

## Congenital malformations in newborns of consanguineous and non-consanguineous parents

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### ABSTRACT

**Objective:** To find out the pattern of different congenital malformation (CM) and to compare the proportion of congenital malformations between consanguineous and non-consanguineous parents.

**Methodology:** This observational study was done in Countess of Dufferin Fund Hospital, (CDF) Hyderabad from July 2006 to June 2008. All newborns with congenital anomaly at birth were included. Complete examination of the newborn after birth and relevant investigations were done. Babies with malformations whose parents were consanguineous were compared with babies having CM whose parents were non-consanguineous. Maternal age, parity, singletons, multiple births, still births and neonatal death were also recorded.

**Results:** Overall prevalence of congenital malformations was 15.7 / 1000 births. Central nervous system anomalies were the commonest (51%). Congenital malformations in the newborns of consanguineous parents were significantly higher than in the newborns of non-consanguineous parents. Still births and neonatal deaths were commoner in the newborns of consanguineous parents.

**Conclusion:** The results of this study show that parental consanguinity is associated with increased congenital malformations; neural tube defect is the most common anomaly seen.

**KEY WORDS:** Congenital abnormalities, Consanguineous marriage, Neural tube defects.

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### INTRODUCTION

Consanguinity is defined as the marriage between individuals who have a common ancestor.<sup>1</sup> Consanguineous marriage (inbreeding) has long been a controversial topic, with particular attention focused on adverse health outcomes.<sup>2</sup> The detrimental health effects associated with consanguinity are caused by the expression of rare, recessive genes inherited from common ancestor(s). In general terms, inbreeding is associated with loss of biological fitness.<sup>3</sup> Congenital malformations are structural abnormalities of prenatal origin that result from defective embryogenesis or deviation from normal development. Offspring of consanguineous parents are at a twofold greater risk than offspring of non-related parents for autosomal recessive disorders.<sup>4</sup> The less common a disorder, the greater is the influence of consanguinity on its prevalence, a generalization that applies to

recessive multi genes disorders as well as to single gene conditions.<sup>5</sup> For this reason, many previously unrecognized genetic diseases have first been diagnosed in highly endogenous communities and in significant portions of cases the underlying mutation may be unique to the community, This community specific patterns of disease leads to major problems when attempting to estimate the burden imposed by consanguinity associated mortality at national or at regional levels.

Consanguineous marriages are preferred in our country and there is a remarkable lack of knowledge about consanguinity associated morbidity and mortality.<sup>2</sup> The purpose of this study was to find out patterns of congenital malformations in the newborns and to see the association of malformations with consanguinity at Countess of Dufferin Fund Hospital Hyderabad. This hospital is located in the centre of the city and provides services to people of low socio-economic group from all parts of District Hyderabad. Such studies are useful for planning health care, including preventive programmes and educational and rehabilitation needs of the population.

#### METHODOLOGY

This observational study was done in Countess of Dufferin Fund Hospital Hyderabad from August 2006 to June 2008. All foetuses with congenital malformations were detected by ultrasound during the ante natal period, obvious visible congenital anomaly at birth or anomaly detected by ultrasound or X-ray after birth was included. All foetuses with congenital malformations of diabetic mothers or whose mothers were exposed to radiation during the first trimester of pregnancy or whose mothers were exposed to infectious agents proven to cause congenital anomaly were excluded. Complete examination of the newborn after birth and relevant investigations, ultrasound and X-rays, with suspected birth malforma-



Fig-1: Anencephalic Baby.

tions were also recorded in the Performa. Babies with malformations whose parents were consanguineous served as the study group and were compared with anomalous babies whose parents were non-consanguineous (control group).

Data was analyzed by SPSS Version 10. Study variables were consanguineous parents and non-consanguineous parents, congenital malformations and no congenital anomaly. Frequency and percentages were calculated for variables like gender, congenital malformations, maternal age, consanguineous marriages, parity, singleton pregnancies, twin /higher order births and mortality in both groups. Chi-Square and Fischer exact tests were used to determine the significance of difference of congenital malformations between consanguineous and non-consanguineous parent groups. P value < 0.05 was taken as significant.

#### RESULTS

The total number of deliveries during the study period of twenty four months was 7614. One hundred and twenty newborns were congenitally malformed. Sixty per cent of the congenitally malformed newborns belonged to consanguineous parents and (40%) belonged to non-consanguineous parents ( $p < 0.05$ ). The most frequent occurrence of consanguineous marriages was between first cousins 967, in 131 cases the consanguineous marriages were between second cousins while 870 marriages were between distant cousins. Overall, the prevalence of congenital malformations was 15.7/1000 births. The frequency of individual malformations is shown in Table-I. Central Nervous System (CNS) malformations were the commonest (62/120) accounting for 51% of malformations. In the CNS, Neural tube



Fig-2: Meningomyelocele.

defects (NTDs) were seen in 46 cases (74% of all CNS malformations). Isolated neural tube defects like anencephaly, encephalocele and Arnold-Chiari malformation were seen in 36 cases; in 10 cases NTD was associated with other structural malformations. Musculoskeletal system 24 cases (20%) was the second common system affected (Figure-1-3).

