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COLLEGE OF HEALTH SCIENCES

COMPARISON OF PREGNANCY OUTCOMES BETWEEN CHRONIC HYPERTENSIVE PREGNANT WOMEN WITH AND WITHOUT SUPERIMPOSED PREECLAMPSIA AT KENYATTA NATIONAL HOSPITAL FROM 2016-2021

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(MMed) in Obstetrics and Gynecology

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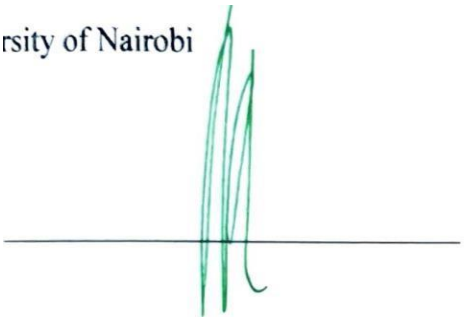
Sign 

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CERTIFICATE OF AUTHENTICITY

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DEDICATION

To my parents Prof. J.J.N. Ngeranwa and Dr. D.C. Kilalo – I stand on the shoulders of giants and recognize “I am” because “you are”; thank you for you encouraged me every step of the way. My siblings Faith, Lulu, Safari and my niece Chao: you have been my rock throughout this process. Thank you for your love, your prayers, your support. Most importantly, I dedicate this to Almighty God in whom all things are possible, and I find my being.

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LIST OF ABBREVIATIONS

ACE I	Angiotensin Converting Enzyme Inhibitors
ANC	Antenatal Clinic
ACOG	American College of Obstetrics and Gynecology
ARB	Angiotensin II Receptor Blockers
BMI	Body Mass Index
CVD	Cardiovascular Disease
CVA	Cerebrovascular Accident
DBP	Diastolic Blood Pressure
FGR	Fetal Growth Restriction
HELLP	Hemolysis, Elevated Liver Enzymes and Low Platelets
IUFD	Intrauterine Fetal Demise
KNH	Kenyatta National Hospital
KDHS	Kenya Demographic and Heath Survey
NBU	New Born Unit
NICE	The National Institute of Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NCD	Non-communicable Diseases
NGO	Non-Governmental Organizations
PPH	Post-partum Hemorrhage
SBP	Systolic Blood Pressure
SDG	Sustainable Development Goals
SPE	Superimposed pre-eclampsia
WHO	World Health Organization

OPERATIONAL DEFINITIONS

Antepartum hemorrhage: Bleeding per vaginum after 20 weeks of gestation and prior to delivery of the fetus

Birth asphyxia: Defined as an Apgar score of less than 7 at 5 minutes after birth with cardio respiratory and neurological depression

Body Mass Index [BMI]: Computed from the height and weight of the respondent - weight divided by height squared [kg/m^2]. The BMI is categorized into four groups; **underweight**-BMI <18.5 Kg/m^2, **normal**-BMI between 18.50 and 24.99 Kg/m^2, **overweight**-BMI between 25 and 29.99 Kg/m^2 and **obese**-BMI is $\geq$ 30 Kg/m^2.

Birth weight: First weight of the fetus or newborn obtained immediately after birth. For live births, birth weight should ideally be measured within first hour of life before significant postnatal weight loss occurs.

Control of hypertension: defined as SBP below 140 mmHg and DBP below 90 mmHg while on treatment among those on treatment.

Early Neonatal Death: death occurring within the first 6 days of life

Fetal Demise: a fetal death in-utero that occurs after 20 weeks of gestation but before birth.

Fetal Growth Restriction: discrepancies between actual and expected sonographic biometric measurements for a given gestational age.

Gestation- the carrying of an embryo or fetus inside a female viviparous animal like a woman.

Gestational age- It relates to the age of an embryo or fetus while still in the uterus measured from the first day of the last normal menstrual period, or if unavailable a best estimate is given based on the history, examination and ultrasound findings

Hypertension: a condition where the blood vessels have persistent raised pressure usually defined as systolic blood pressure of 140 mm Hg or more, a diastolic blood pressure of 90 mm Hg or more, or both.

Hypertensive disorders of pregnancy:

i) **Preeclampsia:** Systolic blood pressure of $\geq$140 mm Hg or diastolic blood pressure of $\geq$90 mm Hg in a pregnant woman with a previously normal blood pressure, taken on 2 occasions at least 4 hours apart on or after 20 weeks of gestation; and demonstration of proteinuria

Preeclampsia with severe features: New onset of any of the following events in the absence of proteinuria: low platelet count: less than 100,000 × 10^9/L , liver impairment: elevated liver transaminases levels twice the normal blood concentration, renal insufficiency: Serum creatinine level greater than 90µmol/L or doubling of the concentration without other renal disease, new-onset intractable headache with

medication and not accounted for by alternative diagnosis, visual disturbances, epigastric and right upper quadrant pain and pulmonary edema

ii) **Gestational hypertension:** Hypertension that develops at or after 20 weeks of gestation and persists de novo in the absence of features of preeclampsia

iii) **Chronic hypertension:** Blood pressure ≥140 mm Hg systolic and/or 90 mm Hg diastolic before pregnancy or, before 20 weeks of gestation, use of antihypertensive medications before pregnancy, or persistence of hypertension for >12 weeks after delivery

iv) **Eclampsia:** Development of grand mal seizures or coma in a woman with gestational hypertension or preeclampsia in the absence of any other attributable cause of seizures.

v) **Superimposed preeclampsia-** Features of pre-eclampsia complicating chronic hypertension in pregnancy. Worsening of the blood pressure, new onset of any of the following: proteinuria, low platelet count: less than $100,000 \times 10^9$/L , liver impairment: elevated liver transaminases levels twice the normal blood concentration, renal insufficiency: Serum creatinine level greater than 90µmol/L or doubling of the concentration without other renal disease, new-onset intractable headache with medication and not accounted for by alternative diagnosis, visual disturbances, epigastric and right upper quadrant pain and pulmonary edema

Live birth: Complete expulsion or extraction of a fetus from its mother, irrespective of the duration of the pregnancy, which after such separation, breathes or shows signs of life.

Low Birth Weight: A newborn weighing less than 2500grams at birth regardless of gestational age

Maternal Death: Death of a woman known to be pregnant within 42 days of termination of the pregnancy, irrespective of the duration or site of the pregnancy, that occurs due to a cause related to or aggravated by pregnancy or its management, but not from an accident or incidental causes.

Non-Communicable Diseases (NCDs): Chronic, slow progression diseases that are not passed from person to person such as Hypertension

Normotensive: Having normal blood pressure; systolic range 90-139 mm Hg and diastolic range 60-89 mm Hg

Perinatal period: the period from 28 weeks of pregnancy up to the end of the 7^{th} day after delivery. For this study it shall evaluate up to immediate neonatal outcomes (first 24 hours)

Perinatal mortality: any death of a fetus that occurs after 28 weeks of gestation, either as a still birth or born alive but died within the first 6 days after delivery.

Placental abruptio: premature separation of the placenta from the underlying myometrium resulting in pain, bleeding, and, potentially, clinical significant interruption of fetal gas and nutrient exchange

Pregnancy Outcomes: Maternal and fetal and neonatal end result in a given pregnancy

Poor pregnancy outcomes: undesirable maternal, fetal and neonatal end results of a pregnancy that are associated with higher incidence of morbidity and mortality

Preterm delivery: a delivery that occurs from a gestation of 20 weeks to a gestational age of less than 37 completed weeks

Pre-viable preterm delivery: a delivery that occurs at a gestational age of less than 24 completed weeks

Small for gestational age: Birthweight $<10^{th}$ centile for a population based on a sex-specific curve

Still births – intrauterine death at delivery resulting in baby born with no signs of life at or after having completed a gestational age of 28 weeks

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ABSTRACT

Introduction: Hypertensive disorders of pregnancy (HDPs) complicate 6-15% of pregnancies globally, and are associated with increased risks of adverse maternal and perinatal outcomes. HDPs are the 3rd leading cause of maternal mortality in Kenya. Chronic hypertension as one of the HDPs affects 3-5% of pregnancies and is gradually becoming common due to increasing incidence of obesity and delayed child bearing. Studies from high income countries have illustrated that pregnancies complicated with chronic hypertension are at a higher risk of adverse maternal and perinatal outcomes such as superimposed preeclampsia (SPE), placental abruption, fetal growth restriction, cesarean sections, preterm deliveries, low birth weight and perinatal mortality. These studies also suggest that the incidence of preeclampsia is higher in chronic hypertension than in the general population with worse obstetric outcomes. There is no study done in our region on chronic hypertension comparing the outcomes between those with and without SPE. It is therefore, not known whether the documented findings apply in low and middle income populations. This study, seeks to determine the association between chronic hypertension with or without SPE and adverse maternal and perinatal outcomes among pregnant women at Kenyatta National Hospital (KNH).

Objective: To determine maternal and perinatal outcomes for women with chronic hypertension, comparing those with SPE with those without SPE at KNH between the years 2016 and 2020.

Methodology: A retrospective cohort study was conducted at KNH. Patient records of pregnant women with chronic hypertension were reviewed from December 31, 2021, working backwards until the desired sample size was achieved. Adverse maternal and perinatal outcomes among those with and without SPE were compared. A total of 162 patients' records were enrolled in the study. Eligibility was determined by the American College of Obstetrics & Gynecology criteria for diagnosis of chronic hypertension. The records were then classified into 2 equal groups: SPE group and no SPE group. Data was extracted using a structured data extraction tool and analyzed using SPSS version 26. Maternal and perinatal outcomes as well as the sociodemographic and clinical characteristics of the two groups were compared. Analysis was done using SPSS Version 26. Categorical variables were summarized as frequencies and proportions and compared using the Chi-square test and Fisher's exact test while continuous variables were summarized as means/median and standard deviations and interquartile range and compared using student-t or Mann Whitney U test as appropriate.

Binary logistic regression was used to evaluate the association between exposure to chronic hypertension (with and without SPE) and the maternal, fetal, and immediate neonatal outcomes. This yielded odds ratios (OR) and corresponding 95% confidence intervals (CI)

Results: Of the 162 patients recruited, the mean age was 34 years, 61% were multiparous, 70% had hypertension before pregnancy, 37% had history of pre-eclampsia, and 93% were on hypertensive drugs during the pregnancy. Only 23% of the study participants were on Aspirin antenatally. Chronic hypertension with SPE was significantly associated with an adverse maternal, fetal, and early neonatal outcome with AOR of 3.81(1.85,7.84), 2.97(1.48,5.96), and 5.63(2.59,12.25) respectively. Mode of delivery and gestational age at delivery were the noteworthy adverse maternal outcomes with SPE, with primary CS being significantly more common in women with SPE (2.43(1.15,5.14)), and preterm delivery (8.74(3.70,20.64)). Adverse neonatal outcomes were significantly more common among women with SPE, including prematurity (8.74(3.70,20.64)), SGA (2.45(1.08,5.56)), LBW (4.91(2.28,10.55)) and admission to NBU/NICU (2.34(1.11,4.93)). The 2 groups were not significantly different with regard to most of their sociodemographic and clinical characteristics except parity, family planning, duration of hospital stay and antenatal BP results.

Conclusion: The study contributes to the current limited local and regional data on the significance of chronic hypertension in pregnancy. There is an overall increased risk of adverse maternal and perinatal outcomes. The incidence of adverse maternal and perinatal outcomes is high with or without SPE, but worsens significantly with SPE than reported in high income countries. This indicates that we should intensify antenatal care of chronic hypertensive women locally and counsel them better on the risk of SPE on their pregnancy outcomes. Further evaluations of factors influencing the development of SPE and factors mitigating poor outcomes should be conducted with a larger multicenter study.

