MEDICATION-RELATED RISK FACTORS FOR PRETERM BIRTH IN KITUI COUNTY, KENYA

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Reg No: U51/64043/2013

A thesis submitted in partial fulfilment of the requirements for award of a Master of Pharmacy degree in Pharmacoepidemiology and Pharmacovigilance of the University of Nairobi

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November, 2014

DECLARATION

This is my original thesis. It has not been submitted for award of a degree or any other award in any University.

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To thelate**Prof. Kurt Frùchtl**

ACKNOWLEDGEMENT

I would like to express my appreciation to my supervisors for their direction and guidance. I am indebted to Dr MN Oluka and Prof C K Maitai for their guidance. I would also like to express my deep gratitude to Dr Rose J Kosgei for her patient guidance, enthusiastic encouragement and prompt useful critiques of this work.

I am also grateful to, Dr. F A Okalebo and to my classmates, Mulwa, Seth, Susan, Margaret, Makori, Kiogora, Annie, Lucy, Christabel and Evans for their understanding and patience.

Finally, I wish to thank my family, Christine, Watson and Sandra for their support and encouragement, and for persevering throughout the period of my studies.

The funding is from the Linked-Strengthening Maternal, Newborn and Child Health Research Training in Kenya. The grant is linked to Partnership for Innovative Medical Education in Kenya (PRIME-K). The project described was supported by Award Number 5R24TW008907 from the US National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the US National Institutes of Health

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Abbreviations and Acronyms

APH	Antepartum haemorrhage
ART	Antiretroviral therapy
ARV	Antiretroviral medication
AZT	Zidovudine
BMI	Body mass index
COC	Combined oral contraceptives
COX	Cyclooxygenase enzyme
HIV	Human immunodeficiency virus
KDH	Kitui district hospital
MCH	Maternal and child health clinic
NSAID	Non-steroidal anti-inflammatory medication
OBA	The outcome based approach programme
OIs	Opportunistic infections
OR	Odds ratio
OTC	Over the counter medicine
PIs	Protease inhibitors
PMTCT	Prevention of mother to child transmission
SSRI	Selective serotonin reuptake inhibitors

Operational Definition of Terms

Medication

Any substance used in treatment, cure, prevention or diagnosis of disease or to enhance general well-being

Preterm labour

Presence of uterine contractions of such frequency and intensity as to cause dilatation of the cervix prior to 37^{th} completed weeks of gestation

Preterm birth

Birth of a baby as a result of premature labour prior to 37 completed weeks of gestation

Herbal remedy

A medication prepared from plants or parts of plants and/or plants extracts intended for treatment of illness, remedying of symptoms or prevention of illness, which is not prescribed by a registered medical professional.

Herbal use

Any report of use of herbal remedies during pregnancy

Self-medication

Acquisition and use of any medicine without supervision of a registered medical practitioner

Prescription medication

Any medication that is used after a valid prescription is issued by a registered medical practitioner

Immediate post-partum mother

Mother of a neonate 24 hours old or less

ABSTRACT

Introduction: Premature infants contribute substantially to infant morbidity and mortality especially in low resource areas. Understanding the factors that contribute to pre-mature labour in these areas would greatly influence infant morbidity, mortality and reduce paediatric healthcare costs.

Objective: To investigate the use of herbal remedies, self-medication and prescription medications in pregnancy as risk factors for preterm birth in Kitui County among the immediate post-partum mothers.

Methods: An unmatched case control (1:4) study was conducted in Kitui and Mwingi District Hospitals in Kitui County. A total of 560immediate postpartum mothers were sampled of which 107 were mothers with preterm birth (Cases) whereas 453 were mothers with term birth (Controls). Retrospective review of medical records was conducted to collect data pertaining to medical history and use of prescription drugs during pregnancy. Structured questionnaires were administered to mothers to collect data on demographic characteristics, socio-economic status, self-medication practices and use of herbal remedies. Data was analyzed to describe the distribution of demographic variables between cases and controls using the Pearson Chi square test. Logistic regression was used to test for association between various predictors such as self- medication, use of herbal remedies and prescription drugs and the main outcome variable, pre-term birth. Multivariate modelling was used to identify the risk factors for preterm birth while controlling for confounding.

Results: Predictors of preterm birth were: Herbal use in the 1st trimester lasting two to five days (OR=11.10 [4.34-28.41], p<0.01), herbal use in the 1st trimester lasting six to 10 days (OR= 44.87 [4.99-403.87], p<0.01) and herbal use in the 2nd trimester for six to 10 days (OR= 16.43 [4.53-59.57], p<0.01). Self-medication with the following medications in the 1st trimester for 2 to 5 days: Chlorpheniramine (OR=2.64 [1.22-19.65], p=0.012), Paracetamol (OR=1.34 [1.09-6.73], p=0.043), Amoxycillin (OR=5.72 [1.60-20.84].

Factors were associated with lower risk of preterm birth: Amoxicillin prescribed in the 1st trimester (OR=0.09 [0.01-0.66], p=0.043), ferrous sulphate, 2nd trimester for more than 31 days (OR=0.22 [0.13-0.35], p<0.001), folic acid from 2nd trimester for more than 31 days (OR=0.20 [0.12-0.34], p=0.02) and FDA category A medications (OR=0.27 [0.07-0.42], p=0.001).

Conclusion and Recommendations: Use of herbal remedies and self-medication in pregnancy is common among the women in Kitui County and it is a major risk factor for preterm birth. Prescribers should be sensitized on safe medication use in pregnancy and prompt management of maternal infections. Folic acid and ferrous sulphate supplementation throughout pregnancy should be strengthened.

CHAPTER ONE: INTRODUCTION

1.1 Background to the study

Preterm labour is defined as the presence of uterine contractions of such frequency and intensity as to cause dilatation of the cervix prior to 37 completed weeks of gestation. Childbirth before 37 complete weeks of gestation is considered preterm birth(1). Preterm birth is associated with increased infant mortality and morbidity. Children born prematurely are also at a higher risk of long-term mental and physical disability, adversely affecting their quality of life (2-4). Moreover, a premature infant requires lengthy hospital stay, close monitoring and expensive management, substantially increasing the overall paediatric medical costs. This may contribute a large portion to the overall cost of health care.

The term medication is used to refer to any substance, other than food, that is used in the treatment, cure, prevention or diagnosis of disease or otherwise to alter a physiological process. Medication use in pregnancy is one of the known risk factors for preterm birth. The risk increases with the number of individual medications, duration of use and early timing (4-7). Exposure to medications in the first trimester may compromise organogenesis in the foetus, leading to congenital malformations. During the second and third trimesters, medications may affect growth and development of the foetus or cause direct toxicity to the foetal organs and tissues. The pattern of use of medicines during pregnancy, therefore, has a direct association with adverse pregnancy outcomes, including preterm birth.

Prescription of medications in pregnancy is a delicate balancing act. As a rule, medications should be prescribed in pregnancy only if the expected benefits to the mother exceed the expected risks to the foetus. The FDA classification of medications use in pregnancy is useful in making a decision on which medicines to use and the ones to avoid in pregnancy. It serves as a handy guide to prescribers in order to enhance medicine safety in pregnancy. Medications used in management of chronic illnesses continue to be used throughout pregnancy. Hypoglycaemic agents, antihypertensives, antipsychotics, and anticonvulsives are routinely used to control maternal illness and cannot be discontinued on account of pregnancy. Chronic

infections such as the Human Immunodeficiency Virus (HIV) and tuberculosis must also be treated regardless of pregnancy status.

Mothers are also routinely medicated because of pregnancy induced health problems. Notable is the common problem of hyperemesis gravidarum (morning sickness) during the first trimester. A wide range of medications is commonly used to manage this condition: Antihistamines, dopamine antagonists and vitamins.Less commonly used, but also significant is ondansteron, a serotonin 5-HT3 receptor antagonist (8, 9). Supplements containing folic acid, ferrous sulphate and mebendazole are prescribed to pregnant mothers as a standard routine of care.

Self-medication is using medicines to alleviate symptoms of illness or condition without a valid prescription from a registered medical practitioner. This is usually common with Schedule IV Medications, also known as Over-the-Counter medicines. Pain medicines, nasal decongestants, antimalarials, antihistamines and antacid preparations are commonly acquired over the counter. Some of these medications may not be safe for use in pregnancy (8).

Herbal remedies are defined as medicinal products containing aerial or underground parts of plants, or combinations of plant materials either in their crude form or as a refined plant preparation. These products may also contain organic or inorganic ingredients that may not be of plant origin, such as honey (9). The use of herbal remedies in Kenya is in an upward trend. In addition to the traditional herbalists in the rural areas, many herbal practitioners are setting up shops in the urban areas as well. This could have led to an increasing number of pregnant mothers accessing and using herbal remedies. Without doubt, some of the ingredients in herbal preparations may contribute to higher incidence preterm birth.

Compounding the problem of risky medication exposure during pregnancy is a high prevalence of medication misuse. Misuse is use of any medication without taking into account the correct indication, dose, route of administration, duration of treatment, dispensing and adherence to treatment. Prescription only medications are commonly available over the counter without prescription. Many medication outlets are neither manned by qualified pharmacists nor are they duly registered.

Prescribers may not always adhere to guidelines in prescribing for pregnant mothers thereby prescribing unsafe medicines in categories C, D, and X of the Food and Drug Administration (FDA)categorization(12).The FDA has established five categories of medications based on their potential risk to cause foetal harm. : **Category A**are medicationswhere adequate studies have failed to show any evidence of foetal harm in the first trimester, and there is no evidence of risk to the foetus in the second and third trimesters. In **Category B, a**nimal studies have failed to show any risk to the foetus but no data exists on the use of the medication in pregnant women. For **Category C** animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans but the medication may still be used in pregnant women if the benefits clearly outweigh the risks. **Category D medications are those where** there is positive evidence of human foetal risk based on adverse reaction data from investigational post-marketing surveillance. For **Category X, s**tudies in animals or humans have demonstrated foetal abnormalities and/or there is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the medication in pregnant women clearly outweigh potential benefits. Unclassified medications were labelled **Category N.**

1.2 Conceptual framework

A conceptual framework linking various exposures with pre-term birth which is the main outcome of this study is shown in figure 1.1.Low socio-economic status is associated with poor access to quality health care services. In a low resource setting, the communities are unable to invest substantially in healthcare and public health interventions. In turn, inaccessibility to proper healthcare leads to ineffective management of maternal infections when they arise. Due to the inflammatory process inherent in infective conditions, the risk of preterm premature rapture of membranes increases, increasing the risk of preterm birth. Chronic illnesses, such as hypertension and diabetes are known risk factors for preterm birth. Due to poor access to healthcare, these disease may not be managed adequately predisposing the mothers to higher risk of preterm birth compared to mothers who are managed promptly and effectively. Herbal remedy use, self-medication and prescribed medications introduces xenobiotics that may be harmful to the foetus or may alter the mothers'

physiological processes so as to increase the incidence of preterm birth. For instance, medications that increase the level of circulating inflammation mediators may facilitate preterm premature rapture of membranes. On the other hand, medications with an anti-inflammatory activity may prove protective against preterm birth.

