Recurrence of Perinatal Death, Preterm Birth and Preeclampsia in Northern Tanzania: A Registry Based Study

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Dedication

To my parents,

Thank you for your decision to send me to school.

To my family,

I really appreciate my beloved wife Aneth for her tender love and support during my study period. To our children; Muhoja, Ndeana, Allen and Adrian, I understand how hard it was to be away from me for such a long time. You have been asking me difficult and challenging questions regarding my absence but at last we reached a consensus. Thank you so much for your patience, I am so proud of you and I love you so much.

To my in-laws: I can hardly express what wonderful and lovely parents you are. You have been in the forefront, taking care of our children during our absence. I really appreciate it so much. May our loving and caring Lord be with you always.

Contributors

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The study was performed under supervision of Professor Rolv Terje Lie (main supervisor), Professor Anne Kjersti Daltveit (co-supervisor) both from the department of Global Public Health and Primary Care, University of Bergen, Norway, and Dr Rachel Manongi (co-supervisor) from Kilimanjaro Christian Medical University College, Tanzania.

KCMC Medical Birth Registry

Table of Contents

List of tables and figures

List of abbreviations

KCMC:	Kilimanjaro Christian Medical Centre
NUFU:	Norwegian Program for Development, Research and Education
	(Nasjonalt program for Utvikling, Forskning og Utdanning)
UK:	United Kingdom
USA:	United States of America
MDGs:	Millennium Development Goals
BMI:	Body Mass Index
UNICEF:	United Nations Children's Fund

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Abstract

Introduction

Some women carry a high risk of adverse pregnancy outcomes. This is reflected in a tendency of these women to repeat outcomes in successive pregnancies. This tendency may be estimated by the recurrence risk. Recurrence risks are well described in high-income countries for several adverse pregnancy outcomes. Little is known about the recurrence risk of pregnancy outcomes in Tanzania and Africa at large.The lack of research on recurrence in low-income countries is striking since they suffer the major burden of these problems. Understanding the recurrence risk of pregnancy outcomes and its underlying risk factors may help clinicians identify and counsel women at particularly high risk of an adverse pregnancy outcome. *Aims*: The overall aim of this thesis was to use recurrence risk estimation to study the heterogeneity in risk of important birth outcomes among women in Tanzania. Specific objectives were: (1) To estimate the risk of perinatal death in a subsequent pregnancy for women who already have experienced a perinatal death; (2) To similarly estimate the recurrence risk of preterm delivery and to estimate the perinatal mortality among the babies of repeated preterm deliveries; (3) To estimate a mother's recurrence risk of preeclampsia in subsequent pregnancies in Tanzania.

Methods

A prospective cohort was designed using maternally-linked records of already collected data from Kilimanjaro Christian Medical Centre (KCMC) Medical Birth Registry. A total of 19,811 women who delivered their first singleton infant at KCMC between 2000 and 2008 formed a cohort, and they were followed for their subsequent births to 2010. At the end of the follow-up period, a total of 3,909 women were recorded with at least one more delivery. These women contributed to 4,053 sib pairs who were studied (Papers **I** & **III**). For Paper **II**,

we further excluded women with missing gestational age for their first and subsequent births from the cohort; the remaining 3,359 women whose pregnancies were followed contributed 3,867 subsequent births. A unique mother identification number was used to link siblings with their biological mother records to create a reproductive history for each woman. All mothers with multi-fetal gestations, referred from rural areas for various medical reasons, and those who did not met linkage criteria, were excluded (Papers **I-III**). Women with an adverse pregnancy outcome in their first recorded pregnancy formed an exposed group, while those with normal pregnancies formed an unexposed group. Data analysis was performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 18.0 and Stata version 12.0. The recurrence risks of perinatal death, preterm birth and preeclampsia were estimated in multivariate analyses using log-binomial regression models with some adjustments. A clustered analysis technique with robust estimation of variances was used to account for correlation between successive births from the same mother.

Results

In Paper I, we found that women who experienced perinatal death in their first recorded pregnancy were more likely to continue to have a next pregnancy, as compared to those whose baby survived (31% vs. 19%). The absolute recurrence risk of perinatal death for women with previous perinatal death was 9.1% (as compared to a risk of 2.8% for women whose previous child survived). This amounted to a relative risk of 3.2 (95% CI: 2.2 - 4.7). Altogether, recurrence contributed 21.2% (31/146) of perinatal deaths in subsequent pregnancies. Some specific maternal and fetal conditions in the first pregnancy such as history of preeclampsia, placental abruption, placenta praevia, induced labor, preterm delivery and low birth weight were also associated with increased risk of perinatal death in the subsequent pregnancy.

In Paper II, we found that the absolute recurrence risk of preterm birth in a subsequent pregnancy for women with a previous preterm birth was 17%. This recurrence risk was 2.7-fold (95% CI: 2.1 - 3.4) compared with women with a previous term birth. The recurrence of preterm birth contributed 15% of the perinatal mortality in the second pregnancy. Babies born at term, who had an older sibling that was born preterm, had a perinatal mortality of 10%. Babies born at term who had an older sibling who was also born at term had a perinatal mortality of 1.7%.

In Paper III, we found that the absolute recurrence risk of preeclampsia was 24.6%, with a relative risk which was 9.2-fold (95% CI: 6.4 - 13.2). Numerous maternal and fetal factors in the first pregnancy were significantly associated with increased risk of preeclampsia in the subsequent pregnancy: preterm birth (RR= 3.1; 95% CI: 2.1 – 4.7), perinatal death (RR= 3.9; 95% CI: 2.9 - 5.9), low birth weight (RR= 3.1; 95% CI: 2.1 - 4.5), chronic hypertension (RR= 8.9; 95% CI: 5.7 - 13.8), and gestational hypertension (RR= 9.8; 95% CI: 4.9 -19.1). Women with a previous history of preeclampsia had increased risks of perinatal death, preterm delivery and delivery of low birth weight infant in their subsequent pregnancy. The risks of these outcomes were only to a little degree explained by recurrence of preeclampsia.

Conclusions

Women who experienced perinatal death in one pregnancy were more likely to lose a child in their next pregnancy. Strategies for perinatal death prevention should consider targeting pregnant women with a previous perinatal loss.

A history of preterm birth is a strong predictor for future preterm birth among women in Tanzania. Recurrent preterm birth increases the risk of perinatal death in the subsequent pregnancy. These women may benefit from more attention during the antenatal care.

Women with previous preeclampsia bear an increased risk of preeclampsia and other adverse pregnancy outcomes in their next pregnancies. This information is important for clinicians to help early identification and to counsel women at risk during prenatal care. Further population-based studies in the region need to examine the recurrence risk of these important pregnancy outcomes to confirm the present findings on recurrence patterns of pregnancy outcomes among Tanzanian women. Clinical studies should address the effect of intervention strategies to prevent recurrence.

List of publications

This thesis was based on the scientific work presented in three papers. These are listed below and are referred to as Paper I, Paper II and Paper III.

Paper I.

Mahande MJ, Daltveit AK, Mmbaga BT, Obure J, Masenga G, Manongi R, Lie RT. Recurrence of perinatal death in Northern Tanzania: a registry based cohort study. BMC Pregnancy Childbirth. 2013 Aug; 13(1):166.

Paper II.

Mahande MJ, Daltveit AK, Obure J, Mmbaga BT, Masenga G, Manongi R, Lie RT. Recurrence of preterm birth and perinatal mortality in northern Tanzania: registry-based cohort study. Trop Med Int Health. 2013 Aug; 18(8):962-7.

Paper III.

Mahande MJ, Daltveit AK, Mmbaga BT, Masenga G, Obure J, Manongi R, Lie RT. Recurrence of Preeclampsia in Northern Tanzania: A Registry-Based Cohort Study. PLoS One. 2013 Nov; 8(11):e79116

1. Introduction

1.1 Perinatal Death, Preterm Birth and Preeclampsia: A Global perspective

The outcomes studied in this thesis are major health problems globally and particularly in Sub-Saharan Africa. Perinatal mortality is an accepted indicator of quality of health care for pregnant women and newborns, and remains a major challenge in low-income countries [1]. The World Health Organization (WHO) has estimated that around 5.9 million perinatal deaths occur each year globally, and the majority (98%) occur in low-income countries particularly in sub-Saharan Africa. Among the main reasons are women´s lacks of access to skilled personnel during pregnancy, delivery and postnatal period [1]. Around 2.6 million of these perinatal deaths are stillbirths [2]. About 60% to 70% of perinatal deaths are assumed to be intrapartum related stillbirths [3]. In addition, about 75% of neonatal deaths occur in the perinatal period [4].

Recent community based studies in Burkina-Faso and Uganda have reported high perinatal mortality rates (79 per 1000 and 41 per 1000 births, respectively) [5, 6]. A recent hospital-based study in Malawi reported a perinatal mortality of 59.9 per 1000 births [7]. Studies identify preterm birth, infections, congenital anomalies, birth asphyxia, hypertensive disorders of pregnancy, diabetes and vaginal bleeding as major causes of perinatal death [8]. As for the causes of maternal deaths, most causes of perinatal deaths are probably preventable. Prevention would include access to quality health care services during pregnancy, child birth and after delivery.

Preterm birth is a major cause of perinatal and infant morbidity and mortality worldwide [9, 10]. It contributes to an estimated 28% of neonatal deaths each year globally [11]. Infants who are born preterm are more likely to have a longer hospital stay and thereby increase health costs both to the family and health care system [12, 13]. Preterm birth is also associated with long term health consequences such as mental retardation, cerebral palsy, respiratory problems, poor academic achievement, chronic lung diseases, and visual and hearing impairments [14, 15].

Globally, the reported prevalence of preterm birth ranges from 5% to 18% [16]. Preterm birth may have increased in the recent years due to increase in induction of labor, cesarean section during the preterm period, use of assisted reproductive technologies and maternal infections [17]. A total of 14.5 million (11.1%) babies have been estimated to be born preterm each year worldwide [18]. The majority (>60%) of these occur in low income countries, especially in sub Saharan Africa and South East Asia [11, 18]. Globally, one million of the babies who are born preterm are assumed to die from preterm-related complications each year, and again the majority of these deaths occur in low income countries [16].

Hospital-based studies in sub Saharan Africa have reported prevalences of preterm birth ranging from 3.8% to 19.9% [19, 20]. Preterm birth has been strongly associated with perinatal mortality in low income countries, especially in sub Saharan Africa [21].

Risk factors associated with preterm birth include previous preterm birth, intrauterine infections, extreme maternal age (≥35 or <20 years), underweight pre-

pregnancy BMI, preexisting maternal medical conditions, fetal anomaly, preeclampsia, placental abruption, intrauterine growth restriction, short interpregnancy intervals, genetic factors, short cervical length and positive fibronectin test [22-25].

Preeclampsia is a multisystem syndrome which complicates up to 4% of all pregnancies [26]. It is associated with increased risks of maternal and perinatal morbidity and mortality [27]. Globally, preeclampsia and eclampsia account for 10–15% of maternal mortality and morbidity [28]. The majority (an estimated 99%) of maternal deaths related to preeclampsia complications occur in low- and middle-income countries, and with a high share in sub Saharan Africa [29].

Preeclampsia is associated with high risks of maternal complications such as abruption placenta, premature delivery, disseminated coagulopathy, pulmonary oedema, acute renal failure, eclampsia, liver failure and haemorrhage [30, 31]. It is also associated with higher risks of adverse perinatal outcomes such as low birth weight, intrauterine fetal growth restriction, hypoxia-neurologic injury and fetal death [30, 31]. In addition, infants who are born after a pregnancy complicated by preeclampsia are at increased risk of metabolic syndrome, stroke and cardiovascular disease later in life [32].

Preeclampsia and eclampsia are among the major public health problem in sub Saharan Africa [28]. A review of preeclampsia studies in developing countries reported prevalences of preeclampsia ranging from 1.8% to 16.7% [33]. A recent report by World Health Organization revealed that preeclampsia and eclampsia are

associated with high risks of maternal death, perinatal death, preterm birth and low birth weight in low and middle income in countries [34].

Risk factors for preeclampsia include first pregnancy, previous history of preeclampsia or eclampsia, long inter-pregnancy interval, multiple pregnancy, obesity or overweight, gestational or pre-existing diabetes, chronic hypertension, family history of coronary heart disease, chronic renal disease, absence of antenatal care, advanced maternal age (≥35 years), change in paternity, genetic factors and immunologic factors [34-40]. Maternal, newborns and newborn health is closely related. The fourth and fifth Millennium Development Goals (MDG 4&5) focus on improvement of maternal, newborn and child health. The MDG-4 aims to reduce child mortality rates by two-thirds from 1990 to 2015, while MDG-5 aims to reduce maternal mortality ratio by three quarters during the same period [41]. However, there is a huge gap between high-income countries and low-income countries in the progress towards achievement of these goals [41, 42].