Key words: Chronic Hypertension, Superimposed Preeclampsia, Maternal Outcomes, Perinatal Outcomes

CHAPTER ONE: INTRODUCTION

HDPs are significant contributors to maternal mortality and morbidity and complicate 6-15% of pregnancies globally(1). In Kenya, studies conducted have demonstrated prevalence rates of hypertensive disorders of pregnancy (HDP) to range from 5-11%(2–4). HDPs are ranked 3rd among leading causes of maternal mortality cases in Kenya.(5). Chronic hypertension in pregnancy is diagnosed in approximately 3% to 5% of pregnancies (6), though recent trends show that the effect of the chronic hypertension on pregnancy might be on the upsurge especially due to increased incidence of delayed child bearing and obesity (7). The burden of hypertension worldwide and in Kenya is also on the increase (8) meaning more women of reproductive age will end up having pregnancies complicated by chronic hypertension.

The definition of chronic hypertension in pregnancy according to the American College of Obstetrics and Gynecology (ACOG) is blood pressure recording of ≥140 mm Hg systolic and/or 90 mm Hg diastolic before pregnancy or, prior to 20 weeks of gestation, use of antihypertensive medications prior to getting pregnant, or persistence of high blood pressure for >12 weeks after delivery(9). Despite the fact most chronic hypertensive women carry the pregnancy to term with minimal complications, they are at an increased risk of developing superimposed pre-eclampsia (SPE), and adverse outcomes such as perinatal mortality and morbidity from preterm birth, and increased incidence of placenta abruption and cesarean section (6).

Incidence rate of SPE has been demonstrated by several studies to range from 25-40% in the high income countries with associated poor obstetric outcomes (10,11), but, there is scarcity of data from middle and low income countries.

This study sought to determine the incidence of poor pregnancy outcomes (maternal and perinatal) in chronic hypertensive women, comparing those with and without SPE. It also compared the differences in the sociodemographic, obstetric and clinical characteristics of the two cohorts.

CHAPTER TWO: LITERATURE REVIEW

2.0 Introduction

Hypertensive disorders of pregnancy (HDP) still contribute significantly to maternal morbidity, long term disability and death. They complicate 6-15% of pregnancies worldwide and are associated with higher risks of perinatal and maternal morbidity and mortality (1). According to a World Health Organization (WHO) systematic review published in 2014, maternal deaths due to hypertensive disorders account for approximately 14% globally (12). In Kenya, studies conducted have demonstrated prevalence rates of hypertensive disorders of pregnancy (HDP) to range from 5-11%(2–4). HDPs are ranked third among leading causes of maternal deaths contributing 16%, with eclampsia being diagnosed in 78% of these deaths (5). According to the International Society for the Study of Hypertension in Pregnancy (ISSHP), HDPs have been grouped into four categories: gestational hypertension, preeclampsia/eclampsia, chronic (pre-existing) hypertension, and preeclampsia superimposed on chronic hypertension (13).

Chronic hypertension is diagnosed in approximately 3% to 5% of pregnancies and is increasingly becoming common due to growing incidence of obesity and delayed childbearing in women of reproductive age (6,14). The definition of chronic hypertension in pregnancy according to ACOG is blood pressure ≥140 mm Hg systolic and/or 90 mm Hg diastolic before pregnancy or, prior to 20 weeks of gestation, use of antihypertensive medications prior to getting pregnant, or persistence of high blood pressure for more than 12 weeks after delivery (7,9). ACOG recommends that the diagnosis of hypertension must include at least two recordings taken 4hours apart, unless when faced with severe hypertension, where a shorter interval [minutes] is acceptable to confirm diagnosis and facilitate timely intervention (9).

2.2 Burden of Hypertension Worldwide and in Kenya

Hypertension, globally, is the main contributor to cardiovascular disease (CVD) and chronic kidney disease, responsible for approximately 9.4 million deaths worldwide (8,15). The prevalence of

hypertension universally in adults older than 18 years was found to be 24% for men and 20% in women in a 2015 pooled analysis, which was a significant increase from 594 million in 1975 to 1.13 billion by 2015(15). In Kenya, data from national surveillance indicates that deaths due to Non-Communicable Diseases (NCDs) have risen between 2003 to 2010 from 35% to 45% respectively, hypertension playing an important role in the trend (8). A study conducted in 2018 on hypertension in Kenya revealed a prevalence ranging from 24% to 32.6% from various settings and populations (8).

The study also identified certain factors associated with the development of hypertension which included advances in age, higher body mass index (BMI), inadequate physical activity, high salt intake, consuming high fat intake and harmful use of alcohol (8,15). The study also observed that hypertension rates in Kenya are higher in the urban setting compared to rural due to the associated lifestyle changes that contribute to less physical activity and unhealthy diets and ultimately result in being overweight or obesity (8).

Additionally, the 2018 study highlighted that there is a low level of awareness of hypertension in the general population at 15.5% and only 26.9% of those aware of their hypertensive state were on treatment (8). This indicates that the burden of hypertension is yet to be adequately addressed leaving many women in the reproductive age at risk of complications in pregnancy without knowing.

2.3 Physiologic Changes in Blood Pressure in Pregnancy

Approaching the end of the first trimester normotensive women typically experience a reduction in blood pressure with its lowest levels at 16–18 weeks of gestation (7). 30% reduction in systemic vascular resistance begins as early as 7 weeks with marked vasodilation that happens regardless of the rise in plasma volume resulting in a fall in blood pressure of 10% (and even more in second trimester) (6,16,17). Blood pressure generally decreases by 5-10 mm Hg and persists at this low level during the course of pregnancy then starts to rise and approach pre-pregnancy values by the third trimester (6,16).

A similar pattern in blood pressure is seen for most women with chronic hypertension and consequently some hypertensive women become normotensive during pregnancy, some requiring their antihypertensive medication tapered (6,16). These normal physiological changes may complicate the recognition of chronic hypertension if a pregnant woman starts antenatal care primarily in the second trimester when the physiological decrease has occurred. These women may be diagnosed, wrongfully, as gestational hypertension in the third trimester when the blood pressure rises to pre-pregnancy levels. In these scenarios, the correct diagnosis of chronic hypertension has to be made in retrospect once the high blood pressures persist more than 12 weeks postpartum (6,9).

2.4 Diagnosing Chronic Hypertension in Pregnancy

Ideally, to diagnose chronic hypertension in pregnancy it is important to have knowledge of pre-pregnancy blood pressure levels. Unfortunately, these pre-pregnancy values are not known for many women and based on self-reporting, the prevalence of hypertension is underestimated as opposed to physician diagnosis or actual documented measurements (6). Chronic hypertension predating pregnancy is estimated to be essential (i.e. cause unknown) in >86% of women and secondary (i.e. associated with underlying conditions- renal, vascular or endocrine) in approximately 11–14% of cases of hypertension (6,14).

During patient assessment, a systematic evaluation of signs and symptoms is critical to reveal the uncommon secondary causes of hypertension as well as the extent of end-organ damage more so in gravid women with longstanding hypertension (6,9). Some of the directed patient investigations, include kidney function tests, liver function tests, a urinalysis and a full blood count. Others like an electrocardiogram and echocardiogram, or a toxicology screen, or ophthalmologic evaluation would be requested as applicable (6,9).

2.5 Classification of Chronic Hypertension in Pregnancy

Generally, in the absence of pregnancy, hypertension is classified into 3 groups: prehypertension, stage 1 hypertension, and stage 2 hypertension (17). Two categories of severity are acknowledged in pregnancy: mild (up to 159mmHg systolic and 109mmHg diastolic) and severe (≥ 160mmHg systolic or 110mmHg diastolic) (9,17,18). Sibai et al, also classified chronic hypertension in pregnancy as high or low risk for counselling and management purposes. Pregnant women were classified a low risk when they presented with mild hypertension, no history of perinatal loss, and without any end organ involvement (left ventricular dysfunction, microvascular disease, stroke, dyslipidemia or retinopathy); whereas high risk was based on presence of secondary hypertension or severe essential hypertension with end organ damage, history of perinatal loss or maternal age greater than 40 years (18).

2.6 Negative effects of Chronic Hypertension on Pregnancy

2.6.1 Maternal Risks

Many studies have demonstrated that the presence of chronic hypertension in pregnancy is associated with poor maternal outcomes. Although mild chronic hypertensives do well in pregnancy with similar outcomes to normotensives they are at greater risks of maternal complications which become amplified in severe, uncontrolled cases (6).Complications for chronic hypertensive women in pregnancy include risk of developing SPE, operational delivery, postpartum hemorrhage and placenta abruption.

Studies done in high income countries indicate the risk of superimposed pre-eclampsia is approximately eightfold higher compared with pre-eclampsia in normotensive women (25.9% vs. 3-5%)(6,10). The presence of pre-eclampsia further complicates the adverse pregnancy outcomes. Sibai et al (19) study of chronic hypertension in pregnant women demonstrated the rate of placental abruption was 1.5%, which increased in those with SPE (3%) compared to those without SPE (1%). Another study conducted in Sweden found similar results with higher rates of abruptio of 1.1% in chronic hypertensive women compared to 0.4% those without chronic hypertension, respectively(20).

Chronic hypertension complicates pregnancies by increasing the risk of preterm delivery. A study piloted in Denmark showed a positive association between having chronic hypertension and term and preterm delivery of small for gestational age (SGA) fetuses independent of other risk factors such as superimposed preeclampsia, smoking, parity and maternal age(21). Worsening maternal and fetal state brought about by endothelial dysfunction naturally results in higher rates of pre-term induction of labor as well as caesarean deliveries(20,21). A 2014 systematic meta-analysis of pregnancy outcomes in chronic hypertension also showed an incidence of caesarean section of 41.4% (10). This indicates 4 out of 10 women with chronic hypertension will undergo Caesarean section.

Previous studies indicate that chronic hypertensive women showing signs of end-organ damage before becoming gravid are at greater risk of hypertensive encephalopathy, acute renal failure, pulmonary edema, cerebrovascular accidents and retinopathy during pregnancy(22). This necessitates proper pre-conception evaluation and counselling. The maternal mortality risk is also heightened in chronic hypertensive women due to the above mentioned end-organ complications which are up to six-fold compared to normotensive women(6,9).

2.1.2 Fetal Risks

A large body of data has indicated that pregnancies of chronic hypertensive women are associated with poor perinatal outcomes. A meta-analysis of 55 studies, spanning 25 countries published in 2014, showed a three times as great risk of preterm delivery earlier than 37 weeks of gestation, neonatal intensive care admission and low birth weight <2500 g. It also indicated a four times as great risk of perinatal death when compared to the general United States population of pregnant women(10). Zetterström et al. also found a higher (2–4 times) perinatal mortality rate in the chronic hypertensive women than that of the normotensive ones, with higher risk of stillbirths and neonatal deaths independent of other influences such as fetal growth restriction, SPE, or gestational diabetes (20).

Often decisions of early delivery have to be made with manifestation of worsening fetal or maternal health, resulting in induction at an early gestational age. This results in preterm delivery with prematurity further complicating the risk of perinatal mortality. Studies indicate that the severity and duration of chronic hypertension, presence of target organ damage, and proteinuria level correlate with the incidence of these poor perinatal effects (9).

2.7 Chronic Hypertension with Superimposed Preeclampsia (SPE)

SPE is simply development of preeclampsia complicating already existing hypertension in a pregnant woman. However, SPE is often challenging to diagnose and tends to be a diagnosis of exclusion [6,7]. According to ACOG, exacerbated increase in blood pressure or increase in proteinuria above the baseline (≥ 300 mg/24-hour collection) should prompt evaluation for superimposed preeclampsia(9). Helpful indicators to point to a diagnosis of SPE include new onset of thrombocytopenia, a sudden rise in liver enzymes, elevated uric acid or rapid onset of symptoms indicative of severe preeclampsia: headaches, visual disturbances, or epigastric pain(9).

A 2014 systematic review carried out in the United States presented the collective incidence of SPE to be 25.9% among chronic hypertensive women(10). These findings were comparable to those reported by Sibai et al in 1998 which followed 763 women prospectively and found the overall risk of SPE to be 25%(19). This is much more elevated than the overall risk of pre-eclampsia in the general pregnant population. Research conducted in Asian women from Thailand, found a higher incidence of SPE (43.3%) suggesting that the results from high income countries were not generalizable to different populations due to different risks and characteristics(11).

