THE PREVALENCE OF OVERT CONGENITAL ANOMALIES IN LIVE BIRTHS AT SELECTED HOSPITALS IN KANO METROPOLIS, NIGERIA

BY

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MAY, 2015

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MSC/MED/2068/2009 -2010

A THESIS SUBMITTED TO THE SCHOOL OF POSTGRADUATE STUDIES

AHMADU BELLO UNIVERSITY ZARIA, NIGERIA

IN PARTIAL FULFILMENT FOR THE AWARD OF MASTER OF SCIENCE DEGREE IN HUMAN ANATOMY

DEPARTMENT OF HUMAN ANATOMY

FACULTY OF MEDICINE

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MAY, 2015

DECLARATION

I declare that the work in this thesis entitled "*The Prevalence of Overt Congenital Anomalies in live Births at Selected Hospitals in Kano Metropolis, Nigeria*" has been performed by me in the Department of Human Anatomy Faculty of Medicine under the supervision of Dr. B. Danborno and Dr. W. O. Hamman. The information derived from the literature has been duly acknowledged in the text and the list of references provided. No part of this thesis was previously presented for another degree or diploma at any Institution.

Lofty-John Chukwuemeka Anyanwu _____ _____

Signature Date

CERTIFICATION

This thesis entitled "THE PREVALENCE OF OVERT CONGENITAL ANOMALIES IN LIVE BIRTHS AT SELECTED HOSPITALS IN KANO METROPOLIS, NIGERIA". By Lofty-John Chukwuemaka Anyanwu meets the regulations governing the award of the degree of Master of Science in the Department of Human Anatomy, Ahmadu Bello University, and is approved for its contribution to knowledge and literary presentation.

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DEDICATION

I dedicate this work to my parents Hon. Nze and Lolo J. C. A. Anyanwu for their prayers and blessings. I also dedicate it to my darling wife Mubo and our lovely sons Ebuka and Ebube and our beautiful daughter, Adachi, for their love and support throughout the rigors of the programme.

Above all, my praise and thanks goes to the Almighty God, my ever present help in times of need.

ACKNOWLEDGEMENTS

I am very grateful to my teachers and supervisors Dr. B. Danborno and Dr. W. O. Hamman for their advice and guidance throughout the program.

I am highly indebted to my lecturers (Dr.A.O. Ibegbu, Dr.U.E. Umana, Dr.J.N. Alawa, Dr. Ikyembe), and the Head department of Human Anatomy Prof. S.S. Adebisi. Great teachers, who have taught me much from their wealth of wisdom. I cannot forget to thank the other members of staff and my classmates in the anatomy department, who helped create a conducive environment for me to learn.

I remain ever grateful to Mr. Taiwo Peter of the Dean's office, Faculty of Medicine for his generosity. I acknowledge the assistance and help of Mr.A. Agbon- my classmate. Who was gracious and assisted me in my data entry.

I also am grateful to my colleagues Dr. Osondu Agu, Dr Theophilus Nwobodo, Dr. Nuhu Hassan and all the medical students who assisted me in my data collection. I am much indebted to my colleague Dr. A.M. Mohammad, who helped cover my duty post. I am much indebted to Mal. Sadiq and Mrs Margaret of Aminu Kano Teaching Hospital, Kano, and Mr. Fidelis who assisted me to type this work.

I am immensely grateful to my darling wife Mubo and children (Ebuka, Ebube and Adachi) for their patience, prayers and support throughout this program. I appreciate my parents Hon. Nze and Lolo JC Anyanwu and family for their understanding and blessings. I acknowledge the love and support of my in-laws Elder and Mrs. Benjamin S. Jegede who were always willing to help. May the Lord bless and keep you all – Amen!

ABSTRACT

Congenital malformations also known as birth defects are structural or functional abnormalities of prenatal origin which result from defective embryogenesis or an intrinsic defect in the developmental process. The birth prevalence of Congenital anomalies varies from country to country, and from region to region within the same country. The objective of this study was to determine the prevalence and spectrum of overt congenital anomalies in live born neonates in selected hospitals in the Kano metropolis of North Western Nigeria, as well as the associated maternal, paternal and neonatal risk factors. A descriptive study design was employed. All live born neonates in three major hospitals in Kano metropolis were prospectively studied from April 2013 to December 2013. Detailed family history and clinical data were recorded in a structured questionnaire for each child. Autopsies and cytogenetic analysis were not done. The congenital malformations were classified as multiple or single-system abnormalities. Of the 1456 live births which occurred during the study period, 41 had congenital malformations, giving a prevalence of 28.15 per 1000 live births. Five (12.20 %) had multiple malformations and 36 (87.80 %) had involvement of a single system. Of the neonates with multiple malformations, two had recognized syndromes. The most common systems involved in neonates with isolated single system malformations were the central nervous system (10 cases), the genitourinary system (10 cases), the dermatological system malformation (6 cases) and the gastrointestinal system (5 cases). The consanguinity rate in the study was 17.83 %. Although congenital malformations were more likely to occur in offspring from consanguineous marriages, this was however not statistically significant ($p > 0.05$). Birth weight of the neonates had a significant but negative association with the likelihood of being born with a congenital malformation [OR = 0.38; (95 %

CI 0.20 – 0.71) $p < 0.01$]. Given the high frequency of central nervous system malformations in this study, the findings suggest that neural tube defects account for a significant proportion of congenital anomalies in the Kano metropolis. Also since the study showed that only 5 % of the mothers commenced use of folic acid containing multivitamin supplements in the first month of pregnancy or before conception, emphasis on the primary prevention of congenital malformations by encouraging peri-conceptional use of folic acid containing multivitamin supplements is recommended.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF PLATES

LIST OF ABBREVIATIONS

AFP	Alpha Feto Protein
AIDS	Acquired Immune Deficiency Syndrome
AKTH	Aminu Kano Teaching Hospital
ART	Assisted Reproductive Technology
BMI	Body Mass Index
CI	Confidence Interval
CMV	Cytomegalovirus
CNS	Central Nervous System
CRS	Congenital Rubella Syndrome
CVS	Chorionic Villus Sampling
DNA	Deoxyribonucleic acid
GNP	Gross National Product
hCG	Human Chorionic Gonadotropin
ICSI	Intra-Cytoplasmic Sperm Injection
IVF	In-Vitro Fertilization
LBW	Low Birth Weight
LGA	Local Government Area
MMSH	Murtala Mohammed Specialist Hospital
MRI	Magnetic Resonance Imaging
NTD	Neural Tube Defect
OR	Odds Ratio

PUBS	Percutaneous Umbilical Blood Sampling
SJSH	Sheikh Jidda Specialist Hospital
SPSS	Statistical Program for Social Sciences
U5MR	Under 5 Mortality Rate
VSD	Ventricular Septal Defect
WHO	World Health Organization

CHAPTER ONE

1.0 INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Congenital malformations also known as birth defects are structural or functional abnormalities of prenatal origin which result from defective embryogenesis or an intrinsic defect in the developmental process (Al-Gazali*et al*., 1995; Sawardekar, 2005; Sallout*et al*., 2008; Ochieng*et al*., 2011). The birth prevalence of Congenital anomalies varies from country to country. It is believed that between 2-4% of the live born infants and 15-20% of stillbirth has a significant birth defect (Kingston, 2002; Dastgiri*et al*., 2002; Muga*et al*., 2009). Birth defects are an important cause of childhood morbidity and mortality as it is estimated that one out of every 3 babies that die in the world has a congenital anomaly (Muga*et al*, 2009; Tomatir*et al*., 2009). The World Health Organization (WHO) estimates that some 260,000 deaths worldwide (about 7% of all neonatal deaths) were caused by congenital anomalies in the year 2004 (WHO, 2010). Apart from the direct impact on affected children and their families, congenital anomalies exert an enormous financial burden on a nation's health, educational and social support services (Penchaszadeh, 2002; Sawardekar, 2005). Studies have shown that of the 8million children born yearly worldwide with a birth defect, 3.3 million die before the age of five and 3.2 million of the survivors may be mentally or physically disabled or both (Sallout*et al*., 2008). Congenital anomalies could be broadly divided into 2 major groups i.e. single system abnormalities affecting a single organ system or body part, and multiple abnormalities – which affect more than one organ system or body part (Al-Gazali*et al*., 1995;Sawardekar, 2005; Walden *et al*., 2007). In the etiology of anomalies approximately 10- 20% were shown to be genetic, 10 – 20% environmental, and 60 – 80% was attributed to unknown factors (Sallout*et al*.,

2008;Tomatir*et al*., 2009). It thus follows that birth defects can be categorized as those of a simple genetic origin (monogenic); or those due to interactions between multiple genetic and non – genetic, usually undefined factors (multifactorial); those associated with chromosomal abnormalities; those attributed to discrete environmental factors as the major cause; and all others with no recognized cause (Sawardekar, 2005; Queisser-Luft and Spranger, 2006). Some malformations however are non- genetic such as the amputations caused by amniotic bands after early rupture of the amnion (Kingston, 2002). The underlying causes for most congenital anomalies remain unknown and for most of the commonly seen anomalies, multifactorial inheritance may be the underlying etiology (Queisser-Luft and Spranger, 2006; Sallout*et al*., 2008).

Birth defects can be life threatening, result in long-term disability, and negatively affect individuals, families, health – care systems and societies (WHO, 2010). Furthermore, major social, educational and economic changes will be needed to cater for the child with a birth defect (Miles, 2006). The WHO has indicated the necessity to evaluate the potential burden of congenital anomalies in every country at whatever stage of development with a view tointroducing preventive measures at the appropriate time (Venter *et al*., 1995; WHO,2010). It is believed that up to 60% of congenital anomalies are potentially preventable (Czeizel, 2005; Dastgiri, 2007). Studies in the early 1990s, showed that 400µg of daily folic acid consumption at least one month before conception and through the first trimester of pregnancy is effective in preventing both the occurrence and recurrence of neural tube defects (Ying Wu *et al*., 2007; Ryan-Harshman and Aldoori, 2008 ;Koren*et al*., 2008; Dunlap *et al*., 2011; Czeizel, 2011).

There is a paucity of information on the incidence of congenital anomalies in sub-Saharan Africa (Delport*et al.*, 1995; Venter *et al*., 1995). The WHO has shown that maternal illnesses

like syphilis and rubella are a significant cause of birth defects in low and middle income countries (WHO, 2010). However, as infectious diseases and malnutrition are brought under control, congenital malformations in 3rd – world countries will begin to assume a greater relative importance as a cause of mortality and mobidity among children, as is currently the case in the developed nations (Delport*et al*., 1995). In the developed nations where the overall infant mortality is low, congenital anomalies are a prominent cause of infant mortality, as it has been noted that as many as 25% of neonatal deaths in the European region are due to congenital anomalies (WHO, 2010).

Prenatal ultrasonography (18+weeks gestation) may identity abnormalities requiring emergency neonatal surgery or severe malformations that have a poor prognosis, however a physical examination of all newborns by trained primary health-care practitioners which is feasible in most health systems will allow for the identification of many birth defects including cardiovascular defects which are associated with a high risk of early mortality (WHO, 2010; Kingston, 2002).

It has been shown that only 43% of all congenital abnormalities are diagnosed at birth, and some internal malformations are only recognized at autopsy (McIntosh *et al*., 1954; Al-Gazali*et al*., 1995;Sawardekar, 2005; Muga*et al*., 2009). Diagnosing multiple congenital abnormality syndromes in children can be difficult but it is important to give correct advice about management, prognosis and risk of recurrence (Kingston, 2002).

The impact of congenital anomalies on childhood morbidity and mortality in Africa is largely unknown, however extrapolation from other studies conducted in developing countries indicates that the cumulative incidence of severe congenital anomalies may affect up to 85 per 1000 children by the age of 5 years (Bickler and Rode, 2002). Delport*et al*, (1995) showed that the incidence of congenital anomalies in black South African neonates

born in an urban setting was 11.87 per 1000 live births, a figure which was comparable to those from first world countries (Delport*et al*., 1995). Bakare*et al* reported a prevalence rate of 6.9% for external congenital anomalies amongst neonates in the Ife-ijesha district of south western Nigeria (Bakare*et al*., 2009). This is in agreement with the reported worldwide prevalence of between 1% and 6%for congenital anomalies amongst all infants (Dastgiri*et al*., 2007).

More than 80% of the world population lives in the developing world (this includes Asia, Africa, Latin America and the Caribbean and Eastern Europe), and also about 90% of births in the world occur in these regions (Penchaszadeh, 2002). Extrapolation from other studies conducted in developing countries indicates that the cumulative incidence of severe congenital anomalies may affect up to 85 per 1000 children by the age of 5 years (Bickler and Rode, 2002). Most children who are born with major congenital anomalies and survive infancy are affected physically, mentally, or socially and can be at increased risk of morbidity due to various health disorders (Tomatir*et al*., 2009). At the rural Ahmadu Bello University Teaching Hospital, Malunfashi in northern Nigeria the most frequent (40%) operations performed were for congenital abnormalities (Bickler and Rode, 2002).

Registration of congenital malformations in any population is important in establishing incidence, types and patterns of malformations seen in that population and such information can be useful as an early warning system of new teratogens in the environment, for example by the appearance of new malformations or an increase in previously rare conditions (Mkandawire and Kaunda, 2002).

1.2STATEMENT OF THE PROBLEM

The incidence of congenital anomalies varies among different ethnic groups. However in Africa south of the Sahara, limited information is available on the incidence of congenital anomalies, especially in the black population. Recorded prevalence rates for congenital anomalies in developing countries is underestimated by deficiencies in diagnostic capabilities, lack of reliability of medical records and health statistics, and by underreporting . In response to this concern, this study is proposedto establish the prevalence and spectrum of overt congenital malformations in selected hospitals in Kano metropolis, Northwestern Nigeria.

1.3JUSTIFICATION FOR THE STUDY

It is commonly believed that the incidence of congenital anomalies varies according to the geographical, socio- economic and ethnic characteristics of the population.

Data collected from a congenital anomaly registry may then be used for identifying prevalence trends, for conducting research on potential risk factors, for public health policy development for planning and implementation of services needed by children with malformations and for evaluating the effects of preventive measures and treatment services. It is important to understand the factors which cause congenital malformations in any particular population with a view to proffer preventive measures. This descriptive study is designed to identify such factors in the neonates born with congenital anomalies inKano metropolis.

1.4AIM AND OBJECTIVES OF THE STUDY

1.4.1Aim:-

The aim of the study was to determine the prevalence and spectrum of overt congenital anomalies in live born neonates in selected hospitals in Kano metropolis, Kano State, Nigeria.

1.4.2 Objectives:-

The objectives of the study are to determine the:

(i) prevalence of congenital malformations.

(ii) common types of congenital malformations.

(iii) possible causes of congenital anomalies in the study population.

(iv) effect of maternal age on the prevalence of congenital anomalies.

1.5SIGNIFICANCE OF THE STUDY

The study will provide information on the prevalence of overt congenital anomalies in Kano metropolis. It will also form the basis for further research into the causes of congenital anomalies in northern Nigeria. This will aid the design of intervention programs and policies which will help reduce the incidence of congenital anomalies in the region.

1.6LIMITATION OF THE STUDY

This study is a hospital based study focused on determining the prevalence of overt congenital anomalies in live-born neonates. This would not reflect the true prevalence of congenital anomalies as covert or internal congenital anomalies will not be assessed. Also it

may not reflect the true prevalence of overt congenital anomalies in the community as certain segments of the population may not be able to access the maternity services of the study hospitals due to their geographical location or due to service charges. Also the study is prospective in nature and may not reflect the seasonal trends of some congenital anomalies which may be better shown by a retrospective study of past data.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 EMBRYOLOGY OF CONGENITAL ANOMALIES

Conception occurs following fertilization, the process by which a spermatozoa fuses with an oocyte. This results in the formation of a one celled zygote. The two-cell stage is reached approximately 30 hours after fertilization. Once the zygote has reached the two-cell stage, it undergoes a series of mitotic divisions, increasing its numbers of cells so that at approximately 3 days after fertilization, the 16-cell (morula) stage is reached (Seiden, 2002; Sadler, 2005; Klein and Enders, 2007; Standring, 2008).

Following implantation into the uterus in the first week of conception, the zygote undergoes a series of developmental processes to form the three germ layers (ectoderm, endoderm and mesoderm) by the third week of development (Seiden, 2002; Sadler, 2005; Scanlon and Sanders, 2007; Klein and Enders, 2007; Standring, 2008).

The embryonic period or period of organogenesis, occurs from the third to the eighth weeks of development, and is the time when each of the three germ layers; ectoderm, mesoderm and endoderm, gives rise to a number of specific tissues and organs. By the end of the embryonic period, the main organ systems have been established, rendering the major features of the external body form recognizable by the end of the second month (Hutson and Beasley, 1988; Seiden, 2002; Sadler, 2005).

The period from the beginning of the ninth week to birth is known as the fetal period. It is characterized by maturation of tissues and organs and rapid growth of the body. Growth in

length is particularly striking during the third, fourth and fifth months, while an increase in weight is most striking during the last 2 months of gestation. In general, the length of pregnancy is considered to be 280 days, or 40 weeks after the onset of the last normal menstrual period (Sadler, 2005; Scanlon and Sanders, 2007; Standring; 2008).

Nearly two thirds of all pregnancies are affected by serious abnormalities which lead to spontaneous abortion in the first three to four weeks, often before the pregnancy has been confirmed. It is estimated that half of these losses are a result of chromosomal abnormalities. Almost 10 % of pregnancies abort in the embryonic stage, from inborn errors or gross malformations. The surviving fetuses now represent about 30% of the original number of fertilized ova. These abortions are a natural means of screening embryos for defects, since without this phenomenon; approximately 12% instead of 2% to 4% of infants would have birth defects (Hutson and Beasley, 1988; Sadler, 2005; Scanlon and Sanders, 2007).

There are four main groups of congenital lesions (Hutsen and Beasley, 1988) when viewed from the chronology of fetal development:

i. Inborn errors affecting the fertilized ovum;
ii. Abnormalities occurring at the time of the three germ layers;
iii. Abnormalities of organogenesis; and
iv. Defects in fetal movement or compression.

Genetic or chromosomal anomalies are present from the one-cell stage, and cellular or germ layer defects occur between one and three weeks after conception. These two groups account for the enormous drop in survival during the early weeks of pregnancy. Only a small percentage of conceptuses with these defects survive to birth (Hutson and Beasley, 1988; Sadler, 2005; Scanlon and Sanders, 2007).

Anomalies occurring during embryogenesis may be caused by innate genetic defects or by extrinsic teratogens. It is during this period of development that most surgically correctable malformations arise (Hutsen and Beasley, 1988).

The genetic control of morphogenesis is a multi-tiered hierarchy within which only certain abnormalities are possible and only a few are common. In other words, there is not an infinite array of possible defects, but only a small number of common lesions sufficiently compatible with survival to reach birth (Hutson and Beasley, 1988; Sadler, 2005; Scanlon and Sanders, 2007). The commonest form of abnormal morphogenesis is incomplete development (Fig. 2.1).

This is a normal process in which only the timing is disrupted. Less common is redundant morphogenesis, where the normal process has been partially or completely duplicated. Truly aberrant morphogenesis is rare, because the abnormality will usually lead to death well before birth (Hutsen and Beasley, 1988).

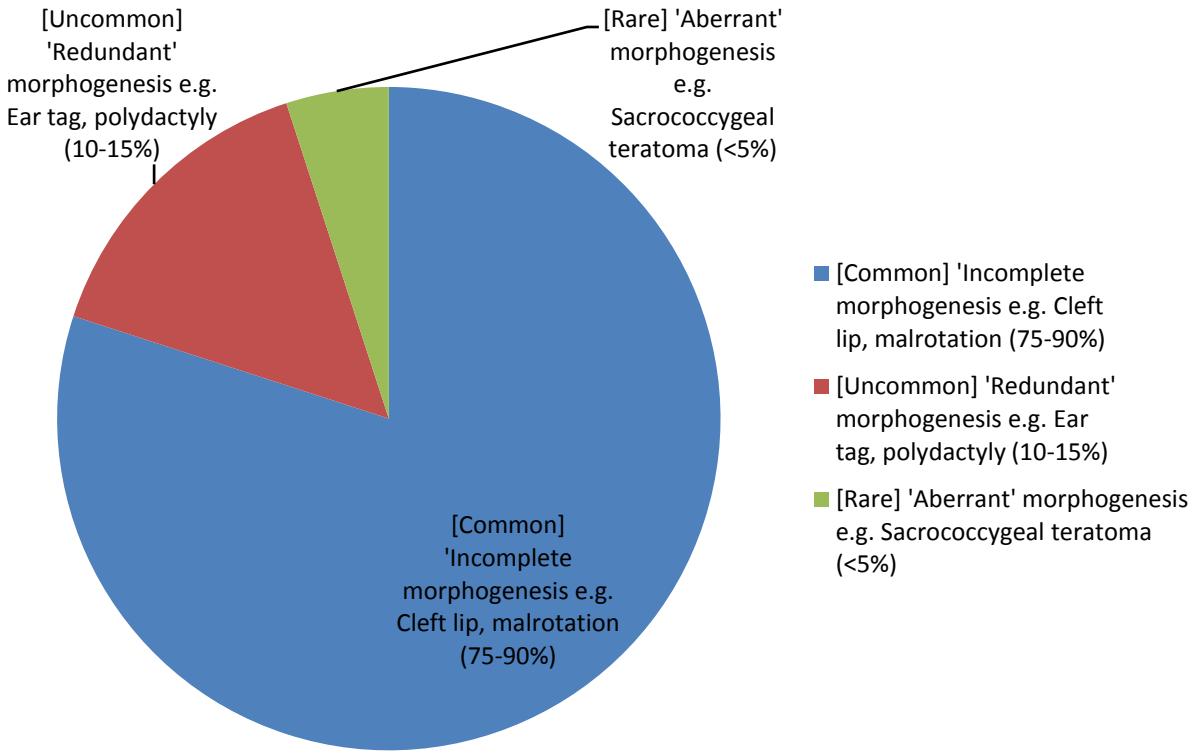

Fig. 2.1: The different types of abnormal morphogenesis that is possible.

Adapted from Hutson and Beasley (1988).

2.2 MECHANISMS OF CAUSATION OF CONGENITAL ANOMALIES

Birth defects can be defined as structural or functional abnormalities, including metabolic disorders, which are present from birth (WHO, 2010). Congenital anomalies, congenital abnormalities, birth defects and congenital malformations are all terms used to describe developmental disorders of the embryo and fetus (Merks*et al*., 2003; Lowry *et al*., 2009; Kurinczuk*et al*., 2010). There is no single agreed definition of what constitutes a congenital anomaly (Merks*et al*., 2003; Kurinczuk*et al*., 2010). It suffices to note however that not all variations in development are anomalies as anatomical variation in humans is common (Kurinczuk*et al*., 2010).

There are four distinct mechanisms of causation of anomalies, which result from different phenomena (Kingston, 2002; Merks*et al*., 2003; Sadler, 2005; Lowry et al., 2009; Iacob*et al*., 2009; Kurinczuk*et al*., 2010).

2.2.1 Phenomena causing congenital anomalies

2.2.1.1 *Malformation*

A malformation is a primary structural defect occurring during the development of an organ or tissue. It is an anomaly of morphogenesis produced through a primary, intrinsic and precocious process of abnormal development (morphogenesis).

The organ does not develop normally (although the tissues are normal) or the differentiation is incomplete. Most malformations have occurred by 8 weeks of gestation. An isolated malformation, such as cleft lip and palate, congenital heart disease or pyloric stenosis, can occur in an otherwise normal child. Although malformations may be mild and have little or no effect on the functioning of the individual, they are always abnormal.

Most single malformations are inherited as polygenic traits with a fairly low risk of recurrence and corrective surgery is often successful.

Multiple malformation syndromes comprise defects in two or more systems and many are associated with mental retardation. The risk of recurrence is determined by the aetiology, which may be chromosomal, teratogenic, due to single gene or unknown.

Most major organs and organ systems are formed during the third to eighth week. This period, which is critical for normal development is called the period of organogenesis. Stem cell populations are establishing each of the organ primordia, and these interactions are sensitive to insult from genetic and environmental influences. Thus this period is when most gross structural birth defects are induced.

2.2.1.2 Disruption

This kind of defect implies that there is destruction of a part of a fetus that had initially developed normally. It can be described as a morphologic defect of an organ, part of an organ or a larger region of the body resulting from the extrinsic breakdown of, or an interference with an originally normal developmental process. Disruption results from destructive events caused by problems of various origin (for instance of vascular, infections, or mechanical origin), commonly affecting several tissue types in a well-demarcated anatomic region; the structural damage does not conform to the boundaries normally imposed by embryonic development.

By definition, disruption is not genetic, although genetic factors may predispose to disruptive events (for example, collagen defects that reduce the resistance of the amnion and make it more vulnerable to spontaneous ruptures). Amniotic band disruption after early rupture of the amnion is a well recognized entity, causing constriction bands that can lead to amputations of digits and limbs. Sometimes more extensive disruptions occur such as facial clefts and central

nervous system defects. Interruption of the blood supply to a developing part from other causes will also cause disruption due to infarction with consequent atresia. Disruptions usually appear in the form of multiple congenital anomalies. The prognosis is determined by the severity of the physical defect.

2.2.1.3 Deformation

This is an abnormal form, shape or position of a part of the body, and result from mechanical forces (Kurinczuk*et al*, 2010). Deformations are due to abnormal intrauterine molding and give rise to deformity of structurally normal parts. They are produced by aberrant mechanical forces that distort otherwise normal structures, resulting from maternal or fetal factors, occurring at any time in gestation.

Deformations affect the musculo-skeletal system and lead to the loss of symmetry, altering the alignment, distorting the configuration and the abnormal position of some structures. They are determined by factors that produce the limitation of the uterine space and/or the inability of the fetus to move, thus giving rise to deformity of structurally normal parts (Iacob*et al*., 2009).

Deformation may occur in fetuses with underlying congenital neuromuscular problems such as spinal muscular atrophy, congenital myotonic dystrophy and spina bifida where positional deformities of the legs and feet may occur. In these disorders, the prognosis is often poor and the risk of recurrence for the underlying disorder may be high.

Oligohydramnios which causes fetal deformation can result from fetal renal agenesis and subsequent absence of urine production by the fetus. Chronic leakage of liquor can also cause oligohydramnios. A normal fetus may also be constrained by uterine abnormalities, breech presentation or multiple pregnancy.

2.2.1.4 Dysplasia

The term dysplasia refers to abnormal histogenesis or function of a specific tissue type, which can be focal or distributed throughout the body, resulting in clinically apparent structural changes, which have a continuing course (Merks*et al*., 2003). It is an abnormal cellular organization or function within a specific organ or tissue type. The causes are generally non-specific and as a consequence often affect several organs simultaneously. Most dysplasias are caused by single gene defects, and include conditions such as skeletal dysplasias and storage disorders from inborn errors of metabolism. Since the tissue itself is intrinsically abnormal, the effect on the clinical symptom may persist or worsen as long as the tissue continues to grow or function. Dysplasia is the mechanism of congenital anomaly in diseases such as Marfan's syndrome and Osteogenesisimperfecta. Monogenic mutations which result in dysplasias are highly recurrent. Unlike the other mechanisms causing birth defects, where the actions causing it are relatively brief in duration, dysplasias may have a progressive effect and can lead to continued deterioration of function.

