ADVERSE BIRTH OUTCOMES ASSOCIATED WITH DRUG USE IN PREGNANCY AT KENYATTA NATIONAL HOSPITAL

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A Thesis submitted in partial fulfillment of the requirements for the award of the Degree of Master of Pharmacy in Pharmacoepidemiology and Pharmacovigilance, School of Pharmacy, University of Nairobi.

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DEDICATION

I dedicate this work to my parents whose encouragement, prayers and good example have taught me to work hard for the things I aspire to achieve. To my spouse Marvin Kabage, who has been a constant support and encouragement during the challenges of school and life.

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LIST OF ABBREVIATIONS AND ACRONYMS

ADBO	Adverse Birth Outcomes
ANC	Ante Natal Clinic
ART	Anti-Retroviral Treatment
CS	Cesarean Section
EDD	Estimated Due Date
ELBW	Extremely Low Birth Weight
FDA	Food and Drug Administration
HTN	Hypertension
FSB	Fresh Still Birth
NRFS	Non-Reassuring Fetal Status
OBS/GYN	Obstetrics and gynaecology
PPH	Post-Partum Hemorrhage
KNH	Kenyatta National Hospital
SGA	Small Gestational Age
UTI	Urinary Tract Infection
WHO	World Health Organization
3TC/TDF/EFV	Lamivudine/Tenofovir/Efavirenz

DEFINITION OF OPERATIONAL TERMS

Adverse Birth Outcomes:	Any condition that is abnormal at birth. This study will focus on preterm birth, stillbirth, and congenital malformations.
Preterm Birth:	Any birth occurring between 24 – 37 weeks gestation.
Still Birth:	Fetus born at 24 weeks gestational age or more with no heartbeat or respiratory effort.
Congenital Malformations:	Single or multiple defects of the morphogenesis of organs or body parts identifiable at birth or during intrauterine life.
Drug:	A medicine or other substance which has a physiological effect when ingested or otherwise introduced into the body.
Medical Error:	Any preventable adverse outcome that results from improper medical management.
Medication Error:	Unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient, or consumer.

ABSTRACT

Background: Drug prescribing and use during pregnancy is common and essential for either treating a pre-existing condition or a condition that develops during pregnancy. Use of various drugs during pregnancy cause possible adverse outcomes. In Kenya, there has been an increase in cases of adverse birth outcomes congenital malformations, neonatal deaths, premature labour, and stillbirths, among others. It is exceedingly difficult to assess the effect of drugs on the fetus during clinical trials due to ethical reasons. Therefore, pregnant women constitute a uniquely vulnerable population for which the risks of medication use must be separately assessed.

Objective: To determine the association between adverse birth outcomes and medication used during pregnancy among mothers who delivered at Kenyatta National Hospital.

Methodology: An unmatched case control study was conducted at Kenyatta National Hospital. The cases were mothers who delivered babies with adverse birth outcomes and the controls were mothers who delivered normal healthy babies. A structured, interviewer administered questionnaire was used to collect data from the mothers and also their medical records including their ANC records were reviewed. The adverse birth outcomes included preterm, birth defects and still birth. Multivariable logistic regression was conducted to assess the relationship between drug use and selected outcome variables.

Results: Preterm birth was the most common adverse birth outcome at KNH with a frequency of 27.6%, followed by stillbirth (15.3%) and congenital malformations (7.14%). Majority (48.4%) of the women received drugs from Pregnancy Risk category A. A few drugs from category D were prescribed and there was a difference in their use with more women in the case group (13.9%) compared to the control group (8.7%) on these medications. The risk of developing ADBOs increased 6-fold with nifedipine (OR 6.42), 4-fold if the mother had used carbamazepine (OR3.97) and 3-fold with magnesium sulphate (OR 3.11) after adjusting for social-demographic, past obstetric history, co-morbidities, pregnancy complications, and maternal delivery outcomes.

Conclusion: Preterm birth is the most common adverse birth outcome among women attending antenatal clinic at Kenyatta National Hospital. Most women are exposed to drugs during pregnancy and there was a risk of adverse birth outcomes due to medication factors. Prescribing medication to pregnant women should be carefully evaluated and measures put in place to monitor and prevent the potential known and unknown medication risks to the developing fetus.

1.0 CHAPTER ONE: INTRODUCTION

1.1 Background

Adverse birth outcomes consist of several undesirable health effects to the newborn infant. They comprise of preterm birth, congenital malformations and still births. Preterm births are live births delivered before completion of 37 weeks of pregnancy. Typical term pregnancies last between of 37 and 41 weeks, permitting complete growth of infant organs and the structural framework. (1). Newborn infants who weigh below 2,500 grams during childbirth are said to be of low birth weight. This can be due to preterm delivery or fetal nutritional supply restriction, or a mix of both. Congenital malformations are undesirable structural changes in at least one or more parts of the infant's body that are present at birth (2).
Still birth refers to death of the fetus while still in the uterus. Every wanted pregnancy needs to culminate in the delivery of a healthy normal baby without posing harm to the mother. To ensure this there is an organized medical service that is responsible for advising pregnant women and conducting medical examination including treatment during the pregnancy; this is referred antenatal care (3) . The most effective method recognized in preventing ADBO in pregnant women and the infants is provision of timely and adequate antenatal care.

Adverse pregnancy outcomes can result from several factors which may be biological, social, economic, or environmental. Inadequate care during pregnancy and delivery has resulted in over 3 million babies deaths yearly, either in the early weeks of life or intrauterine death (4). Pregnant women are intentionally removed clinical trials during development of most pharmaceutical medicines. The woman is usually dropped from the study if gestation occurs during the study and treatment discontinued, although she will be managed to term but different from the study participants. Therefore, at the initial marketing and use many drugs there is no meaningful human data on effects on pregnancy except for the very few medicines specific to a pregnancy condition.

Most women are not aware of the exact conception time or period, therefore exposure of the fetus to drugs during the crucial stage of organogenesis is very common in women of childbearing age. It is approximated 10% of women in the ages between 15 and 44 years unknowingly get pregnant annually (5). Studies indicate that most women take either over the counter or prescribed medicines during gestation period.

This is because some of them get pregnant while they already have preexisting conditions that require continuous or periodic use of medicines such as epilepsy, hypertension, or asthma. Some develop new conditions or worsen the existing ones therefore requiring treatment (6) Total avoidance of pharmacological treatment in pregnancy is not possible and may be dangerous because some women enter pregnancy with medical conditions that require ongoing and episodic treatment (e.g. asthma, epilepsy, hypertension). During pregnancy new medical problems can develop and old ones can be exacerbated (e.g. migraine, headache) requiring pharmacological therapy (6).

Since the thalidomide catastrophe in 1960 and 1971 diethylstilbestrol teratogenic effects, there has been an overwhelming increase on the safety of prescribed drugs to pregnant and breastfeeding women. This has resulted in the US Food and Drug Administration to demand efficacy and safety reports to be shown and approved before introducing a drug to the market (7).

1.2 Statement of the Problem

In Kenya measures of health at birth are depended on birth outcomes, but the cause for adverse birth outcomes such as congenital malformations, stillbirth, and preterm birth among others, is not clearly understood. Genetics, maternal, social factors, and drug use during pregnancy are some of the main factors that have been studied to determine the cause of adverse pregnancy outcomes. There are still significant differences in the birth outcomes between developed and developing countries despite having a huge worldwide improvement in the maternal health and birth outcomes in the past 40 years. In developing countries, the most common adverse pregnancy outcomes are low birth weight, still births, congenital malformations, and preterm births. Many studies have been done to account for maternal and social factors contributing to these birth outcomes, but not much has been done on their association to drug use in pregnancy.

Due to legal and ethical reasons, clinical trials have excluded pregnant women in drug studies and therefore there is no sufficient knowledge on the harmful effects of the medication used in managing pregnancy conditions. Nonetheless drug use is quite common despite the limited information on the safety.

Drugs are commonly prescribed to treat chronic diseases such as hypertension, diabetes, and epilepsy and also those that come as a result of pregnancy or pose an increased risk in pregnancy. For example, hyperacidity, urinary tract infection and gestational diabetes. Iron, folic acid and calcium supplements are also commonly given to women who are pregnant or anticipating pregnancy to improve their nutritional status. Therefore, for good maternal and birth outcome it is important to ensure adequate knowledge, awareness on the safe use medicines during pregnancy.

Though various studies have been done in developing countries on adverse birth outcomes, extremely limited data is available on effects of medication on birth outcomes at Kenyatta National Hospital and in Kenya as a country. Spontaneous adverse events from suspicious findings have been the main source of information on risk of adverse effects of drugs in pregnancy in the past. Rare and undocumented outcomes have been identified through this passive mechanism. However, while trying to evaluate drug risks there are various challenges and limitations to this method that make it problematic. Poor case documentation recall bias due to retrospective reporting, lack of denominator data and controls are some of the major challenges of this method. These challenges can be mitigated through use of prospective pregnancy exposure registries which ascertain major risk factors associated with drug exposure in pregnancy.

Hence this study assessed and determined the adverse birth outcomes and associated drug use patterns among pregnant women who attended antenatal care (ANC) in KNH and also described the pregnancy risk level of prescribed medications according to the US FDA safety rating system. It also gave a measure of the level of compliance to treatment and management of pregnancy-related conditions.

1.3 Study Justification

Prescription drug use has been associated with approximately 1% abnormalities that occur in 2-3% of all infants (8). WHO suggests prescription drugs contribute to about 10% of abnormalities in children. Safety profile of most medicines used in pregnancy is not known and only about twenty drugs or classes of medication have documented teratogenic effects (1). Findings from this study showed the prevalence or the extent of ADBOs at KNH.

It highlighted areas of improvement and provided useful information to healthcare providers for management and counseling of their patients.

Hence promoting safe use of medications in pregnancy which in turn help reduce and prevent adverse birth outcomes associated with drug use during gestation.

The findings also provided individual pregnant woman with important medication information. Quality care during pregnancy ensures all women have a positive pregnancy experience.

Furthermore, the findings of this study reinforced need for pregnancy drug exposure registries which provide clinically relevant human data that can be used in a product's labeling and can also be used to support a change from the originally assigned Pregnancy Category to a different category.

1.4 Research Questions

1. What types of adverse birth outcomes are encountered in babies born to women who deliver at the Kenyatta National Hospital?
2. What socio-demographic, obstetric and medical factors are associated with adverse birth outcomes among women who seek ANC and deliver at Kenyatta National hospital?
3. What types of medications are used for treatment and management of pregnancy related conditions?

1.5 Objectives

The main objective of this study was to determine the association between adverse birth outcomes with medication used during pregnancy among mothers who delivered at Kenyatta National Hospital.

1.5.1 Specific Objectives

The specific objectives of the study were to:

1. To describe the types of adverse birth outcomes encountered in babies born to mothers seeking delivery at the Kenyatta National Hospital.
2. Describe and compare the maternal socio-demographic, obstetric and medical factors associated with adverse birth outcomes.
3. Describe the medication use pattern and pregnancy risk level of prescribed medications according to the US FDA safety rating system.

4. CHAPTER TWO: LITERATURE REVIEW

2.1 Physiological Changes in Pregnancy and Placental Transfer of Drugs

Physiologic changes in pregnancy induce profound alterations to the pharmacokinetic properties of many medications. These changes affect distribution, absorption, metabolism, and excretion of drugs, and thus may impact their pharmacodynamic properties during pregnancy. Pregnant women undergo several adaptations in many organ systems. Some adaptations are secondary to hormonal changes in pregnancy, while others occur to support the gravid woman and her developing fetus (9).

Major physiological changes occur during pregnancy. They include increased cardiac output and glomerular filtration which is caused by increase in plasma volume by 30-50% above normal physiological levels. These changes affect drug pharmacokinetics in pregnant women taking medication. Changes in fat distribution and plasma albumin during pregnancy also affect the metabolism and distribution of fat soluble and protein bound medications such as anticonvulsants (6). The placenta acts as the functional barrier between maternal and fetal blood. Drugs can only cause pharmacologic or teratogenic effects if they can pass through this membrane barrier. Chemical properties of the drug molecule like lipid solubility, protein binding and molecular weight and rate of ionization affect the rate of transfer of the drugs from maternal circulation into fetal circulation. (7) .

In pregnancy there is an increase in fetal albumin whereas maternal albumin is reduced, this causes an increase in the concentration of the drugs that reach the fetus through the placenta. Significant transplacental transfer of drugs is markedly seen in the third trimester due to increased blood flow to the placenta, reduced thickness, and increased surface area of the placenta (10).

2.2 Effects of Drugs on Pregnancy

There are many advantages on the use of drugs in pregnancy, but the main goal is ensuring good health of the mother and the fetus. However, this is achieved only if the drugs are potent, safe and are used in a rational way (11). Drug effects on the fetus are controlled by several factors such as, the dose and strength of the medication, the stage of development of the fetus and length of exposure.

Information and knowledge concerning drug effects during inception of pregnancy and implantation is limited and therefore pregnant women who are planning to get pregnant or at risk of conceiving should avoid medication 3-6 months prior (12).

Certain drugs taken early in pregnancy (15-21 days after fertilization) during the period of blastogenesis may act in an all or nothing fashion; killing the fetus or not affecting it at all. During this early stage the fetus is highly resistant to birth defects. The fetus is highly vulnerable to birth defects between 3rd week and 8th week after fertilization, which is the period of organogenesis. All major organs start developing during this period. Drugs reaching the fetus during this stage may cause a miscarriage, an obvious birth defect, or a permanent but subtle defect, that is noticed later in life (6).