Several studies have shown that the onset of preeclampsia, if present, in chronic hypertension usually occurs earlier (<34 weeks) and is commonly more severe with poor prognosis for the mother and fetus (23). The factors identified to increase the risk of SPE include: duration of hypertension, diastolic blood

pressure greater than 100mm Hg, previous preeclampsia, proteinuria, thrombophilia, diabetes, multiple gestation and use of assisted reproductive technology(19,23,24). Studies also indicate that the risk of SPE is increased in African Americans, smokers, and obese women (19,23,24).

A study conducted in Nigeria that looked at the pattern and factors affecting outcomes in 127 HDPs found an incidence of SPE of 19.7%. In this study, however, there was no distinct chronic hypertension group as all of them either had SPE or eclampsia(25).

2.8 Superimposed Pre-Eclampsia On Chronic Hypertension Is Associated with Poor Maternal and Perinatal Outcomes

HDPs are associated with abnormal placentation and under perfusion arising from the trophoblasts ineffectively invading the maternal spiral arteries(26). Preeclampsia is characterized by several complex placental changes (collectively referred to as placental syndrome) such as lower mean placental weight, area and volume; and histologically more syncytial knots, areas of fibrinoid necrosis, calcified and hyalinised villous spots on the placental villi compared to normotensive women(27).These changes are indicative of the pathogenesis of increased perinatal and maternal morbidity and mortality in pregnant women who develop preeclampsia. A study done in Kenya comparing morphological features of placentae in hypertensive and normotensive women found the above mentioned changes which were associated with a greater incidence of preterm delivery (average 36.3 weeks), low birth weight, fresh stillbirths and admissions to NBU in the hypertensive group(28). SPE worsens chronic hypertension and as can be expected worsens the incidence of poor maternal and perinatal outcomes. A study in Brazil conducted on a cohort of chronic hypertension women, compared the maternal and perinatal outcomes between those who developed SPE versus no SPE. The findings showed higher rates of poor neonatal outcomes in the SPE group including low birth weight, SGA, and need for a neonatal intensive care unit (NICU) admission (29). The study which looked at 385 women

also found higher incidence of cesarean delivery (incidence in SPE 79.64% vs those without 62.38%) and fetal growth restriction in the SPE group (29).

Numerous studies have also confirmed the amplified risk of preterm deliveries and poor neonatal outcomes associated with SPE compared to uncomplicated mild or severe chronic hypertension. Women with SPE were at 43 times higher risk of preterm birth (< 32 weeks) compared to women without chronic hypertension. (30,31). Findings from Nakanishi et al, showed an association between SPE and SGA and preterm deliveries, which resulted in further neonatal complications inclusive of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC), impacting on perinatal mortality (32).

SPE has worse outcomes than preeclampsia possibly due to the pre-existing endothelial dysfunction of maternal vessels that worsens with development of SPE. Studies that compared incidence of adverse events between preeclampsia and SPE found that rates of abruption, eclampsia, SGA, and stillbirth were not markedly different, however, there was increase in preterm delivery earlier than 34 weeks (17.1% in SPE compared to 8.7% in preeclampsia), NICU admission, and cesarean delivery in SPE women (33).

Incidence rates of complications such as eclampsia (0-2.5%) (34), pulmonary edema, placenta abruption, thrombocytopenia, disseminated intravascular coagulation, future cardiovascular disease were found to be higher in women with SPE with severe features compared to chronic hypertension and normotensive patients (9,23,34).

Higher income studies have observed that African-American women with chronic hypertension when compared with their white counterparts have more than two-fold risk of developing eclampsia(35). Studies from northern Nigerian found the incidence of eclampsia to be between 0.42 -2.76% with a mortality of 6.1-42.1%(25). A study conducted in Kenya that looked at 262 patients with eclampsia found a higher risk of mortality in patients aged above 34 years(36)

2.9 Management of Chronic Hypertension in Pregnancy

In high risk patients, studies have shown potential benefits of drug therapy in prolonging the pregnancy, controlling blood pressure and improving perinatal outcomes. The Control of Hypertension in Pregnancy Study (CHIPS) established that severe hypertension resulted in with poor pregnancy outcomes with observed increased risks of maternal death, pregnancy loss, preterm delivery, SGA, or advanced neonatal care for >48 h compared to those with hypertension that is not severe(37). The study also classified the 1000 women enrolled into "less-tight-control" (targeting a diastolic BP value of 100 mmHg) against "tight-control" (diastolic 85 mmHg); and found that those in the former group developed severe hypertension although with not much difference in other outcomes(37).

Many studies and societies including the ACOG Bulletin with the aim to preserve uteroplacental blood recommend a diastolic pressure target of above 80 mmHg to (9,17). They recommend target diastolic BP of 80-105mmHg and systolic BP of 120-155mmHg which is considered well controlled, whereas anything above this is considered poorly controlled and poses a risk for poor maternal and perinatal outcomes(9,38)

Clinically effective antihypertensive drugs of choice that have been studied and found useful in improving the pregnancy outcomes include methyldopa, labetalol, nifedipine, atenolol, oxprenolol, diltiazem; prazosin and hydralazine being preserved for third line use (7,9). The administration of calcium, low-dose aspirin, or other dietary supplements to prevent the development of preeclampsia has been studied(7). Recent studies have revealed the benefits of aspirin in preventing preeclampsia (and SPE) in high-risk populations by 62% as well as a reduction in preterm births earlier than 32 weeks of gestation and the length of stay in the NICU by 68%(39). Prophylactic administration of low-dose aspirin (150mg) has been demonstrated to modify the risk of SPE with a recommendation of initiating the drug before 16 weeks of gestation (7,9,13).

2.10 Conceptual Framework

2.10.1 Narrative

The burden of hypertensive disease worldwide is increasing and some of the risk factors associated with it are black ethnicity, older age (>35 years), higher body mass index (BMI), insufficient physical activity, high salt intake, consuming high fat intake and harmful use of alcohol. The development of chronic hypertension is also influenced by genetics and a previous history of hypertension in pregnancy. The incidence of chronic hypertension in pregnancy is on the rise due to delayed onset of child bearing and the increase in obesity. Hypertension has been demonstrated to affect the uteroplacental flow affecting the growing fetus, as well as cause microvascular injury, vasoconstriction and clot formation leading to end-organ damage. The presence of SPE influences worsened placental insufficiency which increased oxidative stress on the fetus with expected poorer outcomes.

Outcomes expected are either good or adverse maternal and perinatal outcomes. These can be altered by certain factors such as good prenatal blood pressure control, proper antenatal care, use of medication, and good control of blood pressure during pregnancy

2.11.1 Diagrammatic Framework

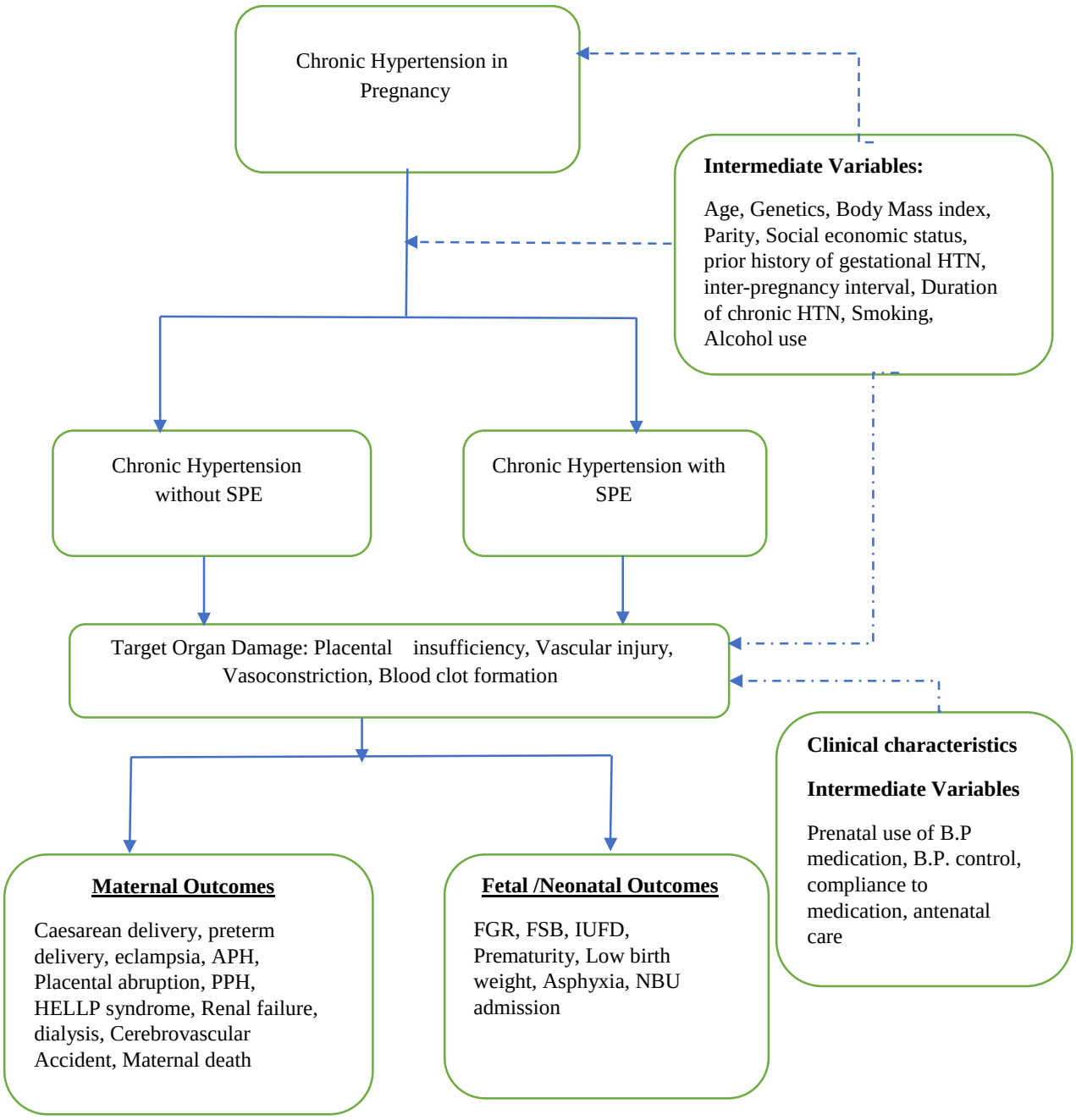

Figure 1: Conceptual Framework

Author's own, 2020

2.11 Problem Statement

Evidence suggests that globally hypertension is on the rise and in Kenya the current prevalence ranges from 24% to 32.6% from various settings and populations (8,14). This coupled with the recent trend of increasing incidence of obesity and delayed childbearing is bound to make cases of chronic hypertension in pregnancy more common (6,14). Studies from high income countries have demonstrated an association between chronic hypertension in pregnancy and several adverse pregnancy outcomes such as SPE, but even in the absence of SPE, a greater risk of perinatal mortality, preterm birth, fetal growth restriction (FGR), placental abruption, and operative delivery still exists in these women (6,10,11).

Hypertension in pregnancy remains ranked as the third leading contributor to maternal deaths in Kenya. It also a major contributing factor to adverse maternal outcomes that result in long term morbidity of the affected women due to end-organ damage. Hypertension has been shown to predispose the pregnant women to long term risk of cardiovascular morbidity and mortality. Since the underlying cause is pre-existing in chronic hypertensives, similar or worse outcomes are to be expected for all the subsequent pregnancies. This brings to attention the need for heightened surveillance for pre-existing hypertension, emphasizing on pre-conception counselling as well as specialized antenatal and postnatal care to prevent adverse outcomes (9).

