FACTORS ASSOCIATED WITH MAJOR STRUCTURAL BIRTH DEFECTS AMONG NEWBORNS DELIVERED AT MUHIMBILI NATIONAL HOSPITAL AND MUNICIPAL HOSPITALS IN DAR ES SALAAM, TANZANIA

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Factors associated with major structural birth defects among newborns delivered at Muhimbili National Hospital and Municipal hospitals in Dar es salaam, Tanzania

By

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance of thesis/dissertation entitled ***Factors associated with major structural birth defects among newborns delivered at Muhimbili National Hospital and Municipal hospitals in Dar es salaam, Tanzania,*** in fulfillment of the requirements for the degree of Master of Science in Applied Epidemiology of Muhimbili University of Health and Allied Sciences.

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DECLARATION AND COPYRIGHT

I, **Rogath Saika Kishimba**, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

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DEDICATION

This work is dedicated to my beloved parents, Mr. Rusk Kishimba Shirima and Mrs. Ernestine Kishimba Shirima for their inspiration in education and tireless effort to send me to school.

ABSTRACT

Background: Birth defects have a great impact in middle and low income countries. Ninety four per cent of birth defects in newborns worldwide and 95 percent of deaths due to birth defects worldwide occur in these countries, Tanzania being among them.

In Tanzania, it is estimated that the prevalence of birth defects is 60.5 per 1,000 live births. Factors affecting birth defects can be genetic and non genetic. There are well established preventive programs which are addressing non genetic factors influencing birth defects in developed countries, however in Tanzania limited prevention strategies of birth defects are in place due to limited information on factors predetermining the occurrence of birth defects.

Objective: To determine factors associated with major structural birth defects (NTD or orofacial clefts or limb defects) among newborns delivered at Muhimbili National Hospital and Municipal hospitals in Dar-Es-Salaam.

Materials and Methods: This was a case control study involving newborns born from October, 2011 through February, 2012 at participating hospitals. A case was defined as any newborn live or stillbirth of a Dar es salaam resident with major structural birth defects delivered at participating hospitals during the study period. A control was defined as any live newborn of a Dar es salaam resident without any birth defects born at participating hospital during the study period. Next three newborns who were delivered after the case and met the control definition were recruited as study controls. Mothers for both cases and controls were asked for informed consent.

Data was analysed using statistical software Epi Info version 3.5.1 and MS Excel. Chi square (χ^2) was used to compare proportions and to assess statistical significance. Confidence level of 95% and p value of less than 0.05 were considered statistically significant. Binary and multiple logistic regressions were employed to quantify and adjust factors influencing occurrence of structural birth defects.

Results: A total of 400 newborns participated in the study, 100 cases and 300 controls. Maternal and paternal mean ages were 25.9±5.9 and 32.5±7.2 years respectively. Among cases, the major structural birth defects found included NTD 39(39%), Limbs defects 50(50%) and Orofacial cleft 11(11%). We found higher odds on maternal fever [AOR=2.00, 95% CI: 1.14-3.52], maternal hypertension [4.00, 95% CI: 1.67-9.54] during

pregnancy, and low birth weight newborns [AOR=3.48, 95% CI: 1.77-6.85]. Antimalarials use during pregnancy had lower odds [AOR=0.48, 95% CI: 0.28-0.84].

Conclusion: Maternal fever and hypertension during pregnancy, and low birth weight newborns are risks factors for developing structural birth defects. While antimalarials use during pregnancy was a protective factors against structural birth defects.

Recommendations: Early screening of pregnant mothers for hypertension and other causes of low birth weight or prematurity is highly needed through strengthening of Primary Health Care where ANC visits are done. We also recommend promotion of utilization of existing reproductive and child health and advocacy strategies to address the identified factors.

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LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
AOR	Adjusted Odds Ratio
ARV	Antiretroviral
CCBRT	Comprehensive Community Based Rehabilitation in Tanzania
CDC	Centre for Disease Control and Prevention
CHD	Congenital Heart Disease
CI	Confidence Interval
COR	Crude Odds Ratio
DMO	District Medical Officer
ECSA-HC	East, Central and Southern Africa Health Community
FA	Folic Acid
GA	Gestation Age
G6PD	Glucose 6 Phosphate Dehydrogenase
HIV	Human Immunodeficiency Virus
IPT	Intermittent Presumptive Treatment
MNH	Muhimbili National Hospital
MOD	March of Dimes
MoHSW	Ministry of Health and Social Welfare
MOI	Muhimbili Orthopaedics Institute
MSP	Muhimbili Sickle Cell Programme
MUHAS	Muhimbili University of Health and Allied Studies
NFFP	National Food Fortification Alliance
NTD	Neuro Tube Defects
PPP	Public Private Partnership
RMO	Regional Medical Officer
SCD	Sickle Cell Disease
TFELTP	Tanzania Field Epidemiology and Laboratory Training Programme
TORCHS	Toxoplasimosis, Rubella, Cytomegalo Virus, Herpes Simplex Virus, HIV and Syphilis
UNICEF	United Nations Children's Fund
WHO	World Health Organization

DEFINITIONS OF TERMS

Birth defect

A birth defect is an abnormality of structure or function in a person which is present from birth.

- Structural birth defects include Neural tube defect (NTD), limbs defects, orofacial cleft, congenital heart defects etc.
- Functional birth defects include haemophilia, sickle cell disease etc.

Outcome variable

The outcome variable (major structural birth defects) was defined as any newborn diagnosis of either neural tube defects or oralfacial clefts or limbs defects or a combination of them.

Neural tube defects (NTD) child

Any still or live birth child with any form of spina bifida, anencephaly or encephalocele

- ✓ Spina bifida
    - Meningocele – An out pouching of coverings of the spinal cord as a result of part of spine bone and soft tissue coverings defects.
    - Meningomyelocele – An out pouching of part of coverings of spinal cord and part of spinal cord itself as a result of spine bone and soft tissue coverings defects.
- ✓ Anencephaly
    - Absence of bony covering over the back of the head or missing bones around the front and sides of the head.
- ✓ Encephalocele
    - Presence of a sac-like protrusion of the brain and the membrane that cover it through openings in the skull.
- ✓ Hydrocephalus
    - Rapid increase in head circumference or unusually large hea

Orofacial clefts child

Any still or live birth child with a visible defect of incomplete upper lip or mouth roof or both of one side of the face or both sides since birth.

