

**ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCE
SCHOOL OF NURSING AND MIDWIFERY**

**DETERMINANTS OF NEURAL TUBE DEFECT AMONG CHILDREN, AT
ZEWDITU MEMORIAL HOSPITAL, ADDIS ABABA, ETHIOPIA ,2018
A CASE CONTROL STUDY**

PRINCIPAL INVESTIGATOR : FILMAWIT AYNALEM (BSc)

ADVISORS: MR. FEKADU AGA (ASS'T PROF, PHD FELLOW)

MR. GRUM SEBSBIE (ASS'T PROF, PHD FELLOW)

**A THESIS SUBMITTED TO ADDIS ABABA UNIVERSITY, COLLAGE
OF HEALTH SCIENCE, SCHOOL OF NURSING AND MIDWIFERY IN
PARTIAL FULFULMENT OF THE REQUERIMENTS FOR DEGREE OF
MASTERS OF SECIENCE IN PEDIATRICS AND CHILD HEALTH
NURSING**

JUNE- 2018

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ACRONYMS/ABBREVIATIONS

AAU: Addis Ababa University

ANC: Ante Natal Care

BMI: Body Mass Index

CDC: Center for Disease Control and prevention

CI: Confidence Interval

CSF: Cerebro Spinal Fluid

DM: Diabetes Mellitus

FA: Folic Acid

ICD: International Classification of Diseases

MTHF: Methylene Tetrahydrofolate reductase

NICU: Neonatal Intensive Care Unit

NTD: Neural Tube Defect

OR: Odds Ratio

SPSS: Statistical Package for Social Sciences

WHO: World Health Organization

ZWH: Zewditu Memorial Hospital

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ABSTRACT

Background: Neural tube defects (NTDs) are one of the commonest malformations with worldwide prevalence of 1-3 per1000 live births. They are resulted by failure of neural tube to close during neurulation in 21-28 embryonic days and it's a multi-factorial in etiology. Currently in Ethiopia there is no published data regarding the determinants of NTDs. Therefore this study was used to assess the determinants of NTDs in Addis Ababa and will serve as base line reference for further studies.

Objective: the objective of this study was to assess the determinant of Neural tube defects (NTDs) among children at Zewditu Memorial Hospital, Addis Ababa, Ethiopia.

Method: A hospital based unmatched case control study was conducted from November to May 2018. The sample size was determined by statistical Openepi version 3 by considering 95% CL at 80% power (case to control ratio of 1:2) and gave a total of 180, out of this 60 cases and 120 controls were selected by lottery method. Data was collected by structured questioner & SPSS version 23 software was used for analysis; results were summarized by descriptive statistics. Bivariate and multivariate logistic regression analysis was done at p -value < 0.05 and OR with 95% CI was used to control for possible confounders.

Results: The bivariate analysis shows that oral contraceptive use, young maternal age, parental low educational status, sauna/hot tub use, passive smoking, caffeine consumption ≥ 3 cup/day, maternal occupation, planned pregnancy, family history of neural tube defects, fever/febrile illness, antipyretic use & being multiparous shows significant association to neural tube defects. The multivariate analysis shows that maternal fever/febrile illness (OR 65.5 CI 4.4 -957.9), family history of neural tube defects (OR 43.5 CI 1.2-1506.9), coffee consumption (OR 18.5 CI 3.7-91.1), antipyretic use (OR 0.01 CI .00 -.53) maternal age < 19 (OR 33.3 CI 2.5-448.4) & 25-29 (OR 9.7 CI 1.3-67.6) shows association to neural tube defects.

Conclusion: in conclusion this study shows that maternal fever /febrile illness, family history of NTDs, coffee consumption, young maternal age, were associated with the increasing risk of NTDs whereas antipyretic drug use had protective effect to NTDs. therefore periconceptional maternal screening for genetic factors and medical illness is important for women's of child bearing age.

Key words: Neural tube defect, periconceptional factors, folic acid

CHAPTER I: INTRODUCTION

1.1 Background of the study

Birth defects are congenital anomalies that are present at birth of the baby, can be structural, functional, or metabolic. Structural birth defects are those that affect the development of body part. They usually develop during the first few weeks of pregnancy when the organs develop. Neural tube defect is a structural defect of the central nervous system that affects the brain, spine and spinal column of the developing embryo during the first month developmental process(1).

The neural tube is part of the central nervous system (CNS), which begins to form during the third week post-conception. The formation of the nervous system (Neurulation) starts with the formation of the neural plate, a thickening of ectoderm located along the middorsal region of the embryo. In humans, the neural plate develops into the neural tube via a two-step process. During primary neurulation, the lateral edges of the neural plate elevate as cells differentiate and migrate toward the neural plate edges forming the neural folds. As the neural folds continue to elevate, they meet at the midline and fuse to form the neural tube and primary neurulation and closure of the neural tube concludes by four weeks post conception. Secondary neurulation or canalization occurs at the caudal end of the primary neural tube when mesenchymal cells form a space that connects to the lumen of the primary neural tube. Open NTDs occur when the neural folds fail to meet and fuse during primary neurulation, whereas incomplete secondary neurulation leads to closed NTDs. Failure of the neural tube to close at different regions results in the clinical variation seen in the anatomical location of open NTDs, these defects are classified as open and closed type, open NTDs , in which the neural tissue is exposed to the environment or covered only by a membrane(e.g. are anencephaly and spinal bifida encephalocele, meningocele) and the rare closed NTDs, the neural tissue is not exposed and the defect is covered by skin(e.g. Lipomyelomeningocele, lipomeningocele) among all NTDs spinal bifida and anencephaly are the two most common forms (2).

Globally, more than 10% of infant mortalities are caused by nervous system defects, Although, the incidence of neural tube defects (NTD) has fallen over recent years in industrialized countries, it still remains high in the less developed countries in Latin America, Africa, the Middle East and Far East Asia, with estimated incidence ranging between 1 to 11per 1000 births(3).

NTDs are multifactorial disorders, arising from a complex combination of genetic determinants (mutations in foliate-responsive or foliate-dependent pathways ,family history),and environmental factors involving nutritional deficiencies, parental education, maternal ages and occupations, smoking, alcohol consumption, maternal reproductive history, a previous NTD-affected pregnancy, Maternal insulin-dependent diabetes, use of anti-seizure medication, obesity, and maternal use of caffeine and medications, and exposure to radiation and hyperthermia during early pregnancy (4).

1.2 Statement of the problem

NTDs are serious birth defects that occur when the neural tube, which ultimately will form a baby's brain and spine, fails to close properly. Although largely preventable, they are a significant cause of death and lifelong disability among children's. The defects occur very early in pregnancy (during the first month of conception); usually before a woman knows she is pregnant. Worldwide it occurs widely among diverse populations, with varying levels of economic development, and geographic variations. Any woman who is capable of becoming pregnant could have an NTD-affected pregnancy. It is not possible to predict which women will have a pregnancy affected by an NTD. Ninety-five percent of women with NTD-affected pregnancies have no personal or family history. The exact cause of NTDs is not known. However, some risk factors are known, According to the WHO, almost all (94%) severe birth defects occur in low- and middle-resource countries, often due to maternal malnutrition and exposure to teratogenic agents, alcohol and tobacco. Other known risk factors associated with birth defects include micronutrient insufficiency and deficiency, maternal illnesses such as diabetes, obesity, chemical and heat/radiation exposure during early pregnancy. As infant mortality due to diarrheal and infectious diseases declines in low and middle resource countries, there is an increasing visibility of under-5 mortality due to birth defects. Morbidity due to birth defects is also an important consideration, since, as medical technology continues to evolve, survival rates among babies born with birth defects will likely increase. This will require that countries allocate significant financial resources to account for the long-term care for individuals with disabilities (5, 6).

NTDs affect not only the life of a child and those of his or her family, but the community as well. As a child with spinal bifida grows older, he or she faces unique economic, educational, medical, health, and emotional issues. Paralysis of the legs and bowel and bladder management problems are common. These problems may affect a person's health, self-esteem, personal interactions, and work and recreational opportunities. Although medical care has greatly improved the survival rates and quality of life of children with spinal bifida, the children and family's life is affected with varying degrees of physical and social challenges today, mental retardation caused by hydrocephalus, is uncommon because of early medical and surgical treatment. However,

Learning disabilities are common. In all instances, anencephaly is fatal, either in utero or shortly after birth(5, 7).

Screening tests for NTDs decreases morbidity and mortality by promoting access to earlier diagnosis. Periconceptional consumption of folic acid and vitamins, have demonstrated important role in the development of neural tube and has been proven to reduce the risk of an NTD affected pregnancy by 50% to 70%.Many countries have reported declines in NTDs incidence after the introduction of folic acid fortification in staple food .However, a large number of NTDs cases still occur and the cause remains unclear. Therefore better understanding and additional research of risk factors will improve interventions aimed at reducing NTD prevalence (7, 8).

