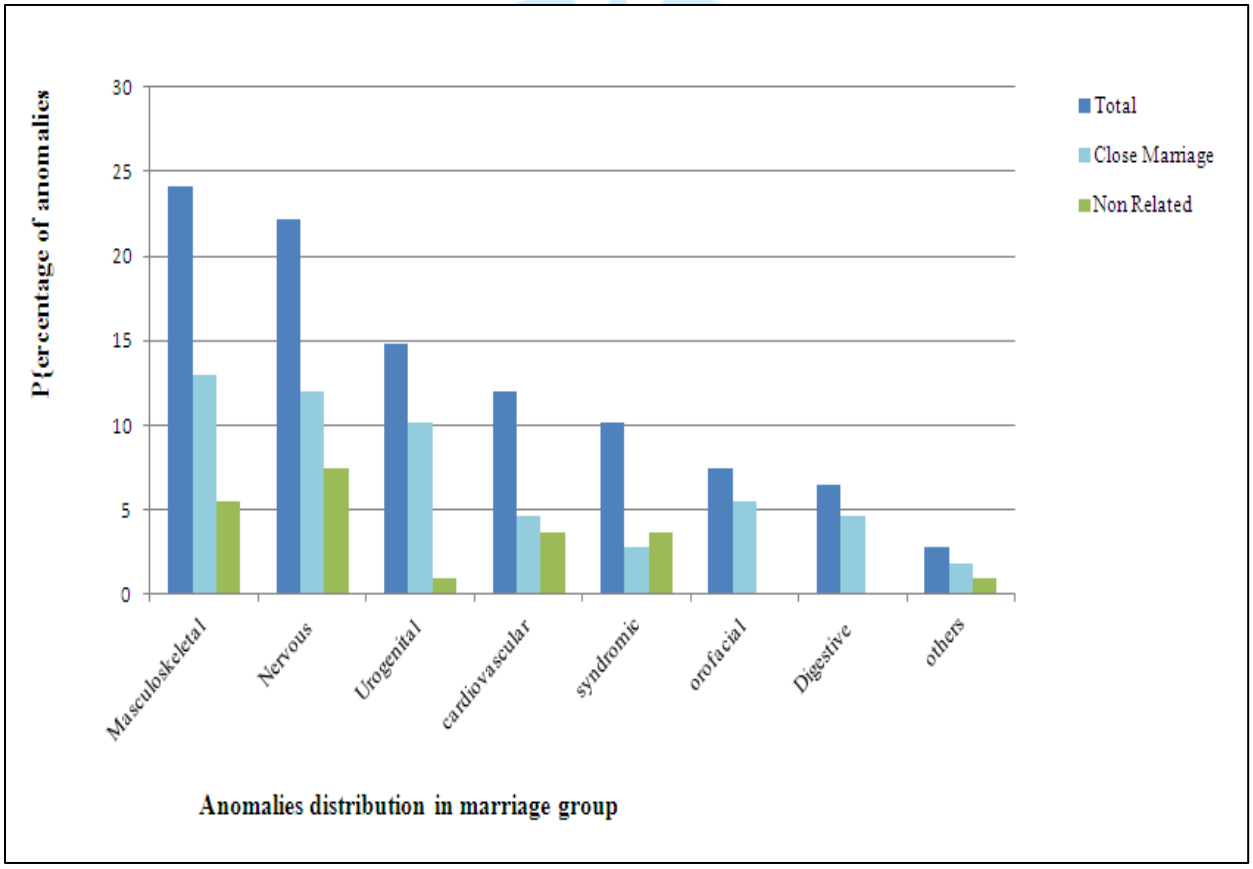


Fig. 3: Distribution of various anomalies in relation to marriage

Discussion

Congenital malformations (CMs) are one of the leading causes of perinatal morbidity and mortality in many countries, with low-income and middle-income countries being under-represented due to the lack of preventive

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

measures and surveillance systems. Congenital anomalies result in 698,000 (6-9) percent of neonatal deaths in Pakistan, which has a significant but underestimated population health issue (Hasan et al., 2010). The current hospital-based research offers valuable information on the occurrence of congenital malformations, pattern and risk factors of congenital malformations among consecutive live births in a tertiary care institution in Islamabad.

The general rate of congenital malformation in this paper (54.9 per 1,000 births) is significantly high compared to other past Pakistani researches (Perveen and Tayyab, 2007; Shamim et al., 2010; Masood et al., 2011). Such disparity could be due to differences in study design, inclusion criteria, diagnostic accuracy and regional population characteristics. Since PIMS is a large referral site with a multiethnic patient population, it is also possible that due to referral bias, more complicated pregnancies will be delivered in tertiary hospitals, resulting in the higher prevalence rate. The same discrepancies in the reported prevalence have been observed across regions and countries highlighting the effect of surveillance systems and methodological heterogeneity on reporting of congenital anomalies (Lechat and Dolk, 1993; Dolk et al., 2010).

