PATTERN AND OUTCOME OF CONGENITAL ANOMALIES AND MATERNAL RISK FACTOR ASSOCIATION

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ABSTRACT

Objective:

1. *To determine the frequency of different congenital anomalies in our hospital population.*
2. *To identity the possible risk factors responsible for these anomalies.*

Study Design: Descriptive cross sectional study.

Place and Duration of Study: Department of Gynaecology and Obstetrics Sharif Medical and Dental College / Sharif Medical City Hospital, from January to December 2012.

Patients and Methods: All booked pregnant females with fetal congenital anomalies diagnosed on antenatal USG during this period were included in study. Frequency and pattern of these anomalies were recorded. Variables studied include parity, age, duration of gestation, education and social status, family history of congenital anomalies, disease in sibling, cousin marriage, relationship with cousin, medical disorders, industrial exposure, and viral infections in early pregnancy. Outcome was determined in terms of frequency and pattern of malformations, male to female ratio, mode of delivery, and severity of congenital anomalies.

Results: Prevalence of congenital anomalies was 21.5 per 1000 total births, with individual incidence of neural tube defect being 18.81 pr 1000 total births. Neural tube defects remain the most common abnormality. Cousin marriages with 1st degree cousin (83.33%) and maternal relationship with cousin (85%) showed significant association as risk factor for congenital abnormalities ($p < 0.350$).

Conclusion: Neural tube defect is identified as major congenital abnormality in this community and consangious relationship being the biggest risk factor associated with it.

Key Words: Congenital anomalies, Neural tube defects.

INTRODUCTION

Birth of abnormal child is a stressful situation for mother as well as for society. About 8 million children are born each years with congenital abnormalities, out of which 3.3 millions die before the age of five while 3.2 million survivors suffers from severe mental or physical disability. Although it is a major global concern but advancing technology and early antenatal diagnosis of birth defects has altered the trends in birth prevalence of the congenital abnormalities.[1]

The prevalence of congenital abnormality in United States and United Kingdom is 2 – 3% and in Pakistan the incidence of congenital abnormalities varies from 11 to 15/1000 total births.[2,3] This geographical variation represents the variation in prevalence of certain causative factor in a population. Causative factor in 60% of cases will be unexplained but well recognized genetic conditions, environmental pollutants, teratogens, infectious agents, drugs and uncontrolled medical disorders like diabetes and epilepsy in antenatal period, and multifactorial inheritance was responsible in most of the anomalies.

Minor abnormalities like cleft lip and palate, diaphgramatic hernias can easily be managed by surgical correction while early identification of lethal abnormalities will reduce the burden to society by early terminations of pregnancy.[4]

The pattern of these anomalies also varies among different population, but neural tube defect remains the most prevalent congenital abnormality in our hospital population. Neural tube defect results from incomplete closure of neural tube at third and fourth week of intrauterine life and defects range from minor anomalies of spina bifida to major anomalies of cranial vault i.e. anencephaly.[5]

Although the prevalence of neural tube defect is decreasing worldwide especially in England and

America with peak at 1930 and 1960 and downward trend since 1970. The situation in developing countries is still devastating. Pakistan is among the countries where congenital abnormalities are still high and the reported incidence is 13 per 1000 in one study. The reason for high prevalence being un-booked status, decrease awareness among pregnant ladies for folate supplementation, food fortification, intermarriages and late marriages, uncontrolled metabolic syndromes like diabetes, lack of dietary nutrients, and pollutants in water in industrial area.[6]

This study aims to determine the magnitude of problem in our hospital population and risk factor analysis in these women so measures will be taken to reduce the prevalence of birth defects in this community.

