Ghana College of Physicians and Surgeons

Faculty of Obstetrics and Gynaecology

Low Dose Aspirin Prophylaxis use among Pre-Eclamptic/Eclamptic women with history-based risk factor(s) in a Tertiary Hospital in Ghana

A Dissertation submitted to the Faculty of Obstetrics and Gynaecology in partial fulfilment of the requirements for the conferment of Fellowship in Maternal-Fetal Medicine of the Ghana College of Physicians and Surgeons (FGCS)

By

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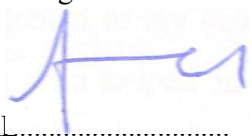
DECLARATION

I declare hereby that except references to other people's work that have been duly noted, the contents of this proposal are my work and have not been submitted to any other institution for the award of a degree nor has it been published in any journal.



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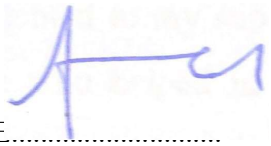

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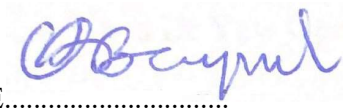

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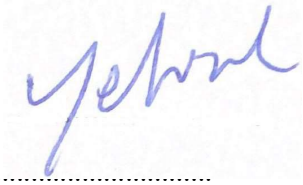

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ABSTRACT

Background

Pre-eclampsia/eclampsia remains a top cause of maternal morbidity and mortality as well as a major cause of perinatal morbidity and mortality at Komfo Anokye Teaching Hospital and the world over. Starting low dose aspirin before 16 weeks in high-risk women prevents preterm preeclampsia. Anecdotal evidence suggests that it is common to find patients admitted with preeclampsia/eclampsia with risk factors at the beginning of pregnancy who would have benefited from low dose aspirin but never received it.

Objective

This study assesses the use of prophylactic low dose aspirin among women admitted to Komfo Anokye Teaching Hospital with pre-eclampsia/eclampsia who had history-based risk factors in early pregnancy.

Methods

This is a cross-sectional analytical study. Women admitted to the obstetric high dependency unit with preeclampsia/eclampsia were recruited consecutively till the sample size of 271 was attained. A structured questionnaire, antenatal care records, hospital in-patient records and discharge notes were used to obtain the relevant data which were analyzed using IBM SPSS version 26.0. Chi square was used to assess associations of adverse maternal and fetal/neonatal outcomes among women that received low dose aspirin compared to those that did not receive low dose aspirin. P-values less than 0.05 were considered statistically significant.

Results

59% of the women with preeclampsia/eclampsia had the risk factors warranting prophylactic low dose aspirin in early pregnancy with only 26.9% of these high-risk women receiving prophylactic low dose aspirin. Low dose aspirin prophylaxis was significantly associated with estimated gestational age of pre-eclampsia/eclampsia diagnosis ($p < 0.0001$). Low dose aspirin prophylaxis was significantly associated with a reduction in the incidence of intra-uterine growth restriction ($p = 0.008$), intra-uterine fetal death/termination of pregnancy ($p = 0.001$), prematurity ($p = 0.001$), neonatal intensive care unit admission ($p = 0.001$), neonatal mortality ($p = 0.023$) as well as the composite adverse neonatal outcome ($p = 0.001$). Low

dose aspirin prophylaxis significantly reduced maternal organ dysfunction ($P = 0.001$) with no significant reductions observed for other maternal outcomes of caesarean section, eclampsia, CVA, maternal mortality as well as the composite adverse maternal outcomes.

Conclusion

Whiles the risk factors for preeclampsia do exist in our women at booking, majority of these high-risk women are not receiving prophylactic low dose aspirin. Prophylactic low dose aspirin reduces the incidence of early onset preeclampsia with a reduction in adverse fetal outcomes but no reductions in adverse maternal outcomes except for maternal organ dysfunction.

Keywords: Preeclampsia, Eclampsia, Prevention, Risk factors, First trimester screening, Low dose aspirin

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Abbreviations/acronyms

A1HDU	A1 High Dependency Unit
ACOG	American College of Obstetricians and Gynecologists
ASPRE	Aspirin for Evidence Based Preeclampsia Prevention
BMI	Body Mass Index
COX	Cyclooxygenase
CVA	Cerebrovascular accident
FPR	False-Positive Rate
FIGO	International Federation of Gynaecology and Obstetrics
FMF	Fetal Medicine Foundation
ICU	Intensive Care Unit
ISSHP	International Society for the Study of Hypertension in Pregnancy
IUGR	Intra Uterine Growth Restriction
IUFD	Intra-Uterine Fetal Death
IVF	In-Vitro Fertilization
KATH	Komfo Anokye Teaching Hospital
LDA	Low Dose Aspirin
LMWH	Low Molecular Weight Heparin
MAP	Mean Arterial Pressure
NICE	National Institute for health and Care Excellence
NICU	Neonatal Intensive Care Unit
NSAID	Non-Steroidal Anti-Inflammatory Drug
PAPP-A	Pregnancy Associated Plasma Protein- A
PG I-2	Prostacyclin

RR	Relative Risk
PLGF	Placental Growth Factor
sFlt-1	Soluble Fms-Like Tyrosine Kinase - 1
SGA	Small for Gestational Age
SMFM	Society of Maternal Fetal Medicine
SOGC	Society of Obstetricians and Gynaecologists of Canada
SOMANZ	Society of Obstetric Medicine of Australia and New Zealand
SPSS	Statistical Package for Social Sciences
TOP	Termination of Pregnancy
TXA-2	Thromboxane-A2
TNF	Tumour-Necrosis Factor
USPSTF	United State Preventive Services Task Force
UTPI	Uterine artery Pulsatility Index
VEGF	Vascular Endothelial Growth Factor
VEGFR-1	Vascular Endothelial Growth Factor Receptor-1
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION

1.1 Background Information

Hypertensive disorders in pregnancy of which eclampsia and preeclampsia are major culprits is a major threat to global health complicating 5.2%-8.2% of pregnancies globally[1]

The World Health Organization (WHO) attributes almost 10% of all maternal deaths in Africa and Asia to hypertensive disorders of pregnancy[2]**.** Preeclampsia/eclampsia have remained a major cause of maternal death in Komfo Anokye Teaching Hospital (KATH) for almost two decades[3]. Statistics from the maternal mortality audit of the Department of Obstetrics and Gynaecology – KATH puts preeclampsia/eclampsia amongst the top two causes of death each year from 2016 to 2020, (Table 1.1 below**)**

Table 1.1: Causes of maternal mortality at KATH, 2016-2020

	CAUSES OF MATERNAL DEATH IN KATH 2016-2020								TOTAL
	HYPERTENSION	HAEMORRHAGE	SEPSIS	BID/ UNEXPLAINED	SICKLE CELL RELATED	HIV RELATED	ABORTION RELATED	OTHERS	
2016	19 (21%)	30 (33%)		10 (11%)	6 (7%)	2 (2%)	2 (2%)	22 (24%)	91
2017	38 (37%)	15 (15%)	8 (8%)	4(4%)	10(10%)	2(2%)	2 (2%)	23(23%)	102
2018	32(24%)	33(24%)	13(10%)	3(2%)	7(5%)	4 (3%)	3 (2%)	41(30%)	136
2019	25(21%)	24(20%)	3(3%)		4 (3%)		7(6%)	35(29%)	120
2020	49(47%)	33(31%)		4(3%)			3 (1%)	18(17%)	107

Table 1.1 ** Reproduced with permission from the maternal mortality audit team of the department of obstetrics and gynaecology -KATH*

Early onset preeclampsia contributes significantly to both maternal as well as perinatal morbidity and mortality. Most of these women who develop preeclampsia/eclampsia are admitted for long periods for management. Those who survive have up to 5 times risk of developing hypertension as well as cardiovascular and cerebrovascular disease later in life when compared with mothers who do not have preeclampsia in their pregnancies.[4 5]

Perinatal mortality is estimated at 2 times higher in pregnancies affected by preeclampsia.[6] Delivery is the only cure for pre-eclampsia and a third of preeclampsia cases require iatrogenic preterm deliveries which accounts for about one-sixth of all premature birth with these babies requiring long periods of stay at the neonatal intensive care units. The preterm babies who survive are at risk of cerebral palsy, neurodevelopmental delay, respiratory disorders, hypertension, diabetes mellitus, obesity, cardiovascular disease, and impaired function later in life.[7] All these make pre-eclampsia/eclampsia such a huge burden on our healthcare system.[8]

An evidence based preventive strategy for preeclampsia is the use of low dose aspirin (LDA) in early pregnancy. The use of LDA before 16 weeks of pregnancy from meta-analyses has shown significant reduction in the risk of developing preeclampsia.[9] [10] There are also well documented predictive tools from various professional organisations such as WHO, American College of Obstetricians and Gynaecologists (ACOG), United States Preventive Services Task Force (UPSTF) that can be used in early pregnancy to identify women who are high risk for developing preeclampsia later in pregnancy who will most likely benefit from LDA use.[11] [12]

1.2 Problem statement

Despite the overwhelming evidence of existing predictive models in picking high risk women for preeclampsia, as well as evidence that starting LDA before 16 weeks in these high-risk women significantly reduces the incidence of preterm preeclampsia, it appears that this preventative strategy has not yet been adopted by KATH and its referring hospitals possibly because the current national safe motherhood protocol[13] do not have a section on screening for high-risk women for LDA prophylaxis in the prevention of preeclampsia.

Most studies in Ghana are on risk factors and outcomes of preeclampsia with none found on LDA use among high-risk women

Hence this study was conducted to generate data on prophylactic LDA use among high-risk women based on maternal risk factors in early pregnancy admitted and managed at KATH for pre-eclampsia/eclampsia.

1.3 Rationale for the Study

The alarming trend in the morbidity and mortality associated with preeclampsia/eclampsia has remained relatively unchanged at KATH over the past 5 years as shown in the maternal mortality audit report above despite the evidence for the cost-effective history-based screening models for LDA prophylaxis in preventing early onset pre-eclampsia.

Data generated on LDA prophylaxis use among high-risk women will serve as the basis for further studies and also serve as a quality assurance measure of the management of preeclampsia at the hospital. It will also help guide the education, recommendation, formulation, and implementation of screening protocols to increase the uptake of LDA prophylaxis in reducing the burden of the disease.

1.4 Research Questions

1. What proportion of women admitted with pre-eclampsia/eclampsia had risk factors at booking warranting aspirin?

2. What proportion of women admitted with pre-eclampsia/eclampsia who had risk factors warranting prophylactic LDA received low dose LDA prophylaxis?

3. Does the gestational age of onset of preeclampsia /eclampsia differ between those women who qualified and received prophylactic LDA and those who qualified and did not receive it?

4. Do the maternal and fetal/neonatal outcomes of those who qualified and received LDA differ from those who qualified and did not receive LDA?

5. What factors determine prophylactic LDA initiation in women with history base risk factors at the booking visit?

1.5 Objectives of the study

1.5.1 Principal Objective

The main objective of this study is to assess the use of LDA prophylaxis among pre-eclampsia/eclampsia women admitted and managed at KATH who had history-based risk factors at the beginning of pregnancy.

1.5.2 Specific Objectives

1 To determine the proportion of women admitted with pre-eclampsia who warranted LDA based on risk factors at booking and the proportion of these women who received LDA.

Null hypothesis: Preeclamptic women who warranted LDA based on risk factors at booking were likely to receive LDA.

Alternative hypothesis: I hypothesized that preeclamptic women who warranted LDA based on risk factors at booking were not likely to receive LDA

2 To determine the factors that influence use of LDA prophylaxis among pre-eclampsia women who warranted LDA based on risk factors at booking

Null hypothesis: There are not likely to be any factors influencing the use of LDA among women at risk of preeclampsia

Alternative hypothesis: Factors influencing LDA use among women at risk of preeclampsia are likely to be the level of the facility and the clinician providing care.

3 To compare the gestational ages preeclampsia was diagnosed in those who qualified and received LDA and those who qualified but did not receive LDA.

Null hypothesis: The gestational ages at diagnosis of preeclampsia in women with risk factors for preeclampsia who receive LDA and those who do not receive LDA will not differ significantly.

Alternative hypothesis: Women with risk factors for preeclampsia who receive LDA are likely to be diagnosed with preeclampsia at a later gestational age than those who do not receive LDA.

4 To compare the maternal and fetal/neonatal outcomes of women who qualified and received LDA and those who qualified but did not receive LDA at booking

Null hypothesis: the adverse maternal and fetal/neonatal outcomes in women with risk factors for preeclampsia who do not receive LDA prophylaxis will not be significantly different from those who received LDA prophylaxis at booking.

Alternative hypothesis: Women with risk factors for preeclampsia who do not receive LDA prophylaxis are likely to have more adverse maternal and fetal/neonatal outcomes than those who received LDA at booking.

CHAPTER TWO

LITERATURE REVIEW

2.0 Overview of preeclampsia

Preeclampsia is the development of new hypertension with/without proteinuria and impaired end organ function occurring after 20 weeks and the postpartum period. Eclampsia is a spectrum of the disease characterised by tonic-clonic seizures not due to other neurological condition. This is a progressive multi organ disease with significant maternal, fetal, and neonatal morbidity and mortality. It is described as having severe features when there is any one of high blood pressure of 160/110 mmHg and above, progressive impaired renal function (creatinine > 90umol/L; 1mg/dL), low platelet below 150,000/uL, impaired liver function (elevated transaminases > double the upper limit of 40 IU/L), neurological disturbance (such as seizures, altered mental status, persistent headaches, blindness, cerebrovascular accidents , persistent visual problems. It normally occurs after 34 weeks and sometimes during labour and postpartum period in over 80 % of the time referred to as the late onset preeclampsia with the rest occurring below 34 weeks of pregnancy described as early onset which is considered to be a more severe disease with life threatening complications and rarely occur around 20 weeks. A systematic review puts global incidence at 4.6 percent in all pregnancies[14].

Many studies have been done on this disease leading to an increasing understanding of the disease aetiology and its effects on the mother and foetus. The huge burden of the disease is reducing in well-resourced countries with well-developed healthcare systems unlike poor resource areas where the maternal and perinatal morbidity and mortality is still very high. Immediate effects on the mother may be hypertension, pulmonary oedema, renal failure, liver failure, haematological complications, cerebrovascular accidents, and mortality whiles that of the foetus may be intrauterine growth restriction, intrauterine fetal death, preterm delivery with prolong stay at the neonatal intensive care unit. Mothers and babies who survive these immediate life-threatening complications are at an increased risk of developing medical disorders in future. Management involves admitting the mother for stabilization which involves blood pressure control with anti-hypertensives, stopping and preventing seizures with Magnesium sulphate (MgS04), assessing mother for organ dysfunction, and managing them and ultimately delivery which is said to be the only cure for the disorder.

2.1 Prevalence and burden of preeclampsia/eclampsia

The WHO in its evaluation of maternal deaths from 2003 to 2009 reported hypertensive diseases of pregnancy which includes preeclampsia/eclampsia as the second highest cause of maternal mortality occurring in 14% of the cases with obstetric hemorrhage as the leading cause at 27%[15]. Preeclampsia account for one in every ten pregnancy related deaths in Africa constituting the third leading cause of death in pregnancy in sub-Saharan Africa.[16] Pratt attributed 14% of maternal mortality to it in low-middle income countries.[15] A recent systematic review of over 40 countries with 39 million women, reported an estimated preeclampsia rate of 4.6% with eclampsia 1.4%[14]. Whiles there is a decreasing trend in the incidence of preeclampsia and its associated complications in well-resourced developed countries recently, the trend is going opposite in the poor middle- and low-income countries[14]. This has been attributed to the difference in access to quality prenatal care as well as adequate management of cases of preeclampsia and eclampsia in these two areas.

The incidence of preeclampsia according to WHO is seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%)[17].

According to Adu-Bonsaffoh et al, the prevalence rate of pregnancy induced hypertensive disorders of which preeclampsia is part in the Korle-Bu Teaching Hospital was 21.4%[18] while Odoi, Opare-Addo and Dassah reported eclampsia/preeclampsia as the leading cause of maternal mortality in KATH accounting for 26.4% of all maternal deaths.[19]
Eclampsia/preeclampsia also account for 29% of all obstetric Intensive Care Unit (ICU) admissions, second only to peripartum hemorrhage in the western world.[20] This is due to complications of preeclampsia which can be fatal sometimes, such as eclampsia, cerebrovascular accidents(CVA), pulmonary oedema and acute renal failure. Mothers who are fortunate to survive this severe maternal morbidity may have psychological consequences in the form of anxiety disorder, breastfeeding issues, depression, issues with future reproductive capacity, isolation among others. The prolonged stays in intensive care units, of the woman herself or the new born, may interrupt the early mother baby bond which has been shown to have health implications[21].

Mothers who survive preeclampsia are 2 to 5 times more likely to develop hypertension, cardiovascular and cerebrovascular disease in the future when compared with mothers who do not have preeclampsia in their pregnancies[4].

It is attributed to almost 18% of intrauterine fetal death and 12% to 25% intrauterine fetal growth restriction.[22] The only known effective treatment of preeclampsia is delivery. Serious neonatal morbidities can occur when delivery occurs far from below 34 weeks of pregnancy. Neonatal morbidity is due to the intrauterine growth restriction and iatrogenic preterm delivery with its associated many issues such as acute respiratory syndrome, intraventricular haemorrhage, bronchopulmonary dysplasia, sepsis, and neuro psychomotor developmental deficits associated with the disease[23]. Children who survive the early neonatal period may have problems with neurocognitive development later in life such as attention-deficit/hyperactivity disorder, autism, epilepsy, intellectual disability, and vision or hearing loss[24].

All these make the disorder a major contributor to perinatal mortality which is about 2 times higher in pregnancies affected by preeclampsia[25]. Short-term healthcare costs of caring for a mother and baby affected by preeclampsia are double those of uncomplicated pregnancy[26]. It is therefore necessary to have effective early screening tools to pick high risk women for an effective preventive measure to reduce the prevalence and burden of the disease.

2.2 Challenges in the Management of Preeclampsia in poor resource settings

There is evidence that the management of women with hypertensive disorders of pregnancy remains suboptimal in most health facilities in Ghana[27]. Frequent stockouts and lack of essential antihypertensives and anticonvulsants for managing hypertensive disorders of pregnancy crisis are not uncommon, and this is often aggravated by inadequate laboratory support in most hospitals in Ghana[27].

Poor health care access, lack of functional healthcare systems and the generally poor infrastructure and human resource development are challenges in the management of preeclampsia in poor resource settings. Generally, there is limited access to proper prenatal and hospital care, and limited access to neonatal intensive care and this explains the higher maternal/perinatal morbidity and mortality associated with preeclampsia.

Inadequate information on when and where to seek help during obstetric emergencies, the lack of decision-making power of the woman in this part of the world, cost of healthcare, poverty, some sociodemographic factors such as level of education, marital status and cultural beliefs on maternal health are documented factors contributing to delays in the woman's decision to seek care during preeclampsia.[28] [29] The unequal distribution of health facilities in favour of urban communities, the distance one has to travel and lack of transport to these urban facilities

cause delay in getting help during preeclampsia.[30] Even for women who reach these facilities, getting care in these emergencies is near impossible for those who are poor and without the national health insurance. Limited trained health personnel, lack of equipment and supplies, poor attitudes of healthcare workers and a perceived poor quality of care are all are shown to be challenges in the management of preeclampsia in these areas[29]. Findings from a study in Nigeria, brings to bare the problems that contribute to the poor management of preeclampsia/eclampsia. Only about 31% of facilities had all the necessary equipment and supplies for diagnosing and managing preeclampsia including MgSO4, with about one-fifth of facilities having the correct guidelines in place for managing preeclampsia/eclampsia[31].

These challenges explain the increased morbidity and mortality associated with the disease in low-income countries. This calls for focussing more attention on prevention to decrease the burden of the disease.