Mothers' ages ranged between 22 - 28 years whilst that of the fathers ranged between 28 - 35 years. Out of 7614 births, 7586 (99.63%) were singletons, 21 (0.27%) were twins with only 5 (0.06%) triplets. Higher order multiple births were 02 (0.02%). During the study period 723 women had miscarriages or abortions. Sixty nine per cent of the women delivered vaginally, 1.35% had assisted vaginal deliveries, and 30% by caesarean deliveries.

In this study the newborns with ambiguous genitalia were 03(02.5%). However, the male gender with CM was more affected 71 (59.16%) than female 46 (38.33%) (n=120), Out of 120 women who gave birth to children with CM, 49 (41%), were primipara, 27 (22%) were second pregnancy & 44 (37%) were multigravida.

Both still births and neo-natal deaths were seen more commonly in the consanguineous group as compared to the non-consanguineous group with a p-value of 0.001 for still births which is statistically significant, and in the ratio of 17:5 for still births and 7:5 for neo-natal deaths. Table-II shows mortality associated with congenital malformations.

**DISCUSSION**

Consanguinity can be a major public health issue because of increased risk of mortality and numerous morbid conditions associated with it. The over all



Fig-3: Harlequin Baby.

prevalence of congenital malformations in this study was 15.7/1000 births. Central nervous system malformations, especially neural tube defects were the commonest.

A study from Pakistan<sup>2</sup> showed that prevalence of congenital malformations was 11.4/1000 births. Most of the affected mothers (55.26%) in the Pakistani study belonged to the age group between 21 to 30 years. A similar maternal age group of 22-28 years was also found to be affected in our study. The male gender was found to have more CM & the similar findings are reported in the study done in Iran.<sup>6</sup>

The most frequently associated risk factor was history of consanguineous marriages in 44.74%. Neural tube defect (NTD) was found to be the commonest (65.8%) type of anomaly. Although consanguinity is more prevalent in Muslim communities, it is linked more to cultural and historical factors than to religious ones.<sup>7,8</sup> Marriages between relatives are favoured by all communities primarily for economic

Table-I: Congenital Malformations during the study period (n=120)

Congenital Malformations	Total		Consanguineous Group		Non-Consanguineous Group		p-value
	n	%	N	%	N	%	
CNS defects	62	51.6	36	30.0	26	21.6	1.61
Musculoskeletal defects	24	20.0	12	10.0	12	10.0	0.65
Genito urinary defects (including Ambiguous Genitalia)	14	11.6	10	8.3	4	3.3	0.14
Isolated Cleft Lip	2	1.6	0	0	2	1.6	0.50
Isolated Cleft Lip and Palate	4	3.3	2	1.6	2	1.6	0.83
Persistent Nuchal translucency	4	3.3	4	3.3	0	0	0.16
Harlequin Fetus	2	1.6	2	1.6	0	0	0.50
Cystic Hygroma	2	1.6	2	1.6	0	0	0.50
Cardiovascular Defects	2	1.6	0	0	2	1.6	0.50
Multiple Congenital Malformations	2	1.6	2	1.6	0	0	0.50
Hydrops Fetalis	2	1.6	2	1.6	0	0	0.50
<b>Total</b>	<b>120</b>	<b>100.0</b>	<b>72</b>	<b>60.0</b>	<b>48</b>	<b>40.0</b>	<b>0.02</b>

Chi square and Fisher exact test was applied between groups

Table-II: Mortality Associated with Congenital Malformations (n= 68)

Type of Mortality	Consanguineous Group	Non-Consanguineous Group	p-value
Still Birth	34 (28.3)	10 (8.3)	0.001
Neonatal Death	14 (11.6)	10 (8.3)	0.52

Fisher exact test was applied

and safety reasons as this practice is believed to strengthen family ties and maintain the family structure and property.

CM was seen more commonly in primigravida. In our study the frequency of CM was more in singleton births as compared to twin and higher order multiple births. Similar findings were reported in one of the studies from Pakistan.<sup>2</sup> In another study from California about 98% of the women with singleton births had babies with congenital malformations as compared to twins and higher order multiple births.<sup>9</sup> Jaber et al.<sup>10</sup> reported significant increase in the incidence of major malformations in relation to the closeness of the parental relationship. For the index group the prevalence of individuals with major malformations were 5.8% in the product of inter-village marriages (mostly first cousins), 8.3% in the intra-village non-related marriages, 15.1% in the distant consanguineous group, and up to 15.8% in the progeny of first-cousin marriages (P < 0.001). Another study from Oman<sup>5</sup> showed that out of 21 988 births, 541 babies (24.6 per 1000 births) had major malformations. Out of these 541 babies, 158 (29.2%) had multiple malformations and 335 (61.9%) had involvement of a single system. Consanguinity rate was 53.1% among total births; it was 76% among those with major malformations. Of the cases with multiple abnormalities, 57 had recognized syndromes, of which 28 (49.1%) were autosomal recessive disorders. Seventy (12.9%) cases had chromosomal abnormalities. The most common systems involved in neonates with single-system malformations were the gastrointestinal system (100 cases), the central nervous system (79 cases) and the cardiovascular system (63 cases). Also, there was an increased clustering of multiple abnormalities and rare recessive disorders in cases with closely related parents and grandparents.<sup>5</sup>