Limb birth defects child

Any still birth or live birth child with a completely absence of limb or overgrowth or undergrowth of limb or duplication of limb or defective in separation of limb either upper or lower or both limbs.

- ✓ Clubfoot (*Talipes equinovarus*)
    - It may involve only one leg or both legs, usually the deformed limb is smaller than usual and the heel appeared to point downwards while the forefoot turns inward.
- ✓ Polydactyly or Syndactyly
    - Polydactyly and syndactyly are congenital irregularities of the hands and feer. Polydactyly is the occurance of extra fingers or toes, and syndactyly is the webbing or fusing together of two or more fingers or toes.
- ✓ Any other form of congenital upper or/and lower limbs irregularities

Isolated birth defects

Birth defects that occur singly without co-existence with any other congenital malformations.

Multiple birth defects

Birth defects that occur in co-existence with one or more other congenital malformations.

Syndrome birth defects

A cluster of symptoms and sign that characterize a given birth defect disease Eg. Down syndrome, Edward's syndrome, Klinefelter's syndrome etc.

CHAPTER ONE

1.0 Introduction

1.1 Background

A birth defect is an abnormality of structure or function in a person which is present from birth. It may be clinically obvious at birth eg. Neural tube defect (NTD) which is a structural defect or may only be diagnosed sometimes later in life when the child is older eg. Haemophilia which is a functional defect [1].

The major structural birth defects include congenital heart disease (CHD), NTD, orofacial clefts and limb birth defects. Neural tube defects are birth defects of the brain and spinal cord. The most common are spina bifida and anencephaly. They result from incomplete development of brain, spinal cord or their protective coverings. Orofacial clefts are birth defects resulted from either cleft lip or cleft palate or both when a baby's lip or mouth was not completely formed in the utero. Limb birth defects are congenital malformations that occurred when the whole limb (upper or lower) or part of the limb fails to develop completely in the utero and clubfoot (*Talipes equinovarus*) is the commonest lower limb birth defect.

It is estimated that 9 million infants (approximately 7% of all births globally) annually are born with a serious birth defect that may kill them or ending with a lifelong disability [2, 3]. The estimated birth prevalence of genetic and partly genetic birth defects ranges from just over 40 per 1000 live births in high income countries to 82 per 1000 live births in some low income countries. Twenty five per cent of these birth defects are accounted by five common defects which are congenital heart defects, neural tube defects, haemoglobin disorders (sickle cell disorder and thalassaemias), down syndrome and G6PD deficiency which lead to neonatal jaundice with kernicterus or significant haemolysis later in life [2]. The mortality associated with birth defects by March of Dimes (MOD) and World Health Organization (WHO) gives an estimate of at least 3.3 million of under-five year children dying from serious genetic or partly genetic birth defects and 3.2 million of those who survive without appropriate care may be disabled for life that exact a harsh human and economic toll on those affected, their families and their communities [2, 3].

In Tanzania, it is estimated that the prevalence of birth defects is 60.5 per 1,000 live births [2]. Studies done at Muhimbili National Hospital neonatal unit in Dar es salaam have shown a birth defects prevalence of 3.3% and neural tube defects rate of 3.02 per 1000 live births. Eight percent overall mortality in the unit was attributed by birth defects [4, 5].

Birth defects may arise either due to problems present before conception i.e genetic causes of birth defects or problems present after conception i.e non genetic causes of birth defects. Other defects may have a multifactorial causes i.e having both genetic and non genetic causes while others the causes are unknown to date. Genetic causes are chromosomal abnormalities, single gene defects and multifactorial disorders. Non genetic causes are due to teratogens and constraints. Teratogens are foetal environmental factors that can cause a defect. They cause most damage in the embryonic phase of development from 4-10 weeks after the start of the last menstrual period. These are maternal infections eg. Toxoplasmosis, rubella, cytomegalo virus, herpes simplex and HIV/AIDS (TORCH); maternal illness eg. diabetes mellitus and epilepsy; radiation in very large doses; drugs eg. alcohol, retinoic acid, some antibiotics (tetracycline streptomycin), anti cancer drugs (methotrexate, thalidomide), warfarin, some anti convulsants (sodiaum valproate, phenytoin), mood stabilizers (lithium); environmental pollutants eg. methyl mercury. Other risk factors for birth defects are maternal medical complications and smoking [1].

Micronutrients fortification to commonly used food stuffs is a major preventive approach against birth defects targeting non genetic factors. Worldwide, UNICEF programme on salt fortification with iodine has been very successful and made a huge impact on the birth prevalence of iodine deficiency disorder in infants over the last 18 years. Recent World bank reported that low income citizen of Tanzania can afford a fortified flour with FA and iron [6]. Tanzania through Ministry of Health and Social Welfare during the 46th Conference of ECSA-HC Health Ministers, had adopted resolution ECSA/HMC46/R10 which among other items urges Member State to adopt and support implementation of ECSA food fortification guidelines. A National Food Fortification Alliance (NFFA) has been established and is in the

process of building a Private Public Partnership (PPP) in food fortification to advance the fortification agenda in the country.

1.2 Problem Statement

The estimated birth prevalence of both genetic and partly genetic birth defects ranges from just over 40 per 1000 live births in high income countries to 82 per 1000 live births in some low income countries. In Tanzania estimated prevalence of birth defects is 60.5 per 1,000 live births [2].

Birth defects have adverse effects on the wellbeing and survival of children born with those anomalies. Almost all birth defects (94%) and deaths due to the birth defects among children (95%) occur in low and middle income countries [2]. Audit in Tanzania carried out at Muhimbili National Hospital indicate birth defects prevalence of 3.3% and 8% mortality in neonatal unit admissions was attributed to birth defects [5].

Birth defects due to teratogens are among the easiest preventable defects and are more likely to be found in middle and low income countries compared to high income countries. This is due to the facts that, pregnancy in these countries is more likely to be at risk from potential teratogens. These potential teratogens/factors that have been found in developing countries to influence birth defect are low socioeconomic and educational levels, increased incidence of malnutrition (mineral and vitamin deficiencies), intrauterine infections, lack of environmental protection policies, high level of environmental pollution, unsafe working conditions during gestation, access to medicines without medical indication nor prescription (self-medication), and common use of home remedies of unknown composition. A clearly documentation of known risk factors that influence birth defects occurrence will help addressing preventive strategies [7, 43].