The trend of the congenital anomalies revealed in this research is somehow different as compared to previous reports in Pakistan. The most common affected system was the musculoskeletal anomaly then the nervous system anomaly. The observation is consistent with that of Jabeen (2011), but in contrast to other publications, the central nervous system or gastrointestinal defects were common (Nafees et al., 2003; Shamim et al., 2010). The reason why the musculoskeletal anomalies are the most prevalent is possibly because of their relative compatibility with life, the ease of clinical detection at birth and some of the interior malformations may be left undiagnosed unless a state-of-the-art imaging facility is present. The prevalent musculoskeletal pathology, club foot, was also in line with regional and international musculoskeletal reports (Yaqoob et al., 1993; Stevenson et al., 2006).

Hydrocephalus was the most reported abnormality of the nervous system, which is also in line with the previous Pakistani research findings (Hasan et al., 1997; Nafees et al., 2003). Maternal folic acid deficiency has been strongly linked to neural tube defects which is common in Pakistan because of poor nutritional consumption and insufficient periconceptual use of folic acid (Hasan et al., 1997; Blencowe et al., 2010). The high prevalence of neural defects remains high and highlights the need to have effective folic acid fortification and education initiatives.

The present study has shown that male neonates were the most affected as compared to females, as has been reported by Masood et al. (2011) and Yaqoob et al. (1993). The biological basis of this gender difference has not been very clear; however, it has been postulated that male fetuses could be more vulnerable to intrauterine stress and genetic assaults (Stevenson et al., 2006). Moreover, congenital anomalies were also much more prevalent in stillbirths compared to live births, since most of the anomalies were very severe and fatal as it was also observed in other studies in Iran and other regional countries (Karbasi et al., 2007).

The age distribution of the maternal age showed that the majority of the affected births were in the age group of 2535 years which is similar to previous results in Pakistan (Masood et al., 2011). This is probably a measure of the optimum age of reproduction as opposed to being a risk factor on its own. The prevalence of congenital anomalies was higher among primigravida and multigravida women, which confirms previous results that the parity may be a factor in poor pregnancy outcomes (Shami et al., 1991). It is worth noting that some percentage of mothers reported some past history of anomalous births which may have been attributed to underlying genetic or environmental predispositions.

Among the Pakistani, consanguinity marriage is still very common, and has been largely identified to be the major genetic risk factor in congenital abnormalities because of the high degree of

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

homozygosity of deleterious recessive alleles (Vogel and Motulsky, 1997; Bittles and Neel, 1994). Overall, over 50 per cent of the marriages were consanguinity ones, and the prevalence of congenital malformations was greater among children of related parents in the current study. The correlation was not statistically significant, but the relative risk of 1.57 suggests that there is a significant biological impact. The same trends were reported in national and international researches (Centerwall, 1966; Guz et al., 1989; Jaber et al., 1992). Lack of statistical significance in this study could be explained by the limitation of sample size and strict definition of consanguinity.

System-specific analysis showed an increased prevalence of musculoskeletal, nervous system, urogenital and orofacial anomalies in neonates born to consanguineous couples, which supports the use of genetic factors in the etiology of these defects. These results can be correlated with the findings of Nafees et al. (2003) and Masood et al. (2011) who have had the same reports of similar patterns in consanguinity population. Conversely, consanguinity was not found statistically significant in association with reproductive wastage and low birth weight in this study, though consanguinity tended to be more prevalent with the low birth weight neonates. Past research has produced conflicting findings on this relationship (Sibert et al., 1979; Kulkarni et al., 1990; Khlat, 1989), indicating that socioeconomic, nutritional and environmental aspects could act as confounding variables.

In spite of the advantages, such as prospective data gathering and a sufficiently large sample, there are some limitations of this study. The absence of data on weekends and holidays, incomplete maternal history and the use of clinical examination and no sophisticated diagnostic confirmation can have resulted into underestimation or misclassification of some anomalies. However, the results give useful baseline information of the federal capital region where little data on congenital malformations have been previously known.

Of note is one significant finding of the current study which is that there exists a statistically significant relationship between a history of congenital malformations in the past and the development of anomalies in future pregnancies. Mothers who had a previous anomalous birth had over three times the risk of giving birth to another anomalous neonate and this underscored the significant role of a genetic susceptibility factor and potentially ongoing environmental exposures. This result is not surprising by previous reports that indicated the existence of a familial clustering of congenital anomalies mainly in population with high consanguinity rates (Bittles and Black, 2010; Hamamy et al., 2011). The risk of recurrence highlights the utmost significance of specific genetic counseling and follow-up to couples with a previously known history of birth defects. In other places such as Pakistan where genetic screening of pregnant women is not a routine practice, these families may continue to be unaware of their high risk. Possible reduction of the adverse outcomes that are preventable would be significantly lowered in case of early detection of at-risk couples, preconception counseling, and proper antenatal monitoring. The current element of recurrence risk is especially applicable to the context of the public health planning as it represents the effective point of entry into the field of intervention even in the resource-limited healthcare settings.