Early exposure of certain drugs to the developing infant in the blastogenesis stage can result in either complete elimination of the pregnancy or having no effect on the embryo at all. This all or nothing concept in the early days of pregnancy makes the fetus less prone to birth defects. However, in the organogenesis stage (between day 21-56 after fertilization) the fetus is extremely vulnerable to congenital malformations and anomalies. This is because all the vital organs develop at this stage (11).

After organogenesis, embryonic development is characterized primarily by increasing organ size. For most human organ systems, this period begins by 8 to 10 embryonic weeks. During this interval, a teratogen can affect the overall growth of the embryo or the size of a specific organ. However, visible malformations are not expected (13).
By the 9th week of pregnancy the embryo has developed to the fetus and exposure to drugs is not linked to major birth defects but can greatly affect growth and maturation of tissues and organs (12).

Table2.1: Major stages of gestation and the drug effects (14) (13)

Pregnancy Stage	Description
Pre-implantation stage (Blastocyst formation)	**From conception to implantation. Shows "all-or-none" effect; that is either killing the embryo or not affecting it at all. No teratogenesis (lasts 16 days)**
Period of organogenesis (from 17th to 56th day)	**Drugs may produce no measurable effect; abortion; sub-lethal gross anatomic defect; or a permanent subtle metabolic or functional defect**
Second and Third trimesters	**Drugs can cause teratogenicity or other effects such as retardation of physical or brain growth, behavior defect, premature labor, neonatal toxicity or even post-natal effects such as cancer in later life.**
Labor-delivery stage	**Danger of toxicity in the neonatal period.**

2.3 FDA Drug Categorization

The teratogenic risk rating system was established by the Food and Drug administration in 1979 (14). The system uses data from clinical trials and studies done both on human and animals. It is an important system that helps in providing clinical guidelines on prescribing and use of medication in pregnancy to both healthcare providers and the pregnant women. Table 2.2 below shows the various categories of drugs used in pregnancy according to the FDA rating system**.**

Table 2.2: FDA Drug categorization for use in pregnancy (15)

CATEGORY	DESCRIPTION
Category A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters.
Category B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women
Category C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Category D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Category X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

During pregnancy drugs from category A are regarded the safest, however use of some drugs from all the other categories B, C and D is still common except for category X that is completely contraindicated. Drugs that have shown no risk to the fetus after sufficient and well controlled studies are classified under Category A. Category B are those that studies have shown no proof of harm or adverse effects to the fetus but there are no adequate and well controlled studies in pregnant women to provide proof of no risk. Drugs in Category C have shown adverse effects in animal studies and there are no adequate and well-controlled studies in pregnant women. Category D drugs have positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk. Drug is Category X are absolutely contraindicated (14).

Though this system has been in use for a long time, questionable records and unclear statements have emerged from this system that make it complicated to use it while making prescribing decisions and counselling pregnant women.

This is mainly due to lack of new data and inconsistent updates on the emerging evidence and data. A clear example is the classification of oral contraceptives as Category X drugs.
However, meta-analyses studies showed that estrogen and progestin combinations were not associated with an increased risk of major anomalies, in general or genitourinary malformations (16). Table 2.3 shows examples of commonly used drugs in pregnancy and their FDA categorization.

Table2.3: FDA categorization of commonly used drugs in pregnancy (15) **.**

No	Drugs (Generic Name)	Category
1	**Analgesics and Antipyretics**	B and C
	Acetaminophen	B
	Aspirin	C
2	**Antiemetics**	B and C
3	**Antibiotics**	B,C and D
	Amikacin	C / D
	Cloxacillin, Cephalosporins	B
	Gentamicin	C
	Penicillin, Ampicillin, Amoxycillin	B
4	**Amoebicides**	B
5	**Anthelmintics**	B
6	**Antimalarials**	C
7	**Antifungals**	C
8	**Vitamins B, C, D, E, folic acid**	A
9	**Antituberculosis**	**B and C**
	Ethambutol	B
	Rifampicin	C
	Isoniazid	C
	Pyrazinamide	C
	P-aminosalicylic acid C	C
10	**Hormones**	**A,X and D**

2.4 Drug Prescribing in Pregnancy

The ideal way to prevent adverse birth outcomes would be complete avoidance of medication use during pregnancy, but this is not possible and may pose harm to mothers who get pregnant with preexisting chronic conditions such as HIV and hypertension that necessitate use of drugs continuously or those that require periodic use of medication like asthma and epilepsy(14). Studies show about 8% of pregnant women require medication treatment due to pregnancy induced complications or chronic disorders (16).

About 59% of pregnant women are prescribed a medication other than a vitamin or mineral supplement. About 13% of pregnant women take a dietary herbal supplement (17). More than 90% of pregnant women take prescription or nonprescription (over-the-counter) drugs or use social drugs such as tobacco or alcohol or illicit drugs at sometime during pregnancy (18).
It has been reported about that 59% pregnant women are prescribed medication other than mineral supplements and vitamins. Use of over the counter or social drugs such as tobacco or alcohol is 90% and about 13% also use herbal medication or supplements (16).Prescribing to this special population has become very challenging due to the fact that one or more of any drug in a prescription maybe hazardous to the fetus.

Studies that have been published on medication use and prescribing patterns differ widely. This is because of variation in medication use between countries, social demographic characteristics and size of the study population. Methodologies of data collection like, patient interviews, use of automated pharmacy records or prescriptions and health records collection has resulted in inconsistent data but some are comparable. Health care setting in which the study is conducted is also a major determinant in the variation (19).

2.5 Use of Herbal Drugs and Self-Medication in Pregnancy

Herbal drugs taken during pregnancy have been associated with conditions such as cancers, congenital malformations, and renal failure. A study done in South Africa showed that 43.7% pregnant women used herbal medication to treat various ailments while 86.3% knew about the use of herbal medicine as a way of cleansing and detoxification. 45.2% used the herbs to ease labour pain and improve birth outcomes of the infant (20).

Over the counter preparations are assumed to be safe and with no risk of ADBO but the opposite may also be true. To ensure safety it is advisable for pregnant women to avoid these medications due to lack of enough safety data. Inadequate health services and ease of availability of drugs has resulted in increased self-prescribing or use of OTC medications in developing countries (19). This poses a great risk of adverse drug reactions, interactions, and poor pregnancy outcomes. For example a case reported by Palatnick and Tenenbein of a 17 year old girl who was 37 weeks pregnant died from use of aspirin daily for a month (20). Autopsy of the fetus showed petechiae of lungs, heart, thymus, and kidneys. This clearly shows that aspirin was readily available and was consumed in excessive amounts. Although use of aspirin is not contraindicated in pregnancy, it is advised that all nonsteroidal anti-inflammatory drugs should be avoided in third trimester aspirin included (21).

Since not much is known on the effects of herbal drugs and supplements on the growing fetus, experts advise that they should be avoided or used with caution in pregnant women and no medication should be assumed to be safe just because it is sold over the counter.

2.6 Adverse Birth outcomes

In many developing countries, adverse birth outcomes remain a major public health concern. There is limited data in Africa and also in Kenya as country on adverse birth outcomes and associated risk factors which makes planning of health services challenging (22). Major adverse birth outcomes include congenital malformations, preterm births and still births.

A congenital malformation is a structural or functional anomaly that occur during intrauterine life and can be identified at birth or later in infancy. Although about 50% of all congenital abnormalities cannot be attributed to a specific cause, several factors have been associated with congenital malformations and they may be either environmental, genetic, or other risk factors such as medication. Figure 2.1 illustrates contribution of various factors to etiologies of congenital malformations.

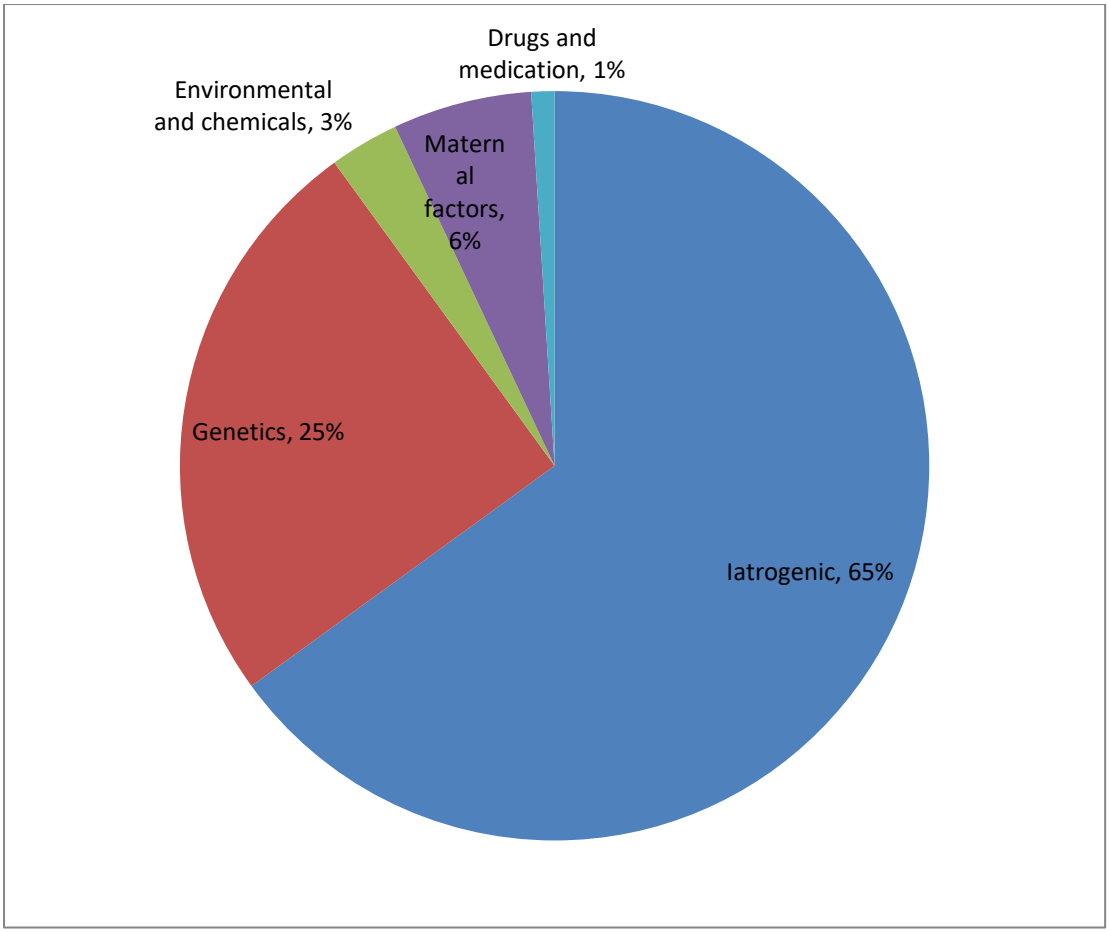

Figure2.1: Percentages of Congenital Malformation etiologies (13).

Most common congenital malformations are caused by either environmental or genetic factors. Approximately 7% of all babies born annually have severe birth anomalies which is about 9 million babies in the world (23). About 3-5% live birth complications are due to presence of a birth defect (24). Although medications have been identified to cause a small proportion of these defects, certain medications have shown to cause an risked risk more than others of developing malformations. The impact of the birth defects may be fatal resulting to death or can also cause a disability that poses major financial, emotional and physical strain to the affected family.

Preterm births can be defined as when a baby is born too early, before 37 weeks of pregnancy have been completed; that is any birth occurring between 24 – 37 weeks gestation. Pregnancy length is calculated from the last day of the menstrual cycle to delivery and its approximately 40 weeks minus or plus 2 weeks. Preterm births can either be indicated or spontaneous.

Indicated preterm birth is where the baby is delivered early (before 37 weeks) because carrying the pregnancy to term would result in harm to the mother or the mother has a severe condition that may be life threating to the child, herself or both. About 20% of preterm births are indicated and the remaining 80% are spontaneous. Spontaneous preterm delivery result from premature labour or rapture of placental membranes before term (25).
Worldwide prevalence of preterm birth by the World Health Organization is approximately 5-18%. Some of the major risk factors for preterm births include, multiple births, previous history of preterm, urinary tract and sexually transmitted infections. Premature births contribute to 40% of neonatal mortality globally and hence a major determinant in accessing mortality and morbidity rates in different study populations (26).

The most important but not well understood adverse birth outcome is stillbirth. It can be defined as loss or death of an infant before 24 weeks of intrauterine life. A study showed that approximately 2.6 million babies born annually in the world are stillborn and 98% of them are from developing countries (27). Antibiotic use in first trimester was shown to be associated with stillbirth in a case control study on association of drug use and stillbirth by Porter et al (28). The etiologies of stillbirth are unknown but there are several factors said to increase the risk for instance, fetal growth restriction, advanced maternal age, birth defects, medical conditions of the mother such as pre-eclampsia and use of alcohol and smoking.

2.7 Global situation of adverse pregnancy outcomes

Adverse birth outcomes can occur in any family, population, or country in the world. It is difficult to give the accurate global prevalence and burden of adverse birth outcomes because most countries do not have the ability to measure and monitor all ADBOs.