2.3 CLASSIFICATION OF BIRTH DEFECTS

2.3.1 Taxonomy

Congenital anomalies can be thus classified based on the number of parts of the body or systems involved (Al-Gazali*et al*., 1995; Kingston, 2002; Sawardekar, 2005).

2.3.1.1 *Single System Defects*

These are abnormalities affecting a single organ, organ system, body part, or local region of the body. They constitute the largest group of birth defects. The commonest of these include cleft lip and palate, club feet, pyloric stenosis, congenital dislocation of the hip and congenital heart defects. Each of these defects can also occur frequently as a component of a more generalized multiple abnormality disorder. When these defects occur as isolated abnormalities, the recurrence risk is usually low (Al-Gazali*et al*., 1995; Kingston, 2002; Sawardekar, 2005).

2.3.1.2*Multiple Abnormalities*

Are those abnormalities that affect more than one body site. Multiple anomalies are related to each other in time or space (Hutson and Beasley, 1988;Kingston, 2002). Different parts of the body may be sensitive to a particular extrinsic teratogen or mutation because they are all undergoing rapid cell division and morphogenesis at the same time. Conversely, several organs in the same part of the body may be affected by a field anomaly of morphogenesis. A good example of time-related defects is congenital rubella: the group of organs involved depends on the age of the embryo at infection. The heart, eyes and teeth will be affected at six weeks, while at nine weeks, the ear will be involved, leading to deafness, but the eye is spared (Hutson and Beasley, 1988; Brent, 2004; Gilbert-Barnes, 2010). Multiple abnormalities are further divided into:

i. Syndromes – The term "syndrome" is used to describe a combination of congenital abnormalities which occurs together repeatedly in a consistent pattern due to a single underlying cause. The literal translation of this Greek term is "running together". Syndromes can be further subdivided according to their aetiology into monogenic, chromosomal, environmental, and syndromes of unidentified aetiology (Al-Gazali*et al*., 1995; Kingston, 2002; O'Neil *et al*., 2003).

ii. Associations – These are disorders characterized by the non-random occurrence of several anomalies but which do not constitute a specific syndrome. The malformations in an association occur together more often than expected by chance alone. There is great variation in clinical presentations, with different children having different combinations of the related abnormalities. The names given to recognized malformation associations are often acronyms of the component abnormalities. Hence the **VATER** association consists of **V**ertebral anomalies, **A**nal atresia, **T**racheo-oesophageal fistula and **R**adial defects. The acronym **VACTERL** has been suggested to encompass the additional **C**ardiac, **R**enal and **L**imb defects of this association. **MURCS** association is the name given to the non-random occurrence of **M**ullerian duct aplasia, **R**enal aplasia and **C**ervicothoracic**S**omite dysplasia. In the **CHARGE** association, the related abnormalities include **C**olobomas of the eye, **H**eart defects, choanal**A**tresia, mental **R**etardation, **G**rowths retardation and **E**ar anomalies (Kingston, 2002;O'Neil *et al*., 2003).

iii. Sequences – The term "Sequence" implies that the associated anomalies can be interpreted as a consequence of a primary initiating abnormality, which may be a malformation, a deformation or a disruption. The features of Potter sequence are

classified as a malformation sequence because the initial abnormality is renal agenesis, which gives rise to oligohydramnios and secondary deformation and pulmonary hypoplasia. Other examples are the holoprosencephaly sequence and the sirenomelia sequence. In holoprosencephaly the primary developmental defect is in the forebrain, leading to microcephaly, absent olfactory and optic nerves, and midline defects in facial development, including hypotelorism or cyclopia, midline cleft lip and abnormal development of the nose. In sirenomalia the primary defect affects the caudal axis of the fetus, from which the lower limbs, bladder, genitalia kidneys, hindgut and sacrum develop. Abnormalities of all these structures occur in the sirenomelia sequence (Kingston, 2002; Sadler, 2005).

iv. Complexes – These are anomalies of several different structures, all of which lie together in the same body region during embryonic development. The term developmental field complex has been used to describe abnormalities that occur in adjacent or related structures from defects that affect a particular geographical part of the developing embryo. The underlying aetiology may represent a vascular event, resulting in the defects such as those seen in hemifacialmicrosomia (Goldenhar syndrome) (Al-Gazali*et al*., 1995; Kingston, 2002).

2.3.2 Severity of Anomalies

Congenital anomalies can thus be divided into groups based on their severity:

i. Minor anomalies are those that cause no significant physical or functional effect. They do not impair viability and do not need to be treated (e.g. epicanthal folds, ocular hypotelorism, preauricular tags and pits, low-set ears, simian crease, etc). They can be regarded as normal variants if they affect more than 4% of the population. The presence of two or more minor anomalies indicates an increased likelihood of a major anomaly being present (Kingston, 2002; Merks*et al*., 2003; Czeizel, 2005; Queisser-Luft and Spranger, 2006).

ii. Mild anomalies are those that require medical intervention (such as congenital dislocation of the hip or undescended testis) but life expectancy is good (Czeizel, 2005).

iii. Major anomalies are structural defects of the body and/or organs that impair viability and require intervention (Czeizel, 2005; Queisser-Luft and Spranger, 2006). Major anomalies have an adverse effect on either function or social acceptability of the individual. They can be subdivided into:

   a. Lethal – If the defects (such as anencephaly or hypoplastic left heart syndrome) cause stillbirth (late fetal death) or infant death or pregnancies are terminated after the prenatal diagnosis of fetal defects in more than 50% of cases (Czeizel, 2005; O'Neil *et al*., 2003).
   b. Severe – If the defects (such as cleft lip or congenital pyloric stenosis) without medical intervention cause handicap or death (Czeizel, 2005).

2.4 FREQUENCY OF OCCURRENCE OF CONGENITAL ANOMALIES

2.4.1 Measure of Frequency

By international convention, the frequency of congenital malformations is reported as prevalence, rather than incidence, as congenital malformations are not newly arising diseases in the usual sense, but rather disorders affecting a given population at a given moment in time (the time of birth) (Queisser-Luft and Spranger, 2006).

The lack of agreement about the definition of congenital anomalies means that the comparison of the birth prevalence of anomalies is problematic as inclusion and exclusion criteria vary between different data sources (Sawardeker, 2005; Kurinczurk*et al*., 2010).

The prevalence of congenital abnormalities depends on the spectrum of congenital abnormalities evaluated, the period of study (only at birth or in early neonatal period or prenatal or the whole infant period are included), the completeness of ascertainment, the diagnostic skill of experts, demographic and genetic characteristics of the study population, whether or not figures relating to pregnancies terminated because of fetal congenital anomalies are included, etc (Czeizel, 2005; Kurinczuk*et al*., 2010; Shawky and Sadik, 2011).

The prevalence and types of congenital malformations differ from one country to another and even in the same country from one region to another. It is reported to be as low as 1.07% in Japan and as high as 4.3% in Taiwan, while in the USA, a 2.3% birth prevalence of congenital anomalies has been reported (Tomatir*et al*., 2009; Francine *et al*., 2014).

2.4.2 Risk of Recurrence

The risk of recurrence for a multifactorial disorder within a family is generally low and mainly affects first degree relatives. Risks are mainly increased for first degree relatives, while second degree relatives have a slight increase in risk only, and third degree relatives usually have the same risk as the general population (Kingston, 2002).

The severity of the disorder and the number of affected individuals in the family also affect recurrence risk. Most isolated congenital malformations, however, follow multifactorial inheritance and the risk of recurrence of some of them is depicted in Table 2.1 (Kingston, 2002; Brent, 2004; Howson *et al*., 2008).

2.5 CAUSES AND RISK FACTORS

Congenital malformations can be inherited or acquired. The etiology of congenital malformations is genetic (30-40 %) and environmental (5-10%). Among the genetic etiology, chromosomal abnormality constitutes 6 %, single gene disorders 25 % and multifactorial 20-30%; however, for more than 50% of congenital malformations, the cause is yet to be known (Mkandawire and Kaunda, 2002; Tomatir*et al*., 2009;Tayebi*et al*., 2010; Francine *et al*., 2014).The causes of congenital malformations can thus be broadly divided into 3 categories: unknown, genetic, and environmental (Table 2.2). The cause of a majority of human malformation is unknown. A significant proportion of congenital malformations of unknown cause are likely to have an important genetic component (Brent, 2004).

Malformations with an increased recurrent risk, such as cleft lip and palate, anencephaly, spina bifida, certain congenital heart diseases, pyloric stenosis, hypospadias inguinal hernia, talipesequinovarus, and congenital dislocation of the hip, fit in the category of multifactorial disease as well as in the category of polygenic inherited disease (Kingston, 2002; Brent, 2004). The multifactorial/threshold hypothesis postulates the modulation of a continuum of genetic characteristics by intrinsic and extrinsic (environmental) factors (Brent, 2004; Howson *et al*., 2008).

Table 2.1: Risk of recurrence in siblings for some common congenital malformations

Types of congenital anomaly	Risk (%)
Anencephaly or spina bifida	5*
Congenital heart disease	1-4
Cleft lip and palate	4
Cleft palate alone	2
Renal agenesis	3
Pyloric stenosis	2.10+
Congenital dislocated hip	1-11+
Club foot	3
Hypospadias	10
Cryptorchidism	10
Tracheo-oesophageal fistula	1
Exomphalos	<1

**Risk reduced by periconceptional supplementation with folic acid*
+Risk affected by sex of index case or sibling, or both .Adopted from Kingston (2002).

Table 2.2: Causes of Human congenital malformations

Suspected cause	% of total
Unknown	≈50
Polygenic	
Spontaneous errors of development	
Synergistic interactions of teratogens	
Genetic	30-40
Chromosomal abnormalities (cytogenetic)	
Single gene disorders	
Autosomal and sex-linked inherited genetic disease	
New mutations	
Multifactorial (gene-environment interactions)	
Environmental	5-10
Maternal conditions: alcoholism, diabetes, endocrinopathies, phenylketonuria, smoking and nicotine, starvation, nutritional deficits	4
Infectious agents: rubella, toxoplasmosis, syphilis, herpes simplex, cytomegalovirus, varicella zoster, venezuelan equine encephalitis, parvovirus B19	3
Mechanical problems (deformations): amniotic band constrictions, umbilical constraint, disparity in uterine size and uterine contents	1-2
Chemical, prescription drugs, high-dose ionizing radiation, hyperthermia	<1

Adapted from Brent (2004)

Spontaneous errors of development may account for some of the malformations that occur without apparent abnormalities of the genome or environmental influence. Spontaneous errors of development may indicate that we never achieve our goal of eliminating birth defects because a significant percentage of birth defects are attributable to the statistical probability of errors in the developmental process, similar to the concept of spontaneous mutation (Brent, 2004).

2.5.1 Genetic Causes

Most birth defects originate before conception and are due to abnormalities of the genetic material – chromosomes and genes. Partly genetic birth defects are due to a combination of genes that puts the fetus at risk in the presence of specific fetal environmental factors. Genetic abnormalities can be inherited (found in families) or they can occur as an isolated event in a particular pregnancy. These abnormalities include chromosomal abnormalities, single gene defects and multifactorial disorders caused by the interaction of genes and the environment (Brent, 2004; Howson *et al*., 2008).

2.5.1.1 *Chromosomal Abnormalities*

These are changes in the number or the structure of chromosomes that result in a gain or loss of genetic material. Down syndrome, generally caused by an extra chromosome 21 (trisomy 21) is the most common chromosomal abnormality (Tagliabue *et al*., 2007; Howson *et al*., 2008; Lowry *et al*., 2009; Yashwanth*et al*., 2010). From 1980-2007 there were 2,455 chromosomal anomalies reported in the Alberta region of Canada. Of these, 1,779 (74%) were either Trisomy 13 (Patau Syndrome), Trisomy 18 (Edward Syndrome) or Trisomy 21 (Down Syndrome). Down syndrome was by far the most commonly ascertained chromosome abnormality – 78% of the above mentioned group of Trisomies and 58% of the total number

of chromosome abnormalities reported. Sex chromosome anomalies accounted for approximately 7% of the total (Lowry *et al*., 2009).

The risk of chromosomal aneuploidies, particularly Down syndrome, increases with advancing maternal age. Middle and low-income countries have a high birth prevalence of chromosomal trisomies. The birth prevalence of Down syndrome can be as high as 2 to 3 per 1,000 live births in middle and low income countries because of limited access to family planning, a high percentage of pregnant women of advanced maternal age (35 year or older) and deficient or absent prenatal screening, diagnosis, and associated services (Howson *et al*., 2008; Yashwanth*et al*., 2010).Chromosomal abnormalities are an important cause of congenital abnormalities, emphasizing the need for cytogenetic evaluation (Yashwanth*et al*., 2010).

2.5.1.2 *Single Gene* Defects

These are caused by alterations in gene structure (mutations) that result in abnormal cell functioning. Single gene defects account for an estimated 7.5 percent of all birth defects in industrialized countries (Howson *et al*., 2008).The population frequency of single gene defects depends mainly on their mode of inheritance, mutation rate, and reproductive fitness. Other factors are defined by population features such as migration, inbreeding, assortative mating, and population size (Cruz-Coke and Moreno, 1994).

The birth prevalence of single gene defects in high-income nations is approximately 3.6 per 1,000 live births (Howson *et al*., 2008). In many middle and low income countries, the rate is higher because of the high birth prevalence of common recessive disorders associated with a selective advantage for carriers to the lethal effects of malaria and because of consanguineous

unions that increase the birth prevalence of autosomal recessive disorders (Howson *et al*., 2008; Shawky and Sadik, 2011; Francine *et al*., 2014).

Single gene defects fall into two broad groups: common recessive disorders (>1 in 10,000 to 1,000 live births) and rare single gene defects (Howson *et al*., 2008). Common recessive disorders include four major disorders: the hemoglobin disorders, G6PD deficiency, oculocutaneous albinism in Sub-Saharan Africa, and cystic fibrosis. The birth prevalence of rare single gene defects is generally more than 1 in 10,000. Hemophilia is an example of a rare single gene defect (Howson *et al*., 2008). Several common disorders thought to follow polygenic inheritance (such as congenital heart disease and Hirschsprung's disease) have been found in some individuals and families to be due to single gene defects (Payne *et al*., 1995; Kingston, 2002).

2.5.1.3 *Multifactorial Disorders*

The concept of multifactorial inheritance was proposed by Boris Ephrussi in 1953 and is now broadly accepted (Howson *et al*., 2008). The concept implies that a disease is caused by the interaction of several adverse genetic and environmental factors (Kingston, 2002; Brent, 2004; Howson *et al*., 2008). This mode of inheritance accounts for an estimated 20%-30% of all birth defects, many of which are lethal (Howson *et al*., 2008; Tomatir*et al*., 2009; Tayebi*et al*., 2010).Multifactorial congenital malformations, involve a single organ, system, or limb, and include some congenital heart disease, neural tube defects, cleft lip and/or cleft palate, and talipesequinovarus (Howson *et al*., 2008).

The liability of a population to a particular disease follows a normal distribution curve, most people showing only moderate susceptibility and remaining unaffected. Only when a certain

threshold of liability is exceeded is the disorder manifest. Relatives of an affected person will show a shift in liability, with a greater proportion of them being beyond the threshold. Familial clustery of a particular disorder may therefore occur (Kingston, 2002).

2.5.2 Environmental Causes

Teratogen induced birth defects are common in middle and low-income countries because of poverty, increased frequencies of intrauterine infection, maternal malnutrition including maternal alcohol abuse, lack of environmental protection policies, poorly regulated access to medication, and lack of availability of health care (Penchaszadeh, 2002; Howson *et al*., 2008).

Labeling an agent as teratogenic only indicates that it may have the potential for producing congenital malformations. Labeling an environmental exposure as teratogenic is inappropriate unless one characterizes the exposure with regard to the dose, route of exposure, and the stage of pregnancy when the exposure occurred (Brent, 2004). Some of the common causes of teratogen-induced birth defect are listed in Table 2.3.

A teratogen is defined as any environmental factor that can produce a permanent abnormality in structure or function, restriction of growth, or death of the embryo or fetus (Brent, 2004; Gilbert-Barness, 2010).

Approximately 1 in 250 newborn infants are estimated to have structural defects caused by an environmental exposure and, presumably a larger number of children have growth retardation or functional abnormalities resulting from non genetic causes, i.e. from the effects of teratogens (Gilbert-Barness, 2010).Most teratogens have a confined group of congenital malformations that result after exposure during a critical period of embryonic development. This confined group of malformations is referred to as the syndrome that describes the agent's teratogenic effects (Brent, 2004).

Table 2.3 Examples of teratogens and their possible fetal effects

Teratogen	*Examples of possible teratology*
Drugs	
• AlcoholFetal alcohol syndrome	
• Anticonvulsants	
Phenytoin	Fetal hydantoin syndrome
Sodium valproate	Neural tube defects (NTD)
Carbamazepine	Facial dysmorphology
• Anticoagulants	
Warfarin	Hypoplasia of nose and stippling of epiphyses
• Antibiotics	
Streptomycin	Congenital deafness
• Treatment for acne	
Tetracycline	Dental enamel staining
Isotretinoin	CNS defects, Cardiac defects, Cleft palate
• AntimalarialsChloroquine causes- auditory, vestibular and retinal defects	
Pyrimethamine	
• Anticancer drugs	Intrauterine growth retardation(IUGR)
• Androgens	Clitoral hypertrophy
Environmental chemicals	
• Organic mercurials	Cerebellar defects, polyneuritis
• Organic solvents	Toluene causes- IUGR, CNS Cardiac and Limb defects
Ionizing radiation	Intrauterine growth retardation(IUGR)
Plant teratogen	
• Mushroom(*Amanita phalloides*)	IUGR, hypospadias, deafness, facial dysmorphology
Maternal disorders	
• Epilepsy	
• Diabetes	NTD, fetal macrosomia
• Phenylketonuria	Mental retardation, microcephaly, cardiac defects
• Hyperpyrexia (Hyperthermia)	Mental deficiencies
• Iodine deficiency	Cretinism
Intrauterine infections	
• Rubella	Cataract, heart defects, deafness
• Cytomegalovirus	Microcephaly
• Toxoplasmosis	Hydrocephalus, cerebral calcification
• Herpes simplex	
• Varicella zoster	Congenital varicella syndrome
• Syphilis	Congenital syphilis, premature delivery

Adopted from Kingston (2002)

Teratogenic exposures during prenatal development cause disruptions regardless of the developmental stage or site of action. Most structural defects caused by teratogenic exposures occur during the embryonic period, which is when critical developmental events are taking place and the foundations of organ systems are being established. Table 2.4 shows that different organ systems have different periods of susceptibility to exogenous agents (Brent, 2004; Gilbert-Barness, 2010).

2.5.2.1 Some significant teratogens

2.5.2.1.1Drugs

Identification of drugs that cause fetal malformations is important as they constitute a potentially preventable cause of abnormality. The current accepted policy is to avoid all drugs if possible during pregnancy. Some of the drugs proven to be teratogenic in humans include:

i. Thalidomide

This has been the most dramatic teratogen identified, and an estimated 10,000 babies worldwide were damaged by this drug in the early 1960s before it was withdrawn from the market (Kingston, 2002).This drug result in an increased incidence of deafness, anotia, preaxial limb reduction defects, phocomelia, ventricular septal defects and gastrointestinal atresias. The susceptible period is from the 22^{nd} to the 36^{th} day post-conception.

A 50mg dose of thalidomide administered on the 26^{th} day post-conception has a significant risk of malformation to the embryo. That same dose taken during the 10^{th} week of gestation will not result in congenital malformations.One milligram of thalidomide taken at any time during pregnancy will have no effect on the developing embryo (Brent, 2004).

Table 2.4 Time specificity of action of some human teratogens

Teratogen	Fertilization age (days)	Malformation
Rubella virus	0-60	Cataract or heart diseases more likely
	0->129	Deafness
Thalidomide	21-40	Reduction defect of extremities
Hyperthermia	18-30	Anencephaly
Male hormones (androgens)<90		Clitoral hypertrophy and labialfusion
	>90	Clitoral hypertrophy
Warfarin (Coumadin)	<100	Hypoplasia of nose and stippling of epiphyses
Diethylstilbestrol	>100	Possible mental retardation
	>14	50% vaginal adenosis
	>98	30% vaginal adenosis
	>126	10% vaginal adenosis
Radioiodine therapy	>65-70	Fetal thyroidectomy
Goitrogens and iodides	>180	Fetal goiter
Tetracycline	>120	Dental enamel staining of primary teeth
	>150	Staining of crowns of permanent teeth

Adopted from Gilbert-Barness (2010)

ii. Alcohol (Ethanol)

Alcohol is currently the most common teratogen, and studies suggest that between 1 in 300 and 1 in 1000 infants are affected (Kingston, 2002). Fetal alcohol syndrome (FAS) consists of microcephaly, mental retardation, growth retardation, typical facial dysmorphogenesis, abnormal ears, small palpebral fissures (Kingston, 2002; Brent, 2004; Gilbert-Barness, 2010). In the newborn period, exposed infants may have tremulousness due to withdrawal (Thomas and Riley, 1998; Kingston, 2002).

The full picture of FAS usually occurs in babies born to alcoholic mothers, or those who drink regularly or binge-drink. However, no amount of alcohol is safe. Structural and functional impairments occur in up to one half of infants born to alcoholic women who drink heavily. Functional and growth disturbances without other morphologic changes can occur in infants whose mothers drink moderately (1 to2 oz of absolute ethanol daily). No malformations have been documented in infants of mothers who drink <1 oz of absolute ethanol daily. However, the risk of spontaneous abortion is twice the normal rate in women who drink 1 oz (28.4ml) of absolute ethanol twice a week (First Nations, Inuit and Metis Health Committee, 2002; Gilber-Barness, 2010).

iii. Antiepileptic drugs

About 1% of pregnant women have a seizure disorder and all anticonvulsants are potentially teratogenic (Kingston, 2002; Brent, 2004; Gilbert-Barness, 2010). There is a two to three-fold increase in the incidence of congenital abnormalities in infants of mothers treated with anticonvulsants during pregnancy (Kingston, 2002). An increased risk of neural tube defect has been documented with sodium valproate and carbamazepine therapy, and other anomalies such as facial dysmorphology and autism have also been reported (Kingston, 2002; Brent,

2004). Phenytoin therapy in the first trimester poses a small risk of development of the "fetal hydantoin syndrome". This consists of developmental delay or frank mental deficiency, dysmorphic craniofacial features, and hypoplasia of the distal phalanges (Gilbert-Barness, 2010).

Periconceptional supplementation with folic acid is advised, as anticonvulsant therapy during pregnancy may be essential to prevent the risks of grand mal seizures or status epilepticus. Whenever possible, monotherapy using the lowest effective therapeutic dose should be employed (Kingston, 2002).

2.5.2.1.2Maternal disorders

Several maternal disorders have been identified in which the risk of fetal malformations is increased. These conditions include:

i. Diabetes mellitus

The risk of congenital malformation in the pregnancies of diabetic women is two to three times higher than that in the general population but may be lowered by good diabetic control before conception and during the early part of pregnancy (Kingston, 2002; Howson *et al*., 2008).

Defects of the heart, central nervous system (CNS), kidneys, and skeleton predominate. Transposition of the great vessels, ventricular septal defect (VSD), and dextrocardia occur with greatest frequency. Anencephaly, spina bifida, and hydrocephaly are the major CNS malformations. Rare malformations include situsinversus and caudal dysplasia, vertebral and renal anomalies, imperforate anus and radius aplasia. Brain development is often impaired and anomalies include those observed in the VACTERL association. Minor physical abnormalities include anteverted nares, flattened nasal bridge, excess skin folds on the neck, and tapered fingers with hyperconvex nail (Brent, 2004; Gilbert-Barness, 2010). Caudal

dysplasia syndrome, with varying degrees of sacral agenesis, is sometimes associated with defects of the palate and branchial arches and occurs in 1% of diabetic offsprings (Gilbert-Barness, 2010).

Although hyperglycemia may be a key in the pathogenesis of diabetic embryopathy, other factors contained in diabetic serum may also contribute to the embryopathy (Cundy *et al*., 2007; Gilbert-Barness, 2010).

ii. Obesity

Obesity (BMI ≥ 30) affects almost one-third of pregnant women in the USA and causes many complications during pregnancy including fetal macrosomia, maternal hypertension, pre-eclampsia, gestational diabetes mellitus, and fetal death (Gilbert-Barness, 2010; Mills *et al*., 2010).

In addition, many investigators have reported an increased risk of birth defects such as congenital heart defects, anorectal atresia, hypospadias, limb reduction defects, diaphragmatic hernia, omphalocoele, neural tube defects, orofacial clefts, cystic kidney and pes equinovarus in babies of mothers diagnosed with pre-pregnancy obesity (Watkins *et al*., 2003; Waller *et al*., 2007; Rasmussen *et al*., 2008; Blomberg and Kallen, 2010; Mills *et al*., 2010). The mechanisms underlying these associations are not yet understood, but may be related to the wide range of abnormalities obesity produces in carbohydrate and lipid metabolism, insulin resistance, and adipocyte hormone action (Waller *et al*., 2007; Mills *et al*., 2010).

iii. Iodine deficiency

This is the cause of endemic goiter and cretinism due to deficiency or of insufficient availability of thyroxine at the feto-placental level. Congenital hypothyroidism associated

with deafness and mental retardation is found in the offspring of hypothyroid mothers. Fetal iodine deficiency results in cretinism characterized by mental retardation, spastic diplegia, deafness, and strabismus (Brent, 2004; Gilbert-Barness, 2010).

Iodine deficiency, common in inland, arid, and mountain regions, causes spontaneous abortion, perinatal death, and childhood intellectual, motor, and auditory disabilities i.e. cretinism (Howson *et al*., 2008).

iv. Hyperthermia

This is defined as a body temperature of at least 38.9^0C and is an antimitotic teratogen after exposure between weeks 4 and 14 of pregnancy (Gilbert-Barness, 2010). The threshold of effect in many species begins at about 1.5^0C over normal core body temperature. In general, higher temperatures and/or longer durations are most likely to cause abortions, while lower elevations cause embryonic death and resorption, or abnormalities of embryogenesis, if exposure occurs at critical stages of development (Graham *et al*., 1998).

Mild exposures during the pre-implantation period and more severe exposures during embryonic and fetal development often result in prenatal death and abortion.

It can also result in a wide range of structural and functional defects such as seen in infants exposed to maternal hyperthermia at 7 to 16 weeks of gestation who have hypotonia, neurogenic arthrogryposis or CNS dysgenesis (Graham *et al*., 1998; Edwards, 2006; Gilbert-Barness, 2010).

In humans, an elevated core body temperature can occur with fever caused by viral or bacterial illness, extreme exercise, saunas, hot tubs, heated beds, electric blankets, etc (Morett*iet al*., 2005; Agopian*et al*., 2013).