In Tanzania there are no enough data on factors predetermining the occurrence of birth defects and hence leading to limited prevention strategies for birth defects. Through this study, we will be able to understand the risk factors and this will help in developing evidence-based birth defects prevention activities. It will also help in supporting the necessity to develop a surveillance system for birth defects.

1.3 Rationale

The estimated birth prevalence of genetic and partly genetic birth defects ranges from just over 40 per 1000 live births in high income countries to 82 per 1000 live births in some low income countries. In Tanzania estimated prevalence of birth defects is 60.5 per 1,000 live births [2], however there are no enough data on factors predetermining the occurrence of birth defects and hence leading to limited prevention strategies for birth defects. A clearly documentation of known risk factors that influence birth defects occurrence is important in addressing preventive strategies [7, 43].

This study intends to come out with additional findings as regard to factors associated with birth defects and hence supplement to the already ongoing strategies. The results of the study will add to the body of knowledge available for the development of a comprehensive intervention package for birth defects.

1.4 Research question

1. What factors are associated with structural birth defects in Dar es salaam, Tanzania?

1.5 Objectives

1.5.1 Broad Objectives

To assess factors associated with structural birth defects among newborns delivered at Muhimbili National Hospital and Municipal hospitals in Dar es salaam, Tanzania

1.5.2 Specific Objectives

1. To describe common types of structural birth defects among newborns delivered at Muhimbili National Hospital and Municipal hospitals in Dar es salaam, Tanzania

2. To assess factors associated with structural birth defects among newborns delivered at Muhimbili National Hospital and Municipal hospitals in Dar es salaam.

CHAPTER TWO

2.0 Literature Review

2.1Overview of birth defects

Neural tube defects (NTD) are serious and commonest structural birth defects that significantly cause perinatal mortality. They affect more than 300,000 newborns Worldwide yearly [2]. In Tanzania there are paucity of data, however the available data shows a neural tube defects rate of 3.02 per 1000 live births [4]. Neural tube defect is also frequently seen and contribute much to the overall mortality in neonatal unit admissions [5].

Cleft lip, cleft palate or both are frequently encountered orofacial congenital malformations and account for 65% of all head and neck birth defects [8]. Unilateral defects with left side predomination had shown to be more common compared with bilateral defects in Tanzania [9].

Limb birth defects are common and their causes are poorly understood. Their frequently occurrence raised a question on the role of prenatal events or exposures. They affect both upper and lower limbs almost proportionally with few having both limbs affected [10].

Recognising and diagnosing birth defects is still a challenge particularly to low income countries and this also can explain the few cases of birth defects seen at clinics. Up to 50% of conditions such as intellectual disabilities, cerebral palsy, deafness and blindness that are commonly seen in clinics are results of birth defects [1, 5].

2.2Factors associated with birth defects

Birth defects due to teratogens are among the easiest preventable birth defects. These are more common in middle and low income countries as compared to high income. The reason been pregnancy in these countries are more likely to be at risk from potential teratogens. Pregnant women in these region are at increased frequency of intrauterine infection, poor maternal

nutrition, low socioeconomic and education levels, lack of environmental protection policies and poorly regulated access to medication [7, 43].

The most common teratogens inducing birth defects are congenital syphilis, congenital rubella syndrome, congenital Iodine deficiency syndrome, foetal alcohol syndrome, maternal insulin dependent diabetes and maternal use of antiepileptic drugs. Maternal illness during pregnancy had shown an association with birth defects. About 54% of mother whose newborns had structural birth defects and participated in a study done in Southern Nigeria had maternal illness [11].

There is a high frequency of reported fever by pregnant women during pregnancy [12]. Several studies have shown that hyperthermia during pregnancy is associated with increased risk of neural tube defects independent of infection status [12, 13]. Women using antifever drugs and folic acid supplementation during pregnancy may have a decreased risk for birth defects [14, 15].

Infection during pregnancy is associated with birth defects, developmental disabilities, and other adverse birth outcomes including preterm birth, pregnancy loss and foetal death [16, 17, 18]. Influenza infection is a relatively a common infection, however recently it has been shown that influenza infection during pregnancy is associated with an increased risk for birth defects [19,20]. Congenital syphilis is the major cause of perinatal mortality and morbidity especially in developing countries. Infants affected and survived are at increased risk for brain damage, blindness and hearing loss. Prevalence of active syphilis in pregnant women in Sub Saharan Africa is between 6-16 percent [21, 22]. It is estimated that about 25 percent of infants born to mothers who contract rubella in the first trimester have congenital rubella syndrome [21, 22]. Infants born to mothers who are insulin dependent diabetic patient have threefold increase risk of having a serious birth defect [23].

Parental consanguineous marriage is accepted by at least 20 percent of the population worldwide. It is a social custom that involve marriage of cousins or uncles and nieces. It increases the birth prevalence of autosomal recessive birth defects and almost doubling the risk of neonatal and childhood deaths from birth defects [24-33].

Advanced maternal age is associated with an increased risk of birth prevalence of chromosomal trisomies particularly down syndrome. In developing countries a health infrastructure is poor there is a high percentage of women who give birth over the age of 35 years. There is no enough coverage of community education, availability and accessibility of family planning services; no medical genetic screening; prenatal diagnosis capabilities or associated services [33, 34].

Alcohol is associated with an increased birth prevalence of birth defects. Maternal alcohol consumption may result into foetal alcohol spectrum disorder that ranges from mild to severe forms. It involves intellectual disabilities, behaviour problems, growth retardation and congenital heart defects [35].

Smoking during pregnancy is a factor which has been reported to increase likelihood of birth defects. Cigarette smoking and tobacco use had widely been implicated in birth defects [36, 37]. A study done in Southern Nigeria to assess antenatal determinants of oral-facial clefts observed an increased risk for oral-facial clefts among those who were cooking indoor compared to those who were cooking outdoor. This had an implication of linking inhaled smoke from the cooking source and cigarette smoking [11].

Infants born to mothers on their antiepileptic medications are at increased risk of developing anticonvulsant embryopathy, major malformations, growth retardation, intellectual disabilities and hypoplasia of the mid face and fingers [38].

Some structural birth defects are affected by newborn sex, with the defects being more common among males. A study done on bilateral renal agenesis, male newborns were more affected than female. Many other studies on structural birth defects had shown a male preponderance as well [39, 40, 41, 42].