Globally, intrapartum fetal deaths are a major cause of child mortality higher than malaria mortality in the recent past. Maternal morbidity is associated with poor birth outcomes, for instance 60-90% of infant death are due to low birth weight (27). In the UK and other developed countries preterm births is still a major challenge contributing to about 6% of the obstetric problems (28). Although less common and poorly understood, stillbirths account for a large proportion of infant morbidity and mortality in the United States (29). About 9 million babies die during the first trimester as stillbirths in Sub-Saharan Africa. Low birth weight and preterm birth as are also major concern in many parts of Africa (28).

2.8 Kenyan situation with regards to adverse pregnancy outcomes

Adverse birth outcomes are a measure of health quality and equity in Kenya. Despite an increased improvement in these measures child mortality and high mortality rates are still alarming (30). Results from a study on pregnancy outcomes in Nyanza showed an increased rate of preterm deliveries especially in adolescents who do not seek antenatal care services (31). Antenatal care seeking behaviors were shown to be highly associated with different birth outcomes, social demographics and other reproductive factors in a study by Magadi et al (32). A study done in Kifili, showed that 53% of all infant deaths were regarded as being caused by labour complications such as obstructed labour, hemorrhage and premature rapture of membranes (33). It is important to note that the uniqueness of congenital abnormalities and other pregnancy complications due to drugs and chemicals exposure is that they are potentially preventable causes of harm to the unborn child.

2.9 Importance of Epidemiological Studies on adverse birth outcomes

Epidemiological studies can be used to show association between drug use and adverse birth outcomes. For instance, in case control studies, mothers of infants with a specific outcome used the drug more than mothers of infants without the specific outcome or cohort studies where pregnant women who took a specific medication during gestation period have a higher number of ADBOs than those pregnant women who did not use the medication. Prospective data collection is gaining popularity and due to promotion of teratology information services which is a new service where pregnant women call drug centers voluntarily to ask questions or for counselling on both prescription and nonprescription medications especially in the first few weeks of pregnancy (34). The challenge of recall bias that is common in most retrospective studies is minimized since exposure data is collected prospectively and follow up of the pregnancy can go on even long after delivery. Rare events and outcomes can be studied effectively through collaboration among these services.

Importance of long-term studies is becoming elaborate by the day since long term drug effects on neurobehavioral can be more catastrophic than physical defects on children and their families.
(35).

CHAPTER THREE: METHODOLOGY

3.1 Study design

The study was hospital based unmatched case control study on adverse birth outcomes and determination of relative contribution of drug associated factors to ADBOs at Kenyatta National Hospital. It entailed collecting data using a combination of structured questionnaires together with review of medical records of women who gave birth during the study period (April to July 2019).

3.2 Study site

The study was conducted at the Obstetrics and Gynaecology wards of Kenyatta National Hospital. It is the largest referral hospital in Kenya and is also the teaching hospital of the College of Health Sciences, University of Nairobi and works in collaboration with many other institutions in offering clinical services. KNH caters for patients from Nairobi and its environs as well as referrals from other hospitals in the country and the greater East African region.

3.3 Study population

The target population was all mothers who gave birth at KNH. The sample population was mothers who had singleton deliveries at KNH during the study period April to July 2019. They formed the population from where cases and controls were recruited.

3.4 Eligibility criteria

3.4.1 Inclusion criteria

1. Live normal infants and infants with ADBOs
2. The mothers of the neonates who must have attended ANC at KNH at had sufficient antenatal data (Antenatal booklet and medical file records)

3.4.2 Exclusion criteria

1. Infants who were multiparous births and their mothers
2. Any postnatal or referral infant delivery to the facility
3. Those mothers who did not consent for both them and their neonates to participate in the study

3.5 The formula for calculation of sample size for case-control studies reported by Kim Kyoungmi (2016) was based on the expected difference between exposure proportions in controls and cases (21). The formula is presented in Equation 1.

Sample size consideration

Equation 1: Formula for sample size computation for case-control studies

$$n = \frac{(p_0 q_0 + p_1 q_1)(Z_{1-\alpha/2} + Z_{1-\beta})^2}{(p_0 - p_1)}$$

n = sample size in each group

P_1= the proportion of exposure among cases

P_0= the proportion of exposure among controls

q_1 = 1- P_1

q_0 = 1- P_0

$Z_{1-\alpha/2}$ = value of the standard normal distribution corresponding to a significance level of alpha (1.96 for α = 0.05)

$Z_{1-\beta}$= value of the standard normal distribution corresponding to the desired level of power (0.84 for power of 80%)

Assuming an expected prevalence of 42% for presence of maternal risk factors among cases of ADBOs as reported for late attendance of ANC by-Niguss at Dessie Referal Hospital (36) the following values were used to compute sample size:

P_1= proportion of cases with maternal risk factors for ADBOs =0.42

P_0 = proportion of controls with maternal risk factor for ADBOs = 0.42- 15 = 0.27

q_1= 1 – 0.42 = 0.58

q_0= 1- 0.27 = 0.73

$Z_{1-\alpha/2}$ = 1.96

$Z_{1-\beta}$ = 0.84

$$n = \frac{[(0.42)(0.58) + (0.27)(0.73)][(1.96 + 0.84)]^2}{(0.27 - 0.42)}$$

$$= \frac{(0.4407)(7.84)}{(0.0225)}$$

= 153.56

= 154 subjects per group

Total sample size = 308 (154 cases, 154 control)

The calculated sample size was inflated by 10% to account for non-response bias. A total of 340 mothers, 170 in case group and 170 in control group were enrolled to the study.

3.6 Participant recruitment and Sampling Method

All deliveries are posted into the maternity register at the time they occur; therefore, the deliveries that were posted during the study period (April 2019 to July 2019) and met the inclusion criteria were included in the study.

Cases were all singleton deliveries of babies born with adverse birth outcomes which included preterm births, still births and those with congenital malformations. Controls were all singleton deliveries of normal healthy babies. Both cases and controls were only included if the mother consented to the study, had attended ANC at KNH and had sufficient antenatal data (the ANC book and patient KNH medical file)

The sampling procedure was unmatched consecutive sampling technique of all ADBOs infants delivered as cases and the next normal born infants after an ADBO infant as the control until sample size was achieved. If the selected case does not meet the inclusion criteria the next ADBO infant will be recruited. If two ADBOs deliveries occur sequentially then the next two normal infants delivered were recruited as controls. The enrollment methodology is as shown in figure 3.1 below.

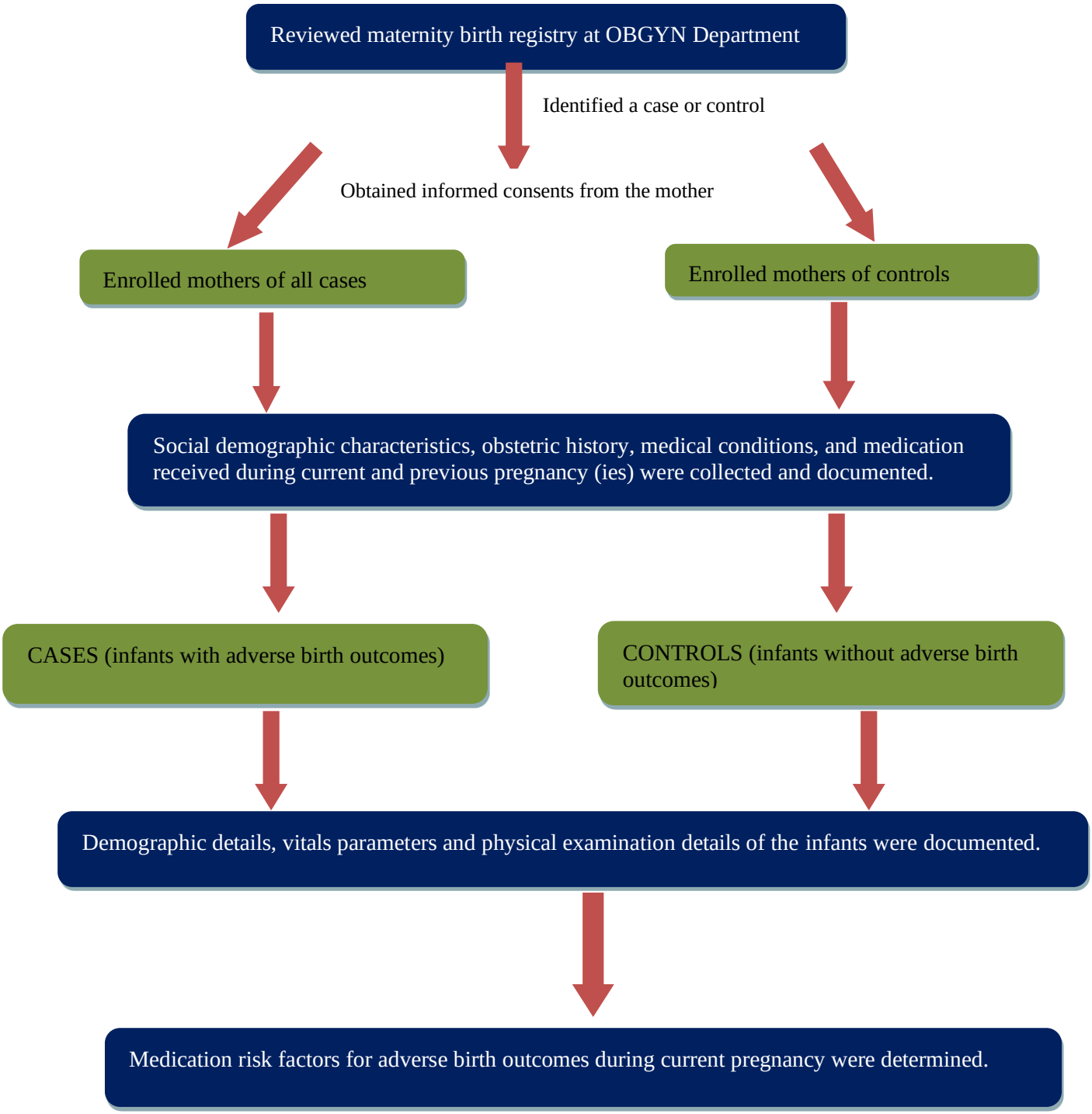

Figure 3.1: Flow chart showing the study methodology procedure.

3.7 Data Collection instruments and procedures

A pretested, interviewer administered questionnaire was used for the data collection from all the relevant sources. It was designed based on the WHO's pregnancy outcome data-sheet (for postnatal data), and antenatal questionnaire (for antenatal data) (32). The following sections were created in the data collection form for capturing the relevant data under each section: social demographic, past obstetric history, pregnancy index, ANC care and medical and medication history, delivery, and fetal outcome (Appendix 3).

Antenatal booklet provided information on recorded last menstrual period, first visit, number of visits, any complications, interventions done and any prescribed medication, quality, and quantity of antenatal care. Each of the women that had met the inclusion criteria had their antenatal booklet with them. They are required to carry them for each hospital visit as per the KNH ANC standard rules for those who did not have, and their ANC patient medical file was not there they were excluded.

Patient admission files provided information on general examination on admission such as height, blood pressure and also provided obstetric information, gestation at labor, onset of labor, maternal/ fetal complications, and mode of delivery. Patient records such as maternity register and patient files were kept in the ward cabinets under a nurse supervision and were accessible to the researcher and the research assistants upon request due to the letter of authorization granted by the head of OBS/GYN department and letter from the ethics and research committee of KNH/UON-ERC (Appendix 1).

After screening the babies with the help of a medical OBS/GYN registrar on shift and their mothers who had met the inclusion criteria for the day, their files and records were set aside. The interviews were conducted in post-natal wards early in the morning before major ward rounds or later in the afternoon. Bedside interview with curtains drawn was done for each of the participant to ensure the privacy. The relevance of the study and how the information they give will be used and protected was explained to each participant before obtaining the consent.

3.8 Variables

The primary outcomes of interest were the prevalence of adverse birth outcomes in KNH and the most common ADBO recorded. Another outcome of interest was drug use during the gestational period and the teratogenic category risk level of the prescribed drugs. The predictor variables were the socio demographic, medical and medication history of the patient. The confounding variables included maternal risk factors (pre-existing conditions), labour complications and a history of ADBO in the family.

3.9 Quality assurance and data management

The screening was solely done by the researcher. All deliveries are posted in the KNH maternity registry as they occur. ADBOs are registered and categorized by an OBS/GYN consultant or OBS/GYN registrar in the ward. The registrar on shift aided and helped the researcher in any clarification or query from the entered data in the maternity birth registry or patient file. Participants admission numbers were entered on a register for serialization to avoid double participation. Research assistants were trained nurses working in the maternity ward, whose role was to assist the researcher in collecting data. Maternity nurses were selected because they were conversant with the study parameters and had access to the patients. Research assistants were trained on ethical requirements like privacy and confidentiality when handling data from the participants and therefore qualified for the job.

The data collection tools were pre-tested and improved appropriately by the researcher. The completed data collection forms were reviewed by the researcher everyday against the source documents for completeness and accuracy. All the raw data collected was entered into Epi-Info version 7(2007-2010) software and a database created. The information in the database was backed up on a daily basis by the researcher using an external flash drive to avoid loss. Hard copies of the data collection form, and the external flash drive were stored in a lockable cabinet to restrict access and enhance confidentiality. Data cleaning and validation was done before being exported into STATA (version 13) for analysis.

3.10 Data analysis

The collected data was checked coded and entered to Epi Info version 7.0 and exported to STATA version 13 for further analysis. Three main approaches were used based on the study objectives. These approaches included both the descriptive(univariate) and inferential (bivariate and multivariable).