A fever can be of varying duration, as with exposure to other potential teratogens. Serious illnesses accompanied by fever (e.g. malaria) may be associated with poor nutritional intake

by the mother, which itself may be associated with poor pregnancy outcome. The infectious agent itself may be teratogenic (such as rubella, varicella or cytomegalovirus) (Morett*i et al*., 2005). The central nervous system (CNS) is most at risk of damage from hyperthermia, probably because it cannot compensate for the loss of prospective neurons by additional divisions by the surviving neuroblasts and it remains at risk at stages throughout pre and postnatal life (Edwards, 2006).

In experimental animals the most common defects are of the neural tube, micropthalmia, cataract and micrencephaly, with associated functional and behavioural problems. Defects of craniofacial development including clefts, the axial and appendicular skeleton, the body wall, teeth, and heart are also commonly found. Nearly all these defects have been found in human epidemiological studies following maternal fever or hyperthermia during pregnancy (Graham *et al*., 1998; Morett*i et al*., 2005; Edwards, 2006; Gilbert-Barness, 2010; Agopian*et al*., 2013).

v. Conception by Assisted Reproductive Technologies

In addition to the problems inherent in multiple pregnancies, children conceived by assisted reproductive technologies (ART) have increased risks for low-birth weight (LBW) and preterm delivery (Gilbert-Barness, 2010).

Consistent evidence from individual studies, including registry-based cohort studies and meta-analyses, has linked assisted conception involving In Vitro Fertilization (IVF) or Intra-Cytoplasmic Sperm Injection (ICSI) with an increased risk of birth defects, with the associations between the use of these techniques and birth defects appearing to be stronger for singleton births than for multiple births (Wennerholm*et al*., 2000; Hindryckx*et al*., 2010; Davies *et al*., 2012; Hansen *et al*., 2012; Hansen *et al*., 2013). The extent to which birth defects after infertility treatment may be explained by underlying parental factors is uncertain as data on birth defects are inconclusive because most available studies, which generally are

observational and based on small sample sizes, do not have the power to control for confounding factors, such as parental age, causes of infertility, the multiple technical variables of the ART regimens, and the causal heterogeneity of infertility (Gilbert-Barness, 2010; Davies *et al*., 2012).

According to Hindryckx*et al*. (2010), the theoretical concerns about the safety and potential risks of ICSI to the offspring can be categorized broadly into the following groups:

- the risks of using sperm that potentially carry genetic abnormalities,
- the risks of using sperm with structural defects,
- the potential for mechanical and biochemical damage and of introducing foreign, material into the oocyte,
- the risks associated with bypassing the process of natural selection by injecting a single spermatozoon into the cytoplasm of the oocyte,
- the risk of transmitting sub-fertility to the offspring.

Although the effects of confounding factors cannot be ruled out, recent well-designed, multicentric, long-term follow up studies indicate that the major malformation rate is increased after ICSI when compared to natural conception but not compared to IVF (Hindryckx*et al*., 2010). Davies *et al*. (2012) however have shown that after multivariate adjustment, the association between IVF and the risk of any birth defect was no longer significant, whereas the increased risk of any birth defect associated with ICSI remained significant.

2.5.2.1.3 Intrauterine infections

Various intrauterine infections are known to cause congenital malformations in the fetus. Maternal infection early in gestation may cause structural abnormalities of the central nervous system, resulting in neurological abnormalities, visual impairment and deafness, in

addition to other malformations, such as congenital heart disease. When maternal infection occurs in late pregnancy the risk that the infective agent will cross the placenta is higher, and the newborn infant may present with signs of active infection, including hepatitis, thrombocytopenia, haemolyticanaemia and pneumonitis (Kingston, 2002).

The lethal or developmental effects of infectious agents are the result of mitotic inhibition, direct cytotoxic effects, or a vascular disruptive event on the embryo or fetus.

However, a repair process may result in scarring or calcification, which causes further damage by interfering with histogenesis (Gilbert-Barness, 2010).

Some teratogenic intrauterine infections include:

i. Toxoplasmosis

Primary maternal infection with *Toxoplasma gondii* occurs in 1 per 1,000 pregnancies in the United States, with infection being disseminated through the placenta to the offspring in 40% of cases (Gilbert-Barness, 2010). Malformations do not occur; however, hydrocephalus and microcephaly result from chronic destructive meningoencephalitis. Chorioretinitis may progress to scarring and loss of vision. Hydrocephalus and cerebral calcifications, hepatitis, and lymphadenopathy are the most common complications in infants infected prenatally (Brent, 2004; Gilbert-Barness, 2010).

ii. Rubella

Approximately 25 percent of infants born to mothers who contract rubella in the first trimester of pregnancy have congenital rubella syndrome (CRS) (Howson *et al*., 2008).

Rubella embryopathy is well recognized, and may manifest with deafness, congenital heart disease, microcephaly, cataracts or mental retardation in affected children (Kingston, 2002; Brent, 2004). The aim of vaccination programs against rubella virus during childhood is to reduce the number of non-immune girls reaching childbearing age. In countries with

successful rubella immunization programs, CRS has been largely eliminated. In the remaining 50 percent of countries, more than 100,000 infants are born with CRS annually (Kingston, 2002; Howson *et al*., 2008).

iii. Cytomegalovirus (CMV)

This is a common infection and 5-6% of pregnant women may become infected. Only 3% of newborn infants however have evidence of CMV infection, and no more than 5% of these develop subsequent problems. Infections with CMV do not always confer natural immunity, and occasionally more than one sibling has been affected by intrauterine infection (Kingston, 2002). Affected infants may have retinopathy, CNS calcification, microcephaly or mental retardation (Brent, 2004). There is no vaccine against this virus currently available.

iv. Herpes simplex

Herpes simplex infection in the newborn infant is generally acquired at the time of birth, but infection early in pregnancy is probably associated with an increased risk of abortion, late fetal death, prematurity and structural abnormalities of the central nervous system or hepatitis (Kingston, 2002; Brent, 2004).

2.5.2.1.4 Ionizing radiation

Ionizing radiation can injure the developing embryo due to cell death or chromosome injury. The most critical exposure period is 8-15 weeks after fertilization (Gilbert-Barness, 2010).

There is no proof that human congenital malformations have been caused by diagnostic levels of radiation. If the threshold of the radiation is greater than 20rad (0.2Gy), it can increase the risk for some fetal effects such as microcephaly or growth retardation, but the threshold for mental retardation is higher (Brent, 2004; Gilbert-Barness, 2010).

Before implantation, the mammalian embryo is insensitive to the teratogenic and growth-retarding effects of radiation and sensitive to the lethal effects. Permanent growth retardation is more severe after mid-gestation radiation (Gilbert-Barness, 2010). Because of its extended periods of organogenesis and histogenesis, the central nervous system (CNS) retains the greatest sensitivity of all organ systems to the detrimental effects of radiation through the later fetal stages (Brent, 2004; Gilbert-Barness, 2010).

2.5.3 Unknown Causes of Birth Defects

As noted in Table 2.2, a specific cause cannot be designated in about 50 percent of all children born with birth defects. Some of these birth defects may be due to new autosomal dominant mutations, submicroscopic chromosome deletions, uniparental disomy or result from an interaction of multiple environmental and genetic factors (Brent, 2004; Howson *et al*., 2008; Rychtarikova*et al*., 2013).

2.5.4 Non Specific Risk Factors for Congenital Abnormalities

Disease prevention has been hampered by a lack of information about modifiable risk factors for abnormalities of fetal development. According to the literature, a number of non-specific risk factors have been identified, and these characteristics need to be taken into account, when possible, in the analysis of the putative risk factors of congenital anomalies (Jenkins *et al*., 2007; Rychtarikova*et al*., 2013). Some identified non-specific risk factors for birth defects include:

i. Parental consanguinity

Consanguineous marriages have been described as an important factor contributing to increased congenital malformations (Sawardekar, 2005; Tayebi*et al*., 2010; Shawky and Sadik, 2011; Francine *et al*., 2014). This social custom accepted by at least 20 percent of the world's population, can be characterized by the degree of relatedness between the spouses: first cousins, double first cousins, half first cousins, first cousins once removed, second cousins, second cousins once removed and third cousins (Howson *et al*., 2008; Tayebi*et al*., 2010). Genetic effects of consanguinity can be traced to the fact that the inbred individual may carry two copies of a gene that was present in a single copy in the common ancestor of his/her consanguineous parents. A recessive gene may thus come to light for the first time in an inbred descendant after having remained hidden for generations. For this reason, consanguinity increases the birth prevalence of autosomal recessive birth defects, almost doubling the risk of neonatal and childhood death from birth defects (Howson *et al*., 2008; Kurinczuk*et al*., 2010; Tayebi*et al*., 2010).

ii. Advanced maternal age

Advanced maternal age (35 or older)is associated with an increased birth prevalence of chromosomal trisomies, particularly Down syndrome (Howson *et al*., 2008; Lowry *et al*., 2009; Springett and Morris, 2012; Rychtarikova*et al*., 2013). There are some specific exceptions to the increase in risk with maternal age, for example, the risk of gastroschisis is inversely related to maternal age, with the peak birth prevalence in women <25 years (Kurinczuk*et al*., 2010; Springett and Morris, 2012).

In middle and low-income countries, a high percentage of women give birth over the age of 35 years without the availability of community education and universally available and accessible family planning services, medical genetic screening, prenatal diagnosis, or

associated services. The prevalence of chromosomal aneuploidies is therefore high in these countries (Howson *et al*., 2008).

iii. Poverty

Reduced socioeconomic circumstances are associated with an increased birth prevalence of birth defects. Mothers in poverty are more likely to be malnourished before and during pregnancy, and are at greater risk of exposure to environmental teratogens such as alcohol and maternal infection (Howson *et al*., 2008; Kurinczuk*et al*., 2010). In starvation and famine, low food intake reduces the glucose stream to the fetus from the mother. It also reduces the concentration of micronutrients in the maternal meal and thus increases the risk of congenital defects, preterm delivery, low infant birth weight, and pre-eclampsia (Scholl, 2008).

An increase in stressful life events as seen in poverty, has been associated with increased risk of cleft palate, cleft lip with or without cleft palate, d-transposition of the great arteries, tetralogy of Fallot, after adjustment for maternal race/ethnicity, education, obesity, age, smoking, drinking intake of folic acid-containing supplements, neighborhood crime, and food insecurity (Carmichael *et al*., 2007).

2.6 CONTRIBUTION OF CONGENITAL ANOMALIES TO GLOBAL CHILDHOOD MORTALITY

The World Health Organization (WHO) estimates that in the year 2004, about 260,000 neonatal deaths occurred worldwide (about 7% of all neonatal deaths) from congenital anomalies (WHO, 2010). At least 3.3 million children under 5 die from serious genetic or partly genetic birth defects each year. An estimated 3.2 million of those who survive without appropriate care may be disabled for life. For those who survive, these disorders can cause

lifelong mental, physical, auditory, and visual disabilities that exact a harsh human and economic toll on those affected, their families, and their communities (Miles, 2006; Howson *et al*., 2008).

Birth defects are a global problem. They are most prominent as a cause of death in settings where overall mortality rates are lower, for example in the European region, where as many as 25% of neonatal deaths are due to congenital anomalies (WHO, 2010). The impact of birth defects on infant and childhood death and disability is particularly severe in middle and low income countries where up to 94 percent of those born with birth defects and 95 percent of the children who die from birth defect occur. The situation in more affluent European nations is strikingly different (Table 2.5). The 142/1000 under 5 mortality rate (U5MR) for Tanzania, in 2003, with a per capita annual GNP of US $290, contrasts with the U5MR of 4/1000 in Norway, having a per capita GNP of US $43,350 (Miles, 2006; Howson *et al*., 2008).

It has been shown that there is an increased risk of first year mortality among infants born preterm with a cardiovascular malformation when compared with those without cardiovascular malformations (Walden *et al*., 2007). Major heart defects are currently diagnosed in 1 in 110 newborns in North America, and account for more than one-third of infant deaths due to congenital anomalies, and for approximately one-tenth of all infant deaths. These estimates are similar for other areas of the world (Botto and Correa, 2003).

Only limited application of what is possible for the care and prevention of birth defects has occurred in middle and low-income countries (Howson *et al*., 2008).

Table 2.5: Estimated number and percentage of annual total birth defects, early deaths due to birth defects, and under 5 deaths for Low, Middle, and High-income countries.

	Low-income Countries	Middle-income Countries	High-income Countries	Total
Annual total birth defects	4.75	2.64	0.49	7.9
(millions)	60%	34%	6%	
Annual early deaths of birth defects (millions)	2.38	0.79	0.14	3.3
	72%	24%	4%	
Annual under 5 deaths	8.8	1.8	0.6	11.2
(millions)	80%	16%	4%	

Adopted from Howson et al., (2008)

2.7 PRENATAL DIAGNOSES OF CONGENITAL ANOMALIES

Prenatal diagnosis is a complex, highly informative medical act, which allows for the diagnosis of numerous congenital anomalies and genetic diseases in the fetal life (Kingston, 2002; O'Neil *et al*., 2003; Iacob*et al*., 2009). Congenital malformations are a diverse group of disorders, with more than 50% of fetal defects affecting the central nervous system (CNS), 20% affecting the genitourinary tract, 15% affecting the gastrointestinal tract, and 8% affecting the cardiovascular system (O'Neil *et al*., 2003). Various prenatal procedures are available (Table 2.6), generally being performed between 10 and 20 weeks' gestation (Kingston, 2002).

2.7.1 Maternal Serum Screening

A combination of tests such as maternal serum α- fetoprotein (AFP) screening alone or combined with human chorionic gonadotropin (hCG) and unconjugated serum estriol (the "triple test"), and inhibin A (the "quadruple test"), amniocentesis, chorionic villus sampling (CVS), percutaneous umbilical blood sampling (PUBS), prenatal ultrasound, and in utero Magnetic Resonance Imaging (MRI) has proved to be effectiveat identifying these abnormalities in utero.

Table 2.6: Techniques for prenatal diagnosis

Ultrasonography

- Safe
- Performed mainly in second trimester

Amniocentesis

- Procedure risk 0.5-1.0%
- Performed in second trimester
- Widely available

Chorionic villus sampling

- Procedure risk 1-2%
- Performed in first trimester
- Specialized technique

Cordocentesis

- Procedure risk 1%
- Performed in second trimester
- Specialized technique

Fetal tissue biopsy

- Procedure risk <3%
- Performed in second trimester
- Very specialized technique
- Limited application

Embryo biopsy

- Limited availability and application

Adopted from Kingston, (2002)

This identification allows for parental counseling, options for intervention or termination, and referral of affected infants to high-risk obstetric delivery centres. The tests also provide answers to stressful questions for parents at high risk for congenital diseases and anomalies. In most developed countries, tertiary hospitals have developed fetal management teams consisting of obstetricians, midwives, radiologists, neonatologists, paediatric surgeons, clinical geneticists and counselors, to provide integrated services for couples in whom prenatal tests detect an abnormality (Kingston, 2002; O'Neil *et al*., 2003).

Screening of maternal blood is recommended for all pregnancies to rule out elevated AFP indicative of neural tube defects and in pregnant women younger than age 35 years to assess for trisomy 18 and 21. Pregnant women who are older than age 35 years and at higher risk of chromosomal abnormalities, should be offered amniocentesis or CVS instead (O'Neil *et al*.,2003; Lowry *et al*., 2009; Springett and Morris, 2012).

AFP is one of the major oncotic proteins in fetal serum. Fetal defects involving lack of effective skin covering (open neural tube defects of abdominal wall defects) allow for this serum protein to be elevated in the amniotic fluid surrounding the fetus (O'Neil *et al*., 2003; Sadler, 2005). Screening by measurement of maternal serum AFP levels should be offered to all women at 15 to 20 weeks' gestation. Maternal serum AFP levels 2 to 2.5times the median are observed in 90% of fetuses with anencephaly and 80% to 85% of fetuses with neural tube defects with a 5% false-negative rate (O'Neil *et al*., 2003).

If theAFP iselevated, ultrasonography (USS) should be performed to assess for fetal demise, gestational age, multiple gestations, neural tube defects and other anomalies.

If the elevated AFP remains unexplained after USS, amniocentesis may be performed to assay the levels of AFP and acetylcholinesterase, both of which may be elevated in fetuses

with spina bifida. Acetylcholinesterase allows identification of increased AFP resulting from fetal blood in the amniotic fluid, because acetylcholinesterase will not be elevated in that setting. Elevated AFP levels also are observed in patients with Turner's syndrome, omphalocoele, gastroschisis, sacrococcygealteratoma, and intestinal obstruction (O'Neil *et al*., 2003).

In contrast to neural tube defects, trisomy 18 and 21 are associated with a decrease in AFP. When combined with elevated hCG and decreased unconjugated serum estriol (the triple test), the sensitivity of detecting trisomy 21 is 65% to 70%, although detection rates are 90% for women 35 years old and older. Trisomy 18 is marked by a low AFP, estriol, and hCG, in contrast to trisomy 21.The second trimester triple test should be offered to all mothers younger than age 35 years, with confirmatory amniocentesis performed if results are consistent with trisomy. If indicated, screening in the first trimester can be performed by using fetal USS to determine nuchal translucency, which is increased in the fetus with chromosomal abnormalities, including Down's syndrome and monosomy X (Turner's syndrome), and in fetuses with a cardiac abnormality. Nuchal translucency measurement may be combined with pregnancy associated placental protein A levels for Down syndrome detection with a sensitivity of greater than 70% (Nicholaides*et al*., 1992; Kingston, 2002; O'Neil *et al*., 2003).

2.7.2 Fetal Imaging

Commonly used modalities for fetal imaging include:

i. Prenatal ultrasonography

This is the most frequently used method of fetal imaging and is effective in determining the gestational age of the fetus, monitoring growth in high-risk pregnancies (including multiple

pregnancies), and detecting many fetal anomalies (Luck, 1992; Todros*et al*., 2001; Kingston, 2002; O'Neil *et al*., 2003; Munim*et al*., 2006; Gliozheni*et al*., 2011).

The availability of advanced real-time scanning equipment and Gray-scale high resolution along with color Doppler evaluation has permitted a more precise assessment of fetal anatomy and activity. Centres specializing in high resolution ultrasonography can detect an increasing number of other abnormalities, such as structural abnormalities of the brain, various types of congenital heart disease, clefts of the lip and palate and microphthalmia. For some fetal malformations the improved resolution of high frequency ultrasound transducers has even enabled detection during the first trimester by transvaginal sonography (Kingston, 2002; O'Neil *et al*., 2003; Mashiach*et al*., 2004; Babu and Pasula, 2013).

It is advised that prenatal ultrasonography (USS) be conducted at least twice during the course of the pregnancy. The first one preferably through the transvaginal route, could be done between 14 and 16 weeks of gestation, while the second one preferably transabdominal USS, could be done after the 26th week of pregnancy (Mashiach*et al*., 2004; Babu and Pasula, 2013). Ultrasound screening for fetal structural abnormalities is generally recommended at 19-21 weeks of gestational age. Data on detection rates using USS for screening for fetal malformations do vary widely, ranging from 8.7% to 85%, and may thus reflect varying criteria for definition of malformation, postnatal examination, selection of study population, prevalence of specific anomalies within a population, skills of operators, etc (Todros*et al*., 2001; Munim*et al*., 2006).

ii. Prenatal magnetic resonance imaging (MRI)

Prenatal MRI may be useful for characterizing an anomaly when ultrasound has identified its presence. MRI is an adjunct to a good prenatal USS. Being free from radiation, this imaging

modality provides high-resolution anatomic images of potential anomalies in a safe manner for the developing fetus (Hubbard, 2003; O'Neil *et al*., 2003). MRI provides significant additional information that improves diagnostic accuracy in evaluation of the fetal brain, spine, neck, chest, abdomen, and urinary tract. It provides important anatomic information that helps in planning delivery and surgical procedures (Hubbard, 2003).

2.7.3 Amniocentesis

Amniocentesis is an invasive procedure that requires the removal of a sample of amniotic fluid to obtain fetal cells for chromosomal analysis. It is generally not performed earlier than 15 weeks gestation, and is done under ultrasound guidance (Kingston, 2002; O'Neil *et al*., 2003; Quinlan, 2008; Fajnzylber*et al*., 2010).The main indications for amniocentesis are for chromosomal analysis of cultured amniotic cells in pregnancies at increased risk of Down syndrome or other chromosomal abnormalities and for estimating α fetoprotein concentration and acetylcholinesterase activity in amniotic fluid in pregnancies at increased risk of neural tube defects (Kingston, 2002; Wilson *et al*., 2007). Maternal risks are limited and include transient vaginal spotting or amniotic fluid leakage (occurring in <1% of cases). Fetal loss is estimated at 0.3% to 0.5%. Although early amniocentesis has been proposed and evaluated, performance before 13 weeks gestation is not recommended because of the 1.3% risk of clubfoot after this procedure compared with the expected 0.1% incidence (Olney *et al*., 1995; Sundberg*et al*., 1997; O'Neil *et al*., 2003).

2.7.4 Chorionic Villus Sampling (CVS)

This is a technique in which fetally derived chorionic villus material is obtained trans-cervically with a flexible catheter between 9 and 12 weeks' gestation or by trans-abdominal puncture and aspiration at any time up to term (Pijpers*et al*., 1988; Olney *et al*., 1995;

Kingston, 2002; O'Neil *et al*., 2003). Dissection of fetal chorionic villus material from maternal decidua permits chromosomal, enzyme, or DNA analysis of the fetal cells.

The rate of fetal loss following CVS seems to be approximately 0.5% to 1% and does not seem to be affected by use of a trans-cervical versus a trans-abdominal approach.There are suggestions that performance of CVS may be associated with an increased incidence of hypoplasia or absence of the fingers or toes at a rate of 1 per 3000 compared with the general population rate. The rate appears to be higher when CVS is performed at less than 10 weeks' gestation, and as such it is recommended that CVS not be performed until later (Olney *et al*., 1995; Kingston, 2002; O'Neil *et al*., 2003).

2.7.5 Cordocentesis

Cordocentesis also called Percutaneous Umbilical Blood Sampling (PUBS) is a procedure through which a sample of fetal blood is obtained from the umbilical vein under ultrasound guidance. This is usually performed at or beyond 18 weeks gestation (Mathur*et al*., 2002; O'Neil *et al*., 2003; Han and Nava-Ocampo, 2005).PUBS can be used for the prenatal diagnosis of many hematologic or genetic abnormalities (Ostlund*et al*., 1997; Kingston 2002; O'Neil *et al*., 2003). The procedure-related rate of fetal loss after PUBS is unclear but may be 1% to 3%. Because PUBS potentially presents a greater risk to the fetus, it should be reserved for situations needing rapid diagnosis or when safer means are unobtainable (O'Neil *et al*., 2003; Kanhai*et al*., 2006).

2.7.6 Fetal Tissue Sampling

Percutaneous placement of a fetoscope into the uterus allows for the visualization of the fetus and the biopsy of fetal tissues such as skin, muscle or liver. This allows the early diagnosis of conditions in which the genetic defect is not expressed in amniotic fluid (e.g. epidermolysis

bullosum and Duchenne's muscular dystrophy) to be made (Quintero *et al*., 1994; O'Neil *et al*., 2003; Yang *et al*., 2010; Deka*et al*., 2012).A fetal loss rate of 2% to 3% is associated with fetal tissue sampling. The need for tissue biopsy is now largely replaced by DNA analysis of chorionic villus material and fetoscopy for direct visualization of the fetus has been replaced by ultrasonography (Kingston, 2002; O'Neil *et al*., 2003). Neither limb anomalies nor neonatal respiratory distress in term births following prenatal fetoscopy have been reported (Iacob*et al*., 2009).

2.7.7 Analysis of Fetal Cells in Maternal Blood

Three types of fetal cells circulate in the maternal blood: lymphocytes, erythroblasts and cells of sincitiotrophoblast. They can be identified and isolated in the maternal blood due to the antigenic differences between the mother and the fetus (Herzenberg*et al*., 1979; Hahn *et al*., 1998; Gussin and Elias, 2002; Iacob*et al*., 2009). The isolation and analysis of fetal cells from maternal blood has allowed non-invasive prenatal genetic screening and diagnosis. Erythroblasts seem to be the most adequate cells for neonatal diagnosis out of the three cell types present in the maternal blood. It is believed that the number of fetal cells in the maternal blood is higher in the case of pregnancies with fetuses having aneuploidy, especially trisomy 21, which would facilitate the detection of such anomalies (Hahn *et al*., 1998; Iacob*et al*., 2009).

A number of techniques have been developed for the analysis of fetal cells in maternal blood. Some of the laboratory analyses that may be performed on these fetal cells include chromosomal analysis, biochemical analysis for metabolic diseases, and DNA analysis (Hahn *et al*., 1998; Gussin and Elias 2002; Iacob*et al*., 2009).

2.7.8 Pre-implantation Genetic Diagnosis

Techniques are now available for evaluating oocytes and embryos 6 days after in vitro conception. The polar body from the oocyte can be biopsied and analyzed. If no known adverse gene or if a normal complement of chromosomes is present in the polar body, the oocyte can be allowed to progress to fertilization and implantation.Following in vitro fertilization and embryo culture, a biopsy of one or two outer embryonal cells at the 6-10 cell stage of development is taken. DNA analysis of a single cell or chromosomal analysis by in situ hybridization is performed so that only embryos free of a particular genetic defect are re-implanted. Sex determination can also be done (Kingston, 2002; O'Neil *et al*., 2003).

2.8 CARE OF PEOPLE WITH CONGENITAL ABNORMALITIES

Care for people with birth defects includes diagnosis and treatment. Treatment of birth defects depends on the level of health care available. It comprises medical therapy, surgery, rehabilitation and palliative care when appropriate (Howson *et al*., 2008; WHO, 2010). Recent advances in prenatal diagnosis have yielded enormous benefits. Anatomic malformations that interfere with fetal organ development and that alleviation of which would allow normal development to proceed should be considered for fetal intervention (O'Neil *et al*., 2003; Gould *et al*., 2011; Zaputovic*et al*., 2012).

The postnatal diagnosis of birth defects comes largely from recognition of certain clinical findings in the neonatal period. Screening of newborn infants for congenital anomalies thus facilitates early detection, treatment and care. Neonatal screening programs (Physical examination of all neonates and screening for congenital hypothyroidism, phenylketonuria, sickle-cell disease and glucose-6-phosphate dehydrogenase deficiency) and training of

primary healthcare providers support the diagnosis and appropriate referral for treatment of infants with congenital disorders.

Physical examination of all newborn infants by trained primary healthcare practitioners is feasible in most health systems and allows the identification of many birth defects, including cardiovascular defects that are associated with a high risk of early mortality and referral (WHO, 2010; Zaputovic*et al*., 2012).

