Study of consanguinity and its relationship with hereditary anomalies in 2,000 births at PIMS, Islamabad

A Dissertation submitted to the Department of Animal Sciences, Quaid-i-Azam University, Islamabad for the partial fulfillment of the requirements of the degree of

Master of Philosophy
in
Human Genetics

by

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And among His Signs is the creation of the heavens and the earth, and the variations in your languages and your colors; verily in that are Signs for those who know [30:22]

DECLARATION

I hereby declare that I have worked on my thesis "Consanguinity and its relationship with Hereditary Anomalies in 2000 newborns and still born babies" independently and the work presented here is original. This thesis has not been submitted in the current or a similar form to any other University.

Kiran Kazmi
Islamabad, 2012

CERTIFICATE

This is to certify that this dissertation entitled "Consanguinity and its relationship with Hereditary Anomalies in 2000 births at PIMS,Islamabad" submitted by Kiran Kazmi is accepted in its present form by the Department of Animal Sciences, Quaid-i-Azam University Islamabad as satisfying the dissertation requirements for the degree of Master of Philosophy in Human Genetics.

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Dedication

Dedicated to my beloved parents and supervisor

Whom I am forever indebted to.....

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*All glories to **Almighty Allah** ,the most Beneficent, the most Compassionate, Who guides and helps everone to solve all problems from simple to the cosmic range. Who bestwoed me knowledge, intelligence and strength to accoplish this difficult task. I pay all of my praises to the Great Prophet **Hazrat Mohammad (S.A.W.W)** Who exhorted His followers to seek for knowledge from cradle to grave and Who is forever a torch bearer to guidance and knowledge for humanity as a whole.*

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Kiran Kazmi

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Abbreviations	Description
APGAR	Appearance,Pulse, Grimace, Activity, Respiration
CI	Confidence interval
CA	Congenital anomaly
CNS	Central nervous system
CTG	Cardiotocography
CVD	Cardiovascular defect
GIT	Gastro intestinal tract
HA	Hereditary anomaly/anomalies
ICD	International classification of diseases
NTD	Neural tube defect
OMIM	Online Mendelian inheritance in man
OR	ODD Ratio
PIMS	Pakistan institute of medical sciences
SD	Standard deviation

Abstract

A marriage is said to be consanguineous when there is a union between two people who are genetically related. In consanguineous marriages, the chances of a pair of identical unfavorable genes meeting are far greater than in an unrelated marriage. Studies has shown that consanguineous marriages are positively associated with low age at marriage, low educational level of the mother, low occupational status of husband, and rural origin. Offspring as a result of consanguineous marriage are having an increased risk of hereditary anomalies, i.e., about 7.9% of the total births. Due to general lack of knowledge of consanguinity associated morbidity and mortality in the populations of Northern cities of Pakistan, the present epidemiological study was conducted at Pakistan Institute of Medical Sciences, Islamabad, and 2,046 deliveries were recorded. Consanguinity rate was observed to be 51.14% among the total marriages; the frequencies of distantly related and non-related unions were 31.70% and 17.15%, respectively. In total, there were 49.98 % first cousin marriages. Distribution of neonatal parameter like birth weight, head circumference, APGAR score, body length and other physical parameters were found to be insignificant in relation to parental marriage type. There were a total of 163 neonates with some hereditary anomaly. Major anomalies observed in the neonates were central nervous system (29.40%) and musculoskeletal malformations (28.20%), followed by anomalies of urogenital (9.21%), cardiovascular (4.29%), syndromic (6.13%), orofacial (9.20%), and digestive system (3.06%).This study finds high prevalence of congenital anomalies in the multiethnic region of Rawalpindi/Islamabad; it is therefore strongly recommend that genetic counseling services supported by the availability of antenatal/prenatal diagnostic procedures should be developed in all major hospitals across Pakistan. There is an urgent need to inform the public properly about the anticipated deleterious effects of inbreeding in societies where intermarriage is widely practiced.

INTRODUCTION

1.1. Congenital anomalies

In Human Genetics, congenital anomalies and consanguinity are fundamental topics to study. Congenital anomalies are transmissible malformations due to certain reasons, current in a neonate at the instance of birth. Consanguinity, "the marital union between closely related persons", may result in the occurrence of hereditary anomalies. Expression of infrequent recessive inherited genes is interconnected with harmful effects consanguinity (Amudha, 2005). Congenital disorders or congenital anomalies due to consanguinity, are structural changes occurred before or at the instance of birth. Such deformity may be either caused by disarray of prenatal developmental events or by some genetic setback Jones, a well acknowledged scientist also defined such changes during prenatal life in 1988, as undying changes shaped by an inherent anomaly of development (Jones, 1988). A congenital anomaly can also be described as a deformation of physical structure or form generally found at birth or during the very early weeks of life; or defined as more broadly to include functional defect, or any irrevocable condition existing in an infant before birth in which there is sufficient deviation in the usual number, size, shape, position or inherent character of any part of organ, cell or cell constituent to justify its designation as abnormal (Hudings et al., 2006). There is an extensive multiplicity of fetal problems which differ reasonably from inconsequential abnormalities to main structural defects (Pure et al., 2003).

Hereditary anomalies (HA) began to appear as one of the main infancy health problems. The prototype and frequency of hereditary anomalies may differ overtime or on basis of environmental location, thereby reflecting a multifaceted relations of known and unknown inherited and ecologicalissues (Birch et al., 2004). It was reported that congenital anomalies come about in 3% of all infants (EUROCAT, 1997).

Minor anomalies involve non-vital organs with little or no practical effects, by not sourcing any distress in the newborn and usually there is no pressure for their correction particularly in the neonatal period. In contrast major or severe anomalies impair functions. They may even be lethal. Thus, they require instantaneous correction. If not treated early major anomalies could be lethal (Balakumar, 2004; Sing et al., 2006).

1.2. Congenital anomalies as morbidity

The bulk of hereditary anomalies are recessive. There are four discrete types of anomalies which fallout from different sets of reasons.

By and large, anomalies are caused by inherently anomalous processes during the development of the ovum or the sperm, or at some phase in fertilization. These consist of the anomalies that are caused by chromosomal abnormalities, for example having an extra chromosome 21 in Down's syndrome, and single gene defects, for example, campomelic syndrome. The other probable type of disruptions refer to defects that are caused by the interference with the formerly normal developmental process. Disruptions can be caused by teratogens such as drugs, for instance alcohol, thalidomide and warfarin; chemicals, for instance polychlorinated biphenyls (PCBs); viruses, for example

cytomegalovirus (CMV) and rubella; and ionising radiation, for example X-rays. Deformation is the other type of abnormality inculding nonstandard forms, shapes or positions of a part of the body and are consequence of mechanical forces. For example, twins can undergo limb deformation such as clubbed foot due to the crowded uterine space. Fourth kind dysplasia refers to the uncharacteristic organisation of cells into tissue. The causes are usually unclear and as a result often affect several organs simultaneously.

The global frequency of inborn disorders has been predictable at 3.7% but definite statistic figure vary extensively between countries (Park, 2005). For example, it is observed as little as 1.07% in Japan and as elevated as 4.3% in Taiwan (Temtamy et al., 1998). The incidence of congenital anomalies in Pakistan has been reported to be variable. For instance, in Liaqat Hospital, Karachi the frequency of anomalies was 15.8/1,000 in live-births (Shamim et al., 2010). A survey from a General Hospital Karachi located in Liyari stated it to be 11.4/1,000 of total births (Perveen and Tyyab, 2007). At the same time a study from a University Hospital in Karachi, Sindh has stated it to be 16% in still births (Khaskheli et al., 2007). This inconsistency from different centers may be due to an assortment of risk factors related to congenital anomalies such as cause, eithnicity, ecological distribution, consanguinity, social and cultural factors (Shamim et al., 2010).

Just about 66% of major CM have no documented etiology and the majority of them have multiple factors for inheritance (Huding et al., 2006; Harris and James, 1997; Bott et al., 2001). These defects can happen for numerous reasons including, reduced

diet, contaminated contact with chemicals, sepsis and in many other anonymous causes (Lee et al., 2000).

Most offspring who are intuitive with major hereditary anomalies and continue to exist infancy are affected physically, psychologically or in a social context and can be at amplified risk of death due to a variety of health disorders. There are many reasons for HA. Anomolies can be classified as those caused by a single gene; those held to be because of interactios of various factors. usually indeterminate factors; either gnetic or ecological grounds (Kalter et al., 1983).