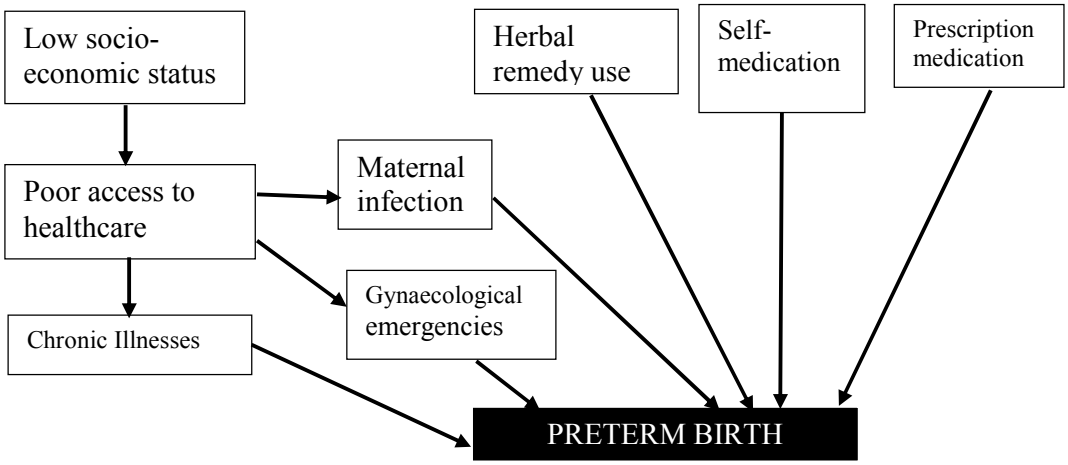

Figure 1.1: **Conceptual framework**

1.3 Problem Statement

Premature infants contribute substantially to infant morbidity and mortality especially in low resource areas. In addition, the cost related to care of preterm infants is very high. Infants may spend many months in the hospital undergoing expensive management. Understanding risk factors posed by medicines is crucial in formulating strategies to reduce the incidence of preterm birth. It would also inform both the health care workers and mothers to avoid medication use patterns that may contribute to preterm birth.

In the recent past, the Kenya Ministry of Health and its partners have put a lot of emphasis on maternal-child health. Attainment of the fourth Millennium Development Goal that focuses on reduction of infant mortality will also require studies into all aspects of child health to inform intervention guidelines in standard paediatric healthcare.

The problem of medication use as a risk factor to preterm birth is real mainly due to widespread irrational use of medicines. Use of herbal remedies in pregnancy is also growing and evidence of safety of herbal remedy in pregnancy is scarce. A study of medication related risk factors for preterm birth, focussing on both conventional medicines and herbal remedies in Kitui County is therefore justified.

1.4 Purpose of the study

To investigate the medication-related risk factors for preterm birth in Kitui County

1.5 Research Question

What are the medication-related risk factors for preterm birth among the immediate post-partum mothers in Kitui County?

1.6 Null Hypothesis

There is no difference in medication related risk factors between immediate postpartum mothers who had preterm term birth compared to those who had term birth in Kitui County, 2014

1.7 Broad Objective

To investigate medication related risk factors for preterm birth among the immediate post-partum mothers in Kitui County.

1.8 Specific Objectives

1. To determine the use of herbal remedies during pregnancy among the immediate post-partum mothers.
2. To determine self-medication practicesin pregnancy among the immediate post-partum mothers.
3. To determine the use of prescription medications in pregnancy among the immediate post-partum mothers.

1.9Study Justification

Infant mortality is a major health problem that required concerted effort to reduce. Preterm birth contributes substantially to infant mortality and morbidity. Premature

infants not only have a lower chance of survival than babies born at term, but they also are more likely to experience long term physical and mental developmental problems. Regions of poor socio-economic status, such as Kitui County, are particularly vulnerable because they report higher incidences of preterm birth than more economically well-off regions. Moreover, poor access to advanced healthcare means that babies born preterm have an even lower chance of surviving and leading a good quality life.Therefore, prevention of preterm birth remains a key intervention in reducing infant mortality and morbidity. A study seeking to identify risk factors for preterm birth is therefore justified.

CHAPTER TWO: LITERATURE REVIEW

2.1 Overview of Preterm Birth

Preterm labour is defined and presence of uterine contractions of such frequency and intensity as to cause dilatation of the cervix before 37 complete weeks of gestation (1). Worldwide, approximately one in 10 babies is born prematurely. This translates into about 15 million premature infants annually (11), making preterm birth a major worldwide paediatric health problem. It is estimated that in developed nations, one third of infant mortality is related to preterm birth (12). Children born prematurely have a higher risk for sensory deficits, respiratory illnesses and learning disability compared to those born at term (13).

Sub-Saharan Africa carries a disproportionately heavier burden of death and disabilities attributed to preterm birth. Estimates of incidence of preterm birth vary widely but are higher than in the developed world (13), averaging about 12% (14) and rising to as high as 25% (15). Unlike the developed nations where most preventable risk factors are easily controlled, mothers in Africa still have to contend with preventable causes of preterm birth.

2.2 Classification of preterm birth

All babies born alive before 37 complete weeks of gestation are classified as premature. The babies are classified by the degree of prematurity as shown in table 1 below. In normal human foetus, several organ systems achieve maturity in the gestation age between the 34^{th} and 37^{th} week. Therefore, children born before the 37^{th} week have immature organ systems, notably the lungs. Premature babies do not have adequate surfactant in their lungs preventing them from remaining expanded between breaths (16). Generally, adverse neonatal outcomes reduce as gestational age increases. Mortality and morbidity of preterm babies gets proportionately higher as the gestational age reduces. Further, for each gestational age, heavier babies are at reduced risk of morbidity and mortality compared to lighter babies (17). Classification of preterm infants on the basis of degree of prematurity is shown in table 2.1.

Table 2.1: Classification of preterm birth by gestational age

Gestational age at birth	Classification
Less than 28 weeks	Extreme preterm
More than 28 weeks to 32 weeks	Very preterm
More than 32 to 37 weeks	Moderate to late preterm

2.3 Aetiology of preterm birth

Preterm birth is a syndrome of multiple patho-physiological pathways and many a times the causal mechanism is not identified. Consequently, an attempt to classify the aetiology of preterm birth groups them into three categories, namely, medically indicated, preterm premature rapture of membranes and idiopathic preterm labour (18).

2.3.1 Medically indicated preterm birth

Medically indicated preterm births account for about a third of all preterm births (19). Maternal and foetal indications may warrant medical intervention to deliver a premature baby. Such conditions as preeclampsia, uterine growth restriction and all conditions that constitute ischaemic placental disease usually lead to medically indicated premature delivery. Severe trauma and shock or acute medical conditions that could cause foetal abruption also usually lead to indicated preterm birth. Mothers who suffer from progressive illness such as cardiac disease may suffer grievous harm by carrying the pregnancy to term. To preserve the well-being of the mother, preterm delivery is indicated (20, 21). There is also sufficient evidence that babies with congenital malformations are twice as likely to be born prematurely compared to infants without congenital malformations (22).

2.3.2 Preterm premature rapture of membranes (PPROM)

Premature rapture of membranes (PROM) refers to a mother presenting with rapture of membranes before the onset of labour. When this occurs before the 37complete weeks of gestation, it is referred to as preterm premature rapture of membranes (PPROM). At term, apoptosis and activation of catabolic enzymes combined with the mechanical action of contacting uterine wall forces the membranes to rapture. However, inflammation of membranes and infection could lead to PPROM. PPROM is estimated to be the cause of about 25% of all the preterm births (23).

2.3.3 Idiopathic preterm birth

About two-thirds of all preterm births are spontaneous, and may not have an obvious cause (19). However, with an exhaustive evaluation plan, some of the causes may be identified. It is quite possible that medications and herbal remedies may be responsible for a significant proportion of these idiopathic preterm births. More work therefore needs to be done to identify any medication related risk factors so as to provide healthcare workers with information required in strategy development to reduce the incidences of preterm birth (24).

2.4 Risk factors for preterm birth

2.4.1 Environmental and socio-economic factors

Low social-economic status is an important risk factor for preterm birth in Sub-Saharan Africa. This is because other controllable risk factors for preterm birth are associated with low income. Poor maternal nutrition is a significant risk factor for preterm birth. In fact, incidence of preterm birth has been known to rise in the months of drought due to poor access to nutrition (25). Moreover, low maternal body mass index (BMI) is an independent determinant of preterm birth (26).

Low social-economic status is also linked to risky maternal lifestyles, such as tobacco use and alcohol consumption, both of which are associated with a higher incidence of preterm birth (27). Mothers in low income settings undergo stressful situations, a significant psychological predisposing factor (28). The burden of preterm birth is higher in settings that have inadequate public health intervention. Weak disease surveillance and control systems allow for frequent disease outbreaks. Since poor access to quality healthcare occurs as a consequence of low socio-economic status, these two factors combine to increase the rate of preterm birth (15).

Kenya suffers from high rate of teenage pregnancy and early marriages. Reports of child brides in some communities are frequent. Girls are thus exposed to sexual debut at a young age (29) and perpetuation of the circle of poverty. Pregnancy occurring within two years of menarche is high risk for adverse outcomes, including preterm birth (30). Other studies report that poor education and single status are risk factors for preterm birth (31). As shown in figure 2.1 below, low socio-economic status influences frequency of preterm birth through a web of pathways, some forming a vicious cycle.

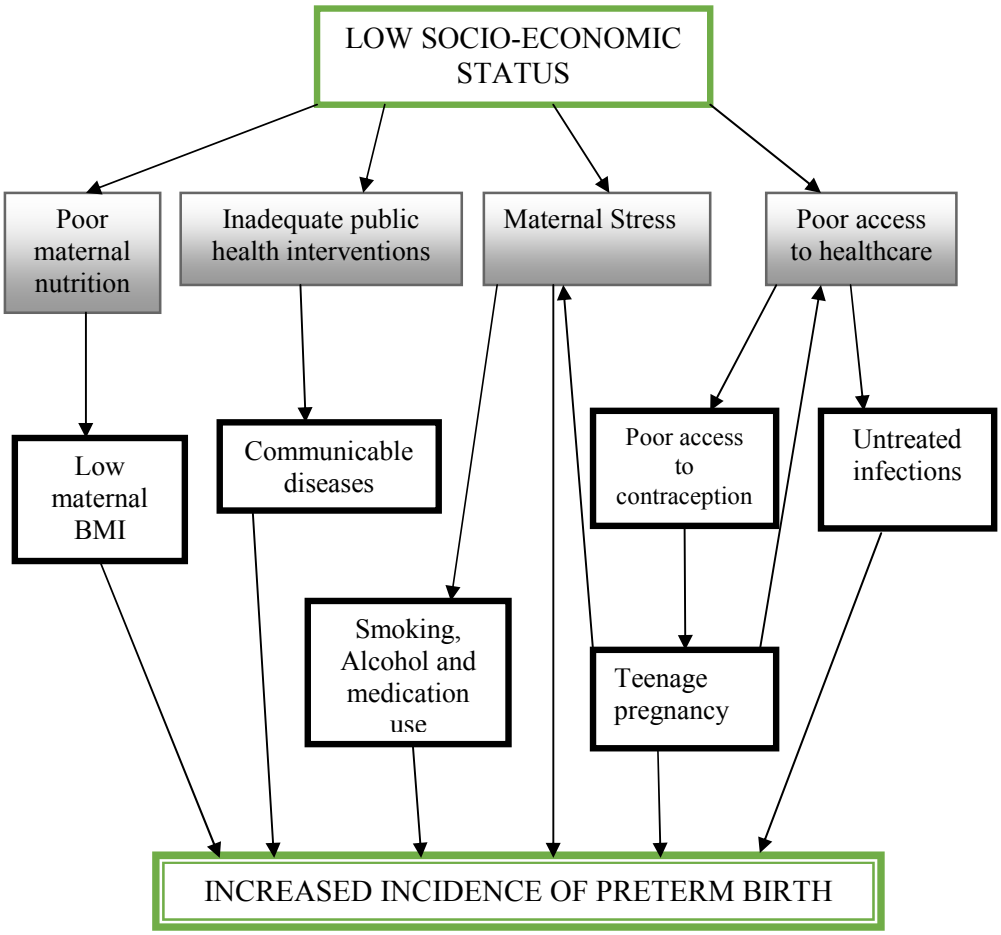

Figure 2.1: Low social-economic status as a risk factor for preterm birth

2.4.2 Maternal illness

During pregnancy, the foetus is completely dependent on the mother and the life and health of the foetus is tied to that of the mother. Any maternal illness is likely to affect the health of the foetus negatively. It is therefore important that maternal health is managed effectively. A number of maternal illnesses have been linked to increased incidence of preterm birth. Chronic illnesses such as Diabetes mellitus, kidney disease, hypertension and HIV infection have been shown to result in higher incidence of preterm birth. It is interesting also to note that the prevalence of some of these diseases are associated with older women, which compounds the problem as older age, of 35 years or more, is an independent risk factor (28,29).