Effective life-saving medical treatment is available for several birth defects, including some common functional single-gene defects. Examples include treatment of neonatal jaundice in glucose-6-phosphate dehydrogenase deficiency and in Rhesus incompatibility, and therapy for congenital hypothyroidism, sickle-cell disorders, thalassaemia,haemophilia, cystic fibrosis, and other inborn errors of metabolism. Other treatment options include postnatal surgical corrections; these are now under research and evaluation in a few selected centres for a number of conditions (e.g. congenital diaphragmatic hernia, congenital heart lesions, myelomeningocele, twin-to-twin transfusion syndrome). As a general principle, as much care as possible should take place close to the patient's home and so should be undertaken in a primary healthcare setting. Referral for treatment should be contemplated only when a diagnosis is not possible or when further management such as pediatric surgery will improve the prognosis (Howson *et al*., 2008; WHO, 2010).

Surgery is an important but largely unheralded component of the services required to treat children with birth defects. More than 60% of children with a birth defect have a congenital malformation of a single organ, system or limb. Between 3 and 10 weeks gestation, the basic shape and organs of the embryo form, and this is when most surgical malformations arise(Hutson and Beasley, 1988).Many birth defects are amenable to cost-effective surgery

that can be life-saving and improve long-term prognosis. Examples are surgery for simple congenital heart defects, cleft lip and palate, club foot, congenital cataracts, and gastrointestinal and urogenital abnormalities (Hutson and Beasley, 1988; WHO, 2010).

Appropriate treatment is also needed for impairments manifesting themselves after the neonatal period. This includes the early detection and treatment of physical, mental, intellectual or sensory impairments. Access to health and rehabilitation services is important to support the participation and inclusion of affected children (Miles, 2006; WHO, 2010).

Effective care depends on accurate diagnosis, which should be possible for most common birth defects. Accurate diagnosis allows practitioners to plan further care, taking into account the circumstances of the family, community, and medical services. Treatment for newborns and children with birth defects can be provided feasibly and effectively in low-income settings. With appropriate training, primary health-care practitioners can offer basic care for children with birth defects. They are able to recognize birth defects, diagnose common problems and identify associated disabilities, which in turn enables them to offer basic treatment and counseling, taking into account family and community circumstances and available medical services. Referral to specialist advice is considered when diagnosis is not possible at the primary healthcare level (Howson *et al*., 2008; WHO, 2010).Antenatal diagnosis together with the improvement of surgical and post operative care of newborns with severe surgically correctable congenital anomalies will enable better survival of live-born infants with birth defects (Zaputovic*et al*., 2012).

2.9 PREVENTION OF BIRTH DEFECTS

The wide range of causes of birth defects means that a portfolio of prevention approaches is needed. Preventive public health measures administered through pre and periconception and

prenatal healthcare services decrease the frequency of certain congenital anomalies. Prevention approaches are classified into three levels:

1. *Primary prevention*: This seeks to ensure that individuals are born free of birth defects by being conceived normally and not being damaged in the early embryonic period (the first eight weeks after conception when the mother may not be aware she is pregnant). The goal of primary prevention is to reduce the incidence of congenital anomalies through the removal of causative factors.

   The primary prevention of congenital anomalies is only possible for a very small range of specific anomalies for which there is either a known cause, or even in the absence of a clear understanding of the cause, a means of prevention has been identified (Pench-aszadeh, 2002; Czeizel, 2005; Howson *et al*., 2008; Kurinczuk*et al*., 2010). On a population level these include childhood rubella immunization, screening and treatment for syphilis during pregnancy, periconceptional folic acid supplementation and/or folate food fortification for the prevention of neural tube defects.

   On an individual level, optimizing the management of women at higher risk, for example, for women who are diabetic or epileptic, is the ideal approach for minimizing the risks of anomalies (Kurinczuk*et al*., 2010). The majority of identified causes of congenital anomalies are non-hereditary and the main preventive measures recommended and being tried in some developing countries include:

a. Expansion of rubella immunization

   The congenital rubella syndrome has been eradicated in the United states by the near universal rubella vaccination as part of childhood immunization programs. By contrast, the burden of congenital rubella in developing countries has been estimated in at least 100,000 cases per year (Howson *et al*., 2008), but only 28% of all developing countries have rubella immunization programs in place, as compared with 92% of industrialized

countries, with worst case scenario being in the continent of Africa, where only one of 47 countries uses rubella vaccine (Penchaszadeh, 2002)

The implementation of immunization programs are a function of political will and appropriate funding. In addition, a minimum of infrastructure, cold chains and adequate organization at community levels are required. This is lacking in most African countries due to poverty and political instability.

b. Folic acid supplementation

Neural tube defects (NTDs) are common and devastating congenital malformations of the central nervous system.The two most common, anencephaly (a total or partial absence of the brain tissue, skull, and overlying skin) and spina bifida (herniation of spinal cord, meninges, or both through a defect in the spine), comprise >90% of cases. Both arise from incomplete closure of the neural tube early in gestation, often before a woman is even aware that she might be pregnant (Koren*et al*., 2008; Dunlap *et al*., 2011; Hoyo*et al*., 2011). Because the neural tube develops during days 22-28 of pregnancy, health ministries in many countries recommend all women of reproductive age consume at least 400 mcg of supplemental synthetic folic acid daily, in addition to a folate rich diet (Meyer and Brown, 2004; Ying Wu *et al*., 2007; Ryan-Harshman and Aldoori, 2008).

There is now strong evidence that adequate periconceptional maternal folic acid supplementation during critical periods of organ formation is associated with reduction in both the occurrence and recurrence of neural tube defects, congenital heart defects (particularly conotruncal heart defects), obstructive urinary tract anomalies, limb deficiencies, orofacial clefts and congenital hypertrophic pyloric stenosis (Hall and Solehdin, 1998; Bailey and Berry, 2005; Joint SOGC-Motherisk Clinical Practice Guideline, 2007).

The bioavailability of naturally occurring folate in foods is very low, so achieving the recommended daily dose of consumption is difficult without supplementation. Folic acid added to foods during fortification is 70-85% bioavailable compared to 50% of folate occurring naturally in foods (Ying Wu *et al*., 2007; Hoyo*et al*., 2011).

In 1996 the Food and Drug Administration (FDA) in USA promulgated a rule requiring all enriched grain products to be fortified with folic acid (FA) at 140mcg FA/100 grams to deliver an additional 100mcg/d of FA to the average adult diet, with effect from January 1998. A similar law is in place in Canada (Meyer and Brown, 2004; Ryan-Harshman and Aldoori, 2008; Hoyo*et al*., 2011).

If continuous supplementation is not possible, experts suggest that women begin folate supplementation at least one month before becoming pregnant (Joint SOGC-Motherisk Clinical Practice Guideline, 2007; Ying Wu *et al*., 2007). Obviously, this approach would be difficult to implement in developing countries, where the overwhelming majority of pregnancies are unplanned.

c. Avoidance of potential teratogens in pregnancy

This is another method of primary prevention. It is an area in which traditions, socioeconomic factors and medical culture coalesce against the goal of avoiding exposure to teratogens. On the one hand, some cultures in developing countries resort to home remedies of unknown composition and teratogenic potential. On the other hand, in some developing countries, pharmaceutical companies market their products directly to consumers, who can purchase most medications over the counter without medical prescription. Compounding these factors are lax environmental quality regulations and unhealthy working conditions which expose pregnant women to environmental

pollutants. Teratogen information services are a valid strategy to counter the above factors and prevent exposure to known teratogens (Penchaszadeh, 2002; Dolk, 2009).

2. *Secondary Prevention*: This consists of early detection, followed by effective early treatment, e.g. neonatal orthopedic screening is very effective for the early detection and treatment of deformities such as congenital dislocation of the hip based on Ortolani click and treated with different conservative methods (e.g. Pavlik pillow) (Czeizel, 2005).

   Secondary prevention encompasses prenatal diagnosis, which must be accompanied by genetic counseling that includes descriptions of the tests available, with their scope and attendant risks. To make informed decisions affecting the outcome of pregnancy, parents need the best information available about their specific set of circumstances. This includes the diagnosis, if possible, affecting their fetus; the cause; the consequences for the fetus; available options for treatment and prognosis as far as this is available; and the risks for recurrence and whether this might be reduced (Howson *et al*., 2008). It should be appreciated that perceptions of a "good" reproductive outcome are very personal and influenced by many social, cultural and religious factors (Kurinczuk*et al*., 2010).

3. *Tertiary prevention*: This aims at complete recovery of congenital abnormalities by early surgical intervention without residual defects or minimal after effects. Interventions include early recognition and diagnosis, including by newborn screening if available; medical treatment of complications; surgical repair of congenital malformations such as cleft lip and palate and congenital heart defects; and neurodevelopmental therapy programs to infants and children with disabilities. It also includes palliative care for children dying from the consequences of their birth defects (Czeizel, 2005; Howson *et al*., 2008).

2.10 ETHICS AND LAW IN CONGENITAL ABNORMALITIES

The discipline of bioethics is a scientific attempt to analyze the problems that often arise in the health field, due to difference of opinion, and at times, conflicting personal and social values. The discipline's fundamental methodology is composed of rational reflection, as well as open dialogue and multidisciplinary approaches. Ethical principles are the ideal. They are what we strive to be, but cannot realize necessarily on a daily basis and cannot expect others to realize.

The term "general ethical principles" refers to the general criteria that serve as a basis for writing and justifying the majority of "good practice" regulations that govern medicine, and which should also be the reference point for legislators. Naturally these principles must adapt themselves to the diverse cultural traditions of each country (Malinowski, 1994; Carrera, 2009).

Legal requirements are the result of society attempting to protect the rights of individuals using laws, as well as trying to determine their duties when faced with specific situations.

Theoretically, the objective of legal requirements is to prioritize and guarantee mutual well-being ahead of private interests, but in practice, these requirement are influenced by prevailing ideology (e.g. political, religious, social elements, and the culture and socioeconomic development level of a country) (Carrera, 2009).

Laws codify what we can expect of ourselves and others, while ethics are aspirations of what we would like and would like others to be. It is thus natural and necessary that generally we maintain a gap between these two levels of behavior. To some extent, this gap is protected by the recognition of individual rights under the constitution, it is a recognition that ethical standards are not always shared and should not be imposed (Malinowski, 1994).

Laws vary in different countries. For this reason, it is important not to confuse ethical principles with legal requirements. In many countries, not all legal requirements are ethical, and in the same way not all ethical principles are necessarily enforced by law.

In democratic countries, the lack of uniformity with regards to ethical values is often manifested through permissive legislation, which tolerates a pluralism of conducts as long as inalienable rights of third parties are not violated. Ethical standards, on the other hand, touch upon personal values and become subjective – a matter of one's own morality. Therefore, even though ethics may by respected and generally aspired to by all, their enforcement is better left to the individual (Malinowski, 1994; Carrera, 2009).Ethics and law converge on morality, the practical guidance that communities of persons create and recreate to use in everyday life to resolve conflicts among desires, goods, principles, and rules (Malinowski, 1994).

2.10.1 Prenatal Ethical and Legal Concerns in Congenital Abnormalities

Prenatal diagnosis is a relatively new medical specialty which includes all medical procedures that lead to the detection or diagnosis of any fetal anomaly. Various prenatal procedures are available, generally being performed between 10 and 20 weeks gestation (Kingston, 2002; Carrera, 2009; Iacob*et al*., 2009).

Prenatal diagnosis of a severe congenital malformation is associated with profound grief, sadness and anger. In many parts of the world, diagnoses of this nature are often followed by decisions to terminate a pregnancy, particularly where the condition is associated with a high rate of prenatal or neonatal death. The increasing availability of prenatal genetic screening and advances in screening technology, coupled with the identification of more gene malfunctions responsible for diseases, now offer prospective parents the possibility of

knowing that their children may suffer from serious physical and mental impairments at a time when abortion is still an option (Malinowski, 1994; Wilkinson *et al*., 2012). The opportunity now associated with this technology is enhanced parental choice. The role of doctors and genetic counselors is to give prospective parents the information about their unborn they seek so that they can make an informed choice (Malinowski, 1994).

According to Carrera (2009), in prenatal diagnosis, some specific ethical principles must be adopted. The vast majority of the ethical principles stated below, are usually also regulated by the majority of national legislation:

i. All pregnant women (and their partners) are entitled to have access to objective information about "congenital defects" (occurrence, prenatal diagnostic possibilities, specific risks, alternative options, etc).
ii. Guided counseling is not ethical. The physician should not attempt to impose his/her personal view over patients.
iii. All examinations should be carried out according to "*Lex artis*" (sufficient expertise, appropriate technology and in a suitable environment).
iv. The examination results must be confidential and access to such results should be restricted.
v. Information provided regarding the results should be adequate, and communicated in a way that can be easily understood by the couple.
vi. Information regarding possibilities and options should be provided objectively, to help the couple reach a personal decision, and in accordance with their needs and beliefs.

In some parts of the world, lethal malformations represent one of the only situations when abortion is legally permitted (Wilkinson *et al*., 2012). In the USA, there is notable accord for

considering the legal induced termination of an established pregnancy (abortion), under the following circumstances:

i. Anatomical malformations that are not compatible with life; as in the case with some structural encephalic defects (anencephaly, porencephaly, hydranencephaly, etc).
ii. Anatomical malformations that significantly compromise quality of life: spina bifida, meningocele, microcephaly, agenesis of the corpus callosum, encephalocele, etc.
iii. Serious congenital defects, associated with chromosome anomalies (aneuploidies, etc).

Specific legislation in the USA provides that the legal interruption of a pregnancy with the aforementioned indications should only be carried out before the 22nd week of pregnancy. Others, on the other hand are more compliant, or on the contrary, more restrictive (Carrera, 2009).

Despite a general discomfort with late term abortions in the USA, several states permit abortion beyond the point of viability when a severe fetal abnormality is detected. Viability is generally considered to occur at the end of the second trimester – that is, during the twenty third or twenty fourth week of pregnancy (Malinowski, 1994).

In Islam and most religions, abortion is forbidden. According to Al-Matary and Ali (2014), the International Islamic Fiqh Council (IIFC), the Sunni Islam authority on Islamic jurisprudence based in Saudi Arabia, has ruled the following:*''If proven by a committee of at least two competent and trustworthy medical experts on the basis of medical examinations with the use of appropriate equipment and laboratory findings before 120 days of pregnancy (19 weeks) that the foetus has serious anomalies that will be present at birth, only then is it permissible to abort after the request of the parents.*

When the pregnancy reaches or is beyond the 120th day (day of ensoulment), abortion becomes totally forbidden and is deemed a form of murder that will result in prosecution

unless the continuation of the pregnancy to full term poses a risk to the mother's life; abortion shall then be considered permissible. This decision must be based on the opinions of at least two competent and trustworthy medical experts in the field.''

There are certain congenital defects sharing in common the fact that they become more severe as pregnancy progresses. Therefore, the possibility of a substantial improvement of the perinatal results exists, if a timely and selective fetal extraction or treatment (surgical or pharmacological) is carried out using proven methods of fetal intervention (Carrera, 2009). Ethical issues arising in such situations pose serious challenges to physicians, politicians, lawyers, and ethicists alike, since justice requires that a pregnant woman, like any other individual, retain the basic right to refuse medical intervention, even if the intervention is in the best interest of her fetus (ACOG committee on ethics, 2005).

Therefore, the availability of prenatal screening for congenital abnormalities and the parental choices it creates are issues that weigh heavily upon procreative liberty and implicate abortion jurisprudence (Malinowski, 1994). Previously the selective abortion, i.e. termination of pregnancy after the prenatal diagnosis of severe fetal defects was also named as secondary prevention. In recent times however, the WHO and other international bodies have excluded this approach from the term "prevention" (Czeizel, 2005).

As evident from the foregoing, it behooves noting that prenatal diagnosis of congenital defects should be carried out under strict ethical criteria that respect the basic rights of mother and baby. However, all prenatal intervention regarding the fetus should take into consideration the condition of the "Patient" and the condition that the fetus reaches when viability increases (Malinowski, 1994; Carrera, 2009).

The choice to interrupt pregnancy (abortion) due to the presence of a congenital defect must adhere to the law, the principle of autonomy of each patient and the possible conscientious objection of practitioners (Malinowski 1994; Carrera, 2009; Al-Matary and Ali 2014).

2.10.2 Postnatal Ethical and Legal Concerns in Congenital Abnormalities

As medicine has improved, there have been unintended consequences. With advanced technology such as assisted mechanical ventilation, it is now possible to keep some terminally or severely ill infants alive for prolonged periods of time. Thus a paradox arises – attempts to save the neonates life, correct malformations, or restore health can initiate new health problems, increase morbidities, or cause further harm to the health of the patient. The result of such treatment is that dying may be prolonged or the infant may survive with profound neurologic or other debilitating problems. This attempt at justice that causes harm then becomes injustice (Barnum, 2009).

There is general agreement within the medical, legal and ethical professions that there are some handicapped newborns in particular situations, whose lives need not be saved. Consensus ends however, when an attempt is made to determine which specific newborns should receive or not receive medical treatment (Clark, 2004; Barnum, 2009).

This diversity of opinions has brought to the forefront the urgent need for a normative moral criterion to assist decision-makers in their discernment of treatment decisions for these never-competent patients (Clark, 2004).

The societal and legally supported opinion is that parents should be able to make decisions for their children because they follow a “best interest” standard. However, what is in the best interest of the child is often debatable, and there are times when good families and good physicians disagree about the appropriateness of continuing or stopping life sustaining treatments (Barnum, 2009).

The bioethicist Richard McCormick proposed a patient-centered, quality of life criterion that can be used by appropriate decision-makers in determining treatment decisions for handicapped newborns. The significance of McCormick's criterion is that it offers the appropriate decision makers a practical beneficial and appropriate moral criterion that is not only reasonable and coherent, but is grounded in a tradition that promotes the "best interest" of handicapped newborns (Smith, 1992; Jones, 1998; Clark, 2004).

The first guideline developed for dealing with never-competent patients focuses on the potential for human relationships associated with the infant's condition.

By relational potential McCormick means "the hope that the infant will in relative comfort, be able to experience our caring and love". Specifically, he proposes that, "if a newborn baby had no potential for such relationships or if the potential would be totally submerged in the mere struggle to survive, then that baby had achieved its potential and further life-prolonging efforts were not mandatory, that is, would no longer be in the ''best interest" of the baby. Therefore, according to this guideline, when a never-competent patient, even with treatment, will have no potential for human relationships, the appropriate decision makers can decide to withhold treatment and allow the patient to die (Smith, 1992; Clark, 2004).

The second guideline of McCormick's quality-of-life criterion is the "benefit-burden evaluation". According to this guideline "where medical procedures are in question, it is generally admitted that the criterion be used in a benefits-burdens estimate''. The question posed is: will the burden of the treatment outweigh the benefits to the patient? The general answer: If the treatment is useless or futile, or it imposes burdens that outweigh the benefits, it may be omitted. Therefore, when a handicapped newborn has the potential for human relationships but after initiating treatment, it becomes apparent that the treatment is medically futile, parents in consultation with health care professionals are not morally obliged to continue medical treatment (Clark, 2004; Wilkinson *et al*., 2012).

McCormick's third norm that further specifies the burden-benefit evaluation states that "life sustaining interventions may be omitted or withdrawn when there is excessive hardship, especially when this combines with poor prognosis''. A "benevolent injustice" occurs when the well intentioned treatment effort of a physician or a medical team produce an outcome that limits the potential of a patient or renders them technologically dependent (Clark, 2004; Barnum, 2009).

CHAPTER THREE

3.0MATERIALS AND METHODS

3.1 STUDY LOCATION AND SUBJECTS

3.1.1Study Location

This study was conducted in three selected major hospitals in the Kano metropolisof Kano State in north-western Nigeria. Neonates born in the labour wards of the hospitals were recruited for the study. The hospitals are situated in the Kano Central Senatorial district, of Kano State.Kano State has a total land area of 20,760 square kilometers, with 44 LGAs and a population of about 9.4 million according to the 2006 National population Census. Kano the State capital is the biggest city in northern Nigeria, comprising of about 8 LGAs. Kano is cosmopolitan in outlook, with a population of about 2.8 million. Urban drift from rural areas within Kano, other states in Nigeria and West Africa, has provided a steady stream of migrants, adding to Kano's growing population. Kano city is characterized by overcrowding and over-burdened social amenities(DRPC, 2005; NPC, 2006; UNESCO, 2007; Dogara*et al*., 2012; Mahmoud, 2012).

Majority of the people are Hausa / Fulani, while other ethnic groups are a minority. Islam is the dominant religion though there are significant groups of Christians and others belonging to traditional African faiths. Most of the indigenous people are farmers and traders.Other residents are mostly traders with some civil servants and artisans. There is a very high concentration of health infrastructure and services in Kano metropolis compared to the rest of the state. There is a total of 28 government hospitals in the state with 43% of them located in the Kano metropolis, 21 primary health centres with 38% located in Kano, 188 private

hospitals and clinics with 91% located in the Kano metropolis (Falola, 2000;Dogara*et al*., 2012; Mahmoud, 2012).

The Aminu Kano Teaching Hospital (AKTH) one of the study hospitals is affiliated to the Bayero University Kano, and provides tertiary health care to its community and to about six neighbouring states in northern Nigeria. The other study hospitals are Murtala Mohammed Specialist hospital (MMSH) and Sheikh Jidda Specialist hospital (SJSH).

The Obstetric and Gynecology Departments of these hospitals provide antepartum, intrapartum and postnatal care to the women in the community.

3.1.2Study Design

This is a descriptive study. The study employed quantitative survey techniques for the collection and analysis of data.

3.1.3Study Subjects

Respondents were neonates born in the labour wards of AKTH, MMSH and SJSHand their mothers. The respondents were identified in the labour and postnatal wards of the hospitals.

3.2SAMPLE SIZE DETERMINATION

To determine the sample size for the study, the formula for estimating single proportions was used (Wingo*et al*., 1994):

$$n = \frac{Z_{\alpha}^2 pq}{d^2}$$

Where:

n = Minimum sample size

α = Level of significance. It will be set at 0.05

1-α = The confidence level that the estimate is within distance (d) of the proportion of interest. It is 0.95.

Zα = Standard normal deviate; at 95% confidence level.

Zα= 1.96 for a two tailed test.

p = Proportion in the target population estimated to have a particular characteristic. It is estimated that about 3% (0.03) of all newborns have a congenital abnormality at birth (Al-Gazali*et al*., 1995;Sawardekar, 2005).

d= Degree of accuracy desired or the distance (or tolerance) - how close to the proportion (p) of interest the estimate is desired to be. It will be within 0.01.

q = 1-p

$$n = \frac{(1.96)^2 \text{ X } 0.03 \text{ (} 1 - 0.03)}{(0.01)^2}$$

$$n = \frac{(1.96)^2 \text{ X } (0.03 \text{ X } 0.97)}{(0.01)^2}$$

n = 1,117.9

n≈ 1,118

The minimum sample size for the study is 1,118 live born neonates.

3.3INCLUSION CRITERIA

Live neonates born in the labour wards of AKTH, MMSH and SJSH.

3.4EXCLUSION CRITERIA

i. Stillborns

ii. Neonates born outside the study hospitals.

iii. Neonates of non consenting mothers.

3.5DATA COLLECTION PROTOCOL

3.5.1Quantitative Survey

Respondents were recruited into the study consecutively until the required sample size was attained.

3.5.2Instrument

A structured interviewer administered questionnaire was used to interview the mothers of the selected neonates and to collect anthropometric data of the neonates. The questionnaire wasalso used to collect socio demographic information and reproductive history of the mothers.

3.5.3Pre -test

The questionnaires were protested in the labour ward of AKTH before the commencement of the study. The following were assessed: - acceptability of the questions and willingness to answer them, whether the questions are appropriate in eliciting responses that are consistent with the study objectives. Following pre-test, ambiguous questions were rephrased.

3.5.4Data Collection

Research assistants who understand and speak the Hausa Language were involved in the collection of data. A workshop for training the interviewers was organized before doing the pre-test and another afterwards to review areas of difficulties. The research assistants were either medical students or medically qualified.

The research assistants were supervised during data collection. As much as possible, care was taken in the field to check the responses.The examination of the neonates was entirely clinical i.e. the examination was by measurements; palpation and observation of the neonate (please see Appendix IV). All the children were examined within 48 hours of birth. Autopsies and cytogenic analysis were not done.

Structural anomalies are considered "overt" or "external" when they are visible on inspection, otherwise they are considered "occult" or "internal" (Abdi – Rad *et al*, 2008; Ochieng*et al*., 2011)

Major congenital anomalies were defined as those abnormalities that if uncorrected or uncorrectable will significantly impair normal body functions or reduce life expectancy, while minor anomalies are those that cause no handicap i.e. they cause no significant physical or functional effect and can be regarded as normal variants if, they affect more than 4% of the population (Al- Gazali*et al*, 1995; Kingston, 2002).

Single – system anomalies are those affecting a single organ, organ system or body part, while multiple abnormalities are those affecting more than one organ system or body part (McIntosh *et al*., 1954; Sawardakar, 2005;Queisser-Luft and Spranger, 2006).

In neonates with congenital anomalies involving two or more systems, a diagnosis was made if the group of malformations constitute a known syndrome or chromosomal disorder, and the child is recorded only once under that diagnose. If no diagnosis can be made, the infant is classified and coded only once as having a multiple congenital abnormality, and the system with the most obvious or major malformation was noted (Delport*et al*,. 1995; Muga*et al*., 2009)

3.6DATA ANALYSES

Field editing was done on the spot following retrieval of the completed questionnaires. Thereafter, office editing was done whereby data were checked manually for error; and coding of questionnaires were done before data entry. SPSS 15.0 (SPSS Inc, Chicago, IL)was used for data entry and analyses. Three levels of analyses were employed, namely, univariate, bivariate and multivariate analyses.Univariate analysis was used in descriptive statistics, to examine background characteristic of respondents, which were expressed in percentages and simple proportions, and displayed on frequency tables.Bivariate analysis was done using chi-square as test statistic to test independence or relationship between the birth of a child with a congenital anomaly and selected factors.Multivariate analysis employed binary logistic regression analysis to assess the effect of socio-demographic independent variables on the birth of a child with a congenital anomaly.Inferential statistics were drawn from the results of both the bivariate and multivariate analysis. Statistical significance was set at $p < 0.05$ for all analyses.

3.7ETHICAL ISSUES

3.7.1Ethical Approval

Ethical approval was sought from the AKTH and the Kano State Hospitals' Management Board research and ethical committeesbefore carrying out the study.

3.7.2Consent

A consent form was administered to the respondents after the purpose of the research had been explained to them. The respondents reserved the right to withdraw from the study for whatever reasons.

3.7.3Confidentiality and Privacy

All information gathered from the respondents was kept confidential.

CHAPTER FOUR

4.0 RESULTS

4.1 UNIVARIATE ANALYSIS

A total of 1456 neonates were included into the study. Table 4.1 shows their characteristics. There were 757 boys (52%) and 699 girls (48%). The Murtala Mohammed Specialist Hospital (MMSH) Kano was the birth place of most of the neonates (828; 56.9%), while 463 (31.8%) of them were born at the Sheik Jidda Specialist Hospital (SJSH) Kano, and only 165 (11.3%) were born at the Aminu Kano Teaching Hospital (AKTH) Kano (Fig. 4.1). Most of the neonates (1334; 91.62%) were products of single gestation, 116 (7.97%) were products of a twin gestation, while 6(0.41%)were products of triplet gestation (Fig.4.2). Delivery was per vaginum for most of the neonates (1242/1451; 85.6%), while for 14.4% of them (209/1451) delivery was by caesarean section (Fig.4.3). Most of the neonates were products of booked pregnancies (1386/1451); 95.52%), while 4.48% (65/1451) were products of unbooked pregnancies (Fig. 4.4).