There is paucity of data particularly in low- and middle-resource countries. This lack of data stems from variability in vital registration, diagnostic capacity, and capability of countries to capture birth defects, and lack of an established birth defect surveillance system. Furthermore, even if birth defects surveillance system exists, prevalence estimates may not include birth defects among stillbirths and elective terminations because no information is collected on stillbirths or elective terminations As a result, the global toll of birth defects remains underestimated (6).

In Ethiopia there is very limited published data regarding the prevalence of NTD. But there is no documented data on the determinant of NTDs in Addis Ababa. Therefore the purpose of this study is to assess the determinants of NTDs among children in Zewditu Memorial Hospital.

1.3 Significance of the study

This study will identify pertinent information on determinant factors of NTDs and the finding will be important to health planner, policy maker, governmental and nongovernmental organizations (NGOs) that are working on the issues of neural tube defect prevention and control and other stake holders such as health professionals in designing interventional project towards improving child health and reducing morbidity and mortality due to neural defect. So that they can put in place research based interventions in order to prevent the problem from its root.

It's expected that findings generated from this study will contribute for policy makers in effort to introduce periconceptional screening and counseling in women's of child bearing age and to revise the existing ANC visit schedule.

It will create awareness for the public about NTDs and its determinant factors. It can also extend the existing knowledge and skill of health professionals about the risky exposures based on our context. Moreover, researcher and practitioners will use this study as base line reference for further development of research on determinant factors.

CHAPTER II: LITERATURE REVIEW

2.1 Magnitude of NTD

Worldwide, it is estimated that more than 300,000 babies are born each year with NTDs, resulting in approximately 88,000 deaths and 8.6 million disability adjusted life years (2). In low income countries, NTDs may account for 29% of neonatal deaths due to observable birth defects. As morbidity and mortality from infectious diseases are decreasing worldwide, the contribution of birth defects to under-5 morbidity and mortality will continue to increase proportionally. In North America, NTDs occur in about 1 in 1000 pregnancies annually(2, 9).

A systematic review on birth defects and developmental disabilities show that there is variation in the prevalence of NTDs worldwide. According to this the highest prevalence in African region (75.4 per 10,000 births), Eastern Mediterranean (124.1 per 10,000 births), Europe estimates (35.9 per 10,000 births)was reported(9).

NTD prevalence rate in live-born neonates of the Kano Metropolis hospital of North-western Nigeria shows that 2.75 per 1000 live birth (10). In Ethiopia the magnitude of birth defects were found 6.07 1000 live birth out of this neural tube was the second most common defect (30.8%) following orofacial defect(11).A retrospective study conducted at two teaching hospitals of Addis Ababa shows that the overall prevalence of NTD was 6.1 per 1000 live birth(11).

2.2: Factors predisposing for the development of NTDs

Congenital abnormalities can develop at any time of the pregnancy, from conception to birth. Neural tube defects are commonest malformations of the brain and spinal cord. Genetic,sociodemographic factors,medical and drug factors, reproductive &obstetric factors, and environmental factors have been implicated in the etiology of NTDs, therefore the embryo and the fetus have to adapt, at a molecular and transcriptional level, to various changes in their cellular milieu (12).

2.2.1 Genetic factors

The genetic mechanisms associated with NTDs have been addressed through studies on associations between NTD risk and variants in genes involved in folate metabolism, chosen because of the protective effect of folic acid on NTDs. Methylene tetrahydrofolate reductase (*MTHFR*) plays an important role in folate metabolism. The *MTHFR*677 TT genotypes in infants and mothers have been associated with increased risk for NTDs. (13) A small proportion of NTDs are associated with known genetic syndromes (Meckel syndrome, and aneuploidy conditions, such as Trisomy 13 and Trisomy 18). Non-syndromic NTDs are also thought to have some genetic basis as evidenced by a 2 to 5% risk of recurrence for mothers with a previous NTD-affected birth, a 50-fold increase over the general population risk. In addition, consanguineous marriages, a positive family history has been associated with an increased risk of an NTD-affected pregnancy (2, 14).

A Population based case-control study conducted in Shanxi province of Northern China showed a history of a previous birth defect-affected pregnancy (OR 5.27, CI 0.98- 28.3) was significantly associated with NTD (15). Another hospital based study conducted at Riyadh and Algeria showed that consanguineous marriage was observed among cases (39.1% and 30%) respectively (3, 16).

2.2.2 Socio demographic factors

Various studies have suggested that NTD risk is higher among families of lower SES. Nutritional deficiency due to poverty and poverty related problems could predispose these mothers to NTDs affected pregnancy and also maternal age (being young and old), parental low educational status, female gender of the offspring, occupational and residential exposure to chemical pollutants are also associated to NTDs (14, 15, 17).

Hospital based case-control study conducted at Genoa, Italy, shows that maternal low educational level (OR=4.87, CI, 2.38–9.97) median annual family income (OR=3.35, CI, 1.34–8.34), maternal age < 25 years (OR=3.36; CI, 1.89–5.36) and >35 years; (OR=5.21, CI, 2.42–11), second and third birth order (OR=2.15, CI, 1.25- 3.6) and (OR=3.93, CI, 1.69–9.17) respectively was among the significant risk factors (17). Northern china studies also show NTD were associated with a primary school education or lower (OR 2.32, CI 1.09- 4.97) (15).

According to study done in Riyadh and Algeria hospitals female gender of offspring's were (36.6% and 70%) respectively and maternal 25-29 was associated to NTDs(3, 16).

2.2.3 Maternal nutrition and folic acid consumption

Among the most notable environmental risk factors for NTDs is maternal pre-pregnancy obesity. Studies showed that being overweight in women was significantly associated with an increase of NTD's rate. It is believed that glucose homeostasis plays an important role in NTD; at the time of neural tube closure, mothers with poorly regulated glucose levels are likely to have an altered intrauterine environment leading to abnormal organogenesis. Greater mean daily consumption of sucrose-containing and high-glycemic index foods was recently shown to be associated with an increased risk of NTD, especially among obese women(16, 18).

Folate status plays a key role in determining the risk of NTDs. Folate is integral to intracellular one carbon metabolism, which produces pyrimidines and purines for DNA synthesis. Both folate and folic acid must be reduced to participate in cellular metabolism. The micronutrient form of folate 5-methyltetrahydrofolate (MTHF) which circulates in plasma, is the physiologically active form of folate that serves as a cofactor for enzymatic reactions. Demands for folate increase during pregnancy because it is also required for growth and development of the fetus. Maternal supplementation with folic acid during pregnancy reduces NTD frequency whereas reduced serum folate and/or elevated homocysteine (an inverse indicator of folate status) is observed in some mothers of NTD affected fetuses, and is considered risk factors for NTDs. FA may not reduce NTD risk to the same degree in all racial/ethnic groups, suggesting that a genetic component may be involved(10, 14).

According to a comprehensive article review of maternal and fetal risk factors associated with NTDs, such as, periconceptional folic acid deficiency, and effects of folic acid supplementation and fortification on rates of NTDs, periconceptional vitamin B12 deficiency maternal auto-antibodies to folate receptors, are an important cause of NTD. About 70% of NTDs in humans are folate-sensitive and can be prevented by 4 mg/day periconceptional folic acid supplementation. The relative risk (RR) estimate for the women who were at high risk of having a pregnancy with an NTD because of a previous affected pregnancy and were allocated to take folic acid was 0.28, indicating a 72% protective effect (RR, 0.28; 95% CI, 0.12–0.71) (4).

A case-control studies conducted in Italy and Algeria shows that significant association to NTDs was observed in mothers who didn't take pre-conception folic acid (OR=27 CI, 9.31–78,& 86%) respectively(16, 17). Another study conducted in Riyadh shows that significant protective effect of periconceptional folic acid consumption both prior to conception (OR 0.02, CI 0.00-0.07) and during the first 6 weeks of conception (OR 0.13, CI 0.04-0.39).According to study conducted in Iran, maternal obesity (OR: 5.4, CI: 1.3-21.8) was significantly associated with NTDs(19).

A six year period hospital based case-control study conducted among all pregnancies with NTD affected newborns (n=91) in Kasha, center of Iran, indicated that maternal obesity (OR: 5.4, CI: 1.3-21.8) was significantly associated with NTDs(19).

2.2.4 Maternal reproductive history

Studies shows that maternal reproductive histories (history of abortion, still birth, early neonatal loss) are associated risks. Parity has also shown to influence NTD risk with being highest number of births or an increasing risk with increasing parity(14, 20).

According to a 4-year period case-control study conducted at King Khalid University Hospital, Riyadh shows that significantly higher proportion case mothers had ,history of stillbirth (case to control ,16% VS 4.1%, P=0.02), neonatal losses (4.2%)(3) .A six year period hospital based case-control study conducted among all pregnancies with NTD affected newborns (n=91) in Kasha, center of Iran, indicated that maternal history of abortion (OR: 4.9, CI: 1.9-12.8), was significantly associated with NTDs(19).

2.2.5 Chemical Exposure

Chemicals used as pesticides (insecticides, herbicides, and fungicides) can cross the placenta and impact embryonic development. In animal studies, these chemicals have been shown to alter neuroepithelial cell proliferation and differentiation during neurulation and lead to excessive neuroepithelial cell death that impacts closure of the neural tube. Pesticide exposure can occur in both the home and the workplace(2). According to Italian study use of pesticides or solvents (OR=10.62, CI, 1.23 91), residence near waste sites or polluting industries (OR=3.57, CI 1.54–8.29) were proved to be a risk factor for spina bifida(17).