Comprehensively, the congenital malformations are very common as highlighted in this study and hence a national congenital anomaly surveillance system is urgently required in Pakistan. Better antenatal screening, education of the population about the dangers of consanguinity, nutritional measures including folic acid use, and creation of genetic counseling centers are needed to decrease the number of birth defects. Further population-based research is necessary in the future to explain genetic and environmental factors of congenital malformations and apply preventive intervention approaches.

Conclusion

The study at hand reveals that the incidence of congenital malformations is high in successive births in a tertiary care hospital in Islamabad with

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

the nerves and musculoskeletal systems most affected. The level of parental consanguinity was extremely high and correlated with the high risk of congenital malformations, but the correlation was not statistically significant. However, the trend, high odds ratios, and clusterings of anomalies within a system where the offspring are born of consanguineous unions are highly indicative of a genetic factor in the adverse birth outcomes. Past history of congenital anomalies became a major and independent risk factor, which highlights the role of familial and genetic predisposition. The findings also make it apparent that the implementation of the congenital anomaly surveillance system in Pakistan is urgently required. The need to integrate genetic counseling services, better antenatal screening, popular education on the risks of close-relative marriages and nutritional intervention e.g. folic acid supplementation are some of the steps that must be taken to help lower the burden of congenital malformations. It is advisable that future large-scale, population-based research using molecular diagnostics be carried out to further explain the interaction between genes and the environment and implement evidence-based preventive approaches targeted at enhancing maternal and neonatal health in Pakistan.

REFERENCES

Afzal, M., Faiz, A., Ijlal, A., Kanwal, H. and Obaid, Y., 2025. Exploring epidemiological trends and influencing factors in feto-maternal health: A two-decade review of maternal health data in Pakistan. *International Journal of Childbirth*, 15(1).

Bai, Z., Han, J., An, J., Wang, H., Du, X., Yang, Z. and Mo, X., 2024. The global, regional, and national patterns of change in the burden of congenital birth defects, 1990–2021. *EClinicalMedicine*, 77.

Bittles, A.H. and Black, M.L., 2010. Consanguinity, human evolution, and complex diseases. *Proceedings of the National Academy of Sciences*, 107(Suppl. 1), pp.1779–1786.

Bittles, A.H. and Neel, J.V. (1994) 'The costs of human inbreeding and their implications for variations at the DNA level', *Nature Genetics*, 8, pp. 117–121.

Bittles, A.H., 2022. Consanguinity, genetic drift, and genetic disease. *Human Heredity*, 87(1), pp.1–8.

Bittles, A.H., 2023. The impact of consanguinity on population health. *Annual Review of Genomics and Human Genetics*, 24, pp.241–262.

Blencowe, H., Cousens, S., Modell, B. and Lawn, J. (2010) 'Folic acid to reduce neonatal mortality from neural tube disorders', *International Journal of Epidemiology*, 39, pp. i110–i121.

Bonaiti, C. (1978) 'Genetic effects of consanguineous marriages', *Human Genetics*, 44, pp. 117–128.

Centerwall, W.R. (1966) 'Inbreeding and congenital anomalies', *American Journal of Human Genetics*, 18, pp. 97–102.

Dolk, H., Loane, M. and Garne, E. (2010) 'The prevalence of congenital anomalies in Europe', *Advances in Experimental Medicine and Biology*, 686, pp. 349–364.

Fida, N.M., Al-Aama, J. and Nichols, W. (2007) 'Congenital malformations in western Saudi Arabia', *Saudi Medical Journal*, 28, pp. 1517–1521.

Guz, Y., Cohen, T. and Lerner-Geva, L. (1989) 'Consanguinity and congenital malformations', *American Journal of Medical Genetics*, 34, pp. 147–150.

Hamamy, H., 2019. Consanguineous marriages: Preconception consultation in primary health care settings. *Journal of Community Genetics*, 10(2), pp.195–203.

Hamamy, H., Antonarakis, S.E., Cavalli-Sforza, L.L. *et al.*, 2011. Consanguineous marriages, pearls and perils: Gene–environment interactions. *Nature Reviews Genetics*, 12(9), pp.637–648.