2.3 Prevention of preeclampsia in high-risk women

The very high burden of preeclampsia coupled with the challenges associated with its management means preventive interventions are necessary to reduce the impact of the disease on maternal and infant health globally. Additionally, because there is no curative treatment other than delivery, an intervention that could prevent preeclampsia would have a significant impact on maternal and infant health worldwide. Many trials have investigated many different preventive interventions for preeclampsia unsuccessfully largely because of the multiple pathways in aetiology. Of the many different strategies studied to prevent preeclampsia, aspirin prophylaxis has been the most consistently useful preventive pharmacologic intervention up to date though the magnitude of benefit is variable and depends on several factors. Studies into the use of LDA in preventing preeclampsia began when evidence emerged that the disease spectrum is as a result of suboptimal trophoblastic invasion leading to an imbalance of angiogenic and antiangiogenic proteins, ultimately causing widespread inflammation and endothelial damage, increased platelet aggregation, and thrombotic events with placental infarcts. Many of these studies hypothesized that the anti-inflammatory effect of aspirin as well as its effect of inhibiting platelet aggregation could be useful to prevent or treat preeclampsia. There is good evidence that aspirin can decrease the occurrence of preeclampsia based on its anti-inflammatory and anti-thrombotic effects.

The WHO and many countries, including the United kingdom, the United states , Canada, New Zealand, Australia now recommend LDA in their guidelines for the prevention of preeclampsia in high-risk pregnant women[32].

2.4 Identification of high-risk women of preeclampsia

Since the establishment that LDA started before 16 weeks' gestation in high-risk women reduces the rate of preterm preeclampsia, it became important to identify pregnant women at risk of developing preeclampsia during the first trimester of pregnancy for this preventive intervention. There are optimal benefit pregnant women who are moderate to high risk of developing the disease receive LDA early in pregnancy. Pregnant women are therefore assessed early in pregnancy for risk factors for preeclampsia. Various maternal socio- demographic and clinical risk factors are used to quantify risk of preeclampsia/eclampsia in a woman during the booking visit. The pregnant woman's estimated risk for preeclampsia may then determine the need for prophylactic low dose LDA. Identifying these high-risk women also provide clinicians with the opportunity to educate the women to address any modifiable risk factors, educate them on the signs and symptoms of preeclampsia they are to notify their provider on as soon as they occur. It may also determine the need for increased surveillance for preeclampsia development during the pregnancy such as accurate determination of gestational age, blood pressure, baseline laboratory values such as platelet count, creatinine concentration, liver chemistries, and urinary protein. This early assessment for preeclampsia risk is also important to determine women who can receive antenatal care and deliver in low risk setting such as midwifery led care, birthing centre, and home birth. Women identified as high risk for preeclampsia are to receive consultation in a high risk setting with specialist obstetricians or consultant led care.

There has been works on the formulation and implementation of screening methods to improve clinicians' ability to identify women at increased risk for preeclampsia in early pregnancy. This largely depends on the risk factors of the disease. There are risk factors of preeclampsia obtained by medical history, physical examination, laboratory testing, and ultrasound imaging. Clinicians use these risk factors either alone or combine them in predictive models to identify pregnant women at increased risk.

The drawback of these risk prediction models is that many pregnant women may be subjected to tests and interventions for a disorder they may not develop.

For clinical use, evidence from external validation and implementation studies to demonstrate the accuracy of these models is limited.[12]

2.5 Screening based on maternal history of risk factors for LDA prophylaxis

Recommendations for screening at the beginning of pregnancy for pre-eclampsia/eclampsia later in pregnancy mostly is from the use of medical, social and obstetric history-based approach. Observational studies has uncovered important risk factors for preeclampsia. These risk factors when present may help identify women in early pregnancy who will subsequently go on to develop preeclampsia later in pregnancy. However there is still little evidence to the best way of combining these risk factors in identifying high risk women for LDA prophylaxis[33].

Predictive models and risk scoring methods that combine these common risk factors to identify women at risk for preeclampsia have been developed by various professional bodies such as ACOG, National Institute for health and Care Excellence (NICE), Society of Obstetricians and Gynaecologists of Canada (SOGC), Society of Obstetric Medicine of Australia and New Zealand SOMANZ , WHO, International Society for the Study of Hypertension in Pregnancy (ISSHP), amongst others as shown in table 2.1 below.

Table 2.1
Risk factors and indications for LDA from selected organisations.
Reproduced from Wertaschnigg et al. (2019)[34].

SOMANZ-RANZOG	NICE 2010	USPSTF 2014	ACOG 2018
Indication for Aspirin:	*Indication for Aspirin:*	*Indication for Aspirin:*	*Indication for Aspirin:*
2 moderate or 1 high risk factor *Dose*: unclear Until 37 weeks or until delivery	*2 moderate or 1 high risk factor* *Dose*: 150 mg/d from 12 weeks Continue daily until delivery. *Consider Aspirin:*	*1 high risk factor* *Dose*: 81 mg/d optimally before 16 weeks Continue daily until delivery. *Consider Aspirin:* If more than one moderate risk factor	*1 high risk factor* *Dose*: 81 mg/d optimally before 16 weeks Continue daily until delivery. Other established medical indications
Risk factors	*High risk factors*	*High risk factors*	*High risk factors*
Previous pregnancy with PE	Previous pregnancy with PE	Previous pregnancy with PE	Previous pregnancy with PE
chronic hypertension	Chronic hypertension	Chronic hypertension	Chronic hypertension
Autoimmune disease	Autoimmune disease	Systemic lupus erythematosus	Systemic lupus erythematosus
Diabetes mellitus	Diabetes mellitus	Diabetes mellitus	Diabetes mellitus
Chronic kidney disease	Chronic kidney disease	Chronic kidney disease	Chronic kidney disease
Multifetal gestation		Multifetal gestation	Multifetal gestation

Nulliparity		Thrombophilia	Thrombophilia
Age >40 years	*Moderate risk factors*	*Moderate risk factors*	*Moderate risk factors*
Inter-pregnancy interval >10 years	Nulliparity	Nulliparity	Nulliparity
BMI at first visit >35 kg/m^2	Age >40 years	Age >35 years	Age >35 years
Family history of PE	Inter-pregnancy interval >10 years	Inter-pregnancy interval >10 years	Inter-pregnancy interval >10 years
Conception by IVF	BMI at first visit >35 kg/m^2	BMI >30 kg/m2	BMI >30 kg/m2
any risk factor	Family history of PE	Family history of PE	Family history of PE
		History of SGA or adverse outcome	History of SGA or adverse outcome
		Sociodemographic characteristics (African American race or low socioeconomic status)	Sociodemographic characteristics (African American race or low socioeconomic status)

BMI: body mass index; IVF: *in vitro* fertilisation; PE: preeclampsia; SGA: small-for-gestational-age;

These bodies use different combinations of these risk factors to assign a woman as low or high risk and LDA is started if the woman is categorised as high risk. This history-based approach although very practical and can easily be implemented even in most low-income countries,

critics of it say the likelihood ratios of the individual risk factors are low. Also, it does not consider how different risk factors interact to either strengthen or weaken the likelihood ratios. There are instances when high risk women are also known to have existing protective factors of preeclampsia such as a multiparous woman with no history of hypertension or hypertensive state in pregnancy or women with a normal weight. These protective factors haven't been shown to decrease the risk of preeclampsia when they are present together with other risk factors that puts a woman as high risk. So, it's important to state that these history-based approach to screening for high-risk women for preeclampsia may have a high screen-positive rate. However, the history-based risk factors present that screen a woman positive are not able to determine the magnitude of risk of preeclampsia developing later in pregnancy.

2.6 Multi modal Preeclampsia Risk Assessment Tool

The complex nature of the pathophysiology of preeclampsia is such that, single maternal factor is unlikely to predict it accurately. Thus, the tendency worldwide is building algorithms and combining multiple factors. Maternal sociodemographic features described above, doppler ultrasound findings, and maternal blood biomarkers are associated with an increased risk of preeclampsia. Each of these have been used as a separate screening test to identify high risk women for preeclampsia. These variables have also been combined to create a prediction tool for a pregnant woman's risk of developing preeclampsia in early pregnancy**.**

The Fetal Medicine Foundation (FMF) developed a model using multiple biomarkers with a combination of maternal risk factors, mean arterial pressure (MAP), uterine artery pulsatility index (UTPI) and serum pregnancy-associated plasma protein A (PAPP-A) between 11 to 14 weeks to improve on detection rate and reduce false positive rates. Combinations of these biomarkers are shown to do better with the disease prediction than single biomarkers[33].

For the FMF model, risks are calculated at 11-14 weeks using maternal risk factors, MAP, UTPI and serum PAPP-A.

A 2008 systematic review reported a higher accuracy of MAP in the prediction of preeclampsia among low-risk pregnant women in the second trimester when compared to using just the measured systolic and diastolic blood pressure. MAP is significantly increased at 11–14 weeks' gestation in women who subsequently develop preeclampsia. An evaluation of MAP in a heterogeneous population of nulliparous and multiparous women had a prediction rate of 58% for early onset preeclampsia and 44% for late onset preeclampsia, with a 5% of false

positives[35]. Accurate assessment of blood pressure is required to get accurate MAP. Wrongly measured blood pressure will affect the results thereby affecting reliability and validity. The recommendation is to measure MAP by validated automated devices with the right cuff size, with women in sitting position with back supported and legs uncrossed, taking two measurements in each arm supported at the level of the heart at the same time, and that the average of the four measurements should be used.

UTPI has become a great screening test for preeclampsia. It serves as a non-invasive method for the assessment of the uteroplacental circulation. A raised UTPI, is associated with the development of preeclampsia later in pregnancy. Result is expressed as multiple of median (MoM). The MoM value of UTPI is significantly increased at 11–13 weeks' gestation in women who subsequently develop preeclampsia. An increase in the UTPI before 23 weeks of gestation in a random heterogeneous population of pregnant women had sensitivity of 77.8% and specificity of 95% for early preeclampsia prediction. This screening tool depends on availability of ultrasound with doppler functions, expertise in the form of well-trained qualified sonographers for a reliable measurement of UTPI. Measurements of the UTPI should be done within acceptable standard ultrasound technique to achieve uniformity of results. This restricts its use on a large scale.

Numerous maternal biomarkers have been studied with placental growth factor (PLGF) and PAPP-A showing promising results in the early prediction of preeclampsia. A low serum PAPP-A in the first trimester is associated with a higher risk for developing preeclampsia later in pregnancy. However, measurement of PAPP-A alone is currently not an effective screening tool for preeclampsia[36]. Moreover, PAPP-A results are influenced by some of the common risk factors of preeclampsia such as diabetes mellitus, parity, multiple pregnancy, advanced maternal age, gestational age at screening, maternal weight, racial origin, cigarette smoking, conception by in-vitro fertilization (IVF)[37]. A low placental production of PLGF is a risk factor for developing subsequent preeclampsia later in pregnancy. Low levels of serum PLGF are shown to precede the clinical onset of preeclampsia and can be detected in the maternal serum in both the first- and second trimesters of pregnancy. When evaluated for early onset preeclampsia, PAPP-A and PLGF had better results[38].

Detection rates using the FMF model is 90% for very early preeclampsia <32 weeks, 75% preterm, and 41% term preeclampsia, with at 10% false positive rate (FPR)[39]. From the results it is obvious that screening between 11 – 13 weeks using a combination of these biomarkers

performs very well in picking women who will develop preeclampsia below 37 weeks with a poor performance for picking cases above 37 weeks. These rates have been prospectively evaluated in many different populations[40] [41] [42] [43] with results of these validation studies comparable to the original study.

Although the screen-positive rate are shown to be lower compared to using maternal socio-demographic clinical risk factors alone , it may have a higher positive likelihood ratio[44]. A sonographer with the expertise in assessing UTPI and additional laboratory testing for the serum PAPP-A and PLGF is required using this model. These are all associated with an increased cost. Also, deficiencies in obtaining UTPI limits reliability and validity.

To find the most effective of these screening tools, many studies have compared the two approaches. A study found that the detection rates for preterm and term preeclampsia were inferior using NICE or ACOG clinical criteria alone to first trimester screening using the MFM multivariable approach. At a screen positive rate of 10%, 370 women would have to be screened, and the 37 identified as being at high risk of pre-eclampsia treated with 150 mg/day of aspirin to prevent one case of pre-term pre-eclampsia[38].

In comparing the detection rates using risks generated through the use of only maternal history verses MAP + UTPI + PAPP-A , maternal history only detected 41.7% whiles that of MAP + UTPI + PAPP-A detected 91.7% of early pre-eclampsia at a false-positive rate of 5% and 10% respectively[40]. Using the NICE type, history-based risk factor approach was compared to the MFM approach of screening between 11 –14 weeks for preeclampsia risk. It was reported that the MFM multi modal approach was superior, with both a significant reduction in screen-positive rate and an increase in detection for pre-eclampsia[45]. This was the tool used in the landmark ASPRE trial which reported a 62% (95% CI 26–80%) reduction in the incidence of preterm pre-eclampsia[46]. A main drawback of this FMF foundation approach is that in low resourced areas where ultrasound scans and laboratory services are not readily available this cannot be used.

Unlike the history-based approach where risk cannot be reduced by the presence of a protective factor in the woman, this could decrease risk based on the factors present in the woman. For example, in many women who were considered high risk based on the NICE approach, the FMF approach reduced this by half.

2.7 Screening in a low resource setting

Though low resource areas have the highest morbidity and mortality associated with the disease, screening of preeclampsia using maternal factors and biomarkers in the first trimester here is a big challenge because, the use of these clinical and biochemical factors remain unrealistic for general use in most of these developing countries. As at now, there is still not a single cost-effective and reliable screening test for preeclampsia recommended for use in most low resourced developing countries[47]. This is largely due to the unavailability of the biomarkers for the prediction of the disease in most of these areas. Tests such as uterine artery doppler studies and placental growth factor assays are not readily available in primary healthcare settings of these areas. Therefore, most of these areas must rely on using just the maternal factors from history at booking in predicting the risk of the disease occurring later in pregnancy for LDA initiation. Using history based maternal factors alone or together with MAP achieves detection rates of 44.8% and 50.5%, respectively, for preterm preeclampsia, at 10% FPR[48]. It seems reasonable to implement this relatively simpler model. This has backing from the International Federation of Gynaecology and Obstetrics (FIGO) who recommends that where resources are limited, modifications of the first trimester combined test can be considered[49]. The important thing according to FIGO is for member associations to ensure that resource-appropriate risk assessment for preterm preeclampsia forms an integral part of routine first trimester evaluation protocol offered at all maternal health services[49].

2.8 Risk factors for pre-eclampsia at antenatal booking for screening

Observational studies have identified various maternal risk factors associated with preeclampsia. These risk factors are assessed at booking to predict a woman's risk of developing preeclampsia.

Of the many maternal risk factors associated with preeclampsia, those found to be independently linked with the highest risks of developing preeclampsia are termed the high-risk factors and include: a history of preeclampsia, chronic hypertension, pregestational diabetes, chronic kidney disease, antiphospholipid syndrome, and systemic lupus erythematosus.

Those modestly associated with increased preeclampsia risk are termed moderate risk factors and include: nulliparity, advanced maternal age, multiple pregnancy, a family history of

preeclampsia in a first-degree relative and obesity. The multiple presence of these moderate risk factors heightens preeclampsia risk.

These risk factors sometimes are present alone or in combination with others. The absolute and relative importance of one risk factor over another was evaluated in a study that estimated the contributions of these common maternal risk factors to the development of pre-eclampsia in terms of each risk factors absolute rate and relative risk of pre-eclampsia[50].

In this meta-analysis of cohort studies that evaluated the risk of preeclampsia in relation to these common clinical risk factors assessed at ≤16 weeks of gestation, the highest rate of preeclampsia occurred in patients with antiphospholipid syndrome (pooled rate 17.3 percent, pooled relative risk [RR] 2.8), and the highest relative risk of preeclampsia occurred in patients with a past history of preeclampsia (pooled rate 12 percent, pooled RR 8.4) with chronic hypertension (pooled rate 16.0 percent, pooled RR 5.1), pre-existing (pregestational) diabetes (pooled rate 11.0 percent, pooled RR 3.7), pre-pregnancy body mass index (BMI) >30 kg/m^2 (pooled rate 7.1 percent, pooled RR 2.8), multifetal pregnancy (pooled rate 6.4 percent, pooled RR 2.9)[50].

This has provided clinicians with knowledge of the magnitude of pre-eclampsia risk by the various maternal risk factors at booking for LDA prophylaxis. For example, antiphospholipid antibody syndrome, chronic hypertension, previous pre-eclampsia, pregestational diabetes mellitus, pre-pregnancy BMI >30 were each found to be associated with a high rate of pre-eclampsia and a low threshold number needed to prevent (NNPT) which would justify consideration for LDA[50]. It is based on this that certain risk factors are suggested to be used alone and others to be used in combination to identify high risk women of preeclampsia.

Nulliparity is found to be a common feature in women who develop preeclampsia. A Nigerian study found 27.7% of women with hypertensive disease in pregnancy to be nulliparous women[51] whiles an Australian population study of women who developed preeclampsia reported 29.2% of these women to be nulliparous[52]. In a meta-analysis of large cohort studies of risk factors for pre-eclampsia where the absolute risk of developing pre-eclampsia in the presence versus absence of a given risk factor, the relative risk of developing pre-eclampsia and the population attributable fraction for pre-eclampsia in relation to each risk factor were determined, nulliparity had the greatest population attributable fraction for pre-eclampsia (32.3%, 95% confidence interval 27.4% to 37.0%)[50]

Multiple pregnancy is an established risk factor and is included in most of the maternal based risk factors for screening for high-risk women at the booking visit. Multiple pregnancy was found to be very common among women with hypertensive disease of pregnancy in a Nigerian study[51]. Other case reports consistently showed multiple pregnancy to be a common risk factor for preeclampsia[53]. A systematic review and meta-analysis of clinical risk factors for pre-eclampsia determined in early pregnancy showed multiple pregnancy to have (RR 2.9, 95% CI 2.6-3.1)[50].

Obesity at the booking visit is also shown to be a common feature of women who develop preeclampsia later in pregnancy. Some studies in a Ghanaian population show obesity to be a significant risk factor for preeclampsia[54]. There are many studies among African populations although using different ranges of obesity consistently finding raised body mass index before pregnancy to be a common feature in women who subsequently develop preeclampsia[55 56]. A systematic review reported obesity as an independent risk factor of preeclampsia with [RR 2.8, 95% CI 2.6-3.1])[50].

Maternal age above 35-40 years is common in women who develop hypertensive disease in pregnancy[55 56 57]. In a study of obstetrical outcomes in women over 40 years of age, (4.6 %) of these women were ≥ 40 years old at the time of delivery[58]. Women aged ≥ 40 years are shown to have almost two times the risk of developing pre-eclampsia, irrespective of parity[59]. A systematic review put maternal age ≥ 40: RR 1.5, 95% CI 1.2-2.0)[50] .

Findings from numerous studies have always demonstrated a positive association between family history of hypertension disease in pregnancy and preeclampsia/eclampsia[60 61]. Ghanaian studies have consistently found family history to be common risk factor for preeclampsia/eclampsia[54]. In a study of over 421 women with early onset preeclampsia, 41 of them representing 9.7% had a maternal family history of preeclampsia[62]. In another study in Brazil, 17% (94 out of 530) women with hypertensive disease in pregnancy had family history (mother and/or sister) of hypertensive state in pregnancy. Another meta-analysis showed that the odds of women who have a family history of hypertensive disease in pregnancy were nearly three times more likely to develop preeclampsia/eclampsia compared with women without a family history of HDP (OR: 2.73; 95% CI:1.85, 3.6).

Inter pregnancy interval of more than 10 years as a moderate risk factor for preeclampsia is supported by a study that showed that preeclampsia risk in a second or third pregnancy was

directly related to the time that had elapsed since the preceding delivery, and when the interbirth interval was 10 years or more, the risk approximated that among nulliparous women[63].

The presence of a single moderate risk factors at booking reportedly puts the incidence of preeclampsia is to be below 8%. In those with multiple moderate risk factors it rises. It's also important to note that these moderate risk factors do not carry the same magnitude of risk for preeclampsia and the frequency of these risk factors varies in different populations. Also, the risk reduction benefits of LDA have not been evaluated in each of these subgroups.