2.2.6 Maternal Fever/febrile illness

Maternal hyperthermia can arise from either febrile illnesses or external exposure to heat, such as prolonged period's use of hot tub or sauna. A recent meta-analysis evaluated that the NTD risk was increased almost three fold in cases of maternal fever during the first trimester. And also strongly implicated that maternal fever in early pregnancy as a risk factor for NTD-affected pregnancies (21). Although it has been proposed that hyperthermia-induced NTDs may arise from changes in metabolism, research indicates that it is the heat that adversely affects development, likely as a result of increased cell death, decreased proliferation, disruption of gene expression, and damage to the embryonic vasculature, leading to induction of apoptosis, inhibition of proliferation/delayed differentiation(22).

A population based case-control study of fetuses and live born infants with NTDs conducted in California showed that, maternal fever or febrile illness episode in the first trimester was associated with an increased risk for having a NTD-affected pregnancy (OR 1.91 CI, 1.35–2.72) &(OR 2.02 CI 1.2-3.34) respectively but risks were lower among women who used a fever-reducing medication (approximately 95% used antipyretic)(23). Study of northern china shows that history of a fever (OR 3.36, CI 1.68, 6.72), use of antipyretic drugs (OR 4.89, 95% CI 0.92, 25.97) were associated to NTDs(15).

2.2.7 Maternal Medical and drug factors

Maternal pregestational diabetes mellitus is an important risk factor for the development of CNS malformations; its teratogenic effect may be due to embryonic exposure to elevated glucose concentrations. Hyperglycemia has been shown to inhibit the uptake of myo-inositol, which is essential for embryonic development during gastrulation and neurulation stages of embryogenesis. It is has been found to cause a 2-fold to 10-fold increase in risk of CNS malformations among the offspring of affected women, relative to the general population(10).

Maternal epilepsy is associated with a 1% to 2% risk for offspring with NTDs and an overall two- to three-fold increased risk for congenital anomalies in the offspring. This risk is considered to be due to anticonvulsant use, in particular valproic acid and carbamazepine(14). Other factors including use oral contraceptives, medical illness (like hyperthyroidism), use of anti seizure drugs may also predispose offspring to NTDs(14, 23).

2.2.8 Maternal life style

Maternal life style factors like alcohol consumption, caffeine consumption, smoking and external exposure to tobacco smoke are associated to NTDs (2).

Maternal caffeine consumption, smoking and external exposure to environmental tobacco smoke (ETS) have also been studied with respect to risk for an NTD-affected pregnancy. Meta-analyses review indicate that maternal smoking confers a small increased risk for spina bifida, and a moderately increased NTD risk in cases of maternal ETS exposure(21). Both smoking and ETS are associated with decreased serum folate levels (22).

According to hospital based study conducted in Italy high caffeine intake (≥ 3 cups per day) (OR=7.78, CI, 4.02–15.05), maternal smoking habits (OR=1.91, CI 1.16–3.14) and alcohol intake (OR= 3.69, CI, 2.12–6.42) were proved to be a risk factor for spina bifida(17). In addition to this northern china study indicated that daily passive exposure to cigarette smoke (OR 1.60, CI 0.94, 2.73) was associated to NTDs (15).

CONCEPTUAL FRAME WORK

This conceptual frame work is developed by reviewing different ideas from several studies (2, 14, 15, 17, 18, 21, 22).NTD is multi-factorial in etiology, according to this conceptual framework shows that genetic factors, reproductive history, medical and drug factors, maternal lifestyle and child characteristics could have direct association with NTDs. However, socio demographic factors, environmental factors, environmental factors and maternal nutrition could have direct and indirect association with NTDs.

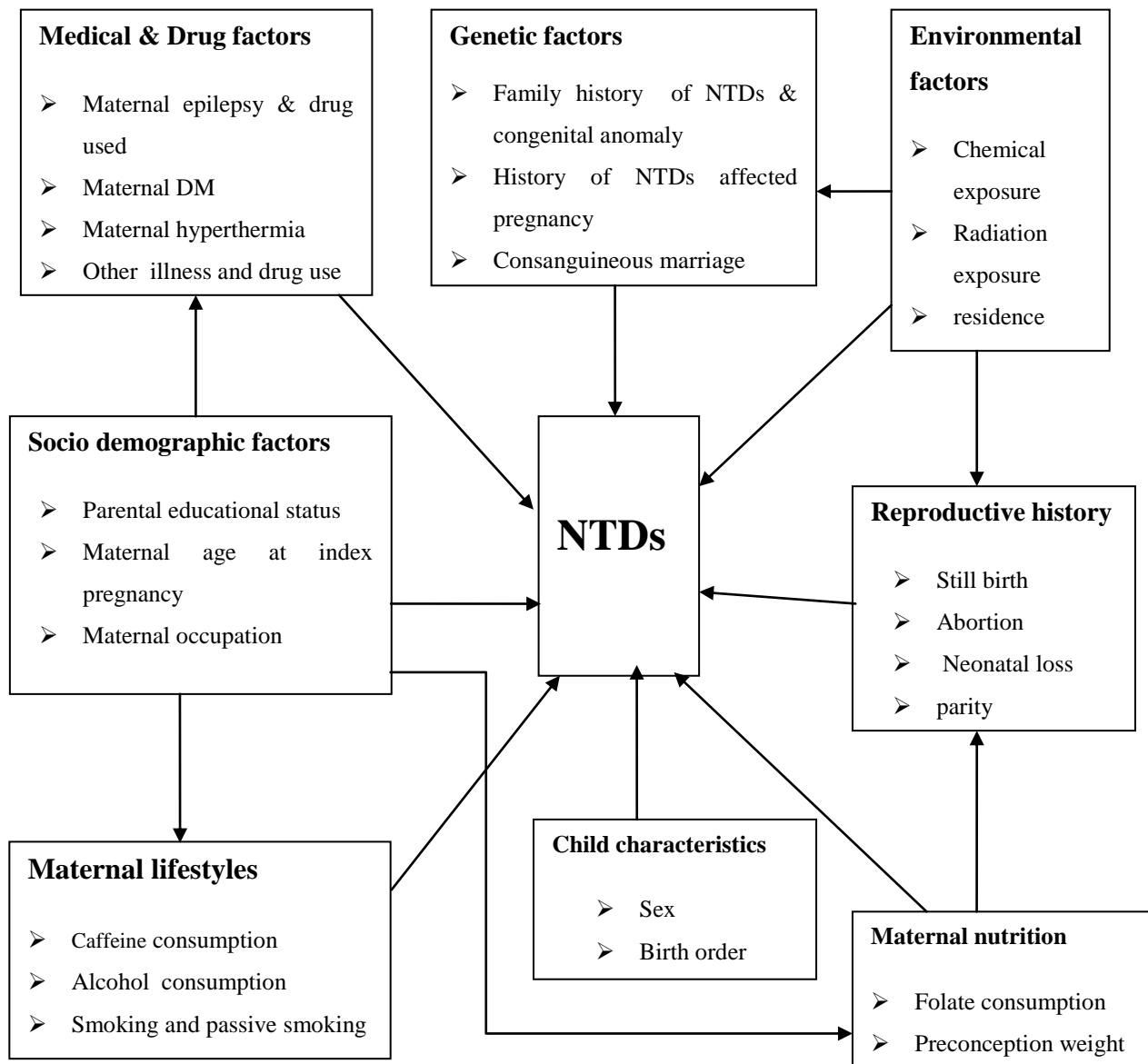


Figure -1: Conceptual frame work of determinants of NTDs among children < 3 years of age, 2018.

CHAPTER III: OBJECTIVES

3.1. General objective

- To assess the determinant factors of NTDs among children < 3 years of age children at Zewditu Memorial hospital, Addis Ababa, Ethiopia, 2018.

3.2 Specific objectives

- To identify parental socio demographic factors associated to NTDs
- To assess parental genetic factors associated to NTDs
- To determine maternal reproductive and obstetric factors associated to NTDs
- To assess periconceptional factors associated to NTDs
- To assess child characteristics associated to NTDs

CHAPTER IV: METHODS AND MATERIALS

4.1 Study Design

Hospital based unmatched case control study was conducted among cases or children's < 3 years of age with NTDs and controls or children's < 3 years of age without NTDs at Zewditu Memorial hospital, Addis Ababa, Ethiopia, 2018.

4.2 Study area and period

Addis Ababa is the capital city of Ethiopia. Based on 2013 population projection the total population of the city is 3,273,001 among this 1,772,001 are women and the rest 1,551,000 are men(24). There are 52 hospitals in metropolis which 6 are administered by Addis Ababa regional health bureau, 5 by federal ministry of health, 3 by NGO, 3 by defense and police and the remaining administered by private owners(25). Zewditu Memorial Hospital is one among the 6 hospitals administered by the AARHB. It is located in the central part of the city. It has a total of 885 staffs 580 of them are health professionals and 305 are supportive staffs and it runs multidisciplinary health service system. The pediatric and NICU of the hospital has a total of 73 beds. Zewditu memorial hospital (ZMW) is one the neurosurgical teaching hospital of AAU where the pediatric neurosurgical cases admitted and treated. So this study was carried out at ZMW from April to May 2018.