Globally, maternal deaths related to pregnancy and childbirth and deaths for under five years of age have declined by almost half for the past 10 years [41, 42]. The maternal mortality rate has dropped by 45 percent between 1990 and 2013, from 380 to 210 deaths per 100,000 live births; while the under-five mortality rate has decreased by 47% from 90 to 48 deaths per 1,000 live births during the same period [41]. However, the decline has not been similar in sub Saharan Africa, where the majority (62%) of maternal deaths occur [43]. Globally, neonatal mortality rate has dropped from 33 deaths per 1, 000 live births in 1990 to 21deaths per 1, 000 live births 2012

(i.e. 37% decline)[41]. However, the share of neonatal deaths among under five deaths has increased from 37% in 1990 to 44% in 2012, and the perinatal mortality rate also has remained high over this period especially in sub Saharan African [41]. Most of these deaths are probably preventable if women had access to quality health care services [44].

1.2 Perinatal Death, Preterm Birth and Preeclampsia in Tanzania

Tanzania has made insufficient progress towards achievement of MDG 4.The under five deaths have declined dramatically by more than fifty percent for the past ten years. However, the share of perinatal and neonatal mortality has remained high over the same period. The overall perinatal mortality rate in Tanzania is estimated to 51 per 1000 live births while the neonatal mortality rate is 26 per 1000 live births [45]. The stillbirth rate is also still as high as 43 per 1,000 live births [46]. Hospital-based studies in Tanzania have reported perinatal mortality rates ranging from 38 to 92 per 1000 births [47-50]. However, lack of population-based studies in Tanzania coupled with the high rate of home delivery may result in biased estimation of the total perinatal mortality rate and its components. Major causes of perinatal mortality in Tanzania include neonatal infection, birth asphyxia, preeclampsia, obstructed labour, antepartum hemorrhage, and preterm-related complications [48, 50].

Two hospital-based studies in Tanzania have reported prevalences of preterm birth ranging from 10% to 16.7% [51, 52]. These figures correspond to an estimate of 14% obtained from Demographic and Health Survey data [46]. Risk factors that have

been associated with preterm birth in Tanzania include maternal occupation, early sexual debut, maternal infections during pregnancy, maternal HIV, malaria and preeclampsia or eclampsia [53].

According to the Tanzania Demographic and Health Survey report 2010, preeclampsia and eclampsia contributes with 17% of all maternal deaths [46]. There is a lack of information on preeclampsia in Tanzania. Most studies on eclampsia in Tanzania have reported adverse maternal and perinatal outcomes. A cross-sectional hospital based study by Ndaboine et al [54], found that eclampsia had maternal and perinatal case fatality rate of 7.9% and 20.7%, respectively. Similarly, Kidanto and colleagues reported that eclampsia had a maternal case fatality rate of 7.7% [55]. There is a strong relationship between preeclampsia, preterm birth and perinatal death. Preeclampsia is an important risk factor for both preterm birth and perinatal death. Similarly, babies who are born preterm are at increased risk of dying during the perinatal period. Understanding the underlying risk factors of these adverse pregnancy outcomes is critical to help designing interventions to improve maternal health and child survival.

1.3 Studies of recurrence of pregnancy outcomes

Studies on recurrence risk of pregnancy outcomes have demonstrated that women with an adverse pregnancy outcome are at increased risk of repeating a similar outcome in their subsequent pregnancies [56-59].

Information on recurrence of pregnancy outcomes is important for clinicians, parents, epidemiologists and health policy makers. Clinicians may counsel women at risk of a particular adverse pregnancy outcome during prenatal care. They may also perform individualized risk assessment for accurate prediction of outcome of a future pregnancy, and guide management for high-risk women and provide referral to more specialized care for close monitoring to prevent recurrence [60].

For epidemiologists, data on recurrence of pregnancy outcomes may help understand the nature of the public health problem and identify risk factors for a particular pregnancy outcome [61]. A high recurrence risk may imply that genetic factors, persistent environmental factors or social factors put some women and their babies at a higher than average risk. For health policy makers, this information provides a basis for evidence-based decisions for allocation of research resources geared to improve maternal and newborns health [61]. Recurrence risk studies provide information about heterogeneity of risk in the general population and underlying risk factors for disease [62]. Recurrence risks between apparently unrelated outcomes may also help to identify that they have common causes [63].

1.4 Birth registration and challenges in Tanzania

Birth registration is the process whereby the country keeps a continuous and complete record of births, deaths and marital status [64]. Birth registration helps the country to understand the proportion of births and deaths that occur each year, as well as causes of deaths. This information is also important for planning and designing public health

policies as well as measuring their impact. Furthermore, birth registration provides a child with several advantages including state legal recognition of existence as a member of society, securing birth certificate, access to civil rights, rights for inheritance, protection from vulnerability and exploitation, especially in case the parents separate [64].

Recent national demographic and health survey showed that only 19% of children under five years age in Tanzania are registered, and about half (10%) of the registered children had received birth certificate [65]. The birth registration rate in Tanzania mainland is lower compared to Zanzibar (17% vs. 95%, respectively), and proportion of the registered children varies between rural and urban areas (13% vs. 53%, respectively) [65].

The lower registration rate in Tanzania has been attributed to lack of a law to enforce compulsory giving of birth certificates, lack of accountability and coordination on birth registration policy, and limited resources in terms of human capacity and materials [66].

Apart from birth registration, Tanzania relies on other sources of information to obtain national health statistics such as Demographic and Health Surveys (DHS) and national censuses. Since most of the deaths are not recorded or unrecognized, especially those which occur at home, there is a problem in estimating the magnitude of health problems with respect to newborns health.

1.5 Importance of record linkage

Data linkage refers to the process of combining information from two or more records which belong to the same person or family, using a unique key identifier or common variable to produce one data set [67]. The linked data permits prospective analysis of individual women's reproductive history. This makes it possible to estimate the recurrence risk of pregnancy outcomes in subsequent pregnancies [68].

Use of linked data provides several advantages, including cost effectiveness, reduced time for data collection, checking of data quality, better use of existing data, conservation of patient privacy and consent, and increased communication between researchers, clinicians and administrators [69]. It also makes data available to researchers and other partners to undertake a range of projects [70]. However, incompleteness of data and unmatched information has been reported as common problems in the data linkage process [71].

Lack of record linkage between mothers and their newborns is a striking limitation for surveys, censuses and vital registration data. Since data exist in isolation, it is difficult to study recurrence risk in subsequent pregnancies for individual women. Some authors have reported limitation in the use of a person's name as a unique identifier in the data linkage process, since there are changes in women's names between pregnancies, as women may change their partner; common names are shared between mothers, and women move to different areas between pregnancies [68].

1.6 Birth registries and recurrence of pregnancy outcomes

Medical birth registries (hospital or population-based) provide important information on mothers' health before pregnancy, during pregnancy, delivery and newborns condition [72]. They also generate information on disease patterns, risk factors and causes [72]. Furthermore, medical registries provide data for future epidemiological research, epidemiological surveillance, and planning for health care services [73, 74]. Therefore, a medical birth registry is an important source of information that may complement other sources of information.

Follow-up studies of recurrence within registry data require that records of subsequent pregnancies have to be linked using a unique mother's identification key to compile the reproductive history for each individual woman in a prospective way. This makes it possible to estimate recurrence risks of adverse pregnancy outcomes in successive pregnancies or across generations for long-standing registries [75]. The data in the registry may have been collected many years ago, and still it is possible to follow women prospectively within the registry data. Some epidemiologists would refer to this as a historic cohort study [76]. Since registry data usually are collected in a standardized and incidence based manner over time and follow-up is secured through record linkage, we could perhaps refer to this study design as a registry-based historic cohort study.

Compared with regular prospective cohort studies, medical birth registry data offers the opportunity to carry out a prospective analysis within a defined period with

existing data and at less cost, while regular prospective cohort studies require individual follow-up into the future and continued tracking of individuals.

Previous authors [77] have reported numerous limitations in using birth registry data, including missing data, loss to follow-up for mothers who do not show up for their subsequent pregnancy, limited number of potential confounding variables, which may open room for residual confounding, reporting error, lack of quality control; and under-reporting of births and deaths, especially in settings with a high prevalence of home deliveries. These limitations affect both prevalence and risk estimates, as well as generalizability of the study findings, especially in hospital-based registry studies. On the other hand, improvement in birth registration and utilization of birth registry data provide important information to clinicians, program health managers and health policy makers which help to provide better care services for mothers and their newborns.

1.7 Epidemiology of recurrence risk of pregnancy outcomes

Reproductive health risks in the general population vary from one woman to another. Some women have higher risk than others and tend to repeat unwanted outcomes [78]. One important method that may help to discover such heterogeneity of reproductive risk in the general population is to identify mothers who experience recurrence of pregnancy outcomes [62]. It has been shown that causes of recurrence risk and general risk are more or less similar, except that the causes of recurrence risk must persist over time [78]. Previous history of adverse pregnancy outcome is an important predictor for future risk [77]. However, high recurrence risk of most pregnancy outcomes has been

associated with genetic or persistent environmental causes [62]. Figure **1** shows a schematic diagram of the concept of recurrence risk as explained by Allen Wilcox [78]. The recurrence risk is a measure of the difference between the population median risk and the median risk of affected persons.

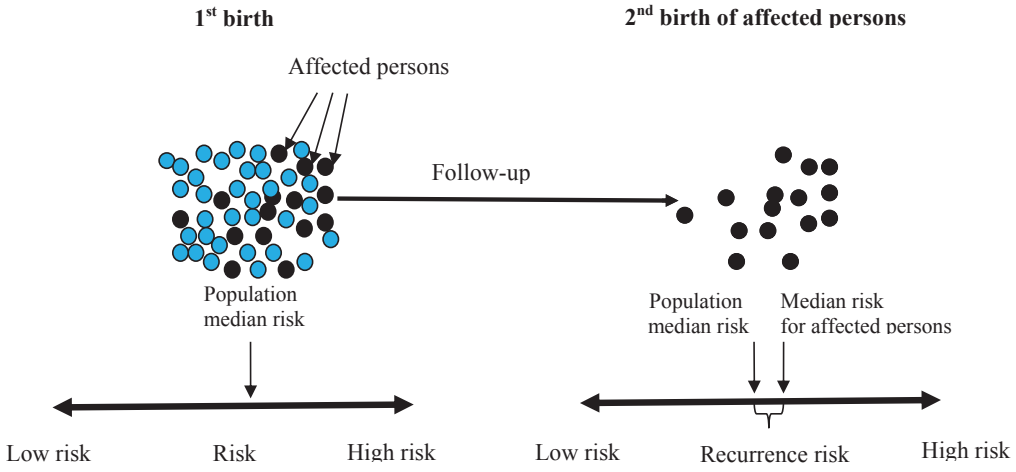


Figure 1. The recurrence risk estimates the heterogeneity in risk (From Wilcox, 2010 [78])

In Figure 1, some women marked with black dots experience an adverse outcome in their first birth. These individuals will typically have higher than average risk, which will be estimated as the recurrence risk when they are followed to their next birth. It is important to understand that the recurrence risk does not represent a direct causal effect from the outcome of the first birth to the outcome of the next birth. In the analysis the outcome of the first pregnancy is treated as if it was an exposure, and the outcome of the second pregnancy is treated as the outcome. The association is

typically measured by a relative risk. This is however not estimating a direct causal relationship but rather the indirect and combined effect of many persistent background factors like genes, persistent environmental exposures, persistent characteristics of the mother's physiology, persistent social conditions and much more. This is illustrated in Figure 2. Recurrence risk may sometimes be interpreted as being caused more by genes or more by the environment. Still, recurrence risk may be viewed as a tool more for prediction and demonstration of heterogeneity than for estimation of direct causal effects between an exposure and an outcome.