In a study on risk factors associated with preeclampsia in Ethiopia, the commonest risk factor at booking was previous hypertensive state in pregnancy which was found in about half (44.6%) of cases[64]. Another study on LDA to prevent preeclampsia in women at high risk had about 23% of the women with preeclampsia in a previous pregnancy as the third commonest risk factor[65]. A Nigerian longitudinal study reported hypertensive disease in a previous pregnancy increased the likelihood of having hypertensive disease in the present pregnancy by four times compared to women without any history of hypertensive disease in pregnancy (RR: 4.2; 95% CI: 2.14, 6.81)[51]. In a systematic review and meta-analysis of clinical risk factors for pre-eclampsia estimating the contributions of several clinical risk factors to the development of pre-eclampsia in early pregnancy , a past history of preeclampsia had an increased risk of developing preeclampsia in a subsequent pregnancy eight times compared with patients without this history (RR 8.4, 95% CI 7.1-9.9) with these women having the greatest pooled relative risk (8.4, 7.1 to 9.9)[50]. Another meta-analysis also reported that based on pooled estimates of OR, the odds of women who had a history of hypertensive disease in pregnancy were nearly four times more likely to develop hypertensive disease in pregnancy compared to women who did not (OR: 3.75; 95% CI: 2.05, 5.45)[66]

Chronic hypertension is a commonly present risk factor during the booking visit in women who develop preeclampsia later in pregnancy. A Nigerian study on factors associated with severe preeclampsia and eclampsia reported 26% of the women with preeclampsia being chronic hypertensives[67]. Evidence for chronic hypertension as a risk factor for preeclampsia is well established. A systematic review and meta-analysis of clinical risk factors for pre-eclampsia that estimated the contributions of several clinical risk factors to the development of pre-eclampsia determined in early pregnancy found chronic hypertension at booking though defined differently by individual studies to have a five times risk of developing preeclampsia compared with patients without this risk factor (RR 5.1, 95% CI 4.0-6.5) making it the second

highest in terms of pooled relative risk and also second highest in terms of pooled rate (16.0%, 12.6% to 19.7%) for preeclampsia [50].

Pregestational diabetes is a known risk factor for preeclampsia and are assessed at booking in screening for preeclampsia. A study in an Australian population found 4.2% of women with preeclampsia being diabetics[52]. Pregnant women with pregestational diabetes mellitus were found to be five times more likely to develop preeclampsia/eclampsia in comparison to women without diabetes (RR: 4.8; 95% CI: 1.91, 6.75) in a Nigerian study[51]. An Ethiopian study reported the odds of having preeclampsia to be 5.4 times higher among diabetic mothers compared to non-diabetic mothers[68]. In a population-based study, pre-existing diabetes was a risk factor for both early onset and late onset preeclampsia[69]. A systematic review and meta-analysis of the clinical risk factors for pre-eclampsia determined in early pregnancy which aimed at developing a practical evidence based list of clinical risk factors that can be assessed by clinicians at ≤16 weeks' gestation to estimate a woman's risk of pre-eclampsia reported a relative risk of (RR 3.7, 95% CI 3.1-4.3) for pregestational diabetes mellitus[50].

Women with chronic kidney disease at the booking visit has gone on to develop preeclampsia. In the systematic review and meta-analysis of the clinical risk factors for pre-eclampsia, chronic kidney disease had a (RR 1.8, 95% CI 1.5-2.1)[50] and can be higher depending on the stage during pregnancy and the presence of an associated hypertension[70].

Women with antiphospholipid antibodies (anticardiolipin antibodies or lupus anticoagulant or both) at booking have significant risk of developing preeclampsia later in pregnancy. A meta-analysis reported women with antiphospholipid antibody syndrome were found to have the highest pooled rate of pre-eclampsia (17.3%, 95% confidence interval 6.8% to 31.4%) [50]

2.9 Proportion of high-risk women at booking based on maternal risk factors

Not many studies were found on the proportion of women with preeclampsia who had risk factors at the beginning of pregnancy. A prospective cohort study on LDA usage among women with an increased preeclampsia risk reported 306 out of 865 representing 35.4% of the women had a predicted increased preeclampsia risk[71].

In a Canadian study between 2012 to 2015, a total of 1727 representing 21% of women were screened as high risk for preeclampsia out of a total of 8176 women having prenatal care[72]

2.10 LDA initiation and usage rates among high-risk women

There is a general knowledge-to-practice gap in the use of LDA prophylaxis to reduce the incidence of preeclampsia. A study on clinical and geographical variation in prophylactic and therapeutic treatments for pre-eclampsia in the United Kingdom reported that of the women with known risk factors at trial entry, 24% (569/2399) received LDA[73]. This same study reported low LDA usage rate based on the locations of these pregnant women which ranged from 8% to 49%. A study in Nigeria showed the administration of prophylactic LDA in the management of preeclampsia/eclampsia to be low with more than four-fifths of healthcare providers not routinely assessing for risk factors for effective preventive measures[31]. A prospective cohort study on the rate of LDA usage among high risk women reported a usage rate of 25%[71]. In a population-based study, where researchers estimated LDA usage rates for preeclampsia prevention among pregnant women with maternal risk factors such as pre pregnancy diabetes, obesity, chronic hypertension, or a combination of these factors. Women with diabetes had LDA usage rate of 17.2% (95% CI, 16.2-18.2), obesity 6.9%(95% CI, 6.7-7.1) and chronic hypertension 27.6% (95% CI, 26.2-29) during the first trimester[74]. When some of these risk factors were combined, the rate of LDA use was 22.2% (95% CI, 20.5-24) among women with both diabetes and obesity, 36.6% (95% CI, 31.9-41.6) in women with both diabetes and chronic hypertension , 32.3% (95% CI, 30.2-34.5) in women with both obesity and chronic hypertension and 38.8% (95% CI, 32.9-44.9) among women with all three risk factors[74]. There is therefore a general low usage rate of LDA in preventing preeclampsia and its incidence.

2.11 Factors influencing initiation and use of LDA prophylaxis among high-risk women

Despite the general low usage rate of LDA in preventing preeclampsia and its incidence, little research has been done on factors that influence LDA initiation in women who are screened to be high risk. Most studies focused on rates of adherence to LDA.

In a Nigerian study, the use of LDA in high-risk pregnant women had most women in higher levels of care (secondary and tertiary care) receiving LDA with high-risk women in primary care least likely to receive LDA[31]. This same study reported that medical practitioners (obstetricians and gynecologists) were more likely to prescribe LDA for high-risk women in pregnancy for preeclampsia prevention compared to midwives/nurses and that years of experience working in a maternity unit was associated with prescription rates[31]. Same study

also reported that training in maternal and child health had a positive effect on the provision of LDA prophylaxis.

In a Netherlands study, LDA usage was higher for women receiving risk-based care compared to usual care (29.4% vs 1.5%, odds ratio 19.1, 95% confidence interval 11.2-32.5)[71].

So, factors found to influence LDA initiation and use in high-risk women are level of care of a hospital and the clinician providing antenatal care. The higher the level of care the more likely LDA will be prescribed for a high-risk woman. Also, high risk women receiving care at booking from medical practitioners with years of experience working in the maternity unit, an obstetrician gynaecologist especially those with training in maternal and child health are more likely to receive LDA. Women attending antenatal care in hospitals where risk-based care is provided are more likely to receive LDA than in hospitals where all the women are seen together.

2.12 Effect of LDA prophylaxis on gestational age of onset of preeclampsia

The evidence for LDA taken in early pregnancy in delaying the gestational age of onset of preeclampsia is well established. LDA effect in reducing the burden of preeclampsia in terms of perinatal morbidity and mortality is largely due to its documented effect in delaying the gestational age of onset of preeclampsia hence a reduction in the iatrogenic preterm deliveries associated with the disease. The landmark ASPRE trial (Aspirin for Evidence-Based Preeclampsia Prevention) reported a significant reduction of 62% for preterm preeclampsia with no reduction in the incidence on term preeclampsia[46]. The ASPIRIN study[75] reported LDA could reduce the incidence of hypertensive disorders of pregnancy before 34 weeks of gestation (0.1% [8/5780] vs 0.4% [21/5764], RR, 0.38; 95% CI, 0.17e0.85; P¼.015)

A systematic review and meta-analysis comparing LDA initiated before 16 weeks to controls reported a major reduction of the risk of preterm preeclampsia < 37 weeks (RR 0.11, 95% CI 0.04–0.33) but had no significant effect on term preeclampsia (RR 0.98, 95% CI 0.42–2.33) and concluded that LDA administrated at or before 16 weeks of gestation reduces the risk of preterm but not term preeclampsia[46].

Another meta-analysis of 31 trials on a combined total of 32, 217 pregnancies reported that use of LDA was associated with a 10% reduction in the prevalence of both preeclampsia and delivery before 34 weeks' gestation[76].

Beaufils et al[77] found strong benefits of LDA initiated at 14–16 weeks for the prevention of severe preeclampsia and preeclampsia diagnosed before 37 weeks in pregnancies at high risk of preeclampsia. Another study also reported preterm births before 32 weeks to be decreased by approximately 60 percent (1.2 versus 2.9 percent, odds ratio [OR] 0.42, 95% CI 0.19-0.93) in high risk women who took LDA[78].

The reported benefits of LDA prophylaxis of reductions in the incidence of preterm birth, perinatal mortality, composite adverse neonatal outcomes in meta-analysis could essentially be attributed to a decrease in early onset preeclampsia at <34 weeks' gestation as reported in a 2021 meta-analysis by the USPSTF[79]

2.13 Effect of LDA prophylaxis on maternal and fetal/ neonatal outcomes

Lots of studies into whether LDA reduce adverse perinatal / neonatal outcomes in pregnant women at high risk of preeclampsia have been done.

Secondary analyses of the ASPRE trial suggest a 68% reduction in length of stay in the NICU mainly due to a decrease in the rate of births at<32 weeks' gestation, mainly because of prevention of early preeclampsia[80].

Duley et al in a 2019 meta-analysis found a (9%) reduction in the RR for preterm birth <37 weeks (35,212 women, 47 trials; RR 0.91, 95% CI 0.87 to 0.95, high-quality evidence), a 14% reduction in fetal deaths, neonatal deaths or death before hospital discharge(35,391 babies, 52 trials; RR 0.85, 95% CI 0.76 to 0.95; high-quality evidence), a reduced risk of small-for-gestational age babies (35,761 babies, 50 trials; RR 0.84, 95% CI 0.76 to 0.92; high-quality evidence), and pregnancies with serious adverse outcome (a composite outcome including maternal death, baby death, pre-eclampsia, small-for-gestational age, and preterm birth) (RR 0.90, 95% CI 0.85 to 0.96; 17,382 women; 13 trials, high-quality evidence)[81].

A meta-analysis by Roberge et al concluded that LDA initiated at ≤ 16 weeks of gestation is associated with a greater reduction of perinatal death and other adverse perinatal outcomes IUGR (RR = 0.46 (95% CI, 0.33–0.64) vs 0.98 (95% CI, 0.88–1.08), P < 0.001) and preterm birth (RR = 0.35 (95% CI, 0.22–0.57) vs 0.90 (95% CI, 0.83–0.97), P < 0.001)[82]

A recent meta-analysis published in 2021 by the USPSTF reported: lower risk of perinatal mortality (RR 0.79), preterm birth (RR 0.80), IUGR (RR 0.82). This however did not find a clear reduction in preterm delivery (RR 0.92, 95% CI 0.83-1.02)[12]

On maternal outcomes, the available studies mainly focused on effect of LDA prophylaxis in the prevention of preeclampsia as well as the composite adverse maternal outcomes. The individual adverse outcomes such as having a cesarean section, organ dysfunction, eclampsia, CVA, maternal mortality was rarely looked at. In an Asian study, LDA prophylaxis did not significantly reduce the risk of caesarean section in either East Asians (OR = 0.67, 95% CI: 0.14–3.22) or non-East Asians (OR = 1.01, 95% CI: 0.86–1.19)[83]

The USPSTF meta-analysis in 2021 did not find a significant association between LDA prophylaxis and the risk of organ dysfunction such as HELLP syndrome (hemolysis, elevated liver enzymes, low platelets; RR 0.77, 95% CI 0.44-1.36) or severe maternal morbidity (RR 1.00, 95% CI 0.72-1.39)[79]. It concluded that the direct maternal outcomes of preeclampsia such as eclampsia, HELLP syndrome, CVA, organ failure, and death were extremely rare so pooled estimates were not possible to compute.

2.14 Guidelines from selected organizations

The United Kingdom's NICE consider a woman at high risk for preeclampsia when she has any one of hypertensive disease in a previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus, any autoimmune disease or more than one of nulliparity, maternal age 40 years and above, BMI of 30 kg/ m2 and above , family history of preeclampsia, or interpregnancy interval of >10 years. They recommend these high-risk women be put on LDA 150mg daily from 12 weeks' gestation until delivery.

In the United States, the USPSTF recommends the use of LDA (81 mg/d) as preventive medication for preeclampsia after 12 weeks of gestation in women who have one or more of history of preeclampsia, multifetal gestation, chronic hypertension, pregestational type 1 or 2 diabetes, kidney disease, autoimmune disease (systemic lupus erythematous, antiphospholipid syndrome) or at least two of nulliparity, obesity(BMI >30), family history of preeclampsia (mother and/or sister), maternal age 35 years or older, personal history factors (low birth weight or small for gestational age, previous adverse pregnancy outcome, >10-year pregnancy interval), in vitro fertilization conception, lower income and black persons[79]. The detection rates using the USPSTF was very high at 90% and 89% for preterm and term preeclampsia, respectively on account of its expanded list of risk factors; this however, increased its false positive rate to as high as 64%[43].

ACOG and the Society for Maternal-Fetal Medicine endorses the USPSTF guideline. These two bodies recommend aspirin (81 mg/day) in women at high risk of preeclampsia to be initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks) and continued daily until delivery.

WHO recommends LDA to be initiated by 20 weeks' gestation or as soon as antenatal care is started for the prevention of pre-eclampsia in women at moderate risk (women with any two primiparity, family history of pre-eclampsia, age greater than 40 years, or multiple pregnancy) and at high risk (diabetes, chronic or gestational hypertension, renal disease, autoimmune disease, positive uterine artery Doppler, previous history of pre-eclampsia, or previous fetal or neonatal death associated with pre-eclampsia) of developing pre-eclampsia [2]

The Society of Obstetricians and Gynaecologists of Canada recommends 75 to 162mg/day LDA for women at high risk of preeclampsia (previous preeclampsia, relevant pre-existing hypertension, renal disease, diabetes, antiphospholipid syndrome, multiple gestation, or two or more lower risk factors[84].

FIGO recommends approximately 150 mg LDA beginning at 11 to 14+6 weeks every night until 36 weeks of gestation, delivery, or diagnosis of preeclampsia for women identified as high risk[49]

2.15 Pathophysiology of preeclampsia

Preeclampsia is the development of hypertension after 20 weeks of pregnancy with proteinuria and/or other signs of end-organ dysfunction. The etiology of preeclampsia/eclampsia is still not entirely known. Many maternal, paternal, and fetal factors have been implicated in its development in a model composed of two interrelated stages. An abnormal placentation in the first stage leading to maternal inflammatory response in the second stage. In normal pregnancy, the placenta is described as a high capacitance low resistance unit with an increase in uterine blood flow for adequate fetal development. In a pregnancy with no preeclampsia, the spiral arteries in the decidua and myometrium at the placental implantation site undergo remodelling in 4 steps as their walls are being invaded by trophoblast. The decidua is first invaded, then intra-arterial trophoblast migration occurs, followed by a subsequent intramural invasion of the vessels, then the middle muscular layer of the vessels are replaced by fibrinoid material and connective tissue, with vessel reendothelialization occurring last. There is an increase in the diameter of these vessels much higher than that observed in uteri of nonpregnant women

resulting in the low resistance to blood flow with a high capacitance intervillous space providing adequate blood supply to maintain pregnancy effectively. This remodelling does not occur from the level of the radial artery so this level outwards will have increased blood pressure in their walls due to the increased blood flow to the uterus during pregnancy. This creates stress from this level which provides the trigger for nitric oxide secretion by the endothelium, which produces a generalized vasodilation of the uterine vessels. In preeclampsia this remodelling may be partial or completely absent resulting in a low capacitance high resistance placental unit. The proportion of remodelled vessels is considerably reduced, mostly in the central areas of the placental bed. In some instances, obstructive lesions forms within these vessels too by a process called atherosis where atheromatous plaques made up of lipid-rich macrophages, perivascular mononuclear inflammatory infiltrate, and fibrinoid necrosis form within the vessels occluding the lumens of these vessels either completely or partially leading to uteroplacental ischemia. The poor perfusion of the intervillous space and the subsequent ischemia triggers the release vasoactive compounds into the maternal circulation, which can produce an exaggerated inflammatory response, vasoconstriction, endothelial damage, capillary leak, hypercoagulability, and platelet dysfunction, all of which contribute to organ dysfunction and the various clinical features of the disease. The oxidative stress results in the release of free radicals which causes the endothelial dysfunction and vascular injury. The oxidative stress increases the levels of antiangiogenic factors vascular endothelial growth factor receptor-1 (VEGFR-1) and the soluble form of the vascular endothelial growth factor, fms-like tyrosine kinase1(sFlt-1). VEGFR-1 block the action of vascular endothelial growth factor (VEGF) a major proangiogenic factor whiles sFlt-1antagonises VEGF action. There is also a decrease synthesis of placental growth factor (PIGF) a proangiogenic factor. Therefore, there is a predominance of antiangiogenic factors (VEGFR-1 and sFlt-1) to the proangiogenic factors (VEGF and PIGF) which characterise preeclampsia. There is also an increased synthesis of Thromboxane A2 which causes vasoconstriction and platelet aggregation and a decreased synthesis of prostacyclin that have a vasodilatory action and inhibit platelet aggregation. Therefore there is an imbalance in thromboxane A2 to prostacyclin leading to the hypertension and platelet consumption which in extreme form present as disseminated intravascular coagulation which are major features of preeclampsia.

So, preeclampsia development is believed to occur in 2-stages. In stage one of the pathophysiology there is suboptimal trophoblastic invasion leading to failure of the spiral arteries to remodel early in pregnancy. This results in the formation of a low capacitance high resistance placenta instead of the normal high capacitance low resistance placenta. Stage 2 of the pathophysiology is due to the abnormal placenta formed in stage one causing suboptimal uteroplacental blood flow which creates a generalized hypoxic state and an oxidative stress in the abnormally formed placenta leading to a continues secretion of antiangiogenic factors which leads to the features of preeclampsia.

It is stage one of the pathophysiology that is targeted for the prediction and stage 2 for prevention of preeclampsia.

Despite this understanding, what really causes some placenta to form normally and others to form abnormally leading to all the sequence of events remains unknown and may differ between everyone. Vascular, genetic, immunologic, environmental and maternal factors, contribute to this abnormal placenta formation[85]

Abnormal differentiation of the trophoblast for myometrial trophoblastic invasion has been suggested as a possible mechanism responsible for defective trophoblast invasion of the spiral arteries leading to preeclampsia[86].

Immunologic factors as a possible cause to abnormal placental development has also been proposed. This came up from observation of epidemiological data that prolonged prior exposure to paternal antigens appears protective against preeclampsia whiles nulliparous women, change in partnership with pregnancy occurring within a year of sexual cohabitation in-between pregnancies, women with long interpregnancy intervals, continuous use of barrier contraception, IVF conception all have reduced exposure to paternal antigens and are all associated with higher risks of developing preeclampsia.

Genetic predisposition to preeclampsia is suggested by the observations that primigravid women with a first degree family history of preeclampsia have a higher risk of the disease than primigravid women with no such history[87]. Also, preeclampsia risk increases in women who have had preeclampsia in a previous pregnancy[88]. A woman pregnant with a man who was the product of a pregnancy complicated by preeclampsia is more likely to develop preeclampsia than with men without this history[89]. Also a woman who becomes pregnant by a man whose

previous partner had preeclampsia is at higher risk of developing the disorder than if the pregnancy with the previous partner was normal[90].

Environmental factors like low calcium intake have also been discussed though causality has been difficult to prove. Epidemiologic studies have linked low calcium intake with increased rates of preeclampsia. Calcium supplementation in areas of low calcium is suggested as a preventive treatment for preeclampsia. The mechanism of this association is not clear.

The development of preeclampsia can be early onset (<34 weeks of gestation) and late onset (≥34 weeks of gestation). Over 85% of women develop preeclampsia at ≥34 weeks of gestation including during labour with about 10% developing it at <34 weeks of gestation[91]. About 5 percent of preeclampsia cases occur postpartum usually within 48 hours of birth[92].Though the clinical features of these two overlaps, the spectrum of disease and outcomes differ. Early-onset preeclampsia has been shown to have more severe clinical findings with poorer maternal/fetal outcomes compared to late onset preeclampsia[69].

