PREVALENCE, RISK FACTORS AND TIMING OF OCCURRENCE OF STILLBIRTHS AMONG PATIENTS WITH HYPERTENSIVE DISORDERS OF PREGNANCY AT KENYATTA NATIONAL HOSPITAL IN 2018-2019; A CROSS-SECTIONAL STUDY

PRINCIPAL INVESTIGATOR:
DR. BILLY MELLA ODHIAMBO
H58/7004/2017
DEPARTMENT OF OBSTETRIC AND GYNAECOLOGY

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DECLARATION

This Dissertation is my original work, drafted under the guidance of my supervisors, and has not been presented for the award of a degree in any other university. References of work done by others have been indicated appropriately.

Signature:..... ..... **Date**...12.04.22.....

Dr.Billy.Mella Odhiambo,

CERTIFICATE OF SUPERVISION

This dissertation has been submitted with our approval as University supervisors:

Signature: **Date:20/06/2022**

Dr Alex Bosire, MBChB, Mmed (Obs/Gyn)

Lecturer, Department of Obstetrics and Gynaecology,

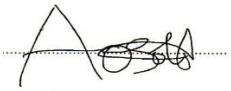
Consultant, Obstetrician and Gynaecologist, Kenyatta National Hospital,

Faculty of Health Sciences, University of Nairobi.

Signature:.... **Date. 20/06/2022**

Professor Omondi OgutuMBChB, Mmed (Obs/Gyn), PGDRM, FCOG (ECSA)

Associate Professor, Department of Obstetrics and Gynaecology,
Faculty of Health Sciences, University of Nairobi.



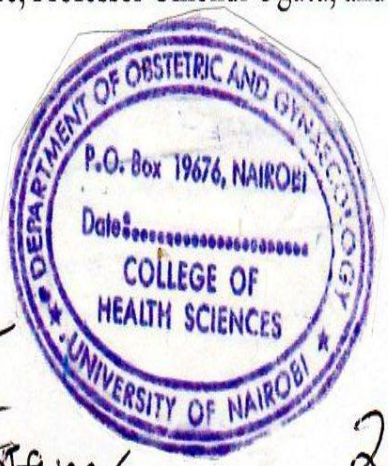
Signature: **Date: 22/06/2022**

Dr. Afried Osti, MBChB, MPH, Mmed (Obs/Gyn), PHD

Senior Lecturer, Department of Obstetrics and Gynaecology,

CERTIFICATE OF AUTHENTICITY

This dissertation is the original work of Dr Billy Mella Odhiambo under the supervision and guidance of Dr. Alex Bosire, Professor Omondi Ogutu, and Dr. Alfred Osoti.



Signature:..... **Date:** 22/06/22

Professor Eunice J. Cheserem,MBChB, Mmed (Obs/Gyn), PGDRM, Fell. (Gyn/Onco)

Associate Professor, Department of Obstetrics and Gynaecology, Faculty of Health Sciences,
Consultant, Obstetrician and Gynaecologist, Kenyatta National Hospital,
Chairperson, Department of Obstetrics and Gynaecology, University of Nairobi.

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LIST OF ABBREVIATIONS

AGA: Adequate for Gestational Age

AOR: Adjusted Odds Ratio

BP: Blood Pressure BPP:

Biophysical Profile CH:

Chronic Hypertension

CODAC Causes of Death and Associated Conditions

DBP: Diastolic Blood Pressure

EmONC: Emergency Obstetric and Neonatal Care

ENAP: Every New-born Action Plan

GA: Gestational Age

GH: Gestational Hypertension

HDP: Hypertensive Disorder of Pregnancy

HELLP: Haemolysis, Elevated Liver enzymes, Low Platelet count

ISSHP: International Society for the Study of Hypertension in Pregnancy

IUGR: Intra Uterine Growth Restriction

MAP: Mean Arterial Pressure

RCOG: Royal College of Obstetricians and Gynaecologists

RI: Resistive Index

SB: Stillbirth

SBP: Systolic Blood Pressure

SGA: Small for Gestational Age

WHO: World Health Organization

OPERATIONAL DEFINITIONS

Hypertensive disorders of pregnancy:
A group of medical conditions in pregnancy characterized by the presence of high blood pressure, systolic blood BP ≥140 mm Hg and / or diastolic BP ≥90 mm Hg on at least two occasions 4 hours apart or systolic BP ≥160mmHg and / or diastolic BP ≥110mmHg confirmed within 15 minutes. (ISSHP)

Stillbirth:
Death or loss of a foetus before or during delivery. Stillborn babies are delivered with no signs of life known to have had a demise after 24 completed weeks of pregnancy (RCOG)

Risk factors: A variable associated with an increased risk of disease or infection

Prevalence: Proportion of a particular population found to be affected by a medical condition

Timing of occurrence of stillbirths: Occurrence of stillbirths as preadmission or post admission, or as either ante partum or intrapartum
Antepartum stillbirth: Death of a foetus before initiation / onset of labour
Intrapartum stillbirth: Death of foetus during labour and delivery
Preadmission stillbirth: Death of foetus before admission to KNH
Postadmission stillbirth: Death of foetus after admission to KNH

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ABSTRACT

Background

Hypertensive disorders in pregnancy (HDP) such as preeclampsia, eclampsia and chronic hypertension complicate approximately 6.5% of pregnancies in Kenya. About 2.6 million stillbirths occurred globally in 2015, with majority in LMIC, according to WHO. HDP contribute to approximately 16% of stillbirths globally. However, the prevalence of HPD related stillbirths has not been addressed comprehensively in Kenya. Further antepartum, intrapartum, preadmission, or post admission timing of occurrence of stillbirths in HDP, critical for targeted interventions, has not been examined in this setting.

Objective

To determine the prevalence, risk factors and timing of stillbirth among Kenyan parturients with HDP admitted at Kenyatta National hospital in 2018 and 2019.

Methods

Study design: A hospital based cross sectional study

Study site setting: Kenyatta National Hospital records department

Study population: Women aged 15-49 years admitted at Kenyatta National Hospital between 1st January 2018 and 31st December 2019 at 24 and above weeks of gestation or referred after delivery with a verified status of hypertension.

Exposure: Hypertensive disorder of pregnancy

Outcomes: Birth outcomes (stillbirth or livebirth), Timing of occurrence of stillbirth

Study procedure: Simple random sampling was used to identify file of patients who met the eligibility criteria until the desired sample of 404 was reached. Files were allotted numbers and a random number generator used to select the 404 randomly. A pretested questionnaire was used to collect demographic, reproductive, and the medical data relevant to the study.

Data analysis and management: The prevalence of stillbirth was estimated using the Clopper-Pearson method. The sociodemographic and reproductive factors associated with stillbirth were summarized using frequency distributions and compared using the Chi-square test for categorical variables and Mann-Whitney U test for continuous variables. Bivariate and multivariable logistic regression and corresponding 95% confidence interval were used to obtain odds ratios of these associations. Timing of occurrence of stillbirths was summarised as frequencies and percentages and 95% confidence intervals calculated using the Clopper Pearson method. P value of < 0.01 was statistically significant. Statistical Package for Social Scientists (SPSS) software version 21 was used for analysis.

Results: Between 1st January 2018 and 31st December 2019, 450 files were screened of which 404 met the eligibility criteria. Of those ineligible files, 28 had missing laboratory data, 16 were of gestational age less than 24 weeks and 2 had foetal anomalies. The mean maternal age was 29 years (SD ±6) and preeclampsia was the most common HDP (79.2%). The prevalence of stillbirths in HDP was 15.8% (95% CI 12.4-19.8). Determinants of stillbirth were non-ANC attendance (OR 17.48, 95% CI 4.16-85.88), low birth weight (OR 7.78, 95% CI 3.70-16.31), preterm birth (OR 3.99, 95% CI 2.21-7.06), DBP ≥ 110mmHg (OR 2.23, 95% CI 1.24-3.92), low platelet levels (OR 5.95, 95% CI 3.36-10.50), and AST ≥ 2-fold rise (OR 4.93, 95% CI 2.71-8.99). Adjusted odds of SB in vaginal delivery was 13-fold higher than for caesarean, (AOR 13.52, 95% CI 3.69-49.50), 10-fold higher for abnormal resistive index compared to normal (AOR 10.78, 95% CI 2.92-39.78) and 15-fold high for abnormal biophysical profile compared to normal (AOR 15.40, 95% CI 3.75-63.15). Most (73.4%) stillbirths occurred in the antepartum period and 53.1% occurred after admission to KNH.

Conclusion: This study revealed a high prevalence of stillbirth in HDP, especially in preeclampsia and eclampsia most occurring in the antepartum period. The mode of delivery, biophysical profile, and resistive index were independent predictors of stillbirths.

CHAPTER 1:INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

1.1.1 Background

The Royal College of Obstetricians and Gynaecologists define stillbirths as fetal deaths that occur at or after 24 weeks of gestation(1). Worldwide, data from the World Health Organization (WHO) indicate that approximately 2.5 million neonatal deaths were reported in 2018, which translates to about 7,000 deaths of new-borns every day(2). Even though neonatal mortality has declined over the years, perinatal mortality remains high at 6 million deaths per year, with 3.3 million cases being stillbirths. The burden of stillbirths is highest in Low- and Middle-Income Countries (LMIC) at 50 per 1000 compared to 10 per 1000 in the high-income settings. Approximately 97% of cases of stillbirths (3.2 million) reported from LMIC (3) are due to the overstretched medical systems, home deliveries, and supervision of pregnancies by unskilled traditional birth attendants (4).