The mean gestational age at delivery for the neonates in the study was 38.73 (SD 2.44) weeks, while their mean birth weight was 3.10kg (SD 1.20kg). For the 1,321 neonates whose weight data were available, 98 (7.42%) were of low birth weight (LBW) i.e. birth weight < 2.5kg, 90.54% (1196/1321) were of appropriate birth weight (2.5 – 4.0kg) and 2.04% (27/1321) were macrosomic (birth weight > 4kg).

The socio-demographic characteristic of the neonates' mothers is shown in Table 4.2. The mean maternal age was 26.49 years (SD 6.38 years). Of the 1446 mothers for whom age was recorded, the majority of them 73.37% (1061/1446) fell within the 20 – 34 years age bracket, while only 4.29% (62/1446) were age 40 years and above at the time of the study. Only

27.36% (392/1433) of the mothers were primiparous, while the majority (1,041/1433; 72.64%) had had 2 or more child births at the time of the study. The ethnic group of the fathers of the neonates (Fig.4.5) was in the majority of the cases Hausa/Fulani (1312/1453; 90.3%). Most of the mothers (661/1450; 45.59%) had attained a secondary school level of education, and only about 1.72% (25/1450) had no formal education (Fig. 4.6).

Table 4.1: Characteristics of Neonates in the Study

Variables	Frequency	Percentage (%)
Gender		
Male	757	52
Female	699	48
Type of Delivery		
Vaginal	1242	85.60
Caesarean Section	209	14.40
Gestational Age (Weeks)		
36 and below	363	25.55
37 – 40	838	58.97
41 and above	220	15.48
Nature of Gestation		
Singleton	1334	91.62
Twins	116	7.97
Triplets	6	0.41
Birth Weight (kg)		
< 2.5	98	7.42
2.5 – 4.0	1196	90.54
>4.0	27	2.04

Table 4.2: Socio-demographic characteristics of neonates' mothers

Variables	Frequency	Percentage (%)
Age (Years)		
19 and below	153	10.58
20 – 34	1061	73.37
35 – 39	170	11.76
40 and above	62	4.29
Highest Level of Education		
None	25	1.72
Primary/Quaranic	552	38.07
Secondary	661	45.59
Post –Secondary	212	14.62
Religion		
Christianity	68	4.68
Islam	1382	95.11
Others	3	0.21
Ethnic Group of Husband		
Hausa/Fulani	1312	90.30
Igbo	21	1.45
Yoruba	24	1.65
Others	96	6.61
Nature of Marriage		
Consanguineous	256	17.83
Non- Consanguineous	1180	82.17
Parity		
1	392	27.36
2 – 4	571	39.85
5+	470	32.80
Booking Status of Pregnancy		
Booked	1386	95.52
Unbooked	65	4.48
Age of Husband (Years)		
19 and below	0	0
20 – 34	498	35.98
35 – 39	309	22.11
40 and above	580	41.91

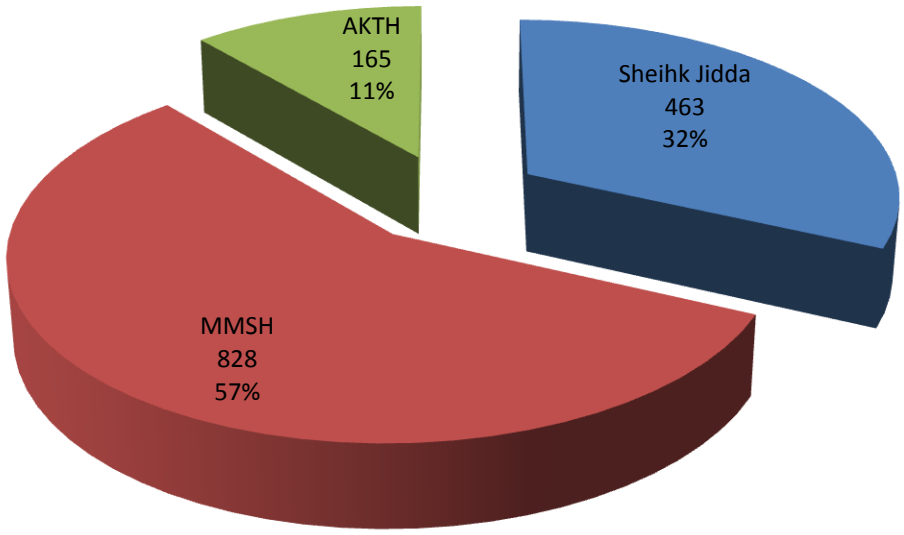

Figure 4.1: Distribution of neonates according to hospital of birth

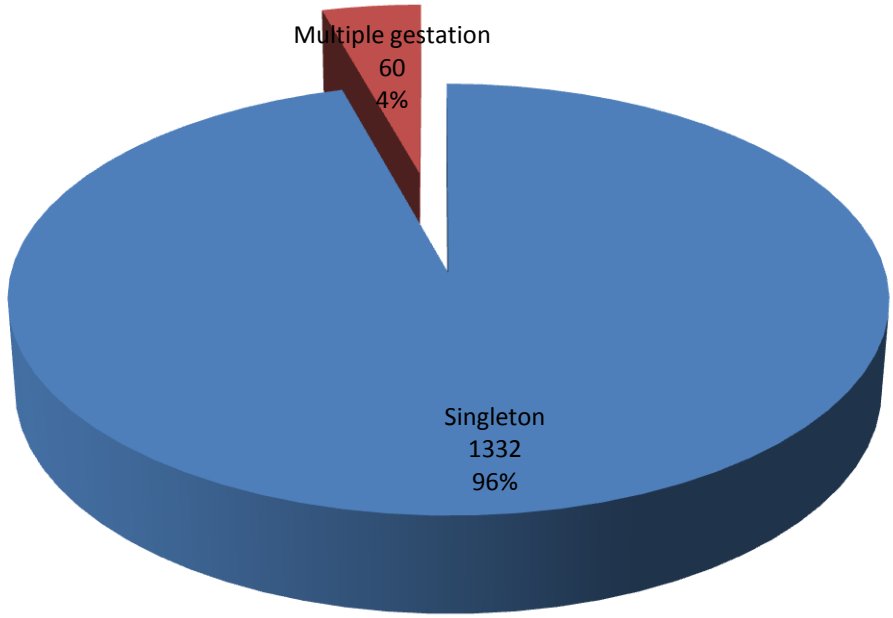

Figure 4.2: Percentage distribution of neonates according to nature of gestation

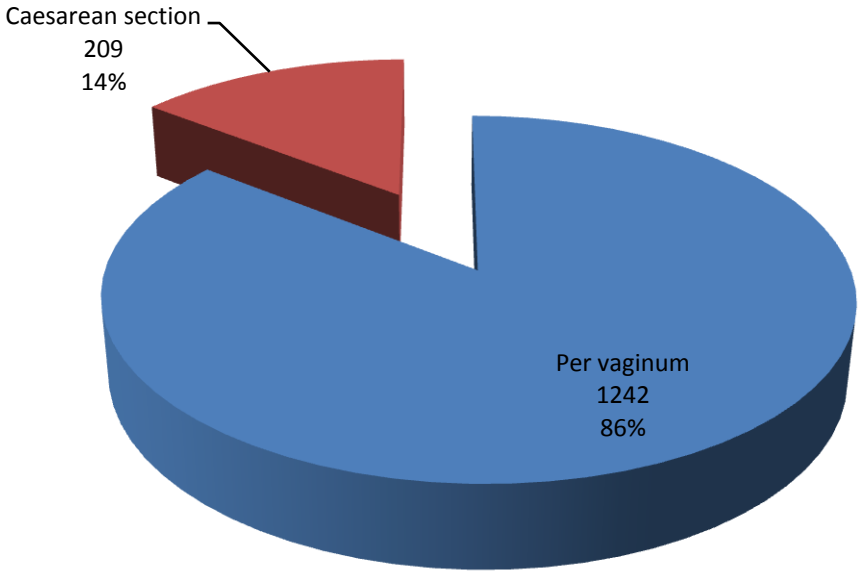

Figure 4.3:Percentage distribution of neonates according to type of delivery

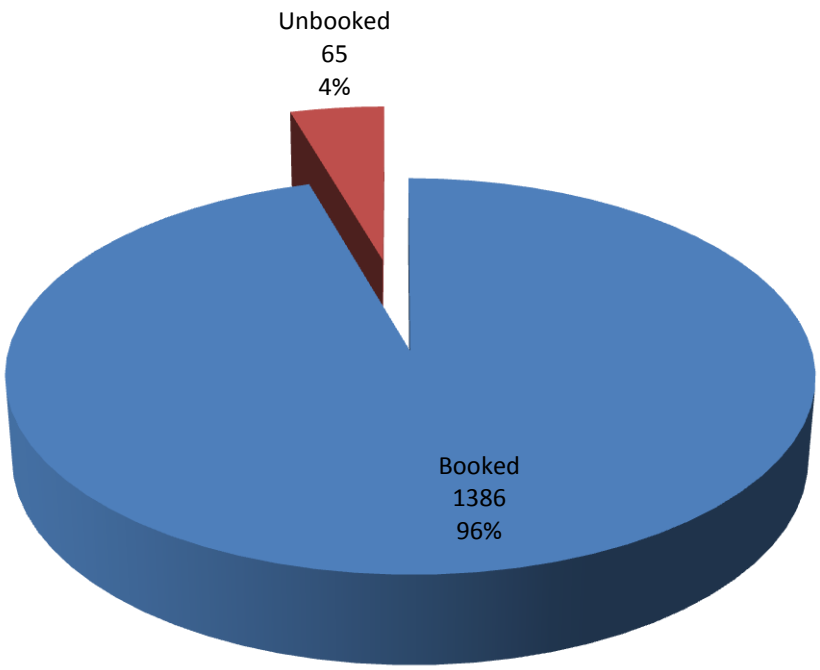

Figure 4.4: Booking status of pregnancy

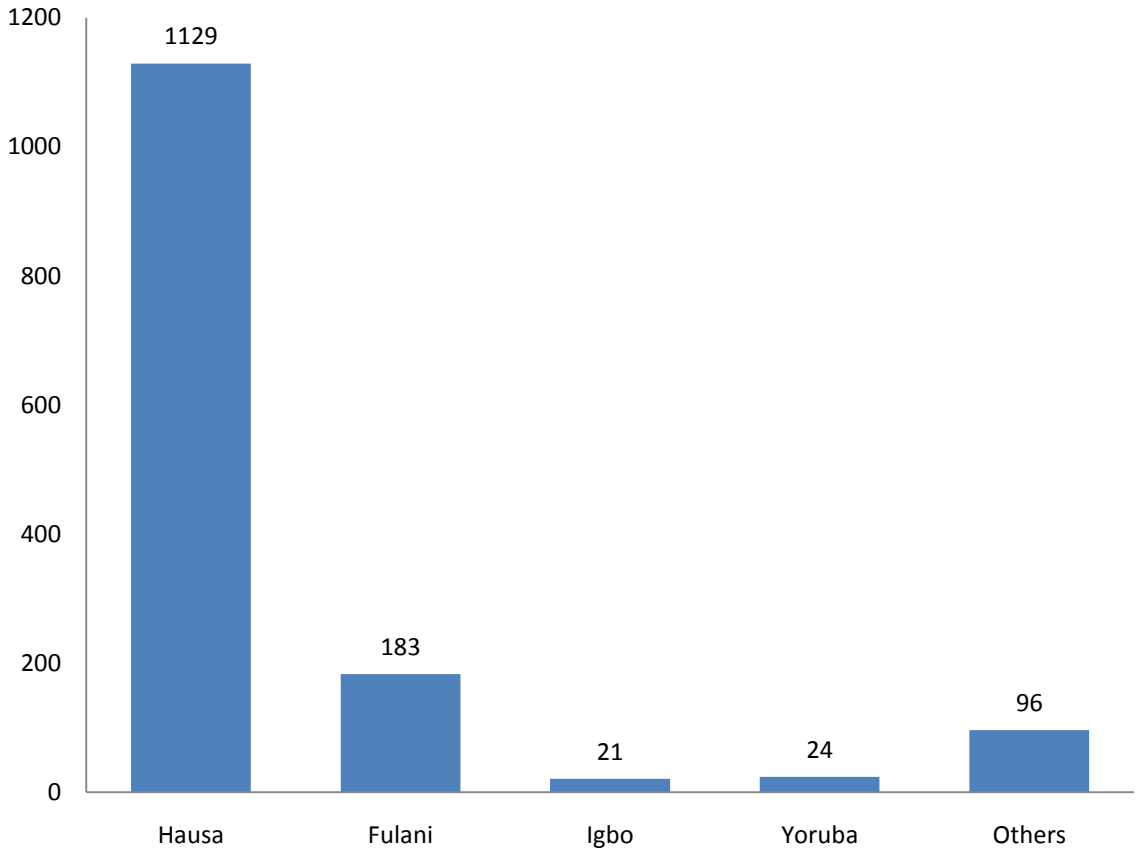

Figure 4.5: Ethnic group of fathers of neonates

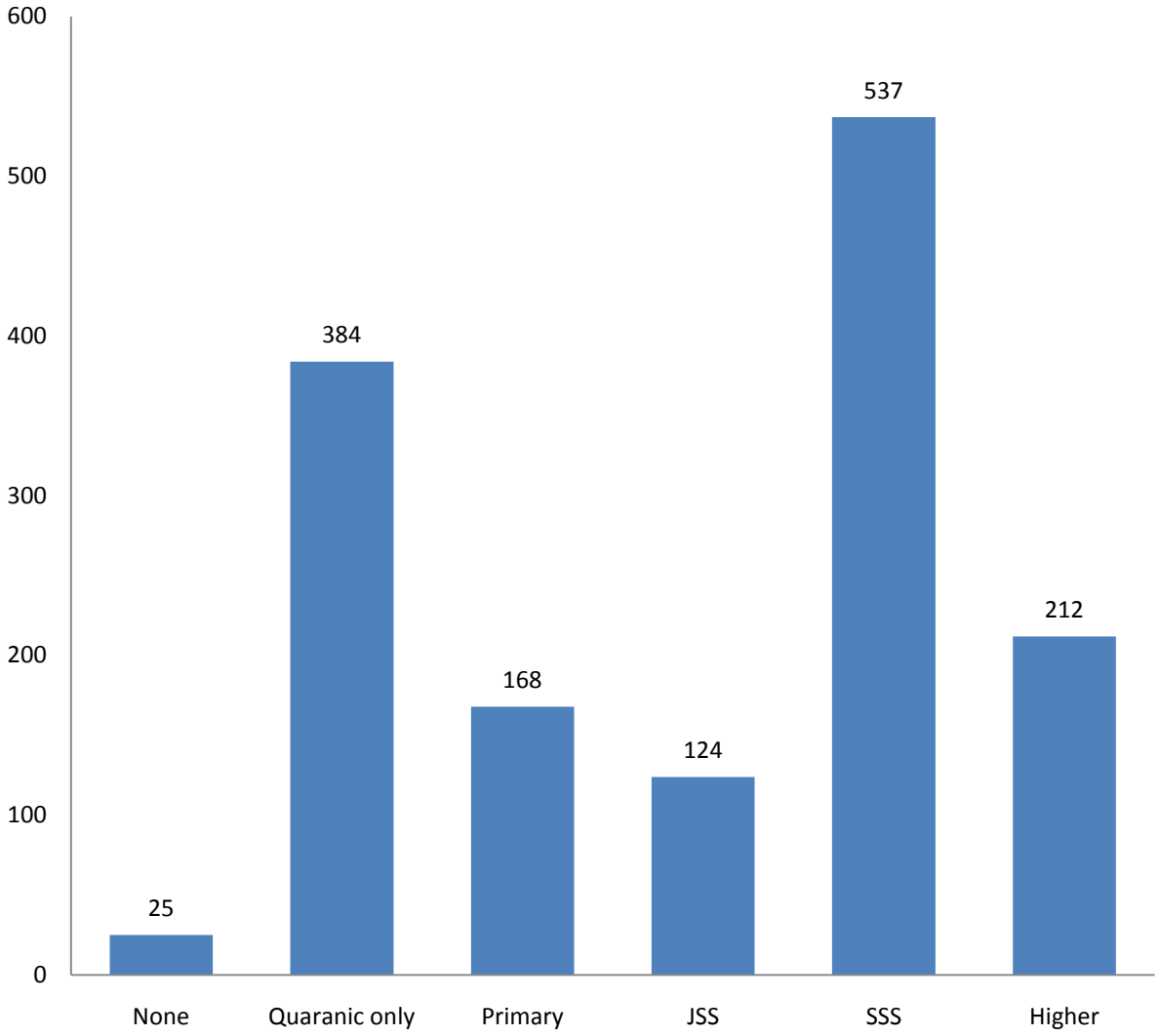

Figure 4.6: Level of Education of neonates' mothers

Most of the mothers (1382/1453; 95.11%) were Muslims. The majority of the mothers belonged to a non-consanguineous marriage (1180/1436; 82.17%) and only 17.83% (256/1436) had a consanguineous marriage (Fig. 4.7). Only 3.24% (47/1450) of the mothers gave a positive family history of the birth of a child with a congenital malformation, while 2.48% (36/1450) were not sure (Fig. 4.8).

The use of folic acid containing multivitamin supplements for the index pregnancy was commenced by most of the mothers (1063/1453; 73.16%) after the third month of pregnancy, while only 5.02% (73/1453) began use at least one month before pregnancy or in the first month of pregnancy. About 10.87% (158/1453) of the mothers reported non-use of folic acid containing multivitamin supplements for the index pregnancy (Fig. 4.9).

Among the neonates' mothers, 24.62% (358/1454) gave a positive history of having a febrile illness in the first trimester of the index pregnancy, 16.71% (243/1454) had a similar complaint in the second trimester, while a similar complaint was noted by 25.79% (375/1454) in the third trimester of the index pregnancy (Fig.4.10). The use of native (non-orthodox) medication in the first trimester of the index pregnancy was reported by 6.74% (98/1454) of the mothers, while 7.98% (11/1454) gave a similar report for the second trimester and 21.94% (319/1454) admitted to using native medication in the third trimester of the index pregnancy (Fig. 4.11).