Univariate analysis was conducted depending on the type of variable being analyzed. For categorical variables that constituted most of the variables like, the prevalence of various types of ADBOs, drugs prescribed per trimester and classification per FDA system, the univariate analysis was presented as a table of frequency distribution containing both the frequency and corresponding percentage. Continuous variables such as weight and age measures of central tendency (mean and median) were calculated along with measures of distribution (standard deviation) to determine the distribution.

The primary outcome in the analysis was adverse birth outcome. The bivariate analysis involved cross tabulating each independent variable against ADBO and comparing the proportion of mothers in the different level of each independent factor who had ADBO delivery. The chi square test was used to test for significant associations between maternal characteristics and ADBO deliveries. For each bivariate comparison, the magnitude of association was also determined by calculating the Odds Ratio (OR) associated with ADBO and presenting the OR along with the corresponding 95% confidence interval.

Binary logistic regression analysis was used to identify the independent risk factors for ADBOs among medications received by mothers during the current pregnancy, after adjusting for cofounding variables like socio-demographic characteristics, other medical conditions and medications received. Strength of association between the risk factors and ADBOs was ascertained by calculating odds ratio (OR) along with 95% CI. For all analyses, a probability value of <0.05 was considered statistically significant.

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3.11 Ethical considerations

Approval to carry out the study was sought from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UON-ERC). Ref: KNH-ERC/A/124 (Appendix 1). Approval to collect data was also granted by from the hospital management authorities at Kenyatta National Hospital. Informed consent for participation in the case control study was also sought from the mothers.

The researcher followed all the necessary procedures to ensure privacy and confidentiality of the information obtained during the study. Patient codes were used instead of patient identifier information. The data instruments were stored in a password-protected database only accessible to the researcher. The data collection instruments and any other materials that were used during the study were kept under lock and key.

3.12 Data Dissemination Plan

It was important to ensure that the findings from the research were disseminated so as to ensure that they inform practice and thereby maximize the benefit to patients, health practitioners and mothers who plan to conceive. This plan involved several activities that included, publishing the findings in a peer reviewed journal, sharing the information with the Medicine and Therapeutic Committee members of KNH, conducting continuing medical education (CMEs) with the OBS/GYN department which is the concerned department in KNH. Sharing the information via electronic media like medical blogs, websites and you tube educative videos also help the information reach a huge number of audiences.

4.0 CHAPTER FOUR: RESULTS

Part One: Baseline Characteristics of the Study Population

A total of 340 mothers, 170 in case group and 170 in control group were enrolled into the study. The study population was from mothers who had delivered at the KNH obstetrics and gynecological wards between 5th April 2019 and 30th July 2019. The selection procedure is as shown below in Figure 4.0

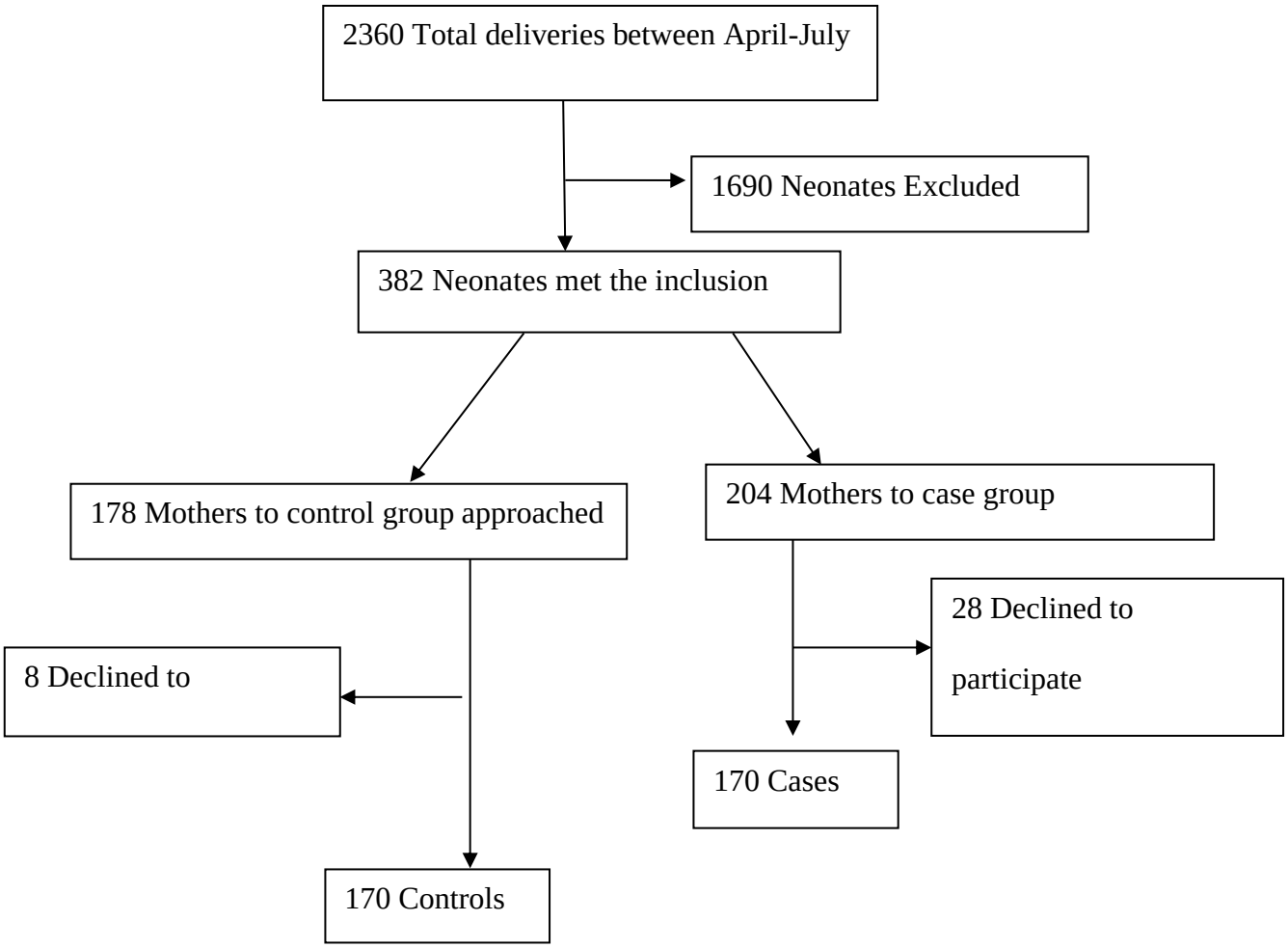

Figure 4.1: Consort diagram for recruitment of case and control groups

4.1 SOCIO - DEMOGRAPHIC CHARACTERISTICS

Majority of the women (51.8%) were aged between 21-30 years in both groups, followed by ages 31-40 at 33.0%. It was noted that (9.8%) young women aged between 10-20 years and (5.4%) were in the 41-50 age category. Regarding marital status most women were married (79.2%) followed by single women at 20.5% and 0.3% were separated. Majority women (49.2%) had attained secondary level education and most of them (46.0%) were unemployed, followed closely by self-employed at 40.0% and only 14% of the total number of women in both groups were employed. Those who had primary school level were (23.8%), (21.3%) had college level and (5.8%) had no formal education. There was no statistically significant difference in the socio demographic traits between the groups. Socio demographic characteristics of the two groups are summarized in the Table 4.1.

Table 4.1 Socio - demographic characteristics in the study population

Characteristic	Cases n (%)	Controls n (%)	p-value
Age group			
10-20	14(8.1%)	18 (11.8%)	
21-30	85(51.7%)	83(52.1%)	0.551
31-40	63(35.6%)	60(29.8%)	
41-50	8(4.6%)	9(6.3%)	
Marital Status			
Single	32(18.6%)	32(22.7%)	0.455
Married	139(80.8%)	109(77.3%)	
Separate	1(0.6%)	0(%)	
Level of Education			
None	10(5.8%)	8(5.6%)	0.505
Primary	41(23.7%)	34(23.9%)	
Secondary	90(52.0%)	65(45.8%)	
College	32(18.5%	35(24.7%)	
Occupation			
Unemployed	69(44.2%)	76(48.3%)	0.200
Self employed	73(42.4%)	53(37.1%)	
Salaried employed	23(13.4%)	21(14.7%)	

4.2 ADVERSE OUTCOMES

The most common adverse birth outcome among the case group was preterm births (27.6%) followed by still birth (15.3%) and the least common was congenital malformations at (7.14%).

Fetal weight of infants was significantly different between the two groups with 80.0% of infants born to mothers in the case group below 2500grammes compared to 2.1% those born to mothers in the control group. Children born to mothers in the case group (30.6%) weighed more than 3500 grams compared to 2.4% of children born to mothers in the control group. The frequency of the ADBOs is presented in figure 4.2 below.

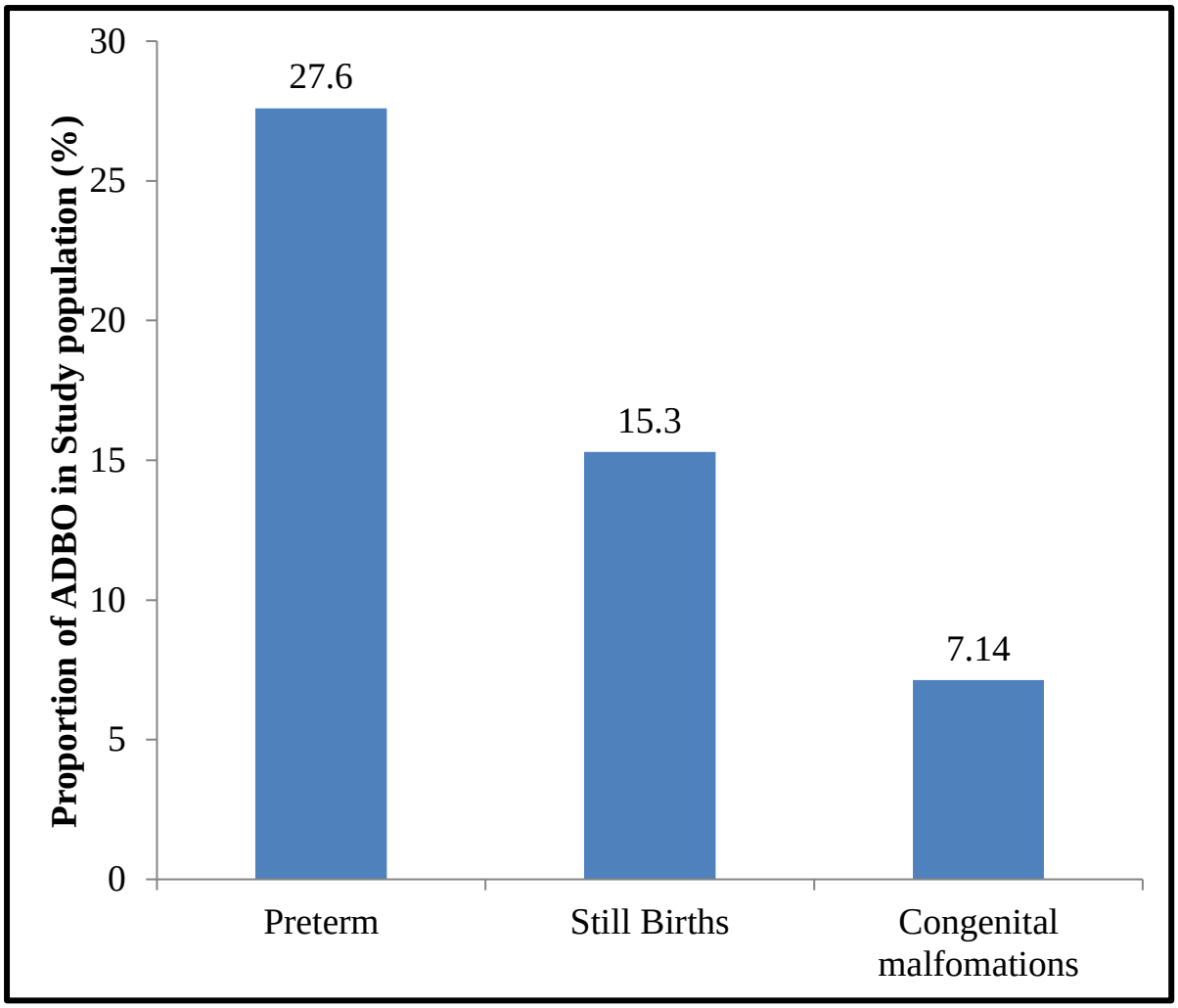

Figure 4.2: Frequency of various types of adverse birth outcomes among case group

The specific congenital malformations were spina bifida (45.8%), cleft palate (16.7%), polydactyl (8.3%), hydrocephalus (8.3%) and others (20.8%) which included hydrops fetalis, ectopic kidney and complete facial deformation. This is shown in figure 4.3 below.