2.16 Mechanism of action of aspirin

Aspirin (acetylsalicylic acid) was theorized to be protective against preeclampsia due to its well-known anti-inflammatory, anti-angiogenesis, and antiplatelet properties. Aspirin inhibits the activity of the platelet enzyme cyclooxygenase (COX) in the production of prostaglandins which mediate pain and induce platelet activation. There are three isoforms of this enzyme: cyclooxygenase 1(COX 1), cyclooxygenase 2 (COX 2) and cyclooxygenase 3 (COX 3). Aspirin mainly irreversibly inhibits the constitutive enzyme COX-1 activity and, to a lesser degree, the inducible enzyme COX-2 activity[93].

COX 1 regulates the production of thromboxane-A2 (TXA-2) a vasoconstrictor and a promoter of platelet aggregation and prostacyclin (PG I-2) a vasodilator and inhibiter of platelet aggregation[94].

It's been observed that whiles higher doses of Aspirin inhibit the synthesis of all these prostaglandins, low dose aspirin only inhibits TXA-2 production whiles keeping PGI 2 synthesis[95]. LDA, therefore, prevents the synthesis of TXA-2 thus preventing its harmful effects on blood vessels and platelets whiles keeping the synthesis of PG I-2 and its beneficial effects on blood vessels and platelets.

Other effects of Aspirin independent of COX are also believed to be implicated in its preventive role in preeclampsia such as its effect in decreasing the formation of thrombin[96] and increasing

fibrinolysis[94] in the endothelium via decreased expression of the tissue factor responsible for platelet adhesion[95]. It's been also shown to biologically prevent tumour-necrosis factor (TNF) induced endothelial cell dysfunction by regulating the NFkB/eNOS pathway[97]. Aspirin has also been shown to reduce oxidative stress in preeclampsia by attenuating the nitrous oxide pathway[97].

In vitro studies have shown that aspirin increases the expression and production of PIGF gene and corrects imbalances in the different cytokines and this effect in regulating cytokines is believed to result in better trophoblastic invasion, which usually occurs before 16-18 weeks of gestation.[98]

2.17 Basis for preventing Preeclampsia with Aspirin

Because the exact pathogenesis of preeclampsia is not fully understood and the understanding that it may be from multiple aetiologies, the mechanism by which aspirin prevents it is also not certainly known. Aspirin largely seems to delay the onset of preeclampsia hence its largely reported effect in reducing the incidence of early onset preeclampsia.

From the pathophysiology, preeclampsia is associated with increased levels of platelet TXA-2 and a reduced level of PGI 2. This imbalance can be observe from 13 weeks of pregnancy in high risk women and is reversed by 2 weeks of treatment LDA[99] which inhibits TXA2 secretion without having any effect on endothelial prostacyclin. Hence there is vasodilation. So LDA prevents the vasoconstriction and platelet aggregation and the resultant placental hypoperfusion that underpins preeclampsia. Aspirin also shows proangiogenic activity by its inhibition of the expression of sFlt-1 a potent anti-angiogenic factor in human trophoblasts[100]. sFlt-1 is present at high levels in the circulation of patients with preeclampsia and is responsible for the angiogenic imbalance seen in the pathogenesis of preeclampsia.

This is the physiological explanation for the preventive role of aspirin in preeclampsia.

2.18 Pharmacokinetics of Aspirin

Aspirin is taken orally, is readily absorbed in the stomach and upper small intestines reaching peak plasma concentrations in 30 to 40 minutes with platelet inhibition occurring within an hour[93 101]. The rate of absorption depends on gastrointestinal pH, the dose and dissolution of the tablet[101]. Aspirin, a weak acid is first hydrolyzed to salicylic acid and then conjugated to

salicyluric acid which is the principal metabolite excreted in urine[102]. Aspirin half-life is about 20 min (13–31 min). It is slowly eliminated due to the high plasma level of protein transporters[101].

2.19 Timing of LDA initiation and discontinuation

Most trials on aspirin preventing placental complications have initiated treatment from 12 weeks of gestation. Convincing evidence shows the reduction of preterm preeclampsia is higher when LDA is started before 16 weeks of pregnancy[9]. It is therefore recommended to initiate therapy after 12 weeks but before 16 weeks. On initiating therapy after 16 weeks, a recent meta-analysis did not show a statistically significant reduction of preterm preeclampsia in patients starting aspirin after 16 weeks.

There is still some benefit in high risk women when therapy is initiate after 16 weeks[103]. The recently updated recommendation statement of the USPSTF in September 2021 based on evidence review says there is no upper gestational age limit for initiating LDA administration (previously 28 weeks)[79].

No consensus exists on the optimal time to stop LDA. Whiles some continue LDA until delivery, others discontinue at 36 weeks of gestation or few days before expected delivery to eliminate the theoretical risk of bleeding during delivery; however, no such adverse maternal effects have been proven[104]. So, it appears there is no benefit to stopping LDA prophylaxis before delivery. When to stop has not been associated significantly to excessive maternal or fetal bleeding. LDA alone do not contradict the use of spinal or epidural block for labour pain management or caesarean sections. Also, data on the effect of starting LDA prior to 12 weeks on mother or fetus.

2.20 Dose, time of day to take LDA and compliance in preeclampsia prevention

Doses of 100 mg/day or more have been shown in studies to be optimal[105]. Caron et al., showed a clear dose-dependent effect of aspirin with pregnant women not responding relatively well to doses below 100mg[106]. In the ASPRE trial a dose of 150 mg of aspirin per day was selected based on previous evidence of a dose-dependent benefit[38]. Since this trial generally provides the basis of recommendations on the use of aspirin in the prevention of preeclampsia, a dose of 150mg aspirin is what is generally recommended.

Specifying the time of the day to take aspirin is not routinely done so there can be morning or evening administration of the drug. However some experts believe that LDA may be more effective if taken at bedtime[107] though this may increase gastric irritation. In a randomized trial, COX-1-dependent platelet activity was significantly reduced upon awakening after LDA taken at bedtime with COX-1-independent platelet activity was not affected. This supports evening or bedtime intake of LDA.

Good antenatal compliance to LDA prophylaxis is important in preventing or delaying preeclampsia. Adherence rates less than 90 percent has been shown not to be effective[108]

2.21 Safety of LDA in pregnancy and contraindications.

Prophylactic LDA for preeclampsia has been found in multiple studies to be safe with no increased risk of congenital malformations throughout pregnancy[76 109].

Use of LDA in the third trimester has also not been associated with premature closure of ductus arteriosus[110] as well as no increased risk of neonatal intracranial hemorrhage[81].

The USPSTF did not find any negative effect on the long term physical and developmental outcomes in a child that has in-utero exposure to aspirin. Likewise, a follow up of the Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) of these infants up to age 18 months did not report differences in gross motor development, height, and weight gain.

For maternal safety, studies found no increased risk in haemorrhagic complications associated with LDA during pregnancy such as placental abruption, postpartum haemorrhage and blood transfusion[12]. However in non-pregnant patients long term use of aspirin has been associated with an increased risk of major gastrointestinal and cerebral bleeding episodes[111].

Because of significant cross-sensitivity between aspirin and other nonsteroidal drugs, LDA is also contraindicated in patients with known hypersensitivity to non-steroidal anti-inflammatory drugs (NSAID). Exposure to low-dose aspirin in patients with nasal polyps may result in life-threatening bronchoconstriction and should be avoided. The same is true in patients with asthma who have a history of aspirin-induced acute bronchospasm.

Absolute contraindications to the use of aspirin in pregnancy includes women with a history of aspirin allergy like an urticaria or hypersensitivity to other salicylates are at risk of anaphylaxis and should not receive LDA previous history of allergy or hypersensitivity to aspirin, women who are known to have hypersensitivity to other NSAIDs and known asthmatics with a history

of aspirin-induced acute bronchospasm. Women who screen positive with these absolute contraindications should be carefully counselled on all features of preeclampsia and should be carefully monitored to make a timely diagnosis to minimise complications. Relative contraindications to LDA include previous history of gastrointestinal bleeding from any source especially if source cannot be determined, active peptic ulcer disease, genitourinary bleeding, and any condition associated with severe hepatic dysfunction. So, for women who screen positive and have these relative risk factors the decision to prescribe LDA must be reviewed by the consultants and considered on a case-by-case basis.

2.22 Long-term child and adult health benefits associated with LDA prophylaxis

Limited studies exist on the beneficial effect of prophylactic LDA to the child or the mother beyond 18 months after birth. Currently no evidence of long-term benefits for the child such as reducing future risk of cardiovascular diseases have been documented.

For the mothers although some studies have found associations between preeclampsia and long-term cardiovascular health as well as an increased risk for early stroke no data exists to show LDA in pregnancy leads to reduction in risk of these conditions associated with preeclampsia.

2.23 Universal LDA approach compared to LDA to only selected high risk women

LDA prophylaxis has been suggested by some authorities to be more cost effective when given to all pregnant women for preeclampsia prevention especially in areas where it's difficult to have effective screening to identify high risk women[112]. Reasons for this suggestion is the evidence of benefit of this low-cost strategy in reducing the incidence of early onset preeclampsia coupled with aspirins safety in pregnancy. Currently there is no such recommendation because of limited data on universal LDA prophylaxis and its immediate and long-term effects. A study assessing LDA for every pregnant woman reported poor compliance without a significant reduction in preeclampsia incidence and increased incidence of bleeding[113]. This raises compliance concerns on universal LDA administration which is likely to be poor when universally given rather than when is given to only high risk women selected by screening and counselling on the need for LDA[114]. Based on these and the inadequate evaluation of the strategy of universal LDA use in randomized trials, a general recommendation cannot therefore be made.

2.24 Cost effectiveness of LDA prophylaxis

There have been studies mostly in well-resourced countries on cost-effectiveness of preeclampsia prevention with LDA. An Israeli study on cost effectiveness of a comprehensive screening in the first trimester to select high risk women for LDA prophylaxis concluded that this approach to screening and prevention is cost effective in various disease prevalence scenarios[115]. The reduced duration of stay in the NICU in high risk women who received LDA resulted significantly in cost saving compared to the cost of screening in the ASPRE trial[80].

Because LDA intervention is very cheap there has also been comparative studies on cost effectiveness of screening and treatment verses universal LDA prophylaxis with varying results. In a study where the cost of screening by risk factors alone for LDA prophylaxis was compared to universal prophylaxis, there was a very significant cost savings with the screen and treat approach as 76.5% of the women would not be prescribed LDA[116]. However in some other studies it was reported that universal LDA use was associated with a better cost saving than the screen-and-treat strategy annually when both were compared to no interventions[117].

It is important to point out that the long-term consequences of preeclampsia for women and children were not adequately considered in all these studies on cost effectiveness of selective or universal LDA prophylaxis.

2.25 Other investigated approaches to preeclampsia prevention

Calcium Supplementation

There is no consensus as of now on prescribing calcium for preventing preeclampsia because of conflicting reports from studies done. The evidence for general calcium supplementation for all women in prevention of hypertensive disorders is conflicting. A controlled trial that was subsequently published by WHO in women taking calcium from 20 weeks of pregnancy only showed a significant reduction of severe hypertension and maternal morbidity but failed to prevent preeclampsia of any form[118]. Another controlled trial focussing on the effect of calcium intake before and during the first half of pregnancy reported 23% of women that took calcium had preeclampsia whiles 29% of those who took placebo developed preeclampsia[119]. A sub analysis of this study reported that the women who took calcium with over 80% compliance, had a statistically significant reduction of preeclampsia (RR 0.66, CI 0.44-0.98; p=0.037)[119].

In a systematic review and meta-analysis, 1g or more calcium a day in the second half of pregnancy in women on a low calcium diet reported a 55% reduction for preeclampsia which was statistically significant, a significant reduction of high blood pressure and a decrease in the composite outcome of maternal death or serious morbidity[120].

Therefore, whiles there are potential benefits of calcium intake especially in women who are high risk of preeclampsia with low calcium intake there is not enough data to support calcium supplementation in the general obstetric population. The ISSHP in its 2018 report however recommended that women considered at increased risk for pre-eclampsia should receive supplemental calcium (1.2 to 2.5 g/day) if their intake is likely to be low (<600mg/day), in addition to LDA and when intake cannot be assessed or predicted it is reasonable to give calcium[121].

Heparin.

Low molecular weight heparin (LMWH) is safe and widely used in pregnancy because it does not cross the placenta. It has long been suggested for the prevention of placental mediated complications of which preeclampsia is one because of its antithrombotic effect, its effect in balancing proangiogenic and antiangiogenic factors and its anti-inflammatory action[122]. Whiles some randomised control trials have provided evidence to this effect, others too have failed to back this evidence. A significant reduction in the rate of recurrent preeclampsia and fetal growth restriction was observed in non-thrombophilic women who were given daily dalteparin injections (OR 0.15, 95% CI 0.03-0.70)[123]. This was collaborated by another study that reported a significant reduction in the overall rate of pregnancy complications including severe preeclampsia[124]. However, another randomized control trial concluded that antenatal prophylaxis with nadroparin a LMWH did not prevent placenta-mediated adverse pregnancy outcomes including preeclampsia[125].

Two meta-analysis was found on this. The first one reported that the use of LMWH had 36% reduction in the risk of recurrence of placental mediated pregnancy complications which was found to be statistically not significant (relative risk 0.64, 95% CI 0.36-1.11, p=0.11)[126]. The second one reported some significant reduction in preeclampsia in some of the trials they considered as high quality[127]. On this inconsistent evidence, heparins are not recommended for use during pregnancy for prevention of adverse pregnancy outcomes including preeclampsia other than its use in cases of antiphospholipid antibody syndrome.

Antioxidants: Vitamins C and E

the antioxidants vitamins C and E were suggested to play a role in preventing preeclampsia because of the documented role of oxidative stress in the pathophysiology of preeclampsia eclampsia. However, randomised controlled trials of Vitamins C and E failed to demonstrate any significant effect on the incidence of preeclampsia[128]. Therefore, antioxidant therapy with vitamins C and E is not recommended as prophylactic treatment of preeclampsia.

Folic acid

Some observational studies suggested taking multivitamins containing folic acid during pregnancy may be associated with a reduced risk of preeclampsia by lowering blood homocysteine levels or by improving placental and systemic endothelial function[129].The Canadian FACT Trial, a randomised controlled trial that looked at this potential preventive therapy did not report any additional benefit of folic acid in his regard[130]. A recent meta-analyses concluded that multivitamin containing folic acid or folic acid alone was not significantly effective in reducing gestational hypertension or preeclampsia incidence[131].

2.26 Quality assurance measure of the management of preeclampsia

Measures that are used in the assessment of the quality of care in the preventive management of preeclampsia according to NICE are :

a) Evidence of local arrangements to ensure that pregnant women have their risk factors for pre-eclampsia identified and recorded at the booking appointment.
b) Proportion of pregnant women who have their risk factors for pre-eclampsia identified and recorded at the booking appointment.
c) Evidence of local arrangements to ensure that pregnant women at increased risk of pre-eclampsia at the booking appointment are offered a prescription of 150 mg of LDA (unless contraindicated) to take daily from 12 to 16 weeks until birth.
d) Proportion of pregnant women at increased risk of pre-eclampsia at the booking appointment who are offered a prescription of 150 mg of LDA (unless contraindicated) to take daily from 12 weeks until birth.
e) Incidence of pre-eclampsia in women at increased risk of developing pre-eclampsia

2.27 Landmark studies on preeclampsia prevention using aspirin

The hypothesis suggesting preeclampsia to be from suboptimal trophoblastic invasion resulting in an imbalance of angiogenic and antiangiogenic proteins, leading to generalized inflammation and endothelial damage with platelet aggregation, and thrombotic events with placental infarcts presupposes the effect of aspirin in inhibiting inflammation and platelet aggregation should prevent or treat preeclampsia**.** The first randomised trial showing a benefit of aspirin in preeclampsia prevention was done in 1985[77]. Numerous studies with different results on the preventive effects of aspirin in high risk women were done with varying gestational age at inclusion and dosages between studies. The EPREDA trial[132] showed a beneficial effect of aspirin in the secondary prevention of intrauterine growth restriction.

The CLASP trial did not show any benefit of aspirin in reducing preeclampsia rates in pregnancy[133]. It was however observed that a correlation existed between rates of preeclampsia and gestational age at delivery; with lower rates of preeclampsia observed at lower gestational ages.

A meta-analysis of the efficacy of aspirin in the prevention of preeclampsia in high-risk patients showed LDA to reduce the risk of preeclampsia by 15% without changing the incidence of intrauterine growth restriction.

The PARIS meta-analysis showed aspirin to have a 10% reduction in preeclampsia rates in 2007[134]. A series of meta-analyses that followed reported aspirin's effect on preeclampsia rates depended on the dose and time of aspirin initiation. Aspirin was found to be effective in reducing preterm preeclampsia rates if initiated before 16 weeks of pregnancy, with no beneficial effect when started after 16 weeks[135] and no beneficial effect on term preeclampsia rates[135 105]. The ASPRE trial concluded that 150 mg of aspirin given at bedtime from 11 to 14 weeks of pregnancy, until 36 weeks, significantly lowered the incidence of developing preterm preeclampsia rate (a 62% reduction) in high-risk women compared to placebo[136]. This provided the basis to unify recommendations on the use of aspirin in the prevention of preeclampsia.

The USPSTF based on an evidence review updated its recommendations on prophylactic LDA use in September 2021

Major changes from the 2014 USPSTF recommendations and the 2018 Committee Opinion by ACOG and SMFM included LDA to be now "recommended" for patients with ≥2 moderate-risk factors (previously "considered"); LDA is now to be considered for patients with 1

moderate-risk factor; IVF has been added to the list of moderate-risk factors; and there is no upper gestational age limit for initiating LDA administration (previously 28 weeks).

Most of these studies, however, were done on Caucasians with very little or no studies in sub-Saharan Africa.

CHAPTER THREE

MATERIALS AND METHODS

3.0 Study design

This is an analytical cross-sectional study conducted among women admitted with pre-eclampsia/eclampsia at KATH from 1st December 2021 to 31st March 2022. This was the most feasible and cost-effective design that could answer the research questions within the time frame.

3.1 Study Site

The study was conducted at the A1 High Dependency Unit (A1HDU) of the Obstetrics and Gynecology Directorate of KATH, Kumasi. This is the designated ward for the management of hypertensive disorders in pregnancy. KATH is a 1300 bed capacity hospital and is the second largest tertiary hospital in Ghana serving as the major referral center for the middle and northern sectors of Ghana. The bed capacity of the Obstetrics and Gynaecology department of the hospital is 160. About 10,000 deliveries are conducted a year with an average admission of 150 patients with hypertensive disorders of pregnancy monthly to its A1HDU. It is in Kumasi, the regional capital of Ashanti.

3.2 Sample size determination

The sample size was calculated using Cochrane's cross-sectional sample size formulae for single estimates:

$n = (z/m)^2 P (1-P)$

Where,

z is the z value (i.e., 1.96 for 95% confidence interval)

m is the margin of error (i.e., 0.05 or ± 2.5%) and

p=17.0% (0.17) is the highest prevalence of preeclampsia amongst the common clinical risk factors assessed below 16 weeks of pregnancy in a 2016 meta-analysis[137].

Therefore, $n= (39.2)^2 \times 0.17(1-0.17)$

$n= 1,536.64 \times 0.1411$

n= 216

Making a 10% allowance for non-response rate or loss of data, 24 is added to the figure giving a sample size of 240. Therefore, n= 240.

3.3 Inclusion criteria

Pre-eclamptic/eclamptic women admitted and delivered or have pregnancy terminated during the study period who gave consent to the study were included.

3.4 Exclusion criteria

The following served as the exclusion criteria:

1. Failure to obtain informed consent.
2. Patients who did not book for antenatal care
3. Women without antenatal care records.

3.5 Pre-testing

Pre-testing was carried out at Agogo Presbyterian Hospital on 20 women admitted and managed for preeclampsia. Issues discovered were age captured in both the sociodemographic as well as the maternal risk factor sections. These were resolved.

3.6 Sampling strategy

Participating patients were recruited consecutively till the total sample size was obtained at A1HDU after they were admitted, delivered/pregnancy terminated, discharged, or died from preeclampsia/eclampsia.

3.7 Data collection procedure

Details of the study were thoroughly explained to them in a language they understood after which signed informed consent was obtained. For patients who died or were not able to provide consent, this was sought from spouses/relatives. All consenting women had their antenatal record booklets, hospital in-patient records and discharge notes reviewed as well as the records of the newborn reviewed at the time of discharge. The pretested structured questionnaire was then administered in vernacular or English confidentially. Information was collected on their socio-demographic characteristics, antenatal characteristics, medical history, family history and their pregnancy outcomes.