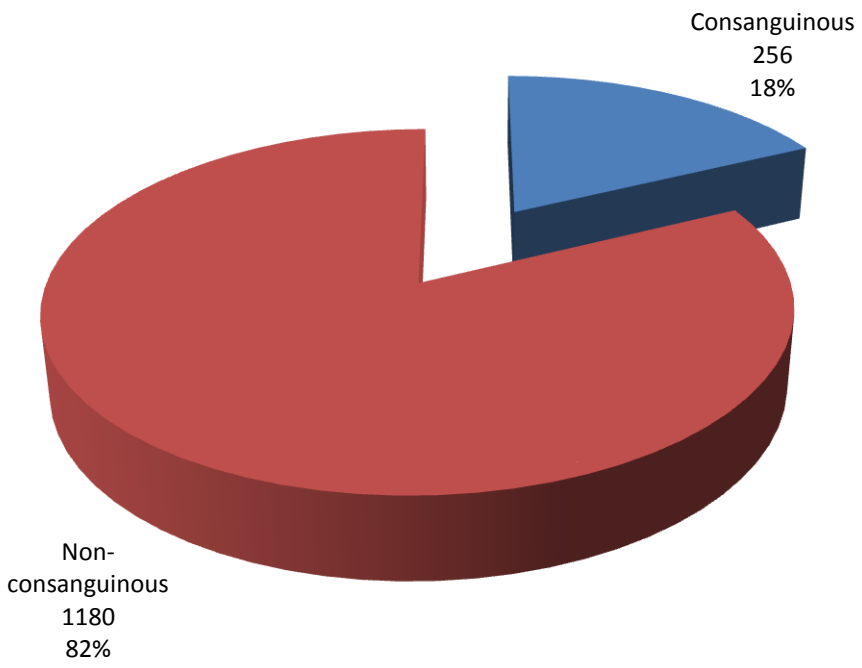

Figure 4.7: Consanguinity rate among parents of the study neonates

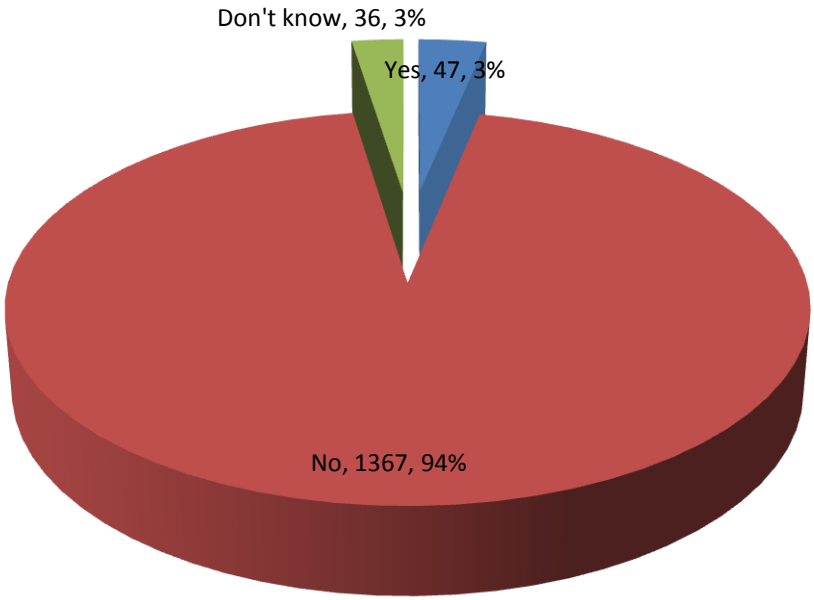

Figure 4.8: Family history of birth of child with a congenital anomaly

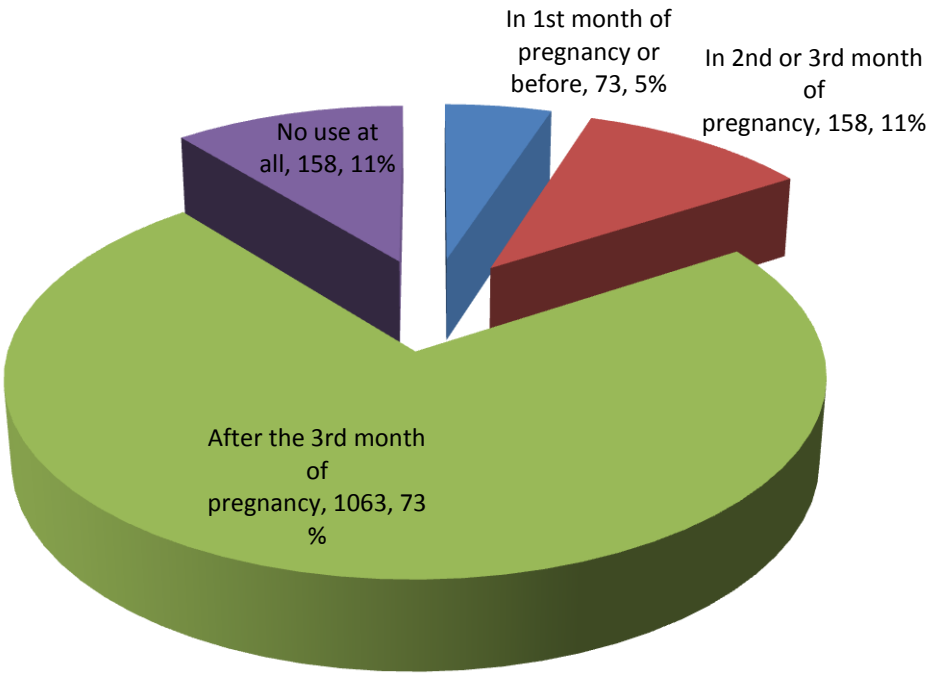

Figure 4.9: Folic acid containing multivitamin supplement use by the mothers

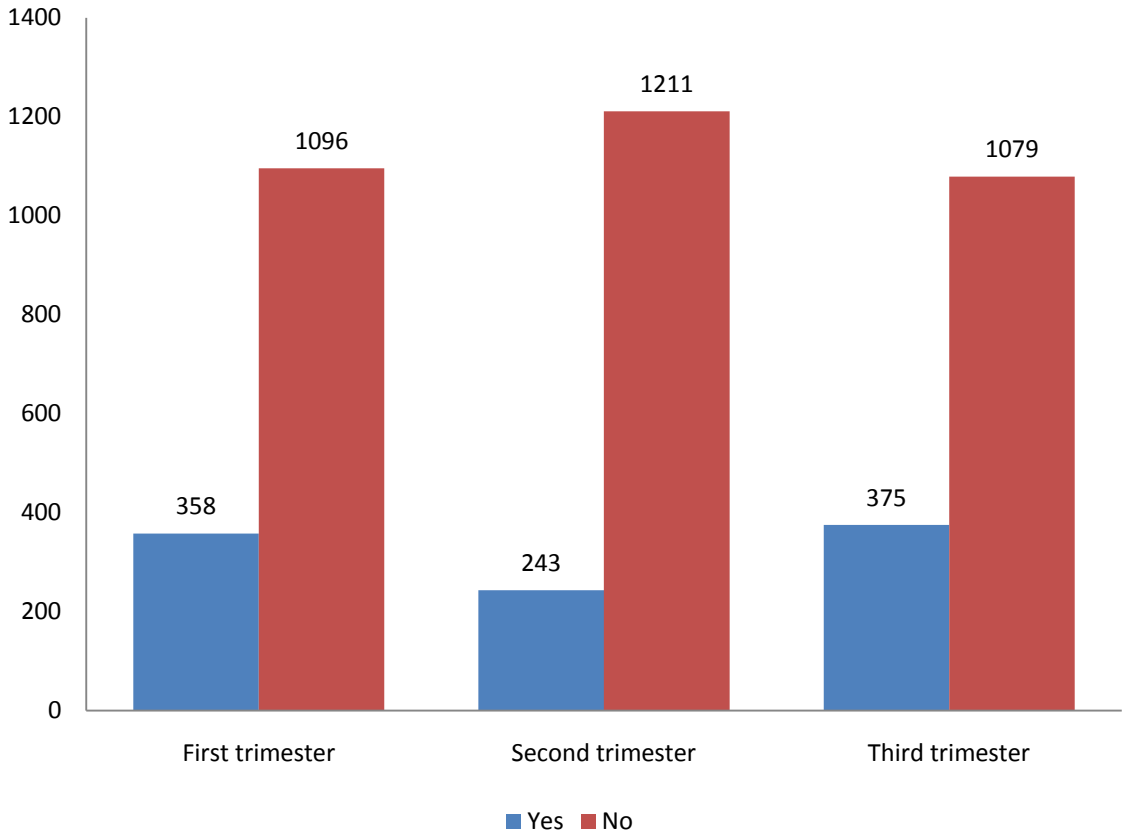

Figure 4.10: History of Maternal febrile illness during pregnancy

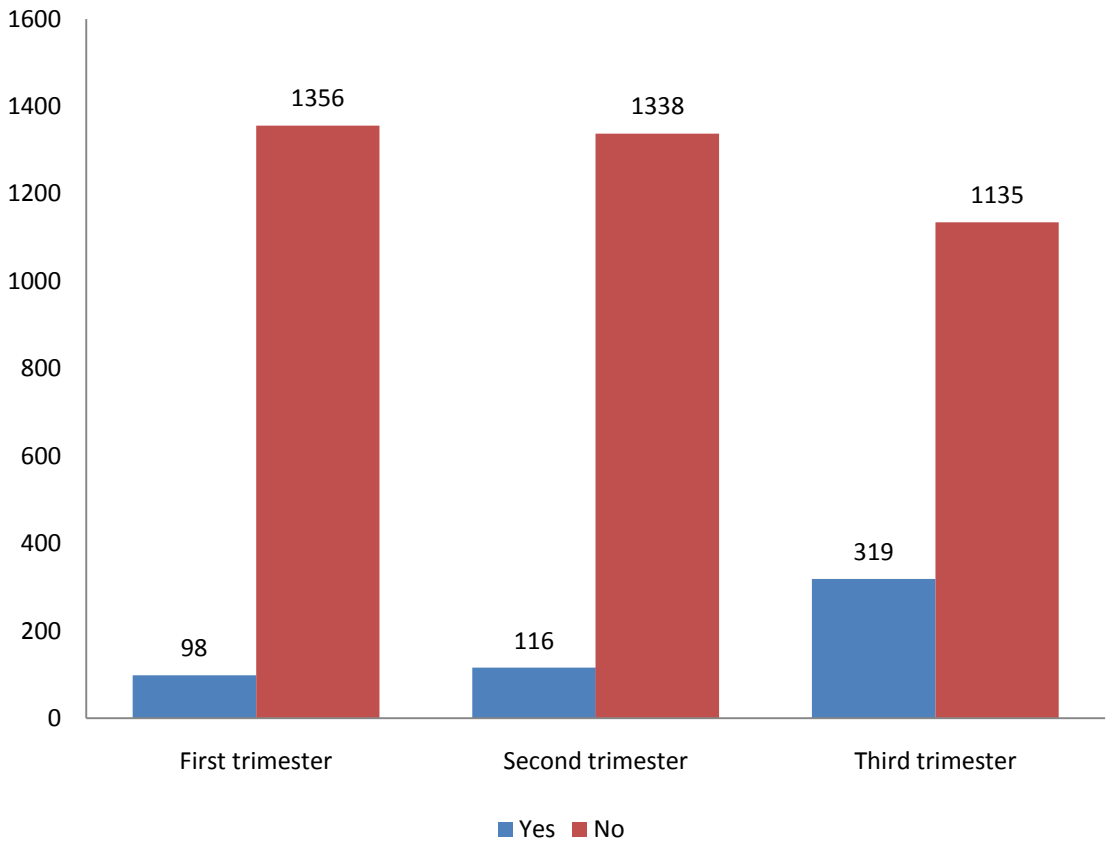

Figure 4.11: History of Maternal use of native medication during pregnancy

Of the 1456 neonates included into the study, 41 babies were found to have an overt congenital malformation (please see appendix V), giving a prevalence of 28.15 per 1000 live births (Fig. 4.12, Table 4.3). Among those with a congenital malformation, 5 (12.2%) had multiple abnormalities, while 36 (87.8%) had involvement of a single system (Fig 4.13). The prevalence for multiple malformations in the study was thus 3.43 per 1000 live births, and that for single-system malformations was 24.72 per 1000 live births. Among the neonates with single-system malformations, the most common systems involved were the central nervous system and genitourinary system with 10 cases each, the dermatological system (6 cases), and the gastrointestinal system (5 cases) (Table 4.3 and Table 4.4). The prevalence of central nervous system and genitourinary system malformations was 6.87 per 1000 live births each. That for dermatological system malformations was 4.12 per 1000 live births and the prevalence of gastrointestinal system malformations was 3.43 per 1000 live births.

Of the 5 neonates with multiple malformations, 2 had recognized syndromes one of which was a case of Down's syndrome and the other a case of Beckwith-Wiedemann Syndrome (Table 4.5). In 3 of these neonates with multiple malformations, a complete evaluation was not possible in order to determine whether they were syndromes, associations, sequences, complexes or chromosomal abnormalities. They were thus classified as "undetermined" (Table 4.5). The birth prevalence of Down's syndrome and Beckwith-Wiedmann Syndrome in the study was 0.69 per 1000 live births each.

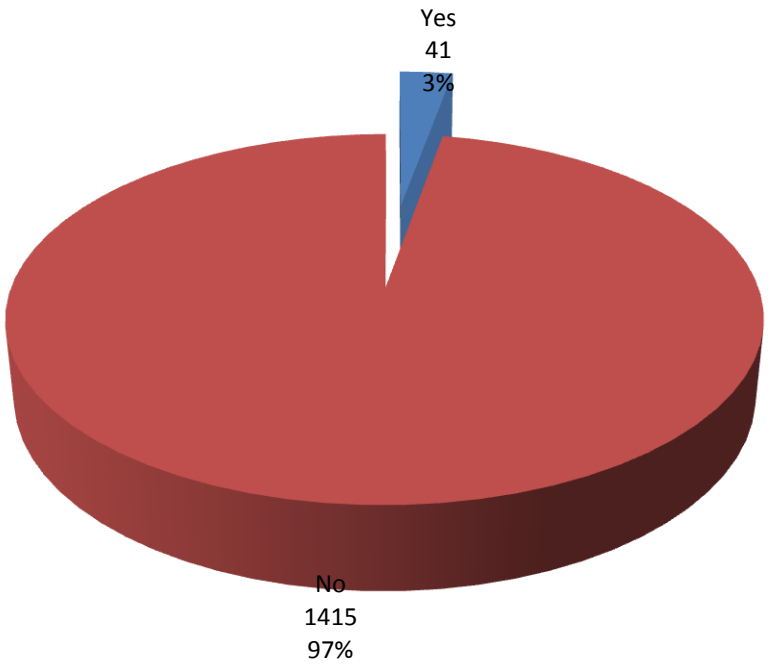

Figure 4.12: Prevalence of External congenital anomalies in the study population

Table 4.3: Summary of congenital malformations in the study

Malformations	No. of Cases	Prevalence/1000 Births
Multiple Malformations		
Syndromes	2	1.37
Undetermined	3	2.06
Sub-Total	5	3.43
Single-System Malformations		
Central nervous system	10	6.87
Mouth	2	1.37
Gastrointestinal	5	3.43
Genitourinary	10	6.87
Musculoskeletal	3	2.06
Dermatological	6	4.12
Sub-Total	36	24.72
Total	41	28.15

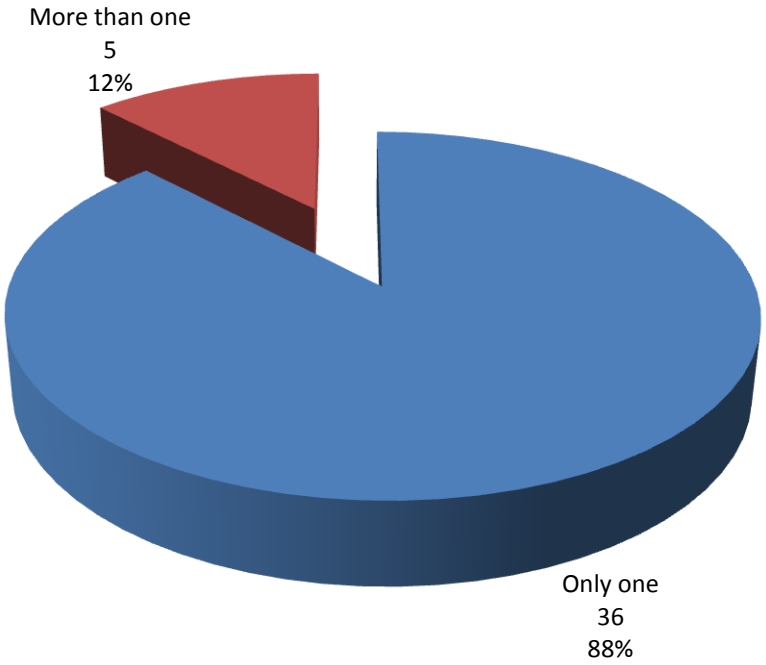

Figure 4.13: Single and multiple system affectation by congenital anomalies

Table 4.4: Single –System involvement among neonates with congenital malformations

	System	No. of Cases
A.	**Central Nervous System**	
	Hydrocephalus	2
	Anencephaly and encephalocoele	1
	Encephalocoele	1
	Microcephaly	6
	Sub Total	10
B.	**Mouth**	
	Cleft lip and palate	1
	Cleft palate	1
	Sub Total	2
C.	**Gastrointestinal System**	
	Intestinal Obstruction	2
	Omphalocoele	1
	Gastroschisis	2
	Sub Total	5
D.	**Genitourinary System**	
	Bladder exstrophy/epispadias complex	3
	Undescended testes	7
	Sub Total	10
E.	**Musculoskeletal System**	
	Polydactyly	3
	Sub Total	3
F.	**Dermatological**	
	Hyperpigmented patches	6
	Sub Total	6
	Total	36

Table 4.5: Multiple congenital abnormalities in the study

	Malformations	No. of Cases
A.	**Syndromes**	
	Down's	1
	Beckwith - Wiedemann	1
	Sub Total	2
B.	**Undetermined**	
	Microcephalous and sacrococcygealteratoma	1
	Hydrocephalus, meningocoele and bilateral talipesequinovarus	1
	Cleft lip, cleft palate and polydactyly of both upper and lower limbs	1
	Sub Total	3
	Total	5

4.2 BIVARIATE ANALYSIS

Table 4.6 presents the results of the bivariate analysis of socio-demographic characteristics of the neonates' mothers in relation to the birth of a child with a congenital malformation. With respect to the age of the mothers, the table shows that among the respondents, the prevalence of congenital anomaly in the offspring increased with increasing maternal age i.e. 19 years and below (3/153; 1.96%), 20 – 34 years (29/1061; 2.73%), 35 – 39 years (5/170; 2.94%), 40years and above (3/62; 4.84 %). This observed increase in prevalence with increasing maternal age was however not statistically significant (p = 0.71). The relationship between the level of maternal education and the birth of a child with a congenital anomaly was not statistically significant (p = 0.65). The mothers from a consanguineous home in the study, were more likely to have a child with a congenital abnormally (8/256; 3.13%) than women from non-consanguineous homes (33/1180; 2.80%). The association between consanguinity and birth of a child with congenital abnormality was however not statistically significant (p=0.94).

The findings show that with regards to parity, the neonates from mothers who have had five or more children, had a higher prevalence of congenital abnormalities (14/470; 2.98%) than the offspring of women with only one child (11/392; 2.81%). The relationship between parity of the mothers and birth of a child with congenital abnormality was not statistically significant (p = 0.94).

Table 4.6: Socio-demographic characteristics of neonates' mothers in relation to birth of a child with a congenital malformation

		Congenital malformation		Statistical significance	
Background characteristics	n	Present	Absent	x^2	p-Value
Age (Years)					
19 and below	153	3	150	1.38	0.71
20 – 34	1061	29	1032		
35 – 39	170	5	165		
40 and above	62	3	59		
Highest level of education					
None	25	0	25	1.63	0.65
Primary/Quaranic	552	17	535		
Secondary	661	20	641		
Post –Secondary	212	4	208		
Religion					
Christianity	68	2	66	0.09	0.96
Islam	1382	39	1343		
Others	3	0	3		
Ethnic group of husband					
Hausa/Fulani	1312	38	1274	1.20	0.75
Igbo	21	1	20		
Yoruba	24	0	24		
Others	96	2	94		
Nature of marriage					
Consanguineous	256	8	248	0.01	0.94
Non- Consanguineous	1180	33	1147		
Parity					
1	392	11	381	0.12	0.94
2 – 4	571	15	556		
5+	470	14	456		
Booking status of pregnancy					
Booked	1386	40	1346	0.07	1.00
Unbooked	65	1	64		
Age of husband (Years)					
20 – 34	498	12	486	0.49	0.78
35 – 39	306	9	297		
40 and above	580	18	562		

Table 4.7 shows that women who commenced use of folic acid containing multivitamin supplement at least one month before pregnancy or in the first month of pregnancy, had a lower prevalence of birth of a child with a congenital abnormality (2/73; 2.74%) than those who reported none use throughout pregnancy (6/158; 3.80%). The study however, did not establish a statistically significant relationship between folic acid containing multivitamin supplement use in pregnancy and the birth of a child with a congenital abnormality (p=0.89). Also, the relationship between maternal febrile illness in the first trimester of pregnancy and the birth of a child with a congenital abnormality was not significant (p=0.48), although the study showed that the birth of a child with a congenital anomaly was more in women who had a febrile illness in the first trimester of pregnancy (12/358; 3.35%) than in those who did not have a febrile illness in the first trimester of pregnancy (29/1096; 2.65%). The analysis revealed that mothers who used native (non-orthodox) medication in the first trimester of pregnancy, had a higher prevalence of birth defects in their offspring (4/98; 4.08%) than women who had not used native medication in the first trimester of pregnancy (37/1356; 2.73%). The study however, did not establish a statistically significant relationship between use of native medication in the first trimester of pregnancy and the birth of a child with congenital abnormality (p=0.44).

Table 4.7: Peri-Pregnancy characteristics of neonates' mothers in relation to birth of a child with a congenital malformation

		Congenital malformation		Statistical significance	
Background characteristics	n	Present	Absent	x^2	p-Value
Folic acid containing multivitamin supplement use in pregnancy.					
≤ 1 month before pregnancy	73	2	71	0.63	0.89
2nd or 3rd month of pregnancy	158	4	154		
After 3rd month of Pregnancy	1063	29	1034		
No use at all	158	6	152		
Pregestational Diabetes mellitus					
Yes	23	0	23	0.68	0.41
No	1431	41	1390		
Febrile illness in first trimester of pregnancy					
Yes	358	12	346	0.49	0.48
No	1096	29	1067		
Native medication use in first trimester of pregnancy					
Yes	98	4	94	0.61	0.44
No	1356	37	1319		

Table 4.8 shows the results of the bivariate analysis of characteristics of neonates in the study in relation to being born with a congenital malformation. With respect to the gender of the child, females had a higher prevalence of birth defects (20/699; 2.86%) than males (21/757; 2.77%). The relationship between gender of the child and being born with a congenital abnormality, was however not statistically significant (p=0.92). The analysis shows that children with a gestational age of 36 weeks or less at birth had a higher prevalence of congenital malformations (11/363; 3.03%) than those who had a gestational age of 41 weeks or more at birth (5/220; 2.27%). There was no statistically significant relationship between gestational age at birth and being born with a congenital anomaly (p=0.86). Singletons in the study had a higher prevalence of congenital anomalies (38/1334; 2.85%) than twins (3/116; 2.59%). The relationship between nature of gestation and being born with a congenital abnormality was also not statistically significant (p=0.90).

With respect to birth weight, children who weighed less than 2.5kg at birth, had a higher prevalence of congenital malformation (8/98; 8.16%) than those who weighed 2.5kg – 4.0kg at birth (29/1196; 2.42%) and those who weighed more than 4.0kg at birth (0/27; 0%). The study showed a statistically significant relationship between the weight at birth of the children and being born with a congenital malformation (p=0.003). The analysis also showed that there was no statistically significant relationship between having a relative with a congenital abnormality and being born with a birth defect (p=0.50). Children who had relatives with a birth defect however, had a higher prevalence at birth of congenital abnormality (2/47; 4.26%) than those who had no relatives with a congenital abnormality (37/1367; 2.71%).

Table 4.8: Characteristics of neonates in the study in relation to being born with a congenital malformation

		Congenital malformation		Statistical significance	
Background characteristics	n	Present	Absent	x^2	p-Value
Gender					
Male	757	21	736	0.01	0.92
Female	699	20	679		
Types of Delivery					
Vaginal	1242	35	1207	0.002	0.97
Caesarean Section	209	6	203		
Gestational age (Weeks)					
36 and below	363	11	352	0.30	0.86
37 – 40	838	23	815		
41 and above	220	5	215		
Nature of gestation					
Singleton	1334	38	1296	0.20	0.90
Twins	116	3	113		
Triplets	6	0	6		
Birth weight (kg)					
< 2.5	98	8	90	11.75	0.003
2.5 – 4.0	1196	29	1167		
>4.0	27	0	27		
Birth defect in a relative					
Yes	47	2	45	1.40	0.50
No	1367	37	1330		
Don’t Know	36	2	34		

4.3 MULTIVARIATE ANALYSIS

Table 4.9 presents the adjusted odds ratios (OR) and 95 percent confidence intervals (CI) for being born with a congenital abnormality, based on the result of a binary logistic regression analysis done using age of mother, nature of parents' marriage, mother's parity, gestational age and birth weight as independent variables.

The findings of this model showed that maternal age of the children, was not an important predictor of being born with a congenital abnormality [OR = 1.04; (95 % CI 0.97 – 1.13); p= 0.28].

A consideration of the nature of parents' marriage showed that mothers who had a non-consanguineous marriage were less likely to have offspring with a birth defect when compared with those who had a consanguineous marriage [OR = 0.81; (95 % CI 0.34 – 1.90); p = 0.63]. This finding however was not statistically significant.

With respect to mother's parity, this model showed that it was not an important predictor of being born with a congenital abnormality [OR = 0.94; (95 % CI 0.79 – 1.12); p= 0.50].

When gestational age of the neonates at birth was considered, this model also showed that it was not an important predictor of being born with a congenital abnormality [OR = 1.00; (95 % CI 0.88 – 1.15) p = 0.95].

With regards to birth weight of the neonates, the findings from this model revealed that it was a significant and important predictor of being born with a congenital abnormality [OR = 0.37; (95 % CI 0.20 – 0.71) p = 0.003].

Thus birth weight has a significant but negative association with the likelihood of being born with a congenital abnormality.

Table 4.9: Multivariate analysis of congenital malformations and other birth characteristics

Explanatory variable	Odds Ratio	p-Value	95% CI (for odds ratio)	
Age of Mother	1.04	0.28	0.20	1.13
Nature of Marriage				
Consanguineous#	-	-	-	-
Non-Consanguineous	0.81	0.63	0.34	1.90
Mother's parity	0.94	0.50	0.79	1.12
Gestational age (weeks)	1.00	0.95	0.88	1.15
Birth weight (kg)	0.37	0.003	0.20	0.71

#Comparison Group

CHAPTER FIVE

5.0 DISCUSSION

Birth defects are an important cause of morbidity and mortality among children worldwide, thus making them a relevant public health concern. It is believed that approximately one-fifth of all birth defects are severe and life threatening, and a considerable uncertainty remains as to the incidence of and mortality attributable to congenital abnormalities in countries of Sub-Saharan Africa that lack adequate registration of deaths (Queisser-Luft and Spranger, 2006; WHO, 2010).

The overall prevalence of birth defects in a given population, tells how many children in that population were born with at least one congenital abnormality. Worldwide surveys have shown that birth prevalence of congenital abnormalities varies greatly from country to country and even within the same country among regions, and this may be attributed to one or more factors such as the design of the study (hospital based or community based, prospective or retrospective), definitions, classifications and inclusion criteria used, end-point of the detection period, type of surveillance system and completeness of patient ascertainment, etiological heterogeneity of malformations, accuracy of diagnosis, prenatal screening policies, the extent of selective termination of affected pregnancies, the gestational age at which these are included in monitoring reports, the extent to which the terminations are notified, social, racial, ecological and economical influences (Sawardekar, 2005;Dastgiri *et al*.,2007; Francine*et al*, 2014). As a consequence of all these factors, estimates of birth prevalence vary from place to place and thus make comparison of rates among studies difficult and probably not very informative (Sawardekar, 2005; Kurinczuk*et al*., 2010).

However, apart from a small number of specific anomalies, any differences in prevalence are thought largely to be due to methodological differences (such as age of study subjects, whether or not stillbirths and abortuses are included, inclusion or exclusion of autopsies and cytogenetic analyses in the study methodology) rather than true differences in underlying population incidence (Kurinczuk*et al.,* 2010).

The prevalence of congenital malformations in this study was 28.15 per 1000 live births (2.82 %). This figure is lower than the figure (6.9%) reported in neonates by Bakare*et al*., (2009) in South Western Nigeria. It is however higher than the figure (0.75%) reported from a hospital based study in neonates by Eluwa*et al*., (2013) in Cross River State of Southern Nigeria. Birth prevalence of congenital anomalies varies appreciably from country to country being as low as 1.07% in Japan and as high as 4.3% in Taiwan (Francine *et al.*, 2014). The prevalence of congenital malformations found in this study falls within this worldwide range. One of the reasons to explain this variation of prevalence figures could be that some degree of selection bias was probably in effect because the study was conducted in 3 major hospitals in the Kano metropolis of North Western Nigeria, which also receive referrals of high risk pregnancies from peripheral hospitals. The exact number of such referrals as well as the number of pregnancies with fetal malformations diagnosed elsewhere and referred to these hospitals for management was not assessed by this study. It is also worthy of note to mention that the rates reported in this study might have underestimated the prevalence of birth defects in the region as not all congenital anomalies could be detected at birth or shortly thereafter because of the lack of cytogenetic and teratology investigations or autopsies for stillbirths and neonatal deaths (Dastgiri*et al.*, 2007).

Longitudinal cohort studies with special follow up examination provide high incidence figures for congenital anomalies as contrasted to studies based on information from hospital

data, because it collects valid information on late manifestation of congenital malformations (Shawky and Sadik, 2011).

The highest frequency of congenital malformations reported in this study involved the central nervous system (CNS) and genitourinary system (GU), followed by dermatological system, gastrointestinal system (GIT), musculoskeletal system, and the mouth. CNS anomalies which occurred both as single system and multiple system malformations are considered the most common anomalies in this study. This finding is similar to what has been reported from Cross Rivers State in the South of Nigeria (Eluwa*et al*., 2013), and from Jos in the North central region of Nigeria (Danborno and Danladi, 2008), as well as workers from other parts of the world (Swain *et al*., 1994; Dastgiri*et al*., 2007; Shawky and Sadik, 2011).The finding is however at variance with the report of Bakare*et al*., (2009) from South Western Nigeria and that of some other workers from outside the region (Sawardeker, 2005; Queisser-Luft and Spranger, 2006; Francine *et al*., 2014). The data however, show that the frequency of anomalies in other systems differ from that reported in different studies done from various regions of the world (Al-Gazali*et al*., 1995; Sallout*et al*., 2008; Tomatir*et al*., 2009).

The geographic variations for some defects may be a reflection of local prevalence rates and risk factors, environmental, genetic and ethnic variations (Shawky and Sadik, 2011). In Western Europe the incidence of live births with spina bifida has diminished in recent years through a combination of primary prevention (folic acid dietary supplements through the first trimester of pregnancy) and secondary prevention (detection of neural tube defects in the fetus at 10 weeks gestation, and abortion), thus the differences in health provision, generate a substantially different context for Western Europe as compared with sub-Saharan Africa (Czeizel, 2004; Miles, 2006).

Neural tube defects (NTD) are malformations of the cranium, spine and nervous system; types of NTDs include anencephaly, spina bifida,encephalocele, and meningocele. Neural tube defects are a major cause of mortality in newborns and have been estimated to affect 0.5 to 8 per 1000 live births (Koren*et al*., 2008). Randomized trials supported by many observational studies have shown that maternal use of at least 400 micrograms of folic acid alone or in multivitamin supplements daily starting at least one month before conception and through the first trimester of pregnancy is effective in preventing both the occurrence and recurrence of neural tube defects (Sawardekar, 2005; Ying Wu *et al*., 2007; Koren*et al*., 2008). Periconceptional use of folic acid alone, or in multivitamin supplements have also been shown to reduce the occurrence of some other congenital abnormalities (Hall and Solehdin, 1998; Czeizel, 2005; Bailey and Berry, 2005). Data from this study shows that only 5.03% of the mothers began the use of folic acid containing multivitamin supplement at least 1 month before or in the first month of pregnancy. In this group, only 2.53% of their offspring had a congenital abnormality. Women who did not use folic acid containing multivitamin supplement at all throughout the duration of the pregnancy constituted 10.88% of the mothers, and in them, 3.80% of their offspring had a congenital abnormality. The relationship between the onset of use of folic acid containing multivitamin supplement and the birth of a child with a birth defect was however, not statistically significant. Other unmeasured confounding factors may be responsible for this finding.

There were two babies in this study who had major congenital malformations associated with chromosomal abnormalities. The birth prevalence of chromosomal abnormalities in this study was 1.37 per 1000 live births, which is lower than 3.2 per 1000 reported by Sawardeker (2005) but higher than 0.87 per 1000 reported by Dastgiri*et al*., (2007). Al-Gazali*et al*., (1995) had earlier reported a prevalence of 1.70 per 1000 for chromosomal abnormalities in

children born in the United Arab Emirates (UAE). The birth prevalence of Down syndrome in the study was 0.69 per 1000 live births, which is lower than the 2.0 per 1000 reported by Sawardeker (2005) and the 1.15 per 1000 reported by Al-Gazali*et al*., (1995). The live birth prevalence of Down syndrome diagnoses in England and Wales in the year 2010 was 1 per 1000 (Springett and Morris, 2012). Lowry *et al*., (2009) had reported that in 2007, the birth prevalence of Down syndrome in the Alberta region of Canada was 1.66 per 1000. The only unequivocally demonstrated risk factor for Down syndrome is an advanced maternal age (more than 35 years) (Queisser-Luft and Spranger, 2006; Lowry *et al*., 2009). In this study only 16% of the mothers were aged 35 years or more. The neonate in this study who had Down syndrome was born to a 45 year old woman. Lowry *et al*., (2009) also reported that 16% of the mothers in the region of Alberta Canada in 2007 were aged 35 years or over. It has been reported that the prevalence at birth of Down syndrome has decreased over the past few years in programs that showed a high rate of termination of pregnancies, and an increase in the terminations year by year; in the same way the highest rates of birth prevalence have been observed in programs where terminations were lowest (Sawardeker, 2005). According to Springett and Morris (2012), in England and Wales, of all the pregnancies in which an anomaly was suspected prenatally in 2010, about 44% resulted in a termination of pregnancyfor fetal anomaly. Termination of pregnancy for prenatally detected fetal anomalies is currently not being practiced in Nigeria.