1.3. Consanguinity

Here in genetical studies,marriages are said to be closeif they share a common blood line, since many couples living in the similar locality possess a shared ancestors. Consanguineous marriages are related to amplified risk for heritable diseases, generally autosomal recessive, but also multifactorial disorders (Kingston, 1989; Schull, 1958, Jaber et al., 1992; Stoltenberg et al., 1997). Khoury and his contemporaries in their study have showed that consanguinity is considerably linked with top rates of still births and HA (Khoury et al., 2000). A description from Kingdom of Saudi Arabia recognized numerous modifable maternal risk factors disturbing infant health (e.g., life phase and baby bearing, little litreacy, joblessness, multiparty), totaling to close marriages (Shawky et al., 2002).

For the reason that most pairs of individuals residing in the same place have a shared predecessor somewhere in their pedigree, as a matter-of-fact the pedegree analysis in such cases does not extend further from parents of great grand parents. Second cousins

add to 1/32 of their genetic constituents from a common predecessor and their childern will be homozygous on average across 1/64 loci (Saggar and Bittles, 2008).

Some anomalies can be inherited, i.e., delivered from parent to infant by genetic coding residing the nucleus. Body cells consist of 46 chromosomes, other than the germ cells.

In a number of cases, one affected parent has an out of order gene which dominates its standard allele, and each child has a 50% probability of inheriting this genetic unit and hence the disorder. This type is dominant inheritance. So each offspring has 25 percent risk, there is one quarter possibility of inheriting un-defective genes; half of a defective and functional gene (Schull,1958; Shull and Neel, 1965, 1972).

From general concerns of health, consanguinity is wider and more multifaceted subject relating major sociological, economical, and demographic influences, differential reproductive behaviors, and pre and post onset of disease and mortality. A systematic approval of the significant non-genetic variables is therefore required in resolving the individual concerns, also of families, and societies in regard of reproductive choices, and in scheming education of genetics and genetic counseling programs for consanguineous couples (Bittles et al., 2002).

1.3.1. Prevalence of consanguineous marriages

The role of consanguinity as a risk factor for congenital anomalies and HA and newborn demise is multifaceted and studies in the past repeatedly failed to account for socio-economic circumstances and other important confounders. Data from Pakistan, in the early 1990s in which 61% of marital unions were between first (50%) and second cousins (11%), enabled fine-tuning for socio-economic and other factors. In opposition to a background infant death ratio of 99 out of 1,000 live births, infants of first cousins had a 42% increased risk of death in the first year and for second cousins the increase was 24% (Grant, 1997). The overall input of consanguinity to infant mortality generally and infant mortality due to congenital anomalies in the UK will inevitably be small since first and second cousin marriages are generally infrequent (Kurinczu, 2010).

Keeping in view the financially viable and safetly reasons approximately all communities are in favour of marriages among relatives (Masood et al., 2011). Although close marriages are more prevailing in Muslim socites, it is associated more to social and chronological factors than to religious concerns (Bittles, 2001). Study into the occurrence and modes of close marriagge in South India verified that the likenessfor close marriages prevails across religious and socioeconomicrestrictions (Sanghvi et al., 1956; Dronamraju and Meera, 1963), conclusion through time were frequent in several other states (Bittles, 1998).

In industrial countries, the charge of consanguineous marriage has decreased to a low balanced level for the reason thatthe existence of diverse racial groups, some of which

carry on the practise conventional social habits. For example immigrants in the England, who are of Pakistani origin, have been observed to have worse consequences as compared to other cultural groups (Bundey et al., 1990). In the Middle East, where the religious conviction of the greater part of the population is Islam, close kin are prevelant (Wong and Frayh, 1989), even high in Egyption population (Hafez et al., 1983), prevelant in Lebanese population (Khlat and Khadr, 1984), Syrians showing prevelance (Prothro and Diab, 1974), Algerian population (Benallegue and Kedji, 1984), Jordanian (Prothro and Diab, 1974), and in Israeli-Arab settlements in Israel within dominant percentages (Jaber et al., 1994).

Pakistan presents a stirring environment to look into the consequence of consanguinity on perinatal mortality. Pakistan Demographic and Health Survey (PDHS), the a unit to assess data on close marriages at national level, observed that more than two fourth of all marital unions were close and about three fourth marriages were between the first cousins (Sathar and Ahmed, 1990).

1.3.2. Consanguinity and congenital anomalies

The proportion of consanguinity connecting any two individuals is reduced four times as themost recent common forefather is different in single step. Consanguinity meansthe sum of matching genetic constituent, which is inherited. For instance, among children of sibs the consanguinity is four folds high as compared to offspring of children of same sibs As a close kinship share a proportion of common set of genes, it is much more probable that related parents will be carriers of an autosomal recessive gene, and as a result there is a chance children are at a higher risk of an autosomal recessive disorder.

The extent to which the risk increases depends on the degree of genetic closeness of relationship between the parents; so the risk is greater in marriages where the parents are close relatives, but for relationships between more distant relatives, such as second cousins, the risk is lower (Kingston, 1989).

Although clinically, the occurrence of an anomaly in a family with first cousin parents suggests autosomal recessive inheritance, it was not clear, what recurrence risks one would expect to find on a large group of people. In their analysis of recurrence, Schull and Neel (1965) focused on the influence of recessive gene inheritance and an expected recurrence risk of 25% for children of consanguineous parents. Different studies report diverging conclusions as to the influence of parental close marriage on rates of birth defects. Methodological issues related to studies of consanguinity and birth defects have been reviewed by Khlat et al. (1991). Given adequate sample sizes, almost all studies that have examined post-natal mortatlity and morbidity, have confirmed that the progeny of consanguineous unions are disadvantages in health terms. Offspring of consanguineous parents are at a two fold greater risk than offspring of non-related parents for autosomal recessive disorders (Fraser et al., 1976). 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 genes conditions (Sawardekar, 2005).

A number of studies have reported a relationship connecting parental consanguinity and higher rates of congenital anomalies (Bromiker et al., 2004). Jaber et al. (1992) reported that offspring born to first cousin parents have 2.4–2.7 times higher risk of having CM or HA as compared to offspring of non-consanguineous parents. In Japan, the incidence of birth defects was 0.7% higher in first cousin progeny (Schull,

1958); however, subsequent investigations have indicated higher levels of malformations. For example, a 26 year study based on the Medical Birth Registry conducted in Norway reported 1.9% higher birth anomalies ratio in Norwegian first cousin couples and 2.4% among Pakistani migrant couples (Stoltenberg et al., 1997), and first cousin progeny had 3.8% excess major malformations in an Arab Community in Israel (Jaber et al., 1992).

Countees of Dufferin Fund Hospital, Hyderabad reported the experiential cases of congenital malformations. From July 2006 to June 2008, identified that overall prevalence of HA was 15.7/1,000 births (Masood et al., 2011). Central nervous system anomalies were the commonest accounting for 51% of total malformations. HA in the newborns of related marriages were significantly more in number than new borns of non-related marriages. Still births and neonatal deaths were regular in the new borns of consanguineous parents (Masood et al., 2011).

The prevalance of closley related marriages was observed in 940 families belonging to multiple socio-economic groups in and around the city of Lahore (Yaqoob et al., 1993). The delevries in these cases from September 1984 to March 1987 were also observed for birth defects. The net prevalence of closely related marriages was 46%. This study concluded that the rate of consanguineous mariages was high, especially in the rural areas (Yaqoob et al., 1993).

Another study was conducted by Hussain (1998) in Karachi to measure the lethel effects associated with closly related marriages and inbreeding while controlling the effects of other potertial conforunders. Data was compiled in 1995 from a sample of 1,021 mothers, comprising a population of multi-ethnic background and living in a

selected squatter settlements in Karachi. The observed odd ratios for perinatal mortality in the progeny of women wedded to their first cousins was 2.0 (95%; CI 1.5-2.6). When parental inbreeding was also taken into account, the adjusted odd ratios for perinatal mortality were raised to higher number further. The study showed that, in spite of variation for important genetic and socio-demographic factors, both closley related marriages and inbreeding remained dominant predictors of perinatal mortality in the progeny (Hussain, 1998).

1.4.3 Impact of Consanguinity

Inbreeding has long been a controversial topic, with special concentrationon undesirable health issues (Perveen and Tyyab, 2007). The undesirable health effects related toclose marriages are caused by the appearance of genes which are recessive in nature. In a broad-spectrum inbreeding is related to loss of biological fecundity (Kanaan et al., 2008). Some investigators are in agreement that fetal growth is compromised (Sibert et al., 1979; Krishan, 1986), while others differ in their findings (Rao and Inbaraj, 1977,1979; Honeyman et al., 1987). Some studies have shown an important effect of consanguineous marriages on reporductive wastage (Al-Awadi et al., 1986).