The overall incidence of HDP in a WHO Multicountry Survey on Maternal and New-born Health is estimated to be 2.73% (5) and many intermediate, distal, and proximal factors have been associated with the high rate of stillbirths reported in LMIC. Poor access to hospitals because of poor familial wealth or overstretched medical systems has been proposed. In Nepal, the adjusted odds for stillbirths among women with a poor familial wealth was 1.8 (95% CI 1.1-3.4)(6). Poor education and poor health-seeking behavior of parturients from LMIC have also been reported (7,8). The WHO country estimates of stillbirths was 32 per 1000 birth in Africa, 27 per 1000 births in East Africa and 29 per 1000 births in Kenya (9) with 3 fold higher odds of stillbirths in preeclampsia compared to normotensive mothers(OR3.12 95% CI 2.77-3.51) and 4 fold higher in eclampsia (OR 3.92 95% CI 3.16-4.87) according to Qureshi Z *et al*(5). HDP contributed to 24.9% of stillbirths according to CODAC system classification of stillbirths in South East Asia(10). National statistics have not described the contribution of HDP on the prevalence and timing of occurrence of stillbirths sufficiently. The risk factors for stillbirth in parturients with HDP are also poorly understood. In this study, we describe the prevalence, timing and risk factors for stillbirths among women with HDP at KNH.

1.2 Literature review

1.2.1 Burden of Hypertension

Recent data from Low and Medium Income Countries (LMIC) has painted Africa as a "hotspot" for hypertension, in which about 40% of adults from the Sub-Saharan region were thought to be afflicted in 2007 (11). This translated to about 80 million cases - which was among the highest globally - and was estimated to double (160 million cases) by 2025 due to stretched medical resources (12,13). In 2010, data from the World Health Organisation (WHO) found a 6% increase in the prevalence of hypertension from 2007, with about 46% of adults thought to be afflicted(14).

1.2.2 Hypertensive Disorders in Pregnancy in Africa

Hypertensive disorders in pregnancy (HDP) are a group of medical conditions that present with elevation of blood pressure with or without proteinuria in pregnancy. In the 1990s, approximately 6% of the burden to parturients, and 13% of maternal deaths were related to HDP(15). To date, pregnancy-related complications lead to about 289,000 deaths of women every year (99% in LMIC) Gudetta and Rugassa (16), with the prevalence estimates for HDP reported to vary markedly in countries and regions in Africa. In a meta-analysis of 17 Ethiopian HDP studies on 258,602 parturients published in HINARI, PubMed, Medline, African journals, and Google Scholar, the overall pooled prevalence for HDP in Ethiopia was 6.07% (17). Pregnant women age ≥ 35 years old were most at risk of HDP, even though no significant association between the number of pregnancies and HDP was reported. Gudetta and Rugassa (16) corroborated the result in 2019 (7.9%), though rates as high as 16.8% have been reported in Gondar, North West Ethiopia(18). In another systematic review and meta-analysis of 13 studies that included 5894 women with HDP in Ethiopia by Mersha *et al.*(19), among the five groups of HDP, preeclampsia/eclampsia syndrome was the commonly reported types of HDP (66.7% - 82.7%) and eclampsia accounted for 27.8% of women admitted for HDP.

The incidence of HDP in a one-year descriptive analysis by Moodley *et al.* (20) in South Africa was 12.5%. In the study, 731 of the 5860 evaluated women (primigravida) developed HDP, with gestational hypertension (GH) contributing the highest number of HDP cases (6.5%) followed by pre-eclampsia/eclampsia (5.9%). In Zimbabwe (21) and Nigeria (22), HDP is estimated to afflict 19.4% and 1.2% of all parturients, respectively. Low income predisposed women to HDP, with the perinatal and maternal mortality rates of parturients with HDP being

the highest. Abu-Bonsaffoh *et al* in 2013 did an analysis of 368 women with HDP in Ghana. In this cross-sectional study(23), the major adverse perinatal outcomes included intrauterine Growth Restriction (6.3%),intrauterine foetal demise (6.8%), preterm delivery (21.7%), low birth weight (24.7%) and birth asphyxia (15.2%)

Even though the literature points to a low-to-moderate prevalence of HDP in middle-income countries such as Rwanda, Nigeria, Ethiopia, and South Africa, (1.0%-12.5%), its prevalence in low-income countries such as Zimbabwe is high at 19.4% because of poor health service coverage and the poor health seeking behaviour of at-risk women. (21). A WHO multicountry survey on maternal and new-born health showed the overall incidence of HDP to be 2.73% with the incidence of preeclampsia being higher in the upper middle income countries and that of eclampsia being higher in the lower middle income countries.(5)

1.2.3 Classification of hypertensive disorders of pregnancy

The recommended classification of hypertensive disorders of pregnancy as per International Society for the Study of Hypertension in Pregnancy (ISSHP) is highlighted in Table 1.

Table 1: ISSHP classification of hypertensive diseases in pregnancy(24)

Hypertension known before pregnancy or present in the first 20 weeks:	
1. Chronic hypertension	a) Essential b) Secondary
2. White coat hypertension	
3. Masked hypertension	
Hypertension arising de novo at or after 20 weeks	
1. Transient gestational hypertension	
2. Gestational hypertension	
3. Pre-eclampsia – de novo or superimposed on chronic hypertension	

1.2.4 HDP and Still Birth

Hypertensive disorders in pregnancy remain a major global health issue not only due to adverse maternal outcomes associated with it but also due to its contribution to significant perinatal morbidity and mortality especially in Sub-Saharan Africa. In 2015, estimates from the World Health Organisation (WHO) indicate that approximately 2.6 million stillbirths were reported globally. This translated to about 7178 deaths of neonates per day, a majority (98%) of which were in LMIC(25). About 50% of stillbirths occur intrapartum with complications such as HDP estimated to increase the risk of neonatal mortality at <28 weeks gestation. In a retrospective

review of singleton deliveries in Haiti (8822) between 2012 and 2014, Bridwell and others reported the prevalence of HDP to be 5.8% with preeclampsia and eclampsia constituting (55.9%) and (23.3%) of cases respectively. The adjusted OR for having a stillbirth was three times higher in women with HDP, while AOR for maternal deaths was slightly higher at 5.13(95% CI 1.53–17.25). Among the reported HDPs, eclampsia contributed the most to adverse pregnancy outcomes with pregnancies of afflicted mothers being 6.34 times likelier to end in a stillbirth, and 12.7 times likelier to result in maternal death. According to Ananth and Basso (26), such complications are even higher in second or third-order births than in first births. In China, the stillbirth rate of women with HDP is 21.9/1000 births as reported by Xiong *et al* (27).

In Africa, a prospective cohort study of 103 pregnant women with new onset hypertensive disorders of pregnancy in Uganda in 2020 by Lugobe *et al.* (28) reported a still birth rate of 203 per 1000 births with antepartum stillbirths being the majority at 76.2% and intrapartum at 23.8%. Edward T. Dassah *et al*.(29) in an analytical cross-sectional study of perinatal outcomes in 451 women with HDP in 2014 found that women with preeclampsia had the highest proportions of stillbirths at 14.2% against eclampsia (13.6%) and gestational hypertension (8.2%) while in Ghana a similar finding was noted in a cross-sectional study by Abu-Bonsaffoh *et al.* in 2013 in an analysis of 368 women with HDP in which the highest proportion of stillbirths were in the preeclampsia group compared to other categories with the lowest rate occurring in the chronic hypertension group(23).

1.2.5 Risk Factors for Stillbirths among women with HDP

In a review of data (2003-2004) by Ananth and Basso (26), a second or higher order of birth was found to be a significant risk factor for stillbirths among women with HDP. In parturient who were having a first birth, the odds of having stillbirth was (OR 1.2, 95% CI 1.40-1.64) compared to women with a high order birth (OR 2.24, 95% CI 2.11-2.37). In the study, being black and multiparity were other predictors for stillbirths among women with HDP. In a review of 6,970,032 births by Xiong *et al*. (27) in China, 66,494 stillbirths were present, with the incidence found to be significantly higher in singleton pregnancies (AOR 3.1, 95% CI 2.85–3.37), superimposed preeclampsia (AOR 6.66, 95% CI 5.57-7.96) and preeclampsia/eclampsia (AOR 4.15, 95% CI 3.81–4.52). In the US Bukowski R *et al* found that SGA pregnancies were associated with a statistically significant 3-fold increased risk of stillbirth compared to AGA

(OR 3.0, 95% CI 2.2–4.0)(30). Kumar *et al* in India in 2019 after conducting an analytical case control study found that maternal complications such as diabetes mellitus, anaemia, placenta abruptio and HELLP syndrome were significantly associated with stillbirth and on multivariate regression analysis, factors that contributed significantly to stillbirths were early onset of hypertension, foetal growth restriction, less than four antenatal clinic visits, vaginal delivery, low birth weight, previous history of abortion, presence of gestational hypertension and chronic hypertension(10).

In Africa several factors have been reported to be associated with stillbirths among women with HDP. In Uganda, a prospective cohort study of 103 pregnant women with new onset HDP by Lugobe *et al*. in 2020 in the adjusted analyses reported that gestational age at birth less than 34 weeks and birth weight less than 2500g were independent risk factors for adverse perinatal outcomes(28). In Ethiopia, the perinatal mortality rate due to HDP was 111.1 per 1000 live births, bivariate logistic regression identified lack of ANC attendance (OR 3.0, 95% CI 1.1–8.2) and diastolic blood pressure more than 110mmHg to be predictors of stillbirth while multiple logistic regression found low birth weight (AOR 4.1, 95% CI 1.0–17.1) and poor maternal outcomes (death and complications) to be independent predictors of unfavourable perinatal outcomes (31).

CHAPTER 2:CONCEPTUAL FRAMEWORK, JUSTIFICATION AND OBJECTIVES

2.1 Conceptual Framework

Socio-demographic factors such as age, marital status, and the education level of parturients have been associated with the risk of developing HDP, with women of extreme of ages, low level of education, and or a poor socio-economic status (lack of employment) estimated to be at a higher risk of developing a HDP (32). These factors may also influence the time at onset of ANC visits and the number of ANC visits that might have an influence on birth outcome and complication of HDP as poor follow up is likely to result in complications. Prenatal factors such as parity, gestational age, birth weight, antenatal care and maternal morbidity may influence both birth outcome and occurrence of complications of HDP. The presence of complications of HDP such as acute kidney injury, pulmonary oedema, and placenta abruption are associated with a high risk of stillbirths. (33–35).