In this study, the prevalence of congenital malformations increased with increasing maternal age, being lowest in mothers aged 19 years and below (1.96%) and highest in mothers aged 40 years and above (4.84%). The relationship between maternal age and the birth of a child with a congenital abnormality was however, not statistically significant. Shawky and Sadik (2011) had earlier reported that the prevalence of congenital malformations was significantly

increased with increased maternal age above 35 years in their study. Springett and Morris (2012) have also shown that the highest prevalence of all anomalies in England and Wales (393 per 10,000 total births, 95% CI: 353, 436) were seen in women aged 40 years and above. Increasing maternal age is the most important, and probably the only documented non genetic risk factor for trisomies in humans, and is believed to result from an increase in chromosomal meiotic errors that occur with age (Shawky and Sadik, 2011). On the other hand, gastroschisis occurs mainly in infants of very young mothers (15 – 19 years), to a lesser degree the increase also occurs among the 20 to 24 years age group with relative stability in prevalence among subsequent maternal ages (Lowry *et al*., 2009; Shawky and Sadik, 2011). In addition, young paternal age has been independently associated withgastroschisis (Shawky and Sadik, 2011). In this study, there were two neonates with gastroschisis, giving a prevalence of 1.37 per 1000 births, which is higher than the prevalence of 0.60 per 1000 reported for the region of Alberta Canada (Lowry *et al*., 2009). The mothers of the neonates were aged 23 and 20 years and their husbands were aged 32 and 30 years respectively. Gastroschisis can occur in conjunction with other malformations such as arthrogryposis multiplex congenita (Khalil *et al*., 2007). The two cases reported in this study were however, isolated cases. Although the exact cause of gastroschisis is not known, there is a positive correlation with a number of risk factors such as the absence of prenatal care, use of vasoconstrictive recreational drugs such as ecstasy, amphetamines and cocaine, smoking cigarettes or marijuana, poor nutrition and genitourinary infections (Lowry *et al*., 2009).

It has been reported that the prevalence of malformations of the extremities and syndromes of multiple systems, as well as Down syndrome, increased with increasing paternal age i.e. 40 years and above (Shawky and Sadik, 2011). Findings from this study showed that the prevalence of congenital anomalies did increase with increasing paternal age i.e. 2.41% for

age group 20 – 34 years, 2.49% for age group 35 – 39 years and 3.10% for age group 40 years and above. The relationship between paternal age and being born with a congenital anomaly was however not statistically significant. This is similar to the findings of Al Bu Ali *et al*., (2011).

Consanguineous marriages are believed to be important in contributing to the risk of being born with a congenital abnormality (Narchi and Kulaylat, 1997; Al-Gazali*et al*., 2006; Fida*et al*., 2007; Al Bu Ali *et al*., 2011). It has been documented that the risk of a child having a recessively inherited condition is higher if the parents are related, and the more closely related the parents are, the higher the risk (Al-Gazali*et al*., 1995; Fida*et al*., 2007). High rates of consanguinity ranging between 25 – 60% of all marriages have been reported for Muslim Arab countries (Sawardeker, 2005; Al-Gazali*et al*., 2006, Shawky and Sadik, 2011). Majority of the mothers in this study (95.11%) were from Muslim homes, and the consanguinity rate in the study was 17.83 %. The rate of malformation was 3.13% and 2.80% in consanguineous and non-consanguineous marriages, respectively. Although, the prevalence of anomalies was higher in consanguineous marriages than non consanguineous marriages, this was however, not statistically significant. This finding is in agreement with the finding of Tayebi*et al*., (2010), but is at variance with the results from the study by Francine*et al*., (2014) who found a statistically significant relationship between parental consanguinity and being born with a congenital abnormality.

In this study, females were more affected with congenital anomalies (2.86%) than males (2.77 %). This difference was however, not statistically significant. Other workers have reported a male excess for congenital anomalies (Shawky and Sadik, 2011, Sokal*et al*., 2014). This finding has raised some speculations i.e. either females are afflicted with a relatively more minor abnormality which they survive with, or they suffer more fatal anomalies (Fida*et*

al., 2007). It is thus recommended that sex distribution should be studied in every congenital malformation separately and not in the whole group, as it is evident from literature that there are large reported variations in pattern of congenital malformations involving different body systems (Fida*et al*., 2007; Shawky and Sadik, 2011).

Multi-parity was associated with increased prevalence of congenital malformations in this study. Women who had 5 or more children had the highest prevalence of births with a congenital malformation (2.98 %). The relationship between parity and the birth of a child with a birth defect was however, not statistically significant. Shawky and Sadik, (2011) had earlier noted an association between multi-parity and an increase in the prevalence of congenital malformations. Muga*et al*., (2009) had also noted in their study that among the babies with a CNS malformation, that birth order "4" contributed 55.2% of the cases. At variance with these observations however is the report by Tomatir*et al*., (2009), who showed that in their series, 78.1% of the mothers who had given birth to a child with a congenital anomaly, were experiencing their first or second live birth.

Findings from this study show that the prevalence of birth defects was higher in the offspring of women who had a history of a febrile illness in the first trimester of pregnancy (3.35%) than those who did not have (2.65 %). The association between the birth of a child with a congenital anomaly and having a febrile illness in the first trimester of pregnancy was however not statistically significant. It has been known for about 100 years now that malformations could be induced in various animal species by exposing the mother to high body temperatures during critical periods of gestation (Graham *et al*., 1998; Moretti*et al*., 2005; Edwards, 2006). Although human data are inconclusive and often conflicting, it is believed that the threshold of effect in many species begins at about 1.5^{o}C over normal core body temperature (Graham *et al*., 1998; Moretti*et al*., 2005). Defects of the CNS,

craniofacial development including clefts, the axial and appendicular skeleton, the body wall, teeth, and heart are commonly found in various animal species, and nearly all these defects have been found in human epidemiological studies following maternal fever or hyperthermia during pregnancy (Edwards, 2006). In a recent study, Agopian*et al*., (2013) showed that the risk for gastroschisis in offspring was increased among women who reported having hot showers lasting $\geq$ 15 minutes compared to < 15 minutes. In addition, they observed modest increase in the risk for spina bifida, cleft lip with or without cleft palate, and limb reduction defects in offspring of women who showered $\geq$ 15 minutes compared to < 15.

Data from this study show that 9.76% of the mothers of the neonates with congenital anomalies had a positive history of use of native medication (non-alcohol, non-orthodox) in the first trimester of pregnancy. The prevalence of congenital anomalies was higher (4.08%) in the offspring of mothers who had used native medication in the first trimester of pregnancy than in those who had not (2.73%). This was however, not statistically significant. Drugs taken by pregnant women can cross the placenta, alter its oxygen transport function by constricting blood vessels, and affect the fetus by acting directly on it, causing damage, abnormal development, teratogenesis or death (Shawky and Sadik, 2011). Francine *et al*., (2014) documented in their series that maternal drug intake during pregnancy was positively associated with congenital malformation in the offspring.

In this study, a high prevalence of birth defects (8.16%) was observed in children whose birth weight was less than 2.5 kg, than in those with a birth weight of 4.0 kg and above (0%). This finding was statistically significant. Multivariate analysis also revealed that birth weight was a significant and important predictor of being born with a congenital abnormality among the neonates in the study [OR = 0.374; (95% CI 0.196 – 0.711) p = 0.003]. Thus among these neonates, every 1 kg decrease of birth weight below the lower limit of normal i.e. 2.5 kg,

increases the odds of being born with an congenital abnormality by 37.4%. A high prevalence of birth defects was also noted in this study for preterm (less than 37 weeks gestational age) neonates than far term (37 weeks gestational age or more) neonates. This finding was however not statistically significant. A high prevalence of birth defects have also been previously reported in other studies among infants with low or very low birth weight as well as in prematures (Melve and Skjaerven, 2002; Fatema*et al*., 2011; Adams – Chapman *et al*., 2013; Francine *et al*., 2014). More than 20 million low birth weight (LBW) infants are born globally each year, consisting 17% of all births in developing countries, which is more than the 7% rate in industrialized nations (Moraes*et al*., 2012). Low birth weight babies basically constitute two groups of babies - those born before 37 completed weeks (preterms) and those born after 37 completed weeks [small for gestational age (SGA)], with the causes and mechanisms involved in LBW being different for premature infants and SGA infants and thus requiring different interventions for prevention (Ugwu and Eneh, 2010). The relationship between growth restriction and malformations may be explained by either the growth restriction as primary and predisposing the fetus to malformations, or as secondary to the presence of malformations, or by coexisting with a malformation due to common etiologic factors (Melve and Skjaerven, 2002).Low birth weight can be caused by various perinatal problems, most frequently by low gestational age (Moraes*et al*., 2012). The prevalence of low gestational age (less than 37 weeks) in this study was 25.55 %.

Shawky andSadik (2011) had earlier shown in their study that family history of congenital malformations was significantly higher among children with congenital malformation than in controls. In this study however, although there was a higher prevalence of congenital malformation in the offspring of mothers who gave a family history of birth of a child with a

birth defect (4.26%) than in those without a similar history (2.71 %) this finding was however not statistically significant.

CHAPTER SIX

6.0 SUMMARY, CONCLUSION AND RECOMMENDATIONS

6.1 SUMMARY

Congenital malformations also known as birth defects are structural or functional abnormalities of prenatal origin. Recorded prevalence rates for congenital anomalies in developing countries is underestimated by deficiencies in diagnostic capabilities, lack of reliability of medical records and health statistics, and by underreporting. The objective of this study was to determine the prevalence and spectrum of overt congenital anomalies in live born neonates in selected hospitals in the Kano metropolis of North Western Nigeria, as well as the associated maternal, paternal and neonatal risk factors.

A descriptive study design was employed in this study. All live born neonates in three selected major hospitals in the Kano metropolis i.e. Aminu Kano Teaching Hospital (AKTH), Murtala Mohammed Specialist Hospital (MMSH), Sheikh Jidda Specialist Hospital (SJSH), were prospectively studied from April 2013 to December 2013. Detailed family history and clinical data were recorded in a structured questionnaire for each child. Congenital malformations were classified as multiple or single system abnormalities.

The prevalence of birth defects in this study was 28.15 per 1000 live births. CNS anomalies were the most common congenital malformations noted in the study population, occurring both as single system and multiple system malformations. Other common anomalies were genitourinary and dermatological system anomalies.

Most of the mothers (73.37%) were aged between 20 – 34 years, and 90.3% of them came from Hausa/Fulani homes, with about 45.59% of them having attained a secondary school level of education.

The consanguinity rate in the study was 17.83%. Only 5.02% of the mothers began use of folic acid containing multivitamin supplement at least one month before pregnancy or in the first month of pregnancy.

Birth weight of the neonates in this study was a significant and important predictor of being born with a congenital abnormality. It had a significant but negative association with the likelihood of being born with a congenital abnormality. Thus, data from the study showed that the lower the birth weight, the higher the likelihood of the neonate having a congenital anomaly.

This study had some limitations in that it sought to detect only external (overt) congenital anomalies in neonates within the first 48 hours of births, relying only on clinical examinations to make a diagnosis. Also neither cytogenetic analysis nor autopsies for stillbirths were done. The study location being an urban setting, would also have introduced a bias, since the results may not be extrapolated to a rural setting with relatively poorer access to modern health care services. It has been documented that a specific diagnosis may not be reached for 30 – 60% of infants with malformations and that diagnosis is not always apparent in the new born period (Sawardekar, 2005). Given that all the study subjects were neonates, the results of the study may not reflect the true prevalence of congenital anomalies in the study population.

Notwithstanding the noted limitations, this study provides some information on the magnitude and spectrum of congenital malformation diagnosed soon after birth in neonates in the Kano metropolis of North-Western Nigeria.

6.2 CONCLUSION

Data from this study show that CNS anomalies were the most common congenital malformations noted in the study population. Also the prevalence of low gestational age (prematurity) in the study was 25.55%. Given the positive association between low birth weight, prematurity and congenital malformations, emphasis ought to be placed on primary prevention of congenital anomalies, targeting those obstetric factors that increase the incidence of prematurity and neural tube defects (such as maternal diabetes mellitus, anaemia in pregnancy, and maternal food insecurity) in the offspring by encouraging routine and comprehensive prenatal care for all expectant mothers, peri-conceptional use of folic acid containing multivitamin preparation, the avoidance of known teratogens (such as alcohol, ionizing radiation and drugs) and probable teratogenic agents, as well as preventing and treating diseases such as malaria and HIV/AIDS.

6.3 RECOMMENDATIONS

The findings of this study show that the birth prevalence of overt congenital malformations in neonates in Kano metropolis is 28.15 per 1000 live births, a figure similar to that reported in international literature. Given that congenital malformations are a leading cause of childhood morbidity and mortality, and thus a public health concern, the following recommendations are hereby proffered:

i. Coordination of medical, social and educational services to raise awareness among health professionals as well as the general public about birth defects, by developing culturally appropriate educational material and involving community and religious leaders in information dissemination.
ii. Emphasizing the importance of timely, accurate and specific diagnosis of congenital malformations in the newborn period to optimize outcome. This can be achieved by

training nurses and midwives to do a complete head to toe examination of all newborns to help detect and document birth defects before the baby is discharged home.

iii. Emphasizing the need for primary prevention measures, which can be incorporated into the existing primary health-care system in the country, such as avoidance of known teratogenic agents, appropriate management of maternal conditions such as obesity and diabetes, and the treatment of malaria and other illness in pregnancy, advice related to maternal nutrition, peri-conceptional use of folic acid containing multivitamin supplements, fortification of flour with folic acid, family planning, counseling in advanced maternal age, and premarital counseling.

iv. The need for further education and training of primary health care providers (and other caregivers) in the field of clinical genetics to develop the necessary expertise in the management of congenital anomalies.

v. The need for surveillance and development of a congenital anomaly monitoring system both at the regional and national levels. This is a pressing need, since for etiological studies, prevention, and management of birth defects, it is important to have population-based monitoring which provides reliable data on the prevalence at birth of such defects and their secular trends.

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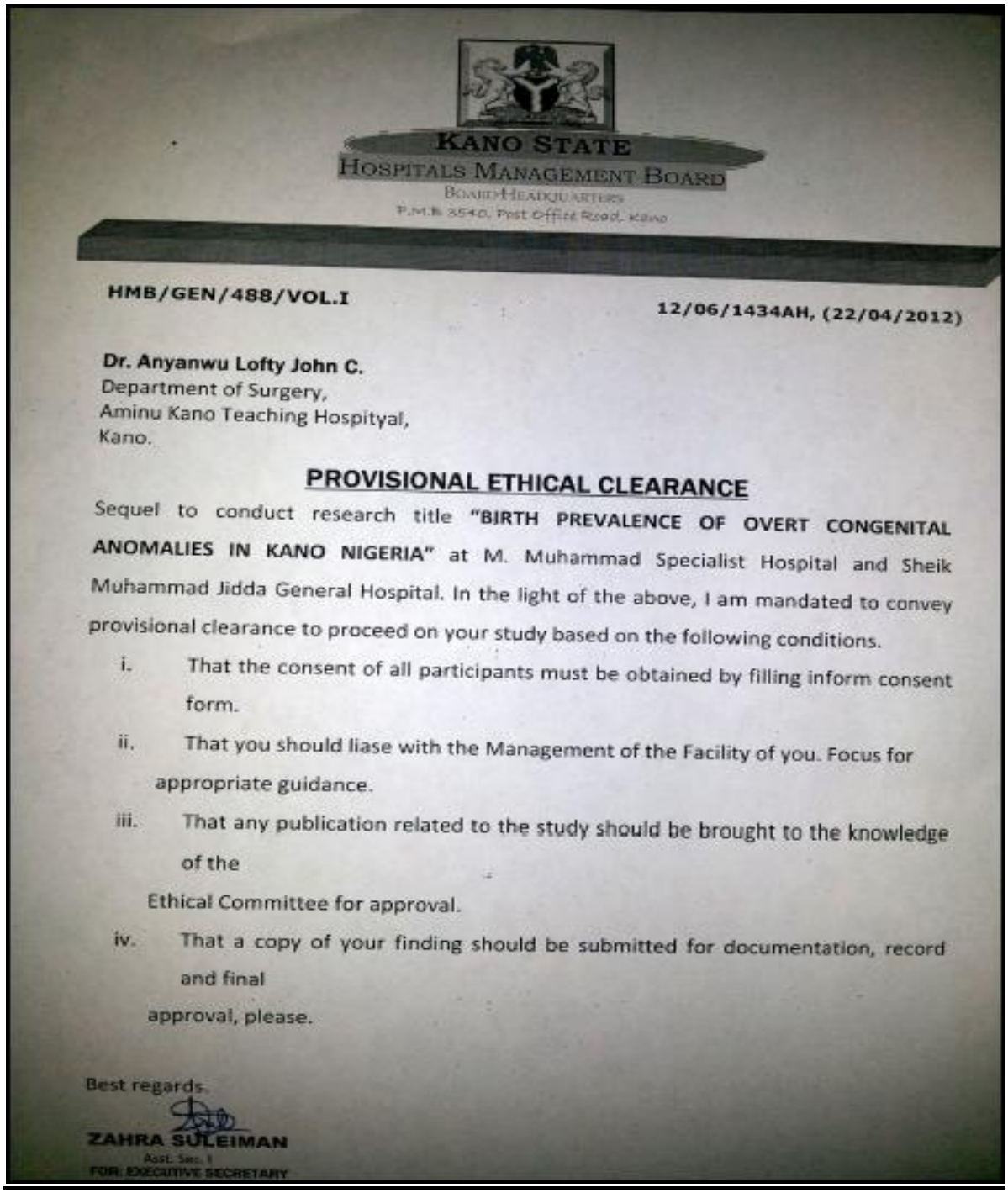
APPENDIX I

ETHICAL CLEARANCE



KANO STATE
HOSPITALS MANAGEMENT BOARD
BOARD HEADQUARTERS
P.M.B. 3540, Post Office Road, Kano

HMB/GEN/488/VOL.I

12/06/1434AH, (22/04/2012)

Dr. Anyanwu Lofty John C.
Department of Surgery,
Aminu Kano Teaching Hospityal,
Kano.

PROVISIONAL ETHICAL CLEARANCE

Sequel to conduct research title **"BIRTH PREVALENCE OF OVERT CONGENITAL ANOMALIES IN KANO NIGERIA"** at M. Muhammad Specialist Hospital and Sheik Muhammad Jidda General Hospital. In the light of the above, I am mandated to convey provisional clearance to proceed on your study based on the following conditions.

i. That the consent of all participants must be obtained by filling inform consent form.

ii. That you should liase with the Management of the Facility of you. Focus for appropriate guidance.

iii. That any publication related to the study should be brought to the knowledge of the Ethical Committee for approval.

iv. That a copy of your finding should be submitted for documentation, record and final approval, please.

Best regards.

ZAHRA SULEIMAN
Asst. Sec. I
FOR: EXECUTIVE SECRETARY

AMINU KANO TEACHING HOSPITAL

P. M. B. 3452, ZARIA ROAD, KANO.

(☎: 07068297399, 08057203531, 064 - 377085 - 8) www.akth.org, E-mail: enquiries@akth.org, email: (akthkano@yahoo.com)

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NHREC/21/08/2008/AKTH/EC/1023

AKTH/MAC/SUB/12A/P-3/VI/1123 — 12th March, 2013

Dr. Anyanwu Lo[illegible]ohn Chukwemeka
Department of Surgery
AKTH, Kano

Ufn.

The Head of Department
Department of Surgery
AKTH, Kano

ETHICAL APPROVAL

Further to the request for approval in respect of your research proposal "Birth Prevalence of Overt Congenital Anomalies at an Urban Tertiary Hospital in Kano, Nigeria". The Committee has reviewed your proposal and noted same as a Prospective study.

Similarly, the Committee requires you to keep Data ananimous and ensure confidentiality on information retrieve in the consent form.

In view of above, Ethical approval is hereby granted to conduct the research.

However, the approval is subject to periodic reporting of the progress of the study and its completion to the Ethical Committee.

Regards

Bara'atu Kabir (Mrs.)
Secretary Ethical Committee
For: Chairman

APPENDIX II

SUBJECT INFORMATION SHEET

My name is Anyanwu LJC; I am a postgraduate student of the Department of Human Anatomy, Ahmadu Bello University, Zaria.

I am conducting a study titled "The Prevalence of overt congenital anomalies in live births at selected Hospitals in Kano metropolis, Nigeria.

The research is to be conducted using interviewer administered questionnaires

The aim of this study is to determine the commonly seen birth defects in children born in this hospital and to be able to quantify the volume of the problem.

I can be contacted for further clarifications on 08037052659. My e-mail address is loftyjohnc@yahoo.com.

Thank you very much.

Yours sincerely

Anyanwu LJC

APPENDIX III

CONSENT FORM FOR RECRUITMENT OF RESPONDENTS INTO THE STUDY OF 'THE PREVALENCE OFOVERT CONGENITAL ANOMALIES IN LIVE BIRTHS AT SELECTED HOSPITALS IN KANO METROPOLIS, NIGERIA' USING INTERVIEWER ADMINISTERED QUESTIONNAIRE.

You are asked to participate in a research study conducted by Anyanwu LJC a postgraduate student of the Department of Human Anatomy Ahmadu Bello University Zaria. The results from this study will contribute to my MSc dissertation in Human Anatomy.

If you have any questions or concerns about the research, please feel free to contact Dr.B. Danborno on 08139429300.

PURPOSE OF THE STUDY

Determine the prevalence and spectrum of overt congenital anomalies in live born neonates in the Kano metropolis .

PROCEDURES

If you volunteer to participate in this study, you would be require to answer some questions bordering on your bio-data, and you would also be required to give permission for a physical examination of your child.

POTENTIAL RISKS AND DISCOMFORTS

This study will be of no potential risk or discomfort to you or your baby. Only the time required to conduct the interview and examination will be required of you.

POTENTIAL BENEFITS TO PARTICIPANTS AND/OR TO SOCIETY

The study will provide information on the prevalence of overt congenital anomalies in Kano metropolis. It will also explain the common causes of congenital anomalies in Kano and will form the basis for further research into the causes of congenital anomalies in northern Nigeria. This will aid the design of programmes and policies which will help reduce the incidence of congenital anomalies in the region.

PAYMENT FOR PARTICIPATION

There will be no payments made to the participants in this study.

CONFIDENTIALITY

Every effort will be made to ensure confidentiality of any identifying information that is obtained in connection with this study. The findings from this study will be submitted as an MSc dissertation to the Postgraduate school of the Ahmadu Bello University Zaria, Nigeria.

PARTICIPATION AND WITHDRAWAL

You can choose whether to be in this study or not. If you volunteer to be in this study, you may withdraw at any time without consequences of any kind. You may exercise the option of removing your data from the study. You may also refuse to answer any questions you don't want to answer and still remain in the study. The investigator may withdraw you from this research if circumstances arise that warrant doing so.

RIGHTS OF RESEARCH PARTICIPANTS

You may withdraw your consent at any time and discontinue participation without penalty. You are not waiving any legal claims, rights or remedies because of your participation in this research study. This study has been reviewed and received ethics clearance through the

Ahmadu Bello University Research Ethics Board. If you have questions regarding your rights as a research participant, contact:

Dr. B. Danborno Telephone: 08139429300

Ahmadu Bello University

Zaria.

SIGNATURE OF RESEARCH PARTICIPANT/LEGAL REPRESENTATIVE

I have read the information provided for the study '**BIRTH PREVALENCE OF OVERT CONGENITALANOMALIES AT AN URBAN TERTIARY HOSPITAL IN KANO NIGERIA'** as described herein. My questions have been answered to my satisfaction, and I agree to participate in this study. I have been given a copy of this form.

…….
Name of Participant (please print)

……..
Name of Legal Representative (if applicable)

…… ……
Signature of Participant or Legal Representative Date

SIGNATURE OF WITNESS

……
Name of Witness (please print)

…… …….
Signature of Witness Date

APPENDIX IV

BIRTH PREVALENCE OF OVERT CONGENITAL ANOMALIES IN KANO, NIGERIA.

