MAKERERE UNIVERSITY

USING ULTRASONOGRAPHY, LABORATORY BLOOD TESTS AND MATERNAL CHARACTERISTICS TO PREDICT PRE-ECLAMPSIA AND ADVERSE PREGNANCY OUTCOMES AT ST. MARY'S HOSPITAL LACOR, NORTHERN UGANDA

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DECLARATION

I declare that the work in this book was done personally at St. Mary's Hospital Lacor Northern Uganda and has never been presented to any institution of learning for any academic award.

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DEDICATION

I dedicate this book to my children: Wennemi, Sibondo, Goodluck, and Prinz, who gave me reasons to study even in times of stress.

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ABBREVIATIONS

AC	Abdominal circumference
BP	Blood pressure
BPD	Biparietal diameter
EFW	Estimated fetal weight
FL	Femur length
HC	Head circumference
HELLP	Haemolysis, Elevated Liver Enzymes, Low Platelets
HIV	Human immunodeficiency virus
ISUOG	International Society of Ultrasound in Obstetrics and Gynaecology
IUGR	Intrauterine growth restriction
NLR	Neutrophil to lymphocyte ratio
PE	Preeclampsia
PI	Pulsatility index
RDW	Red cell Distribution Width
RI	Resistive Index
ROC	Receiver Operating Characteristic

OPERATIONAL DEFINITIONS

Doppler sonography is a test that uses reflected ultrasound waves to see how blood flows through a blood vessel.

Uterine artery Doppler sonography will measure the pulsatility index PI and Resistive index RI and observe whether there is any end-diastolic notch on the flow pattern tracing.

The pulsatility index measures the variability of blood velocity in a vessel, equal to the difference between the peak systolic and minimum diastolic velocities divided by the mean velocity during the cardiac cycle.

The resistive index measures the resistance to blood flow caused by the microvascular bed distal to the measurement site.

End diastolic notch indicates cessation or reduction in blood flow through an artery at the point of measurement during the diastole of the cardiac cycle.

Unilateral end diastolic notch indicates cessation or reduction in blood flow through one of the uterine arteries at the point of measurement during the diastole of the cardiac cycle.

Bilateral end diastolic notch indicates cessation or reduction in blood flow through both uterine arteries at the points of measurement during the diastole of the cardiac cycle.

Adverse pregnancy outcome is an outcome that is not considered normal and, for this study, includes stillbirth, preterm birth, low birth weight and pre-eclampsia.

Pre-eclampsia is any hypertension (BP $\geq$ 140/90mmHg) and proteinuria (urine dipstick +) in a pregnant woman after 20 weeks of gestation.

Stillbirth is the death of a fetus in utero after 22 weeks of gestation and before expulsion of the fetus from the womb.

Preterm birth is the delivery (expulsion) of the fetus between 28 weeks and 36 weeks 6 days of gestation.

Low birth weight is the weight of a fetus less than 2.5Kg at birth at term

Resuscitation is a medication intervention to revive, stabilize or stimulate a newborn with difficulty breathing. It ranges from wiping the face of the baby and deep suction of secretions from the throat and nose, rubbing the skin of the back and limbs, ambu bagging and assisted ventilation.

Validation is a process of assessing a prediction model's performance on new data to ensure generalizability. It is done after the initial model is built and involves a separate dataset not used in the model development to test its performance.

Evaluation is a broader term for the overall assessment of the prediction model's accuracy, sensitivity, specificity, area under curve (AUC) and goodness of fit. It can be done at different stages of prediction model development, e.g. during the development (internal validation) or after the prediction model development (external validation).

ABSTRACT

Background: Preeclampsia causes 12% to 19% of maternal deaths in Uganda. Complications include preterm birth, stillbirth and low birth weight. Early diagnosis and timely delivery improve pregnancy outcomes. Nevertheless, due to poor infrastructure in northern Uganda, early prediction and diagnosis with eventual treatment may save lives. Therefore, we set out to predict pre-eclampsia and adverse pregnancy outcomes using maternal history, laboratory characteristics and uterine artery Doppler indices in northern Uganda.

Methods: This prospective cohort study recruited 1,285 pregnant mothers at 16-24 weeks. Participants' history, physical findings, blood tests (full haemogram, renal and liver function) and uterine artery Doppler indices were recorded. One thousand four (1,004) enrolled pregnant mothers had complete delivery records. Preeclampsia, preterm birth, stillbirth and low birth weight were the desired outcomes. We built models in RStudio for predicting pre-eclampsia, preterm birth, stillbirth and low birth weight.

Statistical analysis: t-tests, Mann-Whitney tests and Pearson's chi-square were used to compare means, medians, and proportions, respectively. We calculated incidences of low birth weight at term, pre-eclampsia, preterm birth and stillbirth. We identified from maternal history, physical examination, uterine artery Doppler indices and blood tests, maternal risk factors for preeclampsia, preterm birth, stillbirth and low birthweight at term using the logistic regression models in RStudio. We re-processed the data using the ROSE package to produce synthetic data (test data) to evaluate the (original) model performance and validated the models using K-fold cross-validation. We weighed each variable contribution in the prediction model.

Results: The incidence of pre-eclampsia, preterm birth, stillbirth and low birth weight at term were 4.3%, 11.6%, 2.5% and 5.7%, respectively. The predictors of these adverse pregnancy

outcomes were Maternal age ≥ 35 years, nulliparity, personal history of preeclampsia, tertiary level of education, BMI ≥ 26.5Kg/m2, diastolic hypertension, bilateral end-diastolic notch, lateral placental location, serum GGT ≥30 IU, serum ALT 12 – 49 IU, white blood cell count ≥ 11,000 cells/µl, lymphocyte count of 800-4000 cells/µl, haemoglobin level ≥ 12.1g/dL and serum ALP <98 IU.

The models had a good fit if McFadden's pseudo-R^2 was between 0.2–0.4. Maternal history, laboratory tests and uterine artery Doppler sonography predicted pre-eclampsia with 84.9% AUC and McFadden's pseudo-R^2 of 0.30. The variables with weights up to ≥6.0 predicted adverse pregnancy outcomes by ≥60% AUC and ≥ 50% accuracy.

Conclusion: The prediction models for preeclampsia had AUC of 71.4% to 84.9%. Since the patients present to prenatal clinics with different predictors, the variable weights adding up to ≥6.0 predicted adverse outcomes by ≥60% AUC. These may help to develop prenatal screening tools for preeclampsia in Uganda. We recommend incorporating the prediction of preeclampsia into prenatal care and strengthening the referral pathways for those found to be at risk.

Keywords: Risk prediction, laboratory tests, uterine artery Doppler indices, maternal characteristics, pre-eclampsia, stillbirth, preterm birth, low birth weight, Uganda, Africa

CHAPTER ONE: BACKGROUND

1.0 Introduction and Background

Preeclampsia (PE) is a human pregnancy-specific syndrome characterised by new onset hypertension (≥140/90mmHg) and proteinuria (++ on urine dipstick) or any end-organ dysfunction in a previously normotensive woman (Ministry_of_Health, 2015, 2019; Uganda Bureau of Statistics, 2016; Uganda, 2011). The exact cause is unknown but thought to result from defective placentation (Brosens et al., 2011) or immune maladaptation (Khalil et al., 2013). This defective placentation is thought to result in "great obstetric syndromes", mainly PE, preterm birth (PB), low birth weight (LBW) and stillbirth (SB) (Caughey et al., 2005; Elosha Eiland, 2012; Gallo et al., 2013; Khalil et al., 2013; Knuist et al., 1998; Nakimuli et al., 2014; Wright et al., 2015; Yasmin Casmod, 2016). The late-onset preeclampsia is more associated with metabolic and cardiovascular disease risks (Culhane & Goldenberg, 2011; Khalil et al., 2013; Kistka et al., 2007; Osypuk & Acevedo-Garcia, 2008). In multiracial communities, women of Afro-Caribbean racial origin are at increased risk of adverse pregnancy outcomes (Fulda et al., 2014; Khalil et al., 2013; Ncube et al., 2019). On the other hand, primary smoking is protective (Khalil et al., 2013; Reddy et al., 2010; Salihu et al., 2004). Nevertheless, we need to find out whether secondary smoking is also protective.

PE affects 2-10% of pregnant women globally, with an average prevalence of 4.6% (Abalos et al., 2013) and a cause of about 10% of maternal deaths, the majority of whom are in low-income countries (Kassebaum et al., 2014). In Africa, it causes 10-15% of maternal deaths (Ediau et al., 2013) and 12% -19% of maternal deaths in Uganda (MoH, 2019).

The predictors of PE and other adverse pregnancy outcomes using maternal demographic and clinical findings include nulliparity or new partner fathering the pregnancy (Hoffman, 2023; Lokki et al., 2018), women of African descent (Nakimuli et al., 2014), previous personal or

family history of PE, maternal age of ≥35 years and raised mean arterial pressure (Gallo et al., 2014), pregnancy at high altitude (Myatt & Roberts, 2015; Powe et al., 2011; Prins et al., 2016b; Robillard et al., 2017), twin pregnancies (Laine et al., 2019) delivery of male babies (Wandabwa et al., 2010) and cardiometabolic diseases (Haymanot et al., 2020; Munazza et al., 2011; Noura, 2015), On the other hand, primary smoking is protective against preeclampsia (Myatt & Roberts, 2015; Powe et al., 2011; Prins et al., 2016a). Nevertheless, we need to find out whether secondary smoking is also protective. Autoimmune diseases and systemic inflammation (Hoffman, 2023; Lokki et al., 2018), high uterine artery Doppler pulsatility and resistive indices, and the presence of end-diastolic notches (Gallo et al., 2013; Wandabwa et al., 2010) are also associated with adverse pregnancy outcomes.

In Uganda, laboratory tests (Amukele et al., 2018) and ultrasound examinations (Gonzaga et al., 2010; Kiguli-Malwadde et al., 2020) are available. These blood tests (Xue et al., 2023) and uterine artery Doppler indices (Tudor et al., 2023) can aid the prediction of preeclampsia and adverse pregnancy outcomes. Xue and colleagues found that a combination of full haemogram, liver and renal function tests predicted preeclampsia by 78% AUC (Xue et al., 2023). Tudor and colleagues found a pulsatility index of ≥95th percentile for their population had either preeclampsia or intrauterine growth restriction (Tudor et al., 2023). However, obstetric ultrasound, full haemogram, liver and renal function tests are not mandatory during pregnancy (MoH_Uganda, 2022), although over 93% of pregnant women come into contact with a skilled healthcare provider at least once during antenatal visits (Ediau et al., 2013; UDHS, 2022).

Routine screening of adverse pregnancy outcomes during prenatal care in the global north uses maternal characteristics, laboratory tests and uterine artery Doppler indices (Muin et al., 2022; The_fetal_medicine_foundation, 2022). These Doppler PI and RI values between

populations decrease with increasing gestation age up to the end of the second trimester (Tayyar et al., 2015). **Figure 1** below is a) normal and b), c) and d) abnormal uterine artery Doppler tracing. The machine automatically gives the PI and RI readings, while the end-diastolic notch is subjective and depends on the characteristics of the tracing seen.

Figure 1a: Normal Uterine artery Doppler

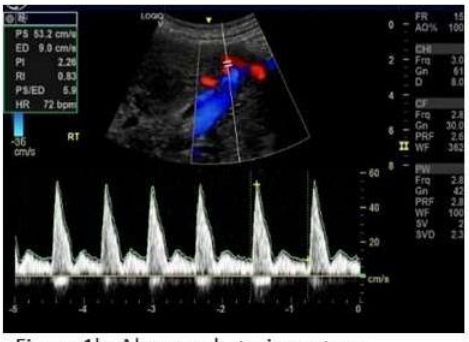

Figure 1b: Abnormal uterine artery Doppler with Severe early and end diastolic notch

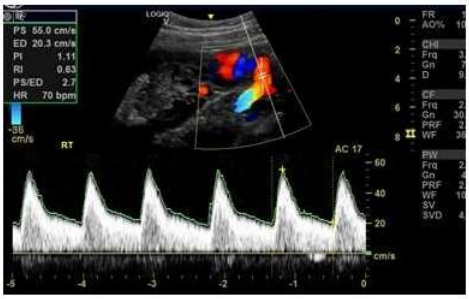

Figure 1c: Mild end diastolic notch without early diastolic notch, angle correction

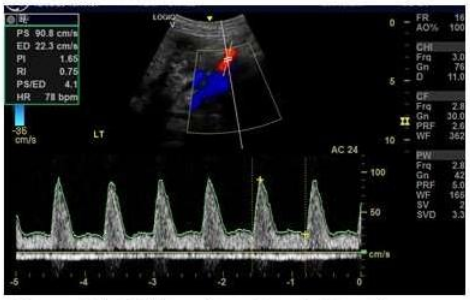

Figure 1d: Mild early and end diastolic notch, angle correction

Figure 1: Normal and abnormal uterine artery flow tracings

The National Institute of Health and Care Excellence (NICE) (NICE, 2021), the American College of Obstetricians and Gynaecologists (ACOG) (ACOG, 2019), the Society of Obstetricians and Gynaecologists of Canada (SOGC) (Laura A. Magee et al., 2022) and Department of Health Australia (Department_of_health, 2019) guidelines for prenatal care advocates for screening for adverse pregnancy outcomes in the first and second trimesters of pregnancy. Those found to be at risk are given frequent follow-up dates and preventive measures according to their protocols, including frequent follow-up visits and low-dose

aspirin (ACOG, 2019; Department_of_health, 2019; Laura A. Magee et al., 2022; NICE, 2021). Those at risk of preeclampsia are given low-dose aspirin starting before 16 weeks to 36 weeks of gestation, and it has been shown to reduce the incidence of preeclampsia by 62%, the majority being early onset preeclampsia (Stubert et al., 2023). In Uganda, we have excellent guidelines for early detection and management of adverse pregnancy outcomes; however, no prediction of those outcomes is made in prenatal clinics (MoH_Uganda, 2022).

Therefore we carried out a prospective cohort study to predict preeclampsia and adverse pregnancy outcomes, built models, and evaluated their accuracy, sensitivity, and specificity of the AUC of second-trimester maternal characteristics, uterine artery Doppler indices (resistive index, pulsatility index, and earl diastolic notch) and maternal blood tests (full haemogram, liver, and renal function tests) to predict pre-eclampsia, low birth weight, preterm birth and stillbirth among women attending antenatal care at St. Mary's Hospital Lacor in northern Uganda. In addition, we determined which models had the best fit for predicting adverse pregnancy outcomes to be used for screening in prenatal clinics by calculating McFadden's pseudo R^2. These may help to develop prenatal screening tools for preeclampsia in Uganda, which may be incorporated into prenatal care.

1.1 Statement of the problem

Maternal mortality in Uganda has remained high over the past decade, reducing from 438 to 189 per 100,000 live births (UDHS, 2011, 2022). Preeclampsia causes 12-19% of these maternal deaths (MoH, 2019). Use of prediction models preventive strategies for adverse pregnancy outcomes has demonstrated to save lives, with current meta-analyses showing a reduction of the risk of the occurrence of pre-eclampsia (RR 0.85, NNT 50), as well as beneficial effects on the rates of preterm birth (RR 0.80, NNT 37), fetal growth restriction (RR 0.82, NNT 77), and perinatal death (RR 0.79, NNT 167) (Stubert et al., 2023).

Pregnant women are encouraged to start prenatal care as soon as they miss their periods (MoH, 2022). Every mother gets a prenatal booklet filled with her history, physical examination and HIV status (MoH, 2022). Prenatal care is free in government health centres and attracts a small fee in private health centres (MoH, 2022). However, prenatal ultrasound is not mandatory; some mothers undergo the whole gestation period without getting a single prenatal ultrasound scan (MoH, 2022; UCG, 2023).

Over 93% of pregnant women come into contact with a skilled healthcare provider at least once during their prenatal visits (UDHS, 2022). The majority return to give birth in the hospital (UDHS, 2022); however, the referral system is tedious and time-consuming for those who eventually require transfer to higher-level health units (Waiswa et al., 2010).

Routine history taking and physical examination for every mother during prenatal care extracts all the maternal demographic characteristics predictors of pre-eclampsia, preterm birth, low birth weight and stillbirth and yet this information is not used for purposes of prediction of these adverse pregnancy outcomes. There are no prediction models specifically developed and validated to predict preeclampsia and other adverse pregnancy outcomes among the black population. These would have aided referral to higher-level hospitals, where uterine artery Doppler sonography, complete blood count, and renal and liver function tests services are readily available. The few available specialist healthcare providers could concentrate care for high-risk pregnancies. The extra vigilance given to high-risk women may lead to early diagnosis and treatment of PE, preterm birth or low birth weight, thereby preventing and reducing morbidity and mortality.

1.2 Hypotheses

Hypothesis 1: Maternal history and physical examination findings at 16 to 24 weeks of gestation predict pre-eclampsia and adverse pregnancy outcomes.

Hypothesis 2: Laboratory blood tests at 16 to 24 weeks of gestation predict pre-eclampsia and adverse pregnancy outcomes.

Hypothesis 3: Uterine artery Doppler indices at 16 to 24 weeks of gestation predict pre-eclampsia and adverse pregnancy outcomes.

Research Questions

1. Which second-trimester maternal socio-demographic and clinical characteristics predict preeclampsia and adverse pregnancy outcomes?
2. Which second-trimester maternal laboratory characteristics predict preeclampsia and adverse pregnancy outcomes?
3. Which second-trimester maternal uterine artery Doppler indices predict preeclampsia and adverse pregnancy outcomes?

1.3 Objectives

1.3.1 General objective

To determine ultrasonography, laboratory and maternal characteristics that predict pre-eclampsia and adverse pregnancy outcomes at St. Mary's Hospital Lacor, northern Uganda.

1.3.2 Specific objectives

1 To determine the second-trimester maternal characteristics that predict pre-eclampsia and adverse pregnancy outcomes at St. Mary's Hospital Lacor, northern Uganda.

2 To determine the second-trimester laboratory characteristics that predict pre-eclampsia and adverse pregnancy outcomes at St. Mary's Hospital Lacor, northern Uganda.

3 To determine the second-trimester uterine artery Doppler Sonography end-diastolic notch, pulsatility index (P.I.) and resistive index (R.I.) that predict pre-eclampsia and adverse pregnancy outcomes at St. Mary's Hospital Lacor, northern Uganda.

1.4 Conceptual framework

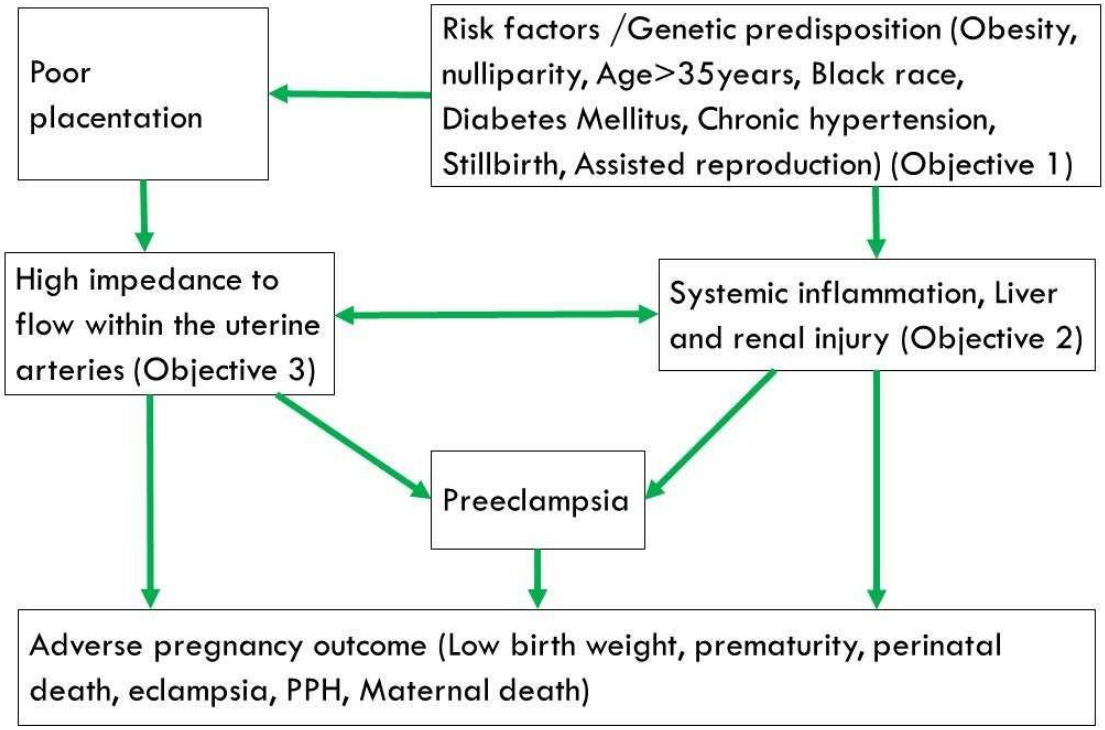

Figure 2: The conceptual framework

Narrative

In this conceptual framework, maternal genetic factors may lead to defective placentation or systemic inflammation, renal and liver injury. These factors may also interact, leading to high impedance to blood flow within the uterine arteries. These high impedance to blood flow within the uterine arteries, systemic inflammation, renal and liver injuries are risk factors for preeclampsia and adverse pregnancy outcomes like intrauterine growth restriction (IUGR), Birth asphyxia, prematurity, perinatal death, eclampsia, postpartum haemorrhage (PPH), abruption placenta, disseminated intravascular coagulopathy (DIC), Stroke, and Maternal death

1.5 Justification of the Study

There are no prediction models specifically developed and validated to predict preeclampsia and other adverse pregnancy outcomes among the black population. This study will significantly benefit pregnant mothers, caretakers, and healthcare providers regarding whom to monitor more closely and who to have timely referrals to higher-level health units. Ultrasound machines are readily available in Uganda, and examination is non-invasive yet very informative to expectant mothers about their unborn babies' health status and structure (Gonzaga et al., 2010; Kiguli-Malwadde et al., 2020). Although obstetric ultrasound scan is not mandatory during pregnancy (UCG, 2023; UDHS, 2022), over 93% of pregnant women come into contact with a skilled healthcare provider at least once during antenatal visits (Ediau et al., 2013). In addition, complete blood count, renal and liver function tests are readily available in most tertiary hospitals and laboratories (UCG, 2023; UDHS, 2022). With the available information, mothers and caretakers are counselled appropriately on what to expect from the findings of their screening during antenatal care. That will enable the few available specialist healthcare providers to care for high-risk pregnancies.