Pregnancies complicated by chronic hypertension have also been demonstrated to have poor perinatal outcomes. Studies from high income countries found a strong association with greater risk of perinatal mortality, NICU admission, prematurity, and low birth weight (6,10,18,20,21). Prematurity leads to several complications in the new born such as RDS, thrombocytopenia, neutropenia, and NEC. These poor outcomes have both immediate and long term health problems and have a negative impact on society.

2.12 Justification

This is a novel study since there is extensive research available locally on pre-eclampsia and eclampsia, but no study was available during literature review that looks at chronic hypertension and superimposed

pre-eclampsia. Most information that we base our practice on locally is obtained from studies done in high income countries. Inadequate data is available from middle and low income countries on the incidence, adverse outcomes, and risk factors of chronic hypertension in pregnancy and SPE. A study in Thailand (11) demonstrated higher incidence of SPE than documented in studies done in the United States suggesting that the results from studies done in high income countries might not be appropriately generalizable to low and middle income populations due to possible differences in characteristics and baseline risks.

The scarcity of local literature on the impact of chronic hypertension and SPE in pregnancy in Kenya makes effective management challenging. The basis of the study is to explore Kenya's clinical spectrum of chronic hypertension in pregnancy and SPE, i.e. from how they present at ANC, and admission, the interventions given in their management, the treatment of complications arising, and compare maternal and perinatal health outcomes between those who develop versus those who do not develop SPE in a setting of a maternity department of a regional referral hospital (KNH). The study will yield novel information locally which will contribute to a greater understanding of the characteristics of pregnant women with chronic hypertension and the possible differences in maternal and perinatal health outcomes when affected by SPE.

Information obtained in this study will be useful to the medical personnel, and health institutions in the region to better understand chronic hypertension in pregnancy, appropriately counsel patients and predict adverse health outcomes in pregnant women with chronic hypertension. This heightened awareness will also influence the standard operating procedures of follow up of patients with chronic hypertension in pregnancy. The information obtained will also serve as a basis of further research into various interventions to alter the management and improve outcomes of pregnant women with chronic hypertension especially in the prevention of SPE. This will contribute in assisting Kenya to achieve SDG 3 and 5 of improving maternal and infant health and reducing deaths (40).

2.13 Study Question

Is there a difference in the incidence of poor pregnancy outcomes between chronic hypertensive pregnant patients with superimposed preeclampsia and those without superimposed preeclampsia at Kenyatta National Hospital between 2016-2021?

2.14 Null Hypothesis

There is no difference in the incidence of poor pregnancy outcomes between chronic hypertensive pregnant patients with superimposed preeclampsia and those without superimposed preeclampsia at Kenyatta National Hospital between 2016-2021

2.15 Research Objectives

2.15.1 Broad objective

To compare the incidence of poor pregnancy outcomes between chronic hypertensive pregnant patients with superimposed preeclampsia and those without superimposed preeclampsia at Kenyatta National Hospital between 2016-2021

2.15.2 Specific objectives

Primary specific objectives

Among chronic hypertensive pregnant patients with SPE and those without SPE at Kenyatta National Hospital between 2016-2021 to:

i) Compare the poor maternal outcomes (Preterm delivery, antepartum hemorrhage, Placenta abruption, IUFD, PPH, Caesarean delivery, eclampsia, HELLP, cerebral vascular accident, kidney injury, dialysis and maternal death)
ii) Determine the differences in poor fetal outcomes (Fetal growth restriction, Stillbirth)

iii) Determine the differences in poor immediate neonatal outcomes (Low birth weight, APGAR Score at 5th minute, Admission to NBU/NICU)

Secondary specific objective

i) To compare the sociodemographic factors, obstetric and medical characteristics between chronic hypertensive pregnant women with SPE and those without SPE

CHAPTER THREE: RESEARCH METHODOLOGY

3.0 Study design

This was a retrospective cohort study. The study was undertaken among chronic hypertensive pregnant women. For this study women with SPE were considered the exposed group, while those without were categorized as the unexposed group. The study examined sociodemographic, obstetric and clinical characteristics (antenatal care, treatment given, BP control, interventions done) of these patients and compared the incidence of poor pregnancy outcomes between the exposed and unexposed groups.

The retrospective nature of this study was most suitable since chronic hypertension in pregnancy and SPE occur rarely and would require a number of years to obtain a suitable sample size for study. By conducting a retrospective study, the records of the patients were obtained from December 2021 working backwards until an adequate sample size was achieved for study.

3.1 Study site and setting

The study was undertaken at Kenyatta National Hospital (KNH) which is the biggest referral and teaching hospital in Kenya and East Africa. KNH has an 1800 bed capacity and primarily serves the residents of Nairobi County as well as referral patients from all other counties of Kenya. The facility caters to women from varying socioeconomic status offering services from Antenatal clinics (ANC) three days a week, to labor ward, to antenatal/postnatal wards (GFA, GFB and 1A) and post-natal clinic (PNC). The Obstetrics and Gynecology department of KNH also has a dedicated Critical Care Unit (CCU) that has a 6 bed capacity and helps serve the critically ill patients from this unit specifically.

The ANC clinic offers services to about 2,000 pregnant women per month while the labor ward conducts approximately 1,250 deliveries in a month. The newborn care unit (NBU) has a capacity of 60 beds/incubators, and the NICU has five incubators and respirators. The NBU admits about 380 babies in a month with an average stay of 14 days.

All pregnant women with HDPs make first contact and are attended to either in the ANC or labor ward, they are then managed (stabilized in case of severity) and taken to the wards or CCU for follow up care

before discharge. The patients are then followed up in the ANC, or PNC for up to 12 weeks after delivery. The facility offers multidisciplinary care to pregnant and postpartum women with various surgical and medical needs. Patients with complications arising from chronic hypertension in pregnancy easily access various disciplines for specialized care such as internists, hematologists, nephrologists, cardiologists, ophthalmologists and neurologists. KNH also offers 24hour radiological imaging (such as ultrasound, CT scan and X-ray) and laboratory services (hematology, endocrinology, biochemistry and immunology) which aid in prompt diagnosis and institution of management.

3.2 Study population

The study population comprised of pregnant women who attended ANC and PNC (up to 12 weeks after delivery) or received intrapartum care at KNH; or women who were referred to KNH prior to, during or immediately after delivery, and were diagnosed with chronic hypertension in pregnancy with or without SPE. The participants selected were of a reproductive age (15-49 years). Pregnant women with SPE were considered the exposed group, while those without SPE were categorized as the comparison/unexposed group.

Inclusion Criteria

This study targeted records of chronic hypertensive pregnant women in KNH. Eligibility criteria included:

i. blood pressure measurement of ≥140 mmHg systolic and/or ≥90 mmHg diastolic at two separate readings before pregnancy or prior to 20 weeks of gestation,
ii. a history of use of antihypertensive medications prior to pregnancy,
iii. persistence of hypertension for >12 weeks following delivery

Exclusion criteria

The study excluded records of pregnant women:

i. with incomplete data (more than 20%)- we anticipated that lack of sufficient variables recorded would have made the data difficult to analyze and derive correct associations

ii. with comorbidities such as diabetes, chronic heart disease, renal disease which have a direct contribution to poor maternal and perinatal health outcomes independent of HDPs, therefore would have acted as confounders and degrade the validity of the data

3.3 Sample size determination and formula

The study considered the use of α = 5% level of significance (type 1 error rate of 5%) and 80% (1-β) power of detecting maternal, fetal and immediate neonatal outcomes between exposed and un-exposed group. P-values less than 0.05 (P-value < 0.05) were interpreted as statistically significant. The study assumed the values of incidences of poor pregnancy outcomes rate from at risk group ($pp_1 = 0.325$) and ($pp_2 = 0.12$) from at no risk group. The values were obtained from the studies done by (Sibai Baha et al, 1999, Casagrande Laura et al, 2020, and Seely EW et al, 2014). There were very limited studies which explicitly gave the incidence rates of the pregnancy outcomes under this study, that could have been directly used to estimate the sample size. Hence, the computation done was based on the averaged values from studies which closely evaluated the outcomes in chronic hypertension with/without superimposed pre-eclampsia. The 3 primary objectives were considered in the computation and the adverse maternal outcomes objective had the highest sample size.

Sample size for the study was computed using Fleiss formula (Fleiss JL 1981 pp. 44-45).

The ratio of exposed versus unexposed was set to be 1:1.

$$n' = \frac{\left[z_{\frac{\alpha}{2}}\sqrt{(r+1)\overline{PQ}} + z_{1-\beta}\sqrt{rP_1Q_1 + P_2Q_2}\right]^2}{r(P_2 - P_1)^2}$$

Where: $z_{\alpha/2} = 1.96$

$z_{1-\beta} = 0.84$ (Power)

$r = \frac{n_1}{n_2}$, The ratio of exposed vs unexposed (Desired ratio 1:1)

$\alpha =$ Type 1 error, level of significance (0.05)

$\beta =$ Type 2 error rate, chance of not detecting a difference (0.2)

P_1 = Rate of poor pregnancy outcome from at risk group = 0.325

$P_2 =$ Rate of poor pregnancy outcome from no risk group = 0.12

$\overline{\mathrm{P}} = (p_1 + rp_2)/(r+1)$ = 0.223

$\bar{Q} = (1 - \overline{\mathrm{P}})$ = 0.777

Hence

$$n' = \frac{\left[1.96\sqrt{(2)\overline{0.1733}} + 0.84\sqrt{0.2194 + 0.1056}\right]^2}{(0.205)^2}$$

$$n' = \frac{[1.1539 + 0.4789]^2}{(0.205)^2}$$

$$\boldsymbol{n' = 63.437}$$

Applying the Fleiss continuity correction to obtain a sample for each group was computed in the equation below to obtain a sample size with continuity correction.

$$n'' = \frac{n'}{4}\left[1 + \sqrt{((1 + \left(\frac{2(r+1)}{n'r|P_2 - P_1|}\right))}\right]^2$$

$$n'' = \frac{63.437}{4}\left[1 + \sqrt{((1 + \left(\frac{4}{63.437 \times 0.205}\right))}\right]^2$$

$$n = 72.867$$

To account for the attrition or incomplete historical information from the data that may lead to a decision to exclude some participants in the analysis, adjustment at rate of 10% (r = 0.1) was computed. The adjusted sample size was finally given as

$$n = \frac{n''}{1-r} = \frac{72.867}{1 - 0.1} = 80.96$$

$$\boldsymbol{n'' \approx 81}$$

$$n_{exposed} + n_{un-exposed} = 81 + 81$$

$$\underline{\boldsymbol{Cohort\ Sample\ size\ = 162}}$$

The cohort sample size for this study was **162;** 81 participants in each arm: exposed vs non-exposed.

3.4 Sampling procedure

Sequential sampling of de-identified records was done until the desired sample size was achieved over the specified time frame: January 2016- December 2021. Since the incidence of chronic hypertension from previous studies was estimated as 3-5%; all records of cases of chronic hypertension in pregnancy within the study time frame who met the inclusion criteria were obtained from ANC, labor ward and PNC units. Continuous recruitment of files was done from December 2021 working backwards until the estimated sample size was achieved. Case files with missing or incomplete data (up to 20%) were excluded such as files in which the main outcome variable was not captured. The sample size of **162** case files was finally subjected to analysis.

3.5 Study Variables

Table 1: Table of variables

Variable Type	Variable Definition
Dependent Variables	**Fetal and Immediate Neonatal Outcomes:** FGR, Prematurity, Low birth weight, Still birth, SGA, APGAR Score at 5th minute, Admission to NBU/NICU **Maternal Outcomes:** Preterm delivery, Placenta abruptio, placenta previa, APH, PPH, Caesarean delivery, eclampsia, cerebral vascular accident, HELLP, acute kidney injury, dialysis, and maternal death,
Independent Variables	Presence of Chronic Hypertension in pregnancy (with and without SPE)
Potential confounders	Maternal age, parity, body mass index, weight, secondary hypertension, smoking, lack of/poor antenatal care

3.6 Data collection procedures

Data was obtained from de-identified ANC, PNC and maternity inpatient records with focus on the time from diagnosis of chronic hypertension and the time of development of superimposed pre-eclampsia as

well as the interventions given that support measurement of clinical care given. Patient names and admission numbers were obtained from the labor ward admission and delivery registries as well as postnatal ward registries. The files were then retrieved using this information from the records department of KNH.