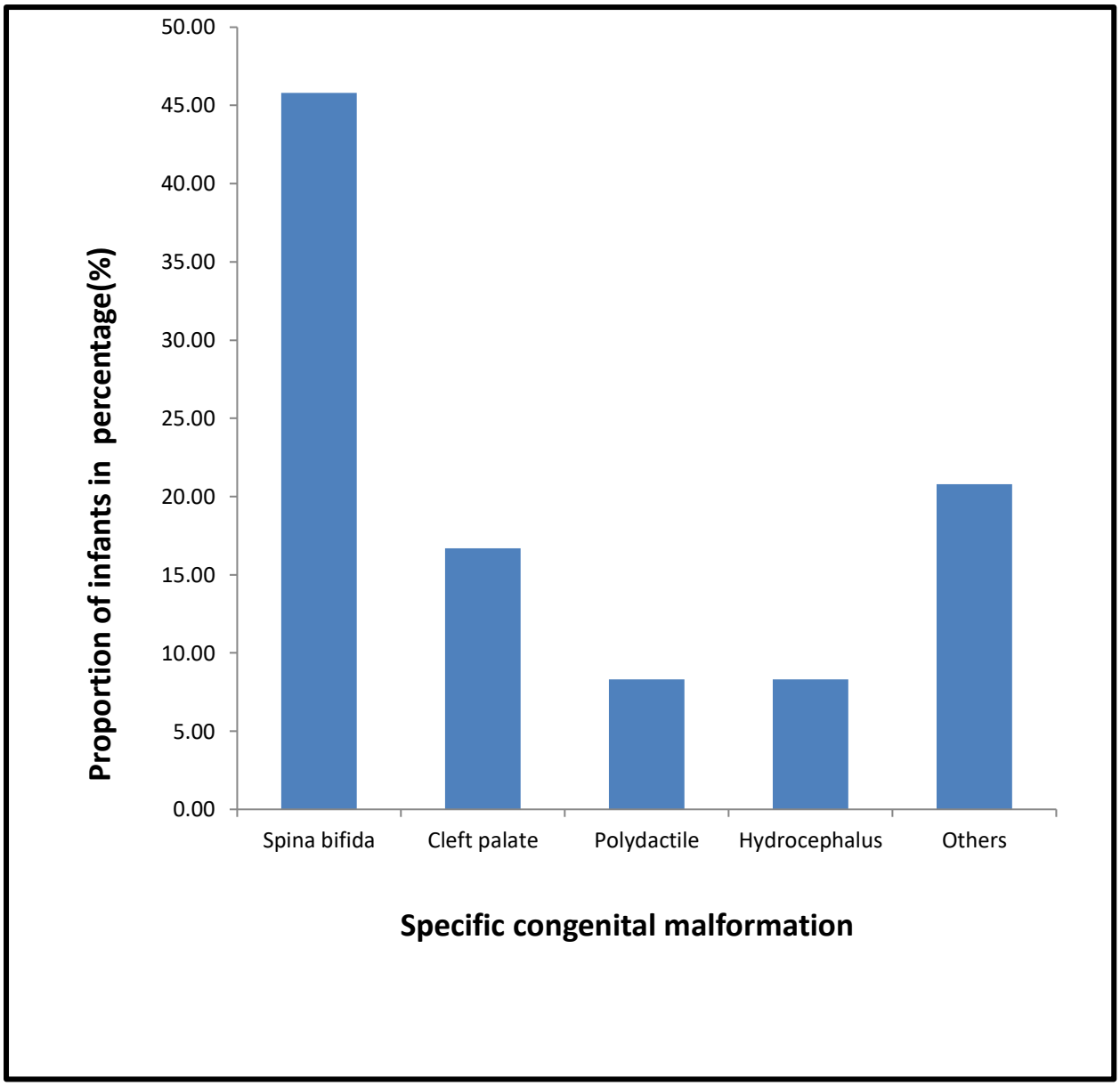

Figure 4.3: Specific congenital malformations of infants born to mothers in the case group.

4.3 OBSTETRIC HISTORY OF MOTHERS IN THE CASE AND COTROL GROUPS

Majority of participants in both groups had one to three previous deliveries (53.5%) in the case group and 51.4% in the control group. There is a significant difference in the outcomes of previous pregnancies between the two groups with the cases having higher incidences of miscarriage (17.8% vs 9.9%), preterm (3.8% vs 0.7 %), stillbirth (6.4% vs 3.7) compared with the control group. Both the cases and controls had normal delivery as the highest mode of delivery for the previous pregnancies at 28.4% and 26.2% respectively which was statistically significant. Overall, there was a statistically significant difference between the two groups in terms of past obstetric characteristics. This is shown in table 4.2 below.

Table 4.2: Past obstetric history of the respondents

Characteristic	Cases n (%)	Controls n (%)	OR (95% CI)	P value
Parity				
Primipara	63(36.2%)	62(43.1%)	1.923(0.668-5.134)	0.200
Multipara	93(53.5%)	74(51.4)		
Grandmultipara	18(10.3%)	8(5.56%)		
Outcomes of Previous pregnancies				
Miscarriage/Abortion	28(17.8%)	14(9.9%)	1.062(0.001-0.486)	**0.001**
Preterm	6(3.8%)	1(0.71%)		
Stillbirth	10(6.4%)	1(0.7%)		
Normal	46(29.3%)	55(39.0%)		
Normal and miscarriage	29(18.5%)	17(12.1%)		
Normal and Stillbirth	16(10.2%)	7(5.0%)		
Stillbirth and preterm	1(0.6%)	0(0.0%)		
Miscarriage and stillbirth	8(5.1%)	2(1.4%)		
None	13(8.3%)	44(31.2%)		
Mode of delivery of previous pregnancies				
Normal	44(28.4%)	37(26.2%)	0.043(0.002-0.521)	**0.001**
Caesarean Section	31(20.0%)	30(21.3%)		

4.3.1 Family planning practices among mother in the case and control groups

Majority of the women (60.3%) in both groups were on family planning prior to the current pregnancy. The implant was the most popular form of contraceptive at 54.6% among cases and 40.2% controls. Use of the daily oral pills was second in both groups at (26.0%), followed by IUCD (11.5%), condoms (9.4%) and others (3.1%) which included counting of days and coitus interruptus. In both groups most women (68.3%) had planned for the pregnancy while 31.7% had not planned.

There was no statistically significant difference between cases and the controls in regard to the planning of the pregnancy and family planning use. Inter-pregnancy interval between the last delivery and the last period was statistically significant different across the two groups (0.002). The cases had longer interpregnancy intervals with 47.6% over 24 months compared to 44.8% in the control group. This is shown in table 4.3 below.

Table 4.3 Family planning practices among mother in the case and control groups

Characteristic	Cases n (%)	Control n (%)	P Value
Family Planning Use Prior to this Pregnancy			
YES	112(64.7%)	79(54.9%)	0.074
NO	61(35.3%)	65(45.1%)	
Type of Family planning used			
Daily oral pills	30(27.3%)	20(24.4%)	0.194
IUCD	8(7.3%)	14(17.1%)	
Norplant	60(54.6%)	33(40.2%)	
Condoms	9(8.2%)	9(11.0%)	
Others	2(1.8%)	4(4.9%)	
Pregnancy planned or unplanned			
Unplanned	53(31.4%)	46(32.2%)	0.212
Planned	116(68.6%)	97(67.8%)	
Inter-Pregnancy Interval			
<6 months	4(2.7%)	5(3.8%)	
6-12 months	16(11.0%)	7(5.3%)	**0.002**
12-24months	29(20.0%)	12(9.09%)	
>24 months	69(47.6%)	59(44.8%)	

4.4 MEDICAL HISTORY OF WOMEN WITH AND WITHOUT ADVERSE BIRTH OUTCOMES

4.4.1 Proportion of participants with co-morbidities in the case and control group

Several participants in both the case and the control groups had preexisting conditions before pregnancy. HIV/AIDS was the most common preexisting condition at 11.5% and 10.4% for the cases and the controls respectively, followed closely by hypertension which was 1.2 times more common among the cases compared to the controls. Among all preexisting medical conditions, there was a statistically significant difference between the cases and the controls in hypertension, diabetes, anaemia and epilepsy. The analysis of the preexisting conditions is shown in table 4. 4 below

Table 4.4 Proportion of participants with Co-morbidities in the case and control group

Characteristic	**Cases n (%)**	**Controls n %)**	**P Value**
Pre-existing Conditions			
Hypertension	13(7.8%)	7(4.5%)	**<0.001**
Diabetes	5(3.0%)	1(0.7%)	**<0.001**
HIV/AIDS	19(11.5%)	15(10.4%)	0.532
Sickle cell	1(0.6%)	0(0.0%)	0.174
Anaemia	5(3.0%)	1(0.7%)	**<0.001**
Epilepsy	1(0.6%)	0(0.0%)	**0.042**
Cardiac dx	2(1.2%)	1(0.7%)	0.652
Depression	1(0.6%)	0(0.0%)	0.346
Asthma	3(1.8%)	2(1.4%)	0.142

4.4.2 Complications and hospital admission during current pregnancy

The frequency for hospital admission was significantly higher among the cases (43.0%) compared to the controls (19.6%). Preeclampsia was the most common reason for admission at 30.3% for cases and almost 10 times less among the control group at 3.0%. Regarding severe malaria the controls had a higher admission rate compared to cases at (6.6 vs 3.3%) respectively.

Urinary tract infection was the most common complication experienced during pregnancy and the difference in the prevalence between the cases and controls was statistically significant p value (<0.001) followed by preeclampsia p value (0.020). There was no significant difference between the groups in women who developed gestational diabetes and upper respiratory tract infection. The complications experienced and hospital admission analysis are shown in table 4.5 below.

Table 4.5: Complications and hospital admission during current pregnancy

Characteristic	Cases n (%)	Controls n (%)	P Value
Hospital Admission			
Admitted	73(43.0%)	28(19.6%)	**0.001**
Not admitted	97(57.1%)	115(80.4%)	
Reasons for admission			
PV Bleeding	7(5.7%)	1(0.7%)	
Preterm labour	13(10.7%)	3(2.2%)	
Psychiatric condition	2(1.64%)	1(0.74%)	
Cardiac Dx	1(0.8%)	1(0.7%)	
Upper Respiratory Tract Infection	2(1.6%)	0(0.0%)	
GI complications	2(1.6%)	2(1.5%)	
Complications experienced during pregnancy			
UTI	29(15.9%)	46(27.1%)	**0.001**
URTI	6(4.3%)	4(5.2%)	0.803
Gestational DM	1(0.7%)	1(1.3%)	0.893
PV Bleeding	14(9.9%)	4(5.2%)	0.043
Anaemia	9(6.4%)	18(23.4%)	**0.020**
Malaria	11(7.8%)	2(2.6%)	**0.004**
Pre-eclampsia	33(23.4%)	10(13.0%)	**0.002**
Febrile illness	8(5.7%)	7(9.1%)	0.912
GI complications	8(5.7%)	0(0.0%)	**0.002**

Dx-Disease, UTI-Urinary Tract Infections, URTI-Upper Respiratory Tract Infections, DM-Diabetes Mellitus, PV-Vaginal bleeding in pregnancy, GI-Gastrointestinal complications

4.5 COMPARISON OF ANTENATAL ATTENDANCE AND LABORATORY TESTS OF WOMEN WITH AND WITHOUT ADVERSE BIRTH OUTCOMES

There were no significant differences between the cases and control group with regard to ANC attendance and the various tests done during the visits. It is important to note that most women had more than 4 ANC visits (59.9% and 68.2% for cases and controls respectively). Majority of the women attended ANC from second trimester, followed by third trimester and only 15.0% in both groups attending in the first trimester.

Regarding the tests done, the cases had the highest number of cases of anaemia both moderate, syphilis (VRLDL positive), seroreactive and also rhesus negative mothers compared to the control group. The ANC comparison data is as shown below in table 4.6

Table 4.6: Antenatal profile data of the study population

Characteristic	Cases n (%)	Control n (%)	P Value
No of ANC Visits			
1	14(8.1%)	7(5.2%)	
2	11(6.4%)	12(8.9%)	0,214
3	44(25.6%)	24(17.8%)	
>4	103(59.9%)	92(68.2%)	
Gestation at 1st ANC visit			
1st trimester	29(17.1%)	18(12.6%)	
2nd trimester	96(56.5%)	85(59.4%)	0.544
3rd trimester	45(26.5%)	40(28.0%)	
Laboratory tests done			
Hemoglobin levels			
Non-anaemia (>11.0)	132(77.7%)	121(85.2%)	
Mild (10.0-10.9)	29(17.1%)	14(9.9%)	0.814
Moderate (7.0-9.9)	9(5.3%)	6(4.2%)	
Severe (<7.0)	0(0.0%)	1(0.7%)	
HIV Status			
HIV positive	23(13.5%)	15(10.6%)	0.438
HIV negative	147(86.5%)	126(89.4%)	
VDRL			
Positive	4(2.4%)	1(0.7%)	0.240
Negative	164(97.6%)	142(99.3%)	
Rhesus Factor			
Positive	114(95.0%)	129(94.2)	0.767
Negative	6(5.0%)	8(5.8%)	

4.5.1 Cravings and substance use during pregnancy

Use of alcohol (7.8%) and pica (33.1%) was higher among the case group compared to the control group 5.8% and 21.2% respectively. However, the association with ADBOs was not statistically significant. The proportion of women who smoked cigarettes in the case and control group was 3.5% and 1.4% respectively. Cigarette smoking conferred almost 3-fold increase in the risk of adverse birth outcome (OR 2.898) which was statistically significant p value (0.017). Table 4.7 shows the association between adverse birth outcomes and substance use in pregnancy.