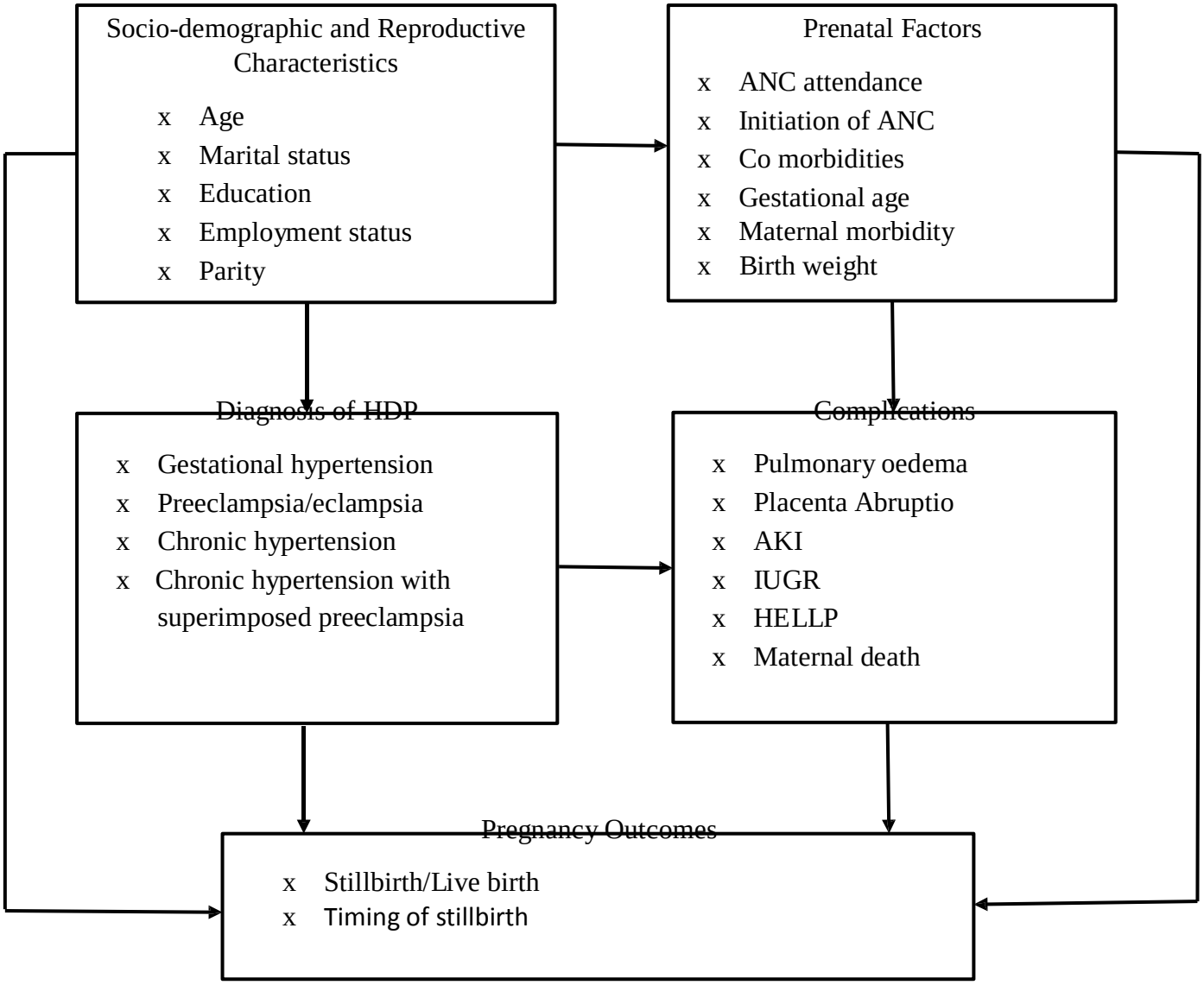

Figure 1: Conceptual framework highlighting the relationship between patient characteristics, the profile of HDP, and the risk and timing of occurrence stillbirths

2.2 Problem Statement

The incidence of HDB is varied with higher incidence of preeclampsia noted in upper middle-income countries and that of eclampsia in lower middle-income countries, the country estimates of stillbirths in Kenya is 29 per 1000 births. HDP contribution to SB has been estimated to be 16% by WHO (5,9). However, national statistics have not described the contribution of HDP on the prevalence and timing of stillbirths sufficiently. The risk factors for stillbirth in parturients with HDP are also poorly understood. In this study, we describe the burden, timing and risk factors for stillbirths among women with HDP at KNH.

2.3 Study Justification and Utility

Hypertensive disorders in pregnancy and its effect on neonatal outcomes is a common problem and afflicts millions of women globally. About 2.6 million stillbirths occurred globally in 2015 and estimated stillbirth rates have remained high in Sub Saharan Africa. As per KDHS report 2014, Perinatal mortality rate in Kenya was high at 29 deaths per 1000 live births (36).

Kenya's plan on Sustainable Development Goals addresses this issue in one of its targets. The World Health Assembly endorsed target of <12 stillbirths per 1000 births in every country by 2030(2) and this has not been achieved yet. Hypertensive disorders in pregnancy are a great contributor to the high perinatal mortality. Although recognised as a major cause of perinatal mortality, there is a paucity of research done to understand the effect of HDP on adverse perinatal outcomes locally, especially its effect on SB has not been comprehensively addressed despite the immediate and long-term effect of foetal loss on maternal health.

This study intends to offer insight on the risk factors of stillbirth in hypertensive disorders and its prevalence. The information gathered in assessment of predictors of perinatal mortality due to HDP may influence management and development of focused and appropriate health interventions leading to better outcomes.

Obstetric and sociodemographic factors that predispose women to stillbirths, for instance, have been poorly explored, limiting early identification of at-rick women. The timing of occurrence stillbirth is also underexplored, which limits early detection and its control further. The finding of this study filled these gaps.

2.4 Research question

What is the prevalence, risk factors and timing of stillbirths among women with HDP admitted at KNH between 1st January 2018 and 31st December 2019?

2.5 Objectives

2.5.1 Broad objective

To determine the risk factors, prevalence and timing of occurrence of stillbirth among women with HDP.

2.5.2 Specific objectives

Among women with HDP who delivered at a gestation of 24 and above weeks and admitted at KNH between 1st January 2018 and 31st December 2019, to

1. Determine the prevalence of stillbirth
2. Determine the sociodemographic and obstetrics factors associated with stillbirth
3. Determine the timing of occurrence of stillbirth as antepartum or intrapartum
4. Compare the prevalence of preadmission and postadmission stillbirths

CHAPTER 3:METHODS

3.1 Study design

This was a hospital based cross-sectional study in which medical records of women with hypertensive disorders of pregnancy (HDP) admitted at Kenyatta National Hospital (KNH) at a gestational age of 24 and above weeks or referred after delivery between 1st January 2018 and 31st December 2019 were reviewed to determine the prevalence of stillbirth, the sociodemographic and obstetrics factors associated with stillbirth, the timing of stillbirth as antepartum or intrapartum and prevalence of preadmission and postadmission stillbirths.

3.2 Study Site and Setting

This study was carried out in Kenyatta National Hospital (KNH) – a tertiary public hospital of the Ministry of Health (MoH), Kenya, which is also the teaching hospital for the University of Nairobi (UoN) College of Health Sciences (COHS). It is located in Upper Hill, approximately 3.5 kilometres from the central business district of Nairobi, the capital city of Kenya. KNH is at the apex of Kenya's health delivery system (level 6) and is mandated to provide specialized health services. It provides services to the population of Nairobi and its environs and receives referrals from all 47 counties in Kenya. The reproductive unit offers both inpatient and outpatient services. The inpatient obstetric department is organised into three antenatal wards, one labour ward and a maternity theatre, it serves up to 1400 patients every month, which translates to approximately 17,000 deliveries per year with the major complication being hypertensive disorders. Each ward has consultant Obstetricians and Gynaecologists among them Feto-Maternal specialists. Other personnel attending to the patients include registrars, reproductive health clinical officers, nurses and consultant physicians who are consulted in case of complications. Moreover, the unit has a registry with an archival system for obstetric data of women, which covers pregnancy and birth outcomes, demographics of patients, and the presence of co morbidities such as HDP. The medical charts of women managed at KNH are available at the medical record departments.

3.3 Study population

Women with HDP who delivered at KNH between 1st January 2018 and 31st December 2019 at 24 and above weeks of gestation or referred after delivery were our study population. Participants were of reproductive age (15-49 years), had data on demographics, medical and reproductive characteristics at the time of delivery.

3.3.1 Inclusion criteria

- Data archived at the KNH registry
- Verified status of hypertension as two elevated blood pressure measurements (systolic ≥140 mm Hg and/or diastolic ≥90 mm Hg) taken at least 4 hours apart with patient on bed rest.
- Delivery at 24 and above weeks gestation as per RCOG cut off gestation for stillbirths.
- Availability of clinical and laboratory data (Full blood count, renal and liver function tests)

3.3.2 Exclusion criteria

- Major fetal anomalies
- Higher order multifetal gestations

3.4 Sample size determination

3.4.1 Calculation

The prevalence of stillbirth in HDP was estimated at 24.9% by Kumar et al in India in 2019 (10). Using the formula by Fisher (1981) (37), the sample size (n) was calculated at 95% CI and a precision of 5%.

Formula:

$$n = \frac{Z^2 x p(1-p)}{d^2}$$

n: Sample size

p: Prevalence of stillbirth in HDP

Z: Normal variate for alpha (1.96)

q: 1-p

d: Precision

Assumptions:

d = 5.0%

p = 24.9% (Kumar et al. 2019)

Z = 1.96

Estimated sample size:

$n=1.96^2 x 0.249\ (1-0.249)/0.05^2$

n = 288, After adjustment by 40% to cater for missing data: *n*= 404 participants

3.4.2 Sampling

A total of 1415 deliveries occurred in patients with HDP between 1st January 2018 and 31st December 2019 (764 deliveries in 2018 and 651 deliveries in 2019). Simple random sampling was employed for those eligible. The files were allotted numbers from 1 to n and a random number generator used to select 243 subjects and 207 subjects randomly from the year 2018 and 2019 respectively. Before recruitment, women who were missing laboratory data (n=28), gestational age < 24 weeks (n=16) and foetal anomaly (n=2) were excluded from the study and a total of 404 women who met the eligibility criteria were included in analysis.