The files were grouped into two groups: those with and those without SPE by harmonized review of the following: medical records (files), antenatal cards, or clinician notes for exposure within the month preceding delivery, gestational age at exposure, and investigation and imaging results. SPE was defined as worsening blood pressure associated with new onset proteinuria (defined as urinary proteins of +1 or greater) or laboratory and clinical findings of end-organ damage. The group without SPE was further divided into those with well controlled blood pressure during admission ($\leq$100 mmHg diastolic BP as adapted from the CHIPS study(37)) and poorly controlled blood pressure.

An online data abstraction form (Google form) was formulated and used to capture the information on the study variables, sociodemographic, obstetric and clinical characteristics of the patients. A process of de-identification of the records was done to preserve the privacy of the research participants. The process involved excluding personal identifiers such as names, in-patient hospital numbers and dates of birth; and instead assigning a unique system-generated identification number to the records included in the study. The information was collected by trained research assistants (2 clinical officers and 2 5^{th} year undergraduate medical students), who were first acquainted with the abstraction tool.

For completeness of data extraction, all records of chronic hypertensive pregnant women retrieved in the records department within the time period (working backwards from December 2021) that met the inclusion criteria was considered for the study until the desired sample size was achieved.

Data was obtained on the maternal socio-demographic characteristics: age, marital status, occupation, smoking and alcohol use. It was not possible to obtain data such as BMI due to 90% of the records missing data on the weight and height of the patients. These were not routinely done in our ANC preceding 2019

and even current records were not keen on it. Obstetric characteristics data was obtained such as parity, attendance of ANC, gestational age at starting ANC, use of family planning, antepartum hemorrhage, fetal monitoring techniques outcomes: ultrasound and non-stress test, and mode of delivery.

Clinical characteristics data included: prior use of BP medication, duration of hypertension disease, use of BP medication antenatally, previous history of pre-eclampsia, history of antenatal admission, presenting symptoms at admission for delivery, mean antenatal systolic and diastolic BP during admission and symptoms of worsening disease such us worsened epigastric or right upper quadrant pain, intractable headache, and visual symptoms; treatment interventions given during admission (medication, induction, Caesarean delivery and its indications or dialysis).

Data on maternal outcomes included timing of delivery (preterm delivery- which will be divided into early onset (<34 weeks) versus late onset (>34-36 weeks + 6 days) and Caesarean delivery as the main outcome variables. Pre-term births were considered as all live births occurring earlier than 37 weeks' and after 20 weeks' gestation. Babies born prior to 28 weeks were classified as extremely pre-term, and between 28 and 32 weeks - very pre-term, whereas between 32 and 37 weeks are moderate (to late) preterm.

The other maternal outcomes included: Placenta abruptio, placenta previa, IUFD, PPH, HELLP, and eclampsia. Data on significant end-organ involvement was also obtained such as cerebral vascular accident, kidney injury, requirement of dialysis, lengthy hospitalization including high dependency or critical care units' admission, and mortality. Data on perinatal outcomes included FGR, and stillbirth as the main outcome variables for poor fetal outcomes and prematurity, SGA (which was arrived at as the weight at delivery on or below the 10^{th} percentile for gestational age using a given population growth curve- INTERGROWTH21^{st}), and Low birth weight as the main outcome variables for poor immediate neonatal outcomes. Data was also obtained on other variables such as APGAR Score at 5^{th} minute, and admission to NBU/NICU. The perinatal outcomes for this study were limited to the immediate neonatal outcomes which is up to the first 24hours after birth.

3.7 Quality assurance measures

So as to ensure the data collected was valid and reliable, the following approach was used:

Pre-testing and validation of data extraction tool

For validation of content and analysis of the internal consistency of the data abstraction form a pre-test and validation procedure was done using the test and retest methods. The data abstract form was reviewed by various health care workers (HCW) such as peers (registrars), medical officers, clinical officers, nurses and consultants at KNH to establish face validity and its suitability and reliability for data collection.

Personnel training

Research assistants were HCWs (clinical officers and undergraduate medical students). They were recruited and trained on use of the data abstraction form and how to go through the file to abstract data from the patient records accurately. They were also trained on how to manage files with missing data and thus improve the integrity of the data collected. Crucially, they were also trained on the importance of ethical consideration in handling the sensitive patient records and maintaining confidentiality.

3.8 Data extraction and analysis

Data was extracted from the files using the online data abstraction form after each record being assigned a unique system generated identification numbers. The Google form was filled in structured sections that had to be completed sequentially before moving to the next section. The data was then automatically uploaded the online which ensured seamless data entry and minimized inaccuracies and inputting errors. The Google form then automatically generated a Microsoft Excel spreadsheet. The data was then checked for completeness, and confirmed to be free of error by the principal investigator. Thereafter, the data was transferred to Statistical Package for Social Sciences (SPSS) Version 26 for analysis. The analysis process was then carried out by an experienced independent statistician.

Demographic and clinical characteristics of the patients was summarized as frequency and proportions for categorical data and as means with standard deviation for continuous data.

For the primary objectives, comparison of the incidences of poor maternal outcomes, fetal outcomes and immediate neonatal outcomes between those with and those without SPE was analysed with the use of Pearson Chi square test and/or Cochran-Mantel-Haenszel method.

The secondary objective of comparing the sociodemographic factors and clinical characteristics between chronic hypertensive pregnant women with SPE and those without SPE was analysed with the use of Chi square for categorical variables and t-test for continuous variables.

Odds Ratio and 95% confidence interval (CI) was calculated where applicable. All tests were considered significant where the p value < 0.05.

Binary multivariate logistic regression model was used to evaluate the association between the exposure to chronic hypertension (with and without SPE) and the maternal, fetal and immediate neonatal outcomes while adjusting for potentially confounding factors (age, smoking, parity etc.) affecting adverse outcomes of interest.

The two sub-groups (with and without SPE) were coded as dummy variable (with SPE taking value 1 while without SPE takes the value 0). The logistic model was applied to evaluate and test for the association between chronic hypertensive conditions (with/without SPE) and maternal, fetal and immediate neonatal outcomes.

$$ln\ (\frac{P}{1-p})) = \beta_o + \beta_1 D_i + \beta_2 X_{dmi} + \beta_3 X_{cli} \ \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \ (1)$$

Where: $X_{dmi}, X_{cli} = demographic\ and\ other\ confounders$

$\beta_0, \beta_1, \beta_2, \beta_3$ = coefficient to be estimated.

$$D_i = \{1\ for\ chronic\ hypertention\ with\ SPE\ and$$

$$\{0{:}\ for\ chronic\ hypertension\ without\ SPE\}$$

Analyzed data is represented using tables, bar graphs and pie charts.

3.9 Ethical consideration

Permission was sought from KNH and UON Ethics Research Committee (ERC) prior to carrying out the study. Permission was also sought from the KNH administration through the Heads of Obstetrics and Gynecology department and the Records department to access the records, obtain and use the data. Confidentiality of the patient's information was observed by de-identifying the record files using an assigned unique identifier, only applicable to the study. None of the participants' personal identifiers were captured on any of the study instruments.

This coded information was then uploaded to an excel sheet that was password protected. Back up data was stored in a password encrypted external hard drive, only known to the principal investigator. Individual patient consent was not obtained because the study used information that had already been volunteered by the patient in their files.

3.10 Data management

Data was collected mainly by the structured online data abstraction form. Data entry and cleaning was undertaken as soon as data was collected. This enabled the principal investigator to recognize gaps in the existing data, and missing data points. The collected data was cross checked for completeness, accuracy and validity by the principal investigator. This was achieved through content validity, involving adherence to the research methodology techniques, collecting data for the intended variables as well as having an adequate sample.

3.11 Study results dissemination plan

The study results will be presented to the department of Obstetrics and Gynecology for input and review from the faculty as partial fulfillment of the Degree of Master of Medicine (MMed) in Obstetrics and Gynecology. The findings will undergo revisions by internal and external examiners. The findings will then be published in peer-reviewed journals to add to the pool of information of the scientific community. The findings will also be disseminated to the KNH/UON reproductive health department through continuous medical education sessions and a report to the KNH management.

3.12 Study limitations and how to minimize them

There is scarcity of information and research on chronic hypertension in pregnancy with and without SPE regionally and on incidence of poor pregnancy outcomes. This posed a challenge in calculation of the sample size. To overcome this, a similar study that was close to our intended was utilized in the sample size calculation and informed the time frame of 6 years. A reasonable sample size was also used. The retrospective nature of the study design introduced the possibility of missing information which may affect the results. This was minimized by excluding patient records that were incomplete or inconclusive. There was selection bias due to conducting this study at a national referral hospital and may not reflect a true picture due to the tendency to receive severe cases. This was minimized by including in our recruitment, diverse patients: those managed primarily at KNH and referrals.

CHAPTER FOUR: RESULTS

A total of 360 of records were obtained during the time period of 2016-2022 of chronic hypertensive pregnant women. Majority of these records 249 (69%) were classified as SPE and the rest didn't have SPE 111 (31%). 100 women were excluded from the study due to comorbidities such as diabetes, chronic heart disease, renal disease which have a direct contribution to poor maternal and perinatal health outcomes independent of HDPs, therefore would have acted as confounders and degraded the validity of the data. The other records were scrutinized for missing data especially on key study variables, and those recruited were 162 with 81 in each group (SPE vs. no SPE) [Figure 2].

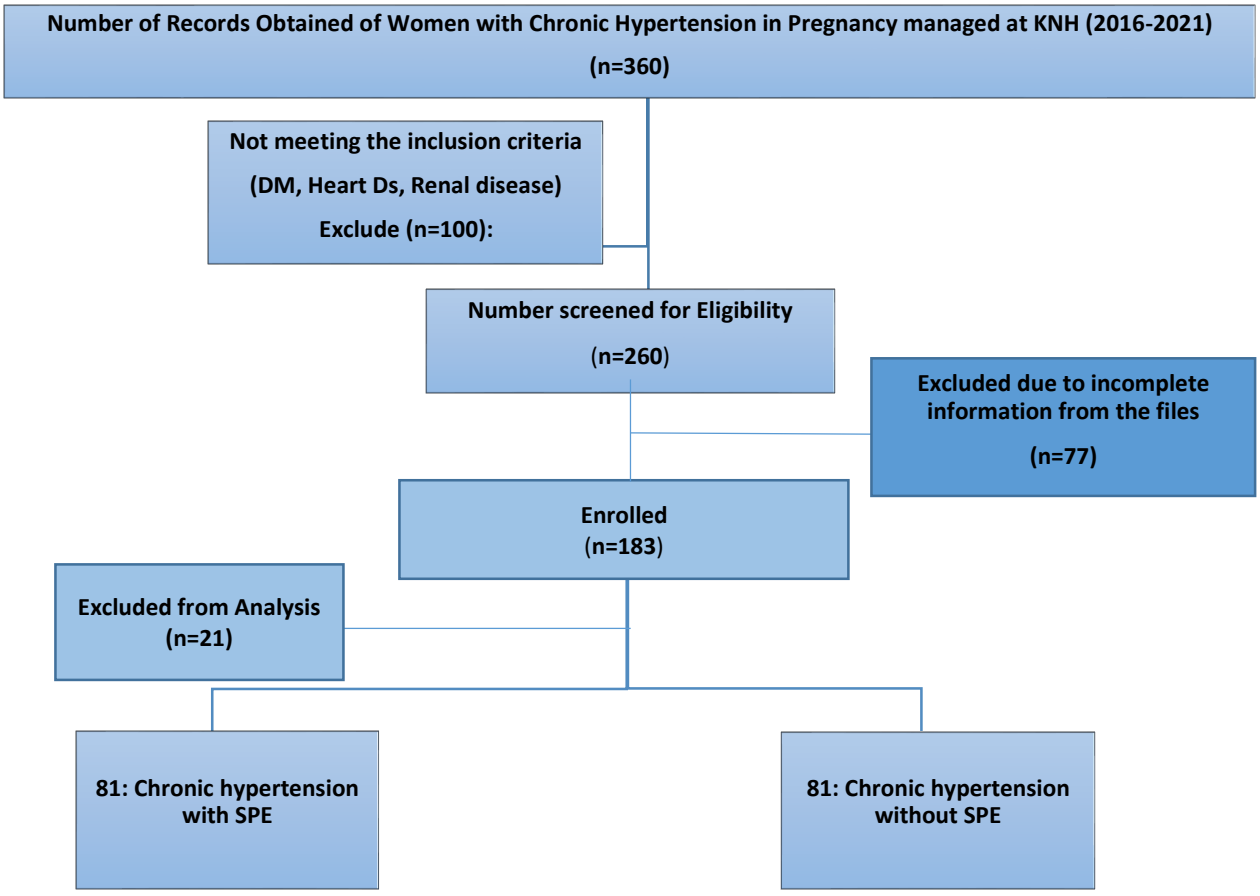

Figure 2: Study Flow chart

The baseline characteristics of the cohort of women is demonstrated in [Table 2]. Mean age was 34 years, and majority of the women were multiparous (which for this study was taken as 2 or more