Table 4.7: Association between Adverse birth outcomes and substance use during pregnancy

Characteristic	Cases n (%)	Controls n (%)	OR (95% CI)	P value
Alcohol use				
Yes	11(7.8%)	10(5.8%)	1.432(0.678- 4.432)	0.343
No	160(94.2%)	159(92.2%)		
Cigarette smoking				
Yes	6(3.5%)	2(1.4%)	2.898(0.547-12.472)	**0.017**
No	164(96.5%)	168(98.6%)		
Pica use				
Yes	57(33.1%)	36(21.2%)	0.512(0.223-1.846)	0.507
No	113(66.9%	134 (78.8%)		

4.6 DELIVERY FACTORS AND COMPLICATIONS DURING LABOUR

Spontaneous vertex delivery (SVD) was 43.6%% in the case group and 56.9% in the control group. More women with adverse birth outcomes were likely to have delivered by caesarean section (52.1%), compared to those without adverse birth outcomes (43.1%). The frequency of labour induction was high among the cases at 22.1% compared to control group at 10.0%. Fewer women among the cases (27.9%) had spontaneous labour onset compared to 46.4% among the controls.

About 15.9% and 14.0% in the case and control group respectively experienced complications during labour. The most common complication was post-partum hemorrhage 10.3% in the case and 5.2% in the control group. However, this was not statistically significant. This is demonstrated in table 4.8 below.

Table 4.8: Delivery factors and labour complications

Characteristic	Cases n (%)	Controls n (%)	P value
Mode of delivery			
SVD	75 (43.6%)	82(56.9%)	
Cesarean	90 (52.3%)	62(43.1%)	**0.018**
Assisted vaginal	6(3.5%)	0(0.0%)	
Breech	1(0.6%)	0(0.0%)	
Labour Onset			
Spontaneous	43(27.9%)	65(46.4%)	
Induction	34(22.1%)	14(10.0)	**0.001**
Not indicated	77(50.0%)	61(43.6%)	
Reasons for Induction			
IUFD	4(4.7%)	0(0.0%)	
Threatened abortion	9(10.6%)	9(6.9%)	**0.010**
Past datism	1(1.2%)	0(0.0%)	
MSB	4(4.8%)	5(3.9%)	
Others	5(5.9%)	1(0.8%)	
Experienced any Obstetric Complications			
Yes	27(15.9%)	20(14.0%)	0.640
No	143(84.1%)	123(86.0%)	
Obstetric Complication			
Retained placenta	2(1.7%)	0(0.0%)	
2nd degree tear	1(0.9%)	0(0.0%)	0.167
PPH	12(10.3%)	7(5.2%)	
Cord Prolapse	10(8.6%)	9(6.7%)	

SVD- Spontaneous vertex delivery, IUFD-Intrauterine fetal death, MSB-Macerated still birth, PPH-Postpartum hemorrhage

4.7 PRESCRIBING PATERN ANALYSIS OF DRUGS USED DURING PREGNANCY

Most women either in the control or case group had used at least one drug during pregnancy. Hematinic were the most prescribed with 59.6% cases and 62.7% controls having taken a combination of iron and folic acid. There was no statistically significant difference between the two groups regarding antibiotic use, antiretroviral therapy, antimalarials, analgesics, antifungals, and respiratory drugs. However, it is important to note total use of antibiotics was higher among the case group (34.4%) compared to the control (29.9%) apart from amoxicillin and cefuroxime. Nitrofurantoin was the most frequently prescribed antibiotic (10.1%) among cases and (7.5%) controls. About 20.0% and 9.6% of women in the case and control group respectively used cotrimoxazole while 4.6% cases and 0.7% controls used fluconazole during pregnancy. For women on antiretroviral therapy the most common regimen was AZT/3TC/NVP 6.1% and 4.2% cases and controls, respectively. This is shown is table 4.9 below.

Table 4.9: Prescribed anti-infective drugs to both women with and without ADBO

Characteristic	Cases n (%)	Controls (%)	
Antibiotics			
Erythromycin	10(6.9%)	8(4.6%)	
Ceftriaxone	6(4.3%)	2(1.4%)	
Amoxicillin	11(6.3%)	12(8.3%)	**0.135**
Nitrofurantoin	18(10.1%)	13(7.5%)	
Cefuroxime	4(2.3%)	6 (3.6%)	
Benzyl penicillin	4(1.7%)	3(2.8%)	
Antiretroviral			
AZT/3TC/NVP	7(6.1%)	6(4.2%)	
AZT/3TC/EFV	5(3.5%)	3(2.6%)	
AZT/3TC/LPV	2(1.7%)	0(0.0%)	**0.143**
3TC/TDF/NVP	4(3.5%)	2(1.4%)	
3TC/TDF/EFV	7(6.1%)	2(1.4%)	
Anti-malarial			
AL	6(4.3%)	2(1.8%)	
Quinine	3(2.7 %)	2(1.4%)	
IM artesunate	4(2.86%)	1(0.92%)	**0.488**
Antifungal			
Cotrimoxazole	20(20.0%)	6(9.6%)	
Fluconazole	5(4.6%)	1(0.7%)	
Hematopoietic drugs			
Iron supplements	36(22.4%)	38(26.7%)	
Folic acid	7(5.8%)	5(4.7%)	**0.217**
Iron/folic acid (IFAAS)	96(59.6%)	89 (62.7%)	
Gastrointestinal drugs			
Antacids	10 (7.1%)	10(8.6%)	
Mebendazole	6 (4.3%)	1(0.9%)	
Metronidazole	7 (3.6%)	2(1.7%)	**0.067**
Probiotics	1 (0.7%)	0(0.0%)	
Metoclopramide	4 (2.8%)	3(2.6%)	
Hyoscine butylbromide	0 (0.0%)	3(2.6%)	
Omeprazole	3 (2.1%)	1(0.9%)	
Respiratory drugs			
Cetrizine	3(2.7%)	6(4.3%)	
Chlopheniramine	2(1.8%)	0(0.0%)	**0.314**
OTC syrups	3(2.7%)	4(2.9%)	

AZT= **zidovudine, 3TC=**Lamivudine,** LVP=**Lopinavir,** TDF=**tenofovir,** EFV=**efavirenz,** OTC=**Over the counter,** NVP= **Nevirapine,** AL=**artemether lumefantintrine ,** AntiD=**Rho(D)immunoglobin***

4.7.1 Prescribed organ system drugs

Use of prescribed antihypertensives, antipsychotics, gastrointestinal drugs, antifibrinolytics, corticosteroids and antidiabetics was different across the two groups. Methyldopa was the commonly prescribed antihypertensive (16.1%) amongst cases and (6.3%) in the control group. About 8.1% cases and 4.9% controls used nifedipine during pregnancy. Use of tranexamic acid was also higher among the cases (12.5%) compared to the control group (1.5%). Anticonvulsants use was significantly different across the two arms (p= 0.001) with 2.1% of the cases and 0.3% controls having used carbamazepine. There was a significant difference in the use of corticosteroids between the two groups (p=0.002) with about 13.2% of the women in the case and 1.5% in the control group having used dexamethasone. Use of insulin was higher among the cases (1.7%) compared to the controls (0.7%) however, this was not statistically significant. Among the study participants, 18.3% used herbal medication during the pregnancy with more women in the control group (22.7%) compared to the case group (14.2%). Table 5.0 below show various organ system drugs prescribed to women in both the case and the control group.

Table 5.0: Organ system drugs prescribed to both the case and the control group.

Drug	Cases n (%)	Control n (%)	P-Value
Antihypertensives			
Methyldopa	28(16.1%)	9(6.3%)	**0.003**
Atenolol	1(0.6%)	0(0.0%)	
Nifedipine	14(8.1%)	7(4.9%)	
Hydralazine	4(2.3%)	0(0.0%)	
HCTZ	1(0.6%)	2(0.7%)	
Carvedilol	3(1.7%)	1(0.7%)	
Digoxin	1(0.6%)	0(0.0%)	
Furosemide	2(1.2%)	1(0.7%)	
Labetalol	3(1.8%)	1(0.6%)	
Magnesium sulphate	4(2.1%)	1(0.6%)	
Ant-diabetics			
Insulin	3(1.7%)	1(0.7%)	0.006
Metformin	2(1.2%)	1(0.7%)	
Anti-fibrinolytics			
Tranexamic acid	13(12.2%)	2(1.5%)	**0.002**
Heparin	0(0.0%)	1(0.7%)	
Vitamin K	4(2.3%)	2(1.4%)	
Anti-convulsants			
Carbamazepine	4(2.1%)	1(0.3%)	**0.001**
Haloperidol	0(0.0%)	0(0.0%)	
Phenytoin	3(1.2%)	0(0.0%)	
Analgesics/Anti-inflammatory			
Paracetamol	46(32.4%)	44(37.3%)	0.284
Diclofenac	4(2.8%)	1(0.9%)	
Ibuprofen	5(3.5%)	1(0.9%)	
Tramadol	4(2.3%)	0(0.0%)	
Corticosteroids			
Dexamethasone	15(13.2%)	2(1.5%)	**0.002**
Hydrocortisone	2(1.8%)	0(0.0%)	
Prednisolone	3(2.7%)	3(2.2%)	
Anti D	3(2.1%)	2(1.2%)	0.067
Duphastone	4(2.3%)	0(0.0%)	
Use of Herbal drugs	21(14.2%)	32(22.7%)	0.062

HCTZ*=hydrochlorothiazide*

4.7.2 Frequency of medication use by trimester.

Most medications excluding iron/folic, and vitamins were taken in the second trimester. About 8.9% of mothers in the case and 5.1% in the control group used medication in the first trimester. The proportion of women who took medication in the second trimester in the case and control group was 36.1% and 22.8% respectively. A bout 5.7% of all the mothers in the two groups took drugs throughout the pregnancy. The difference between the two groups in the trimester in which the medications were taken was statistically significant (p=0.003). This is shown in figure 4.5 below.

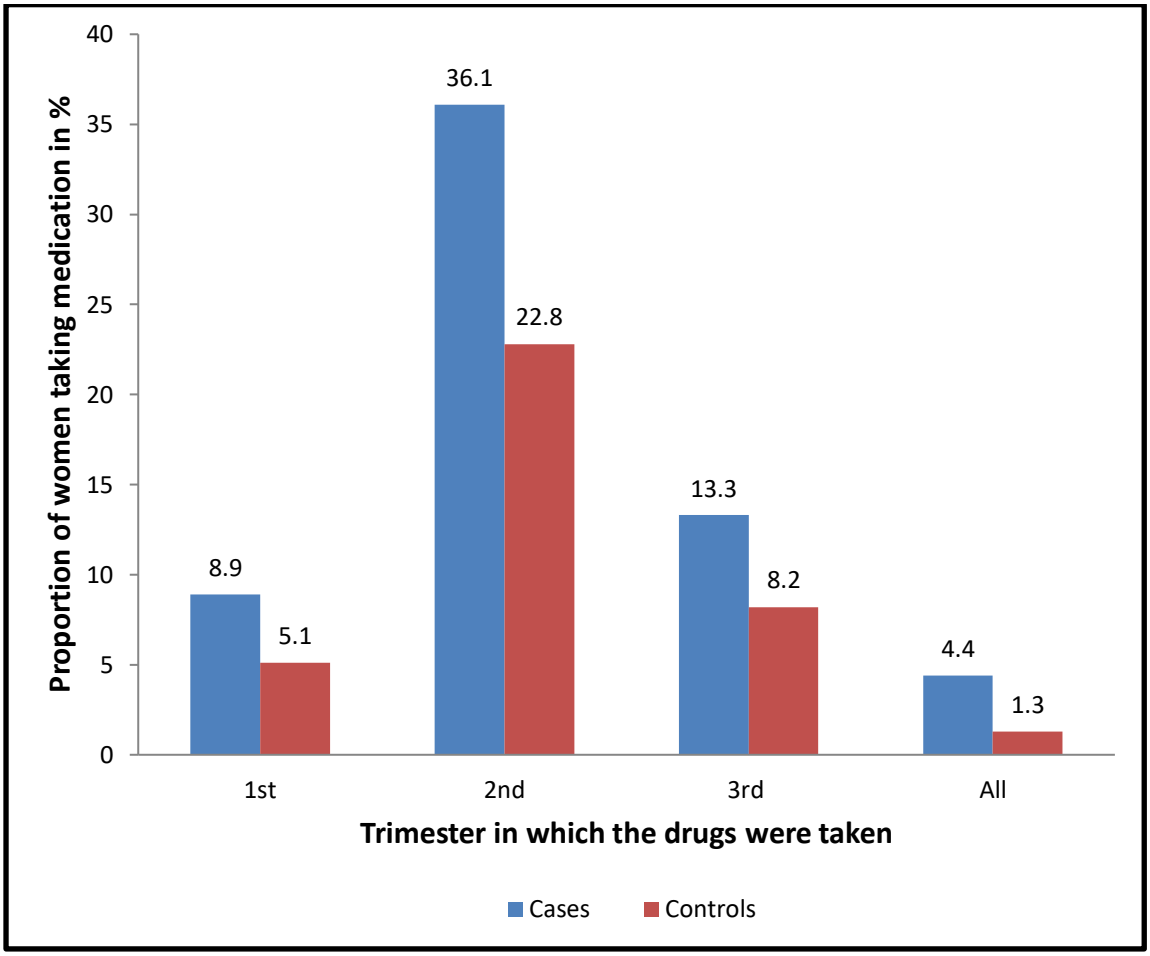

Figure 4.5: Proportion of women taking medication and trimester used.