3.8 Variables measured

The socio-demographic variables obtained were maternal age, educational level, religion, change of partner and/or new partner within 1 year of pregnancy.

The antenatal variables assessed were gestational age of antenatal booking(calculated using first trimester ultrasound scan), the level of care of the healthcare facility where antenatal booking was done and the healthcare provider that saw her at the booking visit.

Variables assessed from obstetric, medical and family history were nulliparity, multiple pregnancy (documented by ultrasound report), interpregnancy interval 10 years and over, BMI 30 kg/m2 and over (BMI determined by the booking weight and height documented in the antenatal record book), first-degree family history of preeclampsia (self-report of this in mother or sister), personal history of hypertensive disease in a previous pregnancy (previous gestational hypertension, previous preeclampsia as determined by medical records or, in the absence of a record, a self-report of these) and the presence of pre-existing medical conditions like chronic hypertension defined as hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or use of antihypertensive-drug therapy by medical records or self-report before the pregnancy or before 20weeks of gestation), chronic kidney disease (determined by medical records or, in the absence of a record, a self-report of these), autoimmune disease (as determined by medical records or, in the absence of a record, a self-report of these) and diabetes mellitus(type 1 and 2)(as determined by medical records or, in the absence of a record, a self-report of these.

Variables on LDA use assessed were number of women who qualified for LDA, number of women who received LDA, the gestational age LDA was started, gestational age preeclampsia/eclampsia developed (Gestational age was determined by a first trimester ultrasound scan or the earliest scan done if no first trimester scan was available) and compliance to LDA (this was assessed by the 4-item Morisky scale).

The maternal outcomes measures were eclampsia, cerebrovascular accidents, caesarean section delivery, organ dysfunction or mortality. These maternal outcomes were put together as composite adverse maternal outcome with a normal outcome being vaginal delivery without any of these adverse maternal outcomes.

Fetal/Neonatal outcomes measured were intra uterine growth restriction (IUGR), intra-uterine fetal death (IUFD)/termination of pregnancy (TOP), prematurity, neonatal intensive care unit (NICU) admission and neonatal death. These were put together as composite adverse fetal/neonatal outcome with a well-baby who did not have any of these outcomes being considered as the normal outcome.

Diagnosis of eclampsia, CVA in the study were made by specialist obstetrician and above who took care of the woman.

Organ dysfunction was picked when there were haematological complications (thrombocytopenia – platelet count below 150,000/uL, haematological evidence of DIC and haemolysis), elevated liver function test (elevated transaminases e.g., ALT or AST >40IU/L), elevated renal function test (creatinine > 90umol/L; 1mg/dL). All these are part of the routine laboratory investigations requested in the management of preeclampsia.

IUGR diagnosis was made by specialist obstetrician level and above based on obstetric ultrasound centiles of estimated fetal weights and doppler studies done by the department's sonographer. This is routinely done for fetal assessment in the management of preeclampsia.

Intrauterine fetal death was confirmed by ultrasound scan.

Prematurity was defined as delivery of a fetus below 37 weeks.

3.9 Data management and statistical analysis

Study data were entered and cleaned with Microsoft Excel. To ensure data security, collected data was handled by the principal investigator, statistician, and supervisor. The ethics committee can also have access to it at any point in time. Statistical analyses were performed on IBM SPSS Version 26.0 (IBM Corporation, Chicago, IL, USA). Continuous variables were presented as means with standard deviations whilst categorical variables were presented as frequencies with percentages. The Chi square was used to assess associations with P-values less than 0.05 considered statistically significant.

3.10 Ethical considerations

Ethical Clearance was obtained for the study from the KATH Institutional Review Board. Participants recruitment and data collection only commenced after this clearance was given.

The study procedure and expected benefits were clearly explained to all recruited participants in simple language they understood after which a thumb-printed or signed informed consent was obtained voluntarily. Participants confidentiality was always maintained during data collection. Participants had the right to opt out of the study at any time with no consequence on their course of treatment. There were no adverse effects of the study. The study period was from 1st December 2021 to 31st March 2022, a period of over 4 months.

CHAPTER FOUR

RESULTS

4.0 Sociodemographic and antenatal characteristics of study participants

The statistical analysis comprised of a total of 271 pre-eclampsia/eclampsia women who were assessed using maternal history-based risk factors for LDA prophylaxis at the A1HDU of KATH. Age, educational level, religion, change/new partner within a year of pregnancy were the sociodemographic factors of preeclampsia/eclampsia women evaluated (Table 4.1 below). The mean age was 31.4(SD±6.0) years with a minimum age of 18years and a maximum age of 47 years.

Majority of women with preeclampsia were more likely to be Christians (75%) within the ages of 30-35 years (35.8%), more likely to have had at least primary education (43.5%) and unlikely to have a new partner or had changed partner within one year of pregnancy (24.0%).

For participants antenatal characteristics, the mean gestational age at booking was 14.0±6.2 weeks with majority of the women booking for antenatal care at $\leq 16^{th}$ week of gestation (73.1%) mostly at the district hospitals (36.5%) and are more likely to be seen by registered nurses and midwives (51.3%).

The mean gestational age of preeclampsia/eclampsia diagnosis/admission among participants was 33.3±4.5 weeks with about (52.4%) being diagnosed with preeclampsia before 34 weeks.

Table 4.1: Sociodemographic and Antenatal Characteristics of Study Participants

VARIABLE	FREQUENCY (n=271)	PERCENTAGE (%)
Age Group (Years)		
18-24	34	12.5
25-29	69	25.5
30-35	97	35.8
36-40	50	18.5
>40	21	7.1
Mean Age 31.4±6.0		
Educational Level		
No formal education	26	9.6
Primary	118	43.5
Secondary	78	28.8
Tertiary	49	18.1
Religion		
Christian	193	75.1
Muslim	42	16.3
Traditionalist	22	8.6
Change/New partner within 1 Year of Pregnancy		
No	206	76.0
Yes	65	24.0
Gestational Age At Booking		
≤ 16 weeks	198	73.1
> 16 weeks	73	26.9
Mean 14.0±6.2		
Estimated gestational age at Diagnosis/Admission of PE		
< 34 weeks	142	52.4
≥ 34weeks	129	47.6
Mean 33.3±4.5		
Level of care at ANC Booking		
Health Centre	54	19.9
Private clinic	53	19.6
District hospital	99	36.5
Regional hospital	16	5.9
Tertiary hospital	49	18.1
Health Worker Providing Care at Booking		
Community health nurse	14	5.2
Registered midwife/nurse	139	51.3
Doctor	118	43.5

EGA: estimated gestational age; ANC: antenatal care; PE: Preeclampsia

4.1 Maternal risk factors at booking visit among pre-eclampsia/eclampsia women admitted and managed at KATH

Table 4.2 below shows the risk factors used to screen for high-risk women for LDA prophylaxis at booking among pre-eclampsia/eclampsia women. The highest occurring moderate risk factor in the study population was nulliparity (27.3%) with interpregnancy interval of more than 10 years being the least occurring risk factor amongst our preeclampsia women. (2.2%).

The highest occurring major risk factor was women with a history of hypertensive disease in previous pregnancy (37.3%) with autoimmune disease such as antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE) seen in very few of our women (0.7%).

Table 4.2: Maternal risk factors at booking visit among pre-eclampsia/eclampsia women admitted and managed at KATH

VARIABLE	FREQUENCY (n=271)	PERCENTAGE (%)
Moderate Risk Factors		
Nulliparous		
No	197	72.7
Yes	74	27.3
Multiple pregnancy		
No	241	88.9
Yes	30	11.1
Age > 40 years		
No	250	92.3
Yes	21	7.7
Interpregnancy Interval > 10years		
No	265	97.8
Yes	6	2.2
BMI At First Visit > 30kg/m^2		
No	244	90.0
Yes	27	10.0
Family History of PE		
No	241	88.9
Yes	30	11.1
High Risk Factors		
History of Hypertensive Disease In Previous Pregnancy		
No	170	62.7
Yes	101	37.3
Chronic Renal Disease		
No	263	97.0
Yes	8	3.0
Autoimmune Disease (APS, SLE)		
No	269	99.3
Yes	2	0.7
Diabetes Mellitus		
No	259	95.6
Yes	12	4.4
Chronic Hypertension		
No	202	74.8
Yes	68	25.2

BMI; body mass index, PE; pre-eclampsia, APS; antiphospholipid syndrome, SLE; systemic lupus erythematosus

4.2 Proportion of women who qualified for LDA prophylaxis at booking among pre-eclamptic/eclamptic women admitted and managed at KATH

Figure 4.1 below depicts the proportion of women with history-based maternal risk factors at booking warranting LDA prophylaxis among women admitted and managed at KATH for preeclampsia/eclampsia. More than half qualified for LDA (59.0%).

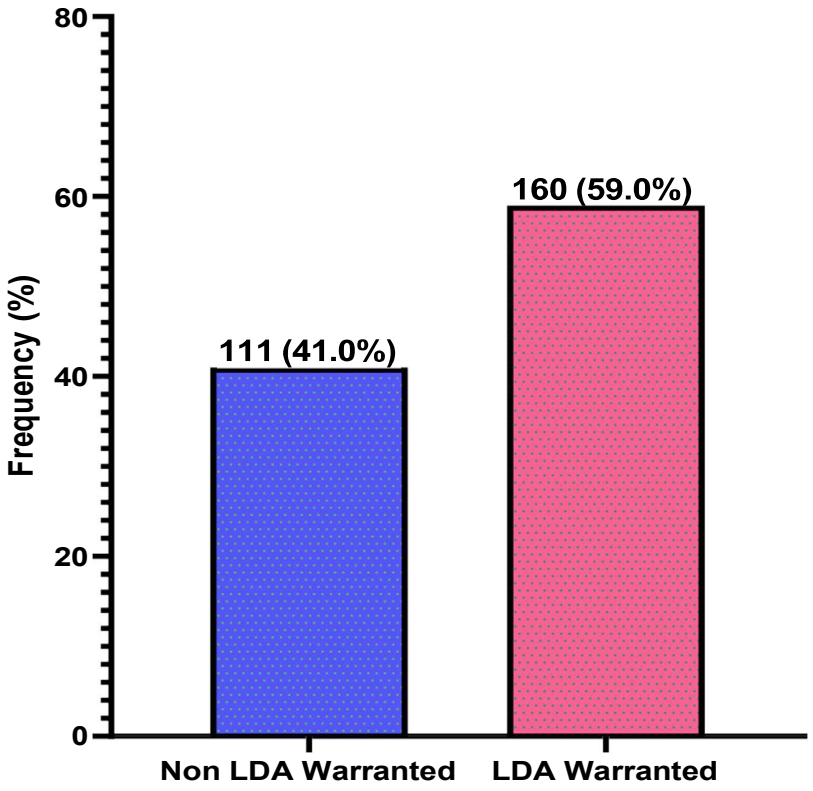


Figure 4.1: Proportion of women with history-based maternal risk factors at booking warranting LDA among pre-eclamptic women admitted and managed at KATH

4.3 Proportion of women who received LDA at booking among pre-eclamptic women admitted and managed at KATH

Of 160 study participants who should have received LDA based on a history-based maternal risk factors at booking, only 43 which is about a quarter received LDA (26.9%) (Figure 4.2).

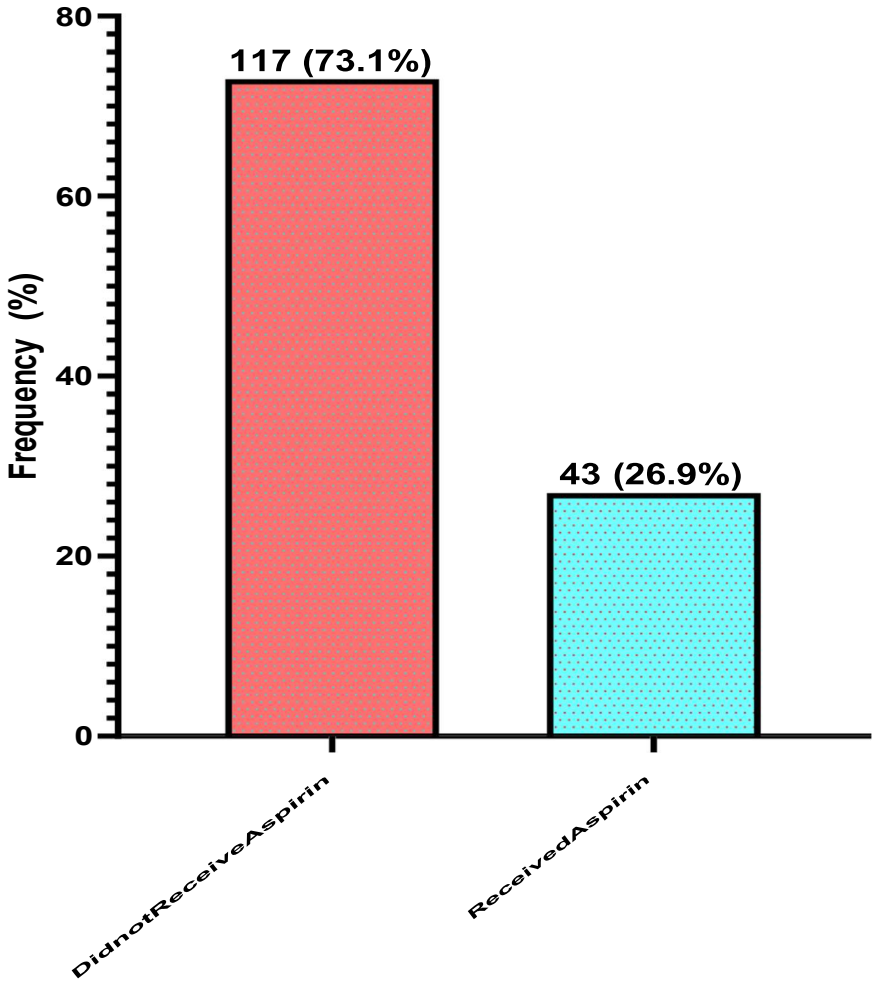


Figure 4.2: Proportion of women warranting LDA who received LDA at KATH.

4.4 Gestational age at LDA initiation among women that warranted and received LDA

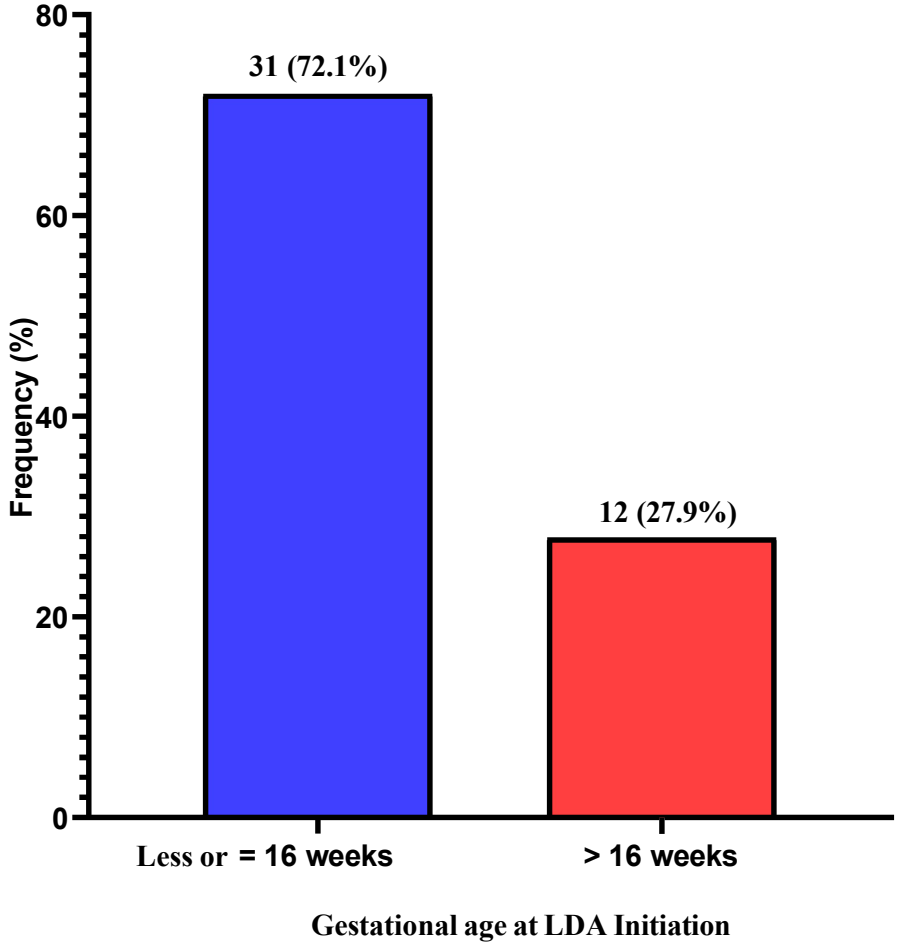


Figure 4.3. Gestational age at LDA initiation among women that received LDA.

Majority of the women that warranted and received LDA started it at gestational ages of ≤ 16 (72.1%) (Figure 4.3).

4.5 Sociodemographic and antenatal factors associated with women who warranted LDA prophylaxis

Table 4.3 below shows sociodemographic and antenatal factors associated with women who warranted LDA prophylaxis and those who did not.

Women who qualified for LDA at booking had 63.7% having preeclampsia below 34 weeks whiles those who did not qualify for LDA had majority being diagnosed or admitted for pre-eclampsia on or after 34 weeks of gestation (64.0%). There was therefore a significant association between estimated gestational age of diagnosis or admission for pre-eclampsia and warranting LDA ($p < 0.0001$).

Also, significant association was shown between level of healthcare facility at antenatal care booking ($p < 0.0001$), health worker providing care at booking ($p < 0.0001$), change of partner or having new partner within one year of pregnancy ($p < 0.0001$) and being LDA warranted.

There was no statistically significant association between being LDA warranted and the sociodemographic factors of age group ($p = 0.6820$), educational level of participants ($p = 0.3490$) and religion ($p = 0.9940$).

Table 4.3: Sociodemographic and Antenatal Factors Associated with women who warranted LDA among Participants

VARIABLE	TOTAL (n=271)	LDA WARRANTED		*p*-value
		NO (n=111)	YES (n=160)	
Educational Level				0.3490
No formal education	26 (9.6)	13 (11.7)	13 (8.1)	
Primary	118 (43.5)	49 (44.1)	69 (43.1)	
Secondary	78 (28.8)	34 (30.6)	44 (27.5)	
Tertiary	49 (18.1)	15 (13.5)	34 (21.3)	
Religion				0.9940
Christian	193 (75.1)	77 (74.8)	116 (75.3)	
Muslim	42 (16.3)	17 (16.5)	25 (16.2)	
Traditionalist	22 (8.6)	9 (8.7)	13 (8.4)	
Change/New Partner In 1 Year Of Pregnancy				**< 0.0001**
No	206 (76.0)	69 (62.2)	137 (85.6)	
Yes	65 (24.0)	42 (37.8)	23 (14.4)	
Gestational Age At Booking				0.3880
≤ 16 weeks	198 (73.1)	78 (70.3)	120 (75.0)	
> 16 weeks	73 (26.9)	33 (29.7)	40 (25.0)	
EGA at Diagnosis/Admission for PE				**< 0.0001**
< 34 weeks	142 (52.4)	71 (64.0)	58 (36.3)	
≥ 34weeks	129 (47.6)	40(36.0)	102 (63.7)	
Level Of ANC At Booking				**< 0.0001**
Health centre	54 (19.9)	33 (29.7)	21 (13.1)	
Private clinic	53 (19.6)	26 (23.4)	27 (16.9)	
District hospital	99 (36.5)	39 (35.1)	60 (37.5)	
Regional hospital	16 (5.9)	6 (5.4)	10 (6.3)	
Tertiary hospital	49 (18.1)	7 (6.3)	42 (26.3)	
Health Worker Providing Care At Booking				**< 0.0001**
Community health nurse	14 (5.2)	13 (11.7)	1 (0.6)	
Registered midwife/nurse	139 (51.3)	60 (54.1)	79 (49.4)	
Doctor	118 (43.5)	38 (34.2)	80 (50.0)	

EGA; estimated gestational age; ANC; antenatal care, PE: Pre-eclampsia

4.6 Sociodemographic and antenatal factors associated with LDA initiation among participants that warranted LDA according to history-based maternal risk factors

Table 4.4 below displays the sociodemographic and antenatal factors associated with receiving or initiation of LDA.