4.4 Source Population: All children < 3 years of age who were admitted to Zewditu Memorial Hospital.

4.5 Study population: All children's < 3 years of age, who full fill the inclusion criteria admitted at Zewditu Memorial hospital for both cases and controls.

4.6 Study unit: All mothers of both cases and controls groups and their medical charts.

4.7 Inclusion and Exclusion Criteria

4.7.1 Inclusion Criteria

- **For Cases:** All children less than 3 years of age with any type of NTDs in both sex who were admitted at Zewditu Memorial Hospital, Addis Ababa Ethiopia, 2018.
- **For controls:** Children under 3 years of age and who were admitted to Zewditu Memorial Hospital at the time of data collection but not having any forms of NTDs and other congenital anomalies.

4.7.2 Exclusion Criteria

- Respondents who can't hear and talk and critically ill during the data collection, and children's admitted with other care giver/other than the mother were excluded. A control group with other congenital anomalies other than NTDs was also excluded.

4.8 Sample Size and sampling procedure

4.8.1. Sample size determination

History of abortion, maternal obesity (>30 BMI) and failure to take periconceptional folic acid, were considered to calculate the required sample size by revising different literatures. Maternal history of abortion is chosen as an independent variable since it gives maximum sample size as compared to other exposure variables. The sample size of the study participants is calculated using OpenEpi, version 3 software by employing two population proportion difference approach by considering the proportion of history of abortion of cases (18.7%) and the proportion of controls exposed is (4.8%) with 4.9 odds ratio from similar study and the following assumptions: 1 to 2 cases to controls ratio will be recruited to achieve 80% power at 95% confidence level. Then it gives a total estimated sample size of 173, (58 cases and 115 controls). By adding a 5% non-response rate, total of 180(60 cases and 120 controls) participants were included in the study.

4.8.2. Sampling technique and Procedures

As it is described in the study area part, among the AAU teaching hospitals ZMH (where the only NTDs referral hospital from the country at all) was purposively selected. And a total of 60 cases with any type of NTDs who fulfill inclusion criteria were included in the study, and 120 controls that fulfill inclusion criteria was selected using simple random sampling technique (lottery method). For each case two consecutive controls were sampled.

4.9 Data collection tools and procedure

Data was collected using pretested a semi structured questionnaire. The questions are developed and reviewed from different study literatures(2, 3, 8, 15, 17, 23) in order to address the objectives of the study contents of data extraction format were reviewed by senior neurosurgeons. The questioner was developed first in English then later translated in to local language (Amharic). Three trained BSc nurses conducted face to face interview with parents of the children and it was supported by review of patient medical chart for confirmation of their diagnosis. Respondents were provided a brief orientation on the purpose of the study and its significance.

4.10 Pretest

Before data collection, pretest was done in 5% (9) of the sample size population (3 cases and 6 controls) at Korea hospital, which is not included in the study area before the actual data collection period and necessary adjustments, was done on the study tool.

4.11 Data quality control

To increase the quality of data properly designed, pretested data extraction tool was used. In order to avoid any confusion and to have a common understanding, training was given to data collectors and supervisors by principal investigator about the objectives of the study, data collection instruments, data collection procedures and the ethical considerations during data collection.

Each respondent's questionnaire was checked for its completeness and its consistency at the time of data collection by collectors, supervisors, and principal investigators. Data coding, entry, and cleaning was performed by the principal investigator.

4.15 Study Variables

4.15.1 Dependent variable

- NTDs (Yes, No).

4.15.2 Independent variable

Socio-demographic

- Parental educational status
- maternal age at pregnancy
- Maternal occupation

Reproductive history

- Still birth
- Abortion
- Early neonatal loss
- Parity
- ANC visit
- Planning of pregnancy

Maternal behavioral factors/lifestyles

- Alcohol consumption
- Smoking/exposure to external smoking
- Other (herbal use)Maternal DM

Environmental factor

- Chemical exposure
- Radiation/heat exposure

Maternal nutrition

Priconception maternal weight
Folic acid supplementation

Genetic factors

History of NTDs affected pregnancy
consanguineous marriage
family history of NTDs or congenital
anomaly

Medical & Drug factors

Maternal epilepsy & drug used
Maternal fever/febrile illness

Child characteristics

Birth index
Gender

4.16 Operational definition

- **NTDs:** are structural defect of the central nervous system that affects the brain, spine and spinal column during the first month of embryonic development.
- **Myelomeningocele:** is a condition where the spinal cord and the tissues covering it protrude out of an opening in the back.
- **Encephalocele:** is a kind of neural tube defect that results in a sac like protrusion of the brain and its surrounding membranes through an opening in the skull.
- **ANC follow up:** a woman who had regular antenatal care during pregnancy.
- **Periconceptional period:** a time one month before conception until 12 weeks of gestation.
- **Pericoceptional folic acid supplementation:** standard recommendation of folic acid (400µg/day) for all women from the moment they begin trying to conceive until 12 weeks of gestation should take a folic acid supplements.
- **Food fortification;** is a practice of deliberately increasing the content of an essential micronutrients (vitamins, minerals) in a food to improve its nutritional quality.
- **Consanguineous marriage:** a union between two individuals who are related by birth as second cousins or closer (familial marriage).
- **Maternal fever/febrile illness:** a febrile condition that increases degree of body temperature $> 38^{\circ} \text{C}$ either internally caused by illness (febrile illness) or external exposures (hot tub use, heated beds....).
- **Close family member:** are individuals who are related by blood and it includes grandparents, parents, siblings and children.
- **Planned pregnancy:** Are deliberate decision /agreement made by family or women to start to become pregnant (includes intentionally stopping of contraceptive use).

- **Body Mass Index (BMI):** BMI is a measurement of persons weight(kg) with respect to his/her height (meter²) based on the WHO BMI score is classified as;
 - ✚ <18.5 under weight
 - ✚ 18.5-24.9 normal weight
 - ✚ 25-29.0 over weight
 - ✚ > 30.0 obese
- **Parity:** the number of times the woman give birth
- **Multiparous:** woman who has given one more birth
- **Grand multiparous:** a woman who has already given five or more birth
- **Living near to waste disposal area:** residents located less than 100 meter from waste disposal area or polluting industries.
- **Pesticides:** are chemical compound used to kill insects, rodents, fungi, weeds
- **Cases:** for this study NTDs includes mylomeningocele and Encephalecle occurring either in isolation or in combination with other congenital malformations.

4.12 Data processing, analysis, presentation

The data will be checked for completeness and consistencies, and cleaned, coded and entered using Epidata version 4.2 and was exported to statistical package for social sciences (SPSS) software version 23 for analysis. Descriptive statistics was used to describe the study population in relation to relevant variable. Odds ratio (OR) with 95% CI was used to assess the relationship between factors associated with the occurrence of outcome variable.

Logistic regression model was used and bivariate logistic regression was done to determine association between each independent variable with outcome variable. All variables with a significant association in the bivariate logistic regression analysis were entered into the final multivariate analysis model to control confounders and identify independent effect of different factors for occurrence of NTDs. variables having $P < 0.05$ were considered as statistically significant.

4.13 Ethical consideration

After approval of the document by Addis Ababa University (AAU) collage of health science, Ethical clearance was obtained from AAU collage of health science research and community service directorate ethical committee and support letter was taken from Addis Ababa health bureau. Letter of permission was obtained from the selected hospital principal. After getting permission to conduct the study, each study subject's selected parents were asked for their willingness by explaining objectives of the study and its significance. During data collection the participation of the respondents was voluntary based and they were free to withdraw their participation at any time they want. Participant's confidentiality was strictly held by research team. Study participants were assured that there will not be any physical and emotional harm resulting from participating in the study.

4.14 Plan for dissemination of result

Final result of the study will be presented and submitted to Addis Ababa University collage of Health Science, School of Nursing and Midwifery to serve as reference material for subsequent researches and teaching purposes. The study finding will be submitted to Addis Ababa health bureau and Ministry of Health. The paper will be presented at different conference in the university and in scientific conferences. Attempt will be made for publication of the research on peer-reviewed Journal.

6. RESULTS

A total of 180 (60 cases and 120 controls) were included with 100 % response rate. As it's shown in table 1; compared to control mothers case mothers were primary school (53%) and house wife (88%). More than half (54%) fathers of controls had diploma /other higher educational status. Maternal age at index pregnancy was ≥ 30 (42.2%) for mothers of controls than cases. Compared to controls, case children's were female (58%), birth order of children's shows that controls were first born (44%) than cases.