4 .7.2 Classification of prescribed drugs according to the US FDA classification system

Majority of the women received drugs from category A, followed by B, C and D respectively. Notably there was an increased use of drugs from category D in the case group compared to the control group (13.9% vs 8.7%). No drug from category X was prescribed**.** More cases than controls were more likely to have taken category C and D drugs. Examples of prescribed drugs from category D included cotrimoxazole, fluconazole, efavirenz, carbamazepine and phenytoin. Figure 4.6 below demonstrates the percentage of drugs prescribed in each FDA category.

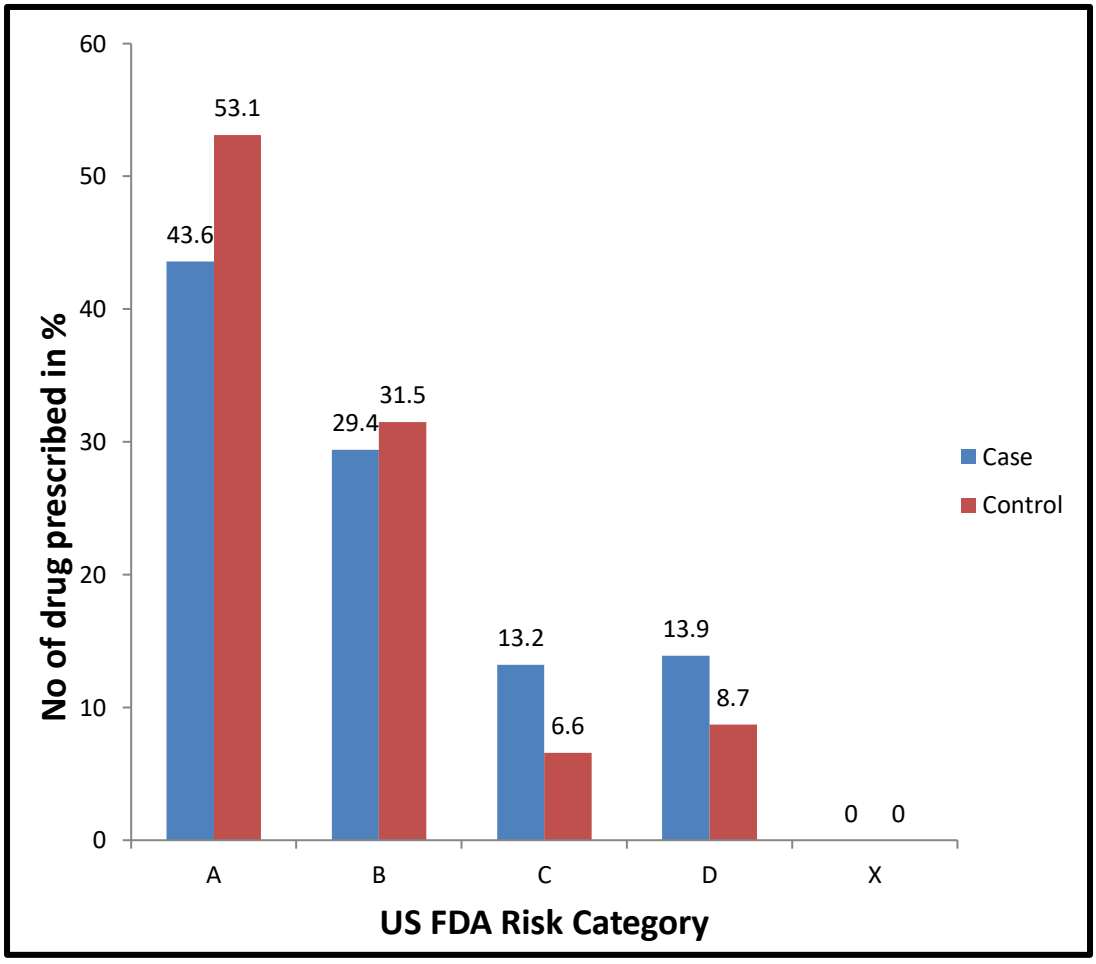

Figure 4.6: Percentage of drugs prescribed according to the US FDA classification system.

4.8 ASSOCIATION BETWEEN MEDICATIONS USED IN PREGNANCY AND ADVERSE BIRTH OUTCOMES

Nifedipine, carbamazepine and magnesium sulphate were found to be significantly associated with adverse birth outcomes. The risk of developing ADBOs increased 6-fold with nifedipine (OR 6.42), 4-fold if the mother had used carbamazepine (OR 3.97) and 3-fold with magnesium sulphate (OR 3.11) after adjusting for social-demographic, past obstetric history, co-morbidities, pregnancy complications, and maternal delivery outcomes. Though not statistically significant, increased risk of ADBOs was identified in the use of nitrofurantoin, labetalol, anti-retroviral (3TC/TDF/EFV) and fluconazole. Notably there was decreased risk of ADBOs with use of insulin, methyldopa, and herbal drugs. This is shown in table 5.1 below.

Table 5.1: Association of medications used in pregnancy and adverse birth outcome

Medication prescribed during pregnancy	**AOR (95% CI)**	**P value**
Nifedipine	6.42(3.14-12.52)	**<0.001**
Carbamazepine	3.97(1.66-18.38)	**0.012**
Magnesium sulphate	3.11(1.93-11.68)	**0.016**
Nitrofurantoin	1.89(0.24-12.45)	0.513
Labetalol	1.72(0.52-4.72)	0.532
3TC/TDF/EFV	1.56(0.82-3.45)	0.672
Fluconazole	1.89(0.47-5.12)	0.150
Insulin	0.89(0.17-4.66)	0.461
Methyldopa	0.73(0.55- 0.97	**0.002**
Herbal drugs	0.56(0.30-1.04)	0.068

AOR *- adjusted odds ratio; adjusted for socio-demographic and past obstetric history of mothers (age, level of education, occupation, weight, parity, outcomes of previous pregnancies)*

4.8.1 Association of medication with specific adverse birth outcome

An expanded bivariate analysis was done to determine which of the identified commonly used medication in pregnancy, was strongly associated with adverse outcome among the mothers who used and those who did not use the specific medication. The risk of developing ADBOs increased 3fold with the use cotrimoxazole (OR 2.84). There was no significant association identified between use of folic acid, nitrofurantoin, and methyldopa during pregnancy and ADBOs after controlling for the confounders. This is summarized in table 5.2 below.

Table 5.2: Association between commonly used drugs and adverse birth outcomes among the case and the control group

Drug	Mothers with ADBO	Mothers without ADBO	AOR	P value
Cotrimoxazole				
Yes	20(11.8%)	6(3.3%)	2.84(1.762-8.976)	**0.004**
No	150(88.2%)	176(96.7%)		
Nitrofurantoin				
Yes	18(10.6%)	13(7.6%)	1.76(0.247-6.452)	0.079
No	152(89.4%)	157(92.4%)		
Methyldopa				
Yes	28(16.5%)	9(5.3%)	0.93(2.786-16.541)	1.000
No	142(83.5%)	161(94.7%)		

***AOR** - adjusted odds ratio; adjusted for socio-demographic and past obstetric history of mothers (age, level of education, occupation, weight, parity, outcomes of previous pregnancies).*

CHAPTER 5: DISSCUSSION

The study assessed adverse birth outcomes (preterm, stillbirth and congenital malformations) and the association with maternal and medication risk factors among women who delivered and had attended ANC at Kenyatta National Hospital.

The most common adverse birth outcome among the case group participants was preterm births (27.6%) followed by still births (15.3%) and congenital malformations (7.14%). This was comparable to a study by Cherie et al in Ethiopia (40) that showed the proportions of ADBO to be preterm (35.0%), still birth (14.0%) and congenital malformations (11.0%).

The frequency of pre-term births (27.6%) was higher compared to 18.3% reported by Wagura et al (2018) in Kenya (28). This is possibly because this study looked at both spontaneous and induced preterm deliveries whereas only spontaneous preterm deliveries were considered by Wagura et al. WHO population based estimates of preterm birth that indicate that most countries with a prevalence of more than 15% are in sub-Saharan Africa.

Stillbirths frequency(15.3%) was lower compared to 23.0% findings of Lucas et al in Kenya(37) .This difference may be due to difference in methodological and population variation between the participants. In this study only participants who had attended antenatal care at KNH were included. Therefore, having attended ANC could have contributed to the lower stillbirth proportion in this study population. Among babies born with congenital malformations spina bifida (45.8%) which involves the musculoskeletal system was the most frequent accounting for 45.8%.This finding was similar to that of Abbey M et al in Nigeria (24). Other congenital malformations included ectopic kidney, heart defects and face deformation.

Majority of the women in the two groups, case (51.7%) and control (52.1%) were aged between 21-30 years which is the peak reproductive age for most women in Africa. Some studies have shown advanced maternal age as a risk for adverse birth outcome but this was not demonstrated in the current study (38) . Most of the women in both groups were married (79.2%), had secondary level education (49.2%) and were either unemployed (46.0)%) or self-employed(40.0%) and only 24.0% had formal employment .Other studies(24,33) had shown conflicting findings on association between ADBOs with education level and employment status but similar to Wagura et al (38) education level and employment status were not associated with ADBOs in this study.

This may be due to increased access to free maternal healthcare and to basic education whether employed or unemployed among mothers in this study whose background was mainly urban.

With regard to past obstetric history, adverse birth outcomes of previous pregnancies were associated with a high risk of ADBO of the current pregnancy. There was a statistically significant difference in the outcomes of previous pregnancies between the two groups with the cases having higher incidences of miscarriage (17.8%), preterm (3.8%), stillbirth (6.4%) compared with the control group with miscarriage (9.9%), preterm (0.7%) and stillbirth (3.7%). This may be caused by persistence of unidentified factors among the women in the case group. This finding are similar to previous studies which showed that increased risk of preterm and stillbirth deliveries in women who had had poor outcomes before (26,39,40).

Complications during pregnancy whether medical or obstetric are of major concern in regard to the pregnancy outcome. In this study urinary tract infection was the most common complication experienced during pregnancy and the difference between the cases and controls was statistically significant (p=0.001) followed by preeclampsia with a (p=0.002).These findings were similar to other studies done in Kenya, Ghana and Nigeria (23,40,41). In terms of preexisting conditions, there was a significant difference between the case and the control group in hypertension, anaemia and diabetes. Studies have shown maternal anaemia being associated with ADBO like premature births and low birth weight (42).Literature has shown congenital abnormalities to the musculoskeletal system are the most common abnormalities among offspring of diabetic mothers (42). Diabetes mellitus during pregnancy has also been linked to structural abnormalities like extra digits to hands, club foot, club foot and high arched palate(13).

Studies that have been published on medication use and prescribing patterns differ widely. This is because of variation in medication use between people living in different geographical areas, difference in social demographic characteristics and size of the study population. This study showed that most women either in the control or case group had used one or more drugs during the pregnancy; this is because iron and folic or a combination of both were prescribed for 96% of all the women in both the case and control groups who attended ANC. This was comparable a study in Ethiopia where all pregnant women (100%) were given prophylactic iron and folic acid .

Regarding patterns of prescribing, women received several medications such as methyldopa, labetalol, nifedipine or hydralazine for the management of hypertension. Insulin and metformin were used for management of gestational diabetes. Magnesium sulphate was administered to those who had signs of pre-term labour and to prevent seizures associated with pre-eclampsia. Corticosteroids like dexamethasone were prescribed for promotion of fetal lung maturation. Anti-emetic drugs were prescribed especially in first trimester to manage nausea and vomiting. Nitrofurantoin was the most prescribed drug for UTI infections; 10.1% among cases and 7.5% controls. Amoxicillin and erythromycin were also widely used as broad-spectrum antibiotics. Most of the medications given were as per the standard guideline for management of various conditions in pregnancy. This is similar to findings of Kodhiambo M et al (33) .

Studies have shown use of herbal medication to be associated with ADBOs like congenital malformations, tumors and childhood malnutrition(17). In this study there was decreased risk of ADBOs with use of herbal drugs (OR=0.56) and more women in the control group (22.7%) were on herbal medication compared to the case group (14.2%). This was different from findings of Mabina et al (19) . Most of them cited reason for use of herbal medication was to make labour easier, improve fetal conditions and to help with nausea, vomiting and hyperacidity in the first trimester. It is possible that herbal medication could have protective risk on ADBOs compared to conventional medicine due to increased awareness in their use and more intensified regulation to ensure their safety.

Most women used medication excluding iron/folic and vitamins in the second trimester 36.1% cases and 22.8% controls and the least use during first trimester case (8.9%) and control group (5.1%). This was inconsistent with previous studies that showed increased use of drugs in the first trimester (36). This may indicate good clinical practice in the study facility to limit use of drugs in first trimester due to increased risk during organogenesis in first trimester compared to the other trimesters.

In terms of US-FDA pregnancy risk classification, majority of the women received drugs from category A, followed by category B, D and C, respectively. It was identified that there are a number of pregnant women who received drugs that ought to be avoided especially from category D (drugs with clear evidence of risk to the fetus) and there was also a difference in the use of category D with more women in the case group (13.9%) compared to the control group (8.7%). None of the FDA Category X drugs was prescribed.