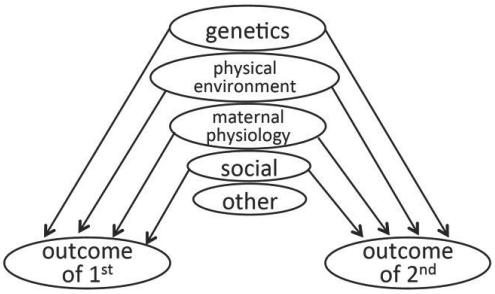


Figure 2. Association between outcomes of 1st and 2nd pregnancy of the same mother as caused by the indirect effect of many factors that persist over time

1.8 Methodological challenges in studying recurrence of pregnancy outcomes

1.8.1 Confounding, adjustments and bias

Since recurrence risks represent the sum of a mixture of indirect effects, the concept of confounding is difficult to define for these associations. The contribution to the association for example from social factors may not necessarily represent confounding

in the common sense, since social factors are just one of many sets of factors that contribute to the association. By adjusting for social factors we may attempt to remove the contribution of social factors to the association. The remaining adjusted estimate would still not represent a causal effect but only the sum of all other indirect contributions to the association. It may therefore be helpful to avoid the term confounding of these association estimates. The looser term of adjustment may apply better to the situation. Adjustment may remove the contribution of specific factors to the association.

In practice one would have to use information either from the first or the second pregnancy for adjustments. Usually adjustments are made for variables that are measured at the first pregnancy [77]. Wilcox suggested that if the aim of the analysis of recurrence risk of a pregnancy outcome is prediction, condition during the first pregnancy could be adjusted for. If the purpose of the analysis is to determine whether there are underlying causal mechanisms, adjustments are not necessary or useful.

In studies of the causal effect of a current exposure on an outcome in the second pregnancy, adjustment for the outcome of a previous pregnancy may introduce bias due to dependency between the current exposure and history of the past pregnancy [77]. Other investigators [62] have also reported that some women with previous poor pregnancy outcomes are more likely to have low socio-economic status or low educational attainment. These women are more likely to have poor quality of information that may lead to underestimation of recurrence risk due to incorrect data

linkage between pregnancies. Basso [77] found that the recurrence risk may also be affected by time-dependent covariates. For example, some women may change their behaviour in subsequent pregnancies as a result of a previous poor pregnancy outcome. Still, it is difficult to determine what the correct target value of estimation of recurrence risk is, except that it should represent the effects that are present in a defined population. The recurrence risk will to a large degree be determined by the indirect effect of a mixed bag of factors present in the population (figure 2). Any direct effects between the exposure (outcome of first pregnancy) and the outcome (outcome of second pregnancy) are likely to be weak. A general recommendation would therefore be to avoid unnecessary adjustments and realize that the concept of confounding is difficult to define in this context.

Selection mechanisms may bias recurrence estimates away from what is the correct value for the population. If only a subset of women with the highest risk is represented in the data, estimates of recurrence risks may be exaggerated.

1.8.2 Selective fertility and heterogeneity

A previous pregnancy outcome is an important determinant for a woman's or couple's decision of whether and when to have a next pregnancy [77]. Selective fertility is a tendency of women or couples with a previous experience of perinatal loss to go on for the next pregnancy after a short period in order to replace the loss of a baby [79]. On the other hand, parents with a previous live child with a birth defect or chronic illness

are more likely to wait a longer time, or choose not to have a next pregnancy [77]. Skjaerven and colleagues [79] found that despite the difference in the risk of perinatal loss between women, selective fertility may result in bias due to overrepresentation of women with high risk at higher birth orders.

1.8.3 Interpretation of recurrence risk of pregnancy outcomes

Epidemiologists and clinicians may have different interpretations of risk measures [60]. One author noted that clinicians often misinterpret the concepts of relative risks and odds ratios, which leads to early change in clinical practice and interventions based on weaker associations, due to clinicians' biased decision when dealing with women with previous adverse pregnancy outcomes [60]. Furthermore, Ananth reported on obstetricians' tendency to focus on modifiable risk factors when counselling women with a previous adverse pregnancy outcome, in order to maintain the physician-patient relationship [80]. The author concluded that, since most of the studies on recurrence risk of pregnancy outcomes are population-based, the population-based recurrence risk cannot be directly translated to the individual patient.

1.8.4 Sample size and statistical analysis

Studies on recurrence risk of pregnancy outcomes require a large sample size in order to have statistical power to estimate the recurrence risk in successive pregnancies and enhance generalizability of the results [80]. Hospital-based birth registry studies may suffer from a selection bias due to over-representation of high-risk women who may

not be representative of other women in the general population. Furthermore, since the analysis of recurrence risk of pregnancy outcomes involves correlated data; this requires a method of analysis that accounts for this correlation. One simple method is to use a robust variance estimates and clustering (available in STATA), using the mother as the unit of analysis. Other challenges include accurate definition of exposure and outcome, and choosing an appropriate study design [80].

1.9 Epidemiology of recurrence of perinatal death

1.9.1 Recurrence of perinatal death

Table 1 shows studies which have reported recurrence risks of perinatal death. Women with a previous history of perinatal death are generally at increased risk of experiencing perinatal death in their subsequent pregnancy [81-84]. Prospective studies typically from high-income countries have reported a high recurrence risk of perinatal mortality in subsequent pregnancies, ranging from 2 to 5-fold [58, 85, 86].

A previous study in Israel reported a recurrence risk of perinatal mortality of two-fold in women whose previous babies died during the perinatal period as compared to women whose first infant survived [58]. In the same study, a previous history of hypertensive disorders, diabetes mellitus and fertility treatment were associated with increased risk of recurrent perinatal mortality. Salihu and coworkers [85] assessed the relationship between maternal age at initiation of pregnancy and recurrence of perinatal mortality using the Missouri maternally-linked longitudinal data. They found that women with a previous history of perinatal mortality, stillbirth or neonatal

mortality had 4 to 5-fold increased risk of recurrence of the similar outcomes. Furthermore, a recent report from a multi-country study in developing countries has reported a recurrence risk of perinatal death of more than two-fold [87]. A previous hospital-based study in Tanzania reported a recurrence risk of perinatal death which was 1.9- fold [88].

1.9.2 Recurrence of stillbirth

Tables 1 also show studies which have reported recurrence risk of still birth. Most of the previous studies are done in high-income countries and have reported on the recurrence risk of stillbirth, ranges between 2 to 10-fold [82, 89-91]. Furthermore, a previous history of stillbirth has been associated with an increased risk of adverse maternal and perinatal outcomes in the subsequent pregnancy, such as infant mortality, neonatal death, preeclampsia, abruption placenta, preterm birth, low birth weight, caesarean section and induction of labour [56, 92-94].

The risk factors for recurrence of stillbirth have been well documented including placental abruption, preterm birth, low birth weight [82, 95], preeclampsia, small for gestational age [95], and obesity [96].

In the Missouri maternally-linked cohort, Salihu and coworkers [85] found that young women who had a previous history of neonatal mortality had a five-fold increased risk of recurrence stillbirths in their subsequent pregnancies compared with their older counterparts. In 2011, August and colleagues [86], using the same data, reported a three-fold increased recurrence risk of stillbirth for women whose first pregnancy ended in infant death, compared with women whose first infant survived.

When the authors stratified the data by race, they found that the risk of stillbirth in the subsequent pregnancy increased by a factor of more than four among black women with a past history of infant death. Moreover, white women whose first pregnancy resulted in infant death had a three-fold increased risk of stillbirth in their next pregnancy [86]

Sharma and colleagues [91] estimated the recurrence risk of stillbirth among relatively low-risk women (less than 35 years) using the Missouri maternally-linked data. They found that the recurrence risk of stillbirth in the second pregnancy was approximately six times higher in women with a previous stillbirth compared with their counterparts who had a previous live birth. When data were stratified by stillbirth subtype, the recurrence of early stillbirth (20–28 weeks of gestation) was10-fold higher compared with a lower risk of 2.5-fold for the late stillbirth (≥ 29 weeks of gestation) [91]. In addition, women with a previous stillbirth had a higher risk of intrapartum stillbirth compared with antepartum stillbirth (Hazard ratio; HR=12.2 vs. 4.2), respectively [91]. Furthermore, Black and colleagues [94] reported that the risk of stillbirth in a subsequent pregnancy among women who had a previous stillbirth was only 1.2-fold compared with those who had delivered a live born baby. The authors concluded that the majority of the women with a previous stillbirth were also likely to have live births in their subsequent pregnancy.

A prospective cohort of 1,688 women attending ANC in Tanzania showed women with a previous history of stillbirth had 7.5-fold increased risk in their subsequent pregnancy as compared to women whose infant survived [53].

Parents who have lost a baby are very anxious to know the causes of death for their baby and the chance of such an event occurring in the next pregnancy. All these questions require answers from the health care givers in a timely manner in order to give assurance and comfort the parents. Furthermore, women with previous perinatal loss require counseling about recurrence risk of perinatal death to prevent future occurrence. In addition, knowing the causes of previous perinatal death enables clinicians to predict recurrence risk and help to guide management of the future pregnancy.

Table 1: Summary of the selected studies on the recurrence risk of perinatal death

Author (year of publication)	Country	Study design	Study population	RR(95% CI)
Salihu HM [85]	USA (1989–2005)	Cohort	152,151 mothers	5.1 (3.91–6.73) †
August EM [86]	USA (1989–2005)	Cohort	320,350 mothers	2.9 (2.02–4.18)*
Weintraub AY [58]	Israel (1988–2004)	Cohort	25,876 mothers	2.2 (1.2–3.9) †
Ouyang F [88]	Low income countries (2004–2008)	Global Survey on Maternal and Perinatal Health	61,780 women	2.35 (1.65–3.37)* 2.82 (1.76–4.52) §
Sharma PP [91]	USA (1978–1997)	Population cohort	261,384 women	5.8 (3.7– 9.0)*
Melve KK [84]	Norway (1967–2004)	Population cohort	574,311 mothers	2.3 (1.2– 4.7)*
Bhattacharya S [82]	UK (1981–2000)	Cohort	309,304 women	1.94(1.29–2.92)*
Black M [94]	UK (1976–2006)	Cohort study	34,079 women	1.2 (0.4–3.4.)*
Hinderaker S [87]	Tanzania(1995–1996)	Hospital-based cohort study	3,512 women	1.9 (1.1–3.2) †

*Stillbirth
§ Early neonatal death
†Perinatal death

1.10 Epidemiology of preterm birth recurrence

Women with a previous preterm birth are at increased risk of a preterm birth in a subsequent pregnancy [97-99] (Table 2).

Table 2: Summary of selected studies on the recurrence risk of preterm birth

Author (year of publication)	Country	Study design	Study population	Recurrence risk of Preterm birth
				RR(95% CI)
Ananth CV [100]	USA(1989–1997)	Retrospective cohort study	154,809 mothers	3.6 (3.2–4.0)^{SPTB} 10.6 (10.1–2.4)^{MPTB}
Simonsen SE [99]	USA(1989–2007)	Historical cohort study	439,067 mothers	1.29(1.04–1.60)^{MPTB} 1.24(1.1–1.40)^{SPTB}
Ananth CV [101]	USA (1988–1999)	Cohort	15,945 mothers	5.6 (4.5–7.0)^{S}
Esplin MS [102]	USA(1989–2001)	Prospective cohort	98,724 women	13.6(11.5–16.0)^{SPTB}
Kistka ZAF [103]	USA(1989–1997)	Population cohort	368,633 mothers	5.4(5.1–5.8^{SPTB} (52.6 % vs. 46.3 %) for black vs. white
McManemy [104]	USA 1989–97	Population based cohort	19,763 women	6.7 (5.7–7.7)^{SPTB}
Meis PJ [105]	USA(1992–94)	Prospective cohort	2929 women	2.3 (1.5–3.4)^{SM}
Ekwo E [106]	USA (1988–93)	Prospective cohort	1,957 women	30.6% vs 11.7% (black vs white)
Adams MM [107]	USA (1980–95)	Population based cohort	178,896 women	26% vs. 19.9% (black vs white)
Carr-Hill [108]	UK, 1980)	Cohort	6572 mothers	15.4%
Di Renzo DC [109]	Italy (2008)	Retrospective cohort	7634 women	3.4 (1.3–8.7)

MPTB: Medically indicated Preterm Birth, SPTB: Spontaneous Preterm Birth, SM: Spontaneous preterm birth in the first pregnancy to medically indicated preterm birth in second pregnancy.

Recurrent preterm birth is associated with an increased risk of maternal complications such as type-II diabetes, thromboembolism, [110] and cardiovascular disease in later life [111]. Furthermore, recurrent preterm birth is also associated with high risk of perinatal mortality, small for gestational age and Apgar score ≤ 7 minutes [112].