Many parts of Kenya are malaria endemic zones. Others, especially the highland areas, are known to experience malaria epidemics. Malaria in pregnancy burden is still a problem in some parts Kenya and is associated with higher risk of preterm birth (34). This is despite efforts that have been made to reduce malaria in pregnancy. Initiatives and Presumptive Malaria Treatment for pregnant mothers, provision of cheaper malaria medications and diagnostic kits have helped but significant proportion of the population is still affected. Other common conditions such as periodontal disease (26) have also been shown to be associated with preterm birth.

Routine early detection and management of infections protects against preterm birth. Bacterial infections of the placenta and chorioamnionitis can lead to production of prostaglandins through the inflammatory process leading to ripening of the cervix and predisposing to preterm birth (35). Not surprisingly then, sexually transmitted infections (STIs) including *Chlamydia trachomatis*, gonococcal infections, syphilis and bacterial vaginosis(36) trigger an inflammatory response that leads to production of cytokines which raise the level of prostaglandins. Screening of mothers for any STIs and prompt treatment should therefore form part of the strategy aimed at reducing the frequency of preterm birth.

2.4.3 Gynaecological risk factors

Gynaecological factors are important as predictors of preterm birth and can be used to identify mothers most at risk. Mothers most at risk should be monitored closely to reduce the frequency of adverse pregnancy outcomes. Antenatal clinic visits should be encouraged for all mothers and especially those that are at risk. Such visits have

been shown to be protective against preterm birth (37), probably due to early identification and management of some of the infections and disorders.

Obstetric and gynaecological history plays an important role in predicting the incidence of preterm birth. History of preterm birth and previous induced abortion are strongly associated with preterm birth. Other conditions such as preeclampsia, ecclampsia, antepartum haemorrhage and placenta praevia put the mother at risk for preterm birth (38). Polycystic ovary syndrome is also a gynaecological problem associated with preterm birth.

Uterine fibroids are benign neoplasms of the uterine smooth muscle. It is estimated that fibroids occur in 30% of women between thirty and forty year of age, rising to 50% by the age of fifty (39). Most uterine fibroids are asymptomatic. They have been associated with poor fertility and increased frequency of preterm birth (40).

2.4.4 Medication-related risk factors for preterm birth

Medication use in pregnancy is common and is associated with many risks and it must therefore be carefully balanced to maximise benefits and minimise the potential risks. Metformin is commonly used in management of women with gestational diabetes mellitus and in combination with clomiphene in the management of clomiphene-resistant polycystic ovarian syndrome. In both cases, maternal and pregnancy outcomes seem to improve with the use of metformin (41). Glibenclamide use to control diabetes mellitus in pregnancy has not been associated with increased incidence of preterm birth (42). Clomiphene, like all fertility treatments is associated with multiple pregnancies, which is an independent risk factor for preterm birth.

Hormonal therapy in women of childbearing age is also common with hormonal contraception being the most prevalent form of contraception in use. Medroxyprogestrerone Acetate (MPA) is used both in combined oral contraceptives and contraceptive depot injections. Intrauterine inflammation, a common pathway of preterm birth, is associated with decreased serum progesterone levels, therefore MPA use may be protective against preterm birth (43).

Pain medications, particularly Non-Steroidal Anti-Inflammatory Medications (NSAID) are probably the most commonly used medications for self-medication.

People take NSAIDS to relieve fever, headaches, backaches, toothaches, sore throat and menstrual pains. Paracetamol is very commonly used in popular medicine brands, either on its own or in combination with aspirin and caffeine. Studies show that paracetamol may be a risk factor for preterm birth (44). Most NSAID are non-selective cyclooxygenase (COX) inhibitors, inhibiting both COX1 and COX2. There is evidence that prostaglandins are involved in the expulsion of preterm foetus, therefore the NSAIDS, such as acetylsalicylic acid and indomethacin, by reducing the inflammatory process may protect against preterm birth (45). Selective COX2 inhibitors such as nimesulide, have however, been linked to constriction of ductusarteriosus and oligohydramnios(46).

Mothers who suffer from epilepsy have a slightly elevated risk of adverse pregnancy outcomes compared to women without epilepsy. Exposure to antiepileptic medications may further increase that risk (47). Benzodiazepines use in pregnancy has been associated with a very high risk of preterm birth, up to 7 fold increase compared to mothers not on benzodiazepines (48). Another common anticonvulsant that is routinely used in pregnancy is phenobarbital. It is routinely included in standard therapy for the management of threatened abortion. It has been thought to reduce periventricular haemorrhage in preterm infants when given to mothers prior to preterm birth (49). But a systematic review of the studies conducted on phenobarbital concluded that its use does not protect the premature infant either from periventricular haemorrhage or neurological disability in childhood (52). It does succeed, however, in sedating the mothers and probably increasing the chance of adherence to complete bed rest.

The first trimester of pregnancy is often characterized by hyperemesis gravidarum (morning sickness) that is characterised by bouts of nausea and vomiting, a very unpleasant experience for most mothers. Therefore, use of remedies for this condition is very common. In the 1960's, thalidomide was marketed to manage this problem. It was certainly effective in reducing nausea and vomiting, so effective, in fact, that it is in use for nausea associated with cancer chemotherapy. However, it resulted in foetal tragedy with numerous miscarriages and neonatal deaths were linked to the use of thalidomide in pregnancy. Many infants that survived were left disabled from severe forms of phocomelia(51). In the present day, antihistamines are frequently prescribed

for this problem. Meclizine is combined with caffeine in fixed dose combination and frequently prescribed for morning sickness (52). It is also widely available for self-medication. Doxylamine and diphenhydramine are less frequently used to control nausea but are common ingredients in cough preparations. Given that a large proportion of women use antihistamines, there is need for a study on their safety in pregnancy especially in the local population (53).

Broad spectrum antibacterial medications are thought to alter the vaginal flora predisposing mothers to preterm birth (54). It is plausible, though, that generally, antibiotic use may reduce prevalence of bacterial infections and the associated inflammation process, protecting against preterm birth.

HIV infection is associated with reduced immunity leading to increased frequency and severity of Opportunistic Infections (OI). This makes HIV disease and independent risk factor for adverse pregnancy outcomes, including preterm birth (55). HIV chemotherapy involves the use of regiments of usually three antiretroviral medications (ARV). Pregnant mothers who are HIV infected are usually put on a cocktail of two or three antiretroviral medications in a bid to reduce HIV vertical transmission risk. Protease inhibitors (PI) tend to be used in second-line antiretroviral therapy (ART). Therefore, advance disease may be a confounder in the association between PI and preterm birth (33). Thankfully, Zidovudine and Nevirapine, commonly used in pregnancy have not been linked to preterm birth. Other medication-related risk factors for preterm birth include tricyclic antidepressants (56) and, not surprisingly cancer chemotherapeutic agents (57) due to their aggressive destruction of rapidly dividing cells of the foetus.

Herbal remedies contain many constituents some of which are biologically active. Plant parts contain many phytochemicals, including carbohydrates, glycosides, sterols, flavonoids, tannins, and alkaloids (8). There is need for studies on the effects of herbal remedies on pregnancy outcomes and specifically preterm birth.

2.5 Diagnosis of preterm labour

In local clinical setting, it is usually difficult to distinguish preterm labour and false labour. Use of clinical laboratory test to predict preterm labour may therefore be useful. Foetal fibronectin is an important biomarker and is gaining prominence in

diagnosis of preterm labour. Its presence in cervical and vaginal secretions indicates a high risk of preterm birth. Cervical sonography has also become a useful tool in assessing cervical incompetence at or before 24 weeks of gestation (58). Elevated inflammation biomarkers in the vaginal fluid such as interleukin-6 can also be used to predict preterm birth. Still, diagnosis of preterm labour is complex and requires diligence and skill.

2.6 Prevention of preterm labour

Due to the adverse outcomes of preterm birth, prevention of preterm birth remains an important measure in obstetric care. Public health strategies are important in reducing incidence of preterm birth especially in low socio-economic settings.

Prevention of preterm labour in the clinical setting is focussed on treating individual mothers who present with symptomatic preterm labour. Though this method in itself does not lead to significant reduction on preterm deliveries, it affords the health professionals time to intervene with antenatal steroids and to refer the mother to a better equipped health facility if need be. This reduces the incidence of infant mortality and morbidity (59).

During pregnancy, avoidance of risk factors such as smoking and alcohol consumption greatly reduces incidence of preterm labour. Knowledge of other common risk factors, such as medication related risk factors would significantly reduce the incidence of preterm labour. Attendance of the antenatal clinic where maternal education and early clinical intervention is done is another effective method. Mothers are educated on proper nutrition, avoiding stressful situations, hygiene and sanitation to reduce frequency and severity of maternal infections.

2.7 Management of preterm labour

Clinical management of preterm labour is symptomatic rather than management of causal factors. However, many medical interventions to manage preterm labour do not result in plausible success. Use of progesterone, for example, to prevent preterm labour in high risk groups has about a 30% success rate (60). Referral of pregnant

women to a health facility with capacity for adequate perinatal care in terms of medical equipment and specialised personnel does improve infant survival.

Tocolysis is a common practice in local clinical setting. A variety of tocolytics with varied modes of action are employed. Commonly used are betamimetics such as salbutamol. Oxytocin antagonists, calcium channel blockers, nitrous oxide donors and prostaglandin synthesis inhibitors are also routinely used. Tocolysis, however, in as much as it affords longer latency and fewer births within 48 hours of administration to allow for steroid therapy, it does not improve perinatal mortality. In fact, it is associated with lower APGAR scores at 5 minutes in the newborn(61).

2.8 Identification of medication related risk factors for preterm labour

In the prevention of any medical condition, it is important to identify the individuals who may be at an increased risk than others. In understanding the risk factors, an opportunity is availed to proactively develop strategies to reduce the occurrence of the problem. Medication related risk factors for preterm birth are best identified in the context of the population. This is so because medication use patterns differ from region to region and is affected by a multiplicity of factors. Health seeking behaviour also differs regionally affected by factors such as socio-economic indicators, accessibly and cultural practices. Use of alternative remedies, such as herbal medicines, and health services also follows a similar pattern.

CHAPTER THREE: METHODOLOGY

3.1 Study Design

The study was a non-matched hospital-based case control study comparing medication use in pregnancy between immediate postpartum mothers with preterm birth (cases) and immediate postpartum mothers with term birth (controls) at the ratio of one case to four controls (1:4). A case control design was deemed best to answer the objectives of the study because preterm birth is a rare outcome. The ratio of 1:4 is justified because preterm birth is relatively infrequent, and therefore, to increase statistical power, a large number of controls were needed.There was also a limit to the number of potential cases and a fixed study time.