Previous study done in Cameroon that showed 17% of women were exposed to at least one FDA category C or D medication (potentially teratogenic) (43).Increased in exposure to drugs in category C and D was highly contributed by use of antimalarials and anti-tuberculosis medication. Although the FDA classifies antimalarials in category C (potentially risky) drugs, no adverse effect has been shown on risk–benefit assessments of quinine use in all trimesters and ACT combinations from second trimester to have no adverse effect on the mother or fetus. Safe use of these medications during pregnancy is depended on severity of the disease or the stage of pregnancy as per the WHO recommendations (3, 44) .

Specific medication association to ADBOs showed that the risk of developing ADBOs increased 6-fold with nifedipine use. Nifedipine has been identified to be associated with preterm births. A prospective observational study conducted by the ENTIS identified more preterm births in the study group compared to the control group (23.8% vs. 6.5%) (44). Nifedipine is used as tocolytic agents to prevent preterm births. It is likely that nifedipine might have been used as a tocolytic in women who were already in preterm labour or as antihypertensive in cases of severe hypertension, that mandated an iatrogenic preterm delivery hence the increased risk of ADBO with use of nifedipine. Similar situation with use magnesium sulphate which is used in severely hypertensive women or as a drug for neuroprotection in premature deliveries.

The study showed 3 fold increased risk of ADBOs in women who used carbamazepine this was comparable to a meta-analysis study that showed use of antiepileptic drugs have been associated with congenital heart disease with 1.8 times risk among the group that used carbamazepine (45). Though not significant the study showed an increased risk of ADBO in the use fluconazole (OR=1.89). Use fluconazole in pregnancy has been associated with stillbirths and linked to a distinct pattern of craniofacial, skeletal and heart defects(50). Some studies have shown no significant increase in the prevalence of birth defects following exposure to EFV-based ART (50).This was consistent with the study findings that identified some risk with use of EFV regimen but it was not significant. There was a 3-fold increased risk with the use of cotrimoxazole. A meta-analysis study showed use of cotrimoxazole in the initial stages of pregnancy to be associated with risk of developing adverse birth outcomes especially congenital malformations but relatively safe in the late pregnancy both in the HIV infected and infected mothers(51). There is need to do further studies to assess safety of cotrimoxazole in pregnancy.

STRENGTHS AND LIMITATIONS OF THE STUDY

The main strength of the study was the inclusion of only women who had attended ANC at KNH for both the case and the control group. This enabled systematic follow up of their records on medical and medication data.

Major limitation encountered was how to directly correlate the adverse birth outcomes with the use of a specific medication.

Recall bias on drugs taken over the counter or self-medication was a also a limitation. These drugs could have easily been missed since they were subject to patient recall which can be biased despite the measures in data collection to minimize it.

CHARPTER 6: CONCLUSION AND RECOMMENDATIONS

Conclusion

Preterm birth was the most common adverse birth outcome at KNH (27.6%), followed by stillbirth (15.3%) and congenital malformation (7.14%). Among babies born with congenital malformations spina bifida was the most frequent (45.8%) followed by cleft palate (16.7%), polydactyl (8.3%), hydrocephalus (8.3%) and others like ectopic kidney, hydrops fetalis and complete face deformation (20.8%).

Maternal factors that could be associated with ADBOs include medical conditions and past obstetric history. Adverse birth outcomes of previous pregnancies and medical complications such as pre-eclampsia were associated with a high risk of ADBO of the current pregnancy. Most drugs were prescribed following the required guidelines. Majority of the women received drugs from category A, followed by category B, D and C respectively. A few drugs from category D (drugs with positive evidence of risk to the fetus) were prescribed. None of the FDA Category X drugs was prescribed. Use of certain medication like nifedipine, carbamazepine and magnesium sulphate were associated with risk of ADBO.

Recommendations

There is essential need for further research on safety of drug exposure during pregnancy. This can be done through establishment of pregnancy drug registries and large cohort studies to provide prospective data. Strategies and policies on prevention of maternal factors such as obstetric complications and chronic diseases like HTN, diabetes and HIV that contribute to ADBOs. Need for continuous review of treatment guidelines of conditions in pregnancy with recent, reliable, and appropriate available data. Campaign for increased pharmacovigilance and monitoring of all medications used during pregnancy will be very necessary.

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APPENDICES

Appendix 1: Kenyatta National Hospital ERC approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
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Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/124

3rd April, 2019

KENYATTA NATIONAL HOSPITAL APPROVED 03 APR 2019 KNH/UoN-ERC P.O. BOX 20723 - 00202 NAIROBI

Muthee Nelly Wambui
Reg. No.U51/7836/2017
Dept.of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Nelly

RESEARCH PROPOSAL: ADVERSE BIRTH OUTCOMES ASSOCIATED WITH DRUG USE IN PREGNANT AT KENYATTA NATIONAL HOSPITAL (P897/12/2018)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 3rd April 2019 – 2nd April 2020.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

Protect to discover

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy , UON
The Chair, Dept. of Pharmacology and Pharmacognosy, UON
Supervisors: Dr. Margaret Oluka, Prof. Faith A. Okalebo

Appendix 2: Consent form for participation in the study for both the case and the control group

Adverse birth outcomes associated with drug use in pregnancy.

Introduction

My name is Dr Wambui Muthee, a postgraduate student in the School of Pharmacy at the University of Nairobi. I am inviting you to take part in this research study. I would like to give you information that will help you decide whether or not to participate in this study. Feel free to stop me and ask any questions about the purpose of this study, any risks or benefits, what happens if you participate and anything else about the study that is not clear. Once I have answered your questions to your satisfaction, you may then decide to sign your name on this form to be in the study. It is also good to understand that the decision to participate in this study is voluntary; you are free to withdraw from the study at any time without giving a reason. Refusal to participate will not affect the services you are entitled to at Kenyatta National Hospital. I will give you a copy of this form for your record.

May I continue? YES/NO

This study has been approved by Kenyatta National Hospital-University of Nairobi Ethics and Research Committee protocol No…….

What is this research study about?

This study is being done to understand what kinds of medicines are used during pregnancy, practices during pregnancy and the outcome of the pregnancy.

What will I be asked to do if I decide to participate in this research study?

I will ask your permission to interview you, review your medical and ANC records and collect any other information about your pregnancy and medication use.

Are there any benefits to me if I decide to take part in this study?

Taking part in this study will not directly help you but it will help the hospital understand the types of medicines that are used during the pregnancy and some of the outcomes associated with medication use. This would help the hospital ensure the medicines are used effectively and in the best way possible and improve quality experience for future pregnant mothers preventing any harmful effects caused by drugs even you as a person has a chance to benefit in the future.

Are there any risks to my participation in this study?

I do not anticipate any risk to you by collecting information from you and your hospital records**.** I will keep everything you tell me as confidential as possible. To protect your privacy, your name will not be filled on the data collection instruments. For this study, you will be assigned a unique number that I will use to identify you in a password-protected database. All the records will be kept under lock and key and only I will be able to access and use it. The results from this study may be published or presented at professional meetings but your name will not be used or associated with the findings.

What procedures are involved in this study?

The study will involve interviewing you and reviewing your medical and ANC records. A data collection instrument will be used to collect information from your file.

What are my rights as a research study participant?

Your participation in this study is voluntary. Withdrawal or refusal to participate in the study will not affect in any way the treatment you are receiving or your hospitalization, both now and in the future.

Are there any costs or payments for participating in this study?

There will be no costs to you for taking part in this study. You will not receive money or any form of compensation for taking part in this study.

Who can I talk to if I have questions?

If you have questions about this study or the information in this form, please contact the person responsible for this research, Dr Wambui Muthee (Tel. +254 728 958 393) at the School of Pharmacy, University of Nairobi. If you have questions about your rights as a research participant, or would like to report a concern or complaint about this study, please contact the

Kenyatta National Hospital / University of Nairobi Ethics Review Committee (KNH–UoN ERC) Tel. 2726300 Ext 44355,Nairobi-Kenya, or E-mail: uonknh_erc@uonbi.ac.ke.

Do you have any questions that I can answer for you now? **YES/NO**

STATEMENT OF CONSENT

I confirm that I have read or had the consent information read to me, that outlines the nature of this study. The researcher has explained the study to me and answered my questions to my satisfaction. The risks and benefits have been explained to me. I understand that I will be given a copy of this consent form after signing. I understand that all effort will be made to keep my personal identity confidential.

I also understand that this is a voluntary exercise and I can withdraw from the study at any time if I choose.

By signing this consent form, I have not given up any of my legal rights as a research study participant.

I give my voluntary permission to take part in this study and allow access to my medical records.

Signature of Patient_____ today's date_____

Name of patient_____

Researcher's Agreement

I confirm that the participant has been given an opportunity to ask questions about the study, and all the questions have been answered correctly and to the best of my ability. I confirm that the participant has understood and knowingly given consent.

Researcher's

signature_____Date_____

You can contact any of following researchers at

DR MUTHEE NELLY WAMBUI
SCHOOL OF PHARMACY, UNIVERSITY OF NAIROBI
mutheenelly@gmail.com
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DR MARGARET OLUKA
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0722 604 216

PROFESSOR FAITH .A. OKALEBO

SCHOOL OF PHARMACY, UNIVERSITY OF NAIROB

0737434204

Appendix 3: Data collecting form

ADVESE BITHOUTCOMES ASSOCIATED WITH DRUG USE IN PREGNANCY AT KENYATTA NATIONAL HOSPITAL

DATE: ☐ SERIAL NO: CASE ☐ CONTROL ☐

I. SOCIODEMOGRAPHIC DATA

1. AGE (YRS): ☐

2. MARITAL STATUS

☐ A SINGLE ☐ B MARRIED ☐ C SEPARATED/DIVORCED ☐ D WIDOWED

3. LEVEL OF EDUCATION

☐ A NONE ☐ B PRIMARY ☐ C SECONDARY ☐ D COLLEGE

4. OCCUPATION

☐ A UNEMPLOYED ☐ B SELF EMPLOYED ☐ C SALARIED EMPLOYMENT

II. PAST OBSTETRIC HISTORY

1. PARITY……..GRAVIDA……

NO	YEAR	PLACE OF DELIVERY	SEX	TYPE OF DELIVERY	0UTCOME

III. INDEX PREGNANCY

1. LMP ____/ /_____ EDD ___/ /_____ GESTATION _____Weeks

2. PREGNANCY

A PLANNED B UNPLANNED

3. INTERPREGNANCY INTERVAL (last delivery to LMP)

A < 6 MONTHS B 6 – 12 MONTHS C 12 – 24 MONTHS D >24 MONTHS.

4. FAMILY PLANNING USE PRIOR TO THIS PREGNANCY

A YES B NO

5. IF YES, SPECIFY METHOD _____

6. HABITS DURING PREGNANCY

A ALCOHOL B CIGARETTES C PICA D OTHERS (SPECIFY)

IV ANTENATAL CARE

1. ATTENDANCE

A YES. B NO

3. NUMBER OF VISITS ☐

4. GESTATION AT FIRST ANC VISIT …… actual weeks

5. ANTENATAL PROFILE

		YES	NO	RESULT
A.	Haemoglobin Level			
B	Blood Group ABO type			
	RHESUS			
C	VDRL			
D	HIV STATUS			
E	Urinalysis			

6. OTHER TESTS DONE

a) Ultrasound A YES B NO If yes indication …….

b) Laboratory test A YES B NO If yes indication …….. .

7. COMPLICATIONS EXPERIENCED DURING INDEX PREGNANCY

		YES	NO
A	ANAEMIA		

B	P.V BLEEDING		
C	HYPERTENSION		
D	URINARY TRACT INFECTION		
E	MALARIA		
F	FEBRILE ILLNESS		

8. HOSPITALADMISSION DURING THIS PREGNANCY?

[A] YES [B] NO

9. IF YES, WHY _____.

10. HEALTH EDUCATION AND COUNSELLING

	YES	NO
NUTRITION		
DANGER SIGNS		
LABOR AND DELIVERY		
FAMILY PLANNING		

11. DRUGS AND NUTRIENT SUPPLEMENTS ADMINISTERED

DRUGS	A= YES /	SPECIFIC DRUG	INDICATION	

	B = NO	NAME/DOSAGE/DURATION		TRIMESTER
HAEMATINICS				
ANTIBIOTICS				
ANTIHYPERTENSIVES				
HAART				
STEROIDS				
ANTACIDS				
OTHERS (specify)				

V NUTRITIONAL ASSESSMENT

1. ANTHROPOMETRIC MEASURES

a. MATERNAL WEIGHT _____ Kgs

b. MATERNAL HEIGHT _____ cms

VI DELIVERY

1. DATE OF ADMISSION _____/__/_____

2. DATE OF DELIVERY ____/__/_____

3. GESTATION AT DELIVERY _____WEEKS

4. MODE OF DELIVERY

A SVD B C/SECTION C ASSISTED VAGINAL D BREECH

5 .IF C/SECTION, INDICATION…….

6. LABOR ONSET

A B

SPONTANEOUS INDUCTION

7. IF INDUCTION, INDICATION ……

8. INTRAPARTUM COMLICATIONS

A YES B NO

9. IF YES, SPECIFY _____ .

VII FETAL OUTCOME

1. INFANT SEX ☐ MALE ☐ FEMALE

2. INFANT APGAR SCORE AT 5 MINUTES_____/5MIN

3. INFANT BIRTH WEIGHT _____GRAMMES

4. OUTCOME AT BIRTH A NORMAL B STILL BIRTH

C PRETERM D CONGENITAL MALFORMATION

IF D SPECIFY THE CONGENITAL MALFORMATION:

6. ADMISSION TO NBU A YES B NO