The study will also open doors to more research to validate the developed model to ensure generalizability, strengthen referral pathways for mothers who have been identified as at risk of developing preeclampsia, identify training gaps for midwives to predict preeclampsia using the available antenatal care cards, training gaps for health care workers especially in prenatal ultrasound to perform sonography routinely as part of prenatal care and increase curiosity for more research into prediction of adverse pregnancy outcomes.

CHAPTER TWO: REVIEW OF LITERATURE

2.1 Aetiology of pre-eclampsia and associated adverse outcomes

At implantation, L-selectin mediates the adhesion of the blastocyst to carbohydrate receptors on the uterine wall (Genbacev et al., 2003; Sadler T.W, 2019). This attachment is the site for the future placenta (Sadler T.W, 2019). As the blastocyst gets embedded into the endometrial wall, it differentiates into the inner and outer cell mass (Sadler T.W, 2019). The inner cell mass forms the embryo, while the external cell mass forms the fetal membranes and placenta (Sadler T.W, 2019). At the embryonic pole, the trophoblasts form villi which invade deeper into the endometrium; vacuoles appear in the syncytium, fuse, and coalesce to form large lacunae (Pijnenborg et al., 1983; Sadler T.W, 2019). This primary trophoblastic invasion occurs at 8 to 10 weeks of gestation (Lyall et al., 2001). At this stage, only the maternal plasma reaches the vicinity of the growing embryo for nutrient exchange (Lyall et al., 2001). The secondary trophoblast invasion occurs at 16 to 18 weeks of gestation (Lyall et al., 2001). The cytotrophoblast cells emigrate from the chorionic villi to invade the inner third of the myometrium (Fisher, 2015; Powe et al., 2011). Cytotrophoblasts migrate up the spiral arteries and replace the maternal endothelial lining in a retrograde fashion. They also insert themselves among the smooth muscle cells that form the tunica media (Fisher, 2015; Redman & Sargent, 2005) of the spiral arteries. These structural modifications of the blood vessels are associated with functional alterations, such that the spiral arteries become low-resistance vessels by 18 weeks of gestation and, thus, less sensitive to vasoconstrictive substances (Fisher, 2015; Redman & Sargent, 2005; Uzan et al., 2011). As a result, invasion of the venous side of the uterine circulation is minimal, sufficient to enable venous return (Fisher, 2015).

Failure of the secondary trophoblast invasion is associated with pre-eclampsia and intrauterine growth restriction (Lyall et al., 2001; Redman & Sargent, 2005). Some vessels retain portions of their endothelial lining with relatively intact muscular coats (Fisher, 2015; Powe et al., 2011; Redman & Sargent, 2005). That results in constricted high-resistance vessels forming (Powe et al., 2011). Moreover, this leads to reduced blood flow to the placental bed, placental insufficiency (Elosha Eiland, 2012), and decreased oxygen tension at the placental bed (Brennan et al., 2014; Possomato-Vieira & Khalil, 2016). The resultant placental ischaemia encourages anaerobic respiration, which produces oxygen-free radicals, causing placental injury and increasing placental debris in maternal circulation (Jain et al., 2014; Redman & Sargent, 2005). The high resistance within the blood vessels, coupled with the production of oxygen-free radicals, leads to endothelial injury, dysfunction, vasoconstriction, and hypertension (Powe et al., 2011).

2.2 Immune maladaptation in pre-eclampsia and adverse outcomes

PE may also arise from an immune maladaptation of the mother to fetal tissues and membranes. Dekker and Robillard (Dekker G.A & Robillard P.Y, 2004) argue that the increased placental tissue in maternal circulation increases inflammation and endothelial injury. Other researchers believe the degree of immune response to the placental debris in maternal circulation determines the severity of pre-eclampsia (Dechend & Staff, 2012; Redman & Sargent, 2003, 2005). This systemic inflammation may result in endothelial injury, vasoconstriction, and hypertension (Dekker et al., 1998), and alters maternal blood cell count, liver and renal function tests, and eventually leads to inadequate invasion of the spiral arteries by the developing placenta (Dekker et al., 1998; Harmon et al., 2016; Laresgoiti-Servitje E, 2011; Myatt & Roberts, 2015; Powe et al., 2011; Prins et al., 2016a; Redman, 2011; Redman et al., 2014), similar to an allograft rejection (Medawar, 1960). That

results in a shallow cytotrophoblast invasion of the spiral arteries, hence endothelial dysfunction and placental insufficiency (Dekker G.A & Robillard P.Y, 2004).

2.3 Genetic origin of pre-eclampsia preeclampsia and adverse outcomes

PE may also have a genetic heritage. KIR2DS5 is an activating human NK cell receptor of lineage killer cell immunoglobulin-like receptors commonly found in families, usually women of African descent (Nakimuli et al., 2015). This cell receptor (C2 epitope of HLA-C), KIR2DS5*006, was protective against pre-eclampsia in African women (Nakimuli et al., 2015). Dekker and Robillard (Dekker G.A & Robillard P.Y, 2004) believed pre-eclampsia inheritance is a single recessive or dominant gene with incomplete penetrance. It is unclear whether the maternal genetic composition is responsible for abnormal placentation or immune maladaptation to pregnancy. PE may also result from the maternal system's inability to cope with the physiologic and genetic conflict (Dekker G.A & Robillard P.Y, 2004). The very low-density lipoprotein versus toxicity-preventing activity theory observes that Free fatty acids increase in the circulation of pregnant mothers 15 to 20 weeks before the onset of pre-eclampsia (Lorentzen et al., 1994), which leads to endothelial injury (Arbogast et al., 1994). The hyper-dynamic disease model found that pregnant women destined to develop pre-eclampsia have increased cardiac output associated with compensatory vasodilation (Bosio et al., 1999; Shakuntala Chhabra et al., 2016). That may be detected as an increased pulsatility index in the high-resistance uterine arteries. The dilated systemic terminal arterioles and renal afferent arterioles may expose capillary beds to high systemic pressures and increased flow rates, eventually leading to endothelial cell injury (Bosio et al., 1999).

2.4 Vascular abnormalities in pre-eclampsia and adverse pregnancy outcomes

The uterine artery is a branch of the internal iliac artery (Rock & Jones, 2008). It divides into arcuate and spiral arteries (Rock & Jones, 2008). During early pregnancy, it undergoes

vascular remodelling to form low-resistance vessels to supply large volumes (500-650ml/min) of blood to the uterus to meet the demands of the growing fetus (Palmer et al., 1992). Therefore, inadequate remodelling is associated with reduced blood flow to the placental site (Redman et al., 2014). Uterine artery Doppler sonography measures blood flow direction, velocity, resistance, and Volume (Nelson & Pretorius, 1988). The pulsatility index (PI) measures the difference between the peak systolic and minimum diastolic velocities divided by the mean velocity during the cardiac cycle (Nelson & Pretorius, 1988), while the resistive index (RI) is a measure of the resistance to blood flow caused by the microvascular bed distal to the site of measurement (Nelson & Pretorius, 1988). End diastolic notch indicates reduction or cessation in blood flow through the artery at the point of measurement during the diastole of the cardiac cycle (Nelson & Pretorius, 1988). That explains the placental site perfusion (Nelson & Pretorius, 1988; Redman et al., 2014). However, different groups and ethnicities of women have other cut-off Doppler PI and RI indices (Papageorghiou et al., 2001; Prajapati & Maitra, 2013; Yasmin Casmod, 2016), making it hard to adopt a guideline from one part of the world to fit another.

2.5 Prediction of preeclampsia and adverse pregnancy outcomes

2.5.1 Prediction of pre-eclampsia and adverse outcomes using uterine artery Doppler sonography

Sonography uses sound waves with frequencies over 20 kilohertz (kHz) (Abu-Zidan et al., 2011) above the audible range. Ultrasound machines produce the ultrasound, receive the reflected waves (echoes) (Abu-Zidan et al., 2011), process the echoes, and display them on the screen to form an image. Doppler sonography uses the principle of the Doppler effect (Maulik, 2005). It measures ultrasound waves' changes in frequency between the source and the echoes whenever there is relative motion (Abu-Zidan et al., 2011; Maulik, 2005; Nelson & Pretorius, 1988). The wave frequency increases when the motion is towards the sound

source and reduces when the movement is away from the sound source (Maulik, 2005; Nelson & Pretorius, 1988). The difference in frequency of the transmitted sound wave and echo usually is within the audible range (Abu-Zidan et al., 2011; Evans, 2006; Maulik, 2005; Nelson & Pretorius, 1988). It measures blood flow direction, velocity, resistance, and volume (Maulik, 2005; Nelson & Pretorius, 1988). It also shows areas of turbulence in the blood vessel. The pulsatility index measures the difference between the peak systolic and minimum diastolic velocities divided by the mean velocity during the cardiac cycle (Maulik, 2005). The resistive index measures the resistance to blood flow caused by the microvascular bed distal to the site of measurement (Maulik, 2005). End diastolic notch indicates cessation or reduction in blood flow through an artery at the point of measurement during the diastole of the cardiac cycle (Maulik, 2005). When applied to the uterine arteries, it gives an idea about the placental site perfusion or insufficiency (Maulik, 2005).

The changes in blood flow in uteroplacental vessels may predict which patients are more likely to develop pre-eclampsia. In the 1980s, Trudinger and colleagues (Trudinger et al., 1985) described uteroplacental blood flow waveforms in 12 normal and 91 complicated pregnancies starting at 20 weeks until delivery in Sydney, Australia. They found reduced diastolic blood flow in the uterine arteries associated with intrauterine growth restriction and hypertensive disorders in pregnancy (Trudinger et al., 1985). This study provided the baseline for more research using Doppler sonography to predict pre-eclampsia and adverse pregnancy outcomes. Similarly, Fleischer and colleagues (Fleischer et al., 1986) assessed uterine artery Doppler velocimetry in pregnant women with hypertension in their second and third trimesters in the USA. They found that normal pregnancy occurred when the systolic-diastolic ratio was less or equal to 2.6. A notch in the waveform would arise when the systolic-diastolic ratio was more than 2.6. Such pregnancies would be complicated by

stillbirth, premature birth, intrauterine growth restriction, and pre-eclampsia, with positive and negative predictive values of 93% and 91%, respectively.

In the 2000s, Papageorghiou et al. did a multicentre screening for pre-eclampsia and fetal growth restriction using transvaginal uterine artery Doppler flow sonography at 23 weeks of gestation (Papageorghiou et al., 2001). They found that the 95th percentile for the pulsatility index for uterine arteries of the women studied was 1.63. A pulsatility index above 1.63 had a sensitivity and specificity of 69% and 95.2%, respectively, to predict pre-eclampsia (Papageorghiou et al., 2001). In addition, Papageorghiou and colleagues (Papageorghiou et al., 2005) repeated a multicenter prospective cohort study to assess the risk for the development of PE by maternal characteristics and second-trimester uttering artery Doppler sonography. PE occurred in 2.2% of their study population, with blacks and obese women more at risk. They found that for a false positive rate of 25%, the detection rate for pre-eclampsia using maternal history alone was 45.3%, with uterine artery Doppler flow pulsatility index was 63.1%, and by combining the tests, it raised to 67.5% (Papageorghiou et al., 2005).

Yousuf et al. determined whether placental laterality associated with abnormal second-trimester uterine artery Doppler flow sonography predicted pre-eclampsia. They found that a laterally situated placenta predicted 52% of pre-eclampsia. Furthermore, a combination of a laterally situated placenta and an abnormal uterine artery Doppler flow sonography predicted 92% of pre-eclampsia (Yousuf et al., 2016).

The prediction of pre-eclampsia is improved if we target high-risk patients for screening. Anafi and Hajian (Asnafi & Hajian, 2011) assessed uterine artery Doppler sonography efficiency in the prediction of adverse pregnancy outcomes in high-risk pregnancies (those with a history of chronic hypertension, pre-eclampsia, diabetes mellitus, gestational diabetes,

intrauterine fetal death, infertility, polycystic ovarian syndrome, and recurrent abortion) at 18 to 24 weeks in it Iran. They found pre-eclampsia in 48% of those with end-diastolic notching as opposed to only 9% without end-diastolic notching (Asnafi & Hajian, 2011).

Similarly, Bhattacharya and colleagues (Bhattacharyya Sanjoy Kumar, 2012) did uterine artery Doppler flow sonography in pregnant women at 24 to 26 weeks in India. They found that a unilateral or bilateral end-diastolic notch or a resistive index greater than 0.6 had a sensitivity and specificity of 73.3% and 86.5% of high-risk pregnancies, and low-risk pregnancies were 57.1% and 95.8%, respectively (Bhattacharyya Sanjoy Kumar, 2012). However, they did not give the cut-off of their pulsatility index. Yasmin Casmod and colleagues (Yasmin Casmod, 2016) did uterine artery Doppler flow sonography in the first, second, and third trimesters of pregnancy in South Africa from 2008 to 2010. They found that the incidence of pre-eclampsia was 5.8%, and the second-trimester early diastolic notch predicted only 50% of cases. Most (73%) of the patients were blacks in their twenties (Yasmin Casmod, 2016).

Likewise, Dutta and colleagues (Amit Dutta & S. K. Rafikul Rahaman, 2017) in India observed accelerated maturation of the placenta in pregnancies complicated with hypertension as detected by the ultrasound scan. Placental lesions found during the ultrasound examination included cystic areas with echogenic borders, the heterogeneous appearance of placental mass, and thick or thin placentae. At histology, they found infarction, calcification, increased syncytial knots, fibrinoid necrosis, perivascular and sub-chorionic haemorrhage in the placentae of pregnancies complicated by hypertension (Amit Dutta & S. K. Rafikul Rahaman, 2017). Similarly, Weiner and colleagues (Weiner et al., 2016) studied the role of placental histological lesions in predicting pre-eclampsia recurrence. They found

that the placentae from the recurrent pre-eclampsia group had a higher rate of maternal and fetal vascular supply lesions than the non-recurrent pre-eclampsia group.

Lopez-Mendez et al. evaluated the uterine artery Doppler ultrasound resistance index, pulsatility index, early diastolic notch, systolic peak, and their combinations in pregnant women with pre-eclampsia (Lopez-Mendez et al., 2013). They found an abnormal general Doppler Ultrasound profile positively associated with adverse outcomes in pre-eclampsia. However, the study did not give the cut-off reading for adverse effects in Preeclampsia and never commented on whether Doppler flow sonography was helpful in the prediction of adverse pregnancy outcomes in pre-eclampsia.

Uteroplacental blood flow abnormalities may also be diagnostic of some adverse outcomes, such as small-for-gestation age. In the 1990s, North et al. (North et al., 1994) found the best screening for PE and small for gestational age (SGA) babies to be a RI or abdominal circumference (AC) above the 90^{th} percentile. Konchak and colleagues (Konchak et al., 1995) found an elevated uterine RI associated with an increased risk for PE and SGA. In addition, a uterine artery notch had an increased risk of PE, preterm birth, and SGA (Konchak et al., 1995). Bower and colleagues (Bower et al., 1998) found that a PI of 1.5 had a sensitivity of 100% and a positive predictive value of 55% while predicting adverse pregnancy outcomes, which included PE and SGA. In Ethiopia, demographic characteristics were used to predict low birth weight and at a 26% false positive rate, they predicted low birth weight with 83% AUC with 82% specificity and 71% sensitivity (Hassen et al., 2020). While in India, Singh et al. (Singh et al., 2014) found a prediction model AUC of 79% with 72% sensitivity and 56% specificity. In the USA, maternal history predicted low birth weight with 75.3% accuracy (Gaziano et al., 1981). In Denmark, the uterine artery pulsatility index predicted low birth

weight with 74% AUC (Sinding et al., 2017), while in Saudi Arabia, the placental thickness of <2cm and diameter of <18cm predicted low birth weight with 88.6% AUC (Habib, 2002).

In a review article, Llurba et al. (Llurba et al., 2009) examined the value of one-step uterine artery Doppler indices at 19-22 weeks of gestation for predicting pre-eclampsia and intrauterine growth restriction. They drew receiver operating characteristic curves to compare uterine artery Doppler sonography and maternal characteristics to predict pre-eclampsia and IUGR. For a false positive rate of 10%, uterine artery Doppler mean PI identified 70.6% of pregnancies that subsequently developed PE and 73.3% of those who developed IUGR. Maternal history alone had a meagre detection rate for PE and IUGR.

In Spain and Sweden, a short cervical length on ultrasound of endo-cervical length of ≤25 mm predicted preterm birth at <33 weeks of gestation with 38.5% sensitivity and 95.8% specificity with an area under the curve (AUC) of about 64% (Burgos-Artizzu et al., 2021; Kuusela et al., 2021).

Meanwhile, a bilateral end-diastolic notch signifies reduced perfusion of the placental site, which may translate into insufficiency (Espinoza et al., 2010). In Australia, they found that a bilateral end-diastolic notch would predict preterm birth by 31.4% sensitivity and 58% AUC (van Zijl et al., 2020). In a systematic review by Meertens et al. (Meertens et al., 2018), most models for predicting preterm birth have an AUC of 54% - 70% for both development and validation.

2.5.2 Prediction of pre-eclampsia and adverse pregnancy outcomes using maternal characteristics in multivariable prediction models

Maternal characteristics, including socio-demographic factors, predict pre-eclampsia or adverse outcomes associated with the disease. In the United Kingdom, David Wright and

colleagues (Wright et al., 2015) developed a model for predicting pre-eclampsia based on maternal demographic characteristics and medical history. They assumed that if the pregnancy continued indefinitely, all women would develop pre-eclampsia. Instead, they found an increased risk for pre-eclampsia, advancing maternal age, increasing weight, Afro-Caribbean and South Asian racial origin, medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, conception by in vitro fertilization, family history and personal history of pre-eclampsia. At a screen-positive rate of 11%, the new model predicted 40%, 48%, and 54% of cases of total pre-eclampsia and pre-eclampsia requiring delivery at <37 and <34 weeks, respectively.

The Fetal Medicine Foundation (Chaemsaithong et al., 2020) developed a triple test for screening for PE before 16 weeks using maternal factors and mean arterial pressure, uterine artery Doppler, and serum placental growth factor. It can detect correctly 90% and 75% of preterm and term PE, respectively, at 10% false positives in the Caucasian population. The detection rates were lower in other races.

North and colleagues (North et al., 2011) found that the area under the receiver operating characteristics curve (AUC) under internal validation was 0.71 for maternal characteristics. The addition of uterine artery Doppler indices at 20 weeks did not improve performance (internal validation AUC 0.71) (North et al., 2011). They developed a framework for specialist referral based on a probability of pre-eclampsia generated by the model of at least 15% or an abnormal uterine artery Doppler waveform in a subset of women with single risk factors (North et al., 2011).

Direkvand-Moghadam and colleagues (Direkvand-Moghadam et al., 2012) found the history of pre-eclampsia, hypertension, and infertility as suitable independent predictor variables for PE using multivariate logistic regression analysis. The area under the Receiver Operation

Characteristics (AUROC) was estimated to be 0.67 (95% CI 0.59–0.67, p<0.01), indicating the efficacy of the model for the prediction. Next, Derekand-Moghadam and colleagues (Direkvand-Moghadam et al., 2013) developed a predictive model using a history of pre-eclampsia, hypertension, and infertility history. The area under the Receiver Operating curve Characteristics (AUROC) was 0.67 (95% CI 0.59–0.67, p < 0.01), which showed that using the model is much better than having a guess.

Wright and colleagues (Wright et al., 2015) developed a model showing increased risk for PE provided by advancing maternal age, increasing weight, Afro-Caribbean and South Asian racial origin, medical history of chronic hypertension, diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome, family history, and personal history of PE and conception by in vitro fertilization. The risk for PE decreases with increasing maternal height and in parous women with no previous PE; in the latter, the protective effect, which is inversely related to the inter-pregnancy interval, persists beyond 15 years. A positive screen rate of 11%, as defined by NICE, the new model predicted 40%, 48%, and 54% of cases of total PE and PE requiring delivery at <37 and <34 weeks gestation, respectively, which were significantly higher than the respective values of 35%, 40% and 44% achieved by application of NICE guidelines.

Gallo et al. (Gallo et al., 2014) screened by maternal history and mean arterial pressure (MAP) at a false-positive rate of 10%, and their detection rate of total pre-eclampsia was 49.3%. Finally, al-Rubaie and colleagues (Al-Rubaie et al., 2016) assessed the performance of risk models. They found four simple models using parity, pre-eclampsia history, race, chronic hypertension, and conception method to predict early-onset pre-eclampsia, achieving the highest AUC (0.76, 95% CI 0.74–0.77).

Al-Rubaie and colleagues (Al-Rubaie et al., 2020) again developed a model for 12,395 births to nulliparous women in 2011–2014. There were 293 (2.4%) pre-eclampsia events. The WS model included maternal age, body mass index, ethnicity, multiple pregnancies, family history of pre-eclampsia, autoimmune disease, chronic hypertension, and chronic renal disease. In the validation sample (6201 births), the model c-statistic was 0.70 (95% confidence interval 0.65–0.75). The observed expected ratio for pre-eclampsia was 0.91, with a Hosmer-Lemeshow goodness-of-fit test p-value of 0.20. In the entire study sample of 12,395 births, 374 (3.0%) women had a WS model-estimated pre-eclampsia risk ≥8%, the pre-specified risk threshold for considering aspirin prophylaxis. Of these, 54 (14.4%) developed pre-eclampsia (sensitivity 18% (14–23), specificity 97% (97–98)). With the NICE screening approach, 107 (9.1%) of the 1173 (9.5%) women classified as high-risk developed pre-eclampsia (sensitivity 37% (31–42), specificity 91% (91–92)). The final model showed similar accuracy to the NICE approach when using a lower risk threshold of ≥4% to classify women as high-risk for pre-eclampsia.

South Korea used maternal history, uterine artery Doppler indices and laboratory tests (Lee et al., 2011) and found maternal age, maternal body mass index (BMI), prior preterm birth, education, occupation, income, and active and passive smoking predicted preterm birth by >90% (Lee et al., 2011). Predictors of preterm birth in Ethiopia were lack of antenatal care visits, having 1–2 antenatal care visits, history of the previous preterm, short inter-pregnancy interval, having reproductive tract infections, history of abortion, urinary tract infection and hypertensive disorders in pregnancy (Regasa et al., 2021; Wakeyo et al., 2020). Attending at least a secondary education and antenatal care was protective (Wakeyo et al., 2020).