3.2 Study setting

The study was conducted in Kitui County, Kenya. Kitui County is located in the South of the former Eastern Province. It is a semi-arid region with sporadic rainfall, which impacts negatively on subsistence farming, which is the major economic activity. This county was selected for this study because none of the studies reviewed have been conducted in this region on risk factors for preterm birth. It was also important because the cultural practices of the people in this region include use of herbal remedies. It has two major urban centres namely, Kitui and Mwingi. Kitui and Mwingi District hospitals are the two largest public hospitals in the county.

Kitui District Hospital is a level 4 medium capacity hospital with 200 beds and 44 neonatal cots. It is reputed to have one of the best run Newborn Units in the county. The Outcome Base Approach (OBA) programme, that reimburses the hospital the cost of maternity services for every cardholder makes it a preferred choice as a maternity services provider in its catchment area before the presidential decree of free maternity services of June 1st, 2013 in all public health facilities.

Kitui District hospital serves the Eastern parts of the county and manages up to 300 deliveries a month. It also serves as a referral hospital for the area with a population that has limited access to healthcare due disadvantaged socio-economic and infrastructural status. Moreover, the hospital is a good representation of the middle level hospitals, which are the majority in Kenya, handling the largest burden of

disease in the population. Mwingi District Hospital is a level 4 hospital in Kitui County. It is a medium capacity hospital with about 170 beds. It serves mainly the Western part of the county. The study was carried out in the maternity and newborn units of the two hospitals between May and August, 2014. Maternal prescription records are contained mainly in the Mother and Child Booklet that is usually in the custody of the mother. Other data elements are captured in paper based Maternity register and individual patients' files.

3.3 Study population

The study was carried out among immediate postpartum mothers who consented and were being cared for in Kitui and Mwingi district hospitals in 2014. Women less than 18 years of age were considered to be emancipated adults and were therefore included in the study.

Inclusion criteria and exclusion criteria

Immediate post-partum mothers who had a preterm birth (delivery at less than 37 completed weeks of gestation) were included as cases while those who had term birth were included as controls. Very sick or unconscious mothers as well as those who could not communicate either in Kiswahili or English were excluded from the study.

3.4 Sample size

Sample size calculation was done as shown in table 3.1, which tabulates the number of cases needed for detection of odds ratio of 1.5 to 4 with 80% or greater statistical power for exposure prevalence of 0.25% to 15%, for a control-to-case ratio of 4:1 (62)**.** The study was designed to detect an Odds Ratio of two or more, exposure prevalence of 15% at 95% confidence level.

Table 3.1: Sample size determination

Exposure prevalence in controls (%)	Minimum Odds Ratio to be detected			
	1.5	**2**	**3**	**4**
15	380	**115***	40	25
10	520	150	50	30
5	950	270	85	45
3	1520	425	130	70
2	2235	620	185	100
1	4395	1205	360	185
0.5	8710	2385	700	360
0.25	17340	4740	1390	710

***115 was the appropriate sample size for the study group**

From the sample size table above, a sample size of cases (n) = 115 and that of controls (n) =460 was selected to be adequate for the detection of odds ratio of two with 80% or greater statistical power for exposure prevalence of 15%.

3.5 Sampling Procedure

All consenting mothers presenting with preterm birth and were eligible to participate in the study were included as cases All consenting mothers presenting with term birth and eligible to participate in the study were included as controls (46).Participants were recruited on a daily bases as they attended the hospitals over a period of three months. To recruit the cases, the researchers visited the postnatal wards that housed mothers who had delivered infants admitted in the Newborn Unit. All mothers with preterm birth within 24 hours were approached to give consent to be interviewed and to have prescription drug information extracted from the Mother and Child Booklet. The mothers in the control group were recruitedfrom postnatal wards. All mothers who had had term birth within 24 hours were approached and those who gave consent were interviewed and prescription data abstraction. From Mwingi District Hospital, 36 cases and 149 controls were sampled, while Kitui District Hospital contributed 71 cases and 304 controls.

3.6 Case definition

The cases were immediate post-partum mothers who presented in Kitui and Mwingi District Hospitals within the study period between May and August, 2014, with a diagnosis of preterm birth, that is, delivery of live infant before 37 complete weeks of gestation. No attempt was made to classify the mothers based on degree of prematurity.

Control group constituted immediate post-partum mothers who present in Kitui and Mwingi District Hospitals within the study period between May and August, 2014, with delivery of live infant at term, that is, after 37 complete weeks of gestation. Mothers of postmature infants were not excluded from the control group.

The level of education of the mothers was classified in to four categories depending on the highest level of education attained by individual participant, none (for those who had had no education), primary, secondary and tertiary.

Type of housing was used as a surrogate indicator for socio-economic status of the mothers. Four levels of housing were determined, with stone housing, tin roof with brick wall, tin roof with mud wall and thatched house representing the highest to the lowest socio-economic status respectively. The number of previous pregnancies, excluding the pregnancy whose outcome was studied, were classified as zero, one, two, three, or more than three. The number of Antenatal Clinic visits during the course of the pregnancy were classified as zero, one, two, three, four, or more than four.

The participants were classified as having used herbal remedy or not. The trimester of herbal use and duration of use in days were combined to make one composite variable. Self-medication was defined as the acquisition and use of any medicine without a valid prescription from a registered medical practitioner. This combined both the over-the-counter medications as well as prescription-only medications that are dispensed and used without a valid prescription. Each generic medication, trimester in which the first dose was taken and the duration of for which the medication was taken were combined to make one composite variable.

Prescription medication use was defined as any use of medicines as a result of a valid prescription by a registered medical practitioner. Each generic medication, trimester in which the first dose was taken and the duration for which the medication was taken were combined to make one composite variable. Medications prescribed in pregnancy were also categorized as per the FDA Categories of medication use in Pregnancy, without regard to the timing or the length of medication use. The medications were divided into four groups, namely group A, B, C and D. None of the medications belonged to category X.

All medications which had been used in pregnancy were recorded in the data abstraction forms. Timing of medication use was classified as first trimester (one to 13 weeks), second trimester (14 to 27 weeks) or third trimester (after 27 weeks). Duration of use was classified as "once to 1 day", "2 to 5 days", "6 to 10 days", "11-30 days" or "more than 31 days". Individual medication or episode of herbal remedy use, timing and duration of its use were combined to make one composite variable. The timing of medication use was defined as the trimester in which the first dose of the medication was taken.

3.7 Data Collection and Management

3.7.1 Data collection

Questionnaires were used in structured interviews to collect maternal baseline characteristics, self-medication and use of herbal remedies. The questionnaires were filled by the investigator or trained research assistant. Every eligible mother underwent a structured interview with the help of a questionnaire, to establish the baseline characteristics and medications that she was exposed to during pregnancy through self-medication. A willing relative or caregiver where available, was enjoined in the interview, with the consent of the mother to aid in recall of self-medication and herbal remedy use in pregnancy. The questionnaire also captured data on herbal remedy use. The mother's *Mother and Child Booklet,* and the patient file records were abstracted using Data Abstraction Form to capture concurrent disease conditions and prescription medication use. The mothers who were not attending ANC in the study hospitals were also asked to produce any medical cards they may have had in their possession and any prescribed medications on them were recorded.

Data abstraction forms were used to gather data on maternal baseline characteristics and prescription medication use in pregnancy. Concurrent medical conditions either pre-existing or diagnosed during pregnancy were also recorded in these forms. The data sources were mainly the patient file and the *Mother and Child Booklet*. Patient files were identified in the health records office using the Inpatient Number. All data abstraction forms were filled in the privacy of the records office and no files were moved from the health records office. However, data abstractions forms were filled in maternity when abstracting data from *Mother and Child Booklet*, as the booklets were in the custody of the mothers.

3.7.2 Pilot Study and Quality Assurance

Ten Questionnaires were pre-tested before the use in the main study to identify the range of possible responses for the open-ended questions. Pretesting also helped to identify and remove ambiguities as well as assess acceptability of the questionnaire. After pretesting, questionnaires were re-designed to make them easier to use. In addition, a data abstraction from was attached to each questionnaire to aid in comprehensiveness in collecting data for each participant. All research assistants involved in the data collection underwent a one-day training so as to aid in accurate data collection. The research assistants were selected from among the interested nursing and clinical medicine students in the third year of their studies. They were briefed on the purposes of the study, the study design and ethical considerations. They underwent training on how to use the data collection tool in data abstraction. They were charged primarily with the responsibility of identifying cases as they occurred throughout the day and night, as well as data abstraction from medical records. The questionnaires and data abstractions tables were designed to create redundancy in collecting the baseline characteristics data and any inconsistencies in variables were verified by the principal investigator.

3.7.3 Data management

Each mother recruited into the study was assigned a participant number. Mothers belonging to the case group were assigned numbers starting with S, for example, S001, S002 and so on. Similarly, mothers belonging to the control were assigned study numbers beginning with C, for example C001, C002 and so on. Data variables from questionnaires and data abstraction forms were organised in Microsoft Excel

2010 spread sheet using the participant number as the identification (ID) number. The table was then exported to STATA version 12 for analysis.

3.8 Data Analysis

Descriptive data analysis was done on socio-demographic variables. The Shapiro-Wilk test was used to determine whether continuous variables conformed to normal distribution. Mean and standard deviation were determined for normally distributed continuous variables. Counts and percentages were used for categorical variables and distribution of variables across the two arms compared using Pearsons Chi square test. 95% confidence intervals were reported. Logistic regression was done to determine significant medication-related risk factors for herbal remedy use, self-medication and prescription medication use. To control for confounding, a multivariate analysis was done by manual forward stepwise model building until a parsimonious model was achieved. Odds ratios and 95% confidence intervals were reported.

3.9 Ethical considerations

The study protocol was submitted to and ethical approval given by the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC) and approved (P77/02/2014). The letter of approval is appended in appendix 1. Written informed consent was obtained from each potential participant before admission into the study using an informed consent form (Appendix 2). All the filled questionnaires were kept under lock and key by the investigator. All electronic data were protected with a password only known to the investigator. All electronic backup devices were stored under lock and key by the principal investigator.

CHAPTER FOUR: RESULTS

4.1 General Sociodemographic Maternal Status

The baseline characteristics are summarized in table 4.1. The mean age of the participants in this study was 25.2 (±5.8) years. Case group had mean age of 25.4 (±7.1) years. The control group had mean age 24.4 (±5.4) years. There was no significant difference in age across the two groups. Concerning level of education, 7 (6.5%) of the cases and 23 (5.1%) of the controls had had no education at all, 63 (58.9%) of the cases and 222 (49%) of the controls had primary level of education. In addition, 29 (27.1%) of the cases and 174 (38.4%) of the controls had secondary education and 8 (7.5%) of the cases and 34 (7.5%) of the controls had tertiary level of education. There was no significant difference across the groups concerning the level of education.

Most of the cases 105 (98.1%) were drawn from rural areas compared to 406 (89.6%) of controls (p=0.005). The cases were more likely to be two lowest socio-economic status (48[44.8%]) than the controls (116[30.1%]p=0.033). Cases were more likely to have had 3 or more than 3 pregnancies (26 [24.3%]) compared to controls (72 [15.9%]) (p=0.04). The controls were more likely to have met the recommended at least four antenatal clinic visits (63) 254 [56.0%] having made four or more antenatal clinic visits compared to 8 [7.5%] of the cases, although there was no significant difference across the two groups.