PATIENTS AND METHODS

This descriptive cross sectional study was conducted in department of Gynaecology and Obstetrics of Sharif Medical and Dental College / Sharif Medical City Hospital using non-probability purposive sampling technique in one year duration from January 2012 to December 2012. All booked pregnant females during this period with fetal congenital anomalies giving birth were included in the study. All un-booked, and those referred from outside with established diagnosis of fetal congenital malformation were excluded from study population. Patients who booked themselves in Sharif Medical City Hospital for delivery purpose undergo booking obstetrical ultrasound from the Radiology Department of Sharif Medical City Hospital as well as anomaly scan at 18 – 20 weeks for detection of congenital anomalies, and routine scan at 28, 34 and 37 weeks respectively. These ultrasound were performed on Toshiba Just Vision using 3.5 MHz probe. Once the diagnosis of congenital anomaly was made at whatever duration of gestation, structured proforma was filled to document the type and the pattern of each anomaly. Congenital anomalies were classified into mild and fatal (operational definition). Mild abnormalities were observed on repeated scans and spontaneous onset of labour awaited. Once delivered these babies were observed in neonatology ward for further management. Fatal anomalies were referred for termination of pregnancy in labour ward. Terminations were performed by using different methods of medical induction, or surgically according to gestational age and obstetrical history.

Variables that were recorded include maternal age, social status (lower who are either unemployed or worked but monthly income less < 8000 Rs, middle class are those whose income is from 10,000 to 20,000 Rs and higher class > 20,000 Rs, educational status of mother as uneducated who never attend school, primary who read up-till class five, secondary six to 9th class and higher education from 10th class to graduation and above), duration of gestation, parity, booking status, presence of risk factors including cousin marriage (1st or second degree cousin), relationship with cousin (maternal i.e. Mother's sister's children, Mother's brother's children, or paternal i.e. Father's sister's children, Father's brother's children, family history of congenital anomalies in first degree relatives, maternal medical disorders like diabetes, thyroid, and epilepsy, previous history of disease in sibling, residential area, exposure of mother to industrial pollutant, viral infections in early part of pregnancy (flue like symptoms and fever), and maternal exposure to any drugs. Exposure of industrial pollutants to pregnant females were asked by asking the residential area in proximity to industrial area by distance from industrial area (3km as near, and > 3 km as distant), presence of industrial waste site near residential area, presence of pollutant smell in air, worker in factory of chemicals or pesticides. Patients were also asked about the intake of folic acid in their antenatal period.

Outcome of fatal anomalies were determined in terms of mode of delivery, and female to male ratio. Descriptive analysis was done using SPP 17. Frequencies, means and standard deviations were calculated. 95% Confidence interval was calculated for proportion. The association of congenital anomalies with risk factor was determined with help of chi-square test of proportion. The results were significant with $p < .05$.

Limitation of study

Chromosomal analysis and Viral infections markers (TORCH) were not conducted in this study due to high cost of these tests which further add burden to the patient so only symptomatology of viral infections were asked to determine the risk in particular patient. In this study we also have not compared risk factors in controls so in future we will conduct study to determine the relative risk of each risk factor with congenital anomalies.

RESULTS

During this study period, the total births were 1116. Eight hundred and fifty ultrasounds were performed and 24 congenital abnormalities were recorded. The overall birth prevalence of congenital anomalies was 21.5 per 1000 total births, with individual incidence of neural tube defect being 18.81 per 1000 total births.

In this study mean age was 26.33 ± 12.63 years among women with congenital anomalies. Most of the women (58.33%) were diagnosed at 27 – 32 weeks of gestation. Mean duration of gestation for the diagnosis of these congenital abnormalities was 25.25 ± 6.916 weeks. Lower social status (70.83%,

95% CI 52.64 – 89.02%), and low education status was observed in most of the women (Table 1).

Among the diagnosed abnormalities neural tube defects remained a leading congenital abnormality. Twenty one (87.5%, 95% CI 74.27 – 100.73%) patients were diagnosed with neural tube defects (NTD). And among the NTD 9 patients (42.86%), 95% CI 21.69 – 64.03) had anencephalic fetus, 6 (28.57%, 95% CI 19.25 – 47.89) had hydrocephalus fetus, 2 patients (9.52%, 95% CI 3.03 – 22.07) each of cleft lip / palate and spins bifida, 1 patient (4.76%, 95% CI – 4.35 – 13.87) each had meningocele and holoprosencephalic fetus. These patients either had single abnormality or multiple neural tube defect. One patient (4.76%, 95% CI 4.35 – 13.87) each had hydrops fetalis, musckuloskeletal defect and genitourinary malformation (polycystic kidney) in fetus respectively (Table 2).