Majority of our women who received LDA booked for antenatal care at the 16th weeks of gestation or below (90.7%). Among those that did not receive LDA, three-quarters booked for antenatal care at the 16th weeks of gestation or below (69.2%). Gestational age at booking was therefore significantly associated with LDA initiation ($p = 0.0050$).

Of the women that received LDA, majority booked for antenatal care at tertiary hospitals (76.7%) with the rest booking outside the tertiary hospital whiles for those who qualified but did not receive LDA largely booked for antenatal care outside the tertiary hospitals in about 92.2%. Level of facility where antenatal care booking was done was found to be significantly associated with LDA initiation ($p < 0.0001$).

On the health worker seeing the woman at the booking visit, women that received LDA had antenatal care from doctors at booking in (93.0%) whereas women that did not receive LDA received antenatal care from registered nurses and midwives at booking (65.0%). A significant association was therefore observed between health worker providing care at booking and receiving LDA prophylaxis ($p < 0.0001$). There was no statistically significant association between age group of participants ($p =0.0580$), educational level ($p = 0.0810$), religion ($p = 0.7870$) and receiving LDA among study participants. Similarly, change or having new partner within one year of pregnancy was proportional among study participants and was not significantly associated with receiving LDA ($p = 0.2680$).

Table 4.4: Sociodemographic and antenatal factors associated with LDA initiation among participants that warranted LDA according to history-based maternal risk factors

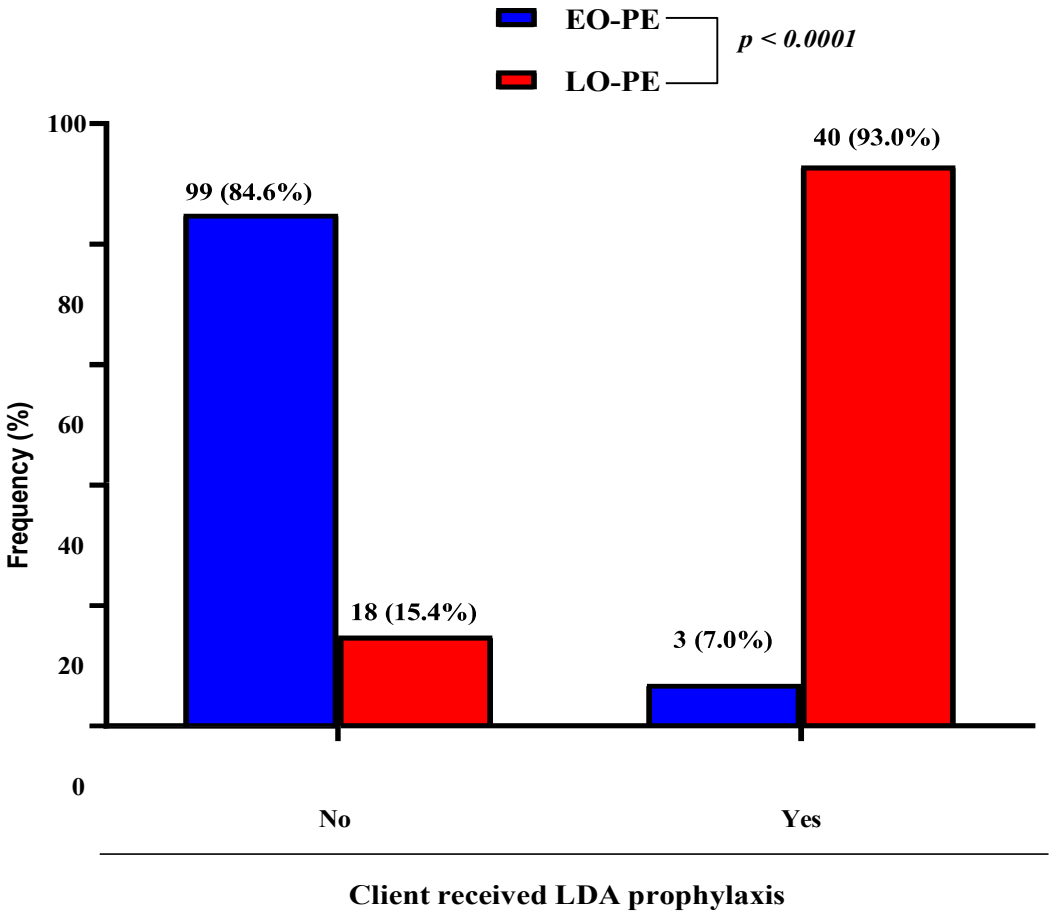
VARIABLE	TOTAL (n=160)	RECEIVED LDA		*p*-value
		NO (n=117)	YES (n=43)	
Educational Level				0.0810
No formal education	13 (8.1)	13 (11.1)	0 (0.0)	
Primary	69 (43.1)	52 (44.4)	17 (39.5)	
Secondary	44 (27.5)	30 (25.6)	14 (32.6)	
Tertiary	34 (21.3)	22 (18.8)	12 (27.9)	
Religion				0.7870
Christian	116 (75.3)	86 (76.8)	30 (71.4)	
Muslim	25 (16.2)	17 (15.2)	8 (19.0)	
Traditionalist	13 (8.4)	9 (8.0)	4 (9.5)	
Change/New Partner In 1 Year Of Pregnancy				0.2680
No	137 (85.6)	98 (83.8)	39 (90.7)	
Yes	23 (14.4)	19 (16.2)	4 (9.3)	
Gestational Age at Booking				**0.0050**
≤ 16 weeks	120 (75.0)	81 (69.2)	39 (90.7)	
> 16 weeks	40 (25.0)	36 (30.8)	4 (9.3)	
Level Of ANC				**< 0.0001**
Health centre	21 (13.1)	21 (17.9)	0 (0.0)	
Private clinic	27 (16.9)	24 (20.5)	3 (7.0)	
District hospital	60 (37.5)	57 (48.7)	3 (7.0)	
Regional hospital	10 (6.3)	6 (5.1)	4 (9.3)	
Tertiary hospital	42 (26.3)	9 (7.7)	33 (76.7)	
Health Worker Providing Care				**< 0.0001**
Community health nurse	1 (0.6)	1 (0.9)	0 (0.0)	
Registered midwife/nurse	79 (49.4)	76 (65.0)	3 (7.0)	
Doctor	80 (50.0)	40 (34.2)	40 (93.0)	

EGA; estimated gestational age; ANC; antenatal care

4.7 Comparison of the gestational age pre-eclampsia/eclampsia was diagnosed (early onset or late onset) in those who warranted and received LDA to those who warranted but did not receive LDA

Majority of the women that received LDA had late onset pre-eclampsia at admission/diagnosis of pre-eclampsia (93.0%) whereas majority of the women that did not receive LDA had early onset preeclampsia (84.6%). LDA initiation was therefore significantly associated with estimated gestational age at pre-eclampsia diagnosis ($p < 0.0001$) (Figure 4.4).

Figure 4.4



EO-PE : Early onset preeclampsia. LO-PE : Late onset preeclampsia

4.8 Compliance to LDA among pre-eclamptic women who received LDA with history-based risks at KATH.

Table 4.5 displays the response to questions on compliance to LDA among pre-eclamptic women who received LDA with history-based risks. Women that received LDA were assessed for compliance to LDA. 7 women did forget to take LDA (16.3%). A few women who received LDA were careless at times about taking their LDA (4.7%), sometimes stop taking LDA when they feel better (7.0%) or sometimes stop taking LDA when they feel worst (7.0%).

Table 4.5. Compliance to LDA among pre-eclamptic women who received LDA with history-based risks at Komfo Anokye Teaching Hospital.

Variable	Frequency (n=43)	Percentage (%)
Did you ever forget to take LDA?		
No	36	83.7
Yes	7	16.3
Are you unconcerned at times about taking your LDA?		
No	41	95.3
Yes	2	4.7
When you feel better do you sometimes stop taking your LDA?		
No	40	93.0
Yes	3	7.0
Sometimes if you feel worse when you take your LDA, do you stop taking it?		
No	40	93.0
Yes	3	7.0

Overall, about two-thirds of the women were complaint to LDA (76.6%) whereas about a quarter of the women were non-compliant to low dose LDA (23.3%) (Figure 4.5).

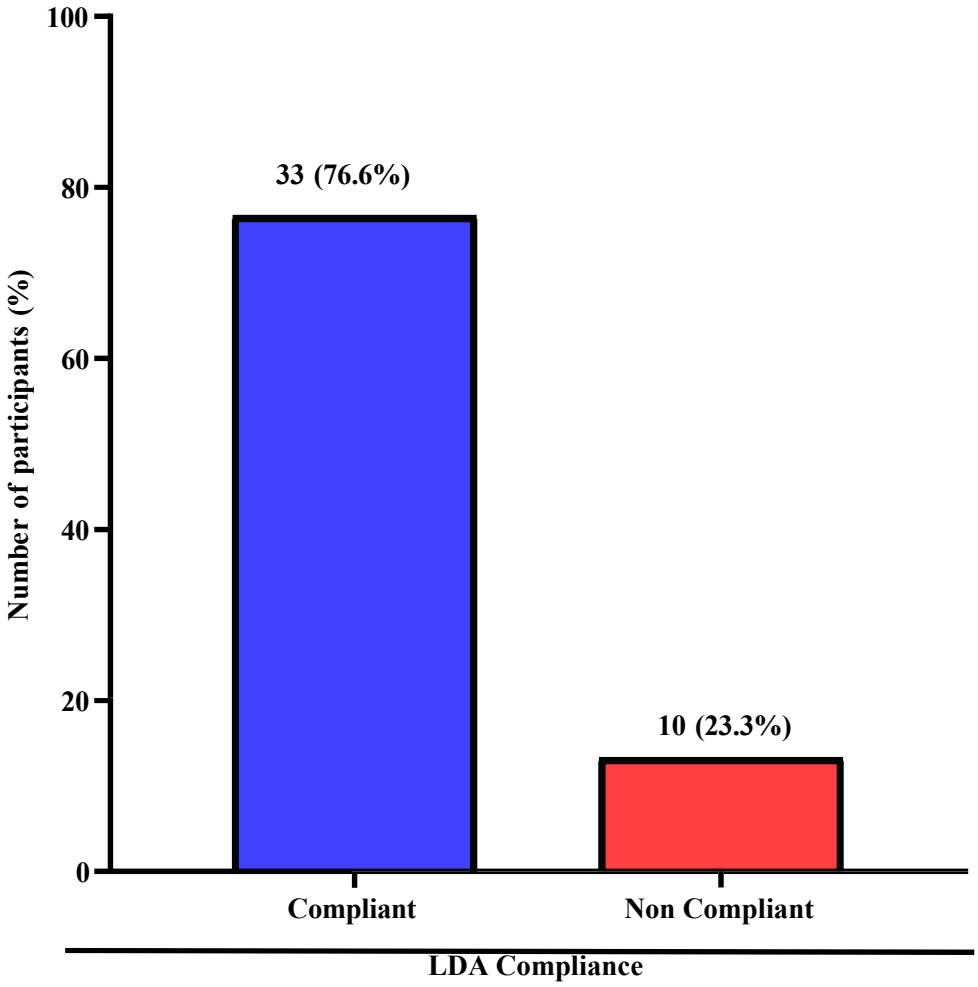


Figure 4.5. Compliance to aspirin among pre-eclamptic women who received LDA with history-based risks at Komfo Anokye Teaching Hospital.

4.9 Maternal and Fetal/Neonatal Outcomes among pre-eclampsia/eclampsia women with history-based risks admitted and managed at KATH.

On the maternal outcomes looked for in the study, majority of the women had caesarean section (69.4%). Organ dysfunction occurred in (48.8%) of the women, eclampsia (8.8%), cerebrovascular accident CVA (1.9%) and 1.9% resulted in a maternal mortality unfortunately.

The common fetal/ neonatal outcomes seen in this study were prematurity occurring in (55.6%) of neonates, followed by NICU admissions (50.0%), IUFD/TOP (19.4%), IUGR (10.6%) and neonatal death (8.1%).

Table 4.7 displays the maternal and fetal/ neonatal outcomes recorded among participants warranting LDA.

Table 4.6. Maternal and Fetal/ Neonatal Outcomes among pre-eclamptic women history-based risks admitted and managed at KATH.

Variable	Frequency (n=160)	Percentage (%)
Maternal outcomes		
Vaginal delivery	46	28.7
Caesarean Section	111	69.4
Organ dysfunction	78	48.8
Eclampsia	14	8.8
CVA	3	1.9
Mortality	3	1.9
Fetal/ Neonatal Outcomes		
Well baby	48	30
IUGR	17	10.6
IUFD/TOP	31	19.4
Prematurity	89	55.6
NICU admission	80	50
Neonatal death	13	8.1

CVA: Cerebrovascular accident; IUGR: Intrauterine growth restriction; IUFD: Intrauterine fetal death; TOP: Termination of pregnancy; NICU: Neonatal intensive care unit. Some women had more than one outcome.

4.10 Association between LDA prophylaxis and adverse maternal and fetal/ neonatal Outcomes among pre-eclamptic participants warranting LDA

Table 4.7 below shows a Chi square analysis of the associations between LDA prophylaxis and adverse maternal and fetal/neonatal outcomes. Results showed a significant association between LDA prophylaxis and organ dysfunction (p = 0.001). Of the women that took LDA prophylaxis, only 20.9% developed organ dysfunction with the large majority not developing organ dysfunction. There was organ dysfunction developing in 58.97% of the women who did not take LDA prophylaxis.

With eclampsia there was no significant association with LDA prophylaxis with our confidence interval set at 95%, however there was an association if the confidence interval was increased to 90% (p = 0.081). 2.33% of the women who received LDA prophylaxis had eclampsia whiles 11.1% of those who did not had eclampsia.

There was no statistical significance observed between LDA prophylaxis and caesarean section (p = 0.273), CVA (p = 0.289) and maternal mortality (p = 0.289).

Putting all the adverse maternal outcomes together into a composite adverse maternal outcome, there was no significant association between the composite adverse maternal outcomes and LDA prophylaxis (p = 0.152).

Table 4.7 Association between adverse maternal outcomes and LDA prophylaxis

Variable	Received Aspirin		Chi Square	P-value
	No (n %)	*Yes (n %)*		
Caesarean section			1.200	0.273
No	33 (28.21)	16 (37.21)		
Yes	84 (71.79)	27 (62.79)		
Organ dysfunction			18.216	**0.001**
No	48 (41.03)	34 (79.07)		
Yes	69 (58.97)	9 (20.93)		
Eclampsia			3.040	0.081
No	104 (88.89)	42 (97.67)		
Yes	13 (11.11)	1 (2.33)		
CVA			1.124	0.289
No	114 (97.44)	43 (100)		
Yes	3 (2.56)	0		
Mortality			1.124	0.289
No	114 (97.44)	43 (100)		
Yes	3 (2.56)	0		
Combine adverse maternal outcome			2.054	0.152
No	30 (25.64)	16 (37.21)		
Yes	87 (74.36)	27 (62.79)		

Table 4.8 below show the fetal/neonatal outcomes and LDA prophylaxis. There was significant association between LDA prophylaxis and IUGR (p = 0.008). None of the women who took LDA prophylaxis had IUGR whiles 14.53% of those who did not take LDA prophylaxis developed IUGR.

A significant association was also observed between LDA prophylaxis and IUFD/TOP (p = 0.001). IUGR/TOP was seen in only 2.33% of the women who took LDA prophylaxis whiles 25.65% was observed in those who did not take LDA prophylaxis.

There was also a significant association observed between LDA prophylaxis and prematurity (p = 0.001). Prematurity occurred in 30.23% of the women who took LDA prophylaxis whiles it was seen in 64.96% of the women who did not receive LDA prophylaxis.

For the admission into the NICU, 23.26% of babies of mothers who received LDA prophylaxis were admitted whiles 59.83% of babies of mothers who did not receive LDA prophylaxis were admitted to the NICU. LDA prophylaxis was therefore significantly associated with NICU admission (p = 0.001).

There was no neonatal death observed in mothers who took LDA prophylaxis whiles 11.11% of neonates whose mothers did not receive LDA prophylaxis died. LDA prophylaxis was shown to be significantly associated with neonatal death (p = 0.023).

Putting all the adverse fetal/neonatal outcomes together into a composite adverse fetal/neonatal outcome, there was a significant association between the composite adverse fetal/neonatal outcome and LDA prophylaxis (p = 0.001). No adverse fetal/neonatal outcome was observed in 76.74% of mothers who took LDA prophylaxis whiles this did not occur in just 12.82% of mothers who did not take LDA prophylaxis.

Table 4.8 Association between adverse fetal/neonatal outcomes and LDA prophylaxis

Variable	Received Aspirin		Chi Square	P-value
	No (n %)	*Yes (n %)*		
IUGR			6.991	**0.008**
No	100 (85.47)	43 (100)		
Yes	17 (14.53)	0		
IUFD/TOP			10.942	**0.001**
No	87 (74.36)	42 (97.67)		
Yes	30 (25.64)	1 (2.33)		
Prematurity			15.360	**0.001**
No	41 (35.04)	30 (69.77)		
Yes	76 (64.96)	13 (30.23)		
NICU			16.824	**0.001**
No	47 (40.17)	33 (76.74)		
Yes	70 (59.83)	10 (23.26)		
Neonatal mortality			5.200	**0.023**
No	104 (88.89)	43 (100)		
Yes	13 (11.11)	0		
Adverse neonatal outcome			61.184	**0.001**
No	15 (12.82)	33 (76.74)		
Yes	102 (87.18)	10 (23.26)		

CHAPTER FIVE

DISCUSSION

5.0 Sociodemographic characteristics

Over 60% of the preeclampsia/eclampsia patients were over 30 years and above. This finding is similar to what Adu-Bonsaffoh and others found in their study on prevalence of hypertensive disorders in Korle-Bu Teaching hospital, Accra[138]. In another study in Korle-Bu Teaching hospital, Accra, Ghana the median age of postpartum women treated for preeclampsia and eclampsia was 32 years (range 18–47)[139]. Results from this study indicates that older age women have a higher risk of developing preeclampsia/eclampsia than younger women. This is supported by several well powered studies. For an example, a case-control study done in Ethiopia reported that pregnant women aged 30 years or older were seven times more likely to develop preeclampsia/eclampsia than younger women[140]. The older the woman is the more likely she may have additional risk factors, such as chronic hypertension, diabetes mellitus, obesity that will predispose them to developing preeclampsia. It's also likely old maternal age may affect the haemodynamic adaption that occurs in pregnancy therefore predisposing the ageing woman to developing the hypertensive state in pregnancy. The increasing trend of rising maternal age due to societal changes thus will impact negatively on the incidence of preeclampsia. A systematic review however had not shown an association between adolescence and risk for preeclampsia[88] .

On the educational status of the women admitted and managed for preeclampsia /eclampsia during the study period, (43.5%) had primary education followed by secondary education (28.8%), then tertiary education (18.1%). A few participants had no formal education (9.6%). This means more of the woman (53%) with preeclampsia/eclampsia had low levels of education in the form of primary education or no formal education at all whiles about 46% had higher education in the form of secondary education and tertiary education. A study reported that women who only have a low level of education were 2.6 times more likely to develop hypertensive disease of pregnancy compared to women who have a higher or above education level (AOR: 2.64; 95% CI: 1.10, 6.32)[64]. In a meta-analysis, there was a significant association between women's level of education and hypertensive disease of pregnancy. The odds of women who had a lower education level were 1.65 times more likely to develop hypertensive disease of pregnancy compared to women who had a higher education level (OR: 1.65; 95% CI: 1.17, 2.13)[66]. The possible explanation may be that the more educated a woman is the more

likely she is to have an increased health seeking behaviour due to adequate knowledge. Highly educated mothers are likely to be aware of pregnancy related complications hence seek help early. These women are also more likely to make decisions on their own hence more likely to meet her reproductive need when she wants. A study in a Brazilian population reported low degree of schooling and socioeconomic status to be factors that hinder access to prenatal care and proposed investments in public health intended to improve the prenatal access, mainly in the group of women with low schooling and socioeconomic status as a way of decreasing the levels of hypertensive disorders of pregnancy[141].

Majority of participants were Christians (75.1%) with the remaining being Muslims (16.3%) and Traditionalists (8.6%). Dassah et al in their study on maternal and perinatal outcomes among women with hypertensive disorders in pregnancy in Kumasi, Ghana which was done in the same hospital as this study similarly had majority of participants being Christians with Muslims in the minority[6]. This largely reflects the religious beliefs of the area which is dominated by Christians.