Table 1: Socio demographic characteristics of mothers of cases & controls at Zewditu Memorial Hospital, Addis Ababa Ethiopia, 2018

| Variables | Cases | | Control | |
|---------------------------------------|-----------|----|-----------|------|
| | Frequency | % | Frequency | % |
| 1. Maternal age | | | | |
| <19 | 10 | 17 | 4 | 3 |
| 20-24 | 17 | 28 | 27 | 22.5 |
| 25-29 | 20 | 33 | 38 | 32 |
| ≥30 | 13 | 22 | 51 | 42.5 |
| 2. Maternal educational status | | | | |
| - Illiterate | 13 | 22 | 9 | 7 |
| - Primary school | 32 | 53 | 44 | 37 |
| - Secondary school | 8 | 13 | 32 | 27 |
| - diploma/Degree | 7 | 12 | 35 | 29 |
| 3. Paternal educational status | | | | |
| - Illiterate | 9 | 15 | 2 | 2 |
| - Primary school | 18 | 30 | 23 | 19 |
| - Secondary school | 21 | 35 | 30 | 25 |
| - diploma/Degree | 12 | 20 | 65 | 54 |
| 4. Maternal occupation | | | | |
| - Housewife | 53 | 88 | 80 | 67 |
| - factory worker | 1 | 2 | 2 | 2 |
| - office worker | 6 | 10 | 35 | 29 |
| 5 Child characteristics | | | | |
| 5.1 Gender - Female | 35 | 58 | 54 | 45 |
| - Male | 25 | 42 | 66 | 55 |
| 6. Birth order | | | | |
| First | 18 | 30 | 53 | 44 |
| Second | 19 | 32 | 35 | 29 |
| Third and above | 23 | 38 | 32 | 27 |

As it's shown in table-2 among a total of NTDs cases 93.7% were Myelomeningecele and 6.7% Encephaloccele. Clubfoot (18.3%) was the only associated congenital anomaly among cases.

Table 2: Child characteristics of NTDs case at ZMH, Addis Ababa Ethiopia, 2018

| Variable | No | % | |
|---|-----|------|------|
| 1.Type of NTDs | | | |
| Myelomeningecele | 56 | 93.3 | |
| Encephaloccele | 4 | 6.7 | |
| 2. Additional congenital anomaly | | | |
| (clubfoot) | Yes | 11 | 18.3 |
| | No | 49 | 81.7 |

I. Logistic regression results of factors and NTDs

Socio demographic factors associated with NTDs

As it is shown in the table 3; the socio demographic factors, maternal age, < 19(OR 9.8CI 2.64 - 36.3, p .0001), maternal age 20-24 (OR 2.4 CI 1.04 -5.83, p0.001) were strongly associated to risk of NTDs. Compared to control mothers cases mothers were not working (OR3.86 CI 1.52 - 9.8 P .005). Parental low educational status, illiterate (OR 7.22 CI 2.23 -23.38 P .001) primary school (OR 3.63 CI1.43 -9.22 P .007) was proved to be a risk factor for NTDs. regarding gender and birth order of the child there was no association to NTDs risk but compared to control children, female cases account 58%.

Table -3 Socio demographic factors and NTDs at ZMH, Addis Ababa, Ethiopia, 2018

| Variables | Cases n | Controls n | OR | CI (95%) | P |
|---------------------------------------|--------------------|-----------------------|-----------|-----------------|-------------|
| 1. Maternal age | | | | | |
| <19 | 10 | 4 | 9.80 | 2.64 -36.33 | .001 |
| 20-24 | 17 | 27 | 2.47 | 1.04-5.83 | .039 |
| 25-29 | 20 | 38 | 2.06 | .914 - 4.66 | .081 |
| ≥30 | 13 | 51 | Ref | | |
| 2. Maternal educational status | | | | | |
| - Illiterate | 13 | 9 | 7.22 | 2.23 - 23.38 | .001 |
| - Primary school | 32 | 44 | 3.63 | 1.43 - 9.22 | .007 |
| - Secondary school | 8 | 32 | 1.25 | .407 - 3.839 | .697 |
| - diploma/Degree | 7 | 35 | Ref | | |
| 3. Paternal educational status | | | | | |
| - Illiterate | 9 | 2 | 24.37 | 4.67 - 127.08 | .000 |
| - Primary school | 18 | 23 | 4.23 | 1.77 - 10.13 | .001 |
| - Secondary school | 21 | 30 | 3.79 | 1.65 - 8.70 | .002 |
| - diploma/Degree | 12 | 65 | Ref | | |
| 4. Maternal occupation | | | | | |
| - Housewife | 53 | 80 | 3.86 | 1.52 - 9.82 | .005 |
| - factory worker | 1 | 2 | 1.16 | .115 - 11.81 | .896 |
| - office worker | 6 | 35 | Ref | | |
| 5 Child characteristics | | | | | |
| 5.1 Gender | | | | | |
| -Female | 35 | 54 | 1.71 | .914-3.20 | .093 |
| -Male | 25 | 66 | Ref | | |
| 6. Birth order | | | | | |
| First | 18 | 53 | .473 | .222 - 1.00 | .052 |
| Second | 19 | 35 | .755 | .348 - 1.63 | .477 |
| Third and above | 23 | 32 | Ref | | |

Maternal reproductive and genetic factors associated with NTDs

Results of maternal reproductive and obstetric history showed that (in table -4), being multiparous (OR .186 CI .035 -.995, P .049), and having planned pregnancy (OR .40 CI .195 - .822, P .031) proved to have an apparent protective effect. History of abortion, still birth, early neonatal loss and having regular ANC follow up had no association to NTDs. but 27% of case mothers had history of abortion. Among the genetic factors, close family history of NTDs (OR 13.2 CI 2.83 -61.6, P .001) was highly associated. Compared to control mothers; cases mothers (22%) had birth relationship with their husband. Neither cases nor controls had previous NTDs affected pregnancy.

Table 4 Maternal reproductive and obstetric history and NTDs at ZMH, Addis Ababa Ethiopia, 2018

| Variables | Cases n (%) | Controls n (%) | OR | CI (95%) | P |
|-----------------------------------|-------------|----------------|--------|-------------|-------------|
| 1.parity | | | | | |
| Multiparous | 55(92) | 118(98) | .186 | .035 - .991 | .049 |
| Grand multiparous | 5(8) | 2(2) | Ref | | |
| 2.history of abortion | | | | | |
| -Yes | 16(27) | 20(17) | 1.81 | .862 - 3.83 | .117 |
| -No | 44(73) | 100(83) | Ref | | |
| 3.History of still birth | | | | | |
| - Yes | 1(2) | 3(2.5) | .661 | .067- 6.493 | .722 |
| - No | 59(98) | 117(97.5) | Ref | | |
| 4.History of neonatal loss | | | | | |
| - Yes | 0(0) | 7(5.8) | .000 | .000 | .999 |
| - No | 60(100) | 113(94.2) | Ref | | |
| 5.Planned pregnancy | | | | | |
| -Yes | 40(67) | 100(83) | .400 | .195 -.822 | .013 |
| -No | 20(33) | 20(17) | Ref | | |
| 6. ANC follow up | | | | | |
| Yes | 56(90) | 113(94) | .867 | .244 - 3.08 | .826 |
| No | 4(10) | 7(4) | Ref | | |
| Genetic factors | | | | | |
| 7.Family Hx of NTDs | | | | | |
| Yes | 11(18) | 2 (2) | 13.245 | 2.83 -61.96 | .001 |
| No | 49(82) | 118(98) | Ref | | |
| 8.Consanguinity | | | | | |
| Yes | 13 (22) | 0(0) | - | .000 | .998 |
| No | 47 (78) | 120(100) | Ref | | |

Maternal periconceptional factors associated with NTDs

From table 5; A significant risk of NTDs was revealed among mothers with hyperthermia (OR 7.93CI 3.87-16.25P.000) and the risk was lower among women's who used antipyretic medications (OR .103 CI .013-.791 P.029). Maternal sauna/ hot tab use was significantly associated to NTDs risk (OR 7.14 CI 3.026 -16.85 P .000) A significantly high risk association

was observed for maternal periconceptional oral contraceptive use (OR 6.9 CI 2.69 – 17.74 P .000). Use of therapeutic drugs with their associated medical illness (history of hypertension, diabetes, UTI,) did not show any association to NTD. Regarding folic acid consumption all case mothers (100%) did not take folic acid supplement at any time of their pregnancy 20% of control mothers take periconceptional folic acid. There was no association to NTDs risk with maternal pregestational weight.