2.5.3 Prediction of pre-eclampsia using maternal laboratory blood tests in multivariable prediction models

Jhee et al. developed a model using systolic blood pressure, serum blood urea nitrogen and creatinine levels, platelet counts, serum potassium level, white blood cell count, serum calcium level, and urinary protein (Jhee et al., 2019). C-statistics for the decision tree model, naïve Bayes classification, support vector machine, random forest algorithm, stochastic gradient boosting method, and logistic regression models were 0.857, 0.776, 0.573, 0.894, 0.924, and 0.806, respectively. The stochastic gradient boosting model had the best prediction performance with accuracy and a false positive rate of 0.973 and 0.009, respectively. The combined use of maternal factors and common antenatal laboratory data of the early second trimester through the early third trimester could effectively predict late-onset pre-eclampsia using machine learning algorithms. However, future prospective studies are needed to verify the clinical applicability of algorithms. Jhee et al. also used a combination of serum urea, aspartate aminotransferase (AST), ALT, creatinine and haemoglobin levels to predict pre-eclampsia. They got an (AUC) above 57% (Jhee et al., 2019). When uric acid, urea thrombocytes, hematocrit, AST and leukocytes were in the regression model, Delic and Stefanovic (Delić & Stefanović, 2010) classified pre-eclampsia with 83.8% accuracy. Elevated levels of AST alone were also predictive of pre-eclampsia (Mei-Dan et al., 2013). An albumin level < 3.3 g/dl had an adjusted risk ratio of 1.87 for the development of pre-eclampsia (Martell-Claros et al., 2019). Yucel and Ustun (Yucel & Ustun, 2017) predicted pre-eclampsia using mean platelet volume (MPV) and platelet crit (PCT) with AUC of 64.1% and 71.2%, respectively.

In a review article by Duckitt and Harrington, the pre-eclampsia risk increases with a personal or family history of pre-eclampsia, antiphospholipid antibodies, pre-existing diabetes, multiple pregnancies, nulliparity, raised booking blood pressure, and increased blood pressure booking body mass index and maternal age ≥ 40 (Duckitt & Harrington, 2005). In addition, individual studies show that risk increases with an interval of 10 years or

more since a previous pregnancy, autoimmune disease, renal disease, and chronic hypertension.

De Kat and colleagues (De Kat et al., 2019) summarized risk factors and models for predicting pre-eclampsia. Black race stood out as a significant risk factor in all the studies where the communities had a mixed race. Studies by Al-Rubaie and colleagues (Al-Rubaie et al., 2016) achieved the highest area under the curve (AUC) for predicting pre-eclampsia at 76% using maternal history.

Darkwa et al. found serum sodium and potassium significantly reduced in women with pre-eclampsia compared to normotensive pregnant women. They concluded that changes in these electrolytes might predict pre-eclampsia (Owusu Darkwa et al., 2017). Kashyap (Kashyap et al., 2006) studied the Role of the anion gap and different electrolytes in hypertension during pregnancy. They found that mean serum sodium, chloride, and bicarbonate levels were significantly higher in proteinuric hypertensive women than in controls. However, they could not confirm whether these findings could be used for prediction purposes and at what gestation age these electrolytes start getting deranged.

Similarly, Girling and Dow (Girling et al., 1997) did a cross-sectional study in London in 1997. They found that the liver enzymes in average pregnant women were lower than the reference values used for Non-pregnant women, whereas those with pre-eclampsia were much higher. However, they did not use these values as predictive tools. Ekun and colleagues (Ekun et al., 2018) found that the plasma sodium, total protein, and albumin in the preeclamptics group significantly decreased compared with control the control group. In the preeclamptic group, there was a significant increase in microalbuminuria, plasma potassium, urea, creatinine, uric acid levels, serum AST, and ALT activities. These parameters may be used for the prediction of PE.

Rodriguez et al. screened 88 normotensive gravid women between 24 and 34 weeks gestation for microalbuminuria and urinary calcium excretion (calcium/creatinine ratio) (Rodriguez et al., 1988). PE subsequently developed in 83% of participants with a high level of micro-albuminuria and a low calcium/creatinine ratio. They concluded that changes in renal function are present in gravid women who are otherwise free of symptoms in whom pre-eclampsia will eventually develop and recommended testing for micro-albuminuria and a calcium/creatinine ratio for predicting the development of pre-eclampsia.

Vahdat et al. found that the mean urine calcium of pre-eclamptic women was significantly lower than normotensive women, and the mean calcium to creatinine ratio was significantly lower in pre-eclamptic women (Vahdat et al., 2012). Ozcan et al. confirmed the findings. Therefore, they concluded that urine calcium and calcium to creatinine ratio might be a screening test to predict pre-eclampsia (Ozcan et al., 1995).

Sultana et al. found that serum calcium levels in the first and second trimesters of gestation were significantly higher than in the Controls. However, the value was substantially lower in the third trimester than in the Controls and the first and second trimesters. In addition, serum phosphate levels in the three trimesters did not show a statistically significant difference compared to the Controls and among the pregnancy groups (Sultana et al., 2012).

Ortner et al. found that mean base excess was similar in pre-eclamptic and healthy pregnant women (Ortner et al., 2015). Quantitative analysis of the base excesses in healthy pregnancies revealed respiratory alkalosis and hypo-albuminaemia, metabolically offset by acidosis (Ortner et al., 2015).

In the 1980s, a fall in the platelet count and a rise in uric acid levels were signs of PE (Fay et al., 1985). However, these were not predictive tools for PE. Yucel and Ustun (Yucel &

Ustun, 2017) evaluated the changes in the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), red cell distribution width (RDW), and plateletcrit (PCT) in pre-eclampsia and their use in predicting the severity of pre-eclampsia in Istanbul Turkey. RDW and MPV were statistically higher in the pre-eclampsia group; PLR and PCT were lower in those with severe pre-eclampsia. They concluded that MPV or PCT might be a useful clinical marker to predict severe Preeclampsia. In a systematic review by Thangaratinam et al., they found that uric acid levels in women with pre-eclampsia are a poor predictor of maternal and fetal outcomes (Thangaratinam et al., 2011).

Maternal obesity, smoking, chronic hypertension, antiphospholipid syndrome, type 2 diabetes, and insulin requirement used in a prediction model risk calculator for stillbirth (The_fetal_medicine_foundation, 2022), predicted stillbirths with 60 - 72% AUC, 75% sensitivity and close to 100% specificity (Akolekar et al., 2016; Muin et al., 2022; Yerlikaya et al., 2016). However, in maternal history and fetal growth rates, the discriminative performance of the model had a C-statistic of 0.80 (Kayode et al., 2016).

In the United Kingdom, stillbirth detection rates ranged from 28 to 48%, with an AUC of 55.0% to 65.8% even after allowing a 10% false positive rate (Akolekar et al., 2016; Yerlikaya et al., 2016). In Australia, the detection rate for stillbirth was 45%, with an AUC ranging from 59% to 84% (Malacova et al., 2020). Similarly, the detection rate for stillbirth in the United States of America has been 64% - 66% AUC (Trudell et al., 2017). Mastrodima et al. used maternal factors, PAPP-A, uterine artery Doppler pulsatility index and ductus venosus pulsatility index. They predicted 40% of all stillbirths and 55% of those due to impaired placentation at a false-positive rate of 10% (Mastrodima et al., 2016).

When using the cervicovaginal thrombospondin 1 level, Stubert et al. got 86% AUC with 94% sensitivity and 77% specificity for predicting preterm birth (Stubert et al., 2021). In Cuba, placental alpha microglobulin-1 (PAMG-1) had 100% sensitivity and 11% specificity (Cnota et al., 2022), with no area under the curve (AUC) recorded. Meertens et al. (Meertens et al., 2018) found, in a systemic review, that most models had an AUC of 54% - 70% for both the development and validation of prediction models for preterm birth.

CHAPTER THREE: METHODS

3.1 Study setting

We researched at St. Mary's Hospital Lacor (LacorHospital, 2020). It is a private, not-for-profit hospital founded by the Catholic Church. It is located six kilometres west of Gulu town along Juba Road in the Gulu district (Longitude 30 – 32 degrees East and Latitude 02 – 04 degrees North). St. Mary's Hospital Lacor is one of the teaching hospitals of Gulu University with a bed capacity of 482. The hospital has specialists, medical officers, midwives, nurses, laboratory and radiology staff, and support and administrative staff.

The hospital receives over nine thousand antenatal mothers yearly and conducts about seven thousand deliveries yearly (LacorHospital, 2020). The standard of care is the Ministry of Health guidelines used by all the different healthcare cadres in the hospital. Where no Uganda ministry of health guideline exists, they use the World Health Organisation (WHO) guidelines (LacorHospital, 2020). This study was done in the general antenatal clinic run by midwives from Monday to Friday, 8 am to 5 pm. The mothers who are found to have any pregnancy complications are referred to the doctor on duty or the labour and delivery ward, where there is always a doctor. The hospital manages two to five mothers with preeclampsia weekly, translating to at least 150 mothers annually. The hospital has an accredited laboratory for general and some specialised tests, especially haematology, serum and urine chemistry, hormonal profile and histopathology.

The hospital has user fees for Antenatal care at five thousand (Ugx 5,000/=) (approximately $1.5), Normal delivery at fifteen thousand (Ugx 15,000/=) (about $4.50) and Caesarean section going for twenty-five thousand (Ugx25,000/=) (about $7.5) Uganda shillings (LacorHospital, 2020).

3.2 Study Design

This research was a Prospective cohort study.

3.3 Target population

We targeted all pregnant women attending antenatal care at St. Mary's Hospital Lacor.

3.4 Selection Criteria

3.4.1 Inclusion criteria

While all expectant mothers attending antenatal care at St. Mary's Hospital Lacor were eligible, we gave those mothers whose pregnancies were less than 16 weeks a return date for the recruitment. We included women of gestational age of 16 to 24 weeks and those who gave informed written consent to participate in the study.

3.4.2 Exclusion criteria

We excluded women carrying fetuses with lethal congenital anomalies and those with preeclampsia at the time of recruitment.

3.5 Sample size estimation

Using Yamane's 1967 formula (V. Kasiulevičius et al., 2006)

Sample size $n = N / 1+Ne^2$

Where N is the finite population size	of 7,000 mothers who come for ANC annually
The margin of error (e)	5%
Therefore	$n = 7,000 / 1+7,000(0.05)^2$
	$n = 379$

The required sample size was **379 mothers** per sub-study and 1,137 from three sub-studies.

Using the online tool for calculating sample size for cohort studies (Riley et al., 2020), the ten known predictors of adverse pregnancy outcomes from literature (obesity, nulliparity,

personal history of preeclampsia, family history of preeclampsia, prenatal hypertension, early menarche and cigarette smoking, high pulsatility index, high resistive index, end-diastolic notch) and global prevalence of preeclampsia estimated at 4.6% (Abalos et al., 2013), we estimated the power at 80%, the confidence level of 95% and margin of error at 5%. Therefore, the sample size was five hundred eighty (580) mothers. Since 580 was way above the 379 mothers, all the mothers were to be recruited for all three sub-studies. However, since it is documented that the hospital delivery rate is 55% in northern Uganda (Ediau et al., 2013), we doubled the sample size to cater for loss to follow-up or withdrawal from the study. That left us with a sample size of **1,160 pregnant mothers**. When using the Riley method (Riley et al., 2020) to calculate sample size for a prediction model development, the more predictors, the bigger the sample size. Other objectives had less than ten predictors, so they would have had a smaller sample size. So, we chose one higher sample size for all the objectives and recruited the same participants to enable us to merge the different objectives during model development.

Research Paradigm

This was a quantitative research and a positivist paradigm, with the belief that there is an objective reality that can be studied using systematic, observable and measurable means to uncover the universal laws and principles governing the physical world (Bourdeau, 2008; Neuman, 2013).

3.6 Data collection procedure

We used consecutive sampling. We informed the mothers about the study during their morning health education meeting on arrival at the hospital. All the women who satisfied the inclusion criteria were approached and requested to give informed consent. All the mothers had their history, physical examination, and uterine artery Doppler ultrasound done. The

mothers recruited after the 1,000th mother did not undergo laboratory tests for logistical reasons. Details are in **Figure 3**.

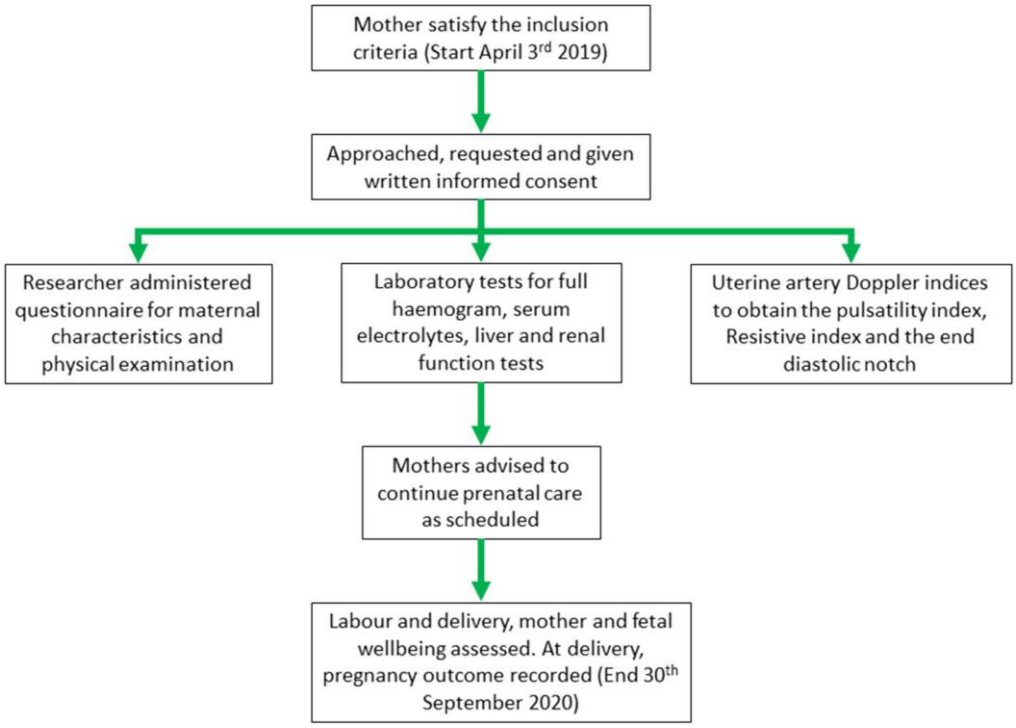

Figure 3: Data collection procedure

3.6.1 Maternal history and Physical Examination

The mothers got questionnaires about their personal history administered by a research assistant (midwife) who helped them understand the questions, fill in their answers, and take their weight and height (to calculate body mass index BMI) and blood pressure.

3.6.2 Laboratory tests

The urine sample: The mother was given a urine bottle and instructed to open the bottle, collect midstream urine, and tighten the bottle cap. She brought the urine sample to the research assistant. The Research assistant dipped the Uri stick into the urine sample and read the results after one minute for the presence of protein, glucose, pH, bilirubin, blood, nitrites,

ketones, specific gravity, and leucocytes, and recorded the results. The urine sample was immediately taken to the laboratory for centrifugation and Microscopy for casts and detection of other cells.

Blood sample: A total of six millilitres of blood was collected. Three millilitres of the blood were put in an EDTA (purple top bottle) and used for full haemogram. The remaining blood sample was placed in a clean vacutainer (red-top bottle), allowed to clot, and used to test for serum electrolytes and liver and renal function tests. We stored the remaining blood and sera in the laboratory refrigerator for any other tests requested for the same patient by the hospital clinical team managing her.

The complete blood count: We put the blood sample in the EDTA bottle in an automated coulter counter, which analyzed it and printed out the results. We shared the result with the patient, and the principal investigator stored a copy.

Renal function test: we used the serum from the red-top bottle to quantify serum urea, creatinine, and electrolytes – sodium, chloride, potassium, calcium, phosphorus, and bicarbonates.

Liver function test: We used another portion of the serum from the red top bottle for quantifying total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and albumin.

3.6.3 Ultrasound examination

The mothers were requested to empty their urinary bladder and lie supine on the examination couch. One Obstetrician & Gynaecologist (trained in advanced obstetric ultrasound equivalent to a diploma at McMaster University, Ontario, Canada) performed the uterine artery Doppler sonography trans-abdominally at 16 to 24 weeks, according to the

international society of ultrasound in obstetrics and gynaecology (ISUOG) guidelines (ISUOG, 2010, 2013), from April 2019 to March 2020 using Logiq V2 ultrasound with a curvilinear transducer 3-5 MHz. If the mother felt uncomfortable during the ultrasound examination, we requested her to lie left lateral or on any side until she felt comfortable.

We measured cervical length trans-abdominally and noted any adnexal masses. In addition, we had a foetal anatomical survey, biometry, fetal heart rate, and calculated amniotic fluid index. The ultrasound probe was placed longitudinally in the lower lateral quadrant of the abdomen and angled medially. We used colour flow mapping to identify the uterine artery as it crosses the external iliac artery. The Doppler sample volume was adjusted to 2 mm and placed about 1 cm downstream on the uterine artery from this crossover point. We corrected the angle of insonation to less than 30 degrees before getting the waveforms. In addition, we obtained automated measurements of the waveforms for pulsatility (PI) and resistive indexes (RI) from the ultrasound machine and observed them for end-diastolic notching (ISUOG, 2013). Finally, we repeated the exact process for the contralateral uterine artery. **Figure 1** shows the appearance of the Doppler flow tracing we obtained from some of the participants we examined. We did Five to ten ultrasound scans daily from Monday to Friday and not more than fifty scans weekly. Pictures of the relevant structures were saved on the hard drive of the ultrasound machine and then later transferred to an external drive.

3.6.4 Validity, reliability and quality assurance

For quality assurance, Dr Rosemary Byanyima from the Department of Radiology at Mulago National Referral Hospital examined the soft copies of 10% of the Doppler sonography waveforms selected randomly and advised accordingly. Validity and reliability of the research result were ensured by strictly adhering to the standard operating procedure set for the research and following the international guidelines for uterine artery Doppler sonography.

3.6.5 Follow up

We advised the mothers to continue their routine antenatal care every four weeks as scheduled by the hospital or return to the hospital each time they were not feeling well. They were encouraged to deliver in the Hospital. These were not research-related visits. Each time they returned to the hospital, their weight, blood pressure, fundal height, and fetal heart rate were checked; any discomfort or illness experienced since the last visit was explored. The research team only waited for the time for admission for labour and delivery.

3.6.6 Labour and delivery

We assessed their urine protein, blood pressure, weight, and fundal height in labour. We recorded at delivery the baby's sex, birth weight, Apgar score, and other associated complications (need for resuscitation, antibiotics, IV fluids, blood transfusion, oxygen therapy). We also assessed the mother for difficulties (need for resuscitation, antibiotics, intravenous fluids, blood transfusion, and oxygen therapy). We examined the placenta under flowing water. We noted the following: Weight of the placenta, Color of the placenta (on the fetal side), Number of cotyledons seen, Extra lobes of the placenta, Cord insertion – central or eccentric, and Cord appearance, coils, and true knots. The total duration of hospital stay and treatment received was also recorded. We followed the participants while they were admitted to the hospital. The mother and baby were discharged from the study on discharge from the hospital or death.

3.7 Duration of the study:

The research started on 3rd April 2019 and ended on 30th September 2020. The first twelve months were for recruitment, and the rest was for follow-up. Therefore, the total duration of the study was eighteen months.

3.8 Data management procedure

3.8.1 Variables collected

Predictors: A questionnaire was completed for social demographic characteristics, physical examination and laboratory tests (complete blood count, urinalysis, and liver and renal function tests), fetal ultrasound anatomy survey, and uterine artery Doppler indices (for Pulsatility index, resistive index, and end-diastolic notch).

Outcomes**:**

(i) Preeclampsia by the time of delivery (or pregnancy termination).

(ii) Other adverse pregnancy outcomes were stillbirth, low birth weight < 2.5 kg, and preterm birth.

3.8.2 Data analysis plan

The study population was analyzed using descriptive statistics as follows:

1. The participants were characterized based on their social demographic characteristics, physical examination findings, laboratory findings, and ultrasound findings using proportions.
2. Determined the incidence of preeclampsia and adverse pregnancy outcomes using percentage
3. Compared the baseline sonographic, laboratory and maternal characteristics of the participants: Those with and those without preeclampsia and adverse pregnancy outcomes using t-tests, Mann-Whitney test and Pearson's chi-square test
4. Did univariable analysis to determine the characteristics associated with the adverse pregnancy outcomes. The characteristics with p-value ≤0.20 were taken for multivariable analysis.
5. Did multivariable analysis to find out whether the characteristics are independent predictors of preeclampsia and adverse pregnancy outcomes.

6. Developed models for the prediction of adverse pregnancy outcomes using maternal demographic and clinical findings, laboratory findings, uterine artery Doppler indices and a combination of the characteristics
7. I validated the models using K (10)-fold cross-validation for accuracy, sensitivity, and specificity of the area under receiver operating characteristic (AUC-ROC) curves.
8. Characteristics with p-value ≤0.05 were independent predictors of preeclampsia and adverse pregnancy outcomes.

3.8.3 Statistical analysis

The datasets were preprocessed in Stata 15, and models were built in RStudio. We combined all four datasets for maternal characteristics, uterine artery Doppler indices, laboratory tests, and pregnancy outcomes. We applied the t-test and Mann-Whitney tests to compare means and medians, respectively, and Pearson's chi-square to compare proportions for categorical variables of those retained in the study and those lost. We also calculated the ratios of women who got preeclampsia and stillbirth at different gestation ages (in weeks). Finally, we analysed univariable and got unadjusted p-values for every variable collected.

We added all variables with p-values ≤0.20 or known risk factors for adverse pregnancy outcomes to a logistic regression model in RStudio. Stepwise, we removed the non-statistically significant predictors in the logistic regression model. We retained the independent risk factors for preeclampsia and adverse pregnancy outcomes for different variables (maternal history and physical examination, uterine artery Doppler indices and laboratory tests). We used these variables to build the models of choice.

The preeclampsia, stillbirth, low birth weight and preterm birth (cases) distribution revealed imbalances in the number of cases and controls. Few mothers with preeclampsia, stillbirth, low birth weight and preterm birth (cases) compared to those without (controls). Such

occurrence often biases prediction models and classification of cases. The remedy was to include the treatment of imbalances in the data sets by using random oversampling examples (ROSE) (Nicola Lunardon, 2014) to overcome the drawbacks of over-and under-samplings.