About a quarter of women with preeclampsia had changed or had new partner within one year of pregnancy (24.0%). However, of the women who had changed partners or had a new partner within a year, 42% were not considered as high risk at booking but went on to develop preeclampsia. These women were not considered as high risk because change in partner and/or new partner within a year of pregnancy is currently not one of the risk factors used in screening for high-risk women though there is evidence for increased preeclampsia in women who have changed partners and/or have new partners. Obed et al in their study in Ghana had a similar rate of (24.9%) of women who had changed their male partners before the pregnancy following the one complicated by eclampsia and further reported that the recurrence rate of preeclampsia among the women who had changed their male partners was more significant than those who had not[142]. This gives credence to the immunological theory and the new paternal contribution to the aetiology of the disease. There is an association of hypertensive states in pregnancy and duration of sexual co-habitation before the first conception. Male ejaculate is said to help protect a woman if she has been repeatedly exposed to it. A study reported new partner was seen in (19.1%) of cases and was found to be statistically significant ($p < 0.01$)[143]. Similarly a Nigerian study observed change of partner in 34 (74%) out of 46 multiparous patients with eclampsia[144]. The` incidence of preeclampsia was reported as 11.9% among primigravidae, 4% among multigravida without a change of paternity, and 24% among multigravida with a new

partner with the report further stating that these numbers depend on the duration of sexual cohabitation before conception[145]. The risk of pregnancy-induced hypertension was increased when conception is within 12 months of sexual cohabitation: 40% in 0 to 4 months, 23% in 5 to 8 months, 15% in 9 to 12 months, and 5% after 12 months[145]. In a further study by same authors it was observed that women with preeclampsia and eclampsia had shorter sexual cohabitation time (9.5 months) compared to those of unaffected women (26.3 months)[146]. Seminal antigens elicit an immune response and when this occurs over a long period leads to hypo responsiveness in the mother and a subsequent maternal-fetal tolerance which is associated with decreased preeclampsia risk. More studies are needed to determine if change in partner and/or new partner within a year of conception should be incorporated into the moderate risk factors for screening for high-risk women for LDA prophylaxis.

5.1 History-based maternal risk factors at booking visit among pre-eclampsia/eclampsia women admitted and managed at KATH

The moderate risk factors associated with preeclampsia/eclampsia that were present during the booking visit of women admitted had nulliparity being the most common moderate risk factor at (27.3%). This was similar to the Nigerian study that reported nulliparous women with the highest incidence of hypertensive disease of pregnancy at 27.7%[51]. Likewise, the Australian population study of women who developed preeclampsia reported 29.2% of these women to be nulliparous[52]. Nulliparity is thus a common risk factor at booking in women who will eventually go on to develop preeclampsia amongst other risk factors. Why nulliparity is consistently found to be the most prevalent moderate risk factor for preeclampsia is unclear[50]. However, nulliparous women are more likely to have a reduced exposure to paternal antigens and so may not be sensitized enough prior to pregnancy hence have an increased risk of developing of preeclampsia. This theory is backed by observation from epidemiological data that preeclampsia risk is reduced with increased sexual activity before pregnancy and protection from preeclampsia in subsequent pregnancies is either reduced or eliminated if there is a change in paternity, or continuous use of barrier methods of contraception.

So, every woman in her first pregnancy is at risk of preeclampsia especially if pregnancy occurred within a year of sexual cohabitation. Therefore, special attention should be given to primipara women during antenatal care visits especially in the presence of other risk factors of preeclampsia.

In this study, multiple pregnancy was found in (11.1%) of the study population making it the second most common of the moderate risk factors in our women with preeclampsia. Multiple pregnancy similarly was found to be a very common risk factor for preeclampsia in other studies such as the Nigerian study[51] and other case reports similarly showing multiple pregnancy to be a common risk factor for preeclampsia[53]. Preeclampsia is 2 to 3 times more common in twin pregnancies compared to singleton pregnancies, has early onset, more severe and rapidly progressive[147]. The rising rates of multiple pregnancy because of the widespread use of assisted reproductive technology may explain the common occurrence of multiple pregnancy as a risk factor in the study participants. The increased risk of preeclampsia in multiple pregnancy is said to be due to the relatively large placental mass releasing increased levels of antiangiogenic factors such as sFlt1[148].

In this study, 11.1% of the women with preeclampsia/eclampsia had a maternal first-degree family history (mother and sister) of pre-eclampsia or other hypertensive state in pregnancy. The presence of this risk factor in our women is consistent with other studies in Ghana that reported family history to be common risk factor for preeclampsia/eclampsia[54]. 9.7% of women with early onset preeclampsia was reported to have a maternal family history of preeclampsia[62] which is almost similar to the finding of this study. The Brazil study reported 17% women with hypertensive disease in pregnancy had family history (mother and/or sister) of hypertensive state in pregnancy. This gives support to the heritable mechanisms of preeclampsia/eclampsia. A limitation here is a potential recall bias since the family history of preeclampsia/eclampsia was based upon self-report that was not verified with medical records.

Obesity was found to occur in 10% of women with preeclampsia/eclampsia admitted to KATH. One of the Ghana studies reported high BMI as an independent associated factor for hypertensive state during pregnancy in both urban and rural pregnant women[54]. This relationship was found to persist in studies that excluded patients with chronic hypertension, diabetes mellitus, multiple gestations, or after adjustment for other confounders. In the United States, obesity appears to be the leading attributable risk for preeclampsia present in 30% of cases[149]. This is way higher than the proportion of women with obesity found in this study (10%). The likely explanation to this is the large proportion of obesity in developed countries like the United States compared to that of Ghana[150]. To explain this causal relationship, obese women are more likely to have higher amounts of serum triglycerides and lipoproteins which

have been suggested to promote oxidative stress, caused by either ischaemia-reperfusion mechanism or activated neutrophils and lead to endothelial cell dysfunction.

Maternal age of more than 40 years was seen in (7.7%) of the study population. The study of obstetrical outcomes in women over 40 years of age reported (4.6 %) of the women with preeclampsia were ≥ 40 years old at the time of delivery[58]. This just like results of this study shows women over the age of 40 years are getting pregnant and since pregnancy in this age group have been shown to be at an increased risk of preeclampsia these women should be looked for and appropriately managed. Older patients are generally more likely to be hypertensive, diabetic, obese, to have had preeclampsia in a previous pregnancy which are all additional risk factors that predispose them to developing preeclampsia. The proportion of women getting pregnant after 40 years will continue to rise with its associated increased risk of preeclampsia. Many women are choosing to pursue higher levels of education and higher levels of work. These high earning jobs may come with fixed-term contracts for entry with a lack of flexible working hours making it difficult for these women to balance work and childbearing. The availability of effective birth control at family planning services and the advancement of assisted reproduction technologies for infertility treatment is increasing the number of women getting pregnant after 40 years. It is therefore now not uncommon to find pregnant women after 40 years[151] as seen in about 7.7% of the women with preeclampsia in this study.

A few women with preeclampsia had interpregnancy interval of more than 10 years (2.2%).

On the major risk factors, the commonest risk factor amongst the study participants was hypertensive disease in previous pregnancy (37.3%). The study on risk factors associated with preeclampsia in Ethiopia similarly had the commonest risk factor being a previous hypertensive state in pregnancy which occurred in about half (44.6%) of cases[64]. The severity and the gestational age preeclampsia occurred in pregnancy are strongly linked with this risk. The highest risk of recurrence in a subsequent pregnancy is seen in severe preeclampsia occurring below 34 weeks with recurrence risk of 25 to 65% reported[152 153]. In contrast relatively lower rates of 5-7% risk of recurrence was seen in subsequent pregnancies in women who develop preeclampsia without severe features after 34 weeks in their first pregnancy[154]. Patients who had a normal blood pressure in first pregnancy develop preeclampsia in less than 1 percent of second pregnancies in same study.

Chronic hypertension also seemed to be a very common risk factor at booking in the woman admitted for preeclampsia with a frequency of (25.2%). A Nigerian study on factors associated with severe preeclampsia and eclampsia also reported a similar frequency of 26% of the women with preeclampsia being chronic hypertensives[67].

Diabetes mellitus was present in (4.4%) of the study participants. Diabetes mellitus was similarly noted to be present in 4.2% of women who had preeclampsia in an Australian study population[52]. This association may be due to factors, such as underlying renal or vascular disease, obesity, high plasma insulin levels/insulin resistance, and abnormal lipid metabolism.

Chronic renal disease was found in just (3.0%) of our women with preeclampsia/eclampsia. This was one of the least occurring major risk factors largely due to the very low incidence of chronic kidney disease in reproductive age women.

The least occurring major risk factor amongst the women with preeclampsia was autoimmune disease of antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE) (0.7%). These are chronic conditions that were less frequently diagnosed in our setting until recently due to the limited laboratory facilities that offer the service and the cost of these investigations.

The incidence of preeclampsia is estimated to be at least 8 percent for pregnant women with any one of these high risk factors[81]. This means that public health strategies used in preventing these diseases will be also helpful in reducing the incidence preeclampsia**.**

This history based maternal risk factors contribute in different proportions to the development of preeclampsia/eclampsia in terms of absolute rate and relative risk of pre-eclampsia. The number needed for LDA prophylaxis to prevent one case of preeclampsia depends on the individual risk factor identified at screening. It was found that the number needed for LDA prophylaxis to prevent one case of preeclampsia was below 250 when antiphospholipid antibody syndrome, chronic hypertension, history of pre-eclampsia, pregestational diabetes mellitus and pre-pregnancy BMI >30 were the identified risk factors whiles the remaining risk factors had thresholds above 250 [50].

5.2 Proportion of women with history-based maternal risk factors at booking warranting LDA prophylaxis among pre-eclamptic/eclamptic women admitted and managed at KATH

More than half (59.0%) of the women admitted for preeclampsia had risk factors that warranted LDA prophylaxis. A Canadian study reported a lower proportion of 21% (1727) of women screened as high risk for preeclampsia out of a total of 8176 women having prenatal care between 2012 to 2015[72]. A prospective cohort study in the Netherland on LDA usage among women with an increased preeclampsia risk reported 306 out of 865 representing 35.4% of the women had a predicted increased preeclampsia risk[71]. These proportions seem lower compared to the proportion in this study. However, whiles the proportion of women with risk factors among women who had preeclampsia/eclampsia was assessed in this study, the Canadian and Netherland studies assessed the proportion of high-risk women among all the women reporting for delivery and not just those who had preeclampsia/eclampsia. Knowing 5.2%-8.2% of pregnancies are complicated by preeclampsia world wide[1], then by extrapolation their proportions could even be higher. Nana Ama Ankumah, MD, a maternal-fetal medicine specialist with McGovern Medical School at The University of Texas Health Science Centre at Houston in a report said, the risk factors for preeclampsia are "extremely common," ranging from high risk factors such as diabetes, chronic hypertension, and autoimmune diseases, to moderate risk factors such as being over the age of 35, obesity, and low socioeconomic status.

It is therefore imperative that the risk factors for preeclampsia are common in our women who will subsequently go on to develop preeclampsia as shown by more than half the mothers with preeclampsia/eclampsia having risk factors that warranted LDA at booking in this study.

5.3 Proportion of women warranting LDA at booking who received LDA among pre-eclamptic women admitted and managed at KATH

Only a quarter (26.9%) of study participants who qualified for LDA prophylaxis received LDA for preeclampsia prevention (Figure 4.2) indicating a very low usage rate for this cheap evidence-based intervention for preeclampsia prevention. This low usage rate was similarly reported in a study in Nigeria that showed the administration of prophylactic LDA in the management of preeclampsia/eclampsia to be low with more than 80% of healthcare providers not routinely assessing for risk factors for LDA prophylaxis[31]. A usage rate of 25% was similarly reported in a prospective cohort study on the rate of LDA usage among high risk

women in Netherlands[71]. The study on clinical and geographical variation in prophylactic and therapeutic treatments for pre-eclampsia in the United Kingdom similarly reported that of the women with known risk factors at trial entry, 24% (569/2399) received LDA[73]. This same study went on to report LDA usage rate based on the locations of these pregnant women to range from as low as 8% to a high of 49%. There is therefore a general underutilization of prophylactic LDA in the management of preeclampsia/eclampsia in high-risk women.

It's obvious from this study that whiles the risk factors for developing preeclampsia/eclampsia are common in our women at the antenatal care booking visit, very few of these women received LDA for the prevention of early onset preeclampsia. This clearly represents a poor-quality control measure of the management of preeclampsia/eclampsia at KATH and its referring hospitals.

The question then is, why is it that despite all the evidence for prophylactic LDA's benefit and safety, over 50% of eligible pregnant women did not start LDA? A possible reason for this underutilization of LDA prophylaxis for preeclampsia could be that care providers at antenatal care booking visits are not screening pregnant women to identify those who are high risk as evidenced by the Nigerian study reporting only 15 percent of healthcare providers at antenatal care look for risk factors related to preeclampsia during antenatal care consultations[31]. It could also be that healthcare providers at antenatal care may possibly not be screening for these high-risk women because they may not be aware of this cheap evidence based preventive measure for preeclampsia. In the same Nigerian study antenatal care providers were asked whether they were aware of, or ever used, prophylactic LDA, to prevent preeclampsia among pregnant women at risk, only 14% of providers were aware of prophylactic LDA to prevent preeclampsia[31]. These may explain the underutilization of prophylactic LDA in preeclampsia management.

Antenatal care providers at the booking visit are required to spend time and effort to identify high risk women for LDA initiation to decrease the morbidity and mortality associated with preeclampsia/eclampsia. This can significantly be improved if antenatal care providers are educated on screening for LDA prophylaxis and a checklist for this screening incorporated into the antenatal protocols to ensure that all women booking for antenatal are screened. Identified high risk women should then receive a clear communication of preeclampsia risk and adequate counselling regarding benefits and risks of LDA. This may positively influence uptake rates of LDA for prevention of early onset preeclampsia

LDA usage was based upon self-report which were not sometimes easily verified reliably with medical records therefore the possibility of a recall bias. It is however assumed that women reporting non-usage are likely to be telling the truth.

The data sampling of this study only focused on whether LDA was given based on existing risk factors. In those who warranted but did not receive LDA, it was not determined whether LDA was discussed and not started or not started because it was not discussed at all. Future qualitative research among both healthcare professionals and pregnant women, may improve our insight and understanding regarding the key elements at play in the decisional process regarding preventive LDA usage.

5.4 Sociodemographic and antenatal factors associated with LDA initiation among participants that warranted LDA according to history-based maternal risk factors

Majority of the women who received LDA booked for antenatal care at $\leq 16^{th}$ weeks of gestation (90.7%). Gestational age at booking is significantly associated with LDA initiation ($p = 0.0050$) among high-risk women who warrants LDA. What this means is that the earlier a high-risk pregnant woman books for antenatal care especially below 16 weeks the more likely that she may be put on LDA. This association may likely be explained by the knowledge of the convincing evidence that the optimal effect of LDA in reducing preterm preeclampsia is achieved with commencement of therapy prior to 16 weeks of gestation. It is therefore likely that the few providers who gave LDA in our study were likely basing the initiation of LDA prophylaxis on the recommendation of initiating therapy before 16 weeks. Preterm preeclampsia may still be reduced when LDA is initiated after 16 weeks of gestation though not optimal. Generally, because LDA has a good safety profile, high-risk women who present for antenatal care after 16 weeks of gestation may still benefit from prophylaxis and so should be counselled and given LDA. ACOG and the SMFM based on new evidence from additional trials recommend LDA prophylaxis for women at high risk of preeclampsia to be initiated between 12 and 28 weeks of gestation (optimally before 16 weeks) and continued daily until delivery[79].

Booking for antenatal care at a higher level of care, such as the tertiary hospital is significantly associated with LDA use in high-risk women for prevention of preeclampsia ($p < 0.0001$). A large majority of women who received LDA prophylaxis booked for antenatal care at tertiary hospitals (76.7%). This was similarly seen in the Nigerian study which showed high risk

women booking for antenatal care at the primary care level were the least likely to receive LDA with women booking at higher levels of care at secondary care and tertiary care more likely to receive LDA prophylaxis[31].

On healthcare worker providing care and LDA initiation, a significant association was observed between health worker providing care at booking and a high-risk woman receiving LDA ($p <$ 0.0001). High-risk women that qualified for and received LDA were those who were largely seen at antenatal care booking by a doctor (93.0%). Those who qualified for LDA but did not receive were largely seen at antenatal care booking by non-doctors (65.0%). This finding was also consistent with findings in the Nigerian study that reported that medical practitioners (obstetricians and gynecologists) were more likely to initiate LDA prophylaxis for high-risk women in pregnancy for preeclampsia prevention compared to midwives/nurses and years of experience of working in a maternity unit was associated with prescription rates[31]. Same study also reported that training in maternal and child health (MCH) had a positive effect on the provision of LDA prophylaxis. LDA usage in the Netherlands study was higher for women receiving risk-based care which is usually done in higher levels of care than usual care usually done at lower levels of care (29.4% vs 1.5%, odds ratio 19.1, 95% confidence interval 11.2-32.5)[71].

In our current antenatal care model, booking visit is mostly done by midwives, nurses, or community health nurses with low-risk women for adverse pregnancy outcomes remaining primarily under the supervision of autonomous midwives and nurses**.** It is therefore not surprising that most women especially those booking at the primary care levels are not routinely assessed for risk factors, let alone deploy this effective preventive measure.

There is no protocol currently in our antenatal care protocols on screening for LDA prophylaxis for preeclampsia prevention, although some obstetric healthcare professionals are familiar with guidelines especially obstetricians. Screening for high-risk pregnant women for LDA currently depends mainly on the discretion of individual healthcare professional and therefore only those who have knowledge on this preventive strategy and remember to do it will offer it. This may explain the higher rates of screening for LDA initiation that occurred at the tertiary hospital where antenatal care is provided by providers with a higher knowledge of screening for LDA prophylaxis in the prevention of preeclampsia. Antenatal care in a tertiary hospital such as KATH is largely by resident obstetrician gynaecologist, specialist obstetrician gynaecologist

and maternal fetal medicine specialist. The low rate of LDA usage mainly reflect a lack of a well-structured maternal risk-based-care models as done elsewhere.

District hospitals, regional hospitals, private hospitals and health centers mostly have non-obstetrician medical practitioners, midwives/nurses and community health nurses providing antenatal care especially the very important booking visit. The knowledge of screening for preeclampsia prevention may not be as high in this group as that of obstetricians which explains the very low screening for prophylactic LDA outside the teaching hospitals. This also highlights the unequal distribution of specialist obstetricians, maternal fetal medicine specialist between the tertiary hospitals and the other levels of care.

There was no statistically significant association between age group of participants (p =0.0580), educational level (p = 0.0810), religion (p = 0.7870) and a high-risk woman receiving LDA among study participants. This is to suggest that high risk women receiving prophylactic LDA largely depends on the health worker providing antenatal care at the booking visit. Therefore, incorporating a screening protocol in the form of a checklist into our current antenatal protocols that will compel all antenatal care providers in all levels of care at the booking visit to screen for high-risk women and not leave it to the discretion of the provider will ensure all women are screened. This will improve utilization of LDA in reducing the morbidity and mortality associated with early onset preeclampsia. Once this is to be done then LDA should be made available at antenatal booking clinics especially at the primary and secondary care level to enable non doctors providing antenatal care to prescribe them for women who need them after the screening.

From the measures used in the assessment of the quality of care in the preventive management of preeclampsia such as evidence of local arrangements to ensure that pregnant women have their risk factors for pre-eclampsia identified and recorded at the booking appointment, proportion of pregnant women who have their risk factors for pre-eclampsia identified and recorded at the booking appointment, evidence of local arrangements to ensure that pregnant women at increased risk of pre-eclampsia at the booking appointment are offered a prescription of 150 mg of LDA (unless contraindicated) to take daily from 12 to 16 weeks until birth, proportion of pregnant women at increased risk of pre-eclampsia at the booking appointment who are offered a prescription of 150 mg of LDA (unless contraindicated) to take daily from 12 weeks until birth and the incidence of pre-eclampsia in women at increased risk of developing pre-eclampsia it's imperative from the findings of this study that the quality of care

in the preventive management of preeclampsia/eclampsia is very poor in KATH and its referring facilities.