Prospective studies from high-income countries have reported high recurrence risk of preterm birth in a subsequent pregnancy, ranging from 1.5 to 14-fold [100, 102]. The risk factors associated with increased risk of recurrent preterm birth have been well documented. These include preexisting maternal medical conditions, short interpregnancy interval, underweight pre-pregnancy BMI, very high pre-pregnancy weight gain, history of miscarriage or stillbirth, fetal anomaly, short cervix, positive results of fetal fibronectin screening and PPROM (Preterm Premature Rupture of Membranes) and gestational age in the previous pregnancy [23, 113, 114].

Previous studies have noted that black women have a higher recurrence risk of preterm birth compared with their white counterparts [107, 103, 106]. The recurrence risk of preterm birth is also dependent on gestational age in the previous preterm birth and number of previous preterm births [100, 103]. McManemy and colleagues [104], using the Missouri maternally-linked data for women who had three consecutive births, found that the recurrence risk of preterm birth in the subsequent pregnancy increased by two-fold in women with two previous preterm deliveries compared with women who had one prior preterm delivery (42% versus 21%) [104]. Furthermore, the recurrence risk of preterm birth was also higher for women who had two previous very preterm births (21-31 weeks) as compared to those who had two previous moderate preterm deliveries (32-36 weeks) (57% versus 33%) [104]. The authors noted that the highest risk of recurrent preterm birth tended to occur around the same gestational age as the previous preterm birth. This observation corresponds with other studies [100, 102-104], but in contrast with other authors [115].

Causes and risk factors of preterm birth are heterogeneous, which leads to variations in recurrence of preterm births [116]. The previous investigators suggested that preterm births should be classified according to underlying clinical subtypes. Women with a previous spontaneous preterm birth are at increased risk of spontaneous or medically indicated preterm birth in the subsequent pregnancy, likewise for medically indicated preterm birth [101]. Previous studies have shown that the recurrence risk of medically indicated preterm birth is higher than for spontaneous preterm birth [100, 117], while other authors have reported similar recurrence risk between two clinical subtypes [99].

Women with a history of preterm birth are of particular concern because they are at higher risk of experiencing preterm birth in their subsequent pregnancies and increased likelihood of adverse perinatal outcomes such as perinatal death. Despite reported high recurrence risks of preterm birth and associated adverse pregnancy outcomes especially among black women. Our literature search did not identify any such studies in African populations including Tanzania. Information about recurrence risks of preterm birth and its underlying risk factors may be important to accelerate the efforts towards achievement of MDG 4 for child survival in 2015 and beyond.

1.11 Epidemiology of preeclampsia recurrence

Prospective studies in high-income countries have reported high recurrence risk of preeclampsia, ranging between 6% and 27% [118-121] (Table 3). Some hospital based-studies in sub Saharan Africa also have reported recurrence risks of

hypertension and preeclampsia ranging from 15.8% to 36% [122, 123]. Women with a recurrent preeclampsia are at increased risk of preterm birth, caesarean section delivery, antepartum haemorrhage, intraventricular haemorrhage, chronic hypertension, intrauterine growth restriction, small for gestational age, low birth weight infants, perinatal death and placental abruption [57, 118, 120, 121].

Several studies have reported risk factors that are associated with recurrent preeclampsia, including a history of a preterm preeclampsia pregnancy, overweight, obesity, previous preterm delivery, long interpregnancy interval, prior stillbirth, miscarriage, history of intrauterine growth restriction, chronic hypertension, multiparity and uric acid levels [35, 119, 124, 125].

A published report from an intergenerational study has demonstrated the influence of both maternal genes and fetal genes in triggering preeclampsia [126]. The authors found that women whose mothers had preeclampsia had a more than two-fold increase of the risk of developing preeclampsia, compared to their counterparts who were born to mothers with a normotensive pregnancy. On the other hand, men who were born after a pregnancy complicated by preeclampsia also had an increased risk of triggering preeclampsia in their partners [126].

Table 3: Summary of the selected studies on the recurrence risk of preeclampsia

Author (year of publication)	Country	Study design	Study population	Recurrence risk of Preeclampsia
				RR(95% CI)
Stekkinger E [127]	The Netherlands ((1996–2004))	Retrospective cohort study	480 women	3.77 (1.6–8.8) 17%* and 45%**
Bhattacharya S [40]	UK (1986–2006.)	Prospective cohort study	24,500 women	5.12 (4.42–6.48)
Brown MA [125]	Australia (1988–98)	Prospective cohort	1,354 mothers	1.08 (1.03–1.13) 14 %
Trogstad L [128]	Norway (1967–98)	Prospective cohort	19,960 women	14.1 % (13.6–14.6)
Mostello D [119]	USA (1989–97)	population-based cohort	6,157 women	8.4 (7.8–9.1) 14.7 %
Bramham M [118]	UK (2003–2005)	Randomized placebo controlled trial	500 women	1.05 (0.96–1.16); 23 %
Van Rijn BB [129]	The Netherlands (1993–2002)	Prospective cohort	120 women	25%
Hernandez-Diaz S [121]	Sweden(1987–2004)	Prospective cohort study	19,540 women	14.7 %
McDonald SD [130]	Canada (1994–2002	Population-based cohort study	1,954 women	6.8 % (5.7–7.9 %)
Melamed N [120]	Israel (1996–2008)	Cohort study	600 cases 1,800 none	8.6 (3.2–23.4); 5.9 %

* Recurrence preeclampsia without metabolic syndromes ** Recurrence preeclampsia with metabolic syndromes.

Previous studies also have shown that women who change partners between two successive pregnancies are at an increased risk of developing preeclampsia, compared to those who remain with the same partner [131, 132]. However, this association disappeared after controlling for interpregnancy interval. A similar finding has been reported elsewhere [40, 119].

Studies from western countries have shown variation in recurrence risk of preeclampsia, preterm birth and perinatal death among black and white women, with the black women bearing a high risk of recurrence than white counterparts. Since preeclampsia, preterm birth and perinatal death are interrelated, recurrence risk

patterns of these outcomes and its underlying risk factors in Africa are important to identify to see if similar risks exist among black African women. There is also limited information about perinatal outcomes among patients with preeclampsia and the implications of recurrent preeclampsia on perinatal outcomes (preterm birth and perinatal death). This information is important for planning maternal, child health and newborn health care services, and if possible to accelerate achievement of MDGs 4 & 5.

2. Study rationale and objectives

2.1 Rationale

Cohort studies in high-income countries have reported high relative risk of recurrence for several adverse pregnancy outcomes. When compared to the lower population risk in these countries, the absolute recurrence risk is, however, still low. If similar levels of relative risk of recurrence exist in Africa against the much higher population risk, some women would carry an exceptionally high risk and might benefit from special prevention strategies. Information about recurrence of adverse pregnancy outcomes and the underlying risk factors may help in designing appropriate prenatal and postnatal care to improve maternal and newborn health. It may also help clinicians to identify sub-groups of women with relatively high risk of recurrence, especially those with a prior history of adverse pregnancy outcome who desire to have a subsequent pregnancy. These women may require counseling about recurrence and close follow-up in their subsequent pregnancies. If, however, recurrence risk is not much higher than the average risk in African women, strategies focusing on the whole population could still be more important.

Most of the studies of recurrence risks have been conducted in high-income countries and little is known about recurrence risks in low-income countries. There are very limited data about recurrence risks of adverse pregnancy outcomes from sub-Saharan Africa including Tanzania. This thesis aimed to use existing data from a hospital based registry in Northern Tanzania to estimate the recurrence risk of

perinatal death, preterm birth and preeclampsia among Tanzanian women. We also assessed risk factors associated with recurrence of these outcomes, and perinatal mortality in pregnancies with recurrent preeclampsia or preterm birth.

2.2 General objective

The main objective of this thesis was to study recurrence risks of selected reproductive health outcomes among women in Northern Tanzania using existing data collected from a birth registry. Using unique identification numbers of women in the registry, a historic cohort-study was designed. An assessment of the completeness of prospective follow-up within the registry data was possible by using retrospective interview data on previous births of each woman at each birth at the hospital.

2.3 Specific objectives

1: To estimate the recurrence risk of perinatal death among Tanzanian newborns by studying births of women who already had experienced perinatal death in a previous birth (Paper I).

2: To investigate the consistency of a prospective estimate of recurrence risk of stillbirth in Tanzania with an estimate based on the mother's recall of their previous births (Paper I).

3: To estimate the recurrence risk of preterm delivery among Tanzanian women and to estimate the perinatal mortality among the babies in repeated preterm deliveries (Paper II).

4: To estimate mother's recurrence risk of preeclampsia in Northern Tanzania and asses the risks to the baby in pregnancies with recurrent preeclampsia (Paper III).

3. Materials and methods

3.1 Literature search strategies

We used Cochrane, PubMed and Google scholar to obtain articles that were potentially relevant for our topic. We also included books when necessary. We searched using key terms such as preeclampsia, recurrence of preeclampsia, recurrence risk of preeclampsia, recurrent preterm labour, recurrent preterm delivery, recurrence of preterm birth, recurrence rate of preterm birth, recurrence risk preterm birth, recurrent premature birth, perinatal death, perinatal mortality, stillbirth and early neonatal death, recurrence of perinatal death, recurrence of adverse perinatal outcomes, recurrence of stillbirth, recurrent foetal death and subsequent perinatal outcome after previous preeclampsia or preterm birth. A manual search among articles identified by this search was performed to obtain the relevant articles.

3.2 Study area

This study was conducted at Kilimanjaro Christian Medical Centre (KCMC), one of the referral hospitals in Tanzania, located in Moshi, Kilimanjaro region in northern Tanzania. According to Tanzania national census, Moshi urban and rural districts all together were reported to have a total population of 651,029 inhabitants [133] (Figure 3). Most births are from these districts; which defines the main catchment area of the hospital is the local population. However, some few births are from Hai district which is close to Moshi. The centre also admits referred cases from six regions; Arusha, Kilimanjaro, Manyara, Tanga, Dodoma and Singida, besides serving the local

community. Referred patients may come from one of four regions comprising Kilimanjaro, Arusha, Manyara and Tanga.

Kilimanjaro region has a fertility rate is 2.8 children per woman, with contraceptive prevalence rate of 50% [133]. The region has high institutional delivery rate as well as proportion of deliveries assisted by skilled personnel (86.7% and 86.1%, respectively) [133]. Overall prevalence of HIV in this region is 3.8% (4.9% vs. 2.2%, for women and men, respectively) which is below the national prevalence of 5.1% [133]. The antenatal care HIV prevalence in the region is 5.4%.The health care system in Tanzania is decentralized and deliveries can occur in any level of health care facilities, starting from the dispensary to health center, district hospital, regional hospital and to referral hospital or consultancy hospital.

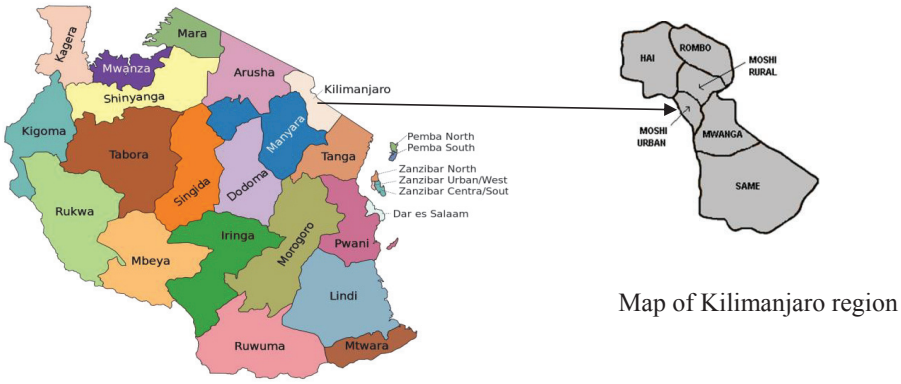


Figure 3. Administrative Map of Tanzania (Source:http://www.tanzania.go.tz**)**

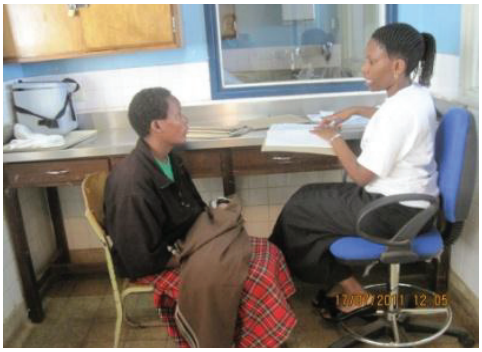
3.3 Data source

The KCMC Medical Birth Registry was established in 1999 in collaboration with the Norwegian Medical Birth Registry, through the University of Bergen in Norway and through Kilimanjaro Christian Medical University College (KCMUC). Initially, it

started as a pilot project between the Norwegian Programme for Development, Research and Education (NUFU) and KCMC in Tanzania; NUFU supported the KCMC birth registry in terms of financing and expertise through the Centre for International Health, at the University of Bergen in Norway. The KCMC Medical Birth Registry started to operate on July, 2000. All birth data are recorded using a standardized form and entered into a computerized database located at the birth registry. The data-base system was specifically designed for the purpose. Approximately 34,000 births were recorded by the end 2010. This is an average of 3,090 deliveries per year for 11 years.