Further 50 contributory disease loci have been traced for autosomal recessive inheritence which is non syndromic. The majority of which were primarily present in closely related families (OMIM). Visual impairment caused by early onset retinal dystrophies (Rahi et al., 1995; Rogers et al., 1999) and childhood glaucoma (Elder and De Cock, 1993) also have an amplified frequency in closely related kinships, and bilateral retinoblastoma appears to be widespread in Arab countries (Al-Idrissi et al.,

1992). High prevelance of major birth defects has been diagnosed in offsprings of close cousin marriages, especially anomalies with a complex aetiology (Schull et al., 1965; Gatrad et al., 1984; Magnus et al., 1985; Kulkarni et al., 1990; Bundey et al., 1992; Jaber et al., 1992; Stoll et al., 1994; Al-Gazal et al., 1995), with a high probability of reappearance (Stoltenberg et al., 1999). Both minor and harsh mental retardation likewise tends to be more prevelant than before in number (Al-Ansari, 1993; Temtamy et al., 1994; Yaqoob et al., 1995; Durkin et al., 1998; Fernell, 1998). In the United Kingdoms Pakistani population suffers more with, cerebral palsy in offsprings of closely related marriages (Sinha et al., 1997), with an autosomal recessive gene mapped to chromosome 2q24-25 identified in progeny of several consanguineous marriages with multiple anomalies (McHale et al., 1999).

In South India highest rates of consanguineous marriages are usually reported in traditional countryside areas and among the poorest and illetrate groups and it may be strongly favoured among major land-lords as a source of ensuring the conservation of their property. The only communities in which closely relatedmarriages appears to be particularly avoided are those with genesis in North India, and which carry on to follow the customs of that area (Rao and Inbaraj, 1977).

Most frequent neural tube defect, Spina bifida, was significantly more common among progeny of consanguineous marriages in numerous populations including Arabia and India (Mahadevan et al., 2005; Murshid, 2000). Congenital heart problems are among one of the widespread birth defects related to consanguinity, with an overall birth prevalence ranging between 4.9 and 10 per 1,000 live births (Yunis et al., 2006).

Merely a minority of the offspring of consanguineous parents experience lethal consequences of on their health (Schull, 1958; Naden, 1979; Magnus et al., 1985; Khoury et al., 1987; Shami et al., 1989; Rstavuj et al., 1994). Even though the comulative effects of consanguinity on infancy morbidity and mortality may be considerable. For example, a 5-year prospective study by Bundey and Alam (1993) projected that there was a three times increase in postneonatal transience and chronic severe childhood morbidity among children of consanguineous Pakistani marriages than the non-related marriages.

The aim of the present study was to understand various aspects of consanguinity in the mothers delivering at PIMS. Data was collected on an assortment of demographic, socio-economic and biological parameters, in order to determine the distribution and dynamics of consanguinity. One of the prime objectives of the current study was to establish the relationship (if any), between consanguinity and the recurrence of hereditary anomalies among the studied mothers.

Subjects and Methods

2.1 Study location and sampling site

One of the major hospitals of Rawalpindi/ Islamabad, Pakistan Institute of Medical Sciences (PIMS), Islamabad was selected for the study of consanguinity and its relationship with hereditary anomalies. PIMS, is the largest tertiary care hospital situated in the centre of Fedral Capital, Islamabad, and was established in 1985. Being in the capital of Pakistan it serves as a prime care centre for the residents of Islamabad and adjoining cities. Providing the best facilities and doctors of the whole country it includes Children's Hospital, Maternal and Child Health Care Centre (MCH), Quaid-i-Azam Posgraduate Medical College (QPGMC) and College of Medical Technologies. It receives a large influx of patients from twin cities Rawalpindi and Islamabad as well as adjoining towns like Bara Kahu. Ali Pur, Ari Syedan, Bani Gala, Pind Bhagwal, Nuilore, Talhaar and Phulgiran, etc. Additionally, a significant number of subjects from sub-urban Districts, i.e., Chakwal, Murree, Wah Cantt, Gujjar Khan, Peshawar, Mardan, Nowshehra, Swat, etc also visit PIMS.

At PIMS, the Maternal and Child Health Care Centre (MCH) was established with the cooperation of Japanese Government. Highly advanced medical facilities are available at the centre and it is able to meet all kinds of emergency situations. These facilities include diagnostic setup, Pathology Lab, Radiology, Blood Bank, CTG (Cardiotocography) machines, and emergency resucitation equipment.

2.2 Ethical committee and consent approval

Before launching the research for my project, the project was approved by Review Committee of Department of Animal Sciences Quaid-i-Azam University (QAU) Islamabad. The research proposal was further evaluated by the Ethical Review Committee of PIMS. After these initial formalities, the project was approved by the concerned authorities of PIMS (i.e., the Director and incharge of General Ward and Nursery), and I was given the permission to collect data at PIMS. For performa filling, consent was also obtained from the mother/family heads of each neonate.

2.3 Study design

This research was designed as a study of consanguinity and its relationship with hereditary anomalies in 2,000 newborns and still born babies delivered at maternity Hospital in PIMS during 5 month period, from February 2011 to July 2011. Examination of demographic factors like age, gender, caste, and language was done. The research team comprising two researchers from Human Genetics laboratory, Department of Animal Sciences, Quaid-i-Azam University, Islamabad including myself was constituted for data collection. Additionally on duty staff at PIMS like resident doctors and nurses were also part of this team.

2.4 Proforma designing and data collection

Standard questionnaires which deisgned for data collection under the light of study objectives and it contained two parts (Annexure I,II). In first part, variables recorded were about demography, maternal age, parental consanguininty and detailed pregnancy record including previous pregnancy detailed, birth order, type of delivery,

gestational age, history of HA in other offspring. The second part was about neonatal characters including live or still birth sex, body length, birth weight, head circumference and APGAR (Activity, Pulse, Grimace, Appearance and Respiration) score and existence of HA and type of it, which were collected from medical records. Pediatricians examined all newborns who were delivered at PIMS and were then screened for hereditary anomalies. Such type of examination included ultrasound during antenatal period, obvious visible congenital anomaly at birth and anomaly detected by ultrasound or X-Ray after birth. The medical record of new borns with hereditary anomalies were extracted for detailed study. A structured interview was carried out to complete the questionnaire. Data was collected and the questionnaires were filled by interviewing the delivering mother and examining the neonates. Questionnaire part 1 (Annexure I,II) were filled by interviewing the mother and then the current pregnancy part was filled depending on the availability of record file. Questionnaire part 2 was filled after examining the neonate. Physical measurements were obtained on the spot or were recorded from the Discharge slips of neonate and medical record.

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

2.5 Dysmorphology record and clinical ascertainment

I was concered about hereditary anomalous condition in the neonates, so to study the relationship between consanguinity and anomalies, 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. Details of every neonate was then carefully discussed with doctors and after having a thorough investigation the diagnosis of anomaly was carefully recorded.

2.6 Classification of anomalies

With the help of gynecologist and neonatologist at the Children Ward, initial ascertainment of the anomaly was done. 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 Inherintance in Man) which is a comprehensive, authoritative compendium of human genes and genetic phenotypes.

2.7 Data entry, storage and analysis

Before any processing and analysis, data were counter checked and its errors were removed. MS Excel 2007, Graphpad and SPSS were used for data analysis. Simple frequency tables, distribution matrices, Chi-square test, ANOVA and ODD ratio, helped in summarizing results and thus, analyzing the data. In order to find out the significance of variables descriptive analysis was performed to calculate frequencies, distributions and percentages. The Chi-square test was used to compare differences between various data groups. Chi-square is actually a statistical test commonly used to compare observed data with data we would expect to obtain according to a specific hypothesis. The level of significance was 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).

Prevalence, proportion and confidence interval were calculated after the classification of anomalies. 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. Proportion was calculated by dividing number of neonates with a specific anomaly by total number of neonates. To identify the significance level Chi-square test was performed again. For the assesment of statistical significance 95% CI (confidence interval) was also calculated.

2.7.1 Statistical expressions used in the analysis

Percentage = (No. of neonates with a specific anomaly × 100) / No. of total anomalies

Prevalence = (No. of neonates with a specific anomaly × 1,000) / No. of total subjects

Proportion = No. of neonates with a specific anomaly / No. of total anomalies

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

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

Results

3.1. Demographic distribution of neonates

A sum of 2,046 neonates was deliveredat PIMS,in the duration of five months of observational study. Various demographic parameters were selected to study the distribution of neonates. Neonates were classified on the basis of their birth status, maternal origin, maternal language and rural urban status of parents.

Among the 2,046 neonates 1,967 were the survivors i.e., live births, 56 stillbirths and 23 were dead (Fig.3.1.1).