We applied the ROSE technique to the combined datasets and obtained a distribution of:

- Normotensive and preeclampsia cases as 399 (51.0%) and 383 (49.0%), respectively
- Live births and stillbirth cases as 400 (51.1%) and 383 (48.9%), respectively
- Normal and low birth weights at term as 349 (51.2%) and 332 (48.8%), respectively
- Term and preterm births as 394 (50.9%) and 380 (49.1%), respectively

We built models from each data sub-group and a combination of sub-groups from the original datasets. In addition, we built similar validation models using the synthetic dataset derived from the ROSE package. Finally, we evaluated the models using K (10)-fold cross-validation into a confusion matrix to obtain the AUC's accuracy, sensitivity, and specificity. We also got the models' coefficients, risk ratio, and McFadden's pseudo R^2 for the model's goodness of fit. For example, the variables were considered independent risk factors for preeclampsia if their p-value <0.05 in the model. The models also had a good fit if McFadden's pseudo-R2 value was between 0.2 and 0.4.

The choice of the statistical method used

The type of statistical analysis used depended on the incidences of adverse pregnancy outcomes and not the dataset collected for the different sub-studies to predict preeclampsia and adverse pregnancy outcomes using maternal history, uterine artery Doppler sonography and laboratory blood tests. The imbalance in the dataset makes the prediction model development difficult because of the risk of overfitting (Demšar & Zupan, 2021).

3.9 Limitations of the study

St. Mary's Hospital Lacor had no electronic medical records, so we could not verify some past medical history. In addition, patients were not motivated by transport refunds or covering hospital bills. The study also coincided with the COVID-19 pandemic lockdowns. These lockdowns increased the number of those lost to follow-up. We used the information we got during recruitment without verifying anything and left out those lost to follow up on the final analysis.

3.10 Dissemination of results

The results of this study are published in peer-reviewed journals. The original document used in the data collection is being kept safe by the PhD student.

3.11 Ethical consideration

Makerere University School of Medicine Research and Ethics Committee (Reference number 2018-105) and Uganda National Council for Science and Technology (Reference number HS258ES) approved the study. We obtained administrative clearance to research at St. Mary's Hospital Lacor (Reference number LHIREC Adm 009/11/18). The midwives informed the participants about the study during the morning health education when they arrived at the hospital. Those who satisfied the inclusion criteria were approached and requested informed consent. We sought written informed consent from every participant in either English or Acholi language. Those with lethal congenital anomalies were referred to the hospital obstetrician on duty for further management.

CHAPTER FOUR: RESULTS

4.0 Introduction

We recruited 1,285 participants, and 1,004 deliveries were obtained at St. Mary's Hospital Lacor. By the end of the study period, two hundred eighty-one (281) participants were lost to follow-up, details in **Figure 4.**

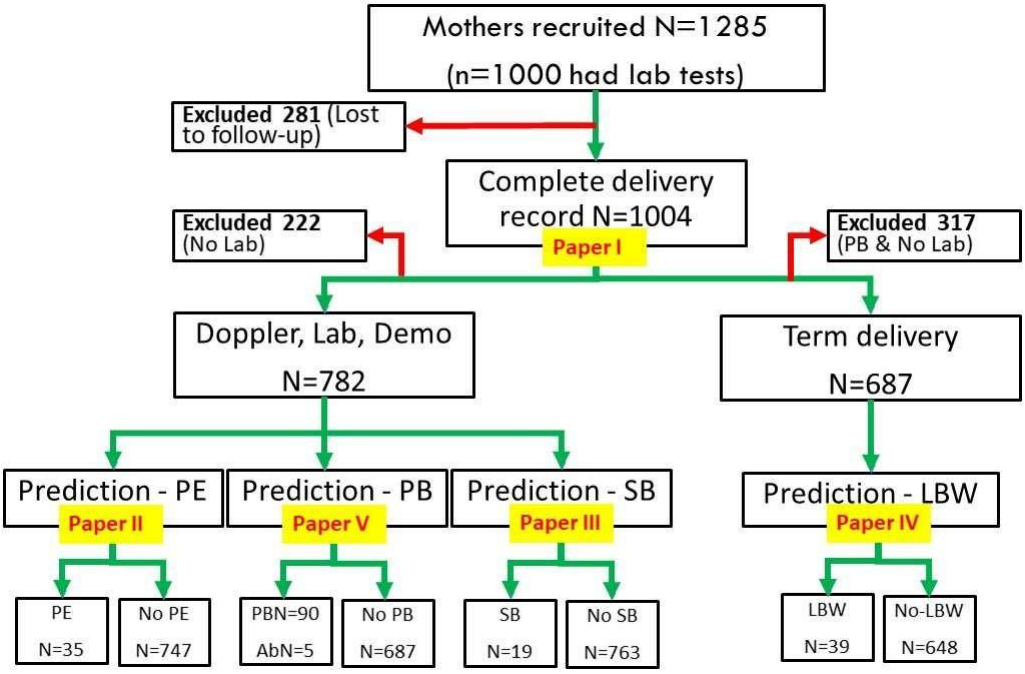

Figure 4: Flow chart of participants through the study

4.1 Maternal characteristics in the second trimester

Of the mothers recruited, the mean maternal age was 26 years, ranging from 15 to 47 years; 1,173 (91.3%) were from 18 to 35 years. The average parity was 1.5, with a range of 0 – 9. Only 0.2% (2 out of 1,285) had smoked cigarettes in their lifetime and were no longer actively smoking at the time of recruitment. The prevalence of prenatal hypertension was 0.5% (7 out of **1**,285) without proteinuria, and 25.9% of participants had an end-diastolic notch (11.0% bilateral and 14.9% unilateral notches). The 95th percentile pulsatility index (PI) and resistive index (RI) were 1.34 and 0.69, respectively. The prevalence of leucocytosis (white blood cell count above 11000 per microliter) was 2.3%. Details are in **Table 1**.

Table 1: Maternal characteristics at recruitment

Characteristics (n=1,285)		
Maternal age ≥35years	111	
Maternal age <35 years	1,174	91.4
: Single	22	1.7
Married / cohabiting	1,263	98.3
Nulliparity	412	32.1
Marital StatusHistory of miscarriage	253	19.7
Multigravida	873	67.9
Unemployed	429	33.4
Informal Employment	777	60.5
Formal (salaried job)	79	6.2
	113	8.8
No previous history of preterm birth	760	59.1%
Personal history of preeclampsia	mean (sd)15	1.2
No Personal history of preeclampsia	858	66.7
No Family history of preeclampsia	1,239	96.4
Family history of preeclampsia	46	3.6
Presence of a chronic illness	113	8.8
Body mass index ≥26.56Kgm^{-2}	322	25.1
Body mass index <26.56Kgm^{-2}	963	74.9
Diastolic Hypertension ≥90mmHg	34	3.3
Multiple pregnancies	28	2.2
Singleton pregnancy	1,257	97.8
No End diastolic notch	953	74.2
Unilateral end diastolic notch	191	14.9
Bilateral end diastolic notch	141	11.0
Average pulsatility index ≥1.34	66	5.1
Average pulsatility index <1.34	1,219	94.9
Average Resistive index ≥0.69	56	4.4
Average Resistive index <0.69	1,229	95.6
Maternal Laboratory tests (n=1000)		
Serum ALP ≥98 IU/L	962	96.2
Serum ALP <98 IU/L	38	3.8
Serum albumin <3.5mg/dL	224	22.4
Serum albumin 3.5 - 4.1mg/dL	714	71.4
Serum albumin >4.1mg/dL	62	6.2
Lymphocyte Count <900 cells/µl	51	5.1
Lymphocyte Count 900-3900 cells/µl	931	93.1
Lymphocyte Count >3900 cells/µl	18	1.8
Total White blood cell count >11000cell/µl	16	1.6
Haemoglobin level <11.0g/dL	515	51.5

4.2 Maternal retention to prenatal care

The mothers who were lost to follow-up were more likely to be younger and unemployed, with a lower body-mass index. The details are in **Table 2**.

Table 2: Comparison of characteristics of individuals retained in the study versus those lost to follow–up

Characteristics	**Retained = 1004 (n, %)**	**Lost =281 (n, %)**	***p*-value**
maternal age ≥35 years	86 (86.5%)	15 (13.5%)	**0.026**
maternal age <35 years	908 (77.3%)	266 (22.7%)	
Unemployed	311 (72.5%)	118 (27.5%)	**0.000**
Informal *Employment*	620 (79.8%)	157 (20.2%)	
Formal *Employment*	73 (92.4%)	6 (7.6%)	
Body mass index mean (sd)	24.7 (3.9)	23.7 (3.1)	**0.000**
Multiple pregnancies	26 (92.9%)	2 (7.1%)	0.057
Singleton	978 (77.8%)	279 (22.2%)	
Average pulsatility index ≥1.34			0.097
Average pulsatility index <1.34	947 (77.7%)	272 (22.3%)	
Maternal Laboratory tests	**Retained = 782**	**Lost =218**	***p*-value**
Serum ALT mean (sd)	30.6 (27.7)	27.9 (23.9)	0.174
Lymphocyte Count mean (sd)	1.8 (0.9)	1.9 (1.5)	0.095

4.3 Pregnancy outcomes of the participants retained to care

PE, preterm birth, low birth weight, and stillbirth incidence were 4.3%, 11.8%, 11.5%, and 2.5%, respectively. The overall perinatal death rate was 3.9%. The details are in **Table 3**. The estimated blood loss at delivery was subjective; any mother with a diagnosis of postpartum haemorrhage was assumed to have lost at least 500 millilitres of blood**.**

Table 3: Pregnancy outcome of participants

Variable	Frequency n=1004	Percentage
Hypertension Bp >=140/90mmHg		
No *Hypertension Bp <140/90mmHg*	939	95.5
Preeclampsia Present	43	95.7
Preeclampsia absent	961	4.3
Caesarean delivery	198	19.7
Normal delivery	806	80.3
Estimated blood loss <500 ml		
Estimated blood loss >=500 ml	71	7.1
preterm <37weeks	128	12.8
Term ≥37	876	87.2
Birthweight (Kg) <2.5		
Birthweight (Kg) ≥2.5	889	88.5
Apgar score of 0/10 at one minute - Dead (Stillbirth*)*		
Apgar score of 1-7*/10 at one minute* Asphyxia	107	10.7
Apgar score of 8-10*/10 at one minute*		
Babies who had resuscitation at birth		
Babies who had no resuscitation at birth	747	74.4
Condition of the baby on discharge from the hospital -Dead	39	3.9
Condition of the baby on discharge from the hospital -Sick	44	4.4
Normal*Condition of the baby on discharge from the hospital* - Normal	921	91.7

4.4 Pre-eclampsia

Pre-eclampsia developed in 43 out of 1004 (4.3%) who returned to deliver in the hospital. However, the overall incidence was higher among those who delivered preterm and lower in term deliveries.

4.4.1 Incidence of preeclampsia

In **Table 4,** the classification of preeclampsia was made according to FIGO (Poon et al., 2019). The calculations were made in ten thousand (10,000) women weeks to produce whole numbers, which are easier to compare. The incidence of pre-eclampsia was 68 per 10^4 women

weeks at <34 weeks and 9 per 10^4 women weeks at ≥34 weeks. That was even lower at term with 9 per 10^4 women weeks.

Table 4: Incidence of preeclampsia

Variables	N	Diseased	% (95% CI)	Incidence of preeclampsia per 10^4 women weeks
Overall preeclampsia				
No preeclampsia	961	0	95.7% (94.3% - 96.9%)	0
Number with preeclampsia	43	43	4.3% (3.1% - 5.7%)	11 (8 - 15)
Early and late-onset preeclampsia				
Early onset preeclampsia <34 weeks	35	7	20% (8.4% - 36.9%)	68 (29 - 126)
Late-onset preeclampsia (Delivery at ≥34 weeks)	969	36	3.7% (2.6% - 5.1%)	9 (7 - 13)
Preterm and term preeclampsia				
Preterm preeclampsia (Delivery at <37 weeks)	128	21	16.4% (10.5% - 24.0%)	48 (31 - 71)
Term preeclampsia (Delivery at ≥ 37 weeks)	876	22	2.5% (1.6% - 3.8%)	6 (4 - 10)

4.4.2 Comparison of second-trimester characteristics of participants who developed preeclampsia and those who did not

The mean PI was 1.092 (95% CI 0.935-1.248) for those who developed PE and 0.796 (95% CI 0.77 - 0.813) for those who did not, with a $p<.001$. The significant differences in maternal characteristics among those who developed preeclampsia and those who did not are listed below. Those who developed preeclampsia were more likely to have a history of preeclampsia, higher body mass index, blood pressure, white blood cell count, neutrophil and lymphocyte count, and a low GGT level. Details are in **Table 5.**

Table 5: Recruitment characteristics of those with preeclampsia and controls

Characteristics	Normal N=961	Preeclampsia N=43	*p*-value
No history of preeclampsia			
Maternal history of preeclampsia	7 (50.0%)	7 (50.0%)	0.000
Body mass index mean (sd)	24.6 (3.8)	26.6 (5.3)	0.001
Diastolic blood pressure mean (sd)	63.7 (10.2)	71.7 (12.1)	0.000
Multiple pregnancies	21 (80.8%)	5 (19.2%)	
Singleton	940 (96.1%)	38 (3.9%)	0.000
No *end diastolic* notch	717 (97.7%)	17 (2.3%)	
Unilateral *end diastolic* notch	147 (94.2%)	9 (5.8%)	0.000
Bilateral *end diastolic* notch	97 (85.1%)	17 (14.9%)	
Average pulsatility index mean (sd)	0.80 (0.28)	1.09 (0.51)	0.000
Average Resistive index	0.74 (0.11)	0.41 - 2.1)	0.000
Lymphocyte Count mean (sd)	1.18 (0.82)	2.33 (2.13)	0.001
Total White blood cell count mean (sd)	6.23 (2.06)	7.93 (10.12)	0.001

4.4.5 Adverse Pregnancy outcomes associated with preeclampsia

Univariable analysis was done. Preeclampsia was associated with preterm birth, low birth weight, stillbirth, caesarean section delivery and postpartum haemorrhage. At multivariable analysis, the mothers who developed preeclampsia were more likely to deliver preterm, get a stillbirth or have profuse blood loss at delivery. Having preeclampsia did not affect the mode of delivery and birth weight. Details are in **Table 6**.

Table 6: Unadjusted and adjusted pregnancy outcomes associated with preeclampsia

Unadjusted pregnancy outcomes associated with preeclampsia		
Variable	**Unadjusted OR (95% CI)**	**p-value**
Stillbirth (Apgar score 0 at 1 minute)	10.19 (3.76 - 25.05)	**0.000**
Blood loss estimate ≥ 500 ml (PPH)	3.84 (1,67 - 8.05)	**0.001**
Preterm <37 weeks	7.62 (4.04 - 14.36)	**0.000**
Low birth weight <2.5Kg	5.17 (2.56 - 10.03)	**0.000**
Caesarean mode of delivery	1.85 (0.92 - 3.55)	0.071
Adjusted pregnancy outcomes associated with preeclampsia		
Preterm <37 weeks	5.70 (2.91 - 11.15)	**0.000**
Stillbirth (Apgar score 0 at 1 minute)	5.25 (1.89 - 14.63)	**0.002**
Blood loss estimate ≥ 500 ml (PPH)	3.75 (1.65 - 8.55)	**0.002**
Intercept	0.02 (0.01 - 0.03)	0.000

4.4.6 Prediction of preeclampsia at St. Mary's Hospital Lacor

4.4.6.1 Unadjusted p-values for prediction of preeclampsia

Maternal history and physical examination showed a significant relationship between preeclampsia and a personal history of preeclampsia, diastolic and systolic hypertension, and multiple pregnancies. All the uterine artery Doppler indices were significantly related to preeclampsia. Serum alkaline phosphatase <98 IU/L, albumin <3.5mg/dL, white blood cell count of >11000 cells/µl, and lymphocyte count of 800 – 4000 cells/µl also had a significant relationship with preeclampsia. Details are in **Table 7**.

Table 7: Unadjusted p-values for prediction of preeclampsia

Variable	Unadjusted Odds Ratio (95% CI)	p-value
Maternal history and physical examination		
Maternal age ≥35 years	1.57 (0.64 - 3.82)	0.321
Para 1 - 2	1.53 (0.60 - 3.90)	0.376
Nulliparity	2.39 (0.94 - 6.08)	0.068
Personal history of preeclampsia	26.50 (8.83 - 79.55)	**0.000**
BMI of 21.92 - 26.56 Kg/m^2	0.63 (0.26 - 1.51)	0.299
BMI of ≥ 26.56Kg/m^2	2.20 (0.99 - 4.88)	0.052
Diastolic blood pressure ≥ 90 mmHg	6.75 (2.35 - 19.40)	**0.000**
Systolic hypertension ≥140mmHg	17.89 (3.87 - 82.60)	**0.000**
Multiple pregnancies	5.89 (2.11 - 16.46)	**0.001**
Uterine artery Doppler indices and sonography		
Average pulsatility index ≥ 1.34	7.88 (3.80 - 16.36)	**0.000**
Average resistive index ≥ 0.69	4.77 (2.46 - 9.24)	**0.000**
Unilateral end-diastolic notch	2.58 (1.13 - 5.91)	**0.025**
Bilateral end-diastolic notch	7.39 (3.65 - 14.96)	**0.000**
Maternal Laboratory tests		
Serum ALP <98 iu/L	5.02 (1.79 - 14.07)	**0.002**
Serum albumin 3.5-4.1mg/dl	1.61 (0.58 - 4.42)	0.359
Serum albumin <3.5mg/dl	2.96 (1.03 - 8.49)	**0.043**
White cell count of (4.0 - 11.0)*10^3	0.70 (0.26 - 1.87)	0.480
White cell count of (> 11.0)*103	5.87 (1.38 - 24.92)	**0.017**
Lymphocyte count of (0.8 - 4.0)*10^3	0.35 (0.13 - 0.94)	**0.038**
Lymphocyte count of > 4.0*10^3	2.63 (0.62 - 11.14)	0.190

4.4.6.2 Models for prediction of preeclampsia

Six models were built from maternal history and physical examination, uterine artery Doppler sonography indices, maternal laboratory blood tests and the combinations of the different datasets.

In **Table 8**, maternal age ≥ 35 years, nulliparity, personal history of preeclampsia, body mass index over 26.5Kg/m2, diastolic hypertension, and multiple pregnancies were independent risk factors for preeclampsia in model 1. The average pulsatility index ≥1.34 and bilateral end-diastolic notch were independent risk factors for preeclampsia in model 2. Maternal age ≥ 35 years, nulliparity, personal history of preeclampsia, BMI ≥ 26.5, diastolic hypertension, and end-diastolic notch remained the independent risk factors for preeclampsia used to build this model 3. The independent risk factors for preeclampsia were a total white blood cell count of over 11,000 cells per microliter and serum ALP <98 IU. In addition, lymphocyte count within the normal range was protective against preeclampsia in model 4.

Table 8: Models for prediction of preeclampsia

Variable		
Model 1, Maternal history and physical examination		**Odds Ratio (95% CI)**
Maternal age ≥ 35 years	4.69 (1.28 - 16.36)	**0.020**
Para 1 - 2	2.36 (0.72 - 8.71)	0.175
Nulliparity	6.13 (1.68 - 26.05)	**0.009**
Personal history of preeclampsia	53.01 (12.8 - 163.7)	**0.000**
BMI of 21.92 - 26.56 Kg/m^2	1.01 (0.33 - 3.51)	0.993
BMI of ≥ 26.56Kg/m^2	3.70 (1.31 - 12.54)	**0.021**
Diastolic blood pressure ≥ 90 mmHg	5.66 (1.47 - 18.26)	**0.006**
Multiple pregnancies	5.16 (1.07 - 18.45)	**0.020**
Intercept	0.00 (0.00 - 0.02)	0.000
Model 2, Uterine artery Doppler indices for prediction of preeclampsia		
Unilateral end-diastolic notch	2.39 (0.92 - 5.78)	0.060
Bilateral end-diastolic notch	3.71 (1.30 - 9.81)	**0.010**
Average pulsatility index ≥ 1.34	3.41 (1.22 - 9.48)	**0.018**
Intercept	0.03 (0.01 - 0.04)	0.000
Model 3, Combined maternal history and uterine artery Doppler indices		
Maternal age ≥ 35 years	4.93 (1.29 - 18.27)	**0.017**
Para 1 - 2	2.13 (0.63 - 8.17)	0.244
Nulliparity	4.39 (1.19 - 19.54)	**0.036**
Personal history of preeclampsia	36.88 (8.40 - 178.40)	**0.000**
BMI of 21.92 - 26.56 Kg/m^2	1.03 (0.33 - 3.71)	0.957
BMI of ≥ 26.56Kg/m^2 (4th quadrant)	3.42 (1.17 - 11.97)	**0.034**
Diastolic blood pressure ≥ 90 mmHg	4.39 (1.06 - 15.21)	**0.027**
Multiple pregnancies	6.22 (1.29 - 18.27)	**0.015**
Unilateral end-diastolic notch	2.39 (0.85 - 6.30)	**0.083**
Bilateral end-diastolic notch	4.40 (1.68 - 11.29)	**0.002**
Intercept	0.00 (0.00 - 0.02)	0.000
Model 4, Maternal laboratory characteristics for prediction of preeclampsia		
White cell count of (4.0 - 11.0)10^3	1.18 (0.40 - 4.25)	0.780
White cell count of (> 11.0)*103	7.38 (1.11 - 46.17)	**0.033**
Serum ALP <98 iu/L	5.84 (1.78 - 16.39)	**0.001**
Serum albumin 3.5-4.1mg/dl	2.01 (0.74 - 6.60)	0.247
Serum albumin <3.5mg/dl	2.84 (0.97 - 9.67)	0.080
Serum urea 11.0 - 44.0 iu/L	4.30 (0.83 - 80.02)	0.158
Serum urea <11.0 iu/L	8.00 (1.02 - 169.30)	0.074
Lymphocyte count of (0.8 - 4.0)10^3	0.29 (0.10 - 1.06)	**0.041**
Lymphocyte count of > 4.0*10^3	1.30 (0.19 - 7.91)	0.705
Intercept	0.01 (0.00 - 0.06)	0.000

Maternal age ≥ 35 years, nulliparity, personal history of preeclampsia, BMI ≥ 26.5Kg/m2, diastolic hypertension, white blood cell count over 11,000, and serum ALP <98 IU were independent risk factors for preeclampsia used to build this model. Maternal age ≥ 35 years, personal history of preeclampsia, BMI ≥ 26.5 kg/m2, diastolic hypertension, bilateral end-diastolic notch, and serum ALP <98 IU were independent risk factors for preeclampsia. Details are in **Table 9**

Table 9: Combination of characteristics for prediction of preeclampsia.