Mothers who had had either previous preterm birth, pregnancy termination or miscarriage were more likely to be cases (12[11.2%]) compared to controls (6 [1.3%]) (p<0.001). Cases were more likely to have used alcohol (11 [10.3%]) compared to controls (23[5.1%]) p=0.043 and cases we more likely to have a diagnosis of preeclampsia (10[9.4%]) compared to controls (5[1.1%]) (p<0.001).Figure 4.1 summarizes the statistically significant baseline characteristics as risk factors for preterm birth.

Table 4.1**:Baseline characteristics of the study population and relation to preterm birth**

Maternal Characteristics	Cases n=107 (%)	Controls n=453 (%)	Total (%)	p value
Mean age [SD]	25.4[7.1]	24.4[5.4]	25.2[5.8]	0.116
Level of education				
None	7(6.5)	23(5.1)	30(5.4)	0.168
Primary	63(58.9)	222(49)	285(50.9)	
Secondary	29(27.1)	174(38.4)	203(36.3)	
Tertiary	8(7.5)	34(7.5)	42(7.5)	
Residence				
Rural	105(98.1)	406(89.6)	511(91.3)	**0.005**
Urban	2(1.9)	47(10.4)	49(8.8)	
Housing				
Stone house	8(7.5)	45(9.9)	53(9.5)	**0.033**
Tin roof with brick wall	51(47.7)	272(60.0)	323(57.7)	
Tin roof with mud wall	41(38.3)	114(25.2)	155(27.7)	
Thatched house	7(6.5)	22(4.9)	29(5.2)	
Previous pregnancies				
0	36(33.6)	142(31.4)	178(31.8)	**0.04**
1	27(25.2)	112(24.7)	139(24.8)	
2	18(16.8)	127(28.0)	145(25.9)	
3	12(11.2)	44(9.7)	56(10.0)	
> 3	14(13.1)	28(6.2)	42(7.5)	
Number of ANC visits				
0	9(8.4)	3(0.7)	12(2.1)	0.085
1	11(10.3)	23(5.1)	34(6.1)	
2	37(34.6)	44(9.7)	81(14.5)	
3	42(39.3)	129(28.5)	171(30.5)	
4	5(4.7)	180(39.7)	185(33.0)	
>4	3(2.8)	74(16.3)	77(13.8)	
Tobacco use				
No	106(99.1)	452(99.8)	558(99.6)	0.266
Yes	1(0.9)	1(0.2)	2(0.4)	
Alcohol use				
No	96(89.7)	430(94.9)	526(93.9)	**0.043**
Yes	11(10.3)	23(5.1)	34(6.1)	
Prior preterm birth, miscarriage or pregnancy termination				
No	95(88.8)	447(98.7)	542(96.8)	**<0.001**
Yes	12(11.2)	6(1.3)	18(3.2)	
Preeclampsia				
No	97(90.7)	448(98.9)	545(97.3)	**<0.001**
Yes	10(9.4)	5(1.1)	15(2.7)	
Vaginal candidiasis				
No	97(90.7)	410(90.5)	507(90.5)	0.963
Yes	10(9.4)	43(9.5)	53(9.5)	

SD standard deviation; Significant p-values in **bold;** CI confidence interval

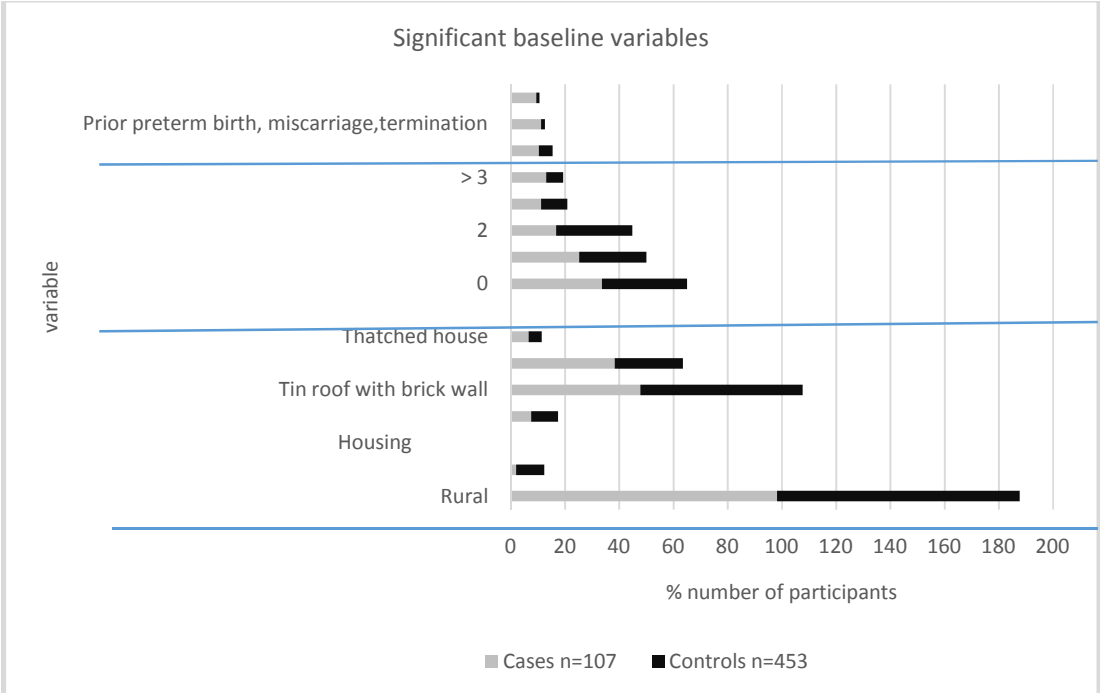

Figure 4.1**: Significant baseline characteristics**

4.2 Herbal remedy use in pregnancy

A logistic regression analysis of herbal remedy use in pregnancy as a risk factor for preterm birth revealed four significant risk factors summarized in table 4.2.The risk for preterm birth due to the use of herbal remedies in the first trimester for two to five days was (OR=12.01; CI 5.1 to 28.3; p<0.001); and for six to 10 days was (OR=36.53; CI 4.52-295.36; p=0.001); second trimester for six to 10 days was (OR=15.7; CI 3.11-34.15; p<0.001). Any herbal use in the first trimester (OR 15.7; CI 7.34-33.6; p<0.001).

Figure 4.2 summarizes the herbal remedy use on pregnancy as risk factor for preterm birth in Kitui County.

Table 4.2**: Herbal remedy use in pregnancy and relation to preterm birth**

Composite Variable	Cases n=107(%)	Controls n=453 (%)	OR (95%CI)	p-Value
Herbal use, first trimester for one day	1(0.9)	1(0.2)	4.26(0.26-68.72)	0.307
Herbal use, first trimester for 2-5 days	19(17.8)	8(1.8)	12.01(5.1-28.3)	**<0.001**
Herbal use, first trimester six to 10 days	8(7.5)	1(0.2)	36.53(4.52-295.36)	**0.001**
Herbal use, second trimester for 6-10 days	9(8.4)	4(0.9)	10.31(3.11-34.15)	**<0.001**

Any herbal use in the first trimester	28(26.2)	10(2.2)	15.7(7.34-33.6)	**<0.001**

Significant p-values in **bold;** CI confidence interval

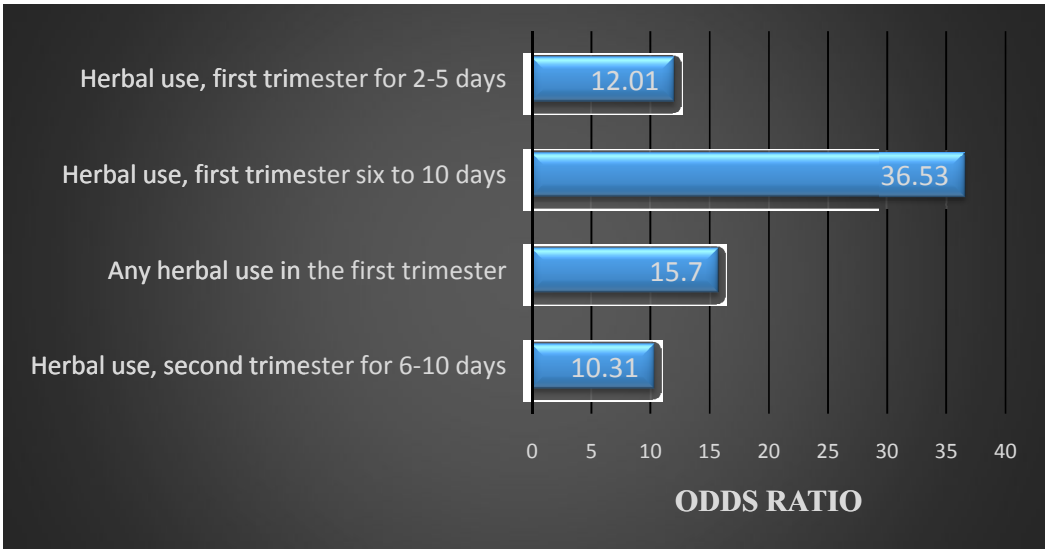

Figure 4.2: **Herbal medication use as risk factors for preterm birth**

4.3 Self-medication in pregnancy

A logistic regression analysis of self-medication use in pregnancy as a risk factor for preterm birth revealed four significant risk factors summarized in table 4.3 below. Self-medication in the first trimester for 2-5 days was associated with significant increase in the incidence of preterm birth for the following medications; Chlorpheniramine (OR=4.36; CI 1.07-17.72; p=0.04), paracetamol (OR=3.79; CI 1.25-11.50; p=0.019), amoxicillin (OR=4.43; CI 1.40-14.01); p=0.011), Magnesium trisilicate (OR=8.91; CI 2.19-36.23; p=0.002). In addition, self-medication at any time during pregnancy for any period of time was also a risk factor for preterm birth (OR= 3.93; CI 1.07-17.72; p<0.001). Figure 4.3 summarizes the significant self-medication risk factors for preterm birth.