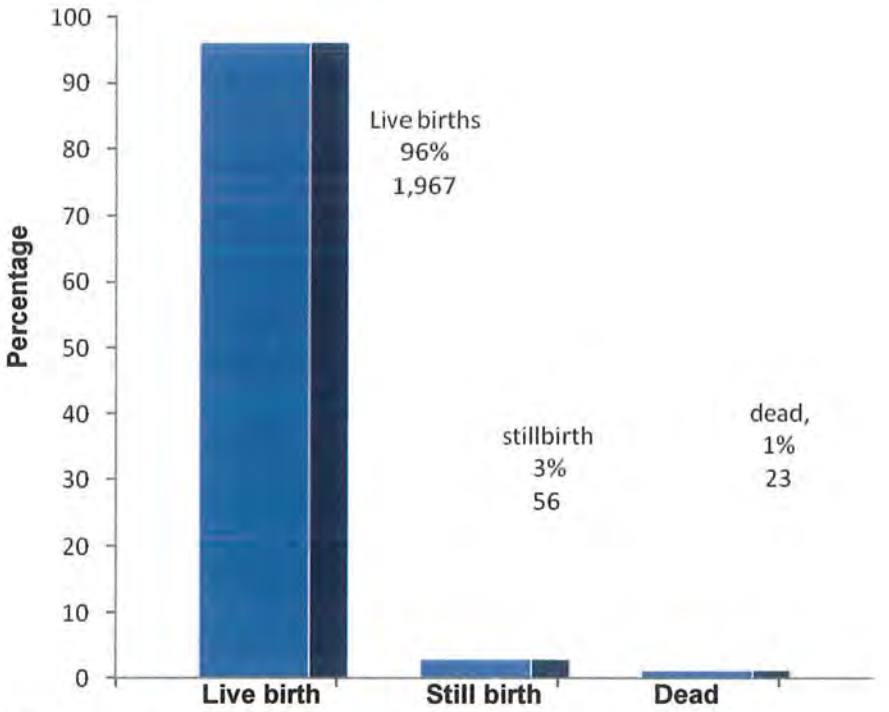

Fig. 3.1.1: Birth outcome of studied neonatal deliveries

The total 2,046 newborns included 1,058 males, 958 females and 30 were of unidentified sex. With respect to pregnancy outcome of the total 2,046 deliveries, 97.34% were singleton and 2.66% were multiple pregnancies (Fig. 3.1.2). Multiple pregnancies comprised of 97.3% births of twins and 8.69% triplets.

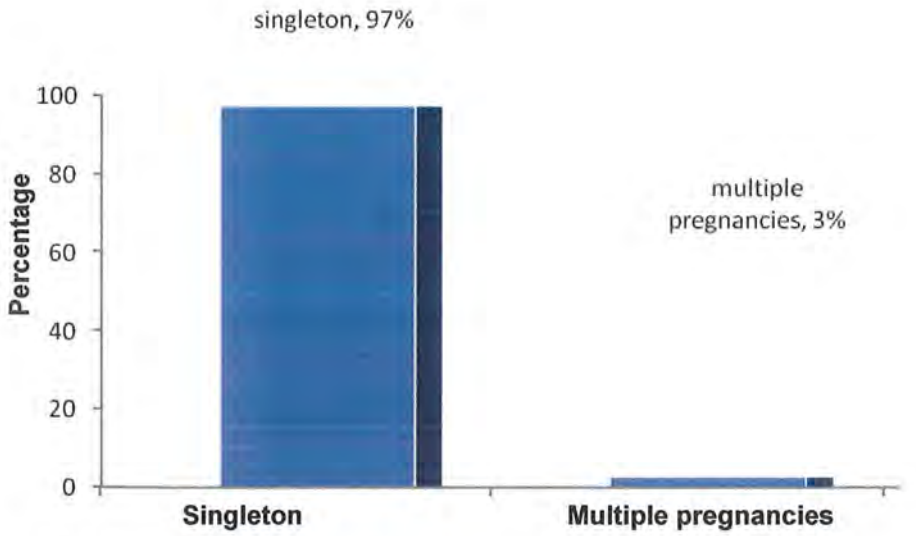

Fig. 3.1.2: Pregnancy outcomes of studied pregnancies.

Parental residence was also observed to categorize neonates (Fig 3.1.3). Federal Capital and Punjab had most number of mothers coming to PIMS for their delivery case. Of the total 1,928 neonates, 43.62% were from Federal Capital, 37.96% were from Punjab, 9.18% from Kashmir, 8.557% from Khyber PakhtoonKhwa (KPK) and 0.675% from Sindh.

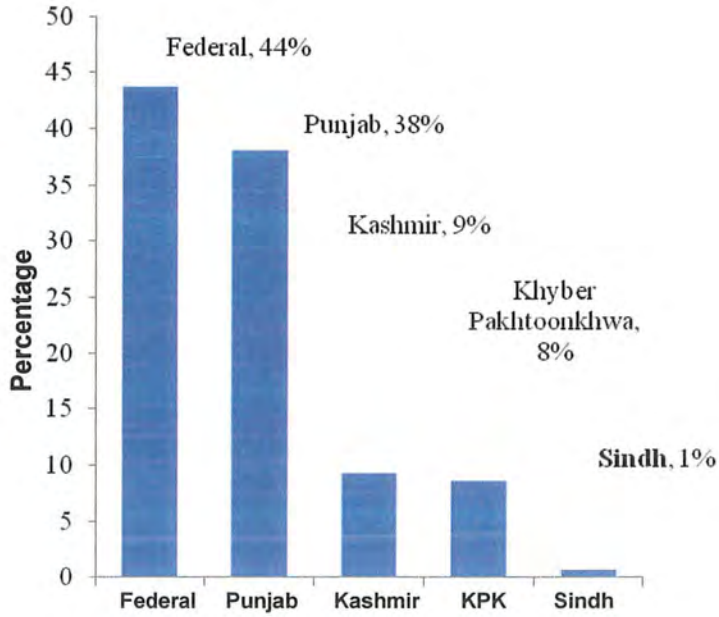

Fig. 3.1.3: Distribution of neonates according to parental residence.

The geographic distribution was studied with respect to parental origin (rural/urban). Most of the subjects delivering at PIMS were from rural areas. 53.46% of the neonates were having rural background from maternal side, whereas 46.25% of the infants were from urban maternal background (Table 3.1.1). Very similar results were observed in paternal records, most of the fathers had rural background, i.e., 53.72%. Fathers from urban background made up 46.28% in the total count (Table 3.1.1).

Table 3.1.1: Distribution of neonates according to rural/urban status of parents.

Province	Father' residence		Mother's residence	
	Rural (%)	Urban (%)	Rural (%)	Urban (%)
Kashmir	60.79	39.21	59.78	40.22
Federal	57.49	42.51	57.53	42.47
KPK	51.87	48.13	53.26	46.74
Punjab	50.82	49.18	50.80	49.20
Sindh	29.17	70.83	43.24	56.76
Others	73.33	26.67	62.50	37.50
Total sample	**53.72**	**46.28**	**53.75**	**46.25**

Distribution of neonates according to maternal linguistics was also studied (Fig. 3.1.4). Punjabi speaking mothers were the most prominent (62.7%). Second and third significant linguistic representatives were Pahari and Pushtoo comprising 14.02% and 11.89% subjects, respectively. The other minor representative language groups were Urdu (1.76%), Potohari(2.35%) and Hindko (5.28%).