Variable	**Odds Ratio (95% CI)**	**p-value**
Maternal history and laboratory tests		
Maternal age Over 34 years	3.88 (1.01 - 14.32)	**0.043**
Para 1 - 2	2.62 (0.77 - 10.15)	0.140
Nulliparity	6.32 (1.69 - 28.11)	**0.010**
Personal history of preeclampsia	48.09 (11.11 - 227.25)	**0.000**
BMI of 21.92 - 26.56 Kg/m^2	1.06 (0.34 - 3.74)	0.923
BMI of ≥ 26.56Kg/m^2	4.41 (1.49 - 15.45)	**0.012**
Diastolic blood pressure ≥ 90 mmHg	7.24 (1.85 - 24.32)	**0.002**
White cell count of (4.0 - 11.0)10^3*	0.52 (0.18 - 1.74)	0.241
White cell count of >11.0*10^3	6.40 (1.13 - 33.82)	**0.028**
Serum ALP <98.0 iu/L	7.77 (2.04 - 25.38)	**0.001**
Intercept	0.01 (0.001 - 0.03)	0.000
Model 6, Maternal history, Doppler indices and laboratory tests		
Maternal age ≥ 35 years	3.88 (0.94 - 15.44)	0.056
Para 1 - 2	2.56 (0.73 - 10.62)	0.144
Nulliparity	4.25 (1.08 - 20.18)	0.051
Personal history of preeclampsia	32.75 (6.59 - 182.05)	**0.000**
BMI of 21.92 - 26.56 Kg/m^2	1.09 (0.34 - 3.98)	0.888
BMI of ≥ 26.56Kg/m^2	3.86 (1.25 - 14.15)	**0.027**
Diastolic blood pressure ≥ 90 mmHg	4.90 (1.15 - 18.01)	**0.022**
Unilateral end-diastolic notch	2.36 (0.81 - 6.39)	0.100
Bilateral end-diastolic notch	4.54 (1.65 - 12.20)	**0.003**
White cell count of (4.0 - 11.0) *10^3 cells /µl	0.85 (0.24 - 3.49)	0.807
White cell count of >11.0 *10^3	8.43 (0.92 - 70.62)	0.050
Serum ALP <98 iu/L	7.14 (1.76 - 24.45)	**0.003**
Lymphocyte count of (0.8 - 4.0) *10^3	0.29 (0.08 - 1.22)	0.074
Lymphocyte count of >4.0*10^3	0.84 (0.09 - 6.96)	0.876
Intercept	0.01 (0.00 - 0.06)	0.000

4.4.9 Evaluation of the Models for prediction of preeclampsia

We evaluated the models using K-fold cross-validation to obtain the classification measures: accuracy, specificity, sensitivity, and AUC, and we presented the performance of each model in **Table 10**. In general, the overall classification accuracy of the models is at least 66%, and the sensitivity is over 73%. Models 1, 3, 5, and 6 had McFadden's pseudo-R-squared value between 0.2 – 0.4, so they had a good fit. They can be used independently for screening for preeclampsia. Therefore, while screening for preeclampsia in antenatal clinics, one can use maternal history and physical findings only or in combination with uterine artery Doppler sonography, blood tests, or both. The uterine artery Doppler indices or blood tests are unsuitable for use alone since their models are not a good fit with McFadden's pseudo-R^2 <0.2.

Table 10: Model performance evaluation using K-fold cross-validation

Model	**Acc (%)**	**Sens (%)**	**Spe (%)**	**AUC (%)**	**McF**
Model 1 (History and physical exam)	66.6	82.7	49.9	78.4	**0.21**
Model 2 (Uterine artery Doppler indices)	68.8	73.7	63.7	71.4	0.09
Model 3 (Combination of models 1 and 2)	76.0	78.2	73.6	80.4	**0.25**
Model 4 (Maternal blood tests)	67.1	76.9	56.9	75.6	0.11
Model 5 (combination of models 1 and 4)	72.7	84.0	61.1	82.2	**0.26**
Model 6 (Combination of models 3 and 4)	77.0	80.2	73.6	84.9	**0.30**

Acc=accuracy, Sens=sensitivity, Spe=specificity, AUC=area under curve,

McF=McFadden's pseudo R^2

4.5 Low birth weight at term

We recruited one thousand pregnant mothers. Six hundred eighty-seven (687) mothers delivered at term. Three hundred thirteen (313) mothers were lost to follow-up or delivered preterm, dropped and not used in the data analysis. The prevalence of birth weight < 2.5 kg at term was 5.7% (39 out of 687). The details are in **Figure 4**.

4.5.2 Unadjusted estimates of the variables against low birth weight.

In **Table 11,** being nullipara or prime gravida was significantly related to low birth weight at term. Lateral placental location, an end-diastolic notch and lymphocyte count (900 - 3900 cells/µl) were significantly related to low birth weight at term.

Table 11: Unadjusted relationships with low birth weight at term

Variable	IRR (95% CI)	p-value
Primi gravida	4.82 (1.13 - 20.49)	**0.033**
Gravida 2-4	2.91 (0.69 - 12.19)	**0.144**
Nullipara	2.71 (1.04 - 7.12)	**0.042**
Para 1 - 2	1.67 (0.63 - 4.45)	0.303
Secondary level of education	1.01 (0.54 - 1.90)	0.975
Tertiary level of education	0.48 (0.17 - 1.42)	**0.186**
Body mass index ≥25 Kgm^{-2}	0.57 (0.29 - 1.11)	**0.098**
Diastolic hypertension ≥90mmHg	2.15 (0.57 - 8.15)	0.260
Lateral placental location	3.66 (1.85 - 7.23)	**0.000**
Unilateral end-diastolic notch	2.47 (1.25 - 4.87)	**0.009**
Bilateral end diastolic notch	2.73 (1.26 - 5.92)	**0.011**
Lymphocyte count of 900 - 3900 cells/µl	0.38 (0.16 - 0.93)	**0.033**
Lymphocyte Count >3900 cells / µl	2.17 (0.68 - 6.96)	**0.192**

4.5.3 Risk prediction models for low birth weight at term

In **Table 12**, model 1, being a Primi gravida, was the only independent risk factor. However, in model 2, lateral placental location is an independent risk factor for low birth weight at term. In model 5, the predictors of low birth weight were gravidity, level of education, serum ALT, GGT, lymphocyte count, placental location and end-diastolic.

Table 12: Models for the prediction of low birth weight at term

Variable	OR (95% CI)	p-value
Model 1: Maternal history and physical examination		
Secondary education	0.92 (0.46 - 1.88)	0.819
Tertiary level education	0.31 (0.07 - 0.97)	0.070
Gravida 2 - 4	3.30 (0.93 - 21.02)	0.113
Prime gravida	5.58 (1.51 - 36.10)	**0.025**
Intercept	0.02 (0.003 - 0.07)	0.000
Model 2: Obstetric ultrasound and uterine artery Doppler indices		
Lateral placental location	2.86 (1.10 - 6.95)	**0.025**
Unilateral end-diastolic notch	1.79 (0.75 - 4.00)	0.171
Bilateral end-diastolic	2.20 (0.82 - 5.26)	0.093
Intercept	0.04 (0.03 - 0.06)	0.000
Model 3: Combination of maternal history, ultrasound and uterine artery Doppler		
Secondary education	0.97 (0.48 - 2.00)	0.931
Tertiary level education	0.23 (0.05 - 0.75)	**0.028**
Gravida 2 - 4	3.56 (0.99 - 22.87)	0.095
Prime gravida	4.97 (1.32 - 32.53)	**0.039**
Lateral placental location	3.29 (1.20 - 8.35)	**0.015**
Unilateral end-diastolic notch	1.98 (0.83 - 4.46)	0.101
Bilateral end-diastolic	2.01 (0.73 - 4.88)	0.141
Intercept	0.01 (0.002 - 0.05)	0.000
Model 4: Maternal laboratory tests		
Serum GGT of 0.0 - 30.0 IU	2.91 (1.01 - 12.27)	0.082
Lymphocyte count of 900 - 3900 cells/µl (normal)	0.30 (0.12 - 0.95)	**0.024**
Lymphocyte count > 3900 cells/µl (high)	2.28 (0.46 - 10.88)	0.295
Serum ALT of 12 - 49 IU	0.33 (0.15 - 0.84)	**0.013**
Serum ALT <12 IU	0.60 (0.17 - 1.98)	0.408
Intercept	0.16 (0.03 - 0.71)	0.026

Footnote: ALT- Alanine Transaminase; AST – Aspartate Aminotransferase; ALP – Alkaline Phosphatase; GGT – Gamma Glutamyl Transferase

In model 5 for prediction of low birth weight at term, maternal history, clinical characteristics and laboratory tests were combined, being a primi gravida was a risk factor while a normal serum ALT and tertiary level of education was protective. In model 6, all the characteristics were combined and found being a primi gravida, lateral placental location, unilateral end diastolic notch were risk factors, while tertiary level of education, normal serum ALT and lymphocyte counts were protective. Details in **Table 13.**

Table 13: Combination models for the prediction of low birth weight at term

Variable	OR (95% CI)	p-value
Model 5: maternal history and laboratory tests		
Secondary education	0.91 (0.44 - 1.92)	0.798
Tertiary level education	0.26 (0.06 - 0.86)	**0.045**
Gravida 2 - 4	3.34 (0.90 - 21.87)	0.119
Prime gravida	6.35 (1.63 - 42.51)	**0.020**
Serum GGT of 0.0 - 30.0 IU	3.22 (1.11 - 13.74)	0.059
Lymphocyte count of 900 - 3900 cells/µl (normal)	0.37 (0.14 - 1.21)	0.070
Lymphocyte count > 3900 cells/µl (high)	3.59 (0.67 - 19.04)	0.128
Serum ALT of 12 - 49 IU	0.31 (0.13 - 0.80)	**0.010**
Serum ALT <12 IU	0.60 (0.16 - 2.06)	0.427
Intercept	0.04 (0.004 - 0.32)	0.005
Model 6: Combination of maternal history, laboratory tests, ultrasound and Doppler indices		
Gravida 2 - 4	3.91 (0.99 - 27.09)	0.091
Prime gravida	5.89 (1.42 -41.94)	**0.032**
Secondary education	1.06 (0.51 - 2.29)	0.876
Tertiary level education	0.16 (0.03 - 0.60)	**0.013**
Serum GGT of 0.0 - 30.0 IU	3.25 (1.11 - 13.96)	0.059
Lymphocyte count of 900 - 3900 cells/µl (normal)	0.30 (0.11 - 1.00)	**0.033**
Lymphocyte count > 3900 cells/µl (high)	2.40 (0.43 - 13.22)	0.310
Serum ALT of 12 - 49 IU	0.22 (0.09 - 0.58)	**0.001**
Serum ALT <12 IU	0.45 (0.12 - 1.59)	0.224
Lateral placental location	3.42 (1.18 - 9.19)	**0.018**
Unilateral end-diastolic notch	2.59 (1.03 - 6.18)	**0.035**
Bilateral end-diastolic	2.58 (0.91 - 6.60)	0.057
Intercept	0.04 (0.003 - 0.31)	0.005

4.5.4 Evaluation of the performance of models 1-6 for the prediction of low birth weight

All the models for predicting low birth weight had their McFadden's pseudo-R^2 value of less than 0.2; therefore, they may not be the best fit. Details in **Table 14**.

Table 14: Low birth weight model performance **evaluation** using K-fold cross-validation

Model	**Acc (%)**	**Sens (%)**	**Spec (%)**	**AUC (%)**	**McFadden's**
Model 1 (History and physical exam)	62.3	37.3	88.3	65.3	0.04
Model 2 (Uterine artery Doppler indices)	59.3	75.4	42.5	62.6	0.04
Model 3 (Combination of models 1 and 2)	62.3	61.8	64.8	71.6	0.08
Model 4 (Maternal blood tests)	59.3	81.7	35.8	66.9	0.07
Model 5 (combination of models 1 and 4)	66.7	73.4	59.6	66.9	0.12
Model 6 (Combination of models 3 and 4)	76.1	79.1	72.9	81.9	0.17

Acc=accuracy, Sens=sensitivity, Spec=specificity, AUC=area under curve, McFadden's=McFadden's pseudo R^2.

4.6 Stillbirth

The prevalence of stillbirth was 2.5% (25 out of 1004). There were 979 (97.5%) live births. Seven (28%) out of the 25 deaths occurred intrapartum. Two (8%) of the 25 mothers who lost their babies had a history of previous stillbirth.

4.6.1 Incidence of Stillbirth

The incidence rates for stillbirth were higher at lower gestation ages, as outlined in **Table 15**. For example, there were 273 stillbirths per 10^4 women weeks at <28 weeks, while only three stillbirths per 10^4 women weeks at ≥37 weeks.

Table 15: Incidence of Stillbirth

Variables	Total Population	stillbirths	% (95% CI)	Incidence of stillbirth per 10^4 women weeks
No stillbirth	979	0	0%	0
Stillbirth occurred	25	25	2.5% (1.6% - 3.7%)	6 (4 - 9)
Stillbirth occurred <28 weeks	9	6	66.7% (22.9% - 92.5%)	273 (94 - 379)
Stillbirth ≥ 28 - <37 weeks	119	9	7.6% (3.5% - 13.8%)	22 (10 - 40)
Stillbirth ≥ 37 weeks	876	10	1.1% (0.5% - 2.1%)	3 (1 - 6)

4.6.2 Unadjusted characteristics for stillbirth

Personal history of preeclampsia and any history of abortion were significantly related to stillbirth while being married or cohabiting was protective. Details are in **Table 16**. Systolic hypertension, end-diastolic notch, pulsatility and resistive indices were significantly related to stillbirth. Most laboratory characteristics had no significant relationship to stillbirth.

Table 16: Unadjusted characteristics for prediction of stillbirth

Variable	OR (95% CI)	p-value
Maternal age (years) ≥35	1.80 (0.63 - 5.14)	0.271
Married/Cohabiting	0.20 (0.50 - 0.77)	**0.020**
Nulliparity	1.82 (0.58 - 5.73)	0.307
Para 1-2	1.38 (0.44 - 4.29)	0.577
Any history of abortion	2.78 (1.30 - 6.10)	**0.011**
Informal (casual labourer)	0.67 (0.28 - 1.57)	0.356
Formal (regular salaried job)	1.89 (0.60 - 5.98)	0.277
Previous history of preterm birth	1.09 (0.25 - 4.76)	0.907
Personal history of preeclampsia	6.15 (1.60 - 23.62)	**0.008**
Family history of preeclampsia	1.06 (0.15 - 7.63)	0.954
Presence of a chronic illness	0.42 (0.06 - 3.09)	0.397
Body mass index >25Kg/m^2	0.76 (0.33 - 1.74)	0.511
Systolic blood pressure ≥140mmHg	5.94 (0.93 - 38.05)	**0.060**
Diastolic blood pressure ≥90mmHg	1.70 (0.24 - 12.08)	0.595
Multiple pregnancies	Too few	
Lateral placental location	1.22 (0.29 - 5.05)	0.788
Unilateral end diastolic notch	1.01 (0.29 - 3.47)	0.990
Bilateral end diastolic notch	3.68 (1.58 - 8.58)	**0.003**
Average Resistive index >0.65 (90th percentile)	3.75 (1.65 - 8.49)	**0.002**
Average pulsatility index >1.19 (90th percentile)	3.82 (1.69 - 8.66)	**0.001**
Serum ALP ≤98 IU (low lab range)	1.44 (0.20 - 10.45)	0.717
Serum albumin 3.5 - 4.1g/dL	0.46 (0.15 - 1.42)	**0.180**
Serum Albumin <3.5g/dL	1.27 (0.43 - 3.70)	0.667
Lymphocyte Count 0.9 - 3.9 cells/microlitre	0.33 (0.10 - 1.12)	**0.075**
Lymphocyte Count >3.9 cells/microlitre	1.89 (0.34 - 10.42)	0.465
Total White blood cell count 4000-11000 cells/microlitre	1.10 (0.26 - 4.70)	0.900
Total White blood cell count >11000 cells/microlitre	2.91 (0.28 - 30.25)	0.372
Haemoglobin level <9.5g/dL (<25th percentile)	2.78 (0.76 - 10.12)	**0.120**
Haemoglobin level 9.5 - 12.1g/dL (25th - 75th percentile)	1.02 (0.27 - 3.89)	0.981

4.6.3 Models for Prediction of Stillbirth

Model 1, the predictors of stillbirth were parity, age ≥ 35 years, history of abortion and personal history of preeclampsia. Model 2 examined the uterine artery Doppler indices. The predictor of stillbirth was the end-diastolic notch on the uterine artery Doppler flow tracing. Model 3, the predictors of stillbirth were history of abortion and end-diastolic notch on the uterine artery Doppler flow tracing. In model 4, the predictors of stillbirth were platelet neutrophil ratio, neutrophil count and haemoglobin level. Details in **Table 17.**

Table 17: Models for prediction of stillbirth

Variable	OR (95% CI)	p-value
Model 1 using maternal history for prediction of stillbirth		
Personal history of preeclampsia	11.08 (1.44 - 57.34)	**0.0075**
History of abortion	2.92 (1.07 - 7.57)	**0.0293**
Age ≥ 35 years	4.29 (0.72 - 20.72)	0.0851
nullipara	5.37 (1.10 - 36.24)	0.0576
para 1 - 2	2.28 (0.48 - 13.67)	0.3284
Intercept	0.005 (0.001 - 0.02)	0.0000
Model 2 using uterine artery Doppler indices		
Unilateral	0.40 (0.02 - 2.09)	0.3843
Bilateral	4.28 (1.54 - 11.19)	**0.0035**
Intercept	0.02 (0.01 - 0.03)	0.0000
Model 3 combination of maternal history and uterine artery Doppler indices		
Variable	**OR (95% CI)**	**p-value**
History of abortion	3.29 (1.24 - 8.41)	**0.0134**
Unilateral	0.38 (0.02 - 2.01)	0.3618
Bilateral	4.49 (1.60 - 11.88)	**0.0029**
Intercept	0.01 (0.006 - 0.03)	0.0000
Model 4 maternal laboratory tests for prediction of stillbirth		
Platelet neutrophil ratio of 47.04 - 83.95	1.80 (0.46 - 9.00)	0.4232
Platelet neutrophil ratio of > 83.95	5.76 (1.12 - 35.90)	**0.0437**
Neutrophil count of (2.63 - 4.54) *1000	2.14 (0.60 - 8.12)	0.2453
Neutrophil count of (>4.54) *1000	4.16 (0.77 - 22.81)	0.0958
Haemoglobin level of 9.5 - 12.1g/dL	0.32 (0.11 - 0.89)	**0.0287**
Haemoglobin level of > 12.1g/dL	0.33 (0.07 - 1.14)	0.1027
Intercept	0.01 (0.001 - 0.06)	0.0000
Model 5 combination of maternal history and laboratory tests		
History of abortion	3.10 (1.11 - 8.26)	**0.0254**
Age ≥ 35 years	4.87 (0.79 - 24.57)	0.0677
nullipara	5.09 (1.02 - 35.71)	0.0715
para 1 - 2	2.51 (0.52 - 15.59)	0.2831
Haemoglobin level of 9.5 - 12.1g/dL	0.33 (0.109 - 0.95)	**0.0411**
Haemoglobin level of >12.1g/dL	0.27 (0.06 - 0.99)	0.0656
Intercept	0.01 (0.001 - 0.005)	0.0000
Model 6: Maternal history, uterine artery Doppler indices and laboratory tests		
Personal history of preeclampsia	5.18 (0.60 - 30.66)	0.0916
History of abortion	3.07 (1.11 - 8.05)	**0.0243**
Unilateral	0.37 (0.02 - 1.98)	0.3507
Bilateral	3.51 (1.13 - 9.92)	**0.0209**
Haemoglobin level 9.5 - 12.1 g/dL	0.33 (0.11 - 0.93)	**0.0375**
Haemoglobin level > 12.1 g/dL	0.30 (0.06 - 1.07)	0.0850
Intercept	0.03 (0.01 - 0.07)	0.0000

4.6.4 Evaluation of the models of stillbirth

The model's AUC ranges from 66.8% to 75.0%, with accuracies of 63.9% to 68.1% (**Table 18)**. Unfortunately, all the models for the prediction of stillbirth had McFadden's pseudo R^2 value less than 0.2; therefore, they may not be of good fit on their own.

Table 18: Evaluation of the models for stillbirth

Models	**Acc %**	**Sens %**	**Spec %**	**AUC %**	**McF**
Model 1 (Maternal history and exam)	65.8	82.4	48.4	71.9	0.08
Model 2 (Uterine artery Doppler indices)	63.9	88.7	37.9	66.8	0.05
Model 3 (History and uterine artery Doppler indices)	67.6	75.9	59.0	69.9	0.08
Model 4 (lab tests)	65.3	71.6	58.7	69.7	0.05
Model 5: (combination of history and laboratory tests)	68.0	67.1	69.0	74.4	0.11
Model 6: (combination of maternal history, Doppler indices and laboratory tests)	68.1	69.1	67.1	75.0	0.12

Acc=accuracy, Sens=sensitivity, Spec=specificity, AUC=area under curve, McF=McFadden's pseudo R^2

4.7 Preterm birth

4.7.2 Unadjusted p-values for prediction of preterm birth

History of previous preterm birth, personal history of preeclampsia, multiple pregnancy, and diastolic hypertension was predictive of preterm birth. Details are in **Table 19**.

Table 19: Unadjusted odds for preterm birth

Variable n=774	Preterm / Term	OR (95% CI)	p-value
Maternal history, physical findings			
Nulliparity	28/217	1.43 (0.86 - 2.40)	0.173
Para 1-2	43/313	1.52 (0.94 - 2.45)	0.090
History of previous preterm birth	16/56	2.07 (1.29 - 3.32)	0.003
History of abortion	23/130	1.37 (0.92 - 2.01)	0.116
Personal history of preeclampsia	6/4	4.72 (2.77 - 8.04)	0.000
Alcohol use in pregnancy	3/45	0.44 (0.15 - 1.35)	0.151
Multiple pregnancies	10/7	4.96 (3.25 - 7.56)	0.000
Diastolic pressure ≥ 90mmHg	7/16	2.53 (1.32 - 4.83)	0.005
Maternal sonographic findings			
Average pulsatility index >1.19 (>90th percentile)	11/71	1.58 (1.01 - 2.47)	0.046
Average resistive index >0.65 (>90th percentile)	11/74	1.45 (0.91 - 2.30)	0.115
Unilateral end diastolic notch	11/116	1.16 (0.72 - 1.86)	0.536
Bilateral end diastolic notch	17/70	1.96 (1.29 - 2.99)	0.002
Cervical length <25mm	1/15	0.53 (0.07 - 3.60)	0.518
Maternal laboratory tests			
Serum albumin 3.5 - 4.1mg/Dl (25th - 75th percentile)	44/366	0.71 (0.45 - 1.11)	0.134
Serum albumin >4.1mg/dL (>75th percentile)	22/169	0.80 (0.47 - 1.35)	0.399
Serum ALP < 98 IU	6/22	1.88 (0.90 - 3.93)	0.093
Lymphocyte count 900 - 3900 cells/µl	77/634	0.48 (0.27 - 0.84)	0.011
Lymphocyte count >3900 cells/µl	4/13	0.99 (0.36 - 2.72)	0.984
PLR of 71.38 - 212.3	76/542	2.30 (0.87 - 6.10)	0.095
PLR of > 212.3	9/70	2.31 (0.76 - 7.06)	0.141
White cell count of 4000 - 11000 cells/µl	72/598	0.70 (0.41 - 1.18)	0.181
White cell count of > 11000 cells/µl	5/11	2.01 (0.84 - 4.81)	0.117

4.7.3 Prediction models for preterm birth

That left only those combinations with the least number of variables with the higher AUC.