Table 5 Maternal periconceptional factors & NTDs, at ZMH Addis Ababa Ethiopia, 2018.

| Variables | Cases n (%) | Controls n (%) | OR | CI (95%) | P |
|----------------------------------|-------------|----------------|-------|--------------|-------------|
| 1.History of hypertension | | | | | |
| Yes | 2(3) | 8(7) | .483 | .099 - 2.34 | .367 |
| No | 58(97) | 112(93) | Ref | | |
| 2. History of diabetes | | | | | |
| Yes | 2(3) | 2(2) | 2.034 | .279- 14.80 | .483 |
| No | 58(97) | 118(98) | Ref | | |
| 3.History of UTI | | | | | |
| Yes | 2(3) | 9(7.5) | .425 | .089 -2.03 | .284 |
| No | 58(97) | 111(92.5) | Ref | | |
| 4.Hx of hyperthermia | | | | | |
| Yes | 35(58) | 18(15) | 7.93 | 3.87-16.25 | .000 |
| No | 25(42) | 102(85) | Ref | | |
| 5.Anti diabetic use | | | | | |
| Yes | 1(2) | 2(2) | 1.00 | .089- 11.25 | 1.00 |
| No | 59(98) | 118(98) | .Ref | | |
| 6. Anti-hypertensive use | | | | | |
| Yes | 1(2) | 7(94) | .274 | .033 - 2.277 | .231 |
| No | 59(98) | 113(6) | Ref | | |
| 7. antibiotic use | | | | | |
| Yes | 7(12) | 11(9) | 1.3 | .480 - 3.56 | .599 |
| No | 53(88) | 109(91) | Ref | | |
| 8.anti pyretic use | | | | | |
| Yes | 1(2) | 17(14) | .103 | .013 - .791 | .029 |
| No | 59(98) | 103(86) | Ref | | |
| 9. Oral contraceptive use | | | | | |
| Yes | 18(30) | 7(6) | 6.9 | 2.69 -17.74 | .000 |
| No | 42(70) | 113(94) | Ref | | |

Environmental factors associated with NTDs

As it is shown in table 6; results for living near to waste disposal area/ polluting industries, Periconceptional maternal exposure to diagnostic radiation, and pesticide exposure were not associated to NTDs risk. No association was found for maternal alcohol consumption, cigarette smoking. But maternal external exposure to cigarette smoke was strongly associated (OR 2.49 CI 1.15 -5.11 P.020). Significantly strong association was revealed for ≥ 3 cups/day caffeine intake (OR 8.14 CI 4.02 -16.4 P .000) and coffee was the most common source of caffeine (OR 34.17 CI 12.08 -96.6 P.000).

Table 6: Environmental factors and NTDs, at ZMH, Addis Ababa, Ethiopia, 2018

| Variables | Cases n (%) | Controls n (%) | OR | CI (95%) | P |
|---|-------------|----------------|-------|---------------|-------------|
| 1. >15 minute sauna/hot tub use | | | | | |
| Yes | 22(37) | 9(7.5) | 7.14 | 3.02 - 16.85 | .000 |
| No | 38(63) | 111(92.5) | Ref | | |
| 2. Pesticide exposure | | | | | |
| Yes | 18(30) | 21(17.5) | 2.02 | .978 - 4.17 | .057 |
| No | 42(70) | 99(82.5) | Ref | | |
| 4. Radiation exposure | | | | | |
| Yes | 2(3) | 3(3) | 1.34 | .219 - 8.27 | .749 |
| No | 58(97) | 117(97) | Ref | | |
| 5. living near to waste disposal area/polluting industry | | | | | |
| Yes | 20(33) | 26(22) | 1.80 | .906 - 3.60 | .093 |
| No | 40(67) | 94(88) | Ref | | |
| 6. folic acid consumption never periconceptional use | | | | | |
| never | 60(100) | 96(80) | - | - | - |
| periconceptional use | 0(0) | 24(20) | - | - | |
| 7. pregestational weight | | | | | |
| Under weight | 6(10) | 11(9) | 1.09 | .153-7.80 | .931 |
| Normal weight | 40(67) | 84(70) | .952 | .167 -5.41 | .956 |
| Over weight | 12(20) | 21(18) | 1.14 | .182-7.19 | .887 |
| Obese | 2(3) | 4(3) | Ref | | |
| 8. Caffeine source | | | | | |
| Coffee | 52(87) | 21(17.5) | 34.17 | 12.08 - 96.64 | .000 |
| Tea | 3(5) | 30(25) | 1.38 | .310 - 6.149 | .673 |
| Both | 5(8) | 69(57.5) | Ref | | |
| 9. Amount of caffeine | | | | | |
| < 3cups/day | 22(37) | 99(82.5) | Ref | | |
| ≥3 cups/day | 38(63) | 21(17.5) | 8.14 | 4.02 - 16.48 | .000 |
| 10. alcohol consumption | | | | | |
| Yes | 6(10) | 20(16.7) | .556 | .210 - 1.46 | .235 |
| No | 54(90) | 100(83.3) | Ref | | |
| 11. Tobacco smoking | | | | | |
| Yes | 0(0) | 2(2) | .000 | | .999 |
| No | 60(100) | 118(98) | Ref | | |
| 12. External exposure to Smoking | | | | | |
| Yes | 18(30) | 18(15) | 2.42 | 1.15 - 5.11 | .020 |
| No | 42(70) | 102(85) | Ref | | |

II. Multivariate analysis

A multivariate logistic regression model constructed by adding all the significant factors from the bivariate analysis to determine variables significantly associated with risk of NTDs. P value <0.05 were used as cutoff point

Table -6 Multivariate analysis of risk factors and NTDs occurrence at ZMH Addis Ababa Ethiopia, 2018

| Variables | OR | 95% C.I. | | P value |
|----------------------------------|------------|----------|--------|---------|
| | | Lower | Upper | |
| 1. Maternal age | | | | |
| <19 | 33.7 | 2.53 | 448.49 | .008 |
| 20-24 | 3.78 | .56 | 25.6 | .172 |
| 25 -29 | 9.7 | 1.39 | 67.65 | .022 |
| ≥ 30 | Ref | | | |
| 2. maternal education | | | | |
| Illiterate | .79 | .044 | 14.29 | .876 |
| Primary school | .80 | .076 | 8.60 | .860 |
| Secondary school | .88 | .08 | 9.6 | .91 |
| Diploma/other higher | Ref | | | |
| 3. Paternal education | | | | |
| Illiterate | .82 | .030 | 22.79 | .911 |
| Primary school | .94 | .135 | 6.66 | .956 |
| Secondary school | 1.19 | .175 | 8.12 | .85 |
| Diploma/other higher | Ref | | | |
| 4. maternal occupation | | | | |
| Housewife | 2.1 | .294 | 16.36 | .443 |
| Factory worker | 1.41 | .004 | 480.9 | .907 |
| Office worker | Ref | | | |
| 5. Family history of NTDs | | | | |
| Yes | 43.5 | 1.25 | 1506.9 | .037 |
| No | Ref | | | |
| 6. Parity | | | | |
| Multiparous | .15 | .000 | 153.72 | .596 |
| Grand multiparous | Ref | | | |
| 7. planned pregnancy | | | | |
| Yes | .41 | .076 | 2.30 | .038 |
| No | Ref | | | |
| 8. History of fever | | | | |
| Yes | 65.5 | 4.48 | 957.9 | .002 |
| No | Ref | | | |
| 9. Anti pyretic use | | | | |
| Yes | .01 | .000 | .538 | .021 |
| No | Ref | | | |

| CONTINUED | | | | | |
|---|-------------|------------|------|------|-------|
| 10.Oral contraceptive use | Yes | 7.1 | .929 | 54.4 | .059 |
| | No | Ref | | | |
| 11.Sauna/hot tub use | Yes | 1.9 | .286 | 12.6 | .506 |
| | No | Ref | | | |
| 12.Amount of caffeine <3 cups/day | | Ref | | | |
| | ≥3 cups/day | 1.9 | .426 | 8.70 | .394 |
| 13.Caffeine source | Coffee | 18.5 | 3.77 | 91.1 | .000 |
| | Tea | .91 | .080 | 10.3 | .939 |
| | Both | Ref | | | |
| 13.passive cigarette smoking | yes | 1.0 | .225 | 9.91 | 492.6 |
| | No | Ref | | | |

7. DISCUSSION

This unmatched hospital based case-control study consisted of 60 case and 120 controls who were admitted at ZMH. Variables such as pericoceptual oral contraceptive use, maternal age <19 & 20-24 , parental low educational status (illiterate and primary school),sauna/hot tab use, external exposure to cigarette smoke consumption of caffeine ≥ 3 cup/day, maternal occupation showed that an increased significant association and having planned pregnancy& being multiparous shows an apparent protective effect to NTDs in the bivariate analysis but these finding were not confirmed in the multivariate regression analysis model.

Results of multivariate analysis of this study shows that maternal preconception hyperthermia, close family member history of NTDs, coffee consumption, maternal age <19 & 25 -29 and history antipyretic use shows association to NTDs after controlling for potentially relevant covariates.

This study revealed that maternal periconceptual hyperthermia was associated to NTDs risk (OR 65.5, CI 4.48 – 957.9 P .002). This result is consistent with other population based case control studies conducted in California and china (15, 23). In addition to those human studies research in animal model indicates that hyperthermia- is a teratogen that adversely affects development, which causes increased cell death, decreased proliferation, disruption of gene expression, and damage to the embryonic vasculature(22).