Nutrition plays a great role in birth defects prevention. Nutritional fortification and/or supplementation have a great impact in controlling birth defects as a public health measure. Reduced socioeconomic status predisposes women of reproductive age to an increased risk of malnutrition before and during pregnancy and at a greater poverty [35].

Maternal Iodine level is an important determinant of foetal wellbeing. Iodine deficiency may result into spontaneous abortion, perinatal death and childhood intellectual, motor and auditory disabilities [43]. Multivitamin and/or folic acid supplementation either preconception and/or periconception have shown to prevent birth defects particularly neural tube defects (NTD). Using of folic acid before and in the first week of pregnancy had shown to prevent neural tube defects by 50-70% [6]. A study done in Atlanta USA assessing the periconceptional use of multivitamin and the occurrence of NTD observed a significant protective effect [44]. Folic acid fortification in maize and wheat flour in South Africa had shown to decrease the burden of neural tube defects by 30.5% with a cost benefit ratio of 1:46 [6,45].

Availability and accessibility of health care particularly reproductive and child health services influence birth prevalence of birth defects. These maternal, newborn and child health services can prevent down syndrome, NTD, other structural birth defects, foetal alcohol syndrome, congenital syphilis, iodine deficiency disorder and congenital rubella syndrome. These can influence infants and childhood mortality rates and thus affecting overall population prevalence of birth defects [7, 8 , 34].

CHAPTER THREE

3.0 Methodology

3.1 Study Design

This was unmatched case control study, conducted in four public hospitals of Dar-es Salaam, from October 2011 to February 2012.

3.2 Study area

Dar es Salaam is one of the 26 administrative regions in Tanzania. It is the commercial city of Tanzania with a population of 3,070,060 people (projection from 2002 Census).

Currently there is no Regional Hospital; however Muhimbili National Hospital (MNH) apart from being a national hospital that receives patients across the country it also serves as a referral hospital for the region Municipal and private hospitals. It has a maternity block with bed capacity as follows; antenatal and postnatal wards 174 beds, Labour ward 20 beds. Monthly, on average it conducts 600 – 900 deliveries. Labour ward has an average of 5 – 4 Registered Nurses, 1 Intern Doctor, 1 Resident Doctor, 1 Registrar Doctor and 1 Consultant in 24 hours every day.

Mwananyamala Hospital is a Municipal hospital for Kinondoni and it serves a population of 1,337,875 people with 267,575 women of reproductive age. It has a maternity block with bed capacity as follows; Antenatal ward 20 beds, Labour ward 10 beds and Postnatal ward 20 beds. Monthly, on average it conducts 1139 – 1396 deliveries. Labour ward has an average of 3 – 4 Nurses midwives, 1 – 2 Registered nurses and 1 – 2 Medical Officers in 24 hours every day.

Amana Hospital is a Municipal hospital for Ilala and it serves 783,687 people with 156,737 women of reproductive age. It has a maternity block with bed capacity as follows; Antenatal ward 21 beds, Labour ward 10 beds and Postnatal ward 27 beds. Monthly, on average it conducted 1470 – 1874 deliveries. Labour ward has an average of 2 – 3 Nurses midwives, 1 – 2 Registered Nurses, 1 Intern Doctor, 1 Registrar Doctor and 1 Consultant in 24 hours every day.

Temeke Hospital is a Municipal hospital for Temeke and it serves 948,498 people with 189,699 women of reproductive age. It has a maternity block with bed capacity as follows; Antenatal and postnatal ward 22 beds, Labour ward 20 beds. Monthly, on average it conducts 1535 – 2198 deliveries. Labour ward has an average of 3 – 4 Nurses midwives, 1 – 2 Registered nurses, 1 Intern Doctor, 1 Registrar Doctor and 1 Consultant in 24 hours every day.

3.3 Study Population

The study included newborns delivered during the study period (October, 2011 to February, 2012) from labour wards at Muhimbili National Hospital (MNH), Temeke, Mwananyamal and Amana Municipal Hospitals.

3.4. Sample Size

The sample size was calculated using Open Epi soft ware version 2.2.1. The following formula was used:

$$n_1 = \frac{\{\mu\sqrt{[\pi_0(1-\pi_0)+\pi_1(1-\pi_1)]}+v\sqrt{[2\pi_2(1-\pi_2)}\}^2}{(\pi_1-\pi_0)^2} \qquad \text{Where } \pi_2 = \frac{\pi_0+\pi_1}{2}$$

$$n_2 = rn_1$$

Where

n_1 = Number of cases

n_2= Number of controls

r= Ratio of controls to case, 3:1

π_0= proportion of controls exposed, 54% [11]

π_1= proportion of cases exposed, calculated from

$$\pi_1 = \frac{\pi_0 OR}{1+\pi_0(OR-1)}$$

OR= Minimum odds ratio to be detected, 2.0

U= One sided percentage point of the normal distribution corresponding to 100% - the power, 80%

V= Percentage point of the normal distribution corresponding to the (two-sided) significance level, 95%.

Therefore the computed sample size was 412, (Cases 103 and Control 309)

3.5 Sampling Procedure

Cases:

A case was defined as any newborn live or stillbirth of a Dar es Salaam resident with major structural birth defects (neural tube defects or orofacial clefts or limb defects) delivered at Muhimbili National Hospital (MNH), Mwananyamala Hospital, Amana Hospital or Temeke Hospital during the study period.

To avoid duplication of interview, if a mother delivered more than one newborn;

- ✓ If all of them met the case definition, only the first born was considered and participated in the study.
- ✓ If only one of them met the case definition while the other did not, only the one who met case definition was considered and participated in the study.

Cases were identified by a trained research assistant (nurse mid-wife) through both newborn medical record file and physical examination before the newborn is transferred to neonatal unit for specialized care.

Newborns who suffered multiple or syndrome defect, the most severe structural birth defect diagnosis present in his/her medical record file was recorded as a primary birth defect and other defects were noted as "others".

Inclusion criteria: All newborns who met the above case definition and were born between October, 2011 and February, 2012 were included in the study until the sample size for the case was attained.

Exclusion criteria: All newborns who met the above case definition and were born between October, 2011 and February, 2012 whose mother's cannot be interviewed because they are either very sick, emotionally upset, mute or died post delivery.