When maternal history and sonographic findings were combined, the sonographic results became statistically non-significant. Without obstetric ultrasound or laboratory tests (model

1), the predictors of preterm birth were personal history of preeclampsia, previous history of preterm birth, diastolic hypertension, and multiple pregnancies. The details are in **Table 20.**

Table 20: shows the models for preterm birth

Variable	Adjusted OR (95% CI)	p-value
Model 1: Maternal history, physical findings		
History of previous preterm birth	2.10 (1.05 - 3.95)	**0.027**
Personal history of preeclampsia	11.94 (3.33 - 48.08)	**0.000**
Diastolic pressure ≥ 90mmHg	3.26 (1.12 - 8.37)	**0.019**
Multiple pregnancies	13.73 (5.08 - 39.11)	**0.000**
Intercept	0.10 (0.07 - 0.12)	0.000
Model 2: Maternal sonographic findings		
Unilateral end diastolic notch	0.76 (0.37 - 1.43)	0.418
Bilateral end diastolic notch	1.95 (1.05 - 3.46)	**0.027**
Intercept	0.13 (0.10 - 0.16)	0.000
Model 3: Maternal laboratory tests		
Serum ALP < 98 IU	2.33 (0.82 - 5.72)	0.082
White cell count of 4000 - 11000 cells/µl	0.91 (0.46 - 1.92)	0.798
White cell count of > 11000 cells/µl	3.90 (0.88 - 16.10)	0.063
PLR of 71.38 - 212.3	6.94 (1.84 - 49.3)	**0.016**
PLR of > 212.3	4.56 (0.92 - 36.86)	0.094
Lymphocyte count 900 - 3900 cells/µl	0.35 (0.14 - 0.92)	**0.029**
Lymphocyte count >3900 cells/µl	2.29 (0.30 - 21.90)	0.432
Serum urea of 11 - 45IU (10th - 90th percentile)	2.65 (1.04 - 8.99)	0.069
Serum urea of <11IU (<10th percentile)	2.23 (0.55 - 9.62)	0.258
Intercept	0.02 (0.002 -0.15)	0.000
Model 4: Maternal history and laboratory tests		
History of previous preterm birth	2.25 (1.11 - 4.32)	**0.019**
Personal history of preeclampsia	10.11 (2.68 - 42.07)	**0.001**
Diastolic pressure ≥ 90mmHg	3.94 (1.34 - 10.39)	**0.008**
Multiple pregnancies	14.17 (5.09 - 41.72)	**0.000**
Serum ALP < 98 IU	2.35 (0.78 - 6.07)	0.098
White cell count of 4000 - 11000 cells/µl	0.63 (0.33 - 1.25)	0.165
White cell count of > 11000 cells/µl	4.02 (0.92 - 16.09)	0.053
PLR of 71.38 - 212.3	3.78 (1.33 - 14.66)	**0.027**
PLR of > 212.3	4.07 (1.13 - 18.06)	**0.042**
Serum urea of 11 - 45IU (10th - 90th percentile)	2.54 (0.96 - 8.97)	0.095
Serum urea of <11IU (<10th percentile)	1.80 (0.39 - 8.52)	0.440
Intercept	0.02 (0.002 - 0.08)	0.000

4.7.4 Evaluation of the models for the prediction of preterm birth

The models had a 56.6% – 69.5% area under the curve (AUC) with 52.2% - 62.4% accuracy and sensitivities of 59.6% - 89.3%. However, their specificities of 20.5% - 47.1% were low. The details are in **Table 21**. All the models for predicting preterm birth had their McFadden's pseudo R^2 value less than 0.2; therefore, they were not a good fit.

Table 21: Model performance evaluation using K-fold cross-validation

Model	Acc %	Sens %	Spec %	AUC %	McFadden's
Model 1 (maternal history)	61.6	87.3	35.0	62.1	0.09
Model 2 (Doppler indices)	55.6	89.3	20.5	56.6	0.01
Model 3 (Laboratory tests)	52.2	59.6	44.5	62.8	0.05
Model 4 (History and Lab tests)	62.4	77.2	47.1	69.5	0.12

4.8 Summary of the prediction models for policy and practice

The models that had a good fit were those for prediction of preeclampsia from maternal history and physical examination, a combination of maternal history and uterine artery Doppler sonography, maternal history and laboratory tests, or a combination of all three, with a McFadden's pseudo R^2 between 0.2 - 0.4. Details are in **Table 8 and Table 9.** However, the rest of the models had their McFadden's pseudo R^2 below 0.2; therefore, they are unsuitable for prenatal clinics. Therefore, we weighted the variables' contributions in the models to determine the threshold for predicting preeclampsia (cran_project, 2022; Park et al., 2021).

The predictors for preeclampsia from maternal characteristics were previous preterm birth, history of abortion, maternal age ≥ 35 years, nulliparity, maternal history of preeclampsia, maternal body mass index > 26.5 kg/m2, diastolic hypertension, multiple pregnancies, end-diastolic notch, white blood cell count over 11,000 cells /µl and serum alkaline phosphatase

(ALP) <98 IU. These predictors' weights are calculated to determine their contribution to each prediction model, as shown in **Table 22**.

Table 22: Weighted predictors of preeclampsia

Variable	**Preeclampsia**
Age ≥ 35 years	2.33
Body mass index (Bmi) ≥ 30 Kg / m^2	2.09
Bmi 25.0 - 29.9 Kg/m^2	2.15
Diastolic pressure ≥ 90mmHg	2.73
Maternal history of preeclampsia	4.77
Multiple pregnancies	2.54
Nulliparity	2.47
Para 1-2	1.40
White blood cell count of 4000-11000 cells/µl	1.36
white blood cell count of >11000 cells/µl	1.86
Serum alkaline phosphatase (ALP) <98 IU	2.77
Unilateral end-diastolic notch	1.87
Bilateral end-diastolic notch	3.19

When combinations of the variables were fitted into logistic regression models, variables whose weighted contributions added up to 6.0 for predicting preeclampsia got AUCs over 60% with an accuracy of ≥50%. Therefore, you can use a combination of any variables whose weights add up to 6.0 to classify a mother as a high risk for preeclampsia.

CHAPTER FIVE: DISCUSSION

Despite nearly 100% retention of prenatal care in the global north, we found a health facility delivery rate of 78% (1,004 out of 1,285). The incidence of preeclampsia was 4.3% (43 out of 1,004). More unemployed, younger, and lighter (low body mass index BMI) women were lost to follow-up. The incidence of preeclampsia in our study was similar to the 4.6% global estimate for preeclampsia despite the expected variation between regions (Abalos et al., 2013). The incidence of preeclampsia was higher at early gestational age compared to term pregnancies, with 20.0% at <34 weeks compared to 2.5% at ≥37 weeks. There is 8.7% to 30.0% for preterm preeclampsia and 2.0% at term in low-risk populations (Poon et al., 2019; Robillard et al., 2020). Most births for early-onset preeclampsia are iatrogenic (induced) (Robillard et al., 2020), therefore adding to the complications of preterm birth. Environmental factors may play a role in the incidence of preeclampsia (Nieves-Colón et al., 2022; Zamudio, 2007). For example, the UK is about 200 meters above sea level, with an incidence of PE at 2% (Khalil et al., 2013). Peru is 2,000 meters above sea level with a 20% incidence of PE, and Colorado on the Rockies Mountains is 3,000 meters above sea level with an incidence of PE of 33% (Bailey et al., 2022; Moore, 2021; Palmer et al., 1999) while northern Uganda at 1,000 meters above sea level is at 4.3%. In Ghana, preeclampsia incidence is 4.6% to 6.6% annually (Adwoa et al., 2022), while in South Africa, it is 5.8% (Yasmin Casmod, 2016).

The prevalence of PE is higher at higher altitudes, probably because of the hypoxia due to low oxygen tension in those areas (He et al., 2019; Tong & Giussani, 2019). Hypoxia is thought to suppress the trophoblastic invasion of the spiral arteries (He et al., 2019). This defective trophoblastic invasion leads to defective placentation (Brosens et al., 2011; He et al., 2019; Hoffman, 2023) and has been implicated in most adverse pregnancy outcomes, including preeclampsia, preterm birth, low birth weight and stillbirth, hence the term “great obstetric syndromes” (Brosens et al., 2011; He et al., 2019; Hoffman, 2023). Placental

insufficiency is thought to lead to massive placental infarct formation, which is shed into the maternal circulation (Hoffman, 2023). That may lead to systemic inflammation, endothelial dysfunction and vasoconstriction with resultant adverse pregnancy outcomes (Hoffman, 2023).

In this community in northern Uganda, hospital delivery rates have been around 55% and increased to 99% when the mothers recruited into one study were given supplies for delivery and their bills covered by the research (Ediau et al., 2013). The researchers used a voucher system where a mother who came for Antenatal care had her bills for delivery covered by the research, which increased the hospital delivery rate (Ediau et al., 2013). That may reflect the enormous poverty level of over 38% of community members living below the poverty line (UBOS, 2020). In contrast, in the developed world, where most mothers have health insurance to cover delivery costs, hospital delivery rates are over 98% (Macdorman & Declercq, 2019). Low socioeconomic status is a known risk factor for preeclampsia (Wandabwa et al., 2010). Khalil et al. (Khalil et al., 2013) found that women of Afro-Caribbean and South Asian racial origin were most at risk of preeclampsia in the global north. Therefore, giving delivery incentives and covering the costs of hospital births may raise the retention rate to prenatal care and community mobilization for poverty alleviation strategies.

While maternal clinical characteristics predicted detected preeclampsia with 66.6% accuracy, 82.7% sensitivity and 78.4% AUC in this research, Antwi et al. (Antwi et al., 2017) predicted pre-eclampsia by 70% AUC and 68% in the development and validation cohort, respectively. Gallo et al. (Gallo et al., 2014) screened by maternal characteristics and mean arterial pressure (MAP) at a false-positive rate of 10%; their detection rate of total preeclampsia was

49.3%. In a systematic review by Al-Rubaie and colleagues (Al-Rubaie et al., 2016), their detection rate was 76%.

Using uterine artery Doppler indices, we could predict over 68% of preeclampsia, although the model did not have a good fit. That was way below Trudinger et al. (Trudinger et al., 1985), who predicted up to 90% of preeclampsia in Australia using an end-diastolic notch. We got an AUC of 80.4% with 76.0% accuracy by combining maternal history, physical examination, and uterine artery Doppler indices. That is comparable to Pedroso and colleagues (Pedroso et al., 2018), who found that a combination of uterine artery Doppler indices and maternal history predicted 75% of PE.

We had blood tests with 67.1% accuracy and 75.6% AUC. Although the model was not a good fit, Jhee and colleagues (Jhee et al., 2019) used a combination of laboratory tests (serum urea, aspartate aminotransferase (AST), ALT, creatinine, and haemoglobin levels) to predict preeclampsia with the area under the curve (AUC) above 57%. Yucel and Ustun (Yucel & Ustun, 2017) predicted preeclampsia using mean platelet volume (MPV) and plateletcrit (PCT) with AUC of 64.1% and 71.2%, respectively. Blood tests with maternal history improved the prediction of preeclampsia to 72.7% accuracy with an AUC of 82.2%. Delic and Stefanovic (Delić & Stefanović, 2010) added uric acid, urea thrombocytes, hematocrit, AST, and leukocytes into the logistic regression model and correctly classified 83.8% of patients with preeclampsia. A combination of maternal history, blood tests, and uterine artery Doppler indices (model 6) only slightly improved the prediction accuracy to 77.0% and 80.2% sensitivity with an AUC of 84.9%. This had a better detection rate compared to 57% in the UK (Wright et al., 2012). A low level of serum ALP may signify a reduced viable mass of placental tissue in pregnancy (Holmgren et al., 1979; Ranganath et al., 2008), which means the reduced surface area for the transfer of nutrients from mother to baby. This reduced

surface area of the functional placenta may increase the number of placental infarcts and, eventually, placental debris released into the maternal circulation. Increased levels of placental tissue in maternal circulation lead to maternal systemic inflammation (Dechend & Staff, 2012). That may result in endothelial injury, vasoconstriction, and hypertension (Dekker et al., 1998).

In a systematic review by Duckit and Harrington (Duckitt & Harrington, 2005), they found that women with a previous history of pre-eclampsia, multiple pregnancies, nulliparity, family history, raised blood pressure (diastolic ≥ 80 mm Hg), increased body mass index before pregnancy at booking, or maternal age ≥ 40 at risk of preeclampsia. Antwi and colleagues (Antwi et al., 2020) reviewed prediction models for preeclampsia between 2000 and 2019 and found diverse prediction accuracy ranging from 45 – 95% in the different world regions. The other prediction rates could explain the differences in the populations studied, the test techniques, and the ultrasound machines used. Our models seem to have acceptable accuracy, although the study population was at high risk. These models will ease the identification of high-risk mothers and referral to specialists' healthcare providers. That may reduce perinatal and maternal morbidity and mortality in the community.

We also developed and validated risk prediction models for low birth weight at term in Northern Uganda from this prospective cohort study. From maternal history, the predictors of low birth weight were education level and gravidity. That predicted low birth weight at term by 65.3% AUC, 62.3% accuracy, 88.3% specificity, and 37.3% sensitivity. In Ethiopia, similar demographic characteristics were used to predict low birth weight. At a 26% false positive rate, they predicted low birth weight with 83% AUC with 82% specificity and 71% sensitivity (Hassen et al., 2020). In India, Singh (Singh et al., 2014) found the prediction

model AUC to be 79% with 72% sensitivity and 56% specificity. In the USA, maternal history predicted low birth weight with 75.3% accuracy (Gaziano et al., 1981).

Considering the uterine artery Doppler indices, the predictors of low birth weight were placental location and end-diastolic notch in the uterine arteries. That predicted low birth weight at term by 62.6% AUC, 59.3% accuracy, 42.5% specificity, and 75.4% sensitivity. For example, Denmark's uterine artery pulsatility index predicted low birth weight with 74% AUC (Sinding et al., 2017). In contrast, a placental thickness of <2cm and a diameter of <18cm in Saudi Arabia predicted low birth weight with 88.6% AUC (Habib, 2002). That probably outlines the population differences and techniques used in the data analysis.

When the maternal history is combined with uterine artery Doppler indices, the predictors of low birth weight were education level, gravidity, placental location, and end-diastolic notch. That predicted low birth weight at term by 71.6% AUC, 62.3% accuracy, 64.8% specificity and 61.8% sensitivity. A combination of uterine artery Doppler indices and maternal history in India predicted low birth weight with 65.9% AUC, 45.4% sensitivity and 84.6% specificity (Deepti Verma, 2016).

While we found the predictors of low birth weight to be serum GGT, serum ALT and lymphocyte count of having predicted low birth weight at term by 66.9% AUC, 59.3% accuracy, 35.8% specificity and 81.7% sensitivity, there is limited data on the prediction of low birth weight using full maternal haemogram, liver and renal function tests. There is no evidence that maternal blood levels of alpha-feto protein (AFP), human chorionic gonadotropin (hCG), or pregnancy-associated plasma protein A (PAPP-A) used as a single predictor help predict low-birth-weight newborns (Goto, 2021). When the laboratory blood tests were combined with maternal history, the predictors of low birth weight were gravidity, level of education, serum ALT, serum GGT and lymphocyte count. That predicted low birth

weight at term by 66.9% AUC, 66.7% accuracy, 59.6% specificity and 73.4% sensitivity. Adding blood glucose levels to maternal history in Mexico predicted low birth weight with 72% AUC (Hernández-Castro et al., 2021).

After combining all the variables from maternal history, laboratory tests, and uterine artery Doppler indices, the predictors of low birth weight were gravidity, level of education, serum ALT, serum GGT, lymphocyte count, placental location, and end-diastolic notch in the uterine arteries. These predicted low birth weight at term by 81.9% AUC, 76.1% accuracy, 72.9% specificity and 79.1% sensitivity. Therefore, considering the few predictors, this model can be used for screening low birth weights in prenatal clinics. That makes our model favourably compared to the other models.

We found that about three in every twenty-five mothers (11.6%) got preterm birth. Without obstetric ultrasound or laboratory tests, the predictors of preterm birth were personal history of preeclampsia, previous history of preterm birth, diastolic hypertension, and multiple pregnancies. That predicted preterm birth with 66% accuracy of those destined to get preterm birth. The addition of laboratory tests to the model only improved it slightly. A bilateral end-diastolic notch was the only statistically significant predictor of preterm birth, with 89.3% sensitivity, 20.5% specificity and 56.6% AUC. However, when combined with a maternal history of laboratory tests, it became statistically non-significant. We combined maternal history and physical examination with uterine artery Doppler indices, anatomical ultrasound survey, and laboratory tests. We found an overall 69.5% AUC, with 62.2% accuracy, 77.2% sensitivity, and 47.1% specificity for predicting preterm birth.

Knowing that preterm birth contributes to over 2% of perinatal morbidity and mortality in the global north (Opondo et al., 2020; Ray et al., 2017) and its management requires a multidisciplinary team and specialized equipment (Mactier et al., 2020), it is necessary for us

in the limited-resource settings to predict it early to arrange for referral to tertiary level hospitals in time. Furthermore, the prognosis of preterm birth depends on the gestational age at birth, duration of contact of the mother with health care providers before delivery, medications received before delivery, and treatment options available to the baby (Berger et al., 2019; Jefferies et al., 2012; Lemyre & Moore, 2017). That predicts preterm birth and referral to specialized centres, one option for reducing perinatal morbidity and mortality. With a 77.2% sensitivity, over two-thirds of those who get preterm birth will screen positive and be referred in time. However, at 47.1% specificity, more than half of the participants will be mistakenly screened positive. That may pressure the already overwhelmed centres unless the healthcare is restructured to handle such screen-positive clients.

The incidence of preterm birth is 6.1% in China (Jing et al., 2020), 9.3% in Nepal (Gurung et al., 2020), and 7.4% in the United Kingdom (Bradford, 2020). The incidence of preterm birth in Gulu city, being 11.6%, perhaps confirms that women of sub-Saharan Africa are more at risk of preterm birth (Tingleff et al., 2021). Without obstetric ultrasound or laboratory tests, the predictors of preterm birth were personal history of preeclampsia, previous history of preterm birth, diastolic hypertension, and multiple pregnancies. Predictors of preterm birth in Ethiopia were lack of antenatal care visits, having 1–2 antenatal care visits, history of the previous preterm, short inter-pregnancy interval, having reproductive tract infections, history of abortion, urinary tract infection and hypertensive disorders in pregnancy (Regasa et al., 2021; Wakeyo et al., 2020). Attending at least a secondary education and antenatal care was protective (Wakeyo et al., 2020). However, that research was cross-sectional and may not reflect the early trimester antenatal characteristics used to predict preterm birth.

Meanwhile, a bilateral end-diastolic notch signifies reduced perfusion of the placental site, which may translate into insufficiency (Espinoza et al., 2010). That may predict the

conditions associated with placental insufficiency, which later leads to iatrogenic preterm birth. A bilateral end-diastolic notch in Australia would predict preterm birth by 31.4% sensitivity and 58% AUC (van Zijl et al., 2020). In a systematic review by Meertens et al. (Meertens et al., 2018), most models for predicting preterm birth have an AUC of 54% - 70% for both development and validation. Since most models had an AUC ranging from 54% to 70% (Meertens et al., 2018), we got an AUC of 69.5%. That makes our models among the higher-performing models for predicting preterm birth.

From the demographic characteristics of our participants, the predictors of stillbirth were parity, age ≥ 35 years, history of abortion and personal history of preeclampsia. That predicted stillbirth with 65.8% accuracy, 82.4% sensitivity, 48.4% specificity and 71.9% AUC. In Niger State, Nigeria, the predictors of stillbirth were maternal comorbidity, rural place of residence, multipara, bleeding during pregnancy, and non-cephalic fetal presentation (Kayode et al., 2016). Maternal employment was protective of stillbirth (Kayode et al., 2016). They predicted stillbirth with a C-statistic basic model = 0.80 (95 % CI 0.78–0.83), and when ultrasound parameters were added, the extended C-statistic model improved slightly to 0.82 (95 % CI 0.80–0.83) (Kayode et al., 2016). In a case-control study in southern Ethiopia, the predictors of stillbirth were women with multiple pregnancies [aOR = 2.98, 95%CI: 1.39–6.36], having preterm birth [aOR = 2.83, 95%CI: 1.58– 508], having cesarean mode of delivery [aOR = 3.19, 95%CI: 1.87–5.44], having no ANC visit [aOR = 4.17, 95%CI: 2.38–7.33], and being hypertensive during pregnancy [aOR = 3.43, 95%CI: 1.93–6.06]. (Abebe et al., 2021). However, these women were recruited after they had given birth. In clinical settings in low-resource settings, one can use the demographic characteristics above as predictors to identify up to two-thirds of mothers at risk of having a stillbirth. Despite the model's sensitivity of 82.4%, the model's specificity of 48.4% is low. One will have to put

more than twice the number of women identified as at risk of stillbirth to get the two-thirds of women who will get stillbirth.

Combining uterine artery Doppler indices and maternal history predicted stillbirth with 67.6% accuracy, 75.8% sensitivity and 69.9% AUC. That may be comparable to Akolekar et al. (Akolekar et al., 2016), who predicted 55% of all stillbirths, including 75% of those due to impaired placentation and 23% of those that were unexplained or due to other causes, at a false-positive rate of 10% using maternal history and uterine artery Doppler indices. Ultrasound examination is not compulsory in Uganda (Ministry_of_Health, 2016). It is reserved for a few referral centres, teaching hospitals and private hospitals (Kawooya, 2012; Ross et al., 2013). Therefore, most mothers go through their gestation without performing a single ultrasound scan.