This study shows that use of Antipyretic drugs had a protective effect (OR 0.015, CI 0.000-0.538, P 0.02) for NTDs. This reduced risk of NTDs among women's who take fever reducing medication is parallel to study conducted in California(23) but it's completely different from study conducted in china(26). This inconsistency can be attributable to the type of anti-pyretic drug used and the nature of the disease that causes hyperthermia. Hyperthermia is condition described by raise in core body temperature and it can be resulted from febrile illness or other external factors (sauna/hot tab use). Therefore it's difficult to determine the resulted hyperthermia that increases the risk of NTDs was attributable to the elevated body temperature by environmental factors or the underlining illness.

In this study close family member with history of NTDs was associated with NTDs risk (OR 43.5 CI 1.25 -1506.9P 0.037);this result is consistent with study conducted in Saudi Arabia(3).NTDs are central nervous system congenital anomalies with multi-factorial causes, and the genetic factors are among the contributing factors. As it is evidenced for couples with previous NTDs affected pregnancy the risk of recurrence for subsequent pregnancy is 2% to 5%. The risk of recurrence for high risk persons (close family member with history of NTDs) is approximately 0.3% to 1.0%, although most human cases are sporadic, with only one affected in family, siblings of a case are on average 32 times more likely to be affected than the general population(2).

This study showed that coffee consumption was significantly associated with NTDs risk (OR 18.9 CI 3.7-91.1 P .000) which is supported by study conducted in Italy (17). The exact mechanism that Coffee consumption and NTDs risk was not clearly stated, several studies show that coffee consumption during pregnancy can cause abortion and low birth weight, and also its consumption during pregnancy can cause alteration in folate metabolism(act as vitamin B₆ antagonist possibly impairing the breakdown of homocysteine) but additional researches must be done to know the exact mechanism. In addition to this coffee consumption can cause a disturbed maternal food intake (maternal diet quality) due to catecholamine secretion.

This study found maternal age <19 (OR 33.7 CI 2.53-448.4P 0.008) and maternal age 25-29 (OR 9.7 CI 1.39 – 67.6P 0.002) was associated for NTDs risks. maternal age 25-29 result was supported by study conducted in Algeria(16).Possible correlation can be established between Pregnancy at lower age groups<19 and NTDs risks, this might be due to low socioeconomic status,low educational level, lack of knowledge regarding potential risk factors and preventive measures(dietary habit, access to health care).

As evidenced in different studies daily periconceptional supplementation with folic acid is effective in reducing the occurrence and recurrence of NTDs but in this study the overall use periconceptional folic acid among cases was 0(0%) this hinders to identify an association between folic acid use and risk of NTDs. In similar way the association between consanguinity and NTDs risks was not determined due to zero cells in control with history of consanguinity.

8. CONCLUSION

In conclusion, results of this study demonstrated that maternal hyperthermia, family history of NTDs, coffee consumption, maternal age <19 and 25-29 were associated with the increasing risk of NTD whereas maternal antipyretic drug use had protective effect to the disease. Therefore preconceptional maternal screening for genetic factors and medical illness is important for women's of child bearing age. Based on this study, future researchers should include genotype screening and maternal nutrition.

9. Strength of the study

This study had several strengths;

- ❖ High participation rate of study groups
- ❖ It tries to examine several potential covariates
- ❖ It is new area of study; since there is no documented data are available on this topic

10. Limitation of the study

- For some potential variables it was difficult to determine their association with the outcome variable due to small sample size. Since it is a hospital based study it makes it difficult represent for the general population.
- Since the exposure status of the study groups were assessed retrospectively there should be a recall bias.

11. RECOMMENDATION

Based on this study its help full to recommend the following efforts from

Ministry of health, and Regional health bureau

- NTDs prevention should be incorporated as part of ANC follow up, therefore in order to achieve this periconceptional maternal counseling and screening for potential medical illness should be introduced because the first ANC visit is too late for prevention of NTDs.

Health care providers

- Health education about NTDs risk factors and preventive measures should be given for all family and women's of child bearing age.
- Periconception counseling and screening should be done when the mother start to plan for pregnancy.

Researchers

- Further research should be conducted on factors which are not included in this study, such as genetic studies (like genotype screening); type of antipyretic used, maternal nutrition and income status needs to be studied.

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13. ANNEXES

ANNEX 1: INFORMATION SHEET (ENGLISH VERSION)

Hello

My name is FilmawitAynalem, I am MSc student at Addis Ababa University Collage of Allied Health, Department of Nursing and Midwifery, and I am conducting a research on determinants of neural tube defect in Zewditu Memorial Hospital, Addis Ababa, Ethiopia, 2018.

The aim of the study is to collect information regarding determinants of neural tube defect in the study area and additionally it will be used by the concerned body to develop a program towards preventing the occurrence, reoccurrence and decrease child mortality and morbidities as a result of neural tube defect. The study will not give any direct benefits to the participants but the information which will be obtained from you will help the researcher to recommend the government and other NGOs to design appropriate interventions to address the problems. The study will not impose any risk and participation is based on your consent and you can quite from giving answers to the questions any time you want. The information's that you give us will not be accessed by anyone other than the study team and will be confidential, and if you are willing the interview may take 20-30 minute and we can proceed.

Consent Form

I give my consent to participate in this study. I have been given the necessary information about the research in a language I understand. I have also understood that I can withdraw my consent any time without penalty or loss of benefits.

1. If yes, proceed to the next page 2. If no ,thank you ,and skip to the next participant

Name of data collector _____

Signature_____

Name of supervisor _____

Signature_____

Date of interview _____

ANNEX 2 QUESTIONER (ENGLISH VERSION)

The questionnaire has four components: part one is about parental socio-demographic factors, part two: genetic factors, part three: maternal reproductive and obstetric factors and finally part four includes the periconceptional factors.

| | |
|---|---|
| Part I: parental socio demographic factors | |
| 1.0 Maternal age at index pregnancy_____ | |
| 1.2 Parental educational status | |
| 1. No education | |
| 2. Primary school | |
| 3. Secondary school | |
| 4. Occupational training | |
| 5. Diploma/degree /other | |
| Mother_____ | father_____ |
| 1.3 Maternal occupation | |
| 1. Housewife | |
| 2. Farmer | |
| 3. Factory worker | |
| 4. Office worker | |
| 5. Other_____ | |
| 1.5Child characteristics | |
| 1.5.0 Gender | female <input type="checkbox"/> male <input type="checkbox"/> |
| 1.5.1 Birth order_____ | |
| 1.5.2 Type of diagnosis (only for case) | |
| _____ | |

Part II: Genetic factors

2.0 Is there any close family member with history of NTDs /other congenital anomalies?

Yes

No

2.1 Do you have history of NTDs affected pregnancy?

Yes

No

2.2 Do you have birth relationship with your husband?

Yes

No

PART III: Maternal reproductive and obstetric history

3.0 Parity_____

3.1 Do you have any history of

Abortion

still birth

early neonatal loss

3.2 Was the pregnancy for the index child planned

Yes

No

3.3 Had ANC follow up (for the index child) Yes No

PART VI: Periconceptional factors

Maternal medical and drug history

4.0 Have you ever been told by a doctor that you had any of these diseases

Hypertension, Hyper/hypothyroidism, bladder /urinary tract infection, tumor, epilepsy, DM

Yes

No

4.1 If the answer is yes did you take any medication (for the medical condition)?

Yes

No

4.2 If "yes" list the medication name_____

4.3 Any Oral contraceptive use?

Yes

No

| | | | | |
|---|-------|--------------------------|------------------------------|--------------------------|
| 4.4 Have you experienced any fever/ febrile illness | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| 4.5 If “yes” did you take any antipyretic (fever reducing medication)? | | | | |
| | yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| Environmental factors | | | | |
| 4.6 Is there waste disposal site or industry near to your residence? Yes <input type="checkbox"/> No <input type="checkbox"/> | | | | |
| 4.7 If “yes” state the distance (meter) _____ | | | | |
| 4.8 Have you used any pesticides (insecticides, herbicides or fungicides) at home /work place? | | | | |
| | Yes | <input type="checkbox"/> | NO | <input type="checkbox"/> |
| 4.9 Have you ever used sauna/hot tub? Yes <input type="checkbox"/> No <input type="checkbox"/> | | | | |
| 4.10 for how long in average(in minutes)_____ | | | | |
| 4.11 Have you experienced any diagnostic/therapeutic radiations? | | | | |
| | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> |
| Maternal nutrition and folic consumption | | | | |
| 4.12 What was your prepregnancy weight (Kg)_____, height (meter)_____ | | | | |
| 4.13 Did you take Folic acid supplements? | | | | |
| | Never | <input type="checkbox"/> | Periconceptional intake | <input type="checkbox"/> |
| | | | After 3 months of conception | <input type="checkbox"/> |
| Maternal life style | | | | |
| 4.14 Did you take any caffeine Yes <input type="checkbox"/> No <input type="checkbox"/> | | | | |
| 4.15 if your answer is yes which caffeine source Coffee <input type="checkbox"/> tea <input type="checkbox"/> | | | | |
| 4.16 How many cups per day (in average)? _____ | | | | |
| 4.17 Other traditional herbal use (specify)? _____ | | | | |

| | | | | | | |
|---|------------|--------------------------|------------|--------------------------|--------------------------|--------------------------|
| 4.18 Do you drink alcohol? | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> | | |
| 4.19 If your answer (amount in average) | >500ml/day | <input type="checkbox"/> | <500ml/day | <input type="checkbox"/> | occasional (<500ml/week) | <input type="checkbox"/> |
| 4.20 Do you smoke? | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> | | |
| 4.21 Did you had any home/occupational exposure to tobacco smoke? | Yes | <input type="checkbox"/> | No | <input type="checkbox"/> | | |