The data from the KCMC Medical Birth Registry were prospectively collected by obstetricians and midwives throughout the period 2000 to 2010. Information from all mothers who deliver at KCMC was recorded at the registry within 24 hours after delivery or later in case a mother had recovered from complications. Trained nurse midwives conducted interviews on a daily basis using a standardized questionnaire to obtain relevant information for the respective mothers. In addition, mothers were asked to provide their antenatal (ANC) cards for more clarification regarding attendance at ANC and number of ANC visits as reported during the interview, referral to ANC (referred from health facility or self-referral), weight at first ANC visit, malaria prophylaxis, drugs, immunization history and condition of the mother during follow-up. The number of ANC visits (were recorded as continuous which) was then categorized with a cut-point at the average number of ANC visits in the studied population (i.e. 5 visits) (paper **I-III**). Verbal consent was sought from each mother

prior to the interview, after the objectives of the registry had been explained to the mother. Data were entered into a computerized data base at the birth registry. The details of the information entered at the medical birth registry has been described elsewhere [135]. The registry was designed for a wide range of purposes including institutional statistics and clinical and epidemiological studies. Several of those were specified in the protocol describing the registry project.



A nurse midwife interviewing a mother after delivery

3.4 Longitudinal record linkage

A unique hospital identification number was assigned to each woman at first admission and used to trace her medical record at later admissions. This identification number was included in the registry's record of each birth and was used to link records of successive births of the same woman. This enabled us to create a historic prospective cohort of women who delivered at least once at the hospital and follow their births at the hospital throughout 2010. In order to ensure that we analysed siblings from the same mother, we used the following two criteria: (1) we matched

year of birth in a birth record with birth years provided by same mother in a reproductive history interview in a subsequent birth; (2) we calculated the interpregnancy interval between two successive pregnancies and compared it with the change in maternal age between two successive pregnancies; a difference of more than two years was considered as an unmatched pair and was excluded from the study. In addition to these criteria, we also checked the correlation of birth weight between linked siblings in our data. A high correlation would imply that siblings in our data belonged to the same mothers and should be included in the cohort. If many unrelated children were included the correlation would be low.

3.5 Study design and study population

A historic cohort study was designed using the KCMC maternally-linked data for women who had delivered their 2 or more singleton babies at KCMC from 2000–2010. Women with multifetal gestations and those who were referred from rural areas for various medical reasons and women from other regions were excluded to minimize overrepresentation of high risk women and loss to follow up (in Papers **I**, **II**&**III**). In addition, women with missing records on gestational age in their first and subsequent recorded pregnancies were excluded in one paper (for Paper **II**). The study population was women with singleton deliveries from the natural catchment area of the KCMC hospital.

3.5.1 Cohort composition

Papers I and III

After the exclusion, we identified all women (n=19,811) who had their first singleton birth at KCMC from 2000–2008. These women constituted our cohort (Figure 4). In Paper I, we included 875 (4.4%) women who experienced perinatal death, as the exposed group, and 18,936 women with a surviving baby as the unexposed group. In paper III we included 736 (3.7%) with preeclampsia as the exposed group and 19,075 without preeclampsia as unexposed**.** These women were then followed for their subsequent pregnancies from 2000 to 2010. The median follow-up was 6.5 years. A total of 3,909 (19.7%) women were recorded with at least one or more births during the follow-up period. This contributed 4,503 siblings during follow-up.

Paper II

To estimate the recurrence of preterm birth and perinatal death in repeated preterm birth, we compared the risk of preterm birth in subsequent pregnancies among women who had complete information on gestational age for the index and subsequent pregnancies (both pregnancies). From the cohort we included women who were identified with singleton babies at KCMC between 2000 and 2008 (n=19,811). We excluded all women with missing gestational age in their first and subsequent pregnancies. The remaining cohort consisted of 18,176 (2,085; 7.2% with preterm births and 16,091 with term births) women who were then followed for their subsequent births up to 2010. Mothers with preterm births formed an exposed group while those who had term births formed an unexposed group. Our final sample was

3,359 (19.7%) women who were recorded with at least one or more births within the follow-up period, and contributed 3,867 siblings.

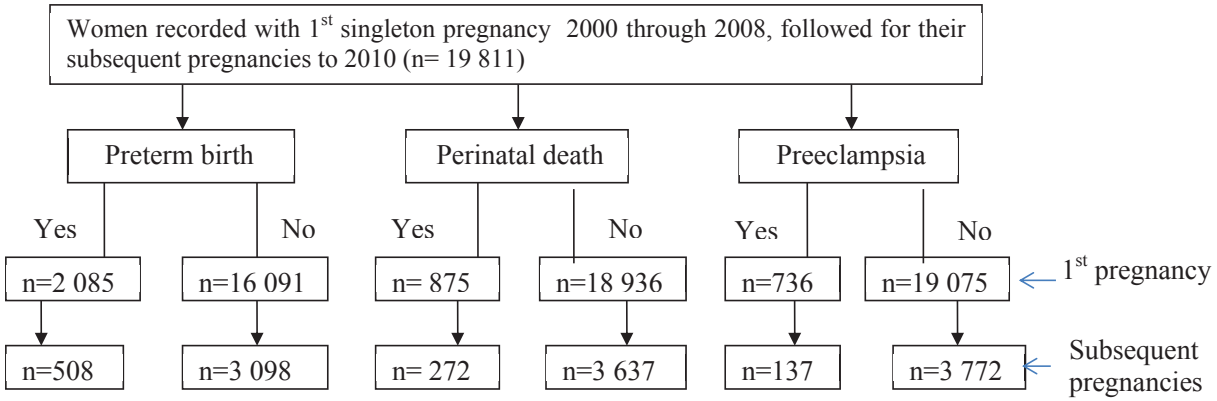


Figure 4. Flow chart showing differences in the three study cohorts

3.5.2 Estimation of loss to follow-up

Our follow-up mechanism to capture mothers who had subsequent births in our health facility may have been incomplete. We used data from the mother's reproductive history that were obtained through interviews with mothers at each delivery. This enabled us to calculate the expected proportion of mothers who had their subsequent births during the follow-up period. Assuming symmetry of the distribution of births within the period 2000 to 2010, we constructed a "backwards cohort". Whenever a mother had one or more babies, we included the most recent baby as the index birth in the construction of a backwards cohort (Figure 5). We identified 21,086 mothers who had the most recent baby in the period 2002–2010.

A total of 7,191 women (34.1%) reported a prior birth in the period 2000–2010 (Figure **5**). When we compared this estimate with the 3,909 (19.7%) of the women who were observed with a subsequent birth using the prospective cohort data, we estimated that the completeness of our follow-up was 58% (19.7/34.1). This implies that about 42% of the women who were expected to be observed with a subsequent pregnancy in our cohort were lost to follow-up. Among the main reasons for loss to follow-up are subsequent births occurring outside the hospital or imperfect record linkage within our data.

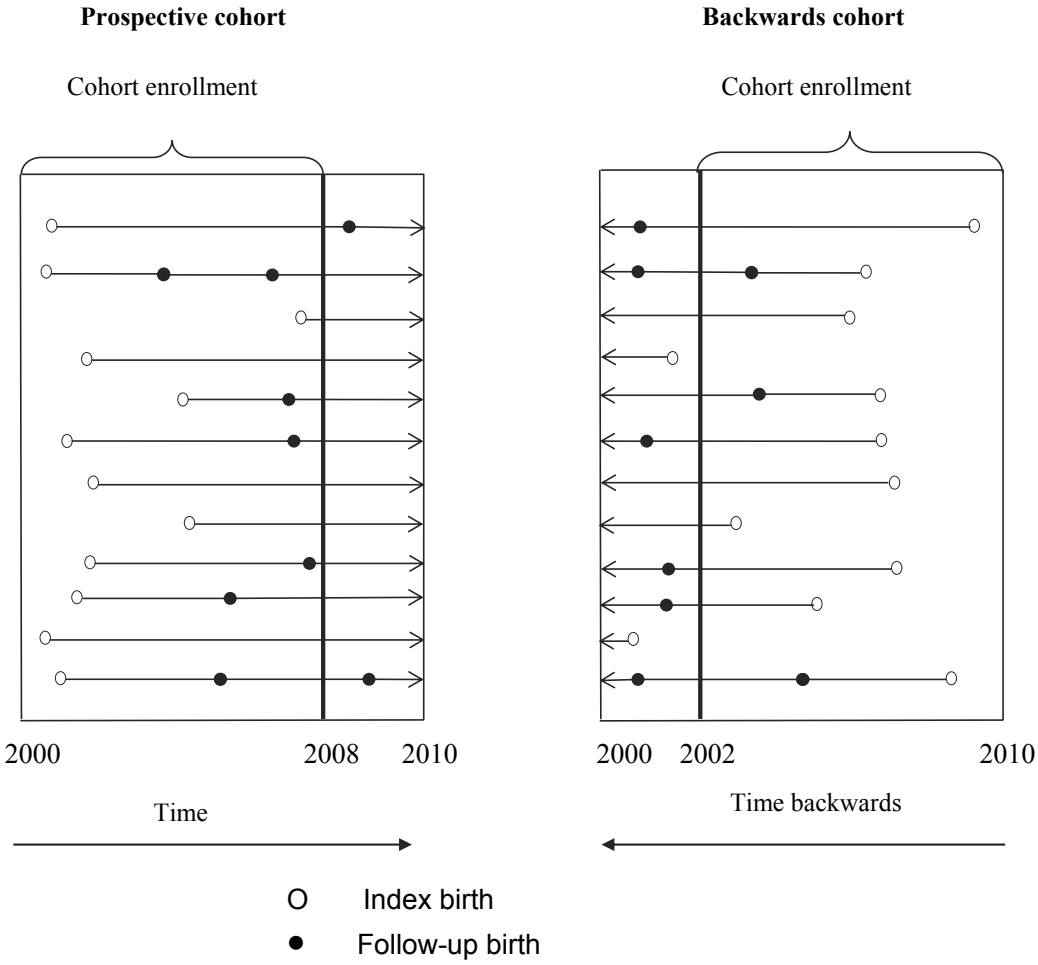


Figure 5: Construction of the "backwards" cohort

3.6 Study variables

Outcome measures

The main outcomes studied were the recurrence risks of perinatal death, stillbirth, preterm birth and preeclampsia in subsequent pregnancies.

Gestational age was calculated as the number of completed weeks between the first day of the last menstrual period (LMP) and date of birth in the subsequent pregnancy.

Preterm birth (PTB) was defined as a birth occurring at less than 37 completed weeks of gestation.

Recurrent preterm birth was defined as two or more consecutive preterm births [115, 136].

Perinatal death was defined as fetal deaths that occurred within a period of 28 weeks of gestation or more (stillbirth), plus infant deaths that occurred at less than 7 days of age (early neonatal death) [137].

Preeclampsia was defined as a new onset of hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg), accompanied by >=300 mg of proteinuria over 24 hours urine collection measured on two occasions, at least 6 hours apart, after 20 weeks of gestational age in a previously normotensive woman .

Secondary outcomes were continuation rate and precurrence risk of stillbirth.

Continuation rate was defined as a proportion of women who were recorded with a next pregnancy conditioned to the outcome of the previous baby.

Precurrence risk of stillbirth was defined as the proportion of previous babies of women that had a poor outcome, given that their current baby also experienced the same problem.

Independent variables

The independent variables were maternal and fetal characteristics in the first pregnancy. These include maternal educational attainment, pre-pregnancy weight, number of antenatal care visits (recorded as continuous), gestational hypertension, chronic hypertension, diabetes, induced labour, caesarean section, preterm birth, birth weight as continuous, then was categorized into low birth weight or normal birth weight, perinatal death (stillbirth and early neonatal death), maternal infections during pregnancy, preeclampsia, placental abruption and placenta previa.