Table 4.3: **Self-medication in pregnancy and relation to preterm birth**

Composite Variable	Cases, n=107 (%)	Controls, n=453(%)	OR (95% CI)	p-value
Ibuprofen, third trimester for 2-5 days	2(1.9)	7(1.5)	1.21(0.25-5.93)	0.811
Paracetamol, second trimester 2-5 days	1(0.9)	6(1.3)	0.7(0.08-5.9)	0.745
Metronidazole, first trimester 2-5 days	1(0.9)	1(0.2)	4.26(0.26-68.72)	0.307
Chlorpheniramine, second trimester for 2-5 days	2(1.9)	3(0.7)	2.86(0.47-17.32)	0.253
Cough mixture, first trimester for one day	2(1.9)	3(0.7)	2.86(0.47-17.32)	0.253
Indomethacin, second trimester for 2-5 days	3(2.8)	4(0.9)	3.24(0.71-14.69)	0.128
Omeprazole, second trimester 2-5 days	2(1.9)	1(0.2)	8.61(0.77-98.84)	0.08
Chlorpheniramine, first trimester for 2-5 days	4(3.7)	4(0.9)	4.36(1.07-17.72)	**0.04**
Paracetamol, first trimester 2-5 days	6(5.6)	7(1.5)	3.79(1.25-11.50)	**0.019**
Amoxicillin, first trimester for 2-5 days	6(5.6)	6(1.3)	4.43(1.40-14.01)	**0.011**
Magnesium trisilicate, first trimester 2-5 days	6(5.6)	3(0.7)	8.91(2.19-36.23)	**0.002**
Use of any self-medication in pregnancy	34(31.8)	48(10.6)	3.93(2.37-6.51)	**<0.001**

Significant p-values in **bold;** CI confidence interval

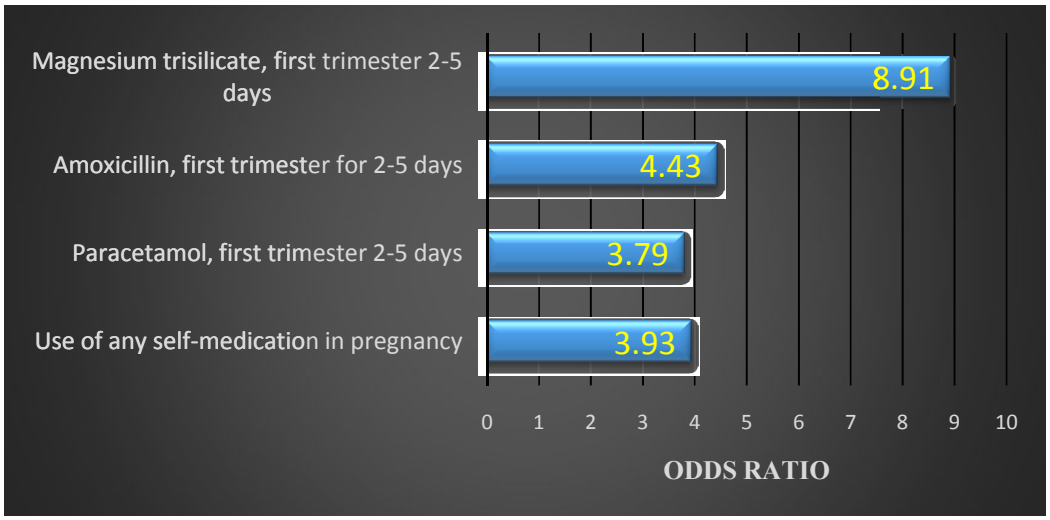

Figure 4.3: **Significant self-medication risk factors for preterm birth**.

4.4 Prescription medication use in pregnancy

A logistic regression analysis of prescription medication use in pregnancy as a risk factor from preterm birth showed 12 significant risk factors for preterm birth as presented in table 4.4.Some prescribed medicines in pregnancy were associated with a reduction in the risk of preterm birth. Amoxicillin prescribed in the first trimester significantly reduced the risk of preterm birth (OR=0.09; CI0.01-0.66; p=0.018), as did ferrous sulphate from second trimester for more than 31 days (OR=0.19; CI0.12-0.30; p<0.001) and folic acid from second trimester for more than 31 days (OR=0.18; CI 0.11-0.28; p<0.001). Omeprazole in second trimester used for 6-10 days was associated with increase in risk of preterm birth (OR=6.50; CI 1.07-39.42; p=0.042) as was metronidazole in second trimester (OR=6.57; CI 2.44-17.69; p<0.001).

Medicines used in management of hypertension and preeclampsia were also associated in very high incidence of preterm birth, both prescribed in second trimester, that is Nifedipine (OR=18.95; CI 5.25-68.44; p<0.001), methyl dopa (OR=11.57; CI 22.16-191.69; p<0.001)) and those prescribed in the third trimester, namely Nifedipine (OR=17.5; CI 1.94-158.69; p=0.011]), enalapril (OR=17.5; CI 1.94-158.69; p=0.011]), methyldopa (OR=22.16; CI 2.56-191.69; p=0.005]), magnesium sulphate (OR=36.55; CI 4.52-295.36; p=0.001]),) and dexamethasone (OR=23.25; CI 5.01-107.79; p<0.001]). Figure 4.4 summarizes the significant prescribed medications as risk factors for preterm birth.

Table 4.4: **Prescription medication use in pregnancy and relation to pretermbirth**

Composite variable	Cases n=107 (%)	Controls n=453 (%)	OR (95% CI)	p-value
Clotrimazolepessaries 3rd trimester for 6-10 days	3(2.8)	13(2.9)	0.98(0.27-3.49)	0.971
Ferrous sulphate 3rd trimester for 11-30 days	2(1.9)	8(1.8)	1.06(0.22-5.06)	0.942
Erythromycin 3rd trimester for 2-5 days	2(1.9)	10(2.2)	0.84(0.18-3.91)	0.828
Paracetamol 3rd trimester for 2-5 days	3(2.8)	11(2.4)	1.16(0.32-4.23)	0.823
Clotrimazolepessaries 2nd trimester for 6-10 days	7(6.5)	33(7.3)	0.89(0.38-2.07)	0.789
Mebendazole 2nd trimester for 1 day	55(51.4)	240(53.0)	0.94(0.62-1.43)	0.769
Carbamazepine 2nd trimester for more than 31 days	1(0.9)	3(0.7)	1.42(0.15-13.74)	0.765
Clotrimazole 2nd trimester for 6-10 days	1(0.9)	3(0.7)	1.42(0.15-13.74)	0.765
RHZE* 1st trimester for more than 31 days	1(0.9)	3(0.7)	1.42(0.15-13.74)	0.765
Paracetamol 1st trimester for 2-5 days	1(0.9)	6(1.3)	0.7(0.08-5.90)	0.745
Ibuprofen 2nd trimester for 2-5 days	1(0.9)	2(0.4)	2.13(0.19-23.68)	0.539
Chlorpheniramine 2nd trimester for 2-5 days	2(1.9)	5(1.1)	1.71(0.33-8.92)	0.526
Erythromycin 2nd trimester for 2-5 days	4(3.7)	26(5.7)	0.64(0.22-1.87)	0.412
Zidovudine 2nd trimester for more than 31 days	2(1.9)	4(0.9)	2.14(0.39-11.83)	0.384
Paracetamol 2nd trimester for 2-5 days	3(2.8)	22(4.9)	0.57(0.17-1.92)	0.361
Doxycycline 2nd trimester for 2-5 days	1(0.9)	1(0.2)	4.26(0.26-68.72)	0.307
Insulin 1st trimester for more than 31 days	1(0.9)	1(0.2)	4.26(0.26-68.72)	0.307
ArtemetherLumefantrine 2nd trimester for 2-5 days	2(1.9)	18(4.0)	0.46(0.11-2.01)	0.303
Cotrimoxazole 2nd trimester for more than 31 days	2(1.9)	3(0.7)	2.86(0.47-17.32)	0.253
Diclofenac 2nd trimester for 2-5 days	2(1.9)	3(0.7)	2.86(0.47-17.32)	0.253
Amoxicillin 2nd trimester for 2-5 days	6(5.6)	43(9.5)	0.57(0.23-1.37)	0.206
Ciprofloxacin 2nd trimester for 2-5 days	2(1.9)	2(0.4)	4.3(0.6-30.84)	0.147
Amoxicillin 3rd trimester for 2-5 days	4(3.7)	6(1.3)	2.89(0.8-10.44)	0.105
Omeprazole 1st trimester for 2-5 days	3(2.8)	3(0.7)	4.33(0.86-21.74)	0.075
Omeprazole2nd trimester for 6-10 days	3(2.8)	2(0.4)	6.50(1.07-39.42)	**0.042**
Amoxicillin 1st trimester for 2-5 days	1(0.9)	43(9.5)	0.09(0.01-0.66)	**0.018**
Nifedipine 3rd trimester for 6-10 days	4(3.7)	1(0.2)	17.55(1.94-158.69	**0.011**
Enalpril 3rd trimester for 2-5 days	4(3.7)	1(0.2)	17.55(1.94-158.70	**0.011**
Methyl Dopa 3rd trimester for 11-30 days	5(4.7)	1(0.2)	22.16(2.56-191.69)	**0.005**
Magnesium Sulphate 3rd trimester for 1 day	8(7.5)	1(0.2)	36.53(4.52-295.36)	**0.001**
Methyl dopa 2nd trimester for 2-5 days	10(9.3)	4(0.9)	11.57(3.56-37.66)	**<0.01**
Dexamethasone 3rd trimester for 2-5 days	10(9.3)	2(0.4)	23.25(5.01-107.79)	**<0.01**
Ferrous sulphate 2nd trimester for more than 31 days	48(44.9)	366(80.8)	0.19(0.12-0.30)	**<0.01**
Folic acid 2nd trimester for more than 31 days	46(43.0)	366(80.8)	0.18(0.11-0.28)	**<0.01**
Metronidazole 2nd trimester for 2-5 days	10(9.3)	7(1.5)	6.57(2.44-17.69)	**<0.01**
Nifedipine 2nd trimester for more than 31 days	12(11.2)	3(0.7)	18.95(5.25-68.44)	**<0.01**

* RHZE a combination of rifampicin, isoniazid, pyrazinamide and ethambutol; Significant p-values in **bold**; CI confidence interval

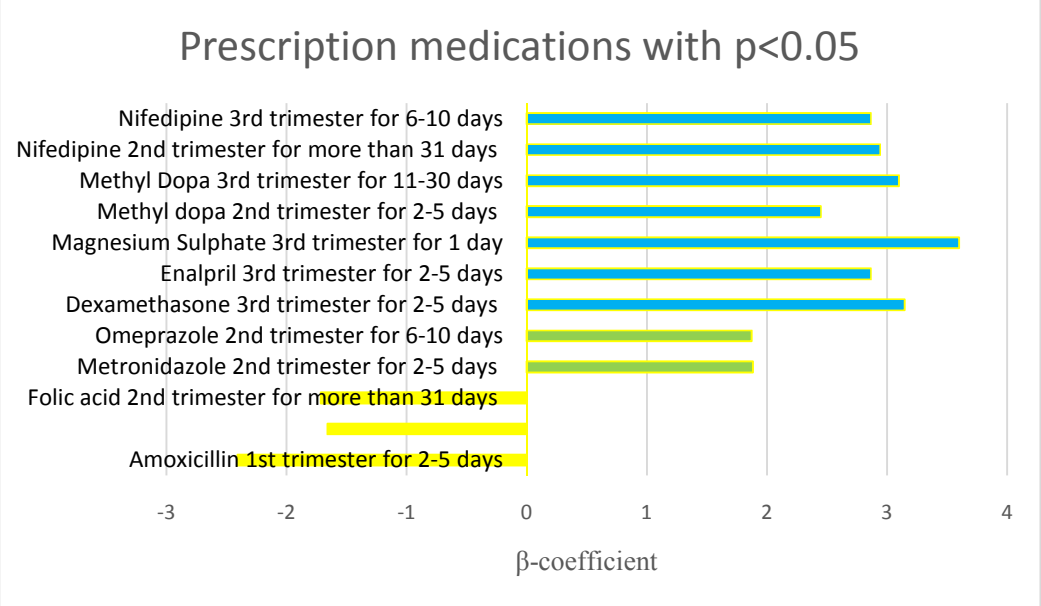

Figure4.4: **Significant prescribed medications as risk factors for preterm birth**

Results of a logistic regression analysis of prescription medication as per FDA categorization are presented in table 4.5 below. Figure 4.5 summarizes the prescribed medications as per the FDA categorization.