previous deliveries of a fetus >28 weeks' gestation whether dead or alive). Prior history of preeclampsia was documented in 37% of the participants, with 63% of the participants starting antenatal clinics before 20 weeks' gestation. The median number of prenatal visits was 4. Hypertension was documented before pregnancy in 70% of the women and 84% of them were on medication preceding pregnancy. The most common medications used pre-pregnancy were Nifedipine-50%, Aldomet-21%, Losartan-30% and Hydrochlorothiazide-28%. Most of the women in our cohort had been diagnosed for over 2 years to 9 years duration (40%) and 29% were newly diagnosed during the pregnancy.

Table 2: Baseline characteristics of the chronic hypertensive women in the study (N=162)

		N(%)
Age (Mean ± SD)		34 ± 5.1
Parity	Nulliparous	25(15%)
	Primipara	38(24%)
	Multipara	99(61%)
History of preeclampsia	Yes	60(37%)
	No	100(62%)
	Not Indicated	2(1%)
Diagnosis of chronic hypertension	Before pregnancy	114(70%)
	During Pregnancy	48(30%)
Duration from year of diagnosis	new	47(29%)
	2-9	66(40%)
	>=10	19(12%)
	Not Indicated	30(19%)
BP medication use during pregnancy	Yes	151(93%)
	No	11(7%)
Aspirin use	Yes	38(23%)
	No	124(77%)
Calcium use	Yes	21(13%)
	No	141(87%)
Gestation at start of ANC	<20 weeks	102 (63%)
BP Medication used	Nifedipine	
	Methyldopa	
KNH clinic attendants		98 (60)

93% of women used antihypertensive medication during pregnancy, with Methyldopa being the most common medication used followed by Nifedipine. ASA prophylaxis was prescribed in only 23% of the

cases and Calcium was utilized by only 13%. 60% of the women in the cohort received antenatal care at KNH.

4.0 Sociodemographic characteristics

The sociodemographic characteristics were comparable between the 2 groups SPE and no SPE [Table 3]. The mean age was 34 years with the age distribution between 26-35 years (49% SPE, 54% no SPE) and > 35 years (44% SPE, 42% no SPE) being comparable in both groups. Most of the patients were married (SPE 89%, no SPE 88%). Most women reported to be unemployed, 52% of the SPE and 62% of the no SPE. Only 1 patient in the study reported smoking and alcohol intake from the SPE group.

Table 3: The distribution of sociodemographic characteristics in chronic hypertensive women with SPE versus no SPE

		Chronic Hypertension			
		With SPE N=81	**Without SPE N=81**		
		n (%)	**n (%)**	**Crude OR(CI)**	**p-value**
Age (Mean ± SD)		34 ± 4.86	34 ± 5.36	-	0.988
Age groups	≤25	5(6%)	3(4%)	Ref	
	26-35	40(49%)	44(54%)	0.55(0.12,2.43)	0.427
	>35	36(44%)	34(42%)	0.64(0.14,2.87)	0.555
Parity	Nulliparous	15(19%)	10(12%)	3.25(1.13,9.31)	**0.028**
	Primipara	12(15%)	26(32%)	Ref	
	Multipara	54(67%)	45(56%)	2.60(1.18,5.73)	**0.018**
Marital Status	Married	72(89%)	71(88%)	0.89(72(89%),0.81)	0.807
	Single	9(11%)	10(12%)	Ref	
Occupation	Yes	39(48%)	31(38%)	0.48(39(48%),0.21)	0.205
	No	42(52%)	50(62%)	Ref	
Smoking	Yes	1(1%)	0(0%)	-	1
	No	80(99%)	81(100%)		
Alcohol Use	Yes	1(1%)	0(0%)	-	1
	No	80(99%)	81(100%)		

Majority of the patients were multiparous (SPE 67%, no SPE 56%), and our analysis found that the odds of developing SPE were higher in the multiparous (OR 2.6, 95% CI 1.18,5.73, p=0.018) and nulliparous (OR 3.25, 95% CI 1.13,9.71, p=0.028) compared to primiparous. The recording of weight and height of the patients was not present in files dating back from 2018, and those thereafter the

findings were not consistent, a lot of missing data (not all patients attended clinic in KNH) so the study was unable to analyze on the impact of BMI on these patients.

4.1 Comparison of maternal outcomes between women with and without SPE

Women with superimposed preeclampsia were significantly more likely to be delivered preterm compared to those without SPE (aOR 8.74, 95% CI 3.70,20.64, *p*=<0.001). Most of these preterm deliveries were iatrogenic. 85% of women without SPE were delivered at term, >37 weeks, compared to 45% of those with SPE. Most of the women with superimposed pre-eclampsia delivered preterm, were delivered in early preterm <34 weeks' gestation (33%) and the other 22% were delivered late preterm between 34 weeks and 1 day to 36 weeks and 6 days [Table 4].

In this study, only 6 patients in the entire cohort developed PPH, 5% of the SPE group and 1% of the no SPE group. Higher odds are seen in the SPE women but the difference due to the few numbers did not attain statistical significance (aOR 4.90, 95% CI 0.43,55.83, *p*=<0.2). Only 5 patients developed Acute kidney injury from the cohort, 3 with SPE and 2 without SPE. Of the 5 women, 4 required to undergo dialysis, the 3 in SPE but the differences in the groups did not attain statistical significance.

3 patients in the entire cohort required admission to the ICU and the common indication necessitating admission for these patients was Eclampsia. There was no maternal mortality in our study participants, and no incidence of placenta previa, CVA or DIC. There were 2 women who were reported to have placenta abruptio and were both from the SPE group.

The number of patients who developed Eclampsia in the SPE group was 21 (26%), with only 3 requiring admission to the CCU. Majority of the women convulsed antenatally, with 5 women experiencing convulsions postnatally. These women received Magnesium sulphate as one of the primary interventions instituted for all the patients. The number of women who developed HELLP syndrome in the SPE group was 8 (10%).

Table 4: Comparison of maternal outcomes in chronic hypertensive women with and without superimposed preeclampsia

		Chronic Hypertension					
		With SPE N=81	**Without SPE N=81**				
		n (%)	**n (%)**	**Crude OR**	**P-value**	**AOR**	**P-value**
Preterm	Yes	45(56%)	13(16%)	7.19(3.38,15.27)	**<0.001**	8.74(3.70,20.64)	**<0.001**
	No	36(44%)	68(84%)				
Gestational Age at Delivery	>37 weeks	36(45%)	69(85%)	-	**<0.001**	-	-
	34 - 36 weeks	18(22%)	4(5%)				
	<34weeks	27(33%)	8(10%)				
PPH	Yes	5(6%)	1(1%)	5.26(0.60,46.09)	0.134	4.90(0.43,55.83)	0.2
	No	76(94%)	80(99%)				
AKI	Yes	3(4%)	2(3%)	1.00(0.14,7.28)	1	0.61(0.07,5.75)	0.666
	No	78(96%)	79(97%)				
Dialysis	Yes	3(4%)	1(1%)	4.16(0.45,38.02)	0.207	6.76(0.51,88.91)	0.146
	No	78(96%)	80(99%)				
Admission to ICU	Yes	3(4%)	0(0%)	-	0.245	-	-
	No	78(96%)	81(100%)				

Overall the odds of a woman with superimposed pre-eclampsia developing a poor maternal outcome was significantly higher compared to those without SPE (aOR 9.33, 95% CI 4.08,21.31, *p*=<0.001) [Table 5].

Table 5: Overall risk of a poor maternal outcome in the pregnant chronic hypertension cohort: with and without SPE

		Poor Maternal outcome					
		No N= 100	**Yes N= 62**	**Crude OR**	**P-value**	**AOR**	**P-value**
Chronic HTN	With SPE	32(32%)	49(79%)	8.01(3.81,16.82)	**<0.001**	9.33(4.08,21.31)	**<0.001**
	Without SPE	68(68%)	13(21%)				

4.2 Comparison of poor fetal outcomes between women with and without SPE

In this study, the adverse fetal outcomes were comparable between the 2 groups. The incidence of FGR was 6% vs 5% and the still birth incidence was 12% vs 10% in those with SPE and in those without SPE respectively.

Table 6: Comparison of poor fetal outcomes between chronic hypertensive women with and without SPE

		Chronic Hypertension					
		With SPE N=81	Without SPE N=81				
		n (%)	n (%)	Crude OR	P-value	AOR	P-value
IUGR	Yes	5(6%)	4(5%)	1.27(0.33,4.90)	0.732	0.99(0.22,4.39)	0.99
	No	76(94%)	77(95%)				
Stillbirth	Yes	10(12%)	8(10%)	1.29(0.48,3.44)	0.618	1.52(0.51,4.54)	0.456
	No	71(88%)	73(90%)				

4.3 Comparison of poor early neonatal outcomes between women with and without SPE

Women with SPE in the study gave birth to neonates with a lower mean birth weight (2192 ± 1017.16g) compared to those without SPE (2862 ± 768.40g), p=<0.001. 56% of the neonates were born premature in the SPE group compared to 16% of the non SPE women.

Table 7: Comparison of poor neonatal outcomes in women with and without superimposed preclampsia

		Chronic Hypertension					
		With SPE N=81	Without SPE N=81				
		n (%)	n (%)	Crude OR	P-value	AOR	P-value
SGA	Yes	25(31%)	14(17%)	2.14(1.02,4.50)	**0.046**	2.45(1.08,5.56)	**0.032**
	No	56(69%)	67(83%)				
Prematurity	Yes	45(56%)	13(16%)	7.19(3.38,15.27)	**<0.001**	8.74(3.70,20.64)	**<0.001**
	No	36(44%)	68(84%)				
Birth weight (Mean ± SD)		2192 ± 1017.16	2862 ± 768.40	-	**<0.001**	-	-
LBW	Yes	45(56%)	19(23%)	4.08(2.08,8.02)	**<0.001**	4.91(2.28,10.55)	**<0.001**
	No	36(44%)	62(77%)				
5-minute Apgar	Normal	60(74%)	69(85%)	2.01(0.91,4.43)	0.082	2.10(0.89,4.94)	0.09
	Poor	21(26%)	12(15%)				
Admission to NBU/ICU	Yes	32(40%)	18(22%)	2.29(1.15,4.55)	**0.018**	2.34(1.11,4.93)	**0.025**
	No	49(60%)	63(78%)				

Neonates of women with SPE had greater odds of being born premature (aOR 8.74, 95% CI 3.70,20.64, p=<0.001) [Table 7]. Poor neonatal outcomes were significantly more common among women with SPE including SGA (aOR 2.45, 95% CI 1.08,5.56, *p*=0.032), low birth weight (aOR 4.91(95% CI 2.28,10.55), *p*=<0.001), and admission to NBU/NICU (aOR 2.34(95% CI 1.11,4.93), *p*=0.025). 26% of the neonates born of women with SPE had a poor APGAR score (<7) at the 5th minute compared to 15% of neonates of women without SPE. The odds are higher for a woman with SPE to have a neonate with a poor score at the 5th minute (aOR 2.10(95% CI 0.89,4.94)), but the difference did not reach statistical significance *p*=0.09.