3.7 Adjustment variables

As suggested in section 1.8.1, we do not interpret recurrence associations as direct causal effects and have decided to avoid the term confounding in this introduction. Still, we decided to adjust for some maternal factors at first birth which may have influence on pregnancy outcomes in a subsequent pregnancy. These adjustment factors were chosen based on their significant association with outcome of interest in a univariate analysis. Adjustment variables were entered in a multiple regression model one at a time to determine its contribution on the association. Adjustment was considered to be necessary when the adjusted relative risk differed from the unadjusted (crude) relative risk by 10% or more. Maternal age, maternal educational attainment and inter-pregnancy interval were adjusted for in most multivariate analyses. Other factors potentially associated with adverse perinatal outcomes were area of residence and infections. These were not significantly associated with any of the studied outcomes in the univariate analysis, and therefore not included as adjustment factors.

3.8 Statistical analyses

Data analysis was performed using the Statistical Package for the Social Sciences for Windows (SPSS version 18.0, Inc., Chicago, IL, USA), and Stata Intercooled version 12.0 (www.stata.com). Comparison of proportions between groups for categorical variables were done using a chi squared (χ^2) test, while comparison of the group means for continuous variables was performed using Student's t-test. The relative risks and recurrence risks with 95% confidence intervals (CIs) for adverse pregnancy outcomes (perinatal death, preterm birth and preeclampsia) were estimated using a log-binomial regression model while adjusting for the potential confounders. Furthermore, the log-binomial model was also performed to test for difference between recurrence risks by introducing interaction terms in the models. A p-value of 5% (2-sided) was considered statistically significant.

The recurrence risks were estimated from the first to any of the successive births (with mothers as the primary unit of analysis instead of births). Since we included recurrence from the first to any of the subsequent births by the same mother, our analysis involved repeated observations (births), whenever a mother contributed more than one follow-up birth. We used a clustered analysis technique with robust estimation of variances to account for repeated observations from the same mother. The continuation rate was expressed as the proportion of women in the cohort who had a second recorded pregnancy within the follow-up period. By using retrospective data obtained by interviewing mothers about their reproductive history, we were able to calculate precurrence rates and compare with our recurrence risks.

We compared the prevalence of preterm birth between women with complete data on gestational age and those who were missing records for the first and subsequent pregnancies. Finally, we identified the risk factors associated with recurrence risk of the studied adverse pregnancy outcomes, and we also explored the adverse birth outcomes subsequent to preeclampsia.

3.9 Ethical considerations

This study was approved by the Kilimanjaro Christian Medical University College research ethics committee. Verbal consent was sought from each mother prior to the interviews. The consent procedure was approved by the research ethics committee as it was part of the medical birth registry study protocol. Ethical approvals were given by the local Institutional Review Board at the hospital and by the Ministry of Health in Tanzania. Since the project was funded by the Norwegian government, the study protocol was sought from Norwegian Institutional Review Board, whereby they did not see the need to approve the project.

4. Results

4.1 Paper I: “Recurrence of perinatal death in Northern Tanzania: a registry based cohort study”

A cohort of 3,909 women who delivered their first singleton infants from 2000–2008 was followed up to 2010 for their subsequent pregnancies. Of these, 272 (6.9%) had experienced perinatal death in their first recorded pregnancy.

The absolute recurrence risk of perinatal death in women with a previous history of perinatal death was 9.1% compared to a lower risk of 2.8% for women whose previous infant survived. This corresponds to a relative risk of 3.2 (95% CI: 2.2 - 4.7). Altogether recurrence contributed 21.2% of the perinatal deaths in subsequent pregnancies.

Some maternal and fetal factors in the first pregnancy were independently associated with increased risk of perinatal death in subsequent pregnancies: preeclampsia (RR=4.5; 95% CI: 2.9 - 7.1), preterm delivery (RR=5.8; 95% CI: 4.1 - 8.0) and low birth weight (RR=6.5; 4.7 - 8.9). These factors were also important predictors for recurrence of perinatal death. Furthermore, women who experienced perinatal death in their first recorded pregnancy were also more likely to have preeclampsia, abruption placenta, induced labour, preterm delivery, maternal underweight, less than five ANC visits and low birth weight babies as compared to women who had a surviving child.

Women who lost their first child due to pregnancy complication by preeclampsia had the highest recurrence of perinatal death (20%). Furthermore, women who delivered a preterm baby or baby with low birth weight in their previous pregnancy also had an increased risk of perinatal death in their next pregnancy (10% to 14%). Women who had a previous normal birth weight baby and did not experience perinatal death had the lowest perinatal mortality in their subsequent birth (1.6%).

In a sub-analysis, we found that women who lost their first baby due to stillbirth were 5.1 times (95% CI: 3.2 - 8.1) more likely to experience stillbirth in their subsequent pregnancy as compared to women who had a live born baby. The recurrence of an early neonatal death was 2.2-fold (95% CI: 1.0-4.9). Women with previous perinatal death were more likely to continue for the next pregnancy as compared to those whose first baby survived (31% versus 19%).

4.2 Paper II: "Recurrence of preterm birth and perinatal mortality in northern Tanzania: registry-based cohort study"

A total of 3,359 women who had singleton deliveries and were recorded with subsequent births were studied. Of these, 479 (14.3%) women had preterm birth in their first recorded pregnancy compared to a 10.8% preterm birth among the women in the cohort who had no recorded subsequent birth.

Compared to mothers who delivered a baby at term in their first recorded pregnancy, mothers who had preterm birth were more likely to have poor attendance at

ANC, low educational level, low BMI, preeclampsia, caesarean section delivery and a low birth weight infant.

The absolute recurrence risk of preterm birth in a subsequent pregnancy was 17.3% in women who had a previous preterm birth in their first recorded pregnancy. This corresponds to a relative risk of 2.7-fold (95% CI: 2.1–3.4). The recurrence of preterm birth accounted for 12% (15/126) of perinatal deaths among all babies in subsequent births. This corresponds to a relative risk of 9.2-fold (95% CI: 5.2–16.1).

Figure **3** shows the effect of preterm birth on subsequent perinatal mortality. The recurrence risk of perinatal death was 5.9-fold (95% CI: 4.1–8.8) among babies who were born at term with an older sibling who was born preterm. This corresponds to an absolute risk of perinatal mortality of 10%. Furthermore, babies who were born preterm with an older sibling born at term had 3.4 fold (95% CI: 1.8–6.5) increased risk of perinatal mortality. The lowest risk of perinatal mortality was observed among babies who were born at term, with an older sibling who was born at term with an absolute risk of perinatal death of 1.7%.

Numerous maternal and fetal factors in the first pregnancy were independently associated with increased risk of preterm birth in subsequent pregnancy. These include low birth weight (RR = 2.9, 95% CI: 2.3–3.6), preeclampsia (RR = 2.5, 95% CI: 1.7–3.7) and perinatal death (RR = 2.5, 95% CI: 1.9–3.5).

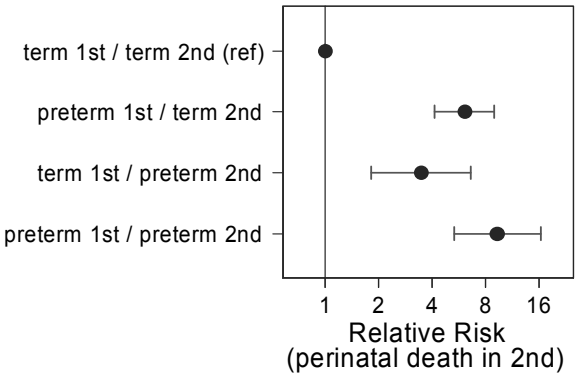


Figure 6: Subsequent preterm birth and risk of perinatal death

4.3 Paper III: "Recurrence of Preeclampsia in Northern Tanzania: A Registry-Based Cohort Study"

In this paper we aimed to estimate the recurrence risk of preeclampsia in subsequent pregnancies among women with a previous preeclampsia. We studied 3,909 women who had singleton deliveries in their first pregnancy from 2000–2008, and who had a subsequent singleton pregnancy in the followed-up period to 2010. Of these, 137 (3.5%) had preeclampsia in their first recorded pregnancy.

Preeclampsia in the first pregnancy was associated with higher risk of chronic hypertension, induced labour, preterm birth, delivery of low birth weight infant's and. perinatal death. The absolute recurrence risk of preeclampsia was 25%, which corresponds to a relative risk of 9.2-fold (95% CI: 6.4 - 13.2) higher compared with women without prior preeclampsia. The highest absolute recurrence risks of preeclampsia in the subsequent pregnancy were observed when the preeclampsia in a

previous pregnancy was accompanied by chronic hypertension (37.5%), previous preterm birth (35.5%), induced labour (32%) or perinatal death (31%).

A number of maternal and fetal conditions in the previous pregnancy were independently associated with higher risk of preeclampsia in the next pregnancy. These included gestational hypertension (RR= 9.8; 95% CI: 4.9-19.1), chronic hypertension (RR = 8.9; 95% CI: 5.7-13.8), diabetes mellitus (RR = 8.4; 95% CI: 2.7-26.3), perinatal death (RR= 3.9; 95% CI: 2.9 - 5.9), preterm birth (RR= 3.1; 95% CI: 2.1 – 4.7) and delivery of low birth weight infant (RR= 3.1; 95% CI: 2.1 - 4.5). Moreover, a previous history of preeclampsia was associated with increased risk of perinatal death (RR= 4.3; 95% CI: 2.7 – 6.8), delivery of low birth weight baby (RR= 3.5; 95% CI: 2.2 – 5.4), and preterm birth (RR= 2.5; 95% CI: 1.7 – 3.6) in the subsequent pregnancy. Much of this risk appeared to be associated with recurrence of preeclampsia. The recurrence risk of the studied pregnancy outcomes remained unchanged also after adjusting for the number of ANC visits in the subsequent pregnancy.

5. General discussion

5.1 Methodological challenges

In this section we discuss methodological problems related our design, sample size representativeness, nature of the population studied and complexity of data analysis that may have influenced internal and external validity of our results. We have also discussed measures taken to minimize sources of bias.

5.1.1 Design

We used a registry-based historic cohort design in all of the three papers constituting this thesis. The cohort was constructed using maternally linked data from the KCMC medical birth registry. Respective siblings were linked using unique identification numbers assigned to each woman who delivers at the KCMC hospital, and the number is supposed to follow the woman through all her births that occur at KCMC. This enabled us to create a reproductive history for each individual woman and made it possible to estimate recurrence risks. This would not be possible for traditional population based repeated surveys where data usually are not linked. Apart from linked data which allows opportunity to study recurrence of pregnancy and birth outcomes, registry-based cohort approach saves time and minimizes costs by using existing data. Medical information is collected prospectively and in a standardized manner. Large registries also confer power to assess rare outcomes. Despite these strengths, registry-based cohort studies have some limitations such as self-reporting bias for interview based data, errors in collected data and data entry, missing

information for some important variables (random or non-random missing), under-reporting of births and deaths, especially in settings with a high prevalence of home delivery like some other areas of Tanzania.

The opportunity to study recurrence was deliberately built into the registry when it was started. A registry is a multi-purpose data-collection and the opportunity to do the recurrence studies we have done in this thesis is a rare opportunity in Tanzania. Overall, the historic prospective design used in this thesis was appropriate for estimation of the recurrence risk of the adverse pregnancy outcomes studied.

5.1.2 Internal validity

Internal validity refers to the extent which the study results are associated with the factors under study and not explained by other extraneous factors such as bias and confounding [138]. As stated in section 1.8.1, confounding may be difficult to define in the context of recurrence risks since it is not trying to estimate a direct causal relationship. A recurrence risk is an association that is mainly caused by a host of indirect effects. The concept is used mainly to demonstrate heterogeneity of risk and for prediction of risk. There are however many potential sources of bias in the estimation.

5.1.2.1 Information / measurement bias

Information bias refers to systematic differences in the way information on exposure and outcome are obtained from study participants, or error in classifying the exposure or outcome status of an individual [138]. In this thesis we discussed four different

forms of information bias that may have influenced validity of our results. These include interviewer bias, recall bias, misclassification bias and ascertainment bias.

Interviewer bias

Interviewer bias occurs when there is systematic differences in the way information is obtained from the studied groups [139]. This may be introduced when the interviewer has a prior knowledge about individual exposure or outcome status. In this thesis, the problem of interviewer bias was minimal because data collection was performed using a standardized questionnaire, and the interviews were conducted by well-trained nurse midwives based on the standardized medical birth registry protocol for data collection. Since the interviews for each woman was performed independently at each delivery between successive pregnancies this ensures that the interviewers were blinded to the exposure and outcome status. Furthermore, the interviewers were not aware of hypothesis under investigation; therefore, the possibility that our results could be explained by the effect of the interviewer bias is unlikely.