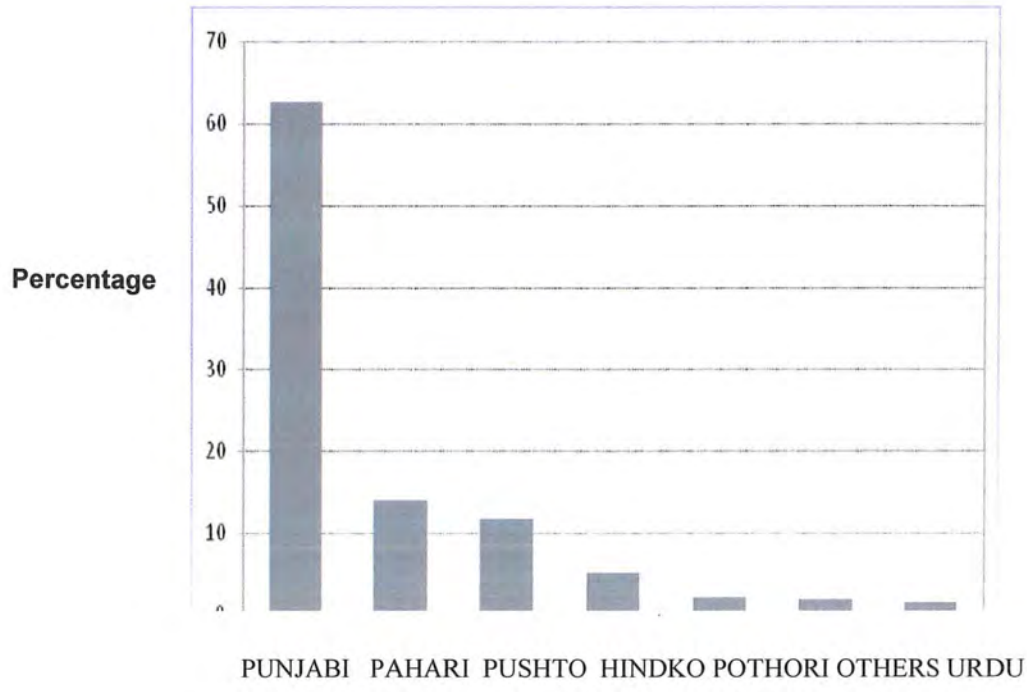

Fig.3.1.4: Distribution of neonates according to maternal language.

3.2 Dysmorphology profile of neonates

Out of 2,046 deliveries, 163 (8.2%) neonates were diagnosed with congenital malformations. These anomalies were categorized according to anatomical systems involved. Distribution of these anomalies is shown in Fig. 3.2.1.

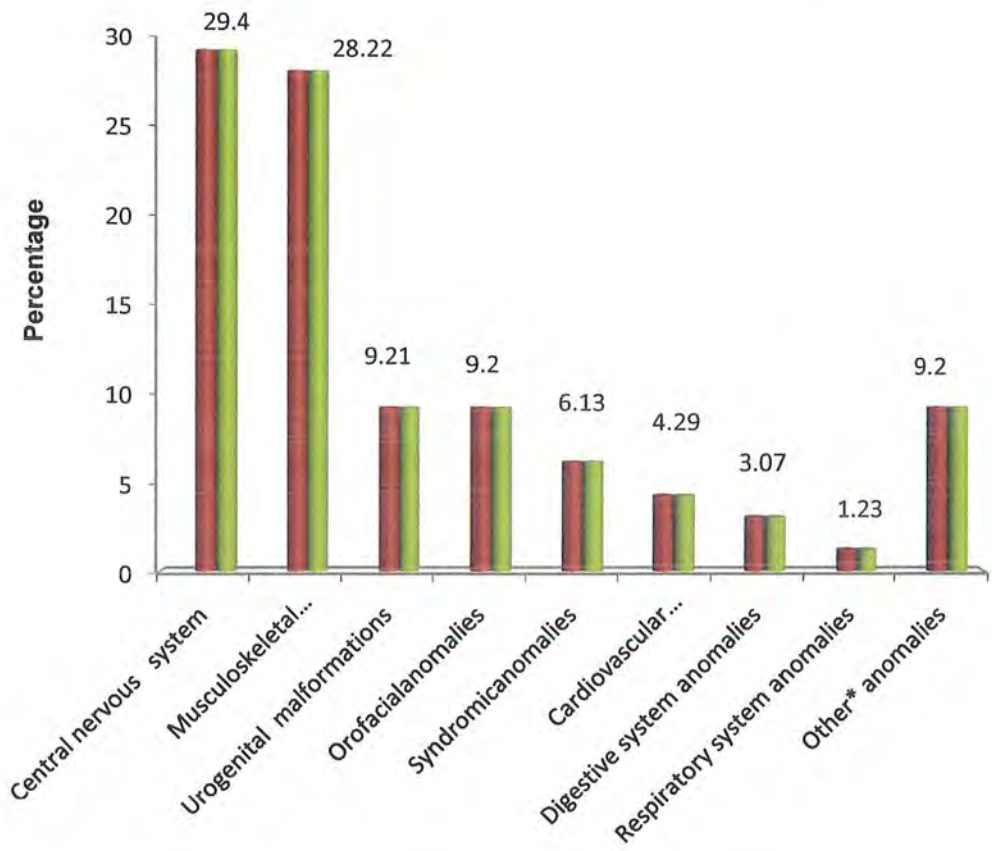

Fig. 3.2.1: Percent distribution of hereditary anomalies

Other* include multiple anomalies.

According to ICD-10 the anomalies were classified and ranked in descending order of frequency which is as follow (Table 3.2.1): central nervous system defects 29.4%, musculoskeletal defects 28.2%. Urogenital system defects 9.21%,orofacial defects 9.20%, cardiovascular anomalies syndromic anomalies 6.13%, 4.3%, respiratory defects 1.22%, and others 9.2%. Multiple congenital anomalies were counted only once by major organ system involved.

Hereditary anomalies of nervous system were most common (48/163) Hereditary anomalies of musculoskeletal were second common anomaly (46/163). Anomalies of urogenital system were third common anomaly types and accounted 15 of the total observed anomalies. In this group the most common anomaly was underdeveloped genitalia. Hereditary anomalies of cardiovascular system, orofacial, digestive and respiratory system were also observed in minor numbers (Table 3.2.1).

Table 3.2.1: Relative proportions of dysmorphologies

Type of anomaly	Total neonates	
	No	%age
Central nervous system	48	29.40
Musculoskeletal malformations	46	28.22
Urogenital malformations	15	9.21
Orofacial anomalies	15	9.20
Syndromic anomalies	10	6.13
Cardiovascular systemanomalies	7	4.29
Digestive system anomalies	5	3.07
Respiratory system anomalies	2	1.23
Other anomalies	15	9.20
Total	163	7.96

Genderwise distribution of neonates with congenital malformations is shown in Table 3.2.2. The total 2,046 newborns included 1,058 males, 958 females and 30 with ambitious gender (included abortion cases also). The male neonates were found to have more congenital malformations than female neonates; out of 1,058 males 96 (9.0%) were observed with congenital malformations and 46 (4.9%) females were diagnosed with congenital malformations of the total 938 females.

Table 3.2.2: Prevalence of congenital malformations by sex of neonates.

Gender	Number of anomalous neonates	Total number of neonates	Percentage
Male	96	1,058	59
Female	60	958	37
Unknown	7	30	4
Total	163	2,046	

Frequency of CA in live birth and still birth showed significant difference which is presented in table 3.2.3. In this study, total still birth/neonatal death among 2,046 neonates were 87. Among live births frequency of CM was 7.55% while in still birth/neonatal death it was 17.24%. A significant statistical difference was found between frequency of CA in still birth and live birth (p=0.0068).

Table 3.2.3 Frequency of congenital malformations in live birth and still birth.

No. of neonates delivered	Total	CM	%age of CM
Live Birth	1,959	148	7.55
Neonatal mortalities/still births	87	15	17.24
All Births	2,046	163	7.966

χ^2=7.314, df = 1; p = 0.0068 (Significant)

3.3 Demographic and maternal risk factors of CA

There are various demographic and maternal factors being associated with CA. Consanguinity,maternal age, education, ethnicity, origin, family structure, pregnancy number, previous birth defect, and previous pregnancy loss, are important predictors of congenital malformations. Some of these factors have been presented in Table 3.3.1 and their association and risk with CA were checked by odd ratio (OR) test.

In this data, 58.3% of the enrolled women were between 25-35 years age range (OR) equal to (0.30), 34.6% women were falling in first category that is <25 years (OR) (0.29), and only 4.1% women were older than 35 years. Maximum number of malformed belonged to mothers in 25-35 years of age group.

Odd ratio for neonates of consanguineous and non-consanguineous mothers were calculated and consanguineous marriages were of (OR) (1.70).

Distribution of anomalies with respect to maternal education was also explored. About 46.4% mothers belonged to the group having at second level or higher education and 43.3% anomalies in neonates are having mothers with primary education and (OR) (1.07 and 1.26.)

The difference between the incidence of hereditary anomalies, babies of primigravida, second gravida and multigravida mothers was not showing any significant association, although both the primigravida and multigravida had significant (OR) equal to (1.16 and 1.04), respectively. Out of 145 women who gave birth to children with CA,

54 were primigravida, 32 were second pregnancy, and 59 were multigravida. The most representative group in data was multigravida (40.6%).

Previous pregnancy loss and previous birth defect were considered as risk factors for congenital malformations. In this study association between previous birth defect and CA showed highly significant risk factor with (OR) (3.25).

Table 3.3.1. Distribution of normal and anomalous neonate and the ODD ratio test statistics with respect to maternal parameters.