Risk factors when inquired in these women it was found that family history of congenital abnormality in first degree relatives was observed in 3 patients (12.5%, 95% CI -.73 -25.73). Maternal medical disorder i.e. diabetes was found in 2 patients (8.33%, 95% CI -2.73 -19.39). Recurrence of disease when observed, 4 patients (16.67%, 95% CI 1.76 – 31.58) had disease in sibling especially neural tube defects. Industrial exposure to pollutant was found in two patients (8.33%, 95% CI -2.73 -19.39). When relationship with husband was studied it was found that 20 patients (83.33%, 95% CI 4.08 – 81.50, p<.0350) were in cousin relationship. And among them 18 (90%, 95% CI 2.1 – 93.4, p < .0682) were first degree cousin, and 2 (10%) were second degree cousin. When maternal and paternal relationship was studied, 17 patients (85%) were in maternal relationship and 3 (15%) were in paternal relationship (95% CI -1 -89.4) p-value < 0.064. Out of 17 maternal relationship, 12 were married to mother's sister's children, 5 patients to mother's brother's children, and 3 patients had marriage with father's sisters children. Viral infection history was not observed in any patient, 3 patients (12.5%, 95% CI -0.73 -25.73) had no risk factor for congenital anomalies (Table 3).

Table 1: *Demographic Characteristics of Patient with Congenital Malformation.*

Variable	*Number*	*Percentage*	*95% CI*
Age years			
< 20	5	20.83	4.58 – 73.08
21 – 25	7	29.17	10.98 – 47.36
26 – 30	5	20.83	4.58 – 37.08
31 – 35	7	29.17	10.98 – 47.36
Mean age: 26.33 ± 12.63			
Duration of Gestation			
< 14 weeks	1	4.17	-3.83 – 12.7
14 – 20 weeks	5	2.083	4.58 – 37.08
21 – 26 weeks	4	16.67	1.76 – 31.58
27 – 32 weeks	14	58.33	38.61 – 78.05
Mean duration: 25.25 ± 6.916			
Parity			
Primigradiva	5	20.83	4.58 – 37.08
$G_2 – G_4$	13	54.17	34.24 – 74.1
$> G_4$	6	25	7.68 – 42.34
Maternal Education			
Uneducated	7	29.17	10.98 – 47.36
Primary	9	37.5	18.13 – 56.87
Secondary	6	25	7.68 – 42.32
Higher education	2	8.33	-2.73 – 19.39
Social Status			
Lower income group	17	70.83	52.64 – 89.02
Middle class	7	29.17	10.98 – 47.36
Upper class	0	0	0

In this study terminations of pregnancy were performed in cases of severe and fatal abnor-

Table 2: *Distribution of Congenital Anomalies.*

Type of Malformation	*Number = 24*	*Percentage*	*95% CI*
Neural Tube Defects	21	87.5	74.27 – 100.75
Acrania	9	42.86	21.69 – 64.03
Hydrocephalus	6	28.57	9.25 – 47.89
Cleft Lip / Plate	2	9.52	-3.03 – 22.07
Spina Bifida	2	9.52	-3.03 – 22.07
Meningocele	1	4.76	-4.35 – 13.87
Hoprosencephaly	1	4.76	-4.35 – 13.87
Cardiovascular malformation	0	0	0
Hydrops Fetalis	1	4.76	-4.35 – 13.87
Musculoskeletal Abnormalities	1	4.76	-4.35 – 13.87
Genitourinary malformation / Polycystic kidneys	1	4.76	-4.35 – 13.87
Digestive System Abnormality	–	–	–

Table 3: *Risk Factors Identified in Congenitally Malformed Fetuses.*

Risk Factor	*Number = 24*	*Percentage*	*95% CI*	*Chi-square Test*	*P-value*
Type of marriage Cousin marriage Non cousin	 20 4	 83.33 16.6	4.089 – 81.50	4.44	.0350
Degree of cousin 1st cousin 2nd cousin	 18 2	 90 10	-2.1 –93.4	3.22	.682
Relationship with cousin Maternal = 17		85	-1 -89.4	3.04	.649
Mother's sister's children Mother's brother's children	12 5				
Paternal = 3		15			
Father's sister's children Father's brother's children	3 0				
Disease in Sibling	4	16.67	1.76 – 31.58		
Family history of congenital abnormality	3	12.5	-0.73 -25.73		
Exposure to Industrial Pollutant	2	8.33	-2.73 -19.39		
Medical disorders	2	8.33	-2.73 -19.39		
Drugs Exposure	0	0	0		
Virus infection	0	0	0		