5.5 Comparison of the gestational ages' pre-eclampsia/eclampsia was diagnosed (early onset or late onset) in those who warranted and received LDA to those who warranted but did not receive LDA

LDA initiation was significantly associated with estimated gestational age of pre-eclampsia/eclampsia diagnosis ($p < 0.0001$) (Figure 4.4) as majority of the women that warranted and received LDA had late onset (≥34weeks of pregnancy) pre-eclampsia (93.0%) with most women (84.6%) that warranted but did not receive LDA developing early onset preeclampsia (< 34 weeks of pregnancy). This study finding support the general evidence that LDA given to high-risk patients identified in the first trimester, reduce the occurrence of early-onset preeclampsia such as the findings of Askie et al who reported use of LDA to be associated with a significant reduction in the prevalence of both preeclampsia and delivery before 34 weeks' gestation in high risk women given LDA before 16 weeks[76] as well as the ASPIRIN study[75] which similarly reported that LDA could reduce the incidence of hypertensive disorders of pregnancy before 34 weeks of gestation .

Another study also reported preterm births before 32 weeks to be decreased by approximately 60 percent (1.2 versus 2.9 percent, odds ratio [OR] 0.42, 95% CI 0.19-0.93) in high risk women who took LDA[78]. Roberge et al in their systematic review and meta-analysis on early administration of LDA for the prevention of preterm and term preeclampsia concluded that LDA administrated at or before 16 weeks of gestation reduces the risk of preterm but not term preeclampsia[155]. Several other studies seems to support the effect of LDA in high risk women in reducing early onset preeclampsia and its associated morbidities such as prematurity, low birth weights, prolonged stay at NICU, perinatal mortality[135 77 46].

This finding is reassuring as early onset preeclampsia is more severe than late onset preeclampsia and is associated with a higher incidence of adverse maternal and perinatal consequences[156]. The likely explanation to this finding is based on the pathophysiology of preeclampsia and the well documented effect of LDA in generally preventing abnormal placentation when given early in pregnancy. The effect is a reduction in the overall risk of the preeclampsia and a shift from early-onset severe disease requiring preterm delivery with its associated maternal and fetal/neonatal morbidity to a milder late onset disease.

This calls for greater efforts in coming up with effective screening strategies to identify high risk women for LDA prophylaxis to decrease the incidence of early onset preeclampsia with its associated morbidity.

5.6 Maternal outcomes and Fetal/ Neonatal Outcomes among pre-eclamptic with history-based risks admitted and managed at KATH.

LDA prophylaxis is shown in this study to be significantly associated with a reduction in the incidence of IUGR, IUFD/TOP, prematurity, NICU admission, neonatal mortality as well as the composite adverse neonatal outcome.

The secondary analyses of the ASPRE trial which only assessed LDA prophylaxis effect on NICU admission reported a significant reduction of 68% in length of stay in the NICU. This is consistent with the finding of reduced NICU admission found in this study[80].

Similarly, Duley et al also reported LDA prophylaxis to have significant reductions in the incidence of fetal death, neonatal death, small for gestational age babies and preterm delivery as well as serious adverse outcome (a composite outcome including maternal death, baby death, pre-eclampsia, small-for-gestational age, and preterm birth)[81].

This is also collaborated by Roberge et al with some similar findings of LDA initiated at ≤ 16 weeks of gestation being associated with a greater reduction of perinatal death and other adverse perinatal outcomes, IUGR and preterm birth[82].

The very recent USPSTF meta-analysis in 2021 similarly reported a lower risk of perinatal mortality, preterm birth and IUGR but not a clear reduction in preterm delivery[79].

These welcomed beneficial effects of LDA prophylaxis on fetal/neonatal outcomes are likely explained by the effect of LDA in preventing early onset preeclampsia.

At the 95% confidence interval the only maternal outcome significantly reduced with LDA prophylaxis was organ dysfunction ($P = 0.001$) with no significant reductions observed for the other maternal outcomes of caesarean section, eclampsia, CVA, maternal mortality. The

composite adverse maternal outcomes also did not show any significant association with LDA prophylaxis.

The Asian study[83] that showed LDA prophylaxis not to significantly reduce caesarean section rates supports the finding in this study of no reduction in the caesarean section rates with LDA prophylaxis.

Just as this study did not find a significant association between LDA prophylaxis and adverse maternal outcomes except organ dysfunction, the USPSTF meta-analysis similarly did not find a significant association between LDA prophylaxis and the risk of organ dysfunction such as HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) or severe maternal morbidity[79]

This may be due to the low numbers of maternal complications such as eclampsia, CVA, and maternal death that occurred in the study as well as the low numbers of women who received LDA prophylaxis.

5.7 Limitations of study

The findings from this work done in a tertiary referral centre cannot be generalized to other facilities especially lower-level facilities across the country. In KATH, pregnant women are attended to by doctors under the supervision of specialist/ consultants and the Maternal Fetal Medicine (MFM) team. In particular, once identified, high risk women are attended to by the MFM team. This is not the case across the majority of health facilities especially lower-level facilities across the country.

There could be a potential recall bias in relation to some of the independent variables such as family history of preeclampsia, a history of hypertensive disease in pregnancy and whether LDA prophylaxis was given or not. This was sometimes solely from information obtained from the patient with no medical records for confirmation. This may be a limiting factor which could affect results. The study assumed that all information provided by the participants were true.

CHAPTER SIX

CONCLUSION AND RECOMMENDATIONS

6.1 CONCLUSION

More than half of the women with preeclampsia/eclampsia had risk factors warranting prophylactic LDA in early pregnancy. However only a quarter of these high-risk women were given LDA. Majority of women with risk factors for preeclampsia at the beginning of pregnancy did not receive prophylactic LDA.

Significant factors associated with LDA prophylaxis initiation and use among high-risk women were early antenatal care booking before 16 weeks, antenatal care at a tertiary hospital and being seen at antenatal care by a doctor especially obstetrician with maternal fetal medicine training.

High-risk women who received LDA prophylaxis developed late onset preeclampsia compared to their counterparts who did not receive LDA prophylaxis.

LDA prophylaxis was significantly associated with a reduction in the incidence of IUGR, IUFD/TOP, prematurity, NICU admission, neonatal mortality as well as the composite adverse neonatal outcome. However, LDA prophylaxis was not significantly associated with a reduction in the composite adverse maternal outcome as well as the individual outcomes of caesarean section, eclampsia, CVA, maternal mortality except for organ dysfunction where there was a significant reduction.

6.2 Recommendations

The Ministry of Health/Ghana Health Service should consider incorporating screening for preeclampsia prevention with LDA into our national safe motherhood protocol to help decrease the disease burden.

The maternal fetal medicine unit of the department of obstetrics and gynaecology of KATH should consider organising training and periodic refresher courses on the preventive management of preeclampsia for all providers of antenatal care in the hospital.

To practically ensure that every woman is screened irrespective of where she books for antenatal care or who sees her at the booking visit, a checklist on screening for high-risk women using the maternal risk factors should be incorporated into a page in the antenatal record book and a care plan clearly outlined for those who screen positive to receive LDA 150mg daily from 12 weeks to 36 weeks. A recommended example to be incorporated into a page of the antenatal book for consideration by the Ghana health service is provided as appendix 5.

6.3 Areas for further research

The current screening tool feasible in our setting only picks less than half of high-risk women, so more local research is needed to develop a more sensitive screening tool specific to our setting that can pick up more women.

More data should also be generated in establishing the most efficient way of improving the uptake of LDA prophylaxis in our high-risk women.

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Appendix 1

PARTICIPANT INFORMATION LEAFLET

INFORMATION SHEET

Title of Research:

Low Dose Aspirin Prophylaxis among Pre-eclamptic /Eclamptic women with history-based risk factor(s) in a tertiary hospital in Ghana

Name(s) and affiliation(s) of researcher(s):

This study is being conducted by Dr. Yaw Gyanteh Owusu, of Directorate of Obstetrics and Gynaecology, KATH.

Background:

You have been diagnosed with preeclampsia which is a dangerous disease. It is a major cause of death or ill-health in a pregnant woman. It may also make your baby not grow well and be smaller than normal or die in your womb. It may also make you deliver a premature baby that may be admitted to the mother-baby unit or may even die. One way that has been shown to prevent the disease mostly in white populations is to be given a drug called aspirin to high-risk mothers before 4 months of pregnancy to be taken throughout the pregnancy until delivery. We are doing this research to find out the proportion of pregnant women admitted here with the disease who were assessed early in pregnancy and put-on aspirin therapy. We will also study the outcomes of the pregnancies between those who had aspirin and those who did not receive aspirin. This will help us determine if aspirin therapy help prevent the disease in our pregnant women with risk factors as has been studied elsewhere.

Purpose(s) of research:

This study seeks to find out the usage of prophylactic low dose Aspirin among pregnant women with a prior history-based risk(s) admitted to KATH for Pre-eclampsia/Eclampsia

Selection of participants:

This study involves study participants with preeclampsia/eclampsia admitted, delivered/pregnancy terminated and discharged at A1HDU of the Komfo Anokye Teaching Hospital (KATH), Kumasi.

Procedure of the research, what shall be required of each participant and approximate total :

On the day your doctors discharge you, we will come to you for a questionnaire interview and in some cases will assess your antenatal care book, hospital in-patient records and discharge notes to obtain and document some information about your pregnancy, the disease that affected your pregnancy and how it affected you and your baby. All this will take a maximum of 15 minutes of your time. In total we expect to recruit about 240 participants into this study during the study period.

Risk(s):

An anticipated small delay in discharge processing as well as loss of privacy during questionnaire administration.

Benefit(s):

There will be no direct potential benefit. Participants however will receive a wide range of education on the disease including how it can be prevented in future pregnancies as well as future health implications as a result of the disease and what can be done to minimize these risks.

Confidentiality:

We will anonymize the patients name, contact details and other identifiers that may point to the patient. All information obtained will be kept under lock, key and password protected electronically and made assess to only the PI, statistician and IRB.

Voluntariness:

Participation in this study is completely voluntary and so you are not under any obligation whatsoever to be part of it.

Alternatives to participation:

You will receive the full treatment you need according to the hospital protocol even if you decide not to participate in this research**.**

Withdrawal from the research:

You may freely withdraw from the study at any point in time during the research and this will not affect any subsequent treatment you will need in the hospital. You will also not be required to explain yourself if you choose not to. You may also decide to abstain from responding to any part of the questionnaire if it makes you uncomfortable.

Consequence of Withdrawal:

There will be no consequence or loss of benefit to you or your baby if you choose to withdraw from the study. However, some information obtained from you before withdrawal may have already been modified and analyzed into reports and may not be undone. Notwithstanding nothing will link you to the study and your confidentiality will be upheld

Costs/Compensation:

For your time and inconvenience, a bottle of canned malt will be given for refreshment in appreciation for your participation.

Contacts:

In case you have any question(s) concerning this study, please do not hesitate to contact Dr. Yaw Gyanteh Owusu the principal investigator on this phoneline **0202536152**

Further, if you have any concern about the conduct of this study, your welfare or your rights as a research participant, you may contact:

The Office of the Chairman,
Komfo Anokye Teaching Hospital Institutional Review Board (KATH-IRB),Research and Development Unit, Kumasi.
Tel: +233 3220 00617.
Email address: kathirb@kathhsp.org or kathirb25@gmail.com

Appendix 2 - Consent Form

CONSENT FORM

Statement of person obtaining informed consent:

I have fully explained this research to _____and have given sufficient information about the study, including that on procedures, risks and benefits, to make an informed decision.

DATE: _____SIGNATURE: _____

NAME: _____

Statement of person giving consent:

I have read the information on this study/research or have had it translated into a language I understand. I have also talked it over with the interviewer to my satisfaction.

I have read the description of the research or have had it translated into language I understand. I have also talked it over with the interviewer to my satisfaction. I understand that my participation is voluntary. I know enough about the purpose, methods, risks and benefits of the research study to decide that I want to take part in it. I understand that I may freely stop being part of this study at any time. I have received a copy of this consent form and additional information sheet to keep for myself.

DATE: _____SIGNATURE/THUMB PRINT: _____

WITNESS' SIGNATURE: _____

WITNESS' NAME: _____

Appendix 3

Ethical clearance

KOMFO ANOKYE
TEACHING HOSPITAL

P. O. Box 1934
Kumasi - Ghana
Tel: +233 - 3200-22301 - 4
Fax: +233 - 3220-24654 / 24621
Website: www.kathhsp.org

Our Ref. No.:....*KATH IRB/AP/109/21*

Your Ref... No:.....

Komfo Anokye Teaching Hospital Institutional Review Board

15th October 2021

Dr. Yaw Gyanteh Owusu
Obstetrics & Gynaecology Directorate
Komfo Anokye Teaching Hospital,
P. O. Box KS 1934,
Kumasi.

Dear Dr. Owusu,

Ethics Approval

Protocol title:	Low Dose Aspirin Prophylaxis among Pre-eclamptic/Eclamptic women with history-based risk factor(s) in a tertiary hospital in Ghana
Study site:	Obstetrics & Gynaecology Directorate of the Komfo Anokye Teaching Hospital
Sponsor:	Self-funded

We write in response to the clarifications and revised documents following review by the Komfo Anokye Teaching Hospital Institutional Review Board (KATH IRB) in respect of the research study referenced above.

We are pleased to inform you that KATH IRB, per your correspondence of 26th September 2021, has given approval for the following study documents:

- *Protocol version 1.0 last updated 20th August 2021*
- *Informed consent form, version 1.0 last updated 26th September 2021*
- *Case report form version 1.0 last updated 26th September 2021*

Approval for the study is in effect until **14th October 2022** and it is the responsibility of the Principal Investigator to maintain the study in good standing at the Komfo Anokye Teaching Hospital. The Board anticipates to be notified of the actual start date of your project.

Prior to the expiration of the study approval, you must submit to the KATH IRB an "Application for Continuing Review" along with provision of "Annual Report" when the study is ongoing, or a "Termination Report" if the research has been completed.

You must hastily report to the KATH IRB should a modification to the research be proposed, and without delay if an unanticipated development occurs before the next required review. Regulations do not permit you to modify conduct of the study in its present form prior to ethics approval; except where urgent action is required to eliminate an apparent immediate hazard to a study subject or other person. It is of utmost importance data generated from this study must be used for the intended purposes only.

Thank you.

Sincerely,

Prof. Kwabena Antwi Danso, BSc, MB ChB, FWACS, FGCS, FACOG
Chairman, KATH-IRB

KOMFO ANOKYE TEACHING HOSPITAL

RESEARCH AND DEVELOPMENT UNIT (R & D)

CERTIFICATE OF REGISTRATION

REG. NO: RD/CR21/151

This is to certify that

Prof/Dr/Mrs/Mr/Ms. Owusu Gyanteh Yaw

has registered his/her proposed study titled Low Dose Aspirin Prophylaxis Among Pre - Eclamptic / Eclamptic Women With History - Based Risk Factor(s) In a Tertiary Hospital In Ghana.

with the Research and Development Unit.

Date of issue: 16-August-2021 Date of expiry: 15-August-2022

Deputy Director for Research

Dr Kwadwo Sarbeng

Signature

K20/0101602

*Receipt number

Note

This certificate does not constitute ethical clearance for the conduct of the study but proof of registration of study with KATH. Ethical clearance from the KATH Institutional Review Board (KATH-IRB) is required to conduct the study at KATH.

Version RD/REG-11TH DECEMBER, 2019

Appendix 4 – Questionnaire

Prophylactic Low Dose Aspirin (LDA) use among pregnant women with a prior history -based risk(s) admitted to KATH for Pre-eclampsia/Eclampsia

BIODATA

Study ☐☐☐☐ ID:

Maternal Age :

Educational level: None ☐ Primary ☐ secondary ☐ Tertiary ☐

Religion : None ☐ Christian ☐ Muslim ☐ Traditionalist ☐

Gestational age at booking: ……..

Estimated gestational age at diagnosis/admission: ……..

Level of care at booking : Health centre ☐ Private clinic ☐

District hospital ☐ Regional hospital ☐ Tertiary hospital ☐

Health worker providing care at booking: Community health nurse ☐

☐ ☐

Midwife/nurse Doctor

Change of partner and/or New partner within 1 year of pregnancy : Yes ☐
No ☐

PART A : ***Moderate-risk factors (tick all that apply)***

☐ Nulliparous

☐ Multiple Pregnancy

☐ Age>40 years

☐ Interpregnancy interval>10 years

☐ Body mass index at first visit >30 kg/m2

☐ Family history of PE

PART B **:** ***High-risk factors (tick all that apply)***

☐ History of hypertensive disease in previous pregnancy

☐ Chronic renal disease

☐ Autoimmune disease (APS, SLE etc)

☐ Diabetes mellitus

☐ Chronic hypertension

PART C

LDA WARRANTED

☐ Yes (2 or more ticks in part A and/or any tick in part B)

☐ No

If Yes did client receive aspirin

☐ Yes

☐ No

If client received aspirin, gestational age of LDA initiation

☐ ≤ 16 Weeks

☐ > 16 Weeks

If client received aspirin, compliance to aspirin until preeclampsia developed ?

Did you ever forget to take your aspirin

☐ *Yes*

☐ *No*

Are you careless at times about taking your aspirin

☐ *Yes*

☐ *No*

When you feel better do you sometimes stop taking your aspirin

☐ *Yes*

☐ *No*

Sometimes if you feel worse when you take your aspirin, do you stop taking it

☐ *Yes*

☐ *No*

Tick one

☐ Compliance to aspirin (ticks **No** for all four above or a **single Yes** tick)

☐ Non-compliance (**more than 1 Yes** tick*)*

Maternal outcome

Vaginal delivery ☐ C/S ☐ Organ dysfunction ☐ Eclampsia ☐

CVA ☐ Mortality ☐

Fetal/Neonatal outcome

IUGR ☐ IUFD/TOP ☐ Prematurity ☐ NICU admission ☐

Neonatal death ☐ Well baby ☐

Contact : Yaw G. Owusu 0202536152

Appendix 5 Recommended checklist for screening

PREECLAMPSIA RISK SCREENING GUIDELINE : TO BE DONE FOR EVERY WOMAN AT BOOKING VISIT

TICK ALL THAT APPLY

PART A : MODERATE RISK FACTORS

Nulliparous	☐	Multiple Pregnancy	☐
Age>40 years	☐	Interpregnancy interval>10 years	☐
BMI at first visit >30 kg/m2	☐	Family history of PE	☐

PART B ; HIGH RISK FACTORS

History of hypertensive disease in previous pregnancy ☐

Chronic hypertension// Booking blood pressure ≥ 140/90 mm Hg ☐

Diabetes mellitus ☐ Chronic renal disease ☐

Autoimmune disease (APS, SLE) ☐

POSITIVE ____ (2 or more ticks in part A and/or any tick in part B)

ACTION IF POSITIVE : Refer/Prescribe Aspirin 150mg daily from 12 weeks to 36 weeks

NB: Positive women with hypersensitivity to aspirin or other NSAIDS, known asthmatics with a history of aspirin-induced acute bronchospasm, active peptic ulcer disease, history of gastrointestinal bleeding, severe hepatic dysfunction is to be seen by specialist obstetrician preferably maternal fetal medicine specialist.

GANTT CHART

ACTIVITY	TIME LINES
1. Proposal writing	JULY-AUGUST, 2021
2. Discussions with reviewers	SEPTEMBER-APRIL, 2021
3. Ethical Clearance.	SEPTEMBER-OCTOBER, 2021
4. Pretesting	NOVEMBER 2021
5.Data Collection	DECEMBER 2021-MARCH, 2022
6.Data analysis	MARCH, 2022
7.Reflective writing	MARCH-APRIL,2022
8.Final write-up	APRIL-MAY 2022
9. Submission of final work	JUNE 2022

5.0 Budget/Resources

The cost of the research including printing, data analysis and other logistics was funded by the researcher.

The table below will outline the budget and resources needed for the study.

ITEM/ SERVICE	UNIT COST GH¢	TOTAL COST GH¢
1. Personnel		
Research Assistant – 1	400	400
Data Entry Clerk - 1	300	300
Data Analyst		1500
2. Materials		
A4 Sheets 1 bundle of A4 sheet	50	50
Pen, Pencil, and Erasers		10
Files and folders (10)	10	10
Staple Machines and Pins		10
Printer Cartridge (4)	75	300
Pen drives (4)	25	100
3. Communication		
Internet data		400
Phone calls		200
Research and development registration/ Ethical Clearance		350
Binding of proposal	30	180
Final dissertation binding	75	300
Refreshment for participants	3.5	965
Miscellaneous		200
GRAND TOTAL		GHS 5275