(QUESTIONNAIRE)

SECTION A

SOCIO-DEMOGRAPHIC CHARACTERISTICS OF MOTHER

No	QUESTION AND FILTERS	CODING CATEGORIES	SKIP TO
1	Age at last birthday	Age in completed years ☐	
2	For how long have you been married?	_____ years	
3	Gravidity/Parity	_____	
4	Nature of marriage	Consanguinous (***AurenZumunci***) -1 Non-Consanguinous-2	
5	Highest level of school attended	None ……1 Quaranic only…….. 2 Primary…… 3 Junior secondary……. 4 Senior Secondary…….5 Higher……..6	
6	What is your Religion?	Christianity……..1 Islam…….2 Traditional……3 Others……..4	
7	How important is Religion to you in helping you deal with problems?	Very important……1 Somewhat important……...2 Not important…….3	

		Neutral…….4	
No	QUESTION AND FILTERS	CODING CATEGORIES	SKIP TO
8	What is your Ethnic group	Hausa……..1 Fulani……..2 Igbo…….3 Yoruba……4 Others…….5	
9	What is your Husband's Ethnic group	Hausa……..1 Fulani……..2 Igbo…….3 Yoruba……4 Others…….5	
10	Booking status of pregnancy	Booked……1 Unbooked……2	
11	Folic acid-containing multivitamin supplement use	Use began at least 1 month before pregnancy or in the first month of pregnancy……..1 Use began in the second or third month of pregnancy…….2 Use began after the third month of pregnancy……..3 No use at all…….....4	
12	History suggestive of prepregnancy obesity	Yes……1 No…….2	
13	Periconceptional smoking	Yes……1 No…….2	
14	Periconceptional binge drinking of alcohol	Yes……1 No…….2	
15	History of pre-gestational insulin treated diabetes	Yes……1 No…….2	

	mellitus	Diabtes treated with oral drug……..3			
No	QUESTION AND FILTERS	CODING CATEGORIES			SKIP TO
16	Use of anti-epileptic drug during pregnancy	Yes……1 No…….2			
17	Any family history of the birth of a child with a congenital anomaly	Yes……..1 No……2 Don't know……..3			
18	History of maternal febrile illness during pregnancy.		yes	No	
		First trimester			
		Second trimester			
		Third trimester			
19	Use of native medication during pregnancy		Yes	No	
		First trimester			
		Second trimester			
		Third trimester			
20	Husband's age	……years			

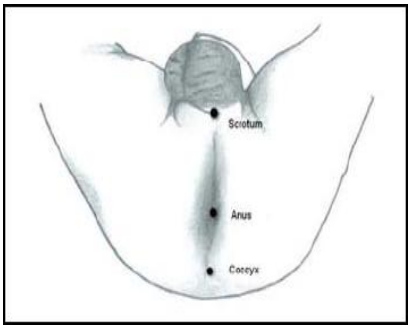
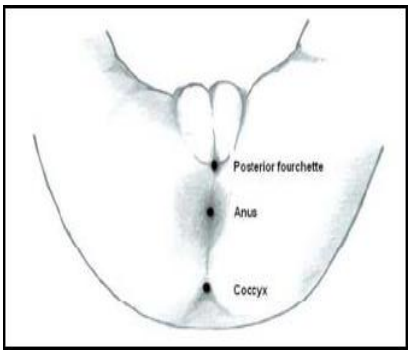
SECTION B

NEONATE'S CHARACTERISTICS

No	QUESTION AND FILTERS	CODING CATERGORIES	SKIP TO
21	Gestational age	Number of weeks of intrauterine life completed (calculated from LMP or US-scan) ……..wks	
22	Birth weight	……kg	
23	Gender	Male……1 Female……2 Indeterminate……..3	
24	Nature of gestation	Singleton……1 Twins……..2 Triplets……3 Others…….4	
25	Type of delivery	Vaginal……1 Caesarean section……2	
26	Head circumference (OFC)	……. cm	
27	Length of child (Distance between vertex and heel in the supine position)	…… cm	
28	Central nervous system	Anencephaly……..1 Meningocoele/spina bifida…….2 Encephalocoele……..3 Hydrocephalus……...4 Microcephaly……..5 Craniosynostosis……6	
29	Neck	Webbed……..1	

		Normal……2	
30	Face	Dysmorphic/syndromic……..1 Normal……2	
No	QUESTION AND FILTERS	CODING CATERGORIES	SKIP TO
31	Eyes	Hypertelorism……..1 Hypotelorism……...2 Exophthalmos……..3 Anophthalmos…….4 Microphthalmos……..5	
32	Ears	Low set……1 Abnormal shape…….....2 Normal…….3 Absent…….4 Accessory auricles……...5	
33	Nose	Absent……..1 Normal……..2 Anteverted (upturned)……..3 Flat nasal bridge……...4 Prominent nasal bridge…….5	
34	Chin	Micrognathia……1 Agnathia……..2 Retrognathia……3	
35	Mouth	Normal……1 Small……...2 Large……...3 Cleft lip……...4 Cleft palate……..5	
36	Gastrointestinal system	Oesophagael atresia…….1	

		Omphalocoele…….2 Gastroschisis……...3 Intestinal obstruction……..4 Imperforate anus…….5				
No	QUESTION AND FILTERS	CODING CATERGORIES				SKIP TO
37	Genitourinary system	Posterior urethral valve…….1 Hypospadias…….2 Bladder exstrophy/epispadias complex……3 Ambiguous genitalia…….4 Undescended testes……..5				
38	Upper limbs			Rt	Lt	
		Humerus absent……	1			
		Ulna absent…….....	2			
		Radius absent……..	3			
		Absent finger……	4			
		Polydactyly……	5			
		Syndactyly……	6			
		Absent nails……..	7			
39	Lower limbs			Rt	Lt	
		Fermur absent……	1			
		Tibia absent……	2			
		Fibula absent……..	3			
		Talipes (club feet)……..	4			
		Syndactyly……	5			
		Polydactyly……	6			
		Absent nail……	7			
40	Skin	Epidermolysis bullosa……1 Congentialicthyosis……..2 Aplasia cutis……...3 Hyperpigmented patches……4				

41	Tumors	Sacrococcygealteratoma……1 Haemangioma……..2 Cystic Hygroma…….....3 Teratoma……..4 Craniopharyngioma……..5	
No	QUESTION AND FILTERS	CODING CATERGORIES	SKIP TO
42	Male Perineum examination  	Penile length (Root to tip of glans not including prepuce)……cm Anus – scrotum distance……cm Anus – coccyx distance……..cm	
43	Female Perineum examination  	Anus – fourchette distance…….cm Anus – coccyx distance…….cm	
44	Does the baby have any recognizable syndrome?	Yes……1 No……2	
45	If “Yes” above name the syndrome.	……	

APPENDIX V
CLINICAL PHOTOGRAPHS

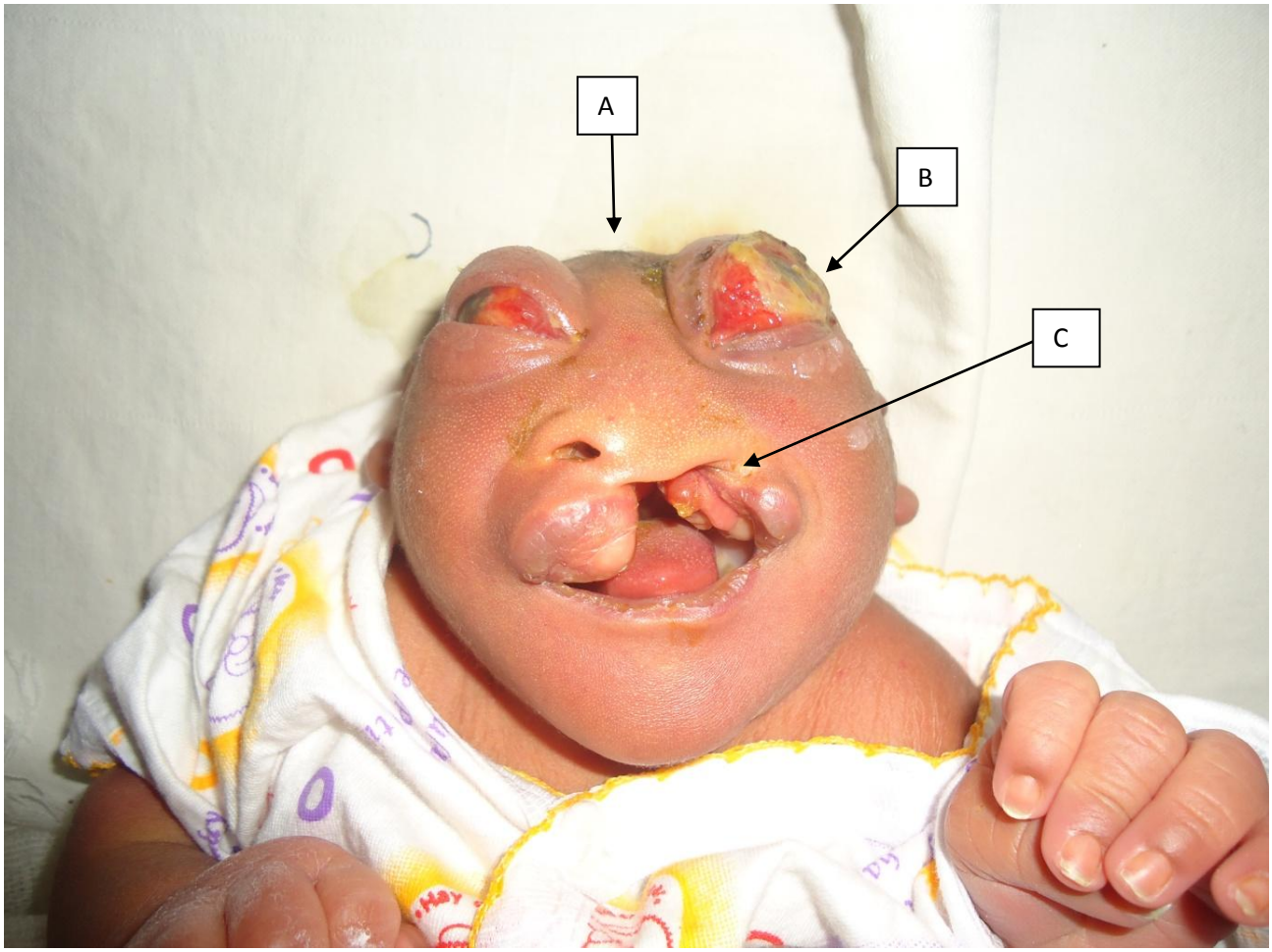


Plate I: A female child with anencephaly (A), a congenital anomaly of the central nervous system. Note the presence of associated congenital exophthalmos (B), and left sided cleft of the lip and palate.

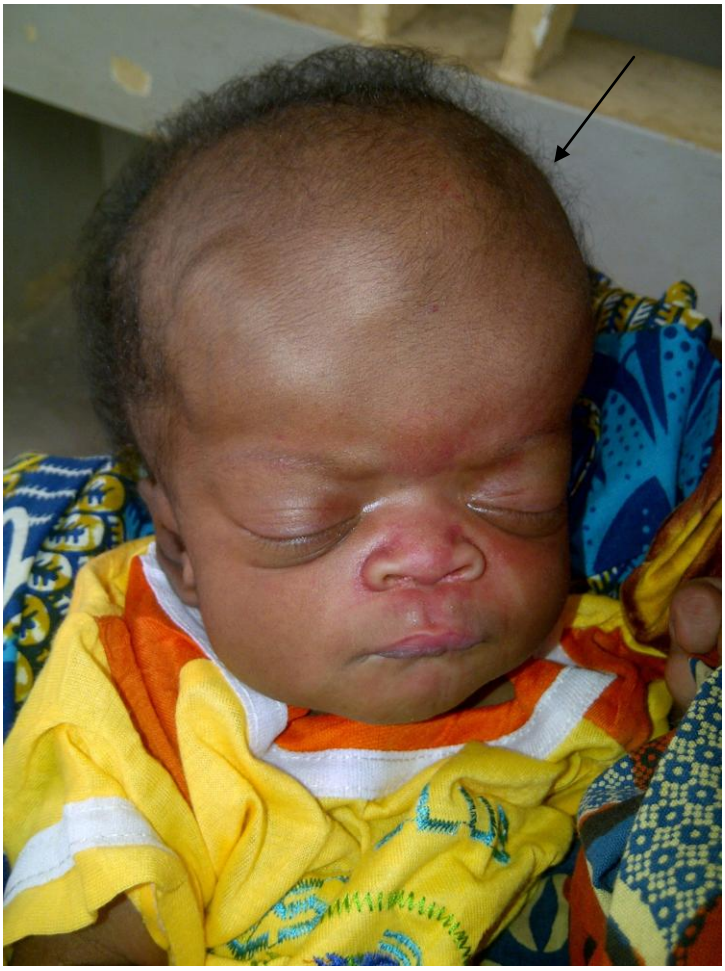


Plate II: A male child with hydrocephalous (arrow), a congenital anomaly of the central nervous system.

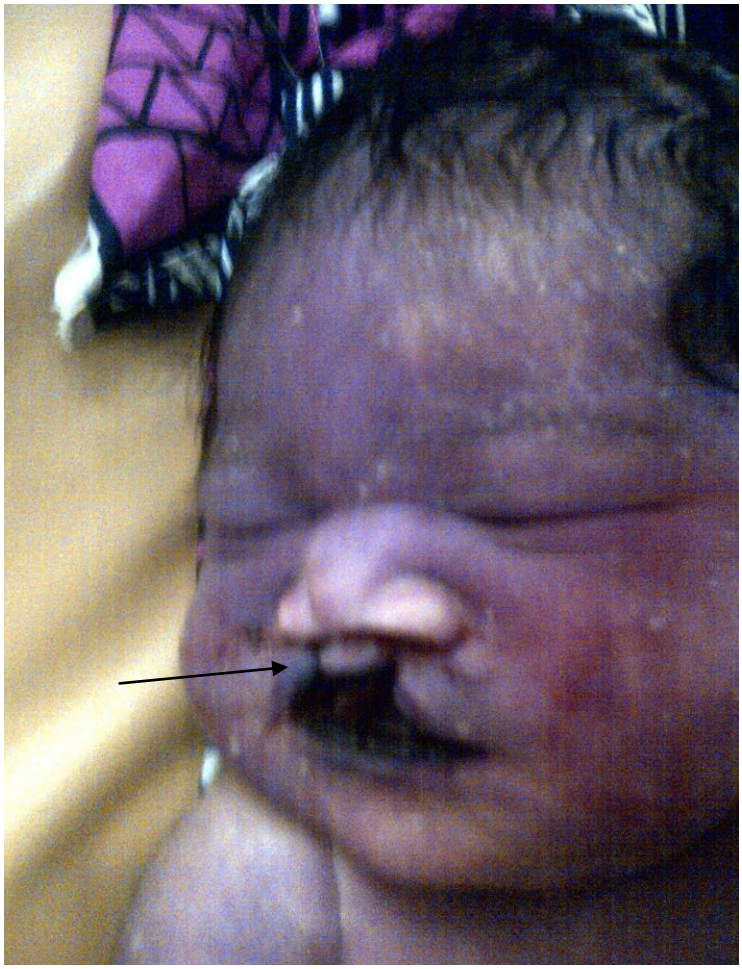


Plate III: Bilateral cleft lip (arrow) in a female child.

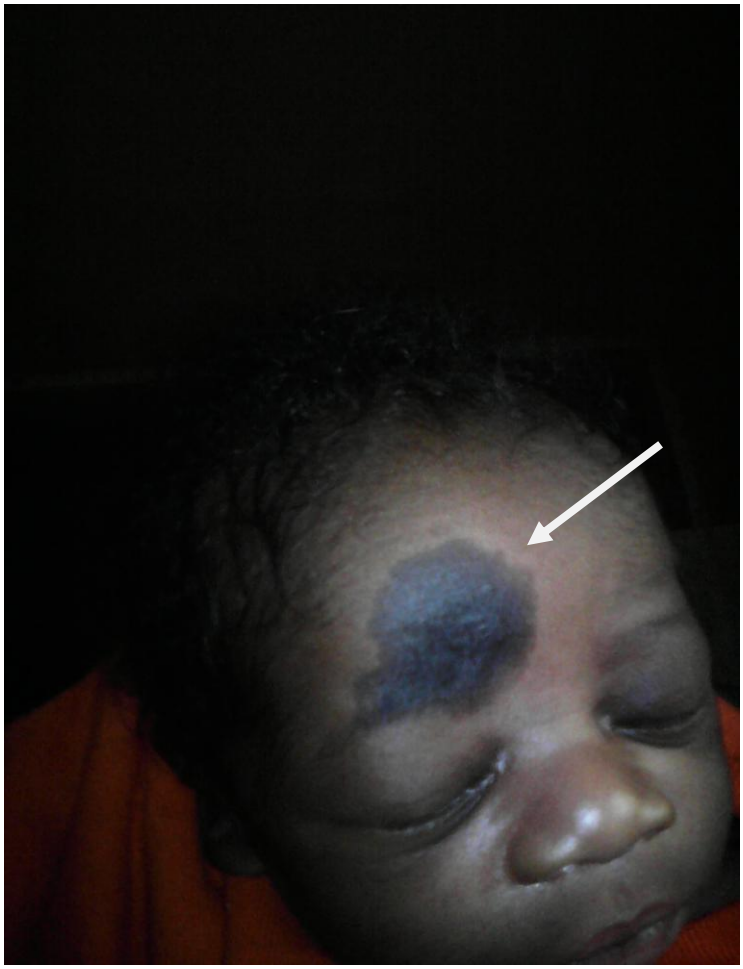


Plate IV: A congenital hyperpigmented patch (arrow) on the face of a female child.

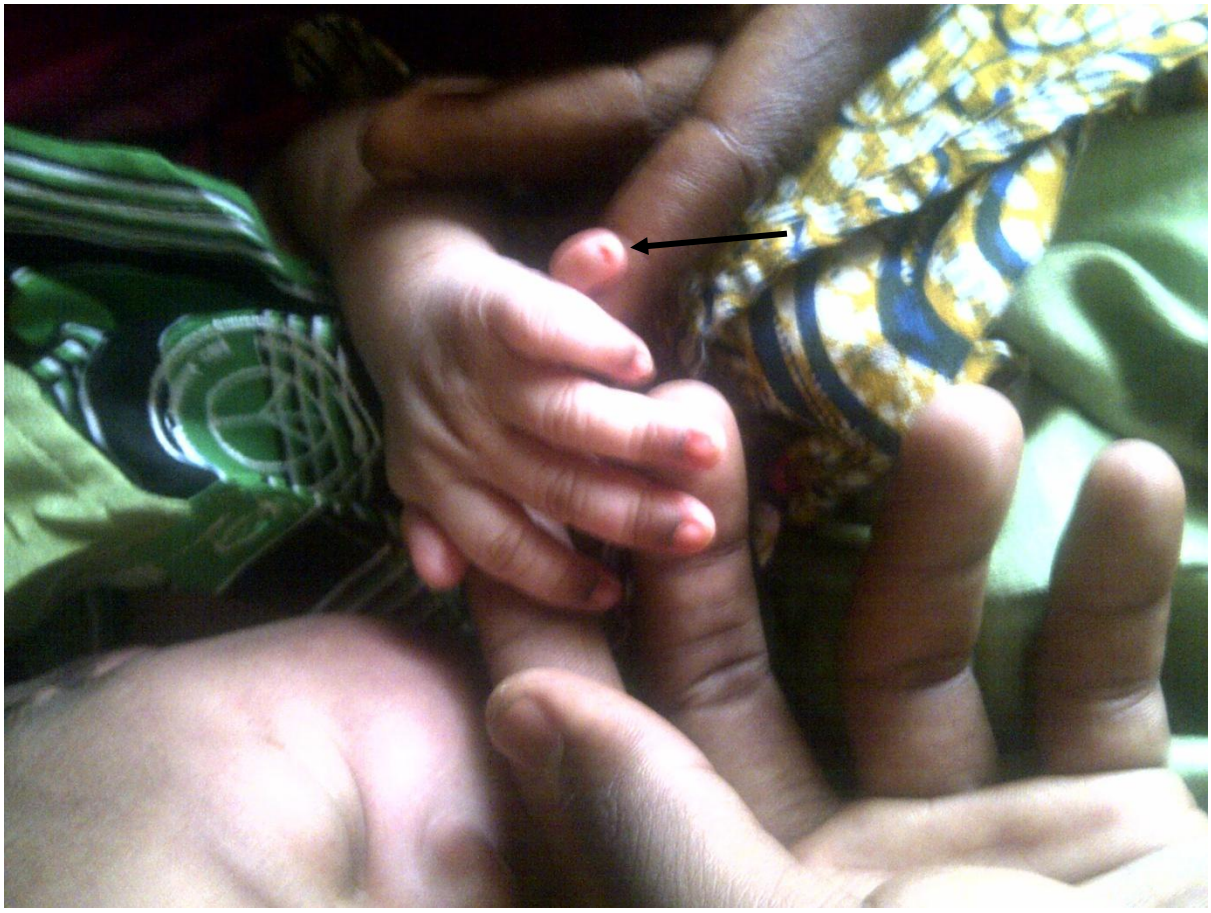


Plate V: Digitiminimi polydactyly (arrow) on the left hand of a male child.

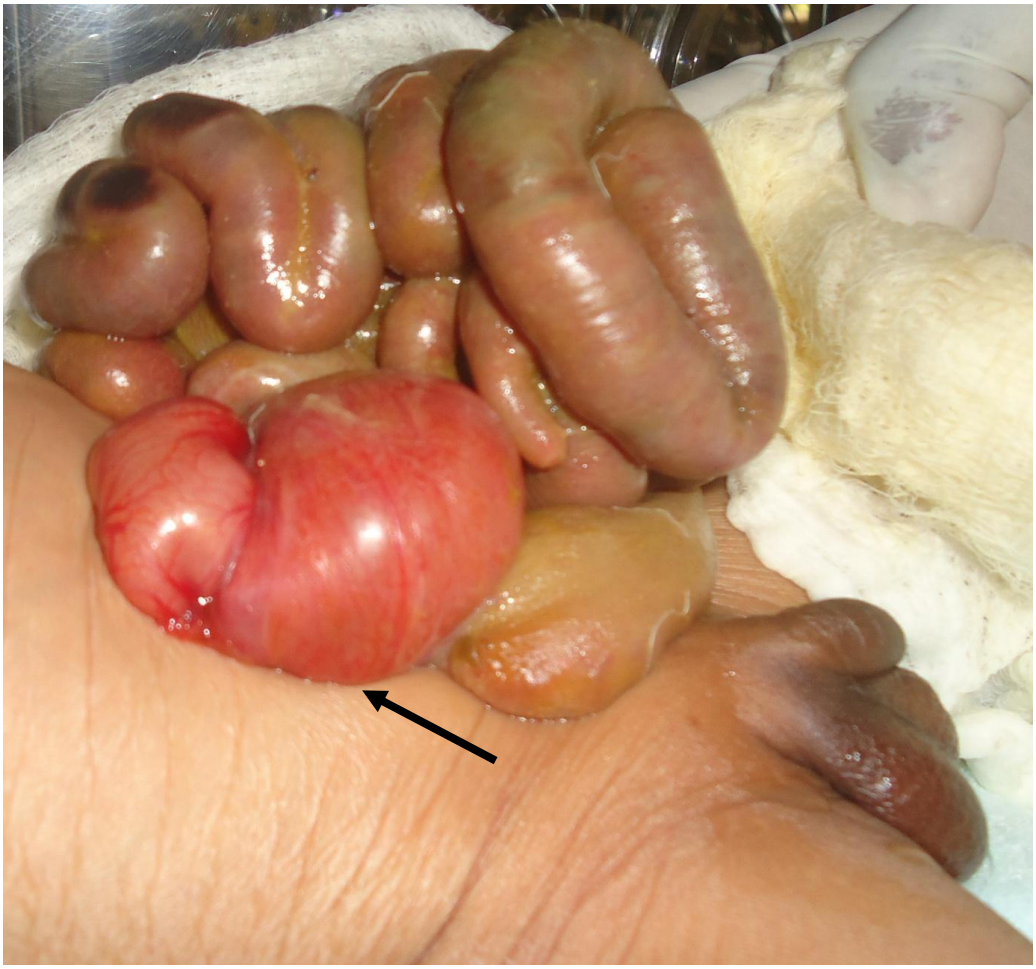


Plate VI: Male child with gastroschisis(arrow) a congenital abdominal wall defect.

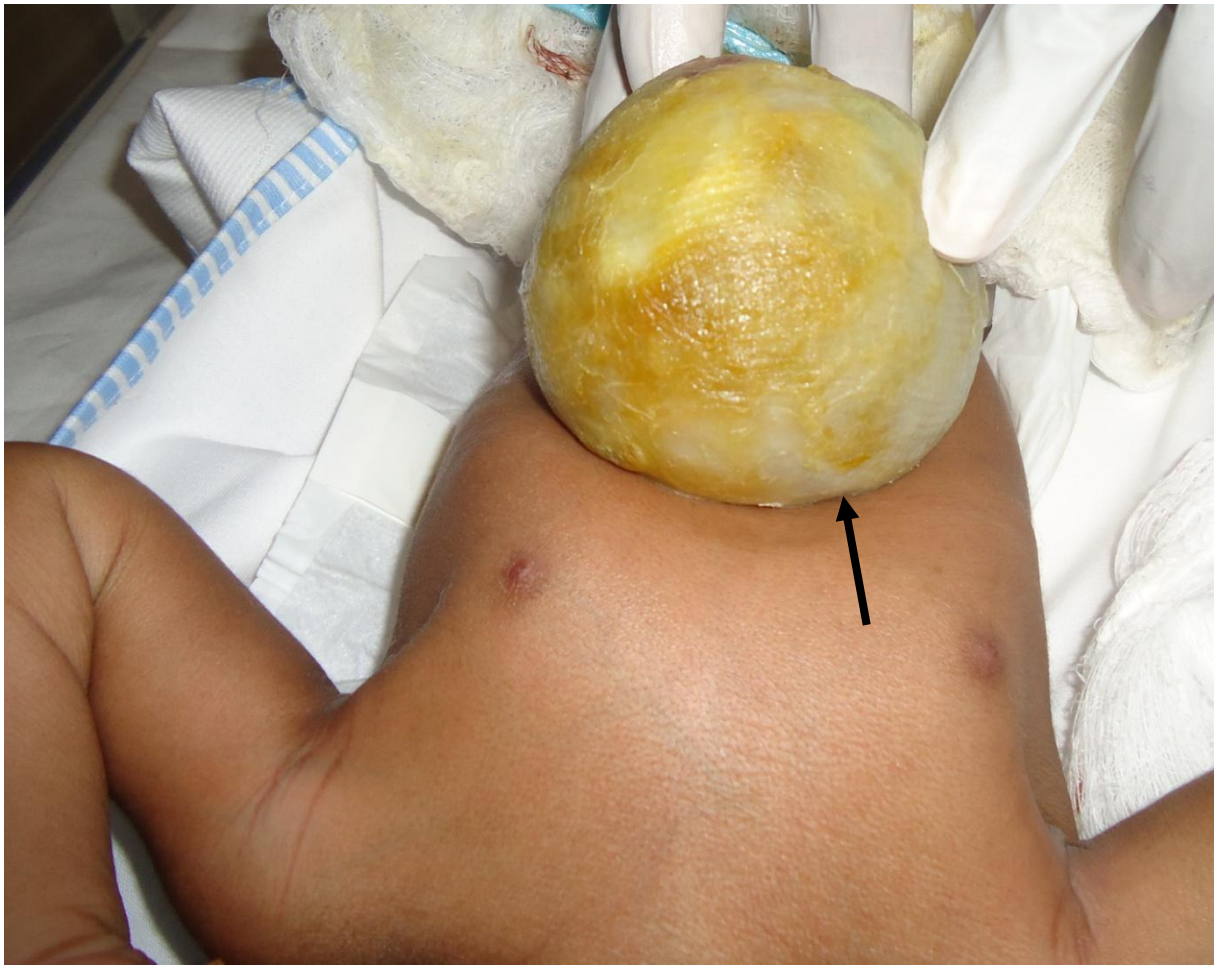


Plate VII: Male child with omphalocoele(arrow) a congenital abdominal wall defect.

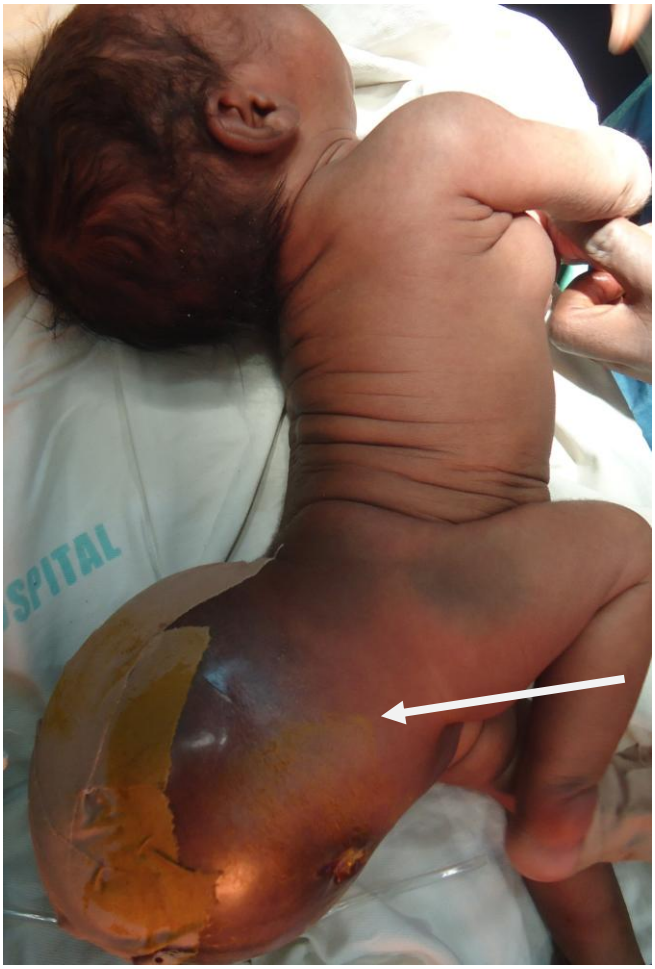


Plate VIII: Female child with sacrococcygealteratoma(arrow) a congenital tumor.