ANNEX 3: INFORMATION SHEET (AMHARIC VERSION)

ለጥናቱ ተሳታፊዎች አጠቃላይ መረጃ

ሰላም

ስሜሬል ማት አይና ለም ይባላል። በአዲስ አበባ ዩኒቨርሲቲ፣ የነርቪንግ እና አዋጅ ነጥብ ምህር ትክክል ውስጥ የሥራ ምረቃ ተማሪ ስሆን በዘውዲቱ መታሰቢያ ሆስፒታል አዲስ አበባ ኢትዮጵያ ውስጥ በ 2018

በህብረሰረሰር ትቦአለ መግጠም ወሳኝ ምክንያቶች በሚል አርእስት የጥናት እና የምርምር ስራ በመስራት ላይ እገኛለሁ።

የጥናቱ አላማም በህብረሰረሰር ትቦአለ መግጠም ምክንያቶች አስመለክቶ መረጃ መሰብሰብ ሲሆን ከዚህም በተጨማሪ የጥናት ውጤት የሚመለከታቸው አካላት በህብረሰረሰር ችግር ምክንያት በህፃናት ላይ የሚከሰተውን የሞት አደጋ ለመከላከል እና ለመቀነስ የሚረዳ ፕሮግራም ለመቅረጽ በግባትነት ያገለግላል።

ጥናቱም ለተሳታፊዎቹ ቀጥተኛ የሆነ ጠቀሜታ የማይኖረው ሲሆን ከእናንተ የሚገኘው መረጃ ውግንተ መራማሪው የመንግስት እና ሌሎች መንግስታዊ ያልሆኑ አካላት ችግሩን ለመፍታት የሚያስችል ተገቢ የሆነ እርምጃ እንዲወስዱ ምክረ ሀሳብ ለመስጠት ይረዳዎል።

ጥናቱ በተሳታፊዎች ላይ ምንም አይነት አደጋ የማያስከትል ሲሆን የሚከናወነው በተሳታፊዎች ፈቃድ ነጥብ ስር ተመሥርቶ በመሆኑ በአስፈላጊው በማንኛውም አይነት ጊዜ ለጥያቄዎቹ ምላሽ አልሰጥም ብለው ማቋረጥ ይችላሉ። የሚሰጡንን መረጃ ከ

አጥኚው ቡድን ውጭ ማንም ሰው የማያውቅ ሲሆን በሚሰጡ ርይዘት እንዲሁም ፈቃድ ከሆኑ ቃለ መጠየቁ ከ 20-30

ደቂቃዎች ውስጥ ሊከናወን ይችላል። ስለሆነም መቀጠል እንችላለን።

የመረጃ ሰነድ

ስለ ጥናቱ በቂ የሆነ መረጃ መረዳት በምችለው ቋንቋ ተሳታፊዎችን በፈቃድ ነጥብ ስር ለመሳተፍ ተስማምቻለሁ።

በተጨማሪም በማንኛውም ጊዜ ቃለ መጠይቁን ማቋረጥ እንደምችል እና በዚህም ምንም አይነት ጉዳት እንደማይደርስብኝ ወይም ጥቅም እንደማያሳልብኝ ተረድቻለሁ።

- 1. አዎ ከሆነ ወደ ሚቀጥለው ጥያቄ ሂድ 2. አይደለም
- ከሆነ ተሳታፊውን በማመስገን ወደ ሚቀጥለው ተሳታፊ ሂድ

የመረጃ ሰብሳቢው ስም _____ ፊርማ _____

መረጃው የተሰጠበት ቀን _____

ANNEX 4: QUESTIONAIRE (AMHARIC VERSION)

መጠየቅ

ክፍል 1: የወሳኝ ችግር ማህበራዊ ደረጃና ህዝብ መጠየቅ

1.0 ህፃን/ህፃና ሲረገዝ/ሱትረገዝ የሆኑት የዋስትማ ስንት ነበር? _____

1.2 የወሳኝ የትምህርት ደረጃ

1. ስለተማሪ ም

2. የመጀመሪያ ደረጃ

3. ሁለተኛ ደረጃ

4. የሱሪሳ ደረጃ

5. ዲግሪ/ ማስተማር/ ስኬት/ ሌላ

ስም _____

ስድስት _____

1.3 የስነ-ምግባር የሰነድ ደረጃ

1. የቤት ስሙ

2. የግብርና ስሙ

3. የፍብረት ስሙ

4. የቤት ስሙ

5. ሌላ _____

የስናትነት የህክምናና የመድኃኒት ስወሳሰድ ታሪክ

4.0 ከሚከተሉት የህመም ስደነት ውስጥ በህክምና ተረጋግጦ ስለሰጡት ብሎተነገር ትያውቃል?

የደምግፊት፣ የታደፎደደመብዛት/ማነስ፣ የፊኛ/የሸንት መቋጠፊያ ሲንፌክሽን፣ ስጢ፣ የሚሞላበሽታ፣ የስኳር ህመም ስዎ ስደደሰም

4.1 መሰረተኛ ከሆነ ህክምና ስደገው ያውቃሉ? (ስህክምና ሁኔታዎች)

ስዎ ስደደሰም

4.2 መሰረተኛ ከሆነ የመድኃኒት ስምደግግር _____

4.3 ማንኛውንም ስደነት በስፍራ የሚወሰድ የወሲድ መከላከያ ተጠቅመው ያውቃሉ?

ስዎ ስደደሰም

4.4 የትኩሳት ስናት ከሌላ የሚያመጡ ህመም ስጋ ሞት ያውቃል?

ስዎ ስደደሰም

4.5 መሰረተኛ ከሆነ የትኩሳት መድኃኒት ተጠቅመው ያውቃሉ?

ስዎ ስደደሰም

ስኳር በሚመስሉ ሁኔታዎች

4.6 በመኖሪያ ስብረት ይኖሩ የቆሻሻ ማስገደድ ደም ሲንፌክሽን ይደረግዎታል?

ስዎ ስደደሰም

4.7 መሰረተኛ ከሆነ ከመኖሪያ ቤታዎ ማንኛውንም ስኳር ትገኛለች? _____

4.8 ስብረት ውስጥ በስራ ቤታዎ ማንኛውንም ስደነት ጸረ-ባዶ/ስራ ምድኃኒት ተጠቅመው ያውቃሉ?

ስዎ ስደደሰም

4.9 ሳውዳ/ ሙቅ-ሳተጠቅሙው ያውቃሉ?

አዎ አይደለም

4.10 መሰረተኛ ስራዎን ከሆነ ስራዎን ያህል ያደረጉት _____

4.11 ማንኛውንም ስራን ተቀባይ መሆኑ/ የህክምና ጠረጎም ለሌሎች ስራዎች ያውቃሉ?

አዎ አይደለም

የስነ-ምግብ ስርዓት ለሌሎች ስራዎች ለመስጠት ያስፈልጋቸዋል

4.12 ከማርባዎች ስርዓት ለሌሎች ስራዎች ያህል ያደረጉት? (ኪ.ግ)

4.13 ማንኛውንም ስራን ተቀባይ መሆኑ/ ማርባዎች ለሌሎች ስራዎች ያውቃሉ?

ፊደሎች ከጽንሰ-ሠራት ስርዓት ለሌሎች ስራዎች 3 የመጀመሪያ ስርዓት ስራዎች

ከጸሐፊው ከ3 ወራት በጊዜ

የስነ-ምግብ ስርዓት ለሌሎች ስራዎች ለመስጠት ያስፈልጋቸዋል

4.14 ማንኛውንም ስራን ተቀባይ መሆኑ/ ማርባዎች ለሌሎች ስራዎች ያውቃሉ? (ቡና ፣ ሻይ) ወስደው ያውቃሉ?

አዎ አይደለም

4.15 መሰረተኛ ስራዎን ከሆነ የትኛውን ስራን ተቀባይ መሆኑ/ ማርባዎች ለሌሎች ስራዎች ያውቃሉ?

ቡና ሻይ

4.16 በቀን ስራዎን ያህል ያደረጉት? _____

4.17 ሌላ የሆነ ስራዎን ተቀባይ መሆኑ/ ማርባዎች ለሌሎች ስራዎች ያውቃሉ? (ደንበኞች) _____

4.18 ስራዎን ያህል ያደረጉት?

አዎ አይደለም

4.19መስጠት/አገልግሎት

በቀን > 500ሚ. ስ. በቀን < 500ሚ. ስ. በሳምንት < 500 ሚ. ስ.

4.20ትምህርት ያጨሳሉ?

አዎ አይደለም

4.21በቤት/ በስራ/ በሌሎች ስራዎች ላይ ተገባዎታል?

አዎ

አይደለም