Recall or reporting bias

Recall bias occurs when there is differences in recall or reporting about the previous exposures with regard to the present outcome between study groups [140]. In cohort studies recall bias can rarely occur; for example, women who experienced poor pregnancy outcomes may try harder to recall their previous exposures that related to outcome in the present pregnancy than women who had healthy pregnancies. This may result in over estimation of the reported outcomes. In this thesis, the possibility that our results could have been influenced by recall bias is less likely because the use of

maternally-linked data in our study enabled us to study each woman in a prospective way; this minimizes the problem of recall bias.

Misclassification bias

Misclassification bias refers to inaccurate classification of an individual by assigning the individual into a wrong category (exposure or outcome status) [141]. Misclassification bias may result in underestimation or overestimation of the measure of association (relative risk or odds ratio).

In Paper II, the estimation of gestational age was based only on the date of last menstrual period (LMP). Since the majority of the women could hardly remember the exact date for their LMP, this may have introduced misclassification bias of preterm birth and influenced our results. However, if this is true, such misclassification bias is likely to be non-differential where some women with term pregnancy may have been misclassified to have preterm birth and vice versa for women with term pregnancy. Therefore, the estimated recurrence of preterm birth in our study may be underestimated. We have discussed on possibility of using birth weight as a proxy measure of gestational age in sub Saharan Africa when the data for gestational age is missing, because these variables are correlated (Paper II).

Ascertainment bias

Perinatal mortality

In this thesis, follow-up was restricted to mothers who stayed in the hospital within seven days after delivery; ascertainment of early neonatal death may not be complete,

as early neonatal deaths that may have occurred outside the hospital within seven days of life for mothers who were discharged earlier than 7 days were not captured in the birth registry. The majority of the women who delivered at KCMC were living in Kilimanjaro region where the institutional delivery rate is 88 percent [133]. But still we don't know the birth characteristics of other women who delivered outside KCMC. This may have resulted to underreporting of true perinatal death and its recurrence (Paper **I**).

Preterm birth

In Paper **II** of this thesis, about 10.8% of the women in the cohort who were recorded with preterm birth in their first pregnancy missed gestational records in their subsequent births. It is possible that some of these women might have preterm births in their subsequent pregnancies. Since these women were not included in the estimation of recurrence risk of preterm birth, we doubt that this could result in underestimation of the reported recurrence risk of preterm birth in the present study.

5.1.2.2 Adjustments

Although we do not consider confounding in the strict sense relevant for recurrence risks, we decided to perform adjustments. Adjustments would in practice work as adjustments for confounding and can be performed by stratification and multivariate techniques [138]. We should note that we did use the term confounding in the papers.

In this thesis, we adjusted some factors in multivariate regression models (Papers I-III). Maternal age, maternal education and interpregnancy interval were adjusted during analysis. However, some variables associated with preeclampsia such as

maternal behavioural factors during pregnancy, immunological factors, paternity change between pregnancies were not captured in the medical registry, and information on body mass index variables was incomplete. The estimated recurrence risk of preeclampsia could therefore be interpreted as including the contribution of these factors. Other causes of perinatal deaths such as birth asphyxia and infections might have contributed to estimated recurrence of perinatal death (paper I).

5.1.2.3 Effect modification

Effect modification occurs when the association between an exposure variable and an outcome of interest varies between levels of a third factor (effect modifier) [138]. In this thesis, we could measure whether the recurrence risk (as a measure of heterogeneity or prediction power) depended on another factor. We found that the association between previous perinatal death and perinatal death in a subsequent pregnancy was modified by preterm birth and preeclampsia in the first pregnancy (Paper **I**). Similarly, the association between previous history of preeclampsia and preeclampsia in the subsequent pregnancy was also modified by chronic hypertension and induction of labour in the past pregnancy (Paper **III**). Even if effect modification existed in our data, our main focus was on average or total recurrence risk.

5.1.3 External validity and selection bias

External validity refers to the extent to which the study findings can be generalized to a large population [142]. Since we wanted our results to be valid and generalizable to a population of women with singleton deliveries in the normal catchment area of

KCMC, we excluded all women who were referred to KCMC from rural areas for various medical reasons and women with multiple gestations to avoid overrepresentation of medical problems among women from more distant areas. It is still difficult to assess whether the heterogeneity we estimate is different from that of the general population in the area. It is possible that women with higher risks are overrepresented in the hospital data. They also get medical support which is different from the population. This causes bias in prevalences, but it is unclear how a relative risk of recurrence, which is our measure of heterogeneity, is affected. There is a potential for bias compared with the population.

Selection bias occurs when there is a difference in characteristics related to exposure or outcome under investigation between individuals who are selected to participate in the study and those who are not selected [143]. Selection bias is a common problem in facility-based studies of prevalence, because women with a history of a pregnancy complication tend to deliver at a higher tertiary hospital for their subsequent pregnancies. In this thesis, selection bias could have influenced our results if women who were included in the study were different from women in the catchment area of KCMC, and if women who came back to KCMC after a previous loss or pregnancy complications are different from those who did not come back or those outside the KCMC catchment area. This could result in errors in the estimated recurrence risks which in turn may affect generalization of our findings to other women in the general population.

In order to minimize the problem of selection bias, we excluded all women who were referred from rural areas for various medical reasons for their first and a subsequent pregnancy in the main analysis to avoid overrepresentation of group of women with high risk pregnancy. In addition, we performed separate sub-group analyses by including group of women who were initially excluded in the main analysis s to determine the possible effect of selection bias. However, we found that the later estimates were comparable to the main results. The observed recurrence risk estimates are less likely to be explained by the effect of selection bias, but estimates may still be biased.

5.1.3.1 Loss to follow up

Loss to follow-up occurs when individuals who were initially enrolled in the study and after the collection of the baseline information withdraw from the study. Loss to follow-up is a common problem in cohort studies

In our study, only 20% of the women in the cohort were recorded with a subsequent pregnancy during the follow-up period. There is a possibility that some of the women who lost to follow-up had further births in other settings. When we compared this figure with 34% women who were expected to have another pregnancy during follow-up (calculated using reproductive history data) (Figure 5), we may assume that we had 58% complete follow-up. This gives an estimated loss to follow-up rate of 42%. Loss to follow-up may lead to biased estimates of the reported recurrence risks in our study if women with previous loss or complications who were followed for subsequent pregnancy had different characteristics from those who did

not show up in the subsequent pregnancy. However, we do not know what are the characteristics of women with and those without previous loss or complications who did not show up in their subsequent pregnancy.

Our findings can not be directly generalized to other women who delivered at lower levels of health care or at home, but may be generalized to other similar hospital settings in Tanzania and perhaps in sub-Saharan Africa. The estimated recurrence risks and the associated risk factors in our study are consistent with other studies in the region, as well as in high income countries, that were conducted in similar settings. This suggests that our findings could be representative also for regular women in the catchment area of KCMC and similar African settings.

5.1.3.2 Role of chance

Chance refers to the degree to which the estimates are affected by random variation, and it is a measure of precision [138]. The role of chance in any epidemiological study can be evaluated by assessing either hypothesis testing (p value at 5% or 1%) or estimated 95% confidence interval (CI) of the measure of effect (relative risk or odds ratio). The precision can be achieved by increasing the sample size.

In this thesis, the sample size was large enough to provide relatively high precision of the recurrence risk estimates. Most of the risk factors for recurrence risks of the studied outcomes were statistically significant with narrow 95% confidence intervals (Papers I-III). Therefore, the possibility that our findings could be explained by chance is unlikely.

5.2 Discussion of the main findings

In this section we discuss our results and compare them with findings from other studies. We studied the recurrence risks of perinatal death (Paper **I**); recurrence risk of preterm birth and perinatal mortality in repeated preterm delivery (Paper **II**); and in Paper **III** we estimated mother's recurrence risk of preeclampsia. The risk factors associated with recurrence risk of the studied outcomes, and subsequent perinatal outcomes after a preeclampsia in the index pregnancy have also been discussed. In general, we found evidence of strong heterogeneity in risk of the studied outcomes.

5.2.1 Overall study outcomes

Paper I

We found that the absolute recurrence risk of perinatal death in women who had previous perinatal death was 9.1% compared with a lower risk of 2.8% in women who had a previous surviving infant. This corresponds to a relative risk of 3.2 (95% CI: 2.2 - 4.7). Altogether 21.2% of all perinatal deaths in subsequent pregnancies were attributable to recurrence of preterm birth.

The absolute recurrence risk of perinatal death estimated in our study was higher as compared to that previously reported in high-income countries [58].The recurrence risk of perinatal death of 3.2-fold in our study was consistent with other studies in high-income countries [56, 58, 85, 86]. But it was higher as compared to a 1.9-fold risk which was previously reported in one hospital study in Tanzania [87], and 1.62-fold among Australian women by Robson et al. [144]. However some studies

have reported slightly higher relative risks [85, 93]. The estimated recurrence risk of stillbirth of 5.1 in our study was in accordance with most studies from high-income countries [86, 145], but higher than some studies [82, 94, 146]. Furthermore, the recurrence risk of early neonatal death in our study was 2.1-fold, which corresponds very closely to the recurrence risk of 2.8-fold that was reported in a recent study from developing countries [88]. The lower absolute recurrence of perinatal death in high-income countries may be explained by heightened antepartum surveillance in subsequent pregnancies among women with a previous history of a perinatal death. These women are considered by the health care providers as a high risk group, and are more likely to be closely monitored or referred to more specialized care in their next pregnancies. Lack of specialized care services in the low-resourced settings could be a possible explanation for the observed differences in perinatal mortality between our study and those of others.

Paper II

We found an absolute recurrence risk of preterm birth of 17%, which was slightly lower compared with 23% that was reported among Missouri women by Ananth et al. [100], 26% by Adams et al. [107] among Afro-American women and 27.9% by Mbah et al. [147] in the USA. The higher recurrence risk of preterm birth reported by the previous studies could be explained by inclusion of severe prior preterm birth which has been associated with high recurrence of preterm delivery. However, other authors have reported that recurrence risk of preterm birth varies depending on the frequency of prior preterm birth, order of occurrence [104] and subclinical type (medically

induced or spontaneous preterm birth) [100, 117]. Unfortunately these factors were not assessed in the present study due to the small number of cases in each category.

Paper III

In our study, we found the recurrence risk of preeclampsia was 9.2 (6.4 - 13.2). This corresponds to an absolute recurrence risk of 25%. The absolute recurrence risk of preeclampsia in our study falls within the range of 15.8% to 36% for recurrence risk of hypertension and preeclampsia that was reported in retrospective cross sectional studies in sub-Saharan Africa [122, 123]. Our absolute recurrence risk of preeclampsia was consistent with other studies in high-income countries [118, 131], but it was higher than previous reports from Scandinavian countries [39, 148], which reported the absolute recurrence ranging between 13% to 15%. Other high-income countries also have reported a lower recurrence risk of preeclampsia of 14% [40, 125]. Our recurrence risk was also higher than 6% that was reported in previous studies in Israel [120], and 6.8% in Canada [130].

The differences between recurrence risk of preeclampsia observed in our study and that of others may be partly explained by the differences in prevalence of the risk factors for preeclampsia among women in the studied populations, such as chronic hypertension and diabetes. On the other hand, the lower absolute recurrence risk of preeclampsia in high-income countries could be attributed to high quality of prenatal care with heightened monitoring and referral for women with a previous history of preeclampsia in their subsequent pregnancies, as they are considered a high risk group

by health care providers, who therefore provide them with the opportunity for interventions to prevent recurrent preeclampsia.

Furthermore, women with a previous history of preeclampsia were more likely to have preterm birth, low birth weight and perinatal death in their subsequent pregnancies. Our finding was consistent with the previous studies [118, 120, 121]. The association between preeclampsia and the reported outcomes may be explained by the shared pathophysiological mechanism as was previously reported elsewhere [149]. This reflects the potential benefits of close clinical follow-up of these women in their future pregnancies.