3.5 Study Flowchart

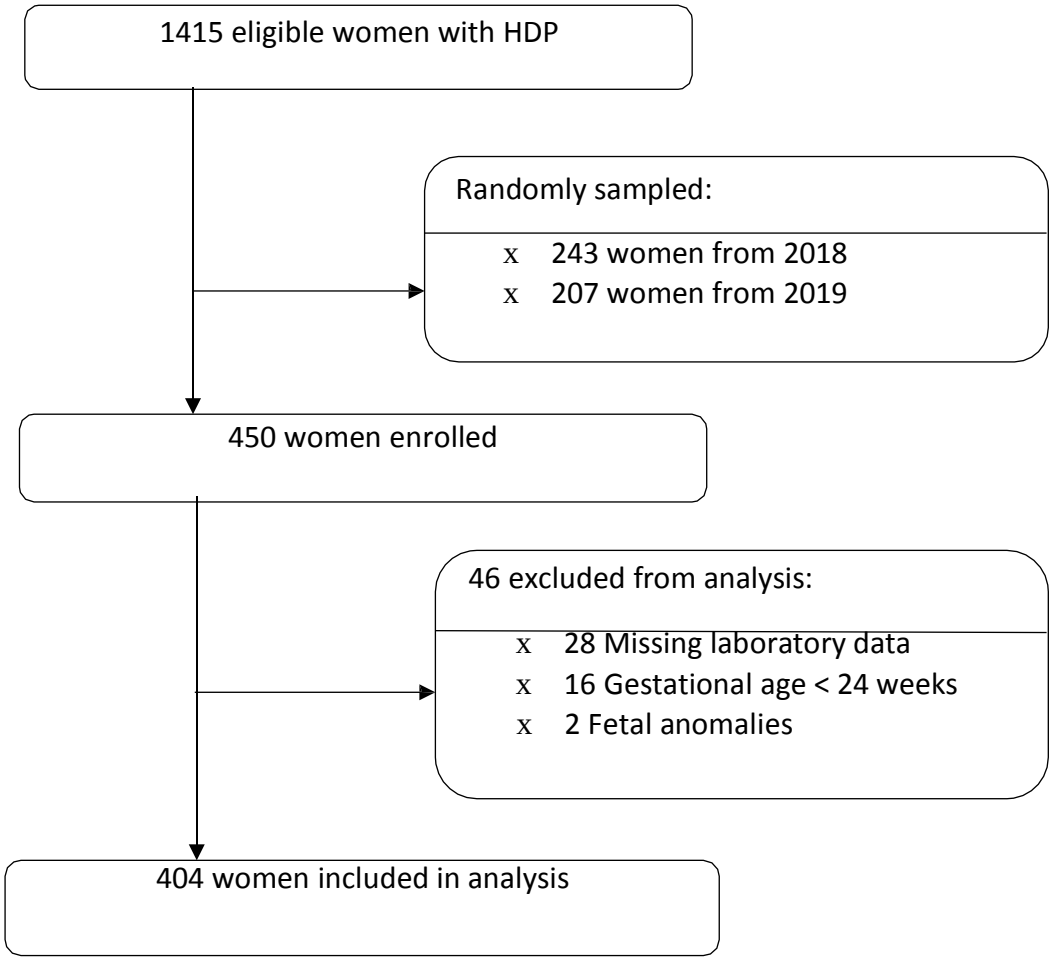

Figure 2 : Study flow chart - To determine the prevalence and timing of occurrence of stillbirth

3.6 Variables

The dependent variable was the birth outcome (stillbirth or live birth) of babies of women with HDPs. HDPs was classified as chronic hypertension, pre-eclampsia/eclampsia, pre-eclampsia superimposed on chronic hypertension and gestational hypertension and was the main independent variables. Other independent variables were the demographics of women such as the age, marital status, and education level; reproductive characteristics such as parity and gestation; the medical characteristic such as the presence of co morbidities such as Diabetes mellitus (DM), ultrasound findings, timing of stillbirths, and severity of HDP (SBP, DBP, and labs).

Dependent and independent variables

Table 2. Prevalence of stillbirths

Type	**Variable**	**Categories**
Dependent	Birth outcome	Stillbirth
		Livebirth

Table 3. Timing of stillbirth

Type	**Variable**	**Categories**
Dependent	Timing of stillbirth	Preadmission
		Post admission
		Antepartum
		Intrapartum

Table 4. Risk factors for stillbirths

Type	**Variable**	**Categories**
Independent	Maternal Age in years	Mean (SD)
	Marital status	Married
		Single
		Divorced/separated/widowed
	Number of antenatal visits	0
		1-4
		>4
	Timing of first antenatal care visit	First trimester
		Second trimester
		Third trimester
	Gestational age in weeks at delivery	Extremely preterm (24-28)
		Very preterm (28-32)
		Late preterm (32 – 37)
		Term (>37)

Type	Variable	Categories
Independent	Birth weight in grams	ELBW <1000
		VLBW (1000-1499)
		LBW (1500-2499)
		>2500
	History of stillbirth	Yes/No
	Twins	Yes/No
	Type of HDP	Chronic hypertension
		Pre-eclampsia/eclampsia
		Gestational hypertension
		Preeclampsia superimposed on chronic hypertension
	Co morbidities	DM, HIV
		Others
	Severity of disease at diagnosis: Highest SBP	
		<140 mmHg
		140 - 159 mmHg
		>160 mmHg
	Highest DBP	<90
		90 – 109
		>110 mmHg
	Labs (TBC, UECs, LFTs, Urinalysis	Platelets
		Urea
		Creatinine
		ALT
		AST
		Proteinuria
	Complications	AKI
		Abruptio
		IUGR
		HELLP
		Maternal Death
	Antihypertensive drug given	Yes/No
	Magnesium sulphate given (where indicated)	Yes/No
	Labour onset	Spontaneous
		Induced
	Mode of delivery	Vaginal
		Caesarean
	Ultrasound findings	RI
		BPP

3.7 Data collection procedures

3.7.1 Data collection tools

A questionnaire was developed and used to collect secondary data from patient files. The tool was closed-ended and organized into sections that captured different sets of information. The demographic characteristics of patients was recorded in section one of the observation checklist. These included age, marital status and education level of participants. The medical and reproductive characteristics of women were captured in section two of the tool. These included the parity of women, the outcome of pregnancy (singleton/ twins), the presence of co morbidities such as HIV and diabetes mellitus, attendance of antenatal care/timing (first, second or third trimester), type of HDP and ultrasound findings. The birth weight and mode of delivery were captured, SGA determined by Alexander et al population norms reported 10^{th} percentile of birth weight for completed weeks of GA, 20-44 weeks(38) and the gestation (if not available on files) estimated from the date of last menstruation or early ultrasound scans (if available) as described by Skupski *et al*. (39) and recorded on the checklist. The third section recorded the timing of stillbirths, which was categorized as ante partum, intrapartum, preadmission, or post admission.

3.8 Data collection

This was done between 5^{th} October and 30th October, 2020 by the Principal Investigator together with research assistants who were a Registered Reproductive Health Clinical Officer and registered Nurse from the department of Reproductive Health trained on research ethics, confidentiality and data collection. Files that met our inclusion criteria were selected from the Records Department and upon selection the files of patients were checked for completeness and information extracted by a trained research assistant. Demographic and reproductive data were recorded. Medical and the reproductive characteristics of women and the timing of stillbirths were also be recorded.

3.9 Data quality assurance

To ensure that the data collection process and the data that we collected was of high quality, we did the following:

1) The Principal Investigator (PI) trained research assistants on data extraction, research ethics and confidentiality.

2) Only files with complete data were included. The completeness of files was checked, and patients with missing clinical and laboratory data excluded.
3) Data analysis was done under the supervision and guidance of a statistician to improve accuracy of results.

3.10 Data analysis

Descriptive statistics were evaluated and presented as charts or tables. The prevalence of stillbirth, including the timing, and prevalence of preadmission and post admission stillbirths was calculated using the Clopper-Pearson method. The demographic and obstetrics factors associated with stillbirth were determined using the Chi-square test and Logistic regression used to adjust for confounding. Analyses was done at 95% confidence interval with a $p<0.01$ considered to be statistically significant. The Statistical Package for Social Scientists (SPSS) software (version 21) was used for date entry and analysis.

3.11 Ethical Considerations

The proposal, study protocol and questionnaire were submitted to the KNH/UoN Ethics Review Committee (KNH/UoN-ERC) for review. The study commenced after formal approval from the committee and only approved protocols and tools were used in the study. Authorization was obtained from KNH administration since it was the study site.

3.11.1 Confidentiality

Personal identifiers of participants such as names or identification numbers were not collected and self-identifying statements and information not be used. Study numbers were used instead.

3.11.2 Privacy

Information was stored securely (password protected) and was not be accessible to anyone else except those involved in the study

3.11.3 Beneficence

Insights into the risk factors of stillbirth in patients with hypertensive disorders will provide information aiming to improve clinical judgement and management of such patients to avoid poor outcomes.

3.11.4 Informed consent

This was not be obtained from patients since information was collected from the files in the records department. However, authorization to collect data was obtained from the records department and the KNH administration

3.11.5 Non-maleficence

There was no physical or psychological harm to patients since information was obtained from the patients records and not patients themselves and there were no personal identifiers to the information obtained.