Variables	Normal alive	Neonate with CA	Dead/abortions	Total sample	OR
Maternal Age					
<25	631	53	23	688	0.29
25-35	1,056	91	42	1,185	0.30
>35	65	19	6	90	1
Total	1,752	163	71	1,986	
Consanguinity					
Yes	870	106	40	996	1.70
No	795	57	38	910	1
Total	1,665	163	78		
Mother Education					
Illiterate	344	37	21	402	1.28
Primary-Metric	825	69	28	922	1
Intermediate and above	587	53	20	660	1.07
Total	1,756	159	69		

Gravida					
1	519	54	20	20	1.16
2	357	32	9	398	1.00
>3	661	59	39	759	1
	1,537	145	68		
Previous birth defects					
Yes	47	13	3	63	3.25
No	1,764	150	78	1,992	1
Total	1,811	163	81	2,055	
Previous pregnancy status					
Dead/Abortion	378	26	20	424	
Alive	1,419	132	63	1,614	1.34
Total	1,797	158	83	2,038	

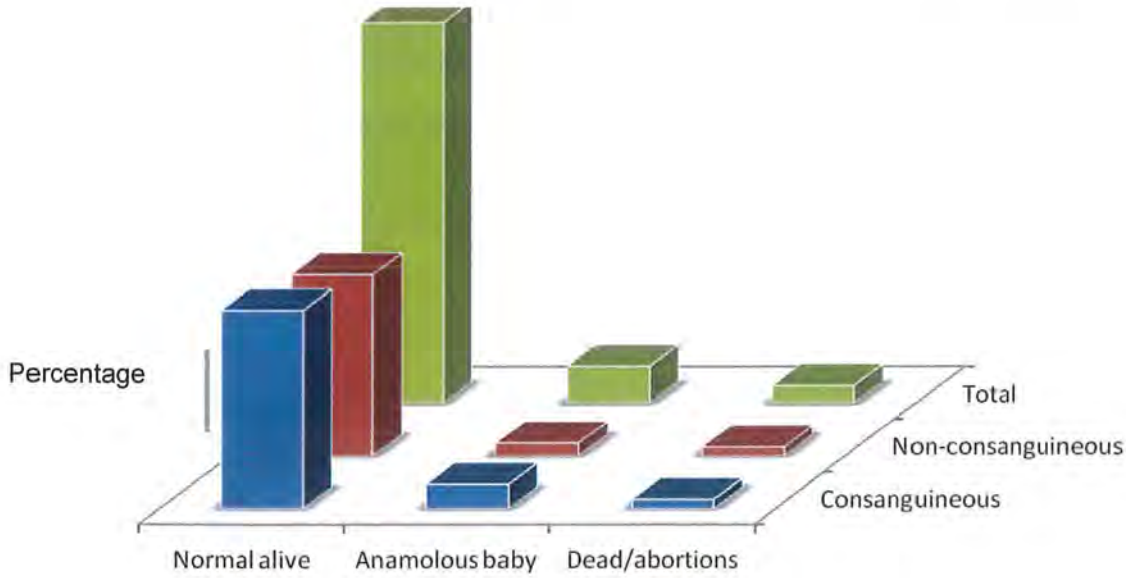

Fig. 3.3.1: Distribution of neonates accordingto consanguinity profile of neonate's parents.

3.3.1 Consanguinity profile of neonate's parents.

Parental consanguinity was the main explanatory variable with respect to congenital malformations. Three broad categories of marriages were defined; close marriages, distantly related marriages, and non related marriages. There were further sub-categories among these three marriage groups. Close marriages included first-cousin (IC), first cousin once removed (1-1/2C) and double first cousin (2-1C). Distantly related marriages include second cousin (2C) second cousin once removed (2-1/2C) and bradari marriages, and in the third category there were non-related marriages (Table 3.3.2).

In accord with the approach adopted by other researcher (Al-awadi et al. 1985; Saugstad, 1977), marriage were also considered as consanguineous when the relationship

between spouses was closer than second-cousin. Different categories of marriages are given in Table 3.3.2. Marriage record of the 1,965 subjects was obtained. About 1% data was missing regarding to marriage type as the subjects did not disclose their relationships. There were 51.15% closely related marriages. The degree of consanguinity among neonate's parents were first-cousin 49.97% (n=982), followed by double first cousin 0.61% (12) and first cousin once removed 0.56% (n=11). Distantly related marriages were calculated to be 17.15%. Among distantly related marriage group, second cousin marriages were 8.19% (n=161) and distantly related marriages 8.95% (n= 176). A total of 31.70% (n= 623) marriages represented the non-related marriages or non-consanguineous group.

Proportion of marriage type by area of living was also explored (Table 3.3.3). The overall rate of consanguineous marriages was 53.5%. The highest rate was found in Punjab 39.4% (n= 426), followed by Federal Capital Islamabad 35.6% (n=385), Khyber Pakhtoonkhwa14.3% (n=155), and Kashmir 9.2% (n=100). One reason for highest rate of consanguinity from Punjab is that in my data set the second most representative group was Punjab after Federal Capital.

Table 3.3.2: Subject's and parental consanguinity.

Marriage Type	No. of neonates	Percentage (%)
Closely related marriages	1,005	51.15
First cousin	982	49.98
Double first cousin	12	0.612
First cousin once removed	11	0.56
Distantly related marriages	337	17.15
Second cousin, second cousin once removed	161	8.19
Distantly related marriages	176	8.96
Non-related marriages	623	31.70
Total	**1,965**	

Table 3.3.3: Distribution of three major types of marital unions.

Province	Total*	Close marriage	Distantly related	Non-related	Total (%age)
Kashmir	208	100	43	65	10.30
Federal	585	385	61	139	29.00
Khyber Pakhtoonkhwa	298	155	47	96	14.77
Punjab	886	426	162	298	43.92
Sindh	40	15	11	14	1.90
Total	2,017	1,081	324	612	

* Data of about 35 subjects was missing as they did not disclose their relationship.

Subject's consanguinity was also compared with parental consanguinity (Table 3.3.4). It was observed that the closely related parents preferred the closely related spouses for their offspring. In distantly related parents, 51.14% subject observed close marriages/cousin marriages, 17.15% distantly related and 31.71% were non-related.

Table 3.3.4: Subject and parental consanguinity record.

Marriage type	Marriages of subject		Marriages of Parents	
	No.	%age	No.	%age
Closely related marriages	1,005	51.14	739	37.61
Distantly related marriages	337	17.15	580	29.52
Non-related marriages	623	31.71	646	32.87
Total	1,965		1,965	

Table 3.3.5 Comparison of subject and parental consanguinity.

Subject's marriages		Parental marriages		
Marriage Type	No.	Close marriages	Distantly related	Non-related
Closely related marriages (51.14%)	1,005	467	318	253
Distantly related marriages (17.15%)	337	100	127	106
Non-related marriages (31.71%)	623	172	135	287
Total	1,965	739	580	646

Neonatal birth status (alive, normal, dead, and anomalous) according to gender has been presented with marriage type in Table 3.3.6. It was observed that in anomalous

male, female and total neonates the percentage was slightly high in close/consanguineous marriage group compared to non- related marriage group. In close marriages the percentage was 9.21%, for distantly related marriages 8.04% and in non-related marriage groups 7.16%. For anomalies distribution, percentage was high for consanguineous marriage groups.

Table 3.3.6 Neonatal outcome (percentage) and marriage pattern.

Neonatal	Close marriages (%age)			Distantly related (%age)			Non- related (%age)		
Outcome	Male	Female	Total	Male	Female	Total	Male	Female	Total
(normal alive single neonate)	34.47	51.10	85.57	38.10	46.50	84.60	43.01	44.02	87.03
Neonate with CM(alive/dead)	2.38	3.20	5.58	5.25	3.15	8.40	2.38	3.15	5.53
Dead/abort excluding CM	1.80	1.80	3.60	2.75	1.31	4.06	3.06	1.36	4.42
Twins/trip/ quadruplets	2.10	0.78	2.90	1.02	0.34	1.36	1.00	0.60	1.60

Physical parameters of neonates were also analyzed (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 observed with respect to the marriage type of mother.

The comparison was done by single factor analysis of variance (ANOVA). The result was statistically non-significant for each of this parameter. 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 almost same in all marriage types (Table 3.3.7).

Table 3.3.7: Physical parameters of neonates and parental marriage types.