Table 4.5**: Prescription medication use as per the FDA categories and relation to preterm birth**

FDA category	Case group n=107 (%)	Control group n=543 (%)	OR(95%CI)	p-value
A	50(46.7)	375(82.8)	0.18(0.12-0.29)	**<0.001**
B	47(43.9)	210(46.4)	0.91(0.59-1.39)	0.65
C	76(71.0)	270(59.6)	1.66(1.05-2.63)	**0.03**
D	11(10.3)	15(3.3)	3.35(1.49-7.51)	**0.003**

CI Confidence interval; Significant p-values in bold; FDA Food and Medication Administration

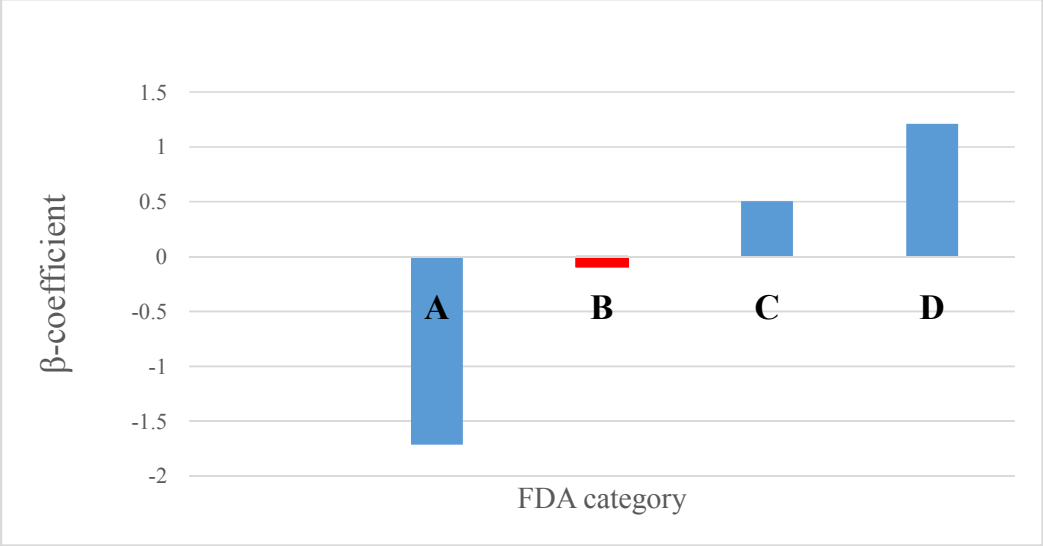

Figure 4.5: P**rescribed medications as per the FDA categorization**

Prescription of category A medications in pregnancy was associated with lower risk of preterm birth (OR=0.18; CI 0.12-0.29; p<0.001). Categories C and D medications were associated with higher risk of preterm birth (category C OR=1.66; CI 1.05-2.63; p=0.03] and category D OR=3.35; CI 1.49-7.51; p=0.003) category D carried the highest risk for preterm birth of all the categories. There was no significant association between prescription of category B medications and preterm birth.

4. 6Multivariate analysis of medication-related risk factors for preterm birth

On multivariate logistic regression analysis, the identified risk factors for preterm birth were as shown in table 4.6. Herbal use in the first trimester lasting two to five days was associated with 11 fold increase in risk for preterm birth. (OR=11.10 [4.34-28.41], p<0.01), herbal use in the first trimester lasting six to 10 days showed nearly 45 times higher risk (OR= 44.87 [4.99-403.87], p<0.01) and herbal use in the second trimester for six to 10 days was associated with more than 16 times higher risk for preterm birth (OR= 16.43 [4.53-59.57], p<0.01). Any herbal use in the first trimester was associated with 7 times the risk of preterm birth (OR=7.10, [3.42-15.80], p<0.01.

Self-medication risk factors for preterm birth were use of the following medications in the first trimester for 2 to 5 days: Chlorpheniramine was associated with nearly 3 fold increase in risk of preterm birth (OR=2.64 [1.22-19.65], p=0.012), exposure to paracetamol was associated with a 34% increase in the risk of preterm birth (OR=1.34 [1.09-6.73], p=0.043), amoxicillin use was associated with nearly six fold increase in the risk of

preterm birth(OR=5.72 [1.60-20.84], p=0.007) while magnesium trisilicate was associated with nearly eight fold increase in the risk (OR =7.66 [2.66-22.32], p=0.011).

Amoxicillin prescribed in the first trimester (OR=0.09 [0.01-0.66], p=0.043), ferrous sulphate, second trimester for more than 31 days (OR=0.22 [0.13-0.35], p<0.001), folic acid from second trimester for more than 31 days (OR=0.20 [0.12-0.34], p=0.02) and FDA category A (OR=0.27 [0.07-0.42], p=0.001) medications were associated with lower risk of preterm birth. Risk factors for preterm birth were: Omeprazole in second trimester used for 6-10 days (OR=7.92 [1.08-58.32], p=0.042), metronidazole use for two to five days in second trimester (OR=3.16 [1.23-12.06], p=0.02), Categories C (OR=3.22 [1.87-6.23], p=0.01) and D medications OR=4.23 [2.10-8.74], p=0.02.

Table 4.6: **Multivariate analysis of medication-related risk factors for preterm**

Variable	Crude OR (95%CI)	p-value	Adjusted OR (95%CI)*	p-value
Preeclampsia	9.21 (3.09-27.63)	**<0.001**	9.06 (2.60-31.63)	**0.001**
Previous preterm birth	9.41 (3.45-25.69)	**<0.001**	9.31 (2.82-30.68)	**<0.001**
Housing	1.45 (1.08-1.95)	**0.013**	1.51 (1.05-2.16)	**0.030**
Residence	0.16 (0.04-0.72)	**0.013**	0.10 (0.01-0.78)	**0.028**
Alcohol use	2.14 (1.11-4.54)	**0.047**	1.20 (0.44-3.27)	0.716
Tobacco use	4.26 (0.26-68.72)	0.307	-	-
Number of Previous pregnancies	1.07 (0.90-1.26)	0.445	-	-
Herbal use in first trimester for 2-5 days	12.01 (5.10-28.30)	**<0.001**	11.10 (4.34-28.41)	**<0.001**
Herbal use in second trimester for 6-10 days	10.31 (3.11-34.16)	**<0.001**	16.43 (4.53-59.57)	**<0.001**
Herbal use in first trimester for 6-10 days	36.53 (4.52-295.30)	**0.001**	44.87 (4.99-403.87)	**0.001**
Herbal use in the first trimester once	4.26 (0.26-68.72)	0.307	-	-
Any herbal use in 1st trimester	15.7 (7.34-33.6)	**<0.001**	7.10 (3.42-15.80)	**<0.001**
Prescribed ferrous sulphate 2nd trimester for >31 days	0.19 (0.12-0.30)	**<0.001**	0.22 (0.13-0.35)	**<0.001**
Prescribed Folic acid, 2nd trimester > 31 days	0.18 (0.12-0.28)	**<0.001**	0.20 (0.12-0.34)	**<0.001**
Prescribed metronidazole 2nd trimester 2-5 days	6.57 (2.44-17.67)	**<0.001**	3.16 (1.23-12.06)	**0.020**
Prescribed amoxicillin 1st trimester 2-5 days	0.09 (0.01-0.66)	**0.018**	0.13 (0.02-0.94)	**0.043**
Prescribed omeprazole 2nd trimester 6-10 days	6.51 (2.03-39.41)	**0.042**	7.92 (1.08-58.32)	**0.042**
Self-medication amoxicillin 1st trimester 2-5 days	4.42 (1.40-14.00)	**0.011**	5.77 (1.60-20.84)	**0.007**
Self-medication chlorpheniramine 1st trimester 2-5 days	4.36 (2.01-17.73)	**0.04**	2.64 (1.22-19.65)	**0.012**
Self-medication mg** trisilicate 1st trimester	8.91 (2.19-36.23)	**0.002**	7.66 (2.66-22.32)	**0.011**
Self-medication paracetamol 1st trimester 2-5 days	3.78 (1.24-11.51)	**0.019**	1.34 (1.09-6.73)	**0.043**
FDA category A	0.18 (0.12-0.29)	**<0.001**	0.27 (0.07-0.42)	**0.001**
FDA category C	1.66 (1.05-2.63	**0.03**	3.22 (1.87-6.23)	**0.010**
FDA category D	3.35 (1.49-7.51)	**0.03**	4.23 (2.1-8.74)	**0.020**

birth

*Pseudo R^2 =0.3168, ** magnesium, CI confidence interval, significant p-values in **bold**

CHAPTER FIVE: DISCUSSION

The main findings of this study are that herbal remedy use, self-medication, certain prescription medications and prescription of categories C and D medications were associated with a higher risk of preterm birth in Kitui County. Use folic acid, ferrous sulphate and amoxycillin in pregnancy was associated with lower risk of preterm birth.

5.1 Determinants of preterm birth

5.1.1 Herbal remedy use in pregnancy

Use of herbal remedies in the first trimester was associated with increased risk for preterm birth. The longer the use of herbal remedies the higher the risk of preterm birth. Exposure to herbal remedies in the second trimester was also associated with increased risk of preterm birth. It was observed that herbal decoctions prepared at home and herbal remedies acquired from herbal clinics were the most commonly used by the mothers. Clearly then, herbal remedy use in pregnancy is a significant risk factor for preterm birth, especially in the first and second trimesters. Herbal remedies contain many unstandardized bioactive xenobiotics and secondary plant metabolites many of which may have toxic effects to the developing foetus. In addition, herbal decoctions preparation at home may not adhere to stringent good manufacturing practices. Microbial contamination may occur during extraction, packaging and while dispensing, exposing the mother to dangerous infections. Due to the wide range of bioactive xenobiotics and possibility of contamination of herbal preparations, it is very difficult to attribute a biological mechanism of action in causation of preterm birth.

The results of this study corroborates findings of an Italian study by Cuzzolin et al, (2010) that showed herbal remedy use is associated with increased adverse pregnancy outcomes, including preterm birth (64). Another study on use of Chinese herbal medicines in pregnancy among the Taiwanese reported that pregnant women with threatened abortion were more likely to have used herbal remedies than other pregnant women (65). It is therefore important for health providers to be sensitized on local herbs and their use in pregnancy.

5.1.2 Self-medication in pregnancy

Generally, the prevalence of self-medication in the study population was low at 14.6% compared to reported prevalence of between 12.5% (66) and 80% (67). A third of all the cases reported use of at least one medication without a valid prescription compared to about a tenth of the controls. Of the medications associated with increased risk for preterm birth, three were OTC medicines (paracetamol, chlorpheniramine maleate and magnesium trisilicate), while one, amoxicillin was a prescription-only medication. Curiously, use of amoxicillin for self-medication was associated with increased risk for preterm birth, but it was associated with lower risk of preterm birth when used under supervision of registered medical practitioner. A study done on self-medication practices in rural India reported that self-medication was common. This was due to mothers' urge for self-care, lack of adequate healthcare services, poverty and ignorance of medication risks. Medicines were also readily available from numerous unlicensed medicine outlets (68). Countries with properly regulated pharmaceutical sector may have lower prevalence than those with challenges in regulating the sector. A study done in Northern Uganda reported a prevalence of 75.7%. Antimalarial medications, anthelminthic medications and antibiotics were commonly used for self-medication. Among the antibiotics, amoxycillin was the most commonly used (69). A study on prescription, over-the counter and herbal medicine use in rural obstetric population, concluded that self-medication use was very common. The study also showed that paracetamol use in pregnancy could be a risk factor for preterm birth. This could be due to the fact that it readily crosses the placenta barrier and may be toxic to hepatocytes (5). The liver functions as the main haematopoietic organ during foetal development. Moreover, paracetamol possesses very weak anti-inflammatory action (70) and therefore not useful in preventing inflammatory processes associated with premature labour. Use of paracetamol also greatly reduces the chance that a mother would use an NSAID, which would benefit her by its anti-inflammatory action.