Central Nervous System defects like neural tube defects are very common, with an incidence ranging from 1.3/1,000 to 1.6/1,000 in Arab countries (Saudi Arabia, Kuwait, Bahrain, and Iran)<sup>11</sup> and 5.7 /1,000 in India.<sup>12</sup> Spina bifida, the most common neural tube defect, was significantly more frequent among

Table-III: Single vs Multiple Births 2006 - 2008 (n= 7614)

Births	No.	%
Single	7586	99.63
Twins	21	0.27
Triplets	05	0.06
Higher Order Births	02	0.02
Total	7614	100%

consanguineous parents in many populations, including Saudi Arabian and Indian.<sup>12,13</sup> The frequency of parental consanguinity in babies with CNS malformations in this study was about 30%. This is similar to the findings of a study conducted at the Ganga Ram Hospital Lahore, where involvement of CNS was seen in 25.7% of newborns and the overall rate of consanguinity was 42.12%.<sup>14</sup> A similar study conducted at the King Khalid University Hospital Riyadh, Saudi Arabia<sup>13</sup> also showed consanguinity of parents as a significant risk factor for spina bifida in offspring.

Congenital heart diseases are among the most common birth defects associated with consanguinity, with an overall birth prevalence ranging between 4.9 and 10 per 1,000 live births.<sup>15</sup> Studies showed that first-cousins marriage is a risk factor for congenital heart disease.<sup>16</sup> Congenital heart disease was noticeably uncommon in our study population and only two babies, who were diagnosed to have CHD were born to non-consanguineous parents. This may be in part due to lack of universal availability of diagnostic facilities like Echocardiography and thus diagnosis of subtle cardiac malformations may have been missed in this study.

Different studies analyzed the potential effect of consanguineous marriages on mortality among Indians, Pakistanis, the immigrant Pakistani in Norway, and Bedouins in Lebanon.<sup>1</sup> Commonly, after adjustment, consanguineous parents were found to be at twofold greater risk of having a loss among their progeny in the perinatal and neonatal period than unrelated parents.<sup>17,18</sup> Both still births and neo-natal deaths were seen more commonly in the consanguin-

Table-IV: Gender distribution in CM 2006 - 2008 (n= 120)

Gender	No.	%
Male	71	59.16
Female	46	38.33
Ambiguous Genitalia	03	02.05
Total	120	100%

eous group as compared to the non-consanguineous group in our study. Stoltenberg et al.<sup>19</sup> showed that the risk of an early death for a newborn whose sibling had died was 29/1,000 to 116/1,000, a rate significantly higher than that observed among non-consanguineous parents (17/1,000 to 67/1,000).

It is worthwhile to remember that one of the most important criteria of health promotion is to be born healthy. To achieve this, increasing awareness among general population about the harmful effects of consanguinity is a simple prevention strategy that can be done through educational programs. Premarital screening is another effective strategy for preventing few disorders such as beta-thalassemia, sickle cell anemia. In 2003, premarital screening became mandatory in Saudi Arabia for hemoglobinopathies.<sup>1</sup> Similar programs exist in Bahrain, UAE and Jordan.<sup>20</sup> In Iran, a recent amendment of the law, originally forbidding the medical termination of pregnancy, contributed to a 70% reduction in the annual birth rate of affected infants.<sup>20</sup> However, even if medical termination of pregnancy is legally allowed, it remains unacceptable in some communities due primarily to religious beliefs. Most couples from the Muslim world prefer not to undertake prenatal diagnosis because it is linked with the concept of abortion which is ethically, religiously and legally not an acceptable option for them.

*Limitations of the Study:* There is a well known association of NTD with folic acid deficiency. Serum and red blood cell folate levels could not be done due to high cost of these tests and low socio-economic class attending the public sector hospital. Additionally, definitive diagnosis of chromosomal abnormalities could not be made because of non-availability of these tests and cost constraints.

### CONCLUSION

The overall prevalence of congenital malformations was 15.7/1000 births. Sixty percent of the newborns with congenital malformations were born to consanguineous parents as opposed to 40%, which were born to non-consanguineous parents. The most common anomaly seen in the newborns was neural tube defect. Further studies at national level are required to validate findings of this study and to elucidate factors other than consanguinity which may contribute to congenital malformations in Pakistani population are required.

Genetic counselling to prevent consanguineous marriages may have an important impact in prevention of congenital malformation and it should be offered to the couples before marriage.

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