5.2.2 Interrelationship between preeclampsia, preterm birth, perinatal death and its recurrence

Preeclampsia, preterm birth, and perinatal deaths are closely linked due to some shared etiological pathways. Preeclampsia can lead to both preterm birth and perinatal death, while infants who are born preterm are at greater risk of dying during the perinatal period. In the present study, women with previous preeclampsia had increased risk of preterm birth and perinatal death in their subsequent pregnancies. Our finding is consistent with previous studies [118, 120, 121]. Mothers with a previous history of preeclampsia had a three-fold increased risk of preterm birth in the subsequent pregnancy. A history of preeclampsia contributed with 12% of the preterm births and 15% of perinatal deaths in the subsequent pregnancy. It also accounted for 18% of perinatal mortality among preterm babies in the subsequent pregnancy. The increased

risk of preterm birth and perinatal mortality in a subsequent pregnancy for women with previous preeclampsia could be explained by recurrent preterm preeclampsia [57, 59, 118, 120] or recurrence of perinatal death [149]. However, high perinatal mortality among preterm infants is an indication of lack of health workers skills in caring for preterm babies.

On the other hand, the increased risk of preterm birth in the subsequent pregnancy could be attributable to physicians' tendency for early interventions such as labour induction or caesarean section to prevent maternal and fetal complications related to preeclampsia. It is worth noting that increased rates of preterm birth as a result of medical interventions in a low resource setting like Tanzania may increase newborn deaths due to lack of special neonatal care services.

Overall, recurrent preeclampsia contributed with an estimated 19% of perinatal deaths in subsequent pregnancies. This corresponded to a relative risk of 7.2 (95% CI: 3.6-14.2). Similarly, recurrent preeclampsia also accounted for 28.2% of preterm births in the subsequent pregnancies. This corresponds to a relative risk of 4.7 (95% CI: 2.7-8.1). Our findings were consistent with previous studies in the USA [159, 160]. The possible explanations for high proportions of preterm birth and perinatal deaths in subsequent pregnancies among women with recurrent preeclampsia could be due to the severity of recurrent preeclampsia which could lead to medically indicated preterm birth performed by the care givers purposely to reduce adverse maternal and perinatal morbidly and mortality, while high perinatal deaths could be partly attributed to prematurity which increases the risk of perinatal death.

In our data, the recurrence risk of preeclampsia was dependent on indicators of the severity of preeclampsia and presence of other maternal conditions in the first pregnancy, such as chronic hypertension and diabetes mellitus. The estimated recurrence risk of preeclampsia in women with a previous preterm preeclampsia was 35.5%, which was higher than reported in previous studies [59, 119 - 121], and was in contrast with van Rijn et al. [129], who found no such association. In our study, the recurrence risk of preeclampsia in women who had chronic hypertension in the index pregnancy was 37.5%, which was higher than 5.9% which was reported in Israel by Melamed et al. [120], and that of van Rijn et al. [129]. But it was consistent with a previous cross-sectional study in Africa [158]. The risk of preeclampsia in a subsequent pregnancy among women who had diabetes in the index pregnancy in our study was in contrast with previous studies [129, 130], which showed that recurrent preeclampsia was not predicted by either preexisting diabetes mellitus or gestational diabetes. However, the association between diabetes and subsequent risk of preeclampsia in our study should be interpreted with caution due to the small number of cases. One possible reason for difference between the estimated recurrence risk of preeclampsia in our study and those of some other studies may be explained by the differences in the severity of preeclampsia among women in the studies. On the other hand, lower recurrence of preeclampsia in the previous study may be attributable to intensified surveillance of women with a chronic condition, including diabetes, between pregnancies; which is not the case in low-resource settings. Our hospital data may contain more women with serious preeclampsia than in the general population.

In this study, the recurrent preterm birth accounted to 21.2% of all perinatal deaths in subsequent pregnancies. The risk of perinatal mortality in subsequent pregnancy was 9.2 (95% CI: 5.2–16.1) times higher in women with recurrent preterm birth than in women who had term baby after adjusting for confounders. The risk of perinatal mortality in the subsequent pregnancy remained higher (5.6-fold) for babies who were born at term with older sibling who was born preterm, but risk of perinatal death was slight lower (3.4-fold) for babies who were born to women who had a preterm birth in the subsequent pregnancy with a previous baby who was born at term. Our result is in contrast with previous reports from Norway by Melve et al [156] who reported lower perinatal mortality in subsequent pregnancies among babies born to mother with previous preterm birth than those with term birth. The difference in perinatal mortality could be explained by the differences in recurrent underlying causes of preterm birth, perinatal care, close followed for high risk mothers during prenatal care, and quality of care of babies who are preterm between developed and developing countries. We considered that high perinatal mortality could be attributed to shorter interpregnancy interval following a preterm birth. However, when we performed sub analysis by adjusting for interpregnancy interval, the estimates remains unaffected. Therefore, the higher perinatal mortality among babies of women with previous preterm babies is not likely to be explained by short interpregnancy intervals.

Our data showed that women with a previous preterm birth, preeclampsia and low birth weight in their first pregnancy had a significantly higher risk of perinatal death in a subsequent pregnancy, regardless of whether the previous child survived or

died in the perinatal period. This was consistent with previous studies [87, 155]. The recurrence of perinatal death was high for women with prior preeclampsia (20%), preterm birth or low birth weight (14%), as compared to women who did not experience these conditions in their first pregnancy. The recurrence risk of perinatal death was not affected by caesarean section, induction of labour, infections during pregnancy or number of antenatal care visits of the previous pregnancy. The observed high perinatal death in subsequent pregnancy could perhaps be explained by the persistent or shared recurrent underlying pathophysiological mechanism between preeclampsia, preterm birth and low birth weight, which is also associated with perinatal death [121, 152-154]. However, Rasmussen et al. [151] reported that women with a previous history of preeclampsia and preterm birth had an excess risk of perinatal death in their subsequent pregnancy even in the absence of recurrence of these factors. This also could be the case in our study.

Apart from preterm birth, infections and birth asphyxia have been reported as main causes of perinatal death in sub-Saharan Africa [162, 163]. Birth asphyxia and infections (especially neonatal sepsis) were not studied in this thesis. These factors may have contributed the recurrence of perinatal death estimated in our study. Infection risk may persist from one pregnancy to the next and similarly for the risk of asphyxia.

Given the multifactorial set of background conditions that shape the recurrence risk of preeclampsia, preterm birth and perinatal death, there is currently no single screening test that can identify pregnant women who are at greatest risk. Therefore,

improvement of general health care and enhancing care of pregnant women with history of adverse pregnancy outcomes may contribute to reduction of preeclampsia complications, preterm birth, and perinatal death. Intervention programs should include providing comprehensive obstetrics and newborn care, perinatal mortality audits, in-service training of health care workers in care of preterm infants, and early recognition of pregnancy complications; all of which have been associated with a 40% reduction of perinatal mortality [164].

6.0 Conclusions

1. Women with a previous perinatal loss had a much higher risk of losing a baby in their next pregnancy than those whose previous baby survived.
2. Also women who had lost their baby in a perinatal death after a term delivery and a normal birth weight in their first pregnancy had increased risk of delivering babies that suffered a perinatal death in subsequent pregnancies.
3. A history of preterm birth is a strong predictor for preterm birth in a subsequent pregnancy in the studied population.
4. Recurrent preterm birth increases the risk of perinatal death in the subsequent pregnancy and may be a reason for heightened clinical follow-up of these women.
5. Preeclampsia in one pregnancy is a strong risk factor for preeclampsia in subsequent pregnancies.
6. The increased risk of preeclampsia in a subsequent pregnancy was dependent on markers of the severity of the condition such as preterm preeclampsia, chronic hypertension and diabetes.
7. Previous preeclampsia is associated with increased risk for adverse pregnancy outcomes in subsequent pregnancies, such as preterm birth, low birth weight and perinatal death.
8. Recurrent preeclampsia is associated with high risk of preterm birth and perinatal death.

9. These conclusions are valid for women who deliver in a hospital facility in Northern Tanzania, but may be generalized to similar settings in sub-Saharan Africa.

7 Recommendations

7.1 Clinical implications

Prenatal and neonatal surveillance for women with a previous perinatal death, preterm birth and preeclampsia may help to provide individualized assessment and clinical counseling regarding recurrence, especially for women who desire to continue for a subsequent pregnancy; and provide specialized care for mothers at risk to reduce future recurrence. The potential should be studied in intervention studies.

Due to high recurrence risk of preeclampsia and its associated adverse perinatal outcomes observed in our study, early identification of high-risk mothers during prenatal care services may help to provide special care and close clinical follow-up in their future pregnancies, and thereby contribute to reducing the risk of adverse maternal and fetal complications.

In this study we found a high risk of perinatal death in subsequent pregnancies among mothers who had previous babies born at term with normal birth weight, suggesting that clinicians need to be aware of the risk of perinatal death in the subsequent pregnancy in these women.

The high perinatal mortality among babies who are born preterm may be improved by implementation of cost effective interventions like Kangaroo Mother Care, antenatal corticosteroid treatment, ventilator support, breast feeding support and treatment of infections. The effect of clinical interventions needs to be studied in future studies.

7.2 Policy implications

Considering maternal health services in Tanzania where only 43% of the pregnant women receive four or more antenatal care visits and 51% have access to skilled during labour and delivery, and a low coverage of emergency obstetric care services, it is important to improve the overall quality of the health care system. Improvement in care and care coverage could be achieved by focusing on enhancing services provided by the existing zonal consultant and regional referral hospitals where high risk obstetric women are referred. Some of these services could be directed specifically towards women who are known to carry high risks.

Nevertheless, continued efforts to invest in skilled birth attendance and developing community based interventions for improved access and health service seeking behaviour to facility based delivery and immediate neonatal resuscitation can significantly improve the neonatal health. These will enable early identification of high risk women, especially those with previous perinatal death, preterm birth and preeclampsia, to reduce risk of recurrence in their future pregnancies.

A medical birth registry is an important tool in monitoring performance of the health care and may provide bench marks for comparison with population based data. Analysis of registry data may provide an opportunity for surveillance of trends of risk factors, clinical management, causes of diseases and adverse pregnancy outcomes. Birth registry data may be linked to allow studies of recurrence of different reproductive outcomes Therefore, establishment of medical birth registries, especially population based registries in sub Saharan Africa, could be of great importance and

enable generalization of the results to large populations. Such registries may also allow studies of long term health outcomes and may save time and costs by using existing data as an alternative or supplement to targeted surveys or new prospective cohort studies. Medical birth registry data makes each baby count and should be used in combination with other data sources to influence policy decision making.

Despite the strengths of registry-based data, some limitations need to be taken into account which may affect data quality and validity of results. Self-reporting bias as a result of recall bias, errors in collected data due to lack of medical knowledge among data collectors or interviewers and data entry clerks as well as missing data (random or non-random missing) may affect some variables in the data.

Furthermore, we found some problems with data incompleteness and lack of information on important variables related to outcomes of interest. This requires efforts to standardize data collection methods, regular data quality check and rigorous analysis to enhance validity of the data. In addition, there is a need to add contact information for each woman in the questionnaire, like a phone number, to facilitate easy tracing of these mothers hence reduce loss to follow up and enable studying long term maternal and offspring outcomes.

Hospital based registry data suffer from selection problems and may not be representative for the entire population. This is definitively a problem for studies of prevalence. It is less clear how association measures are affected, and also how recurrence estimates are affected. Still, this is a limitation that could only be overcome

by access to data with population based coverage. Policymakers should consider standards for data collection both for clinical facilities and populations.

7.3 Future research

Since this was a hospital based study, the population of pregnant women may have different birth characteristics to other women in the general population. Therefore, further population/community-based study is needed for comparison to confirm the estimated recurrence risks of pregnancy outcomes and risk factors associated with the recurrence risks observed in our study. This would be an important study to reveal the true picture among African women in comparison with women in high income countries. Implications for clinical strategies for follow-up could then be generalized to women outside a health facility like KCMC.

More investigation should attempt to identify the underlying causes of recurrence of perinatal death, particularly in women with term birth and perinatal death in their previous pregnancy. Future studies should also aim to identify women with a tendency to deliver preterm and who may benefit from heightened clinical follow-up. Our study had limited information on potential causes of recurrent problems for these women. An assessment of the effect of closer clinical follow-up for women at risk was not possible in the present observational study. This would require further clinical research and intervention studies.

Previous studies in high income countries have reported variations in recurrence risk of preterm birth by clinical subtypes (spontaneous or medically indicated preterm birth). This was not investigated in our study due to difficulties in identification of

these subtypes. Further research in African settings should attempt to estimate the recurrence risk patterns of preterm birth by clinical subtypes to enable comparison with previous studies in the high income countries.

Previous studies in high income countries also have reported differences in recurrence of stillbirth according to time of occurrence (i.e. antepartum or intrapartum stillbirths). This was also not attempted in our data due to small sample size of subjects in each category. Future studies in African populations should also take into account the analysis of stillbirth recurrence by time of delivery to make good comparison with other studies high income countries.

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