malities. Nineteen patients suffered from severe to fatal abnormalities. Out of these 21 (87.5%, 95% CI 74.27 – 100.73) were delivered by spontaneous vaginal delivery while 3 (8.33%, 95% CI -2.73 -19.39) de-

livered by cesarean section. While 5 cases of mild congenital abnormal babies were observed for spontaneous onset of normal labor and after delivery were observed in neonatology unit and referred for surgical treatment where required.

When female to male ratio was compared 14 (58.33%, 95% CI 38.61 – 78.05) female fetuses were delivered as compared to 10 (41.67%, 95% CI 21.95 – 61.35 males.

DISCUSSION

Birth defects are a major cause of perinatal and neonatal deaths. Worldwide, the prevalence rates of all genetic birth defects combined range from a high of 82/1,000 live births in low – income regions to a low of 39.7/1,000 live births in high – income regions.[7] These malformations have multi-factorial etiologies and 40% of cases are idiopathic but there is an impression that they are more prevalent in populations with consanguineous marriages.[8]

Despite amazing advances in science and technology, detection of causes of congenital malformation still remain obscure in most of the cases and only few identifiable factors led the scientist to rethink the situation which is global burden. The epidemiological survey of pattern and prevalence of congenital anomalies not only helps in understanding the frequency of malformations in specific area but also contribute to the general knowledge about the predisposing factors and different patterns of birth defects.

The prevalence of congenital malformation in our study was 21.5 per 1000 total births. The results were comparable to study by P. Tootoonchi in which the prevalence in Tehran population was 24.1 per 1000 total live births, although our figure was higher than studies performed in the United Arab Emirates (10.5/1000), China (11.5/1000) (2) and Lebnan (16.5/1000): the reason for large difference being many refer and complicated pregnancies admitted in our hospital.[9,10] The results are also comparable WHO mortality country fact sheet 2006 on Pakistan with deaths of 21/1000 (2%) from congenital anomalies.

The pattern of congenital malformation varies among different region of world. In our study population out of 24 patients 21 (87.5%, 95% CI 74.27 – 100.73) had neural tube defect. The birth prevalence of neural tube defects in this study was 18.81 per 1000 total births. Creasy and Alberman performed a large study in London, a region with a fairly high NTD prevalence at birth, they estimated that the prevalence of NTDs (anencephaly or spina bifida) at 8 weeks' gestation (an estimate of true incidence) was 5.3 per 1,000 population. The concurrent prevalence of NTDs at birth was 2.8 per 1,000. A similar study of spontaneously aborted fetuses in Northern Ireland estimated the prevalence of NTDs at 8 weeks to be 10.8 per 1,000, compared with the birth prevalence of 7.1 per 1,000. The results of study are also high as compared to study by Samina in Peshawer in which forty – six patients with neural tube defects were seen among 3310 deliveries with birth prevalence of 13.90 per 1000 deliveries. The reason for large difference being: exposure of risk factors in this geographic area, variation in prevalence by race, socioeconomic status, time trends and consanguineous marriages.[10,11]

Among the neural tube defects 9 (42.86%) patients had anencephalic fetus followed by 6 (28.57%) hydrocephalus fetuses reflecting the fact that the prevalence of anencephaly was higher as compared to other abnormalities. The results are comparable to study by Ahmad Behroze in which frequency was anencephaly with 22.6 per 10,000 births.[2]

Neural tube defects in contrast to other CNS abnormalities has multifactorial inheritance pattern. Large number of demographic factors like, age, parity, geographical location, residence, dietary deficiencies, time, sex, social class, ethnic group was involved in pathogenesis.

Sex difference clearly exists in the birth prevalence of neural tube defects more girls are affected than boys.[12] In our study the prevalence was higher among females 58.33% (95% CI 38.61 – 78.05) as compared to 41.67% (95% CI 21.95 – 61.35) males.