Controls:

A control was defined as any live newborn of a Dar es Salaam resident without any birth defects born at Muhimbili National Hospital (MNH), Mwananyamala Hospital, Amana Hospital or Temeke Hospital during the study period.

To avoid duplication of interview, if a mother gave birth to more than one newborn;

- ✓ If all of them met the control definition, only the first born was considered and participated in the study.

Inclusion criteria: Next three newborns delivered after the case between October, 2011 and February, 2012 and who met the control definition were recruited as study controls.

Exclusion criteria: All newborns who met the above control definition and were born between October, 2011 and February, 2012 whose mother's cannot be interviewed because they are either very sick, emotionally upset, mute or died post delivery.

3.6 Variables measured

Dependent Variable

- ✓ Major structural birth defects

Independent Variables

- ✓ Social Demographic characteristics Mother and/or Father
  - Age
  - Marital Status
  - Residence
  - Occupation
  - Level of education
- ✓ Factors influencing birth defects
  - Maternal Age
  - Paternal Age
  - Consanguineous Marriage
  - Sex of the child
  - Maternal Nutrition during pregnancy
  - Maternal Fever during pregnancy
  - Maternal Infection (Malaria, HIV/AIDS, Syphilis) during pregnancy
  - Maternal alcohol consumption during pregnancy
  - Maternal smoking habit during pregnancy
  - Maternal Diabetes during pregnancy

- Maternal Hypertension during pregnancy
- Maternal Drug use (ARVs, Antiepileptic drugs, tetracycline, streptomycin, anticancer drugs, antidepressant drugs and Vitamin A supplementation) during pregnancy

3.7 Data collection and management

A Structured questionnaire was used to collect information through interviewing the mother whose child fit a case or control definition during data collection period. The information included maternal and paternal demographic data and also information on factors that influence structural birth defects. The questionnaire was prepared in English and thereafter translated into a Swahili language which was then used to interview mothers whose newborns participated in the study.

Data were collected by Research assistants and the Principal Investigator. Research assistants were trained for one day on how to collect the needed data. They were trained on how to interview mothers whose newborn participated in the study and how to abstract daily data on newborns with birth defects. A one day pretesting of questionnaire was conducted at Tumbi hospital. After pretesting, data collection tool was modified and shifted all measurements to the end of the interview.

Labor ward admission and discharge procedures were similar to all study sites. Every pregnant woman who was in labor pain, had to be admitted and registered. Her particulars like name, age, place of residence, gravity and parity were recorded. Thereafter a Medical Officer reviewed her clinical condition before she is given a bed. Monitoring was done until she delivered. After giving birth to her baby, the complete clinical evaluation of the mother was done again by the Medical Officer and the mother was later sent into the recovery room within the labor ward for 12-24 hours observation. The baby also underwent clinical examination by the Medical Officer and if he/she had any medical problem including birth defects, he/she was sent to neonatal unit for further care and treatment. If he/she had no problem, the baby was given to his/her mother. The mother was then sent to the postnatal ward for further observation

for at least 24 hour before being discharged. Depending on the condition of the mother or child, she might stay longer in postnatal ward.

Research assistants interviewed mothers who gave informed consent and whose newborn qualified to participate in the study at least 12 hours post delivery just before sent to postnatal ward. They cross checked the information obtained after interview using the interviewee antenatal clinic visit card.

3.8 Data quality assessment

The principal investigator collected all questionnaires on the same day from research assistants, checked them for completeness and proper filling. For questionnaires with incorrect entries or missing information, the Principal Investigator made efforts to trace back the respective respondent and completed the needed information.

3.9 Data analysis

Data were entered, cleaned and analysed using Epi Info version 3.5.1 software and MS Excel. Bivariate analysis was done using Chi square (χ^2) test for comparison of proportions and logistic regression models for obtaining ORs and corresponding 95% CI. Multiple logistic regressions models were employed to assess individual contribution of each independent variable in predicting birth defects while adjusting simultaneously for potential confounding factors. Maternal, paternal and newborn factors which had a p-value of ≤ 0.2 in the bivarite analysis were included in the multiple logistic regression models. P - value of less than or equal to 0.05 were considered statistically significant.

3.10 Ethical considerations

The research protocol was reviewed by MUHAS ethical review board and ethical clearance was obtained. Informed consent was requested to all mothers who were interviewed. Confidentiality was ensured as names were not revealed. No personally identifying information was collected.

3.11 Permission to conduct the study

Permission to conduct the study was sought from the Muhimbili National Hospital (MNH), Dar es Salaam City Director of Health and Municipal Directors of Health for Kinondoni, Ilala and Temeke Municipalities. Finally permission was sought from respective Municipal hospital authorities.

CHAPTER FOUR

4.0 Results

A total of 400 newborns participated in the study with a response rate of 97.1%. Cases were 100 and controls were 300.

4.1 Socio demographic characteristics of the study sample

Out of the 400 mothers whose newborns were studied, 310 (77.5%) were aged between 20 to 35 years with a mean age of 25.9±5.9 years and 361(90.3%) were married. More than half ie 293 (73.3%) of the 400 mothers had primary education. Most 140 (35%) of study participants came from Temeke and Muhimbili National Hospital had the lowest. Table 1 shows the social demographic characteristics of cases and controls. None of the socio demographic characteristics showed a statistical significant difference between cases and controls.

Table 1 Socio demographic characteristic of case and control groups

Characteristics	Cases (N=100)	Controls (N=300)	Total (N=400)	p-value
Study Site				
Muhimbili National Hospital	14 (14.0%)	42 (14.0%)	56 (14.0%)	
Temeke Hospital	35 (35.0%)	105 (35.0%)	140 (35.0%)	
Mwananyamala Hospital	34 (34.0%)	102 (34.0%)	136 (34.0%)	
Amana Hospital	17 (17.0%)	51 (17.0%)	68 (17.0%)	0.99
Maternal age(years)				
<20	15 (15.0%)	40 (13.3%)	55 (13.7%)	
20 – 35	75 (75.0%)	235 (78.3%)	310 (77.5%)	
>35	10 (10.0%)	25 (8.4%)	35 (8.8%)	0.78
Paternal age (years)				
< 25	13 (13.0%)	26 (8.7%)	39 (9.8%)	
25-30	40 (40.0%)	124 (41.3%)	164 (41.0%)	
>30	47 (47.0%)	150 (50.0%)	197(49.2%)	0.45
Maternal education				
None	7 (7.0%)	25 (8.3%)	32 (8.0%)	
Primary school	74 (74.0%)	219 (73.0%)	293 (73.3%)	
Secondary school or higher	19 (19.0%)	56 (18.7%)	75 (18.7%)	0.91
Maternal marital status				
Non married	11 (11.0%)	28 (9.3%)	39 (9.7%)	
Married	89 (89.0%)	272 (90.7%)	361(90.3%)	0.63
Newborn sex*				
Female	48 (49.5%)	166 (55.3%)	214 (53.5%)	
Male	49 (50.5%)	134 (44.7%)	183 (45.8%)	0.32