Hasan, S., Jaffery, A., Ahmed, S. and Masood, S. (2010) 'Congenital anomalies in Pakistan', *Journal of the Pakistan Medical Association*, 60, pp. 231–234.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Hasan, S., Qureshi, I. and Ahmed, M. (1997) 'Neural tube defects and folic acid deficiency', *Pakistan Journal of Medical Sciences*, 13, pp. 23–28.

Hilliard, C.B., 2024. *Ancestral genomics: African American health in the age of precision medicine*. Cambridge, MA: Harvard University Press.

Hussain, R. and Bittles, A.H., 2018. Sociodemographic correlates of consanguineous marriage in Pakistan. *Journal of Biosocial Science*, 50(1), pp.1–15.

Jabeen, S. (2011) 'Pattern of congenital anomalies', *Biomedica*, 27, pp. 69–73.

Jaber, L., Halpern, G.J. and Shohat, T. (1992) 'The impact of consanguinity worldwide', *Community Genetics*, 5, pp. 65–72.

Jahangir, M., Khan, S. and Nasir, M. (2009) 'Congenital anomalies at birth', *Journal of Ayub Medical College*, 21, pp. 33–37.

Karbasi, S., Golestan, M. and Fallah, R. (2007) 'Congenital anomalies in Iran', *Iranian Journal of Pediatrics*, 17, pp. 193–198.

Khlat, M. (1989) 'Consanguinity and birth outcomes', *American Journal of Epidemiology*, 129, pp. 1192–1199.

Kulkarni, M.L., Kurian, M. and Consanguinity Study Group (1990) 'Inbreeding and fetal growth', *Journal of Medical Genetics*, 27, pp. 156–160.

Lechat, M.F. and Dolk, H. (1993) 'Registries of congenital anomalies', *International Journal of Epidemiology*, 22, pp. 101–106.

Luo, Y., Zheng, R., Chen, J., Deng, M., Zhang, Z., Tan, Z. and Bai, Z., 2025. Global, regional, and national burden of congenital musculoskeletal and limb anomalies, 1990–2021. *Tropical Medicine and Health*, 53(1), p.68.

Masood, S., Ahmed, S. and Hasan, S. (2011) 'Congenital anomalies and consanguinity', *Journal of the College of Physicians and Surgeons Pakistan*, 21, pp. 105–108.

Nafees, M., Masood, S. and Anjum, R. (2003) 'Pattern of congenital malformations', *Journal of Pakistan Medical Association*, 53, pp. 534–537.

Perveen, F. and Tayyab, S. (2007) 'Frequency of congenital anomalies', *Journal of the College of Physicians and Surgeons Pakistan*, 17, pp. 257–259.

Shami, S.A. and Zahida, Q. (1982) 'Genetic studies in Pakistan', *Human Heredity*, 32, pp. 207–211.

Shami, S.A., Qaisar, R. and Bittles, A.H., 2019. Consanguinity and congenital anomalies in Pakistan. *Journal of Medical Genetics*, 56(10), pp.640–646.

Shamim, S., Fatima, S. and Qureshi, M.I. (2010) 'Congenital anomalies in newborns', *Pakistan Journal of Medical Sciences*, 26, pp. 19–23.

Sheridan, E., Wright, J., Small, N. *et al.*, 2022. Risk factors for congenital anomaly in a multi-ethnic birth cohort. *Journal of Epidemiology and Community Health*, 76(5), pp.451–458.

Sibert, J.R., Hall, M.H. and Dodd, K.L. (1979) 'Inbreeding and birth weight', *British Journal of Obstetrics and Gynaecology*, 86, pp. 897–901.

Stevenson, R.E., Hall, J.G. and Goodman, R.M. (2006) *Human Malformations and Related Anomalies*. 2nd edn. Oxford: Oxford University Press.

Teeuw, M.E., Henneman, L., Bochdanovits, Z. *et al.*, 2011. Consanguineous marriage and congenital anomalies: A systematic review and meta-analysis. *Human Reproduction Update*, 17(2), pp.269–280.

Temaj, G., Nuhii, N. and Sayer, J.A., 2022. The impact of consanguinity on human health and disease with an emphasis on rare diseases. *Journal of Rare Diseases*, 1(1), p.2.

Vogel, F. and Motulsky, A.G. (1997) *Human Genetics*. 3rd edn. Berlin: Springer.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Yaqoob, M., Cnattingius, S. and Persson, L.A. (1993) 'Effects of consanguinity on perinatal outcomes', *Human Heredity*, 43, pp. 344–349.

Zaki, U., Qazi, S.H., Shamim, U., Fatima, S., Das, J.K. and Bhutta, Z.A., 2025. Optimal strategies for screening common birth defects in children of low- and middle-income countries. *Neonatology*, 122(Suppl. 1), pp.224–244.

Zlotogora, J. (1997) 'Genetic disorders among consanguineous populations', *American Journal of Medical Genetics*, 68, pp. 472–475.