Overall the odds of a neonate born to a woman with SPE having a poor neonatal outcome were higher (aOR 3.30(95% CI 1.64,6.65), *p*=0.001) [Table 8].

Table 8: Overall odds of an adverse neonatal outcome in women with and without SPE

		Adverse Early neonatal outcome			
		No	**Yes**	**AOR**	**P-value**
		N= 76	**N= 86**		
Chronic HTN	With SPE	27(36%)	54(63%)	3.30(1.64,6.65)	**0.001**
	Without SPE	49(64%)	32(37%)		

4.4 Comparison of various obstetric and clinical characteristics between women with and without SPE

The diagnosis of chronic hypertension before and during pregnancy was comparable between the 2 groups. More women with superimposed preeclampsia had a previous diagnosis history of preeclampsia (43% vs 31%) however, the differences in the two groups were not statistically significant. 58% of the women with SPE and 60% of women with chronic hypertension were on medication before pregnancy. The most common medications in the cohort were Nifedipine, Losartan and Hydrochlorothiazide, though a significant number (21%), were also on Methyldopa pre-pregnancy. An average of 93.5% of the patients were on medication during pregnancy. The most common being Methyldopa used by 80% of the women in the cohort, followed by Nifedipine 60%, and others e.g. Labetalol, and Hydralazine were reported in the SPE group. 67% of women in SPE used 2 or more

drugs to control blood pressure antenatally compared with 38% of those without SPE. The most common drug combination regimen was Nifedipine and Methyldopa.

Family planning use was higher in the group with SPE (53% vs 35%) with a crude OR 1.75(95% CI 0.83,3.68). Majority of the patients started ANC <20 weeks' gestation comparable within the 2 groups (63% vs 62%, SPE and no SPE respectively). The ANC attendance of the cohort was majorly in KNH 75%, with many having being referred for admission due to worsening BP antenatally and continued their care in KNH. In the study, 28% of the women with SPE had at least one admission in the antenatal period other than for delivery, while only 16% of women without SPE were admitted antenatally (cOR 2.07(95% CI 0.97,4.46), *p*=0.062). 5 patients in the cohort had APH, with 3 being from the SPE group. The mean systolic/diastolic antenatal blood pressure of the SPE group was significantly higher than those without SPE (164.1/105.3 vs 147.4/92.9). Poor antenatal BP control was associated with increased risk of SPE OR 1.04(95% CI 1.02,1.05), *p* <0.001 [Table 10].

Table 9: Mode of delivery in the study cohort

		Chronic Hypertension					
		With SPE	**Without SPE**				
		N=81	**N=81**				
		n (%)	**n (%)**	**Crude OR**	**P-value**	**AOR**	**P-value**
Primary CS	Yes	37(46%)	23(28%)	2.12(1.11,4.07)	**0.024**	2.43(1.15,5.14)	**0.02**
	No	44(54%)	58(72%)				
Mode of delivery	Primary CS	37(46%)	23(28%)	-	**0.042**	-	-
	Repeat CS	21(26%)	34(42%)				
	Vaginal	23(28%)	24(30%)				

The mode of delivery for the patients in the cohort was predominantly Caesarean delivery (72% in SPE vs.70% without SPE) [Table 9]. The incidence of primary CS was 46% in the SPE group compared with 28% of no SPE. A primary CS was significantly more common in the SPE group than those without SPE (aOR 2.43(95% CI 1.15,5.14), *p*=0.02). The most common indication for cesarean

delivery in the SPE group was described as “worsening maternal condition” necessitating urgent delivery vis-a-vis a poor Bishop score. This indication was followed by a history of previous cesarean delivery and lastly acute fetal distress. The common indications for caesarean delivery in the no SPE group were fetal distress, prolonged labor and failed induction of labor.

Duration of hospital stay was significantly longer in the SPE group with 2.5 times higher odds of staying 5-10 days (cOR 2.58(95% CI 1.28,5.20), p=0.008) and 14 times higher odds of staying >10 days (cOR 14.74(95% CI 3.90,55.66), p=<0.001).

Table 10: Comparison of various obstetric and clinical characteristics between women with and without SPE

		Chronic Hypertension			
		With SPE N=81	**Without SPE N=81**		
		n (%)	**n (%)**	**Crude OR(CI)**	**p-value**
History of pre-eclampsia	Yes	35(43%)	25(31%)	1.70(0.90,3.25)	0.105
	No	46(57%)	56(69%)	Ref	
Family Planning	Yes	43(53%)	28(35%)	**2.14(1.14,4.03)**	**0.018**
	No	38(47%)	53(65%)	Ref	
Duration of hospital stay in days	2-4	19(23%)	42(52%)	Ref	
	5-10	42(52%)	36(44%)	**2.58(1.28,5.20)**	**0.008**
	>10	20(25%)	3(4%)	**14.74(3.90,55.66)**	**<0.001**
Duration from year of diagnosis of chronic HTN	≤1	23(28%)	24(30%)	0.75(0.36,1.59)	0.455
	2-9	37(46%)	29(36%)	Ref	
	≥10	9(11%)	10(12%)	0.71(0.25,1.96)	0.504
Diagnosis of chronic hypertension	Before pregnancy	60(74%)	54(67%)	1.43(0.73,2.82)	0.303
	During Pregnancy	21(26%)	27(33%)	Ref	
Medication used before pregnancy	Yes	47(58%)	49(60%)	0.90(0.48,1.69)	0.749
	No	34(42%)	32(40%)	Ref	
BP medication use during pregnancy	Yes	75(93%)	76(94%)	0.82(0.24,2.81)	0.755
	No	6(7%)	5(6%)	Ref	
Aspirin use	Yes	19(23%)	19(23%)	1.00(0.48,2.07)	1
	No	62(77%)	62(77%)	Ref	
Calcium use	Yes	11(14%)	10(12%)	1.12(0.45,2.79)	0.815
	No	70(86%)	71(88%)	Ref	
Gestation at start of ANC	≤20	8(10%)	16(20%)	0.49(0.19,1.25)	0.135
	>20	51(63%)	50(62%)	Ref	
Admission during antenatal period	Yes	23(28%)	13(16%)	2.07(0.97,4.46)	0.062
	No	58(72%)	68(84%)	Ref	
APH	Yes	3(4%)	2(2%)	1.52(0.25,9.34)	0.652
	No	78(96%)	79(98%)	Ref	
Systolic BP (Mean ± SD)		164 ± 23.33	147 ± 20.04	-	**<0.001**
Diastolic BP (Mean ± SD)		105 ± 16.33	93 ± 14.62	-	**<0.001**

CHAPTER FIVE: DISCUSSION

The study demonstrated that the overall risk for development of poor maternal outcomes was higher in pregnant women with superimposed preeclampsia. This was comparable to other studies conducted in both HICs and LMICs. Our study findings showed a higher odds of preterm delivery <37 weeks in women with pregnancies complicated by SPE compared to those with chronic hypertension only (aOR 8.74, 95% CI 3.70,20.64, *p*=<0.001). Chappell et al(23) demonstrated a higher incidence of preterm delivery <37 weeks in women with SPE; OR 5.23 (95% CI 3.96 to6.90). Similar to these studies the preterm deliveries in our study were iatrogenic. This implies that patients need proper counselling on the risk of preterm delivery with SPE and interventions need to be put in place to optimize the preterm neonate for delivery (such as Dexamethasone and Magnesium sulphate for neuroprotection).

Our findings however, showed that the incidence of preterm deliveries was higher in early preterm <34 weeks compared to the other studies in both HICs and LMICs where the deliveries were conducted in late preterm. The findings could be different since the studies like Boriboonhirunsarn et al. (11), Chappell et al(23) and Casagrande and colleagues (29) showed higher utilization of Aspirin (ASA) prophylaxis in their study participants (> 80%). This was significantly different from ASA use in our participants at 23%. Aspirin trial that studied nulliparous women from LMICs, concluded that low-dose aspirin initiated in the first trimester resulted in a reduced incidence of preterm delivery before 37 weeks, and reduced perinatal mortality(40).

The blood pressure control also has been shown to have an impact on pregnancy outcomes, and our study participants blood pressure was poorly controlled in the SPE group. CHAP study 2022 demonstrated that antihypertensive treatment targeting a BP <140/90 mm Hg reduced the incidence of iatrogenic preterm births <35 weeks' gestation, and fetal/neonatal death(41).

The study findings did not demonstrate a statistical significance in the incidence of poor fetal outcomes between SPE and no SPE. The incidence of Stillbirths was higher in our studies (12% in SPE vs. 10% in no SPE) compared to those of HICs. Abdelazim I *et al*.(42) demonstrated a stillbirth incidence of 1.4% vs 1.3% p=0.7 while Yanit et al.(43) had an IUFD incidence of 0.8%. Our study findings compare to other regional studies like Adu-Bonsaffoh *et al*.(44) in Ghana which reported a stillbirth incidence of 6.8% stillbirths. This could be speculated to be due to poor control of hypertension antenatally, and inadequate access to the antihypertensive medications in low social economic settings. Preterm delivery <34 weeks which is a risk for stillbirths and poor utilization of ASA among our participants could explain the findings. These factors also play a role in development of FGR.

The study found the overall risk of an adverse neonatal outcome to be higher in women with SPE. (aOR 3.30(95% CI 1.64,6.65), *p*=0.001). The preterm deliveries common to women with SPE were similar to other studies(10,11,23,29,32,45). It noted that the SPE group in our study had more deliveries in early preterm compared to other studies. The poor neonatal outcomes of this study are to be expected with the early preterm deliveries resulting in higher rates of SGA, very low birth weights, asphyxia and NBU/NICU admission. The study findings revealed low mean birth weights for both groups SPE and no SPE compared to other literature. The study is the first of its kind in our region and the overall low birth weights in both groups could be a reflection of the low social economic status, poor BP control substandard care brought about by intrinsic challenges in our local health systems and issues related to quality of care.

The understanding of these poor outcomes emphasizes the impact of SPE which has a financial, mental and physical bearing. The findings heighten the need for close surveillance of patients with SPE during pregnancy and delivery to determine suitable timing of delivery and optimize neonatal outcomes.

The CS delivery rate was high in both groups but primary CS rate was significantly elevated in the women with SPE. This was similar to other LMICs studies(11,29) where primary CS rates in

women with SPE were higher. The most common indication for these CS deliveries were worsening maternal condition necessitating early delivery. The study data suggests that chronic hypertension contributes to the rising rate of CS delivery. Further evaluation of why this is so on an institutional level is necessary, and establishing standard operating procedures to mitigate this high incidence such as offering induction of labor where the mother and fetus are stable.

The present study showed no difference in the sociodemographic characteristics of those chronic 2020 hypertensive women who developed SPE and those who didn't. Previous studies suggested that the risk of SPE increased with every additional year > 34 years(46,47), and in nulliparous women(48). Our findings contrast this as the ages and parity of the 2 groups were comparable. Our results also show that multiparous women had some higher odds of developing SPE compared to primiparous. These findings are similar to more recent studies done in HICs where age and parity had no substantial risk of SPE. Chappell et al(23) and Sibai et al(19) demonstrated that lower maternal age and multiparity were not protective in pregnant women with chronic hypertension. This implies that there is a need for heightened surveillance for development of SPE in younger women and multiparous women with chronic hypertension.

The study found higher utilization of family planning among the women in the SPE group compared to those without SPE. This was an interesting difference that was statistically significant p=0.018. The trend is not demonstrated in any of the other literature reviewed. The retrospective nature of the study did not allow to probe into the specific type of family planning used. Further studies would be necessary to determine whether a type of contraceptive used had an impact in development of severe hypertension and SPE.