We predicted stillbirth by 75.0% AUC with 68.1% accuracy, 69.1% sensitivity and 67.1% specificity. That was comparable to the stillbirth-risk calculator (The_fetal_medicine_foundation, 2022) validated in Austria at 72% AUC (Muin et al., 2022). In the United Kingdom, stillbirth detection rates ranged from 28 to 48%, with an AUC of 55.0% to 65.8%, even after allowing a 10% false positive rate (Akolekar et al., 2016; Yerlikaya et al., 2016). In Australia, the detection rate for stillbirth was 45%, with an AUC ranging from 59% to 84% (Malacova et al., 2020). Similarly, the detection rate for stillbirth in the United States of America has been 64% - 66% AUC (Trudell et al., 2017).

Mastrodima et al. (Mastrodima et al., 2016) used maternal factors, PAPP-A, Doppler pulsatility index and ductus venosus pulsatility index for veins (DV-PIV). They predicted 40% of all stillbirths and 55% of those due to impaired placentation, at a false-positive rate of 10%. Within the impaired-placentation group, the detection rate of stillbirth<32 weeks' gestation was higher than that of stillbirth ≥ 37 weeks (64% vs 42%). That makes the study

compare favourably to those conducted in the global north. Perhaps the differences are due to the differences in the population and the technology used to predict stillbirth.

Since patients present to prenatal care with different adverse outcome predictors, we weighted each predictor's contribution in the prediction model. We found that variables whose weights add up to >6.0 predicted adverse pregnancy outcomes by ≥60% AUC and ≥50% accuracy. That may be the beginning of developing a more robust screening method for adverse pregnancy outcomes in the region, as hinted at by other researchers (Ji & Kattan, 2018; Pavlou et al., 2015), and that is also the basis of most risk calculators ever developed (Al-Rubaie et al., 2016; Ji & Kattan, 2018; Robillard et al., 2020; Wright et al., 2012).

The adverse pregnancy outcomes associated with preeclampsia were preterm birth, stillbirth and postpartum haemorrhage. Low birth weight and mode of delivery were not associated with preeclampsia in this community of northern Uganda. These are the already-known complications of preeclampsia found in reference documents (*Creasy and Resnik's maternal-fetal medicine, Principles and practice*, 2014; *William's Obstetrics*, 2018). However, many preterm births associated with preeclampsia may be iatrogenic (Uzan et al., 2011). Therefore, since the preeclampsia prediction models are a good fit, and the other adverse pregnancy outcomes are associated with preeclampsia, it is easier to predict preeclampsia. Hopefully, you will have predicted its adverse outcomes, too. Adding uterine artery Doppler indices to the routine ultrasound scan takes less than five minutes and improves the prediction model's sensitivity. That may improve the prediction of multiple adverse pregnancy outcomes.

METHODOLOGICAL CONSIDERATIONS

We built models from the original data we collected in the prenatal clinic for each pregnancy outcome. The incidences of preeclampsia, preterm birth, low birth weight and stillbirth were 4.3%, 11.6%, 5.7% and 2.5%, respectively. That means the data was imbalanced, with fewer adverse pregnancy outcomes than normal ones. That imbalance makes developing any prediction model difficult because of the risk of overfitting (Demšar & Zupan, 2021). Therefore, we envisaged that this might bias our prediction model when we test for sensitivity, specificity, and accuracy. Therefore, the data was balanced by over-sampling the adverse pregnancy outcomes and under-sampling the normal outcomes to produce a nearly equal number of outcomes in the new (synthetic) dataset using the ROSE package in RStudio (Menardi & Torelli, 2014; Nicola Lunardon, 2014). We created a new dataset from the original using the ROSE package (Menardi & Torelli, 2014; Nicola Lunardon, 2014) in RStudio. The resultant dataset has approximately 50% of the adverse outcome (cases or exposed group) and normal outcome (non-exposed, non-cases), respectively. We used the synthetic (new) dataset as the validation dataset to obtain the AUCs' sensitivity, specificity and accuracy.

Due to the limited sample size for machine learning purposes, we could not divide the sample size into training and test datasets; we opted for K (10) – fold cross-validation (Fushiki, 2011; Jung, 2018; Meijer & Goeman, 2013; Moreno-Torres et al., 2012), with the model from the original dataset being the training dataset, and the synthetic (ROSE-derived) data as the test dataset to generate the accuracies and sensitivities in the confusion matrix in RStudio. This method divides the new (artificial) dataset into ten folds, and each fold is tested against the original dataset. The average sensitivities, specificities, and accuracies are generated and displayed. Since our outcome was binary (cases vs controls), we used McFadden's pseudo R^2 of 0.2 – 0.4 to estimate the goodness of fit (Veall & Zimmermann, 1994, 1996).

STUDY LIMITATIONS

- Only one person was skilled in doing the uterine artery Doppler sonography during the data collection. Moreover, each sonography took about one hour per client. That provided time constraints because doing repeat ultrasound scans for follow-up purposes was impossible, especially for those with an end-diastolic notch.
- We did one measurement of uterine artery Doppler indices, blood pressure, and weight during antenatal care at recruitment. So, we could not determine the rate of change of maternal parameters or the pre-pregnancy values. However, these changes could later be used to calculate risk factors for some adverse pregnancy outcomes.
- We discharged mothers from the study at the baby's discharge from hospital. Therefore mothers who developed preeclampsia after discharge were not captured.
- Finally, there were many losses to follow up, which could have skewed these results differently.
- We could not develop prediction models for adverse preeclampsia-related outcomes because of the few participants who developed preeclampsia (early or late onset). However, the overall incidence of adverse pregnancy outcomes was less than 12%.

STRENGTHS AND CONTRIBUTION OF THE STUDY

- This research was a baseline study in northern Uganda. Therefore, our result could be used to determine the nature of subsequent studies regarding adverse pregnancy outcomes in this under-researched community.
- The study generated prediction models for adverse pregnancy outcomes with high AUCs and good fit, which can be used for screening in prenatal clinics.
- Since not all patients present with all the predictors of adverse pregnancy outcomes, patients with any variable weights adding to ≥6.0 are at high PE risk and need close follow-up.

CONCLUSIONS

1) The incidence of PE was 4.3%, Preterm birth 11.6%, Low birth weight at term was 5.7% and Stillbirth was 2.5%.
2) The predictors of preeclampsia from maternal history and physical examination were maternal age ≥ 35 years, nulliparity, maternal history of preeclampsia, body mass index ≥ 26.56 Kg/m^2, diastolic hypertension, and multiple pregnancies.
3) The Preeclampsia prediction models had accuracies of >66% and AUCs of >71%.
4) Models for prediction of PE using maternal characteristics or a combination of maternal characteristics with lab, maternal characteristics with Doppler or maternal characteristics with lab and Doppler had a good fit with McFadden's pseudo R^2 between 0.2-0.4 and, therefore, are suitable for screening of preeclampsia in prenatal clinics.
5) Patients with any of the predictors of preeclampsia weighting ≥6.0 are considered at high risk.

RECOMMENDATIONS

a) For Future research

i. We recommend validating these models with datasets from other regional health units to ensure generalisability.

ii. Future studies should do serial measurements at intervals during the prenatal period.

iii. Motivate more mothers to deliver in the hospital to reduce loss to follow-up.

b) For Practice

i. Incorporate screening for preeclampsia into routine prenatal care

ii. Strengthen referral pathways for mothers who have been identified as at risk of developing preeclampsia

c) For Policy

i. Train midwives to predict preeclampsia using the available antenatal care cards

ii. Train health care workers, especially in prenatal ultrasound, to perform sonography routinely as part of prenatal care.

iii. Support more research into the prediction of adverse pregnancy outcomes

iv. There should be a public-private partnership to promote the prediction of adverse pregnancy outcomes in Uganda.

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ANNEX 1: CONSENT FORM

Title of the study:

Using ultrasonography and maternal characteristics to predict preeclampsia and adverse pregnancy outcomes at St. Mary's Hospital Lacor

INVESTIGATORS:

1. Dr Awor Silvia from Gulu University, PhD student at Makerere University Tel: +256782 841168 Email: aworsyl@gmail.com

SUPERVISORS:

2. Prof. Dan K. Kaye, School of Medicine, College of Health Sciences, Makerere University. Email: dkaye0700@gmail.com Tel: +256 772 587 952
3. Prof. Annettee Nakimuli, School of Medicine, College of Health Sciences, Makerere University. Email: annettee.nakimuli@gmail.com Tel: +256 772 471 618
4. Prof. Jasper Ogwal-Okeng, Vice Chancellor, Lira University. Email: jogwal.okeng@gmail.com Tel: +256 775 330 389

Background and rationale for the study:

Preeclampsia (PE) is a new onset of high blood pressure (Blood pressure of ≥140/90 mmHg) and proteinuria (≥ + urine dipstick or 0.3 grams per 24-hour urine) after 20 weeks of gestation in a previously normotensive woman. The cause is not known. The incidence ranges from 3% to 10% in nulliparous women and 1% to 3% in multiparous women. It is a major cause of maternal death, especially in sub-Saharan Africa. In Uganda, it causes 12% to 19% of maternal deaths. Delivery of the fetus is the only known cure for preeclampsia. We hope that by conducting this study, we shall be able to identify mothers at risk of preeclampsia early and contribute to the existing strategies available for the reduction of maternal death in Uganda.

A description of the sponsors of the research project and the organizational affiliation of the researchers:

The PhD study is sponsored by SIDA – Makerere University bilateral research program. They provide part of the research fund, tuition fees, and stipends. St. Mary's Hospital Lacor has provided space for my rented ultrasound machine, a laboratory facility at a fee, and office space for data collection. Gulu University provides some laboratory reagents, and Family members have provided office furniture.

Purpose:

This study will examine whether ultrasound examination and maternal characteristics can predict the development of preeclampsia and adverse pregnancy outcomes at St. Mary's Hospital Lacor. That is meant to help identify women who are more likely to suffer from pregnancy complications in future.

The estimated duration the research participant will take in the research project:

You will be in this study from the recruitment day until the baby's delivery and discharge from the hospital.

Procedures:

You will be given a study number and asked personal questions, which will be recorded in a questionnaire. You will undergo physical, laboratory and ultrasound examinations to assess your well-being and the baby's. You will then be followed up every month until delivery, and each time you return to the hospital, you will be asked some questions and examined. If you are already admitted to the hospital, the research team will frequently visit you until you are discharged.

Who will participate in the study

We expect all pregnant women attending antenatal care for St. Mary's Hospital Lacor to participate in the study from about 20 weeks of the pregnancy until the delivery of their babies. Therefore, we expected to recruit over 644 mothers in this study over two years.

Risks/Discomforts:

This research will cause no risk or pain to you or the baby.

Benefits:

The laboratory results and the ultrasound findings will be given to you and may be shared with the doctors and healthcare givers to help decide on the best care for you. In addition, you will have a group of people to attend to you each time you are in the hospital.

Confidentiality:

The Principal investigator, Dr Awor Silvia, will keep the research record confidential and safe. Everything said during the research will be kept confidential according to Ugandan laws. The laboratory and ultrasound results will be shared with you and among the healthcare providers so that they may decide on the best treatment for you. Your name will not appear on any publication arising from this research. However, the Makerere University School of Medicine Research Ethics Committee (REC) and Uganda National Council for Science and Technology (UNCST) may have access to private information that identifies you by name.

Alternatives:

This study is voluntary. If you are not interested in participating, you can continue with your usual antenatal care. This will not affect the nature of care you will get at St. Mary's Hospital Lacor.

Cost:

You will not be asked to pay any money to be part of the research. The laboratory and ultrasound examination will all be done for free.

Compensation for participation in the study:

You will not be paid any money to participate in the study. In case of injury during the study, you will be referred to the Emergency wards of St. Mary's Hospital Lacor for treatment. You will not be compensated in case of permanent damage during the research.

Reimbursement:

You will not be refunded any transport, time, meals or opportunity costs during the study period.

Questions about the study:

If you have questions about the study, you can contact Dr Awor or her supervisors using the abovementioned contacts.

Questions about participants' rights:

You have a right to withdraw from the study at any research stage. However, suppose you have queries about the conduct of the research or your rights. In that case, you can ask the Chairman of the School of Medicine research and ethics committee, Prof. Ponsiano Ocama, by Telephone number +256772421190 or the School of Medicine, Makerere University, P. O. Box 7072 Kampala.

Statement of voluntariness:

Participation in this study is voluntary, and you can join of your own free will. You also have a right to withdraw from the study without penalty.

Dissemination of results:

You will get feedback on the findings and progress of the study. In addition, any new information that affects the study or data that has clinical relevance to you (including incidental findings) will be made available to you and your healthcare providers. Findings from the study will also be published in peer-reviewed journals.

Ethical approval:

This study has been approved by the Makerere University School of Medicine Research and Ethics Committee and the National Council for Science and Technology.

STATEMENT OF CONSENT

..... has described to me what is going to be done, the risks, the benefits involved and my rights regarding this study. I understand that my decision to participate in this study will not alter my usual medical care. In the use of this information, my identity will be concealed. I am aware that I may withdraw at any time. I understand that by signing this form, I do not waive any of my legal rights but merely indicate that I have been informed about the research study in which I voluntarily agree to participate. A copy of this form will be provided to me.

Name ……Signature/thumb print of participant ..... Date ……

Name ……Signature of parent/guardian for minors (If applicable)…Date ……...

Name……Signature of witness (if applicable)……Date…….

Name ……. Signature of interviewer/ ……Date……..….

YEE ME PIME

Gin akweda: Tic ki maraya (Ultrasound) ki kit yotkom lunywal acel acel me niang ka twero nyuto ka two kero me wot pa remo obi mako dako ma oyac ma pwodi peya onywal i ot yat Lacor.

Lakwed lok:

1. Dr. Awor Silvia me Gulu University, Latin kwan i Makerere University Cim cing: +256782 841168 waraga: aworsyl@gmail.com

Ludito ma ngiyo kor tic pa lakwed lok:

1. Prof. Dan K. Kaye, School of Medicine, College of Health Sciences, Makerere University. Waraga: dkaye0700@gmail.com Tel: +256 772 587 952
2. Dr Annettee Nakimuli, School of Medicine, College of Health Sciences, Makerere University. waraga: annettee.nakimuli@gmail.com Tel: +256 772 471 618
3. Prof. Jasper Ogwal-Okeng, Vice Chancellor, Lira University. Waraga: jogwal.okeng@gmail.com Tel: +256 775 330 389

Kit ma te kwedo lok man ocake kwede: Two ma lube ki kero me wotpa remo (pressa) ikom mon ma oyac cake idwe me abic me yacu ikom dako ma ononGo kero me wot pa remone tye maber. Ngo makelo two ne pwodi pe kingeyo. Two ne mako mon 3 onyo 7 ikin mon mia acel ma guyac wang me acel, onyo mape kato adek ikom mia acel pi mon ma dong onywalo lutino mukene. Two man neko mon mapol ilobo pa wan del-col. I Uganda, two ni neko mon ma oo 19 ikom mia acel ma guyac mapwodi peya gunywal. Kadong ocake, ci pecang. Nywalo latin keken aye weko two man dok piny.

Watamo ni ka wakwedo kor lok me two man ci wabekonyo mon mapol ki ngeyo anga ma obi nongo two man ma pwodi peya ocake.

Lucul pi kwedo lok man: Kwedo lok man obedo ma lube ki kwan madit igang kwan Makerere. Lucul pire obedo gamente me lobo pa otara ki me Uganda ma woto ki Makerere University. Gin culu cente me kwan, bute me kwedo lok ki dong we wot ikin yoo bene. Ot yat madit Gulu gumiyo marayo me menyo ii mon ma oyac, pimo remo ki lac, ki kagwoko jami mukene me kwedo lok man. Gang kwan madit me Gulu kany bene guyee miyo but jami mukene ma mitte lapim remo ki kabedo.

Pingo wamito kwedo lok man: Me kwedo man wabitiyo ki maraya ki ngec me yotkom pa dako acel acel ma oyac me neno ka twero nyuto anga ma obi nongo two me kero me wot paremo ma pwodi peya ocake ii otyat madit i gulu. Watamo ni man obikonyo wan me biiko mon mukene ii anyim ma ca gwoki gibinongo two man, wek gunong yat oyot oyot mapwodi two peya obwoyo gin.

Ibibedo ikwedo lok man pi kare ma rumani: Icako bedo nicake tin nioo wa inino ma inywal dok kikwanyi ki otyat**.**

Loke kibi kwedo nining: In kibi tito boti lok kom kwedo lok man kore ki kore. Kibi miyo boti nama ki dong kibipenyi ki lapeny ma kwako kwoo ni. Ci kibipimi, kikwanyo remo ki lac ka kicwalo in imarayo ka pimo latin ma ii ni. Kibi miini nino me dwogo ka mede ki pimme nioo wa nino nywal-li. Ka kigengi iwii kitana, ci lukwed lok bene bi mede ki limi kunu wang ma in inywal ki nioo ka kikwanyi bene ki otyat.

Anga ma kibi kwedo lok ikome: Wamito kwedo lok ikom mon weng ma gubino kapime iotyat Lacor kany ma pwodi peya yacu gi okato dwe abic. Wamito mon 644 imwaka aryo.

Arem: Arem moo keken bibedo peke ikom in onyo latinni ma obi aa ki ikom kwedo lok man.

Ber pa kwedo lok man: Adwogi me pimo remo ki me maraya kibimyo boti. Ngec meno bene kibimiyo ne bot daktare me otyat kany magitye katic ikomi ni. Ka in ibino iotyat ibinongo joo magubibedo ka tic ikomi ki limo in iotyat nioo wang ma kikwanyi ki ii otyat kany.

Mung: Lok ma kibinongo ki ikom kweda man Dr. Awor Silvia obigwoko maber dok kama ding. Lok ma iwaco kany weng kibigwoko imung malube ki pen cik me Uganda kany. Adwogi me pimme ki menye ii maraya kibipoko bot daktare me tye kagwoko yotkomi ii otyat kany wek gumiini yat maber. Nyingi pe bikati igin acoya moo keken mabikati ki ikom kwedo lok man. Twero me kwedo lok man wapenyo dok wanongo ki igangkwan madit ii Makerere ki bot joo maloyo lok kom kwedo lok ducu ii Uganda kany. Gin joo man tye ki twero me ngiyo kor tic me kwedo lok man dok bene giromo neno lok maromo nyutu nyingi.

Yoo mukene: Yee kwedo lok eni tye itwero ni me yee onyo me kwero ne bene. Dic peke iye. Ka ikwero bene ci ibimede ki pimme ii otyat kany kit ma jwii ni.

Cul: In pe ibi culo cente moo wek ibed ikin joo ma ki kwedo lok ikomgi ni. Pimo remo ki menyo maraya malube ki kwedo lok man kibitimo ne me nono.

Dwoko cente ma itiyo kwede me bino ikwedo lok man: Pekibi dwoko cente ni moo keken pi bino ikwedo lok man. Ka inongo awanu moo keken ci wabicwali kama kitiyo iye ikom luret kit ma joo mukene bene cito kunu ni.

Peny ikom kwedo lok man: Ka itye ki lapeny moo keken ikom kwedo lok man iromo penyo lakwedo lok matye kalok kwedi ni onyo igoyo cim cing bot Dr. Awor onyo ludito maloye inama cim makicoyo malo ni.

Peny ikom twero pa joo ma kitye kakwedo lok ikomgi ni: Ka in itye ikin joo makikwedo lok ikomgi ni itye ki twero me aa woko ki ikwedo lok man cawa moo keken. Ka itye ki lapeny moo keken ikom kwedo lok man onyo twero ni ci iromo penyo wonkom maloyo lok

kom kwedo lok igangkwan madit Makerere Prof. Ponsiano Ocama inama +256 772 421 190. Iromo bene coyo waraga igangkwan madit Makerere icanduk nama 7072, Kampala.

Nyutu peke pa dic moo keken: Bedo ikwedo lok man dic peke iye. Iromo aa cawa moo keken labongo obal-tic moo keken.

Poko adwogi me kwedo lok man: Wabimiyo kit ma kwedo lok man tye kawot kwede anyim boti. Adwogi me kwedo lok man wabicoyo pire ikaratac mapatpat. Jami manyen mawabinongo ki ikom kwedo lok man bene wabi tito ne boti.

Twero me kwedo lok: Twero me kwedo lok man wanongo ki igangkwan madit Makerere ki bot joo maloyo lok kom kwedo lok ii lobo Uganda lung.

Nyutu Yee

..... otita ngo ma kibitimo, rac-ce, ber-ne ki twero na malube kikwedo lok man. Aniang maber ni bedo ii kwedo lok man pe obiloko gwok ma anongo ii otyat kany. Lok ma abiwaco kany ki pime weng kibi gwoko ne imung. Aniang maber ni aromo aa cawa moo keken. Aniang bene ni ka aketo cinga ikaratac man, pe obikwanyo twero na ducu ento nyutu keken ni aye bedo ikin joo ma kibikwedo lok ikomgi ni. Waraga ni mukene bene kibimiyo ne bota.

Nyinga ……Cinga.....Nino dwe ……

Nying Lakwed lok……. Cing lakwed lok……Nino dwe ……

ANNEX 2: QUESTIONNAIRE

At 18 – 20 WEEKS (To be filled by the patient in the presence of a Research assistant)

ANC / OP No……. IP No…… Study number …… Phone Number……

Characteristics of respondents

1. Physical address ……..
2. Age *(Fill completed years)……*
3. Nearest Health centre (Name and distance from Home) ……

   ……...……...……
4. Parity: Gravida…….…Para…..…+Abortion / Ectopic pregnancy ……
5. Your Tribe ……
6. Give the name of the place where you were born. ……
7. Country where you were born……
8. In which place and country were your parents born?

   Mother..... Country

   ……..

   Father …… Country …….

Socio – economic status

9. Marital status *(please circle):*
   a. Single=1
   b. Married / cohabiting=2
10. Highest Level of education and number of years*(circle below)*

a. In primary=1(……yrs.);

b. In ordinary level=2(……yrs.);

c. In advanced level=3(……yrs) ;

d. Tertiary institution=4*(..... yrs);*

e. Other type of education=99 *(specify)……*

11. Main occupation *(circle below)*

    a. Unemployed=1;

    b. Farming and selling crops=2;

    c. Own self-business =3;

    d. Private job=4;

    e. Government job=5;

    f. Other job=99 *(Specify……*

12. Who is the main income earner in your household?

    a. Parent=1;

    b. Husband=2;

    c. Child=3;

    d. Self =4;

    e. Other=99*(specify.....)*

Presenting complaints today

13. Why have you come to the hospital today:

    a. Antenatal care =1

    b. I am not feeling well =2

    c. I was told to come to be checked = 3

14. How are you feeling today?

    a. I am well =1

    b. I have a fever =2

    c. I have a headache =3

    d. I have abdominal pain =4

    e. Other = 99 (Specify) ……

History of present pregnancy:

15. LNMP
    a. (write the date if the patient knows) …….
    b. Gestation age today ……
    c. Gestation age at first antenatal care …….
16. Did you go for fertility treatment before getting pregnant? Yes / No
17. If yes to q16, what treatment did you get? ……..