Age and parity association in prevalence of neural tube is not clearly recognized in most of studies but both monotonic and U – shaped relationships (high prevalence in primipara, low prevalence in second births and again increasing prevalence with increasing parity) have been found, the former occurring mainly in low – risk, the latter in high – risk areas.[13,14] The results are comparable to this study in which the prevalence of birth defects was higher among women 21 – 25 years and again at 31 – 35 years with mean age group for the diagnosis of congenital malformation was 26.33 ± 12.63 years.

The effect of maternal parity on NTD risk is probably stronger than that of maternal age. Studies have shown both a "modest risk in mothers of parity three or more" and an increased risk in primiparous mothers. In this study the prevalence was higher 54.17% (95% CI 34.24 – 74.1) in G_2 – G_4.

Higher rates of NTDs have been reported in populations with lower socioeconomic status.[15] This has been true in Europe, North America, and several other regions. In this study 17 patients (70%, 95% CI 52.64 – 89.02) belong to lower socioeconomic status. The biological significance of socioeconomic status is unknown. Factors such as housing conditions, frequency of infections, and age at marriage, alcohol consumption, and smoking may be partly responsible for the association with neural tube defects. In

addition, deficiency of dietary factors such as the intake of vitamins and folic acid and Zinc, exposure to physical and chemical agents at work, lead and high levels of organic matter in drinking water and environmental pollution may be logical explanations for the different prevalence rates of neural tube defects among lower socioeconomic class.[16]

Once a mother has had a child with an NTD, the recurrence risks are markedly higher than reported population risks of a first NTD – affected pregnancy and risk triples with each subsequent NTD – affected pregnancy. In this study the disease in sibling was observed in 4 patients (16.67%, 95% CI 1.76 – 31.58). The results were comparable to study by P. Tootoonchi, Waqss Jehangir and Firouzeh Nili.[9,17,18]

Relatives of people with a neural tube defect face higher risks of having a child with a neural tube defect than the general population. This risk will depend on the number of predisposing genes they have in common with the patient 50% for first – degree relatives, 25% for second – degree relatives, and 12% for third degree relatives.[19] In this study family history of congenital malformation was observed in 3 patients (12.5%, 95% CI -0.73 -25.73).

Consanguinity of parents has also been found to the risk increase 2 – folds in high prevalence areas. Studies on large families with recurrent NTDs have reported an excess of affected family members on the maternal side compared with the paternal side.[20,21] The results of this study suggest that 20 patients (83.33%), 95% CI 4.08 – 81.50, $p < .0350$) were in cousin relationship. And among them 18 (90%, 95% CI 2.1 – 93.4, $p < .0682$) were first degree cousin, and 2 (10%) were second degree cousin. When maternal and paternal relationship was studied, 17 patients (85%) were in maternal relationship and 3 (15%) were in paternal relationship (95% CI -1 -89.4) $p < 0.064$. Out of 17 maternal relationship, 12 were married to mother's sister's children, 5 patients to mother's brother's children, and 3 patients had marriage with father's sisters children. Thus more maternal than paternal side was involved.

Maternal diabetes has long been considered a risk factor for NTDs, although the association has seldom been tested in multivariable analysis. In one study, after control for other potential confounding factors, the risk associated with diabetes was not significantly elevated.[22] However, hyperinsulinemia has been found to be a significant risk factor in Hispanic women in Texas. In this study the risk of diabetes was higher among congenitally malformed fetus and 2 patients (8.33%, 95% CI -2.73 -19.39) had diabetes when analyzed for risk factors.

A "flu" or "cold" syndrome or a febrile illness in the first trimester has been associated with a two – to threefold increase in risk for NTD. In this study we did not use viral marker to see the association however flue like symptom in early part of pregnancy was observed in none of our patient.

In future large study will be required for genetic association to see family trends in this population and viral marker till that time consanguineous marriages will be considered as major risk factor in this population for increased risk of congenital malformation especially neural tube defect.

It is ***concluded*** that neural tube defects with preponderance of females gender are the major anomalies identified in this area. Consanguineous marriages with first degree cousin and maternal relationship identified as major contributor and risk for congenital anomalies so discouraging intermarriages, and early termination of pregnancies in fatal cases will definitely reduce birth defects in community.

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