Self-medication in the first trimester was associated with a significant increase in the risk for preterm birth. The first trimester of pregnancy is a period of rapid foetal growth, rapid cell multiplication and differentiation. For this reason, the foetus is

most vulnerable to xenobiotic during this period. Lack of proper clinical assessment for mothers, as is the case in self-medication, to use medicines when only required, exposes the foetus to harm. Lack of knowledge of adverse medication reactions and medication-medication, medication-herbal and medication-food interactions may also have serious implications in pregnancy. Therefore, a medication use process that involves a proper diagnosis, appropriate prescription, dispensing and adherence is important. Self-medication lacks the benefit of a proper diagnosis process and appropriate prescription, a factor that may be associated with adverse pregnancy outcomes, including preterm birth.

5.1.3 Prescription medication use in pregnancy

From the results of the study, 12 medications formed part of the composite variables that had significant association with the incidence of preterm birth. However, many of these medications were prescribed to manage hypertension in pregnancy, preeclampsia or preterm labour. Hypertension in pregnancy and preeclampsia were identified as independent significant risk factors for preterm birth enalapril, nifedipine and methyldopa were used to manage pre-existing hypertension in pregnancy, or pregnancy induced hypertension. Magnesium sulphate was commonly used in the treatment of preeclampsia during pregnancy but was also be used as a tocolytic. Dexamethasone was used prenatally to speed up foetal lung development and production of surfactant.Therefore, apparent increase in the risk of preterm birth associated with nifedipine, enalapril, methyldopa, magnesium sulphate and dexamethasone could have been due to confounding by indication. For this reason, these medications were not included in the multivariate analysis.

Hyperacidity and acid reflux are very common in pregnancy, therefore the use of acid reducing medicines was expected. Omeprazole, a proton pump inhibitor, was the most prescribed medication for this condition. Its use in pregnancy was associated with increased incidence of preterm birth, but with a wide confidence interval and borderline p-value of 0.042. A meta-analysis on safety of proton pump inhibitors in pregnancy by Gill et al, 2009. They concluded that there was no increased risk of preterm birth with the use of proton pump inhibitors (71).

Use of amoxicillin in the first trimester showed a marked reduction in the risk of preterm birth. Noting that this was the most prescribed antibiotic in the study population, it is therefore plausible that management of maternal infections early could have a protective effect. Although a study by Jepsen et al, 2003 in Denmark showed no association, in a population in a developing country where public health interventions are still inadequate, mothers may clearly benefit from early management of infections (72).

Use of iron sulphate and folic acid in pregnancy for more than 31 days was associated with decreased risk for preterm birth. Iron and folic supplementation is standard practice in antenatal care. However, iron and folic acid supplementation was not prescribed to all mothers. This could be because some prescribers did not always adhere to the guidelines or the health facility that the mothers attend may on occasion have run out of stock of either or both commodities. Ferrous sulphate needed to be used for more than 31 days to confer protective effect against preterm birth. A randomized controlled trial by Cogswell et al, 2003, showed that iron supplementation during pregnancy reduce incidence of preterm birth (73). Along with ferrous sulphate, folic acid also associated with lower incidence of preterm birth. Mothers needed to use folic acid for more than 31 days for any distinct advantage to be noted. This agrees with Mantovani et al, 2014 and Bodnar et al, 2010 who concluded that folic acid in the second and third trimesters appeared to be protective against preterm birth (66, 67). However, a Bangladeshi cohort study reported a slight increase in the risk of preterm birth with folic acid use (76), though this study only assessed mothers on basis of whether they had received ferrous-folic supplementation or not.

Metronidazole use in second trimester for two to five days was associated with increased risk of preterm birth. Studies reviewed showed that there was no association between metronidazole and preterm birth (77), however, most of these considered metronidazole use for treatment of trichomoniasis in pregnancy. In this study, metronidazole was primarily used for management of gastroenteritis.

The Food and Medication Administration (FDA) categorizes medications in categories depending on safety in pregnancy. In this study, prescription of category A medications was associated with a lower risk of preterm birth, while categories C and

D were associated with higher risk of preterm birth. Therefore, adhering to the classification is useful to prescribers. Avoiding or limiting prescription of categories C and D medications would prevent prescribers from putting the pregnant mothers at risk.

5.2 Strengths and limitations

Preterm birth was relatively infrequent and there was a limit to the number of potential cases available in the relatively short study duration. The method chosen for this study enabled simultaneous investigation of many risk factors using the same population sample. It was quick and inexpensive.

The information collected on episodes of medication and herbal remedy use allowed for the assessment of many aspects of use. The timing of use was also relevant because pregnancy is vulnerable to medication use at varying degrees across the three trimesters. Information on dose of medications was not collected, as sampled mothers were unable to recall exact medication strengths. Duration of use of medication or herbal remedy provided a useful measure of intensity of exposure.

This study targeted total sample size of 575 mothers (115 in study arm and 460 in the control arm) but due to time constraint, 560 mothers were included in the study (107 cases 453 controls).

Misclassification of mothers may have arisen due to differential recall of self-medication and herbal medication use among mothers with preterm birth compared to mothers with term birth, or refusal by mothers to disclose herbal use. A definition of "herbal medication use" to the mothers was done during the interview to help in recall. Furthermore, a willing relative or caregiver where available, was enjoined in the interview with the consent of the mother to aid in recall of medication use in pregnancy.

The study was hospital based and the mothers sampled from the public hospitals may have differed from mothers seeking healthcare in private facilities, those delivering at home and the general population.Mothers were classified as either having used herbal medication or not having used herbal medication, the timing of use and duration of use without determining the identity of the herbal remedies, how they were prepared, source or total dose.

This study did not intend to identify the individual herbal remedies used in pregnancy and how they are prepared. No attempt was made to record the total dose of herbal remedies mothers were exposed to but length of use of herbal remedy in days was used to assess intensity of exposure. Some medications, particularly the non-prescription medications, such as paracetamol and herbal remedies, were often used sporadically, which probably could not be reported accurately.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

This study has established that herbal remedy use in pregnant mothers in Kitui County was common and was a risk factor for preterm birth. Self-medication in pregnancy with over-the-counter and misuse of prescription-only medications was a major risk factor preterm birth. Prescription of FDA categories C and D medications for pregnant mothers was a common practice in Kitui County and it continually posed risks to the mother and foetus. There was as positive correlation between and use of medications in categories C and D of the FDA categorization and increase in incidence of preterm birth. Folic acid and ferrous sulphate supplementation throughout pregnancy of for at least more than 31 days played a major role in reduction of risk of incidence of preterm birth.

RECOMMENDATIONS

Maternal education programmes should be instituted and strengthened to educate mothers on the dangers of using herbal remedies. Prompt and effective management of maternal infections is beneficial and should be strengthened. A Deliberate effort should be made by all pregnant mothers to consult registered medical practitioner to avoid use of medicines without a valid prescription. Prescribers should be sensitized on the local herbs and their use in pregnancy, to equip them to educate mothers on the risks that their use poses. They should also be knowledgeable on safe use of medicines in pregnancy, and consistent use of clinical guidelines and other reference materials that can help them avoid use of harmful medicines in pregnancy.

Universal folic acid and ferrous supplementation should be encouraged. The percentage of mothers getting at least two months of folic acid and ferrous sulphate should form a key indicator to be monitored.

A cohort study on the effect of specific medications that are commonly used in pregnancy on pregnancy outcomes in Kenya is warranted, as it would provide valuable information to further improve prescription practices for pregnant mothers.

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APPENDICES

Appendix 1: Ethics and Research Committee Approval

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KENYATTA NATIONAL HOSPITAL APPROVED 15 MAY 2014 P.O. BOX 20723-00202 KNH/UON-ERC

Ref: KNH-ERC/A/140 Link:www.uonbi.ac.ke/activities/KNHUoN 15th May 2014

Albert Ndwiga Kaburi
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
University of Nairobi

Dear Dr. Ndwiga

RESEARCH PROPOSAL: DRUG-RELATED RISK FACTORS FOR PRETERM BIRTH IN KITUI DISTRICT HOSPITAL: A CASE CONTROL STUDY (P77/02/2014)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 15th May 2014 to 14th May 2015.

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 severe 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) 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*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
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.

For more details consult the KNH/UoN ERC website **www.uonbi.ac.ke/activities/KNHUoN.**

Protect to Discover

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Chairperson, KNH/UoN-ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chairman, Dept.of Pharmacology and Pharmacognosy, UoN
Supervisors: Prof. Charles K. Maitai, Dr. Margaret O. Oluka, Dr. Rose J. Kosgei

Appendix 2: Volunteer Information and Consent Form

Preamble

Premature birth is a bad pregnancy outcome. It has wide-ranging effects both on the mothers and the newborn babies. Babies who are born before they are mature enough have a hard time and may get sick often. Many may not survive. This causes pain and discomfort, hospitalization and mental anguish for the mother. Due to its nature, premature labour also leads to increased expenses in health care for both the family and community. Many infants who are born prematurely may develop complications to their health later in life. It is therefore important to identify of the medicines that we take may contribute to this problem and we are convinced that use of certain remedies in pregnancy may have an effect.

We therefore wish to carry out a study to compare the patterns of medication use among mothers with preterm birth and those with normal pregnancy outcome to understand if significant differences exist and identify any high-risk medications or combinations of medications.

We are requesting you to volunteer freely in this study. Before you decide to agree to our interview, we would like to provide you information about the study, with the use of this document, which is a consent form. Please study it carefully and feel free to ask for any clarifications on any element of the study that may not be clear to you. If you agree to our interview, you will be asked to kindly sign this consent form and a copy will be provided to you for safekeeping. Please also note that:

i. Your agreement to participate in this study is voluntary
ii. You may withdraw from the study at any time without necessarily giving a reason for your withdrawal
iii. Refusal to participate in the research will not in any way affect the treatment that is being given in the hospital

Purpose of the study

The Purpose of this study is to understand which of the medications mothers use in pregnancy or combinations of medications are likely to lead to preterm birth, hoping to avoid their use in future in pregnant mothers.

Procedure

During the interview with an investigator, you will be asked a few questions about the medications that you are using or have used in the past during your latest pregnancy including any use of herbal remedies. You will also be asked if you smoke or drink alcohol. In addition, the researchers will also check your medical records to see the medications that have been prescribed to you.

In order to participate in the study, you should meet the following criteria:

1. You must have agreed to take part in the study
2. You must be able to communicate with the researcher.

Risks and discomfort

The study carries no risk or discomfort to you whatsoever. However, the researcher will have access to sensitive and confidential information. However, maximum confidentiality will be maintained and neither your name nor contents of your medical file will be revealed to anyone.

Benefits

The findings in this study will inform the healthcare workers in making evidence-based prescribing for pregnant mothers to reduce the occurrence of preterm birth and consequently reduce infant mortality. The findings will also be used to educate pregnant mothers to reduce medication-related risk factors associated with pre-term labour.

Assurance of confidentiality

All information obtained from your file will be kept confidential and used for the purpose of this study only. Your name will not be used during data handling or in any resulting publications, codes will be used instead. Your medical records will be kept under lock and key and information will be accessible to authorized persons only.

Voluntary participation

The decision to take in this study is your choice. You may choose not to participate without any consequences as to the quality of care you will receive in the hospital. Furthermore, you are free to ask questions about the study.

Contacts

For any further information about this study you may contact me, my academic department or the Kenyatta National Hospital/University of Nairobi Ethics and research Committee using the contacts provided below:

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CONSENT FORM

I, the undersigned, willingly undertake to participate in this study whose purpose has been explained to me. I understand that any information obtained for the purposes of this study will be held in strict confidentiality.

Name …… Signature …… Date ……

Witnessed by:

Name …… Signature …… Date ……

(Investigator)