*Three newborns had ambiguous sex and were not included in this table

4.2 Description of common types of structural birth defects

Description of major structural birth defects was done by their types and their class of occurrence (Isolated, Multiple, Syndrome). Table 2 shows types of major structural birth defects by sex.

Table 2 Types of structural birth defects by sex

Birth Defect	Male (%)	Female (%)	Ambiguous sex (%)	Total (%)
NTD	**18 (36.7)**	**19 (39.6)**	**2 (67)**	**39 (39)**
Anencephaly	5 (10.2)	8 (16.7)	2 (67)	15 (15)
Spina Bifida	5 (10.2)	4 (8.3)	-	9 (9.3)
Encephalocele	0 (0.0)	3 (6.3)	-	3 (3.1)
Isolated hydrocephalus	8(16.3)	4 (8.3)	-	12 (12.4)
Orofacial defects	**7 (14.3)**	**3 (6.3)**	**1 (33)**	**11 (11)**
Cleft palate	2 (4.1)	1 (2.1)	-	3 (3.1)
Cleft lip	3 (6.1)	0 (0.0)	-	3 (3.1)
Cleft palate with cleft lip	2 (4.1)	2 (4.2)	1 (33)	5 (5)
Limbs defects	**24(49)**	**26(54.2)**	**-**	**50 (51.5)**
Talipes equinovarus	10 (20.4)	8 (16.7)	-	18(18.6)
Polydactyly	12 (24.5)	16(33.3)	-	28(28.9)
Other limbs defects	2 (4.1)	2 (4.2)	-	4(4.1)
Total	**49 (49)**	**48 (48)**	**3 (3)**	**100 (100)**

Limbs defects had high proportion 50 (51.5%) followed by NTD 37 (38.1%) and orofacial defects had the lowest 10 (10.3%). There was almost equal distribution of males 49 (50.5%) and females 48 (49.5%). Table 3 shows different types of birth defects by their class (Isolated, Multiple, Syndrome).

Table 3 Distribution of specific types of birth defects by their class (Isolated, Multiple, Syndrome)

Type of Birth Defect	Isolated N=80	Multiple N=15	Syndrome N=5	Total N=100
NTD	28 (35.0%)	9 (60.0%)	2 (40.0%)	39 (39.0%)
Limbs defects	43 (53.7%)	4 (26.7%)	3 (60.0%)	50 (50.0%)
Orofacial defects	9 (11.3%)	2 (13.3%)	0 (0.0%)	11 (11.0%)
Total	80 (100.0%)	15 (100.0%)	5 (100.0%)	100 (100.0%)

Out of the 100 birth defects, isolated birth defects were 80 (80%), multiple were 15 (15%) and syndromic were 5 (5%) respectively. Among the multiple birth defects, neural tube defects had highest proportion (60%) while among isolated and syndrome, limb defects were the most common.

4.3 Factors associated with structural birth defects

Bivariate analysis of structural birth defects by maternal factors, paternal factor and newborn characteristics

Bivariate analysis was used to assess crude association between various factors and major structural birth defects. Table 4 shows crude odds ratios (COR) for different maternal and paternal factors. Mothers who reported to have fever during pregnancy had more than twice odds of giving birth to a defected newborn compared to those who did not suffer fever during pregnancy (COR=2.17, 95% CI: 1.30-3.61). Mothers who reported hypertension during pregnancy were more than four times more likely to give birth to a defected child (COR=4.28, 95% CI: 1.87-9.77) than non hypertensive mothers. Mothers who took folic acid supplementation tablets during pregnancy were more than 50% less likely to have structural birth defected child as compared to those who did not took supplemental folic acid tablets (COR=0.56, 95% CI: 0.32-0.96), and those who reported to use antimalarials during pregnancy had almost 60% less likely to have a structural birth defected child as compared to those who did not use antimalarials and the effect was significant (COR=0.57, 95% CI: 0.34-

0.94). Low birth weight babies were almost four times more likely to have structural birth defects compared to the normal weight babies, (COR = 3.97, 95% CI: 2.09-7.55).

Paternal age, consanguineous marriage, maternal HIV/AIDS, maternal Syphilis, maternal use of; alcohol, multivitamin, antiepileptic, antihypertensive, antibiotics and antiretroviral drugs during pregnancy, newborn sex and prematurity were not seen to have significant association with structural birth defects.

Multivariate analysis of structural birth defects by maternal factors, paternal factor and newborn characteristics

Factors which had a p-value of ≤ 0.2 in the bivarite analysis were included in the multiple logistic regression to assess for their individual effect on structural birth defects while controlling for other factors. Factors which were not considered in the multivariate analysis were consanguineous marriage, maternal HIV/AIDS and maternal Syphilis. Others were maternal use of alcohol, multivitamin, antiepileptic, antihypertensive, antibiotics and antiretroviral drugs during pregnancy.

Table 4 shows the adjusted odds ratios (AOR) for factors which were considered. After adjusting for other factors, the odds of being a case were two times higher among mothers reported unexplained fever during pregnancy compared to those without unexplained fever (AOR=2.00, 95% CI: 1.14-3.52); Mothers reported hypertension during pregnancy were four times more likely to give birth to a child with birth defects than pregnant mothers who were not hypertensive (AOR=4.00, 95% CI: 1.67-9.54); Newborns with low birth weight (<2500grams) were three times more likely to have structural birth defects as compared to those with normal weight (AOR=3.48, 95% CI: 1.77-6.85) and mothers who reported to use antimalarials during pregnancy had almost 50% less likely to have a structural birth defected child as compared to those who did not use antimalarials during pregnancy (AOR=0.48, 95% CI: 0.28-0.84).