Neonatal Parameters	Parental marriages		
	Close marriages	Distantly related marriages	Non-related marriages
Mean Weight (Kg)			
Male	2.82±0.51^{ns}	2.92±0.62 ^{ns}	2.90±0.50^{ns}
Female	2.83±0.55^{ns}	2.82±0.56 ^{ns}	2.84±0.59^{ns}
Total	2.83±0.51^{ns}	2.87±0.59 ^{ns}	2.87±0.55^{ns}
Mean Length (cm)			
Male	48.71±2.69	48.60±2.59	48.91±2.59
Female	48.20±2.68	47.20±2.77	48.28±2.68
Total	48.45±2.69^{ns}	47.89±2.68^{ns}	48.61±2.63^{ns}
Mean OFC (cm)			
Male	33.78±1.86	33.80±1.92	33.70±1.42
Female	33.45±1.91	33.55±1.71	33.60±1.35
Total	33.61±1.88^{ns}	33.68±1.38^{ns}	33.65±1.31^{ns}
APGAR score at 1 min			
Male	6.79±1.24	6.89±1.30	7.10±1.10
Female	6.89±1.04	6.26±1.40	6.66±1.20
Total	6.89±1.04^{ns}	6.26±1.40^{ns}	6.66±1.20^{ns}
APGAR score at 5 min			
Male	8.14±1.11	8.14±1.11	8.14±1.11
Female	8.26±0.89	8.264±0.89	8.26±0.89
Total	8.20±1.14^{ns}	8.20±1.35^{ns}	8.20±1.32^{ns}

^{ns}= Non-significance

Table 3.3.8 illustrates the still births/neonatal death (reproductive loss) associated with marriage pattern. Of the total 70 mortalities, 48 were attributed to close marriages and in distantly related marriages 22 mortalities occurred, whereas, 4 cases of mortality were recorded for non-related marriages. The p value calculated for this data was less than 0.0001 thus interpreting the results significant.

Table 3.3.8: Distribution of deceased and alive neonates in relation to parental marriage type.

Marriage Type	No. of deceased neonates	No. of alive neonates	Total
Closely related marriages	48	856	904
Distantly related marriages	22	409	431
Non- related marriages	4	611	615
Total	74	1,876	1,952

$\chi^2 = 33.27$, df= 2; $p<0.0001$ (significant)(Including all dead neonates, abortions and miscarriage)

Distribution of low birth weight (LBW) neonates is shown in Table 3.3.9. Closely related marriages showed maximum LBW response, whereas the overall result was non-significant with p value 0.7146. Chi-square value of these results turned out to be 0.67.

Table 3.3.9: Distribution of low birth weight neonates, in relation to parental marriage type.

Marriage Type	Total deliveries	Male	Female	Total
Closely related marriage	1,012	136	112	248
Distantly related marriage	349	34	35	69
Non- related marriage	615	58	50	108
Total	1,976	228	197	425

$\chi^2 = 0.67$, df = 2; p = 0.71 (non-significant)

3.3.2 Frequencies of congenital malformations with respect to parental marriage type.

Frequencies of 'congenital malformationsof 163 neonates with respect to parental marriage type were presented in Table 3.3.10. The number of major congenital malformations was 60 (36.80%) in babies of close marriage parents compared with 46 (28.37) and 42 (25.70%) among babies of distantly related and non-related couples, respectively.

Of the 60 (36.80%) anomalies resulting from consanguineous marriages29.44% of nervous system, 28.22% were found to be of musculoskeletal system. 9.21% of urogenital system, 9.20% orofacial,6.13% syndromic,4.29% of cardiac system, 3.06% digestive system, and others (thalasemia, hypothyroidism) 9.20%.

Table 3.3.10: Distribution of various anomalies with respect to mother's marriage type

Type of anomaly	Total neonates		Close marriage		Distantly related		Non-related	
	No.	%age	No.	%age	No.	%age	No.	%age
Central nervous system	48	29.40	19	11.7	8	4.91	21	12.9
Musculoskeletal	46	28.22	22	13.50	9	5.52	12	7.36
Urogenital system	15	9.21	3	1.84	10	6.13	2	1.23
Orofacial	15	9.20	2	1.23	11	6.75	2	1.23
Syndromic cases	10	6.13	4	2.45	4	2.45	2	1.23
Cardiovascular system	7	4.29	7	4.29	0	0	0	0
Digestive system	5	3.07	2	1.23	3	1.84	0	0
Respiratory system	2	1.23	0	0	1	0.61	1	0.61
Others	15	9.20	1	0.61	0	0	2	1.23
Total	163	7.96	60	36.8	46	28.20	42	25.80

Discussion

Consanguinity and its relationship with hereditary anomalies can be explained by associating the maternal parameterswith the neonatal parameters. Consanguinity may be the one of the major cause of heridetry anamolies.Consanguineous marriages are associated with an increased risk of genetic diseases, an increased risk of recessive anomalies is considered to be the main cause of congenital defects among offspring of closely related parents (Vogel and Motulsky, 1997). Parental close marriage increases the chace of homozygosity at any given locus or simultaneous homozygosityat multiple loci may trigger the risk of congenital anomalies among consanguineous children (Bonaiti, 1978; Zlotogora, 1997; Bittles and Neel, 1994).The causes of congenital anomalies could be close marriages or repeated pregnancy due to low contraception (Khaskheli et al., 2007).

Most of the mothers delivering here were from Federal Capital (43.62%) due to locality of the hospital, then Punjab (37.96%) and minor representatives were from Kashmir (AJK) and Khyber Pukhtoonkhwa. Up till now, work done in Pakistan on the prevalence of CA was mostly restricted to major cities like Karachi, Lahore, Hyderabad, Multan and Rawalpindi. From the Federal Capital of Pakistan no study has been reported on the prevalence of HA; only two studies conducted were in Rawalpindi by Hasan et al., (2010), and Masood et al., (2011).In the present study, among the 2,046 neonates 1,967 were live births, 56 stillbirths and 23 were dead.The total 2,046 newborns included 1,058 males, 958 females and 30 were of unidentified sex.

With respect to pregnancy outcome of the total deliveries, 97.34% were singleton and 2.66% were multiple pregnancies. Multiple pregnancies comprised of97.3% births of twins and 8.69% were triplets.The studied subjects were mainly belonging to low and middle socioeconomic status, as the data was collected only from the general ward and not from the private ward. There were 53.72% subjects from rural areas and 46.27% from urban area. One reason for the high proportion of rural representative in this study is that PIMS Hospital is located in the hub of twin cities Rawalpindi/Islamabad and being a public sector hospital, is relatively less expensive. So, people of different ethnic and social backgrounds from the rural areas surrounding the capital attend this hospital.

In general, an accurate assessment of the incidence of congenital abnormalities is difficult because there are the prenatal death of fetuses, abortions and ectopic pregnancies. Thus the term (live- and stillbirths) prevalence was used in the earlier period. However, in recent times the different methods of prenatal diagnoses ha, been used widely for the detection of congenital anomalies and pregnancies are frequently terminated if the fetus is severely affected. Thus, the rate of defects is calculated for offspring including (i)alive neonates, (ii) still births, and (iii) prenatal screened and aborted affected fetuses and the term total (birth and fetal) prevalence of congenital anomalies is used. Limited data is available on the frequency, prototype and neonatal outcomes of inbred anomalies in Pakistan. Though, with the improvements in strategies for neonatal survival in Pakistan the problem of congenital anomalies and related complexities are likely to emerge soon (Robert, 2004). For reasons, consanguineous marriages are preferred in our county and there is a remarkable lack of knowledge of consanguinity associated morbidity and mortality (Perveen and Tayyab, 2007).

Out of 2,046 deliveries, 163 (8.2%) neonates were diagnosed with congenital malformations. These anomalies were categorized according anatomical systems involved. In present study common anomalies were of central nervous system (29.4%) followed bymusculoskeletal malformations(28.2%), followed by anomalies of urogenital (9.2%), cardiovascular (4.29%), syndromic (6.13%). orofacial (9.2%) and digestive system (3.06%).

The patterns of malformations observed in the current study were similar to the reported studies. The most common anomalies witnessed by Jahangir et al., (2009) were central nervous system (38.88%), cleft lip and cleft palate (11.11%), musculoskeletal anomalies (5.55%), ear-face-neck malformations (5.55%) and gastrointestinal tract problems (GIT; 5.55%). According to a data collected by Hasan et al., (1997) high percentage of nervous system anomalies arises due to malnutrition, mainly the folic acid deficiency.

While the differences in the reported birth prevalence rates of HA over time and among different regions, or even within the same region, may be due to multiple factors such as design of the study (Hospital-based or population-based, prospective or retrospective), definitions, classifications and inclusion criteria used, type of surveillance system, etiological heterogeneity of malformations, accuracy of diagnosis, gestational age at which these are included in monitoring reports, and extent to which these terminations are notified (Lechat and Dolk, 1993).