CHAPTER 4:RESULTS

4.1 Socio-demographic characteristics of the study population

Between 1st January 2018 and 31st December 2019, 450 files were screened of which 404 met the eligibility criteria. Of those ineligible files, 28 had missing laboratory data, 16 were of gestational age less than 24 weeks and 2 had foetal anomalies. The sociodemographic characteristics are summarized in table 5 below. The mean maternal age was 29 years (SD ±6). Majority were aged <35 years (77.5%), married (84.3%), and had secondary education (45.0%)

Table 5. Socio-demographic characteristics of patients with HDP admitted at Kenyatta National Hospital in 2018-2019

		n (%)
Age	mean	29.28 (SD 6.18)
Age group	<35	313 (77.5)
	≥35	91 (22.5)
Marital status	Married	340 (84.2)
	Single	63 (15.6)
	Widowed	1 (0.2)
Education level	No formal education	2 (0.5)
	Primary	94 (23.3)
	Secondary	182 (45.0)
	Tertiary	126 (31.2)

4.2 Reproductive Health characteristics

The reproductive health characteristics are summarized in table 6. Majority of patients were multipara (60.4%), while 35.9% were primigravida and 3.7% were grand multipara. Of the 404, 42 (10.4%) had a maternal comorbidity, mainly anemia (23.8%), diabetes (21.4%), HIV (16.7%), and cardiac disease (7.1%). Attendance of antenatal care (ANC) was almost universal (98.0%), mostly beginning in second trimester (14-27 weeks) of the pregnancy (87.9%), and a majority (96.5%) had less than eight antenatal care contacts. The mean number of ANC contacts was 4.22±1.98. Twenty-five pregnancies (6.2%) were twin, while small for gestational age (SGA) was reported in 79 (19.6%). In 71.5% of the cases, a caesarian delivery was done with the main indication (38.1%) being Non-Reassuring Fetal Status (NRFS). 54.0% of the deliveries were at term (≥37 weeks). During pregnancy and delivery, 138/404 patients (34.2%) developed a maternal complication like HELLP syndrome (70.3%), acute kidney injury (34.8%), post-partum hemorrhage (12.3%), and maternal death (9.4%)

Table 6. Reproductive health characteristics of patients with HDP admitted at Kenyatta National Hospital in 2018-2019

		n (%)
Parity	Primigravida	145 (35.9)
	Multipara (1-4)	244 (60.4)
	Grand multipara (≥5)	15 (3.7)
Maternal comorbidity present		42 (10.4)
	Preexisting anemia	10 (23.8)
	Diabetes	9 (21.4)
	HIV	7 (16.7)
	Cardiac disease	3 (7.1)
	Hyperthyroidism	3 (7.1)
	Asthma	2 (4.8)
	Epilepsy	2 (4.8)
	CVA	2 (4.8)
	CKD	1 (2.4)
	DVT	1 (2.4)
	Dilated cardiomyopathy	1 (2.4)
	Giant fibroadenoma	1 (2.4)
	Hepatitis B	1 (2.4)
	ITP	1 (2.4)
	Liver cirrhosis	1 (2.4)
	Malaria	1 (2.4)
	Psoriasis	1 (2.4)
	Renal stenosis	1 (2.4)
	Pneumonia	1 (2.4)
ANC attendance		396 (98.0)
Timing of first ANC visit	First trimester (0-13 weeks)	26 (6.6)
	Second trimester (14-27 weeks)	348 (87.9)
	Third trimester (≥28 weeks)	22 (5.6)
Number of contacts	Mean (SD)	4.22 (1.98)
	≥8	14 (3.5)
	<8	390 (96.5)
Twin pregnancy		25 (6.2)
Fetal growth	Small for gestational age (SGA)	79 (19.6)
	Adequate for gestational age (AGA)	325 (80.4)
Labor onset	Induced	111 (27.5)
	Spontaneous	66 (16.3)
	No labor	227 (56.2)
Mode of delivery	Caesarian	289 (71.5)
	vaginal	115(28.2)
Gestation of delivery	Extremely preterm (24-27 weeks)	20 (5.0)
	Very preterm (28-32 weeks)	70 (17.3)
	Late preterm (33-36 weeks)	96 (23.8)
	Term (≥37 weeks)	218 (54.0)

Birth weight	Mean (±SD)	2344.95 (900.97)
	Extremely low	29 (7.2)
	Very low	47 (11.6)
	Low	141 (34.9)
	Normal	187 (46.3)
Maternal complications due to HDP		138 (34.2)
	HELLP	97 (70.3)
	Acute Kidney Injury	48 (34.8)
	Post-partum hemorrhage	17 (12.3)
	Maternal Death	13 (9.4)
	Pulmonary edema	10 (7.2)
	Placenta Abruptio	9 (6.5)
	Sepsis	7 (5.1)
	Acute respiratory distress syndrome	2 (1.4)
	Disseminated intravascular coagulation	2 (1.4)
	Ascites	1 (0.7)
	Cerebrovascular accident	1 (0.7)
	Placenta previa	1 (0.7)
	Pleural effusion	1 (0.7)
	Puerperal psychosis	1 (0.7)
	Stroke	1 (0.7)

4.3 Selected laboratory and ultrasound findings, blood pressure, and treatment modalities

The selected laboratory and ultrasound findings, blood pressure, and treatment modalities are summarized in table 7. Majority (95.0%) had proteinuria. Thrombocytopenia (platelet count $<100 \times 10^9$/L) was observed in 36% of mothers. The mean urea level was 5.77 (±8.56) with 38.1% reported to have a high urea level (≥4.6uMol/L). The mean creatinine level was 115.96 (±103.95) uMol/L with 39.6% found to have an abnormal level (≥97.26uMol/L). 71 (17.6%) had a ≥2-fold rise (≥80U/L) in AST levels and 66 (16.3%) a ≥2-fold rise (≥70U/L) rise in ALT level. 56 (25.6%) had abnormal restrictive index and 67 (30.6%) abnormal biophysical profiles. Preeclampsia was the commonest HDP (79.2%) followed by eclampsia (8.2%), superimposed preeclampsia (7.2%), gestational hypertension (4.0%), and chronic hypertension (1.5%). In terms of management, 60% of the patients received magnesium sulfate for seizure preventive prophylaxis, 88.6% were on multi-agent antihypertensive drugs, the commonest combination being Nifedipine + Methyldopa (72.5%) while 46 (11.4%) were on single agent treatment. Those on Methyldopa only were 52.2% while Nifedipine only were 45.7%. 15.2% needed Hydralazine for immediate control of hypertension.

Table 7. Selected laboratory and ultrasound findings, blood pressure, and treatment modalities of patients with HDP at Kenyatta National Hospital in 2018-2019

		n (%)
Proteinuria	Yes	384 (95.0)
	No	20 (5.0)
Platelets	Very low (<50)	50 (12.4)
	Low (50-100)	55 (13.6)
	Normal (>100)	299 (74.0)
Urea	Mean (±SD)	5.77 (±8.56)
	<4.6uMol/L	250 (61.9)
	≥4.6uMol/L	154 (38.1)
Creatinine	Mean (±SD)	115.96 (±103.95)
	<97.26uMol/L	244 (60.4)
	≥97.26uMol/L	160 (39.6)
Aspartate aminotransferase (AST)	Mean (±SD)	67.90 (±118.13)
	<2-fold rise (<80U/L)	333 (82.4)
	≥2-fold rise (≥80U/L)	71 (17.6)
Alanine aminotransferase (ALT)	Mean (±SD)	51.26 (±80.821)
	<2-fold rise (<70U/L)	338 (83.7)
	≥2-fold rise (≥70U/L)	66 (16.3)
Systolic blood pressure	Mean (SD)	170.09 (±21.75)
	<140mmHg	22 (5.4)
	140-159mmHg	118 (29.2)
	≥160mmHg	264 (65.3)
Diastolic blood pressure	Mean (±SD)	112.52 (±15.07)
	<90mmHg	5 (1.2)
	90-109mmHg	163 (40.3)
	≥110mmHg	236 (58.4)
Resistive index (RI) evaluated		216 (53.5)
	Normal	160 (74.1)
	Abnormal	56 (25.6)
Biophysical profile done		219 (54.2)
	Normal	152 (69.4)
	Abnormal	67 (30.6)
Hypertensive disease in pregnancy	Chronic hypertension	6 (1.5)
	Gestational hypertension	16 (4.0)
	Preeclampsia	320 (79.2)
	Superimposed preeclampsia	29 (7.2)
	Eclampsia	33 (8.2)
Treated with antihypertensive drug (s)		402 (99.5)
Treatment modality	Single agent	46 (11.4)
	Multi-agent	356 (88.6)
Received magnesium sulfate		240 (59.4)

The distribution of stillbirths by HDP types is shown in figure 4 below. Majority of stillbirths occurred in the preeclampsia group (60.9%). Stillbirths in other groups were Eclampsia (28.10%), Superimposed preeclampsia on chronic hypertension (7.8%) and Gestational hypertension (3.3%). No stillbirth occurred in the Chronic hypertension group.

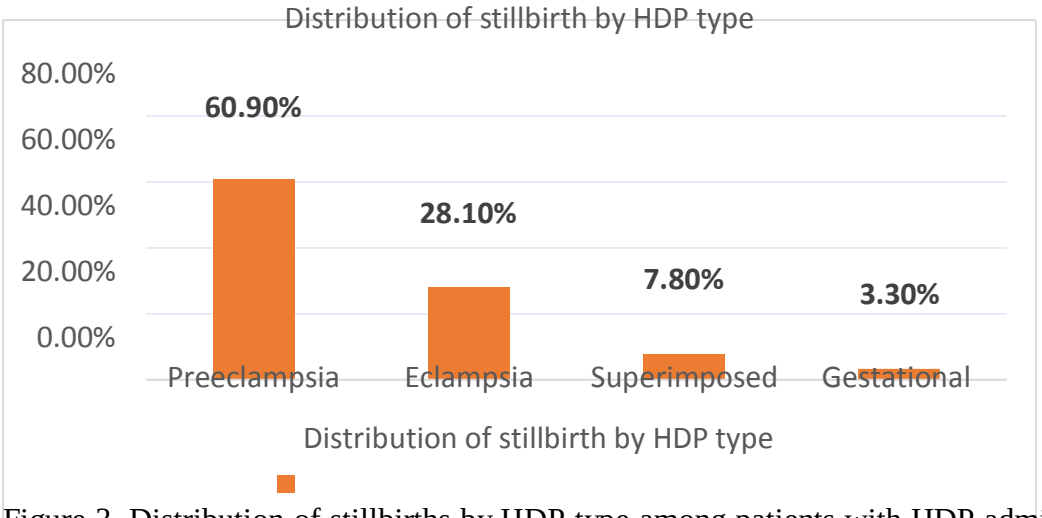

Figure 3. Distribution of stillbirths by HDP type among patients with HDP admitted at KNH in 2018 – 2019.