Studies have demonstrated the risk of SPE is higher in women with previous pre-eclampsia(19,29,46) and early onset pre-eclampsia is more strongly associated with recurrence, and severity of disease(29). Our findings showed a higher incidence of previous history of preeclampsia in the SPE group (43% vs

31%) but the difference was not statistically significant. Many studies still show the risk of recurrence with preeclampsia, development of early-onset preeclampsia in subsequent pregnancy with severe outcomes(49). The findings necessitate counselling of patients with previous history of preeclampsia about recurrence and utilizing interventions such as ASA and Tight BP control to prevent severe outcomes.

The duration of hospital stay was higher in the group with SPE with an average stay of 5-10 days (cOR 2.58(95% CI 1.28,5.20), p=0.008) or > 10 days (cOR 14.74(95% CI 3.90,55.66), p=<0.001). This was similar to the study by Chappell et al.(23) that showed a higher mean number of days of admission in the group with SPE. The average inpatient stay was 12 days. The results also showed women with SPE had higher odds of being admitted antenatally due to complications of hypertension. These findings reflect the financial impact of the disease together with NBU/NICU admission, and strain to health infrastructure.

Mean antenatal systolic and diastolic BP were elevated in the SPE group participants. This is in-keeping with available literature that poorly controlled BP was associated with SPE and adverse outcomes(10,11,41). The health care provider attending to the chronic hypertensive pregnant woman should therefore be aware that an elevated BP poses a risk for development of SPE. Early diagnosis, close surveillance of women on antenatal follow up, counselling on adherence to medication and aiming for good control of BP could help minimize complications of SPE.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

The study has demonstrated that overall SPE is associated with increased incidence of poor maternal, and early neonatal outcomes. These include preterm delivery with consequent adverse neonatal outcomes such as SGA, low birth weight, and admission to NBU/NICU. The incidences of these poor outcomes are higher locally comparable to the reported incidences in HIC/LMICs. SPE was associated with increased incidence of primary CS delivery and increased duration of hospital stay. Poor antenatal BP control was associated with SPE and poor pregnancy outcomes. The utilization of ASA prophylaxis among women with chronic hypertension in pregnancy is very low in our setup.

6.2 Recommendations

- Women with Chronic Hypertension should be counselled appropriately from pre-conception and during antenatal care of the possible development of SPE and the poor pregnancy outcomes
- Educate Healthcare workers on the poor outcomes and need for providing proper counselling and close surveillance of patients with SPE and on the benefits of early initiation of ASA prophylaxis and ensuring adherence, to prevent poor events such as SPE and preterm delivery
- Close surveillance of fetal condition to ensure timely delivery of fetus and minimize poor neonatal outcomes
- Close surveillance of maternal BP (more ANC contacts, 2 weekly interval), better control of BP, and aggressive interrogation and emphasis on compliance to anti-hypertensive medication
- Future prospective multicenter studies are needed to establish incidence of SPE, compare the maternal and perinatal outcomes of SPE to other HDPs
- Further studies are necessitated on the quality of antenatal care, and implementation of newer interventions such as Aspirin use and Calcium Prophylaxis in this cohort aiming to reduce incidence of poor outcomes in SPE

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APPENDICES
Sample data extraction tool

Sociodemographic characteristics

1. Maternal age:
2. Parity:
3. Marital status: Single_____ Married_____
4. Education level:
5. Occupation: Yes_____ No_____ Not indicated ____
6. Smoking: Yes_____ No_____ Not indicated ____
7. Alcohol use: Yes____ No_____ Not indicated ____
8. Weight: _____
9. Height: _____

Past Medical History:

10. Is there a prior history of chronic HTN before pregnancy? Yes: __ No: __ Not known: __

    If yes, how long____(years)

    If on medication before list here _____

11. Is there a history of pregnancy induced hypertension (preeclampsia/eclampsia/gestational hypertension) in previous pregnancy? Yes: __ No: ____
    If yes, indicate type: _____
12. Does the patient have other comorbidities? Yes __ Indicate type _____

Family History of chronic illness:

13. Is there family history of the following
    a. Hypertension: Yes: ___ No: ____ Not indicated ____
    b. Diabetes: Yes: ___ No: ____ Not indicated ____

Previous Obstetric History:

14. Is there prior history of:
    a. Abortions: Yes: ___ No: ____
    If yes, how many _____
    b. Vaginal deliveries Yes _____ how many? (1) (2) (3) (4) (Above 5)
    c. Previous history of C/sections: Yes ___ No ____
    If yes, how many? (1) (2) (3) (4)
    If yes, indication: _____
    History of VBAC Yes: _____
15. Is there history of perinatal death (death of a fetus that occurs after 28 weeks of gestation, either as a still birth or born alive but died within the first 6 days after delivery)?
    Yes: _____ No: _____
    If yes, how many ____

Current pregnancy

16. When was the diagnosis of chronic hypertension made
    Before pregnancy _____ During pregnancy _____
    If during pregnancy at which gestation _____ weeks, Not indicated ____ Diagnosing BP Systolic_____ Diastolic _____
17. Is the current gestation: Singleton? _____ Twins? ____ other Multiples? _____
18. What was the gestation of starting ANC _____ (weeks)
19. How many ANC visits has the patient had: _____ Were ANC visits in KNH Yes: ____ No: ___
20. What was the ANC Hb level:
21. What was the BP range during ANC:
    a. Systolic (Lowest) _____ (Highest) ____
    b. Diastolic (Lowest) _____ (Highest) ____
    c. Not indicated ____
22. What BP Medication did the patient use during Antenatal period: (1) _____ (2) _____ (3) _____ (4) _____
23. Did the patient use Aspirin during antenatal period: Yes ___ No: ___ Not indicated ____ If yes, dose? ____ mg, Not indicated ____
24. Did the patient use Calcium tablets during antenatal Period Yes: ___ No: _____ Not indicated ____
25. Was the patient admitted during the antenatal period (other than for delivery) Yes: ___ No: _____ Not indicated ____
    If yes, indication _____
    Duration of hospital stay _____

Imaging

26. Did the patient have an Antenatal ultrasound Yes: _____ No_____ If yes, How many? _____
27. Did the patient have a diagnosis of IUGR on Ultrasound: Yes ____ No_____
    a. If yes: Gestation ____ weeks
28. Did the patient have a diagnosis of IUFD on ultrasound: Yes ____ No _____
    a. If yes: Gestation ____ weeks
29. Did the patient have a diagnosis of Placenta abruption on ultrasound: Yes ____ No _____
30. What was the Resistive Index on ultrasound: ____ Not indicated: _____?
31. Was there Reversal of umbilical flow on ultrasound: Yes; _____ No: _____

Lab Investigations:

32. Did the patient have admission lab investigations Yes: _____
    Indicate the following
    a. FHG – Hb ____ Plts ___
    b. LFT- AST ____ ALT____ GGT ____
    c. UEC – Urea ____ Creat ____ K+ ____
33. Did the patient have worsening lab functions Yes: ____ No: _____

Admission and Delivery

34. What was the indication for admission_____?
    (labour, late/post term, worsening BP, IUGR, IUFD, Eclampsia, HELLP, CVA, APH, SPE)
35. What was the BP at admission Systolic_____ Diastolic _____
36. What medication was given during admission: (1) _____ (2) _____ (3) _____ (4) _____
37. Were there other interventions during admission _____ (induction)
38. What was the duration from admission to delivery_____?

Maternal outcomes:

39. Did the mother have APH: Yes_____ No_____ If yes, indicate cause _____ previa/abruptio/unknown
40. Did the mother have IUFD: Yes: ___ No: ____
41. Did the mother have a Preterm delivery: Yes ____ No ____ If yes, Gestation _____ weeks
42. What was the mode of delivery: Vaginal: ___ CS: _____ If CS, indication _____
43. Did the mother have PPH: Yes; _____ No: _____
44. Did the mother have AKI Yes: ____ No: _____
45. Did the mother require dialysis: Yes; _____ No: _____
    If yes, how many sessions_____
46. Did the mother have a Cerebrovascular Accident: Yes; _____ No: _____ If yes, type _____ (stroke/Hemorrhage)
47. Did the case end in a Maternal death: Yes; _____ No: _____ If yes, cause _____
48. Did the patient have Eclampsia: Yes: ___ No: ____
49. Did the patient have HELLP syndrome: Yes: ___ No: ____
50. Did the patient develop DIC: Yes: ___ No: ____?
51. Did the patient require ICU admission: Yes; _____ No: _____
52. Duration of hospital stay _____days (admission to discharge/Death)

Perinatal outcomes

53. Did the fetus have FGR: Yes: ___ No: ____ Gestation _____weeks
54. Was the fetus born a Stillbirth: Yes: ___ No: ____ Indicate whether FSB/MSB
55. Did the neonate have Prematurity: Yes: ___ No: ____ Gestation _____ weeks
56. What was the Birth weight of the neonate? _____ grams
57. What was the Apgar score at 5^{th} min? _____
58. Did the neonate require Resuscitation? Yes: ___ No: ____
59. Did the neonate require NICU/NBU admission: Yes: ___ No: ____

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5th November 2021

Dr. Grace M. Ngeranwa
Reg. No.H58/11343/2019
Dept. of Obstetrics and Gynaecology
Faculty of Health Sciences
University of Nairobi

Dear Dr. Ngeranwa

RESEARCH PROPOSAL: COMPARISON OF PREGNANCY OUTCOMES BETWEEN CHRONIC HYPERTENSION PREGNANT WOMEN WITH AND WITHOUT SUPERIMPOSED PREECLAMPSIA AT KENYATTA NATIONAL HOSPITAL FROM 2016-2020: A RETROSPECTIVE COHORT STUDY (P493/06/2021)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P493/06/2021.** The approval period is 5th November 2021 – 4th November 2022.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification
iv. Any changes anticipated or otherwise that may increase the risks or affected 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
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. 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.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

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20th May, 2022

Dr. Grace Ngeranwa
Reg. No. H58/11343/2018
Dept. of Obstetrics and Gynecology
Faculty of Health Sciences
University of Nairobi

Dear Dr. Ngeranwa,

Re: Approval of modifications- study titled, "Comparison of pregnancy outcomes between chronic hypertensive pregnant women with and without superimposed preeclampsia at Kenyatta National Hospital from 2016- 2021" (P493/06/2021)

Your communication dated 9th March 2022 refers.

The KNH- UoN ERC has reviewed and **approved** the following modifications made to the study:

1. Change of study period from '2016- 2020,' to '***2016- 2021'*** to achieve study sample size.
2. Change of study title from, 'Comparison of pregnancy outcomes between chronic hypertensive pregnant women with and without superimposed preeclampsia at Kenyatta National Hospital from 2016- 2020', to '***Comparison of pregnancy outcomes between chronic hypertensive pregnant women with and without superimposed preeclampsia at Kenyatta National Hospital from 2016- 2021***'.

The requested modifications have been adequately justified and are incorporated in the revised research proposal.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH- UoN ERC

cc. The Dean, Faculty of Health Sciences, UoN
The Senior Director, Clinical Services, KNH
The Chairperson, KNH- UoN ERC
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KNH/HOD-OBS&GYN/07/VOL.11/ Date: 18th November, 2021

Dr. Grace M. Ngeranwa
Reg. No.H58/11343/2018
Dept of Obstetrics and Gynaecology
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RE: RESEARCH PROPOSAL – COMPARISON OF PREGNANCY OUTCOCOMES AND CHRONIC HYPERTENSION WITH SUPERIMPOSED PREECLAMSIA AT KNH FROM 2016-2020 (P493/06/2021)

This is to inform you that the department has given you permission to conduct the above study which has been approved by ERC.

Liaise with HOD – Health Information to facilitate your study.

You will be expected to disseminate your results to the department upon completion of your study.

Dr. Maureen Owiti
HOD-OBSTETRICS & GYNAECOLOGY

Cc.

HOD - Health Information