Table 4 Crude and Adjusted Odds Ratios for factors associated with birth defects

Characteristics	Case, N=100 n (%)	Control, N=300 n (%)	COR(95% CI)	AOR(95% CI)
Maternal age(years)				
<20	15 (15.0)	40 (13.3)	1	
20 – 35	75 (75.0)	235 (78.3)	0.85 (0.45-1.63)	0.95 (0.42-2.13)
>35	10 (10.0)	25 (8.4)	1.07 (0.42-2.73)	1.19 (0.37-3.87)
Unexplained maternal fever				
No	67 (67.0)	242 (80.7)	1	
Yes	33 (33.0)	58 (19.3)	2.17 (1.30-3.61)	2.00 (1.14-3.52)*
Malaria				
No	60 (60.0)	211 (70.3)	1	
Yes	40 (40.0)	89 (29.7)	1.58 (0.99-2.53)	1.02 (0.55-1.92)
Epilepsy				
No	98 (98.0)	299 (99.7)	1	
Yes	2 (2.0)	1 (0.3)	6.1 (0.55-68.02)	7.60 (0.68-85.41)
Hypertension				
No	86 (86.0)	289 (96.3)	1	
Yes	14 (14.0)	11 (3.7)	4.28 (1.87-9.77)	4.00 (1.67-9.54)*
Folic acid intake				
No	25 (25.0)	48 (16.0)	1	
Yes	73 (73.0)	252 (84.0)	0.56 (0.32-0.96)	0.59 (0.33-1.06)
Antimalaria				
No	31 (31.0)	61 (20.3)	1	
Yes	69 (69.0)	239 (79.7)	0.57 (0.34-0.94)	0.48 (0.28-0.84)*
Newborn birth weight (grams)				
≥2500	77 (77.0)	279 (93.0)	1	
<2500	23 (23.0)	21 (7.0)	3.97 (2.09-7.55)	3.48 (1.77-6.85)*
Newborn sex				
Female	47 (47.0)	166 (55.3)	1	
Male	53 (53.0)	134 (44.7)	1.40 (0.89-2.20)	1.54 (0.94-2.49)
Prematurity				
No(Born>37[a])	55 (55.0)	189 (63.0)	1	
Yes(Born<37[a])	45 (45.0)	111 (37.0)	1.39 (0.88-2.20)	1.55 (0.94-2.57)
Paternal age(years)				
25-30	40 (40.0)	124 (41.3)	1	
<25	13 (13.0)	26 (8.7)	1.55 (0.73-3.29)	1.39 (0.57-3.45)
>30	47 (47.0)	150 (50.0)	0.97 (0.59-1.58)	0.94 (0.54-1.64)

*Statistically significant [a] Gestational age in weeks

CHAPTER FIVE

5.0 Discussion

Findings showed that major structural birth defects encountered between October 2011 and February 2012 were limbs defects, neural tube defects and orofacial clefts. Limbs defects had a higher proportion followed by neural tube defects (NTD) and orofacial clefts had the lowest. There was almost equal distribution of female and male among the newborns diagnosed with major structural birth defects in the study.

Mothers who reported hypertension, maternal fever during pregnancy, and low birth weight newborns had higher odds of developing structural birth defects. While antimalarials use during pregnancy was a protective factors against structural birth defects.

5.1 Description of structural birth defects

Studies have found that limbs defects are the commonest structural birth defects affecting both upper and lower limbs almost proportionally with few having both limbs affected [10, 47]. This study also finds the same results, ie limbs defects had a higher counts than the rest of defects studied. The study done in Entebbe also had similar findings [46]. Among the limbs defects, this study showed that polydactlyl count is high followed by talipes equinovarus. This trend was also observed in studies done among South African black population [47,48]. However a study conducted in Nigeria, West Africa among children with congenital orthopaedic malformations attending orthopaedic clinic at one of the teaching hospital revealed a different trend with talipes equinovarus having the highest rate [47]. This could be probably due to the differences of study population. Nigeria study population involved majority of limbs defects which need orthopaedic specialized care as it was an orthopaedic clinic based study as compared to this study which involve all limbs defects ascertained from birth.

We found that there is almost equal composition of female and male among the observed major structural birth defects newborns participated in our study. This is inconsistent with

other studies on structural birth defects which had shown a sex disproportionate with the defects being more common among males [39, 40, 41, 42].

This study found isolated birth defect had a high proportion than multiple and syndrome birth defects. Among the multiple birth defects, neural tube defects showed to have a higher proportion than the rest of studied defects. A prospective neurosurgical observational study done in Nigeria to assess central nervous system congenital anomalies resulted into a similar observation as in this study. NTD was shown to have a higher rate of been co-existed with other anomalies [49].

The study also found that Cleft palate co-existence with cleft lip had a higher prevalence than standalone Cleft lip or Cleft palate which had equal prevalence. Males had higher prevalence compared to females. A systematic review of the birth prevalence of cleft lip with or without cleft palate (CLP) and cleft palate (CP) in Africa had similar results as this study except it had an overall orofacial cleft prevalence of female preponderance [50]. A population based case control study done in Shenyang China to explore risk factors for oral clefts had shown a consistent result with our findings [51]. Other studies done in Rift Valley Kenya and Mwanza Tanzania resulted in a higher prevalence of standalone cleft lip compared to cleft palate with cleft lip and standalone cleft palate [9, 52].

5.2 Factors associated with structural birth defects

Mothers who reported to suffer from fever during pregnancy had significantly more than twice a risk of giving birth to congenital defected babies even after adjusting for other factors. Studies conducted in various parts globally had observed a significant association between maternal fever and birth defects in both bivariate and multivariate analysis which is consistent to our findings. A population based case control study done in Shanxi province Northern China on risk factors for neural tube defects found that, a history of fever during periconceptional period was associated with almost a threefold increase NTD risk which persisted even after controlling with other covariates[53]. Hyperthermia was also implicated as a risk for oral cleft in one of the highest reported prevalence rates of oral cleft in the World, Shenyang-Northern China[51]. Several other studies have shown that hyperthermia during

pregnancy is associated with increased risk of neural tube defects independent of infection status [54, 55].