4.4 Prevalence of stillbirths

There were sixty-four stillbirths, resulting in a prevalence of 15.8% (95% CI 12.4-19.8). This translates to a prevalence rate of 158/1000 total births. The distribution of stillbirths by HDP type was Preeclampsia 39 [60.9% (95% CI=47.9-72.9%)], eclampsia 18 [28.1% (95% CI=17.6-40.8%)], chronic hypertension with superimposed preeclampsia 5[7.8% (95% CI=2.6-17.3%)] and gestational hypertension 2[3.2% (95% CI=0.4-10.8%)].

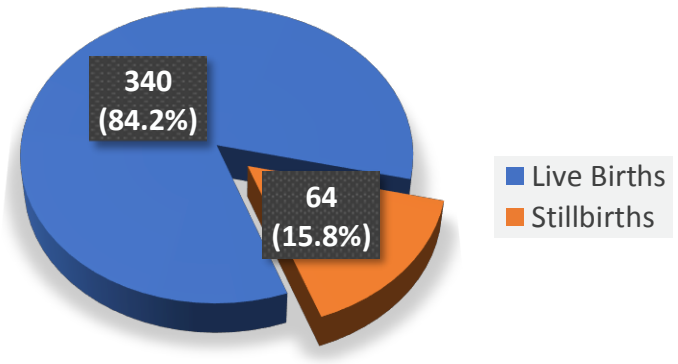

Figure 5. Prevalence of stillbirths among patients with HDP admitted at KNH between 1st January 2018 and 31st December 2019.

4.5 Factors associated with stillbirth

The demographic factors associated with stillbirth are summarized in table 8. 75.0% of patients were young (<35 years), association of maternal age with stillbirth was not significant (OR=1.17, 95% CI=0.63-2.14, P=0.60). Single compared to married women had 86% greater odds of having a stillbirth, however this was also not statistically significant (OR=1.86, 95% CI=0.99-3.60, P=0.06).

Table 8. Demographic factors associated with stillbirth among patients with HDP admitted at Kenyatta National Hospital in 2018-2019

		Stillbirth N=64	Live birth N=340	OR (95% CI)	P value
Age group	<35	48 (15.3)	265 (84.7)	Reference	
	≥35	16 (17.6)	75 (82.4)	1.17 (0.63-2.14)	0.60
Marital status	Married	49 (14.4)	291 (85.6)	Reference	
	Single	15 (23.8)	48 (76.2)	1.86 (0.99-3.60)	0.06
	Widowed	0 (0.0)	1 (100)	-	-
Education	Non formal	0 (0.0)	2 (100)	-	-
	Primary	15 (16.0)	79 (84.0)	Reference	
	Secondary	32 (17.6)	150 (82.4)	1.12 (0.58-2.15)	0.73
	Tertiary	17 (13.5)	109 (86.5)	0.82(0.39-1.78)	0.61

The reproductive health factors associated with stillbirth are summarized in table 9.

Stillbirth was found to be strongly associated with lack of antenatal care visits (OR 17.48, 95% CI=4.16-85.88). Other variables which had strong association with stillbirths were maternal comorbidities (OR 2.38, 95% CI=1.16-4.81), vaginal delivery (OR=8.93, 95% CI=4.85-16.59), complications due to HDP (OR 4.47, 95% CI=2.56-7.94), preterm delivery (OR 3.99, 95% CI 2.21-7.06), ANC contacts <4 (OR=7.91, 95% CI=4.29-14.23), and low birth weight (OR 5.95, 95% CI 3.36 – 10.50)

Parity, timing of ANC, twin pregnancies, and number of ANC contacts were not statistically significant factors associated with stillbirths.

Table 9. Reproductive factors associated with stillbirth among patients with HDP admitted at Kenyatta National Hospital in 2018-2019

		Stillbirth N=64	Live birth N=340	OR (95% CI)	P value
Parity	Primigravida	17 (11.7)	128 (88.3)	Reference	
	Multipara	45 (18.4)	199 (81.6)	1.70 (0.93-3.04)	0.08
	Grand multipara	2 (13.3)	13 (86.7)	1.16 (0.24-4.77)	0.18
Comorbidity(s)	Yes	12 (28.6)	30 (71.4)	2.38 (1.16-4.81)	**0.02**
	No	52 (14.4)	310 (85.6)	Reference	
ANC attendance	Yes	58 (14.6)	338 (85.4)	Reference	
	No	6 (75.0)	2 (25.0)	17.48 (4.16-85.88)	**<0.01**
				1.45 (0.57-3.89)	
First ANC	1st (0-13 weeks)	5 (19.2)	21 (80.8)	Reference	
	2nd (14-27 weeks)	49 (14.1)	299 (85.9)	0.68 (0.25-1.74)	0.47
	3rd (28+ weeks)	4 (18.2)	18 (81.8)	1.36 (0.48-3.81)	0.59
ANC contacts	≥4	17 (6.3)	252 (93.7)	Reference	
	<4	47 (34.8)	88 (65.2)	7.91 (4.29-14.23)	**<0.01**
Twin pregnancy	Yes	2 (8.0)	23 (92.0)	0.44 (0.10-1.72)	0.27
	No	62 (16.4)	317 (83.6)	Reference	
Fetal growth	Small for gestational age	18 (22.8)	61 (77.2)	1.79 (0.99-3.23)	0.05
	Adequate for gestational age	46 (14.2)	279 (85.8)	Reference	
Labor onset	Induced	39 (35.1)	72 (64.9)	3.03 (1.41-6.33)	**<0.01**
	Spontaneous	10 (15.2)	56 (84.8)	Reference	
	No labor	15 (6.6)	212 (93.4)	0.39 (0.17–0.93)	
Mode of delivery	Caesarian section	19 (6.6)	270 (93.4)	Reference	
	Vaginal	44 (38.6)	70 (61.4)	8.93 (4.85-16.59)	**<0.01**
Gestation (birth)	Extremely preterm (24-27)	12 (60.0)	8 (40.0)	17.74 (6.15- 51.63)	**<0.01**
	Very preterm (28-32 weeks)	22 (31.4)	48 (68.6)	5.42 (2.67-10.70)	**<0.01**
	Late preterm (33-36 weeks)	13 (13.5)	83 (85.5)	1.85 (0.88-3.96)	0.11
	Term (≥37 weeks)	17 (7.8)	201 (92.2)	Reference	
Birth weight	Extremely low	21 (72.4)	8 (27.6)	58.73 (20.17-163.9)	**<0.01**
	Very low	13 (27.7)	34 (72.3)	8.56 (3.42-21.95)	**<0.01**
	Low	22 (15.6)	119 (84.4)	4.14 (1.84-8.99)	**<0.01**
	Normal	8 (4.3)	179 (95.7)	Reference	
Complication(s)	Yes	41 (29.7)	97 (70.3)	4.47 (2.56-7.94)	**<0.01**
	No	23 (8.6)	243 (91.4)	Reference	

The association of stillbirths with selected laboratory and ultrasound findings, blood pressure and treatment modalities are summarized in table 10.

There was a statistically significant association of stillbirths with highest DBP ≥110mmHg (OR 2.23, 95% CI 1.24-3.92), other variable with statistically significant association with stillbirths were low platelet count (OR 5.95, 95% CI 3.36-10.50), high creatinine level (OR 3.31 95% CI 1.92-5.83), high urea level (OR 3.30 95% CI 1.92-5.75), ≥2-fold rise AST level (OR 4.93 95% CI 2.71-8.99), ≥2-fold rise ALT level (OR 5.13 95% CI 2.75-9.37), eclampsia (OR 8.40 95% CI 1.82-40.23) and magnesium sulphate administration (OR 3.50 95% CI 1,84-6.72). Proteinuria was associated with 3.73 higher odds of stillbirth (95% CI=0.64-39.55) but was not statistically significant (P=0.17).

Table 10. Association of stillbirths with selected laboratory and ultrasound findings, blood pressure and treatment modalities of patients with HDP at KNH in 2018-2019