In the present study, total number of anomalies was 163, out of which maleneonates were found to have more congenital malformations i.e. 96 than female

neonates'i.e.60 and 7 were of unknown sex. This finding is consistent with other studies (Masood et al., 2011; Yaqoob et al., 1993).

In present study, HA were seen more often in still births i.e. 17% as compared to live births 7%,with a significant p value (p=0.0068), which is in concordance to study carried out in Iran (Karbasi et al., 2007).

Distribution of normal and anomalous neonate and the ODD ratio test (OR) statistics with respect to maternal parameters was also observed. Most of the affected neonate's mothers (55.26%) in the Pakistan belonged to the age group between 22-28 years (Masood et al., 2011). A nearly similar maternal age group 25-35 years was also found in presentstudy, having 91 out of 163 babies malformed and 42 deceased.

Congenital malformations were seen more commonly in primigravida and multigravida. In multigravida the number of CA was 59 and dead/aborted babies were 49, which is in agreement with the observation by Masood et al., (2011), where more defects were observed in multigravida. Of the mothers who experienced anomalous births, 3% were found to have had a previous anomalous baby.

Consanguinity by itself is not responsible for the incidence of birth defects, but facilitates the progress and expression of homozygous states of harmful recessive genes responsible for such defects. If it is true then consequently, the frequency of birth defects should be more prevalent among children of consanguineous parents ascompared to those of non-consanguineous parents: an observation of many research scholars (Guz et al., 1989, Centerwall, 1966). Previous as well as present study supports this notion (Masood et al., 2011; Nafees et al., 2003; Shami et al., 1997). Jaber et al.,

(1992)reported that offspring delivered by first-cousin parents have 2.4 to 2.7 times higher risk of congenital anomalies.

The present study identifies a high frequency of consanguineous marriages in PakistanConsanguinity rate was 51.14% among total marriages; the frequency of distantly related and non-related marriages was 17.15% and 31.70%, respectively. The overall rate of closely related marital unions in this study was high than rate reported by Yaqoob et al., (1993), and Shami and Zahida, (1982).

The proportion of marriage type by area of living was also explored (Table 3.3.3). The overall rate of closely related marriages was 53.5%. The highest ratio was present in Punjab 39.4% (n= 426), followed by Federal Capital Islamabad 35.6% (n=385), Khyber Pakhtoonkhwa14.3% (n=155), and Kashmir 9.2% (n=100). One reason for highest rate of consanguinity from Punjab is that in my data set the second most representative group was Punjab after Federal Capital.

The frequency of HAbetween the consanguineous parents and non-related parents was analyzed, and the difference was statistically non-significant. The reason for non-significant association might be that in the present study consanguinity was considered when the marital union was closer than second cousin, while in some other studies the investigators considered the marriage as consanguineous even when the relationship between the spouses was distant (Masood et al., 2011).

Physical parameters of neonates were also analyzed (alive, normal, singleton) in relation to marriage type. The comparison was done by single factor analysis of variance (ANOVA). The result was statistically non-significant for each of this parameter. 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 almost same in all marriage typesi.e. close marriages, distantly and non-related marriages.

Reproductive wastage wasnon-significant between closely related and non-related couples. Contrastingly other studies observed the potential effect of consanguineous marriages on mortality (Masood et al., 2011). The divergence from other studies could be due to small sample size.

Weight of neonate is an important pointer of health terms. Data on the association between close marriages and birth parameters have been observed, with a number of studieswhich suggested that babies born to closely related parents are smaller and lighter (Sibert et al., 1979; Kulkarni et al., 1990; Shami et al., 1991), on the other hand many other studies failed to detect a significant difference (Rao and Inbaraj, 1980; Khlat, 1989; Saediand Al-Frayh, 1989). Although the percentage of LBW neonates was high in consanguineous parents as compared to non-consanguineous parents,yet this study like others, could not find the significant relationship between low birth weight (LBW) neonates and consanguinity.

Frequencies of 'congenital malformationsof 163 neonates with respect to parental marriage type were presented. The number of major congenital malformations was 60 (36.80%) in babies of close marriage parents compared with 46 (28.37) and 42 (25.70%) among babies of distantly related and non-related couples, respectively.

Of the 60 (36.80%) anomalies resulting from consanguineous marriages29.44% of nervous system, 28.22% were found to be of musculoskeletal system, 9.21% of

urogenital system, 9.20% orofacial,6.13% syndromic, 4.29% of cardiac system, 3.06% digestive system, and others (thalasemia, hypothyroidism) 9.20%.

However, there were few deficiencies in this study design;some data on weekends and holidays were missing, some performas remained incomplete due to lack of cooperation of medical and paramedical staff, and lack of interest by the subjects.

Future perspectives and Recommendation

It is believed that a large multicentre cohort study can optimally address some issues raised in this review.

i. Specifically, the inclusion of a large number of neonates with CA in a prospective fashion will also enable the evaluation of other important maternal (e.g. spontaneous abortion, Caesarean delivery, toxemia) and perinatal (e.g., preterm birth, gestational period, adjusted birth weight, diseases of prematurity) outcomes.

ii. Most of the major anomalies in our study could be prevented by using methods of pregnancy screening for neural tube defects, screening of older mother for Down syndrome, assessing family history and prenatal diagnosis, and by avoiding the malnutrition.

iii. In Pakistan still there are no well-accepted preventive measures despite the high risk of recurrence of single gene conditions, which indicate the strong need for comprehensive preventive measures for congenital abnormalities in our country.

iv. There have been some efforts to address this issue, such as maternal care during pregnancy and educational programs on congenital anomalies and the consequences of consanguineous marriages.

v. Since consanguineous marriages in our society are integral part of social and cultural life, so in this regard social sciences should be merged with genetics to have better results.

vi. An approach to identify familiesat increased risk and to provide them withgenetic counseling should be followed. This approach can be unusually effective in populations

that favor consanguineous marriage like ours, and development of genetic services is a particularly high priorityfor such communities.

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Maternity and Pregnancy Record

Date_____ Location: PIMS Islamabad / _____ Proforma No. _____

A: Personal data

Name_____ Father name _____
City of residence Married _____ Ph. / Cell: _____
Address _____

Parameter	Subject / Mother	Spouse
Age		
Blood group		
Caste (Major)		
Caste (Minor)		
Mother Tongue		
Origin / birth place		
Rural / Urban		
Education		
Occupation		
Any disease (Congenital / acquired)		

B: Consanguinity and Marriage Record

B1. Subject's marriage record

First Cousin:	M1	Double first cousin	M6
• Brother's children	M2	First cousin once removed	M7
• Sister's children	M3	Second cousin	M8
• Brother's on & sister daughter	M4	Second cousin once removed	M9
• Brother's daughter & sister son	M5	Distantly related (*Bradari*)	M10
		Non-related	M11

Marriage year:_____

Family type:

Single: F1 Nuclear F2 Grand parent & one couple F3 More than one couple F4

Extended family F5

B2: Subject's Parental Relationship

First Cousin:	P1	Double first cousin	P6
• Brother's children	P2	First cousin once removed	P7
• Sister's children	P3	Second cousin	P8
• Brother's on & sister daughter	P4	Second cousin once removed	P9
• Brother's daughter & sister son	P5	Distantly related (*Bradari*)	P10
		Non-related	P11

C: Pregnancy / reproductive record

Gap between marriage and 1st pregnancy ____

Preg. No.	Year	S	D	Pregnancy outcome	Mode of delivery	Duration of pregnancy	Reason	Blood Grp.	Pesticides/ Fertilizers/ Smoking	Remarks
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										

D: Current pregnancy record

	Date / 1st observation	Date / 2nd observation
Blood urea (10-50 mg/dl)		
Creatinin (0.4-1.3 mg/dl)		
Blood sugar (random) 80-160 mg/dl		
Uric acid 2-6		

E: Medical Record of subject – family history

History of any disease / defect

RECORD OF BABY

Date_____ Location_____ S. no_____

Sex: _____

Mother's Name: _____

Father's Name: _____

Date Of Delivery: _____

Time Of Delivery: _____

Length	Weight	OFC	APGAR score	Bgrp	Ear lobe M	Ear lobe B	Respiratory Rate	Heart Rate	Maternal parameter	Diagnosis

D: Current pregnancy record

Date	Getationall Period	Bp	Pulse	Temp	Height	Weight		
						Date	Wk	Kg

Dates	**Renal Function Test(RFT)**		Blood sugar (random) 80-160 mg/dl	**Liver Function Test(LFT)**		
	Blood urea (10-50 mg/dl)	Creatinin (0.4-1.3 mg/dl)		Bilirubin	SGPT	Alkaline Phosphatase

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