The study also found that mothers who reported hypertension during pregnancy had more than four times risk of giving birth to defected child than the non hypertensive ones. Our results are consistent with findings of a study done in USA looking on maternal factors and disparities associated with oral cleft [55]. This can probably be explained by the fact that hypertension in pregnancy compromise uteroplacental perfusion and hence interfered with foetal development. Hypertension in pregnancy had also been shown to significantly increase risk for other birth defects such as hypospadias, aesophageal atresia/stenosis and congenital heart disease [56-59].

In this study, antimalarials use had a significant protective effect over birth defects and this remained even after controlling with other covariates. A study done to evaluate toxicological consequences of chloroquine and ethanol on the developing rat foetus had shown a teratogenic effect of antimalarials on structural birth defects such as cleft palate, wrist drop, clubbed foot and brain liquification [60]. However there are no enough evidences for teratogenic potentials for antimalarials other than tetracycline at standard doses in human [61].

Mothers who reported to take folic acid supplementation tablets during pregnancy were more than 50% less likely to have structural birth defected child as compared to those who did not take supplemental folic acid tablets; however in our multivariate analysis the association was not significant. This study shows that folic acid supplementation is protective against having birth defects [6, 62-66]. The results in our study might be due to the fact that we omitted women who took multivitamins (which might also contain folic acid) as this is not in our standard Reproductive and Child Health Antenantal care recommendation. Neural tube defects had shown an increased rate in places where there were no preconception or periconception use of folic acid supplements [62]. On the other hand, places where there is preconception use of folic acid supplementation had shown a decreased rates of neural tube defects[64-66]. In our environment, preconception use of folic acid supplementation is not an effective approach as majority of pregnancies is unplanned. Nevertheless, periconceptional folic acid

supplementation is in practice for all pregnant women attending antenatal clinic to counteract anaemia in pregnancy.

There was an association between Newborn birth weight and having structural defects. Low birth weight babies (<2500 grams) were almost four times more likely to have congenital defects than normal birth weight babies (≥2500 grams). This can be explained by several factors. Some birth defects may increase the risk of polyhydramnios that can result into preterm labour [67-69]. Preterm labour and birth defects may also share other risk factors such as maternal fever, maternal hypertension and different maternal infections. Contrast to our findings, risk of birth defects had been observed to significantly increase in premature infants [67, 70]. A significant association which we found between low birth weight and birth defects can not necessarily be implied to a relationship between prematurity and birth defects due to the fact a third variable ie intrauterine growth retardation can distort this relationship [70].

Studies done in various parts of the World have found association between structural birth defects and advanced maternal age (≥35 years), paternal age >30 years, consanguineous marriage, alcohol consumption and antiepileptic drugs use during pregnancy [25, 33, 38, 71]. However our study did not found advanced maternal age to be associated with major structural birth defects and this can be possibly due to the fact that we had few women who were above (≥35 years) ie only 9%. Other factors like paternal age >30 years, consanguineous marriage, alcohol consumption and antiepileptic drugs use during pregnancy did not also show a significant association to birth defects. Some of these factors like consanguineous marriage and women alcohol consumption during pregnancy can be accounted by the fact that is uncommon in our population.

None of our respondent reported to smoke cigarette, however cigarette smoking and tobacco use had widely been implicated in birth defects [36, 38]. A study done in Southern Nigeria to assess antenatal determinants of oral-facial clefts had similar results for the respondent, however an increased risk for oral-facial clefts that was observed among those who were

cooking indoor compared to those who were cooking outdoor had an implication of linking inhaled smoke from the cooking source and cigarette smoking [11].

5.3 Strengths and limitations of the study

One of the major strengths of this study is to include all births with studied structural birth defects from birth. This made it possible to capture birth defects which were stillbirths or had survived less than a day. This could have not been possible if our study would ascertain birth defects by either retrospective review of data from neonatal units or collecting data from either neonatal admission units or birth defects clinics alone which could have resulted into underestimation of the burden of major structural birth defects. Another strength is the involvement of multiple sites for data collection. This study involves three Municipal hospitals and one National hospital. These are public hospitals and have majority of deliveries of this region with coverage of people with diversity of demographic characteristics or health related behaviours.

This study had several limitations, one being rely on self reported mother's information of the risk factors and hence possibilities of recall bias. Mothers with defected newborns are likely to remember more easily about everything that happens to her during pregnancy as compared to mothers with normal newborns and yet asymptomatic infections or infections with mild symptoms cannot be remembered easily. The second is the study population. This study involves newborns whose mothers residing in only one region out of twenty six regions of this country; this may have decreased the precision of our estimates of prevalence of birth defects and measure of effects of associated factors. Our last limitation is data collection period and following time. This study took a five months data collection period and not more than 24 hours post delivery follow-up time. This may result in inclusion of few number of cases and captured only death resulted from birth defects that occurred within 24 hour.

CHAPTER SIX

6.0 Conclusion and Recommendations

6.1 Conclusion

This study showed that among the major structural birth defects, limbs defects had a higher proportion followed by neural tube defects (NTD) and orofacial clefts had the lowest. There was almost equal sex distribution among the observed major structural birth defects newborns participated in the study. Among NTD, Limbs defects and Orofacial defects the commonest defects for each type were anencephaly, polydactyl and cleft palate co-existence with cleft lip respectively.

Maternal hypertension, maternal fever during pregnancy, and low birth weight newborns were risks factors for developing structural birth defects. While antimalarials use during pregnancy was a protective factor against structural birth defects.

6.2 Recommendations

- Strengthen the Primary Health Care centres where ANC visits are done so that early screening of pregnant mothers for hypertension and other predisposing factors for low birth weight or prematurity is done.
- Ensure there is availability of antimalarial and folic acid tablets at Primary Health Care centres where ANC is done.
- Health education should be continuously given to pregnant mothers on the importance of use of antimalarial prophylaxis during pregnancy ie Intermittent Presumptive Malaria Treatment(IPT)
- Establishing strategies for improving health of women before and during pregnancy. This includes periconception folic acid supplimentation and other preconception simple screening methods.
- Paediatric clinicians/physicians should thoroughly investigate low birth weight newborns against birth defects and maintaining a follow-up after they are discharged from neonatal units.

- Advocacy should be given to the MoHSW on importance of taking birth defects a priority and this should include having allocated budget for comprehensive women's, maternal, newborn and child health programs and provision of basic medical genetic services to ensure that people with birth defects or at reproductive risk of having children with birth defects can live and reproduce as normally as possible.

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