		Stillbirth N=64	Live N=340	OR (95% CI)	P value
Proteinuria	Yes	63 (16.4)	321 (83.6)	3.73 (0.64-39.55	0.17
	No	1 (5.0)	19 (95.0)	Reference	
Platelets	Very low (<50)	22 (44.0)	28 (56.0)	8.25 (4.15-16.41)	**<0.01**
	Low (50-100)	16 (29.1)	39 (70.9)	4.31 (2.14-8.64)	**<0.01**
	Normal (>100)	26 (8.7)	273 (91.3)	Reference	
Urea	<4.6uMol/L	24 (9.6)	226 (90.4)	Reference	
	≥4.6uMol/L	40 (26.0)	114 (74.0)	3.30 (1.92- 5.75)	**<0.01**
Creatinine	<97.26uMol/L	23 (9.4)	221 (90.6)	Reference	
	≥97.26uMol/L	41 (25.6)	119 (74.4)	3.31 (1.92-5.83)	**<0.01**
AST	<2-fold rise (<80U/L)	34 (10.2)	299 (89.8)	Reference	
	≥2-fold rise (>/80U/L)	30 (42.3)	41 (57.7)	4.93 (2.71-8.99)	**<0.01**
ALT	<2-fold rise (<80U/L)	38 (11.2)	300 (88.8)	Reference	
	≥2-fold rise (>/80U/L)	26 (39.4)	40 (60.6)	5.13 (2.75-9.37)	**<0.01**
Systolic	<140mmHg	2 (9.1)	20 (90.9)	Reference	
	140-159mmHg	13 (11.0)	105 (89.0)	1.24(0.27-5.86)	0.79
	≥160mmHg	49 (18.6)	215 (81.4)	2.28 (0.56-10.13)	0.26
Diastolic	<90mmHg	0 (0.0)	5 (100)	-	-
	90-109mmHg	17 (10.4)	146 (89.6)	Reference	
	≥110mmHg	47 (19.9)	189 (80.1)	2.23 (1.24-3.92)	**<0.01**
Resistive index	Abnormal	31 (55.4)	25 (44.6)	38.44 (14.07-95.48)	**<0.01**
	Normal	5 (3.1)	155 (96.9)	Reference	
	not done	36	180		
Biophysical profile	Abnormal	33 (49.3)	34 (50.7)	35.91 (12.42-97.47)	**<0.01**
	Normal	4 (2.6)	148 (97.4)	Reference	
	Not done	37	182		
HDP	Chronic	0 (0.0)	6 (100)	-	-
	Gestational hypertension	2 (12.5)	14 (87.5)	Reference	
	Preeclampsia	39 (12.2)	281 (87.8)	0.97(0.24-4.44)	0.97
	Superimposed preeclampsia	5 (17.2)	24 (82.8)	1.46 (0.24-8.03)	0.67
	Eclampsia	18 (54.5)	15 (45.5)	8.40 (1.82- 40.23)	**<0.01**
Antihypertensive drugs	Single agent	5 (10.9)	41 (89.1)	Reference	
	Multi-agent	59 (16.6)	297 (83.4)	0.61 (0.25-1.54)	0.31
	No treatment		2		
Magnesium sulfate	Yes	52 (21.7)	188(78.3)	3.5(1.84-6.72)	**<0.01**
	No	12 (7.3)	152 (92.7)	Reference	

The predictors for stillbirths after multivariable analysis with backward elimination are summarized in table 11.

Resistive index, biophysical profile, and mode of delivery were predictors for stillbirth. An abnormal resistive index was associated with a 10.78-fold statistically significant higher adjusted odds of stillbirth (95% CI=2.92-39.78). Others variables with significant association were abnormal biophysical profile [AOR 15.40 (95% CI=3.75-63.15)] and vaginal delivery [AOR 13.52 (95% CI=3.69-49.50)]. Complications due to HDP, labor onset, gestation, SGA, marital status, parity, and laboratory findings were not predictors for stillbirths (P>0.05).

Table 11. Predictors for stillbirths among patients with HDP admitted at Kenyatta National Hospital in 2018-2019

		95% C.I. of AOR		
	AOR	Lower	Upper	P value
SVD (caesarian section=reference)	13.52	3.693	49.501	<0.001
Abnormal Resistive Index	10.78	2.920	39.782	<0.001
Abnormal Biophysical Profile	15.40	3.756	63.156	<0.001

Variable(s) entered on step 1: Marital status, Parity, Presence of comorbidities, ANC attendance, SGA, Labor Onset, Mode of Delivery, Gestation in weeks at Delivery, Birth Weight, Maternal complications, Platelets, Urea, Creatinine, AST, ALT, Highest Diastolic blood pressure (mmHg), Restrictive Index (on ultrasound), Biophysical Profile, Magnesium Sulphate, HDP, number of ANC visits.

4.6 Timing of occurrence of stillbirths

The timing of occurrence of still births has been summarized in table 13. Most stillbirths were antepartum [73.4% (95% CI=60.9-83.7%)] and post admission [53.1% (95% CI 40.2-65.7%)].

Table 12. Timing of stillbirths among patients with HDP admitted at Kenyatta National Hospital in 2018-2019

		Frequency (n)	%
During pregnancy	Antepartum	47	73.4
	Intrapartum	17	26.6
Admission status	Post admission	34	53.1
	Preadmission	30	46.9

The timing of occurrence of stillbirth and ultrasound findings are summarized in table 14. In majority of cases where there were abnormal findings in the ultrasound, stillbirths were common in the antepartum compared intrapartum period. Odds of antepartum stillbirths were higher with an abnormal biophysical profile compared to normal [OR=3.71, 95% CI=0.49-25.82] and higher with abnormal resistive index compared to normal [OR=6.25, 95% CI=1.01-38.61] but the difference was not statistically significant.

Table 14. Timing of occurrence stillbirths and ultrasound findings among patients with HDP admitted at Kenyatta National Hospital in 2018-2019

		Antepartum	Intrapartum	OR (95% CI)	P value
Biophysical Profile	Normal	2 (50.0)	2 (50.0)	Reference	
	Abnormal	26 (78.8)	7 (21.2)	3.71 (0.49-25.82)	0.205
Resistive Index	Normal	2 (40.0)	3 (60.0)	Reference	
	Abnormal	25 (80.6)	6 (19.4)	6.25 (1.01-38.61)	0.051

Comparison of timing of occurrence of stillbirths is shown in figure 5. Antepartum stillbirths were more common before admission to the facility while majority of the intrapartum stillbirths were after admission to our facility.

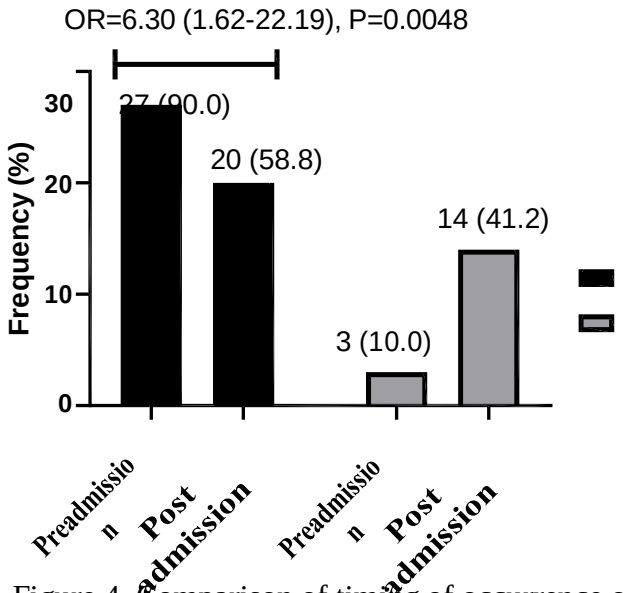

Figure 4. Comparison of timing of occurrence of stillbirths

CHAPTER 5:DISCUSSION, CONCLUSION, AND RECOMMENDATIONS

5.1 Discussion

This study has shown a high prevalence of stillbirths in patients with HDP in Kenya (158 per 1000 births). This is comparable to a local study done in Uganda, a prospective cohort study of 103 pregnant women with new onset HDP in 2020 by Lugobe *et al.* (28) which reported a still birth rate of 203/1000 births. The similarity may be due to the fact that both setting are in LMIC with relatively same quality of follow up of patients and given that they were referral facilities and women seeking care had been managed in other lower level facilities hence deterring early detection and management.(40). A study done by Mekoya D *et al.* in Ethiopia showed a lower prevalence rate of 38/1000 births(41), the difference might be because we included preadmission stillbirths in our analysis hence the higher rate. Hossain *et al*.(42) reported a prevalence rate of 153/1000 births in a population-based study of pregnant women from Dhaka, Bangladesh. The prevalence is comparable to this study and is expected since the study area was a tertiary referral hospital in a LMIC.

This still birth rate is higher than that reported in Asia, Europe, and America. Xiong *et al*. (27) reported a significantly lower prevalence of 21.9 per 1000 births in a retrospective review of 6970032 births data in China. In the USA, the prevalence of stillbirths with pregnancy induced hypertension was between 3.2 and 4.8 per 1000 live births between 2004 and 2005 in a population study of 57 million singleton births by Anath and Basso (26). The prevalence in Canada was 0.52% in a population study of 13,940 hypertensive and 122-394 normotensive women by Allen et al. (43). The disparity in the prevalence rate may be explained by difference in quality of follow up of pregnant women between high income countries and LMIC like Kenya.

In this study the factors independently associated with stillbirths were mode of delivery, abnormal foetal ultrasound findings and maternal complications due to HDP. Other strong associations were lack of antenatal care, comorbidities, preterm delivery, low birth weight, elevated liver enzymes, thrombocytopenia and eclampsia. Eight-fold higher odds of stillbirths were observed in women with eclampsia compared to gestational hypertension, 54.5% v/s 12.5 which was consistent with a study in Bangladesh in which stillbirths were higher with eclampsia (18.%) compared to gestational hypertension (5.9%) (44). The finding is probably due to the fact that preeclampsia/eclampsia causes uteroplacental insufficiency and intrauterine

asphyxia leading to more stillbirths. Abnormal biophysical profile was associated with fifteen-fold higher odds of SB while abnormal resistive index was associated with nine-fold higher odds of SB. This finding is similar to a findings by Shen *et al* in China(45) who found a higher resistive index to be associated with high risk of stillbirth, premature pregnancy termination and a birth weight less than 2500g.

This study found that patients with HDP who had no antenatal care visits had seventeen-fold greater odds of stillbirths compared to those who had attended an antenatal clinic. Sharma *et al.* reported similar findings in India in 2019 in which stillbirths were significantly higher with no antenatal clinic attendance (13.7 per 100 births) compared to at least one antenatal care visit (2.0 per 100 births) (46). In Ethiopia, lack of ANC follow up not only contributed to development of HDP but also stillbirths among women with a pre-existing or newly diagnosed HDP (47). Lack of antenatal care means a delay in making the diagnosis therefore the disease is likely to become severe or progress to eclampsia which has a strong association with stillbirths. Gestational age at 1st ANC visit was not statistically significant factor associated with stillbirths in our population, this is consistent with a retrospective cohort study by Greg Petro *et al.*(48) in Cape Town, South Africa which demonstrated no significant effect of gestational age at first ANC visit on the odds of having a still birth after adjusting for maternal characteristics.

Socio-demographic factors such as age and education level were not predictors of stillbirths. However, when patients presented with comorbidities such as anemia, diabetes and HIV, there was two-fold higher odds of a stillbirth. There were five-fold higher odds of stillbirths in patients with complications of HDP compared to those without, with HELLP syndrome, AKI, PPH, and placenta abruptio contributing the most to morbidity and the overall risk of a stillbirth. Sharma *et al*. (46) reported similar results in a retrospective study in India, in which illnesses such as diabetes and hepatic encephalopathy were strongly linked with an increased risk of stillbirths in women with HDP. Xiong *et al*. (27) and Ye *et al*. (49) had similar findings in Sichuan and Beijing China respectively where HIV infections complicated the pregnancies of women with HDP in sub Saharan Africa (SSA) in a HPTN024 trial in Zambia, Malawi, and Tanzania. This finding can be explained by the fact that complication such as placenta abruptio compromise blood supply to the fetus thereby leading to stillbirths. Attention should be paid to women with comorbidities such as diabetes and those with complications due to HDP during antenatal clinic visits and delivery.

Vaginal delivery was associated with nine-fold higher odds of stillbirths. This association may not necessarily show an increased risk of stillbirths in babies delivered vaginally and should be interpreted with caution because 73.4% of stillbirths occurred in the antepartum period and there was no need to expedite delivery via a caesarian section. A study by Yifru *et al* (50) in Ethiopia showed a similar finding in which vaginal delivery was associated with a five-fold higher odds of stillbirth in HDP. As much as there is strong association, caesarian delivery should only be done when there are indications and when there is need to expedite delivery to save the life of the mother and/or the baby.

As expected, there was significantly higher odds of stillbirths among low birthweights and preterm babies. Extremely preterm births had up to eighteen-fold higher odds of stillbirth, while very preterm and preterm births had nine and six-fold higher odds of stillbirths respectively. Birth weight was also a major prognostic factor for stillbirth with extremely low weight having eighteen-fold higher odds of stillbirths. Nine and four-fold higher odds in stillbirth was reported with very low and low birth weight respectively compared to normal birth weight, a finding consistent with a study by Lugobe *et al* in Uganda which found a two-fold higher odds of stillbirths in birthweight less than 2.5kgs and 3-fold higher odds of SB in preterm births less than 34 weeks(28). This might be related to the scientific fact that HDP is associated with preterm deliveries and low birth weight as delivery is expedited in severe cases before term to save the life of the mother as it takes precedence.

Among selected laboratory and ultrasound findings, odds of stillbirths were five-fold higher with low platelet count, ≥2-fold rise in ALT and ≥2-fold rise in AST. High creatinine levels also had three fold greater odds for stillbirths, these findings are consistent with those of Endeshaw *et al.*(50)in Ethiopia where low platelets and high creatinine were predictors of stillbirths in an unadjusted analysis except for ≥2-fold rise in SGOT that was an independent predictor of stillbirths in their study. This finding can be explained by the fact that low platelet and elevated SGOT are a component of HELLP syndrome which may increase the risk of stillbirths(51) but this association needs further investigations.

Most stillbirths occurred in the antepartum period (73.4%). This is similar to a prospective cohort study of 103 pregnant women with new onset hypertensive disorders of pregnancy in Uganda in 2020 by Lugobe *et al.* (28) who reported antepartum stillbirths to be the majority at 76.2% and intrapartum at 23.8%. This might be related to the poor antenatal follow up as

severity of disease that increased the risk of stillbirths was not picked in time and proper management to avert the poor perinatal outcomes was not instituted. A retrospective chart review in Ethiopia in 2018 reported different findings where two thirds of stillbirths happened intrapartum (52). This inconsistency might be related to difference in quality of intrapartum care between the facilities. Preadmission and postadmission stillbirths were comparable in our study 53.1% versus 46.9%. The slightly higher percentage in the postadmission stillbirths could be due to the severity of disease in referred cases and could also reflect on the quality of antepartum and intrapartum care though this was not assessed. Other studies have however compared referred cases and those who directly visited the hospital and found a difference in the perinatal outcomes(28)

5.2 Study Strengths and Limitations

This study provides insight into the risk factors of stillbirth in HDP and aims to improve clinical judgement and management of such patients to avoid poor outcome. Since this was a cross-sectional study association were not causal. Moreover, because it was retrospective in nature, some patient files had missing and or limited data especially referred cases and were excluded. Quality of intrapartum care was not assessed and this could have probably contributed to some intrapartum deaths. To minimize bias and get accurate data that was able to answer our research questions, sample size was adjusted by 40% to improve statistical power of the study. Instead of recruiting 288 patients as determined using sample size calculation, 404 patients were recruited. Before inclusion, the principal investigator checked all patient files for completeness to lower bias further. Multivariable analysis was also done to account for confounders such as parity and gestational age. Stillbirths that occurred at home were also not included as patients were either not admitted of were missing crucial data needed for analysis. The findings in this study may not be generalizable as this was a referral hospital and our study population may have been skewed towards women with more severe disease.

5.3 Conclusion

Our study is the first in the country to investigate the prevalence and factors associated with stillbirths in HDP and found a relatively high prevalence rate compared to some neighboring countries in Africa and high-income countries. Stillbirth is still therefore a significant health problem for women with HDP, especially preeclampsia/eclampsia. Presence of comorbidities and complications, preterm births, non-attendance of ANC, pre-eclampsia/eclampsia, and low birth weight were identified as risk factors for stillbirths in HDP. However, only the mode of delivery, biophysical profile, and resistive index could be used to predict the occurrence of a stillbirth in HDP.

5.4 Recommendations

- There is high prevalence rate of stillbirths in HDP, we recommend that a prospective study be conducted to determine incidence of stillbirth in HDP and any associated preventable factors.
- There is need for further evaluation of quality of intrapartum care to establish any association with stillbirths in HDP for the postadmission stillbirths
- Almost half of the stillbirths happened before admission to our facility, this may indicate inefficiency and lack of capacity at lower levels. This demands for dissemination of guidelines on management of HDP and improved knowledge of risk factors for adverse birth outcomes to lower-level facilities.

5.5 Study timelines

	2019	2020									
	Dec	Jan	Feb	Mar	April	May	June	July	Aug	Sept	Oct
Concept development	■										
Proposal development		■	■								
Ethical approval				■	■	■	■	■			
Data collection									■	■	
Data analysis										■	
Presentation/dissemination											■

5.6 Study budget

Activity	Item	Kshs
Proposal Development	Printing costs	10,000
Data Collection	Two research assistants @1000/day for 30 days	60,000
Data Analysis	Statistician	40,000
Thesis Development	Printing costs	6,000
PI's Payment	Kshs 1000 per day for 30 days	30,000
	Contingency fund (10% of total budget)	14,600
	TOTAL	160,600

5.7 Funding

This study was sponsored by the Principal Investigator.

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APPENDICES

Appendix 1. Study Questionnaire

PREVALENCE, RISK FACTORS AND TIMING OF STILLBIRTHS AMONG PATIENTS WITH HYPERTENSIVE DISORDERS IN PREGNANCY AT KENYATTA NATIONAL HOSPITAL IN 2018-2019

Study questionnaire (complete all sections)

Study number: ……. Year: …….

Section 1: Demographic characteristics

1. Age……
2. Marital status

☐Married

☐Single

☐Divorced/separated

☐Widowed

3. Education level

☐Non-formal education

☐Primary

☐Secondary

☐Tertiary

Section 2: Reproductive and Medical characteristics

4. Type of HDP

☐Chronic hypertension

☐Gestational hypertension

☐Preeclampsia/eclampsia

☐Chronic hypertension with superimposed preeclampsia

5. Parity

☐Primigravida

☐Multipara (1-4)

☐Grand multipara (≥5)

6. Comorbidities

☐Yes ☐No

If yes, specify…….

7. ANC visit

☐Yes ☐No

If yes, timing of initiation (weeks)

☐First trimester (0 weeks - 13 + 6/7 weeks)

☐Second trimester (14 weeks - 27 + 6/7 weeks)

☐Third trimester (28 weeks - 40 + 6/7 weeks)

8. Number of visits …….

9. Highest Systolic blood pressure (mmHg) …….

10. Highest Diastolic blood pressure (mmHg) ……

11. Labs

Lowest Platelet level…….
Highest Urea level…….
Highest Creatinine level…….
Highest ALT level……
Highest AST level……
Proteinuria ☐Yes ☐No

12. Twins

☐Yes ☐No

13. Gestation in weeks at delivery (in weeks) ……

14. Mode of Delivery

☐SVD ☐C/S

15. Outcome of birth

☐Livebirth ☐Stillbirth

16. Birth weight in grams .....

17. Small for Gestational Age

☐Yes ☐No

18. Timing of stillbirth

☐preadmission ☐Ante partum

☐post admission ☐Intra-partum

19. Type of Stillbirth

☐FSB ☐MSB

20. Maternal complications due to HDP

☐AKI ☐Abruptio ☐Sepsis ☐HELLP ☐Pulmonary Oedema

☐ARDS ☐DIC ☐PPH ☐Death ☐None

☐Other (specify)…….

21. Antihypertensive drug given

☐Yes ☐No

If Yes, specify……...

22. Magnesium Sulphate given (where indicated)

☐Yes ☐No

23. Labour onset

☐Spontaneous ☐Induced

24.Ultrasound Findings:

Resistive index…….

Biophysical Profile……

Notes……

Appendix 2. KNH/UoN ERC Approval

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

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

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

APPROVED 23 JUL 2020

Ref: KNH-ERC/A/238

23rd July 2020

Dr. Billy Mella Odhiambo
Reg. No.H58/7004/2017
Dept.of Obstetrics and Gynaecology
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Odhiambo

RESEARCH PROPOSAL – PREVALENCE, RISK FACTORS AND TIMING OF STILLBIRTHS AMONG PATIENTS WITH HYPERTENSIVE DISORDERS IN PREGNANCY AT KENYATTA NATIONAL HOSPITAL IN 2018-2019 (P176/03/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above research proposal. The approval period is 23rd July 2020 – 22nd July 2021.

This approval is subject to compliance with the following requirements:

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