    ……..

    ……
18. Have you ever been admitted to the hospital during this pregnancy? Yes / No
19. If yes to question 18, when and why? ……

    …….

    ……
20. At what gestation age did you start antenatal care? …….
21. What medication have you been on from the beginning of this pregnancy?

    ……

    ……..

    ……

Obstetric history:

22. How many children have you delivered? .....
23. What were the birth weights of your children? ……..

    ……..

    …….

24. At what gestation age did you deliver them? …….

……..

……..

25. How many live children do you have? ……..

26. What highest level of education are the children?

……

……

……..

27. What happened to the children who are no longer alive? ……

……

……..

……..

28. What was the previous pregnancy outcome with the current partner?

……..

……..

……

29. What pregnancy complications did you have in the previous pregnancies?

    a. Preeclampsia
    b. Eclampsia
    c. Gestational Diabetes Mellitus
    d. Other (*specify*)……

Gynaecological history

30. How many miscarriages have you had? ……

31. Have you ever had an ectopic pregnancy? Yes / No

32. If yes to Question 31, When..... How were you treated for it?

……

……..

33. Have you ever been screened for cancer cervix? Yes / No

34. If yes to question 33, when?..... What was the result?

……..

Menstrual history

35. At what age did you begin getting your periods? ……

36. For how many days was the blood flowing? ……

37. Was it painful? Yes / No

38. If yes to Question 37, what medication did you use to soothe the pain?

……

……

Sexual history

39. How many sexual partners have you had in your lifetime? …….

40. How long have you lived with your current partner before becoming pregnant?

……..

41. Are you the only spouse to your husband? Yes / No

42. If No to Question 41, how many sexual partners does your husband have?.....

Medical history

43. Do you have any chronic illnesses? ……

…….

44. Are you on any long-term medication? Yes / No

45. If yes to question 44, which drugs are you on? …… …….. …..

……

Surgical history

46. Have you ever had a blood transfusion in your lifetime? Yes / No

47. If yes to question 46, when? ……

48. Have you had broken bones before? Yes/no

49. If yes to question 48, When? ……..

Family History

50. Has anyone in your family ever suffered from Hypertension during pregnancy?

    Yes/no

51. If yes to question 50, what is your relationship to this person? …….

52. What chronic illness do you know of in your family line? …….

Social history

53. Have you ever smoked tobacco in your lifetime?

54. Do you smoke tobacco during this pregnancy? Yes / No

55. If yes to question 54, how do you usually use tobacco?

    a. Snuff user

    b. Chew the tobacco

    c. Cigarettes

    d. Other specify ……..

56. If you use cigarettes, how many sticks per day? …….

57. Does anyone in your household smokes? Yes / No

58. If yes to question 57, How are you related to this person?……

    ……

59. Have you ever drunk alcohol? Yes No

60. Did you drink alcohol during this pregnancy? Yes / No

61. If yes to question 60, how much and how regular do you take it?

……..

……..

62. Which other recreational drugs do you use? ……

…….

…….

Physical examination:

63. Height in meters ……..

64. Today's Weight in Kg ……..

65. First visit weight in Kg

66. Today's Blood pressure …….

67. First visit bp ……..

68. Pulse rate …….

69. Respiratory rate ……..

70. Temperature …….

71. Fundal height in Centimeters …….

72. Foetal heart rate ……..

73. Any other organomegaly? ……..……

……

74. Any other finding worth noting ……

…….

…….

ANC / OP No……. IP No…… Study number …… Phone Number……

Laboratory results

75. Hiv Status ……. Hepatitis B surface antigen …….

76. Urine protein ……

77. Urine red blood cells ……

78. Urine pH ……..

79. Urine specific gravity …….

80. Urine leucocytes……

81. Urine glucose ……..

82. Urine Nitrites ……..

83. Urine ketones ……..

84. Hb level……

85. Haematocrit ……

86. MCV …….

87. MCHC …….

88. White cell count ……..

89. Neutrophil count ……

90. Lymphocyte count …….

91. Platelet count …….

92. Serum Creatinin level ……..

93. Serum urea …….

94. Sodium …….

95. Potassium……

96. Chloride……..

97. Calcium …….

98. Phosphorus …….

99. Bicarbonate ……

100. Serum albumin level …….

101. ALT……

102. AST……

103. ALP

104. GGT

105. Bilirubin ……

ANC / OP No……. IP No…… Study number …… Phone Number……

Ultrasound examination findings

106. Gestation age …. Weeks

107. EDD ……..

108. Percentile on growth curve ……

109. BPD..... cm

110. HC..... cm

111. AC..... cm

112. FL..... cm

113. AFI..... cm

114. Right uterine artery PI …….

115. Right uterine artery RI …….

116. Right uterine artery End diastolic Notch Yes / no

117. Left Uterine Artery PI ……

118. Left Uterine Artery RI ……

119. Left Uterine Artery End diastolic notch yes/no

120. Other features observed on Ultrasound

a. Intact cranium…….
b. Cavum septi pellucidi……
c. Midline falx……
d. Thalami…….
e. Cerebral ventricles…….
f. Cerebellum…….
g. Cisterna magna…….
h. Nuchal fold…….

i. Both orbits present…….

j. Median facial profile……

k. Mouth present……..

l. Upper lip intact….

m. Neck Absence of masses (e.g. cystic hygroma)…….

n. Normal appearing shape/size of chest and lungs……

o. Heart activity present…….

p. Four-chamber view of heart in normal position…….

q. Aortic and pulmonary outflow tracts……

r. No evidence of diaphragmatic hernia……

s. Stomach in normal position……

t. Bowel not dilated…….

u. Both kidneys present……

v. Cord insertion site……..

w. No spinal defects or masses (transverse and sagittal views)……

x. Arms and hands present, normal relationships……..

y. Legs and feet present, normal relationships……..

z. Placenta Position……..

aa. No placental masses present……

bb. Accessory lobe of placenta…….

cc. Umbilical cord Three-vessel cord.....

dd. Genitalia Male or female…….

ANC / OP No……. IP No…… Study number …… Phone Number……

Second and subsequent visits

121. How are you feeling today?

a. I am well =1

b. I have a fever =2

c. I have a headache =3

d. I have abdominal pain =4

e. Other = 99 (Specify) ……

122. Gestation age today ……

Physical examination:

123. Weight in Kg ……..

124. Blood pressure …….

125. Pulse rate …….

126. Respiratory rate ……..

127. Temperature …….

128. Fundal height in Centimeters …….

129. Foetal heart rate ……..

130. Any other organomegaly?

……..……..

131. Any other finding worth noting

……

Laboratory results

132. Urine protein ……

ANC / OP No……. IP No…… Study number …… Phone Number……

Ultrasound examination findings (for those classified as exposed or had abnormal uterine artery Doppler PI of >1.40 or RI of >0.58, or had early diastolic notch)

133. Gestation age .....Weeks

134. Percentile of growth curve ……..

135. BPD..... cm

136. HC..... cm

137. AC..... cm

138. FL..... cm

139. AFI..... cm

140. Right uterine artery PI …….

141. Right uterine artery RI …….

142. Right uterine artery End diastolic Notch Yes / no

143. Left Uterine Artery PI ……

144. Left Uterine Artery RI ……

145. Left Uterine Artery End diastolic notch yes/no

146. BPP score …… Tone…. Breathing …. Movement ….. AFI …..

147. Umbilical artery PI ……..

148. Umbilical artery RI …….

149. Mid cerebral artery peak systolic velocity ……..

ANC / OP No……. IP No…… Study number …… Phone Number……

Labour and Delivery

150. Weight in labour

151. Gestation age at delivery ……

152. Urine protein in labour……

153. Blood pressure ……

154. Highest recorded blood pressure in labour ……..

155. Mode of delivery ……

156. Estimated blood loss ……..

157. The placenta

f. Weight of the placenta……..

g. Colour of the placenta…….

h. Number of cotyledons seen……..

i. Extra lobes of placenta…….

j. Cord insertion – central or eccentric ……

k. Cord appearance ……

l. Cord coils present / absent……..

m. True knots present / absent…….

158. Drugs given to mother during labour and delivery

……

159. Baby's birth weight …….

160. Apgar score ……

161. Resuscitation given to baby …….

…….

162. Drugs that are given to baby

……

……

……

On discharge from the hospital

163. Condition of the mother …….

164. Condition of the baby ……

165. Duration of hospital stay

n ..... days before delivery.

o ..... days after delivery

ANNEX 3: PUBLISHED PAPERS

The printed articles included in this thesis are reprinted with the consent of the scientific journals where they were initially published.

1. Awor S, Byanyima R, Abola B, Nakimuli A, Orach CG, Kiondo P, J. Ogwal-Okeng, D. Kaye. Incidence of preeclampsia and retention to prenatal care in Northern Uganda. East African Medical Journal. 2022; 99(6):4885 - 96.
2. Silvia Awor, Rosemary Byanyima, Benard Abola, Paul Kiondo, Christopher Garimoi-Orach, Jasper Ogwal-Okeng, Annettee Nakimuli, Dan Kaye. (2022): Prediction of low birth weight at term in low resource setting of Gulu city, Uganda: a prospective cohort study. PAMJ - Clinical medicine 2022, 10(28). doi:10.11604/pamj-cm.2022.10.28.37102
3. Awor S., Byanyima R., Abola, B., Kiondo P., Orach, C. G., Ogwal-Okeng J., Kaye Dan, Nakimuli, A. (2022).: Prediction of stillbirth low resource setting in Northern Uganda. BMC Pregnancy and Childbirth 2022, 22(1). doi:10.1186/s12884-022-05198-6
4. Awor S, Abola B, Byanyima R, Orach CG, Kiondo P, Kaye DK, Ogwal-Okeng J, Nakimuli A: Prediction of pre-eclampsia at St. Mary's hospital lacor, a low-resource setting in northern Uganda, a prospective cohort study. BMC Pregnancy and Childbirth 2023, 23(1).
5. Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. Journal of African Interdisciplinary Studies. 2022, 6(1), 109 – 126.
6. Prediction of preterm birth (Accepted for publication in the African Health Sciences)

Awor et al. BMC Pregnancy and Childbirth (2022) 22:855
https://doi.org/10.1186/s12884-022-05198-6

BMC Pregnancy and Childbirth

RESEARCH Open Access

Prediction of stillbirth low resource setting in Northern Uganda

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Abstract

Background: Women of Afro-Caribbean and Asian origin are more at risk of stillbirths. However, there are limited tools built for risk-prediction models for stillbirth within sub-Saharan Africa. Therefore, we examined the predictors for stillbirth in low resource setting in Northern Uganda.

Methods: Prospective cohort study at St. Mary's hospital Lacor in Northern Uganda. Using Yamane's 1967 formula for calculating sample size for cohort studies using finite population size, the required sample size was 379 mothers. We doubled the number (to > 758) to cater for loss to follow up, miscarriages, and clients opting out of the study during the follow-up period. Recruited 1,285 pregnant mothers at 16–24 weeks, excluded those with lethal congenital anomalies diagnosed on ultrasound. Their history, physical findings, blood tests and uterine artery Doppler indices were taken, and the mothers were encouraged to continue with routine prenatal care until the time for delivery. While in the delivery ward, they were followed up in labour until delivery by the research team. The primary outcome was stillbirth 24 + weeks with no signs of life. Built models in RStudio. Since the data was imbalanced with low stillbirth rate, used ROSE package to over-sample stillbirths and under-sample live-births to balance the data. We cross-validated the models with the ROSE-derived data using K (10)-fold cross-validation and obtained the area under curve (AUC) with accuracy, sensitivity and specificity.

Results: The incidence of stillbirth was 2.5%. Predictors of stillbirth were history of abortion (aOR = 3.07, 95% CI 1.11—8.05, $p = 0.0243$), bilateral end-diastolic notch (aOR = 3.51, 95% CI 1.13—9.92, $p = 0.0209$), personal history of preeclampsia (aOR = 5.18, 95% CI 0.60—30.66, $p = 0.0916$), and haemoglobin 9.5 – 12.1 g/dL (aOR = 0.33, 95% CI 0.11—0.93, $p = 0.0375$). The models' AUC was 75.0% with 68.1% accuracy, 69.1% sensitivity and 67.1% specificity.

Conclusion: Risk factors for stillbirth include history of abortion and bilateral end-diastolic notch, while haemoglobin of 9.5—12.1 g/dL is protective.

Keywords: Stillbirth, Risk factors, Prediction models, Uganda, Africa

Introduction

Stillbirth is the death of a fetus before birth after 20 weeks of gestation [1]. In the early twentieth century, stillbirth was any child who exhibits no sign of life by crying or breathing, or by pulsation in the cord at its attachment to the body of the child, or by beating of the heart and measuring more than 13 inches in length from the top of head to the heel at birth [2]. In the late twentieth century stillbirth was defined as any baby born at 24 weeks of gestation without a sign of life [3]. It can be classified as an early (24 – 27 weeks), late (28 – 36 weeks), or term (37 weeks) stillbirth [4].

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The global prevalence of stillbirth is approximately 2% [5], with 0.3% occurring in the global north [6, 7], and more than 2% in the global south [5, 8–10]. Women of Afro-Caribbean and Asian origin are more at risk of stillbirths [7, 11–14] and this may be associated with racial disparities in accessing health care [12]. Incidence of stillbirth in Uganda is about 2.0%—3.6% [15, 16]. However, due to challenges in access to care and policies on death registration in the global south, most stillbirths are not registered [17].

When maternal obesity, smoking, chronic hypertension, antiphospholipid syndrome, type 2 diabetes, and insulin requirement are used in a prediction model risk calculator for stillbirth [18], it predicted stillbirths at 60—72% AUC at 75% sensitivity and close to 100% specificity [6, 7, 19]. When maternal history and fetal growth rates were added to maternal history without using the risk calculator, the discriminative performance of the model had a C-statistic of 0.80 [8].

There are limited number of tools built for risk-prediction models for stillbirth within sub-Saharan Africa. With the problems of access to hospital delivery and African ancestry being a risk factor for stillbirth, we set out to develop and validate a prediction model for stillbirth in Northern Uganda.

Materials and methods

Study design

A prospective cohort study at St. Mary's Hospital Lacor, which is one of the teaching hospitals of Gulu University. Using Yamane's 1967 formula for calculating sample size for cohort studies using finite population size, St. Mary's hospital Lacor delivers approximately seven thousand mothers per year. Since my study duration was 12 months for recruitment of the mothers, the finite population I could access was about 7,000 mothers. Yamane 1967 formula:

$$\text{Samplesize} n = \text{N}/1 + \text{Ne}2$$

where N is the finite population size 7,000 mothers.
Margin of error (e) 05%
Therefore $n = 7{,}000 / 1 + 7{,}000(0.05).^2$
$n = 379$.

The required sample size was 379 mothers. We doubled the number (to > 758) to cater for loss to follow-up, miscarriages, and clients opting out of the study during the follow-up period. Recruited 1,285 pregnant mothers 16 – 24 weeks from April 2019 to March 2020. Excluded all with lethal congenital anomalies diagnosed on ultrasound scan especially molar pregnancy, anencephaly, and cystic hygroma. A questionnaire was filled, and uterine artery Doppler sonography was done on all the mothers. The ultrasonography was done by one trained obstetrician. A full foetal anatomical survey was done in addition to the uterine artery Doppler indices (pulsatility and resistive indices, end-diastolic notch). Blood samples were taken for complete blood count, liver and renal function tests, from one thousand (1,000) mothers. The mothers were encouraged to continue with routine antenatal care until the time for delivery. While admitted to the delivery ward, the mothers were followed up by the research team until delivery of the baby. The last mother was delivered at the end of September 2020.

Outcome

The Apgar score of zero within the first minute of birth at 24 + weeks was taken as stillbirth.

Statistical analysis

One thousand four (1,004) complete delivery records were obtained. Data were pre-processed using Stata 15.0 and built models using RStudio R version 4.1.1 (2021–08-10). Univariable analysis was done, and all variables with p-values ≤ 0.20 or were known risk factors for stillbirth like age and maternal comorbidities were put together into a logistic regression model. Since the data was imbalanced with few stillbirths, we applied the ROSE technique [20, 21] to create a new dataset by over-sampling stillbirths and under-sampling live births, and obtained a distribution of live births and stillbirth cases as 400 (51.1%) and 383 (48.9%), respectively. The ROSE-derived data set was fitted into a confusion matrix to evaluate the performance of our models (accuracy, sensitivity, specificity) using K-(10)-fold cross-validation. Variables were said to be independent risk factors of stillbirth if their p-value < 0.05 in the model. Six models were built.

Results

One thousand four (1004) complete delivery records were obtained at the end of the study period.. Of these, seven hundred eighty two mothers had laboratory blood tests done with 2.4% (19) stillbirths and 97.6% (763) live-births. Prevalence of stillbirth was 2.5% (25 out of 1004). There was 979 (97.5%) live births. Seven (28%) out of the 25 deaths occurred intrapartum. Two (8%) of the 25 mothers who lost their babies had a history of previous stillbirth. Two hundred eighty-one mothers were lost to follow-up. Details are found in Fig. 1.

The incidence rates for stillbirth were higher at lower gestation ages, as outlined in Table 1. There were 273 stillbirths per 10^4 women weeks at < 28 weeks while only 3 stillbirths per 10^4 women weeks at ≥ 37 weeks.

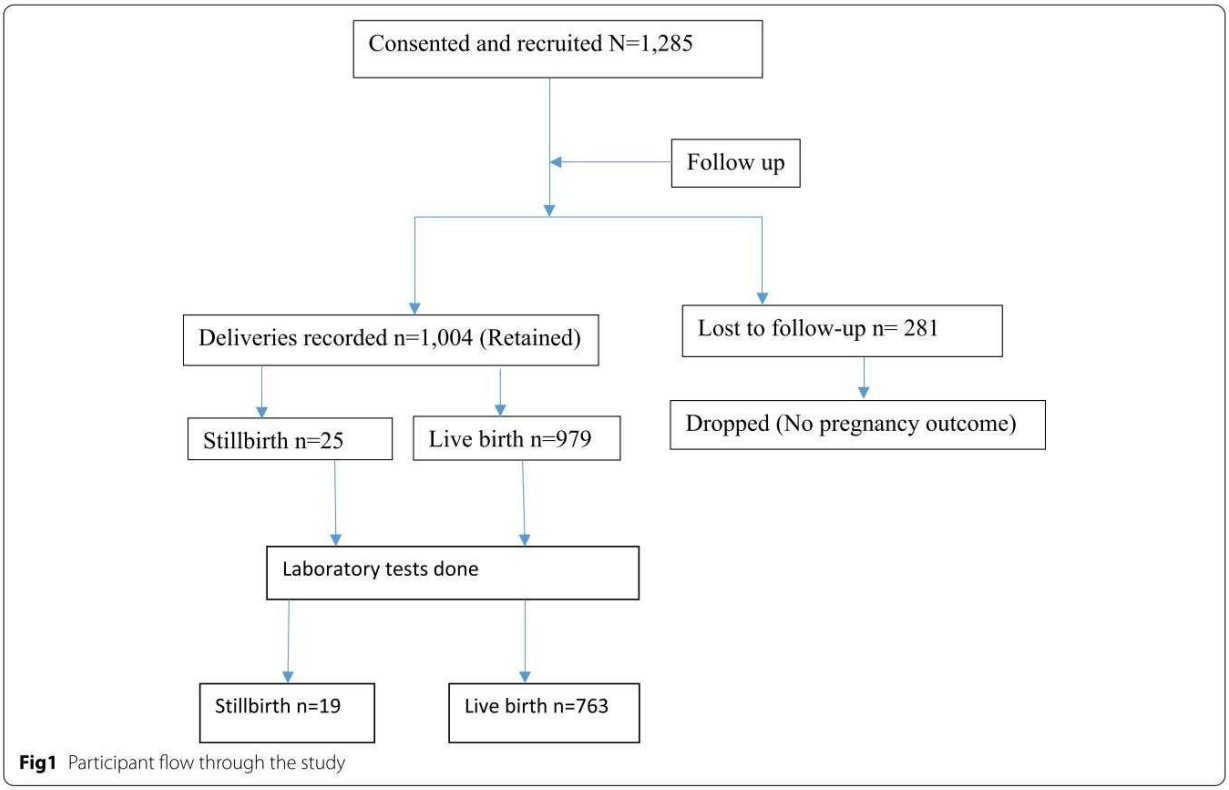

Fig1 Participant flow through the study

Table 1 Incidence of stillbirth

Variables	Total Population	Number of stillbirth	% (95% CI)	Incidence of stillbirth per 10^4 women weeks
No stillbirth	979	0	0%	0
Stillbirth occurred	25	25	2.5% (1.6%—3.7%)	6 (4—9)
Stillbirth occurred < 28 weeks	9	6	66.7% (22.9%—92.5%)	273 (94—379)
Stillbirth ≥ 28—< 37 weeks	119	9	7.6% (3.5%—13.8%)	22 (10—40)
Stillbirth ≥ 37 weeks	876	10	1.1% (0.5%—2.1%)	3 (1—6)

Second trimester characteristics of the women who returned to deliver in hospital

Mean maternal age was 26.3 years while 316 participants were first time mothers. Details in Table 2.

Average body-mass index (BMI) was 24.7, and prevalence of multiple pregnancy was 2.4%. Only 0.6% (6) of participants had prenatal hypertension at the time of recruitment. Details in Table 3.

Prevalence of anaemia in pregnancy was high with a mean haemoglogin level of 10.7 g/dL and haematocrit levels of 32.6%. Details in Table 4.

Unadjusted logistic regression for stillbirth with demographic characteristics

Personal history of preeclampsia and any history of abortion were significantly related to stillbirth while being married or cohabiting was protective. Details in Table 5.

While for the clinical characteristics; systolic hypertension, end diastolic notch, pulsatility and resistive indices were significantly related to stillbirth. Details in table 6.

When laboratory characteristics were used, there were no significant relationship to stillbirth. Details in Table 7.

Table 2 Social demographic characteristics of the study population at recruitment

Characteristics ($n=1,004$)	Mean (sd) / Median (IQR) / Proportion (%)
Maternal age (years) mean (sd)	26.3 (5.5)
Maternal age (years) median (IQR)	26.0 (22.0—30.0)
Single	17 (1.7%)
Married/Cohabiting	987 (98.3%)
Nulliparity	316 (31.5%)
Para 1–2	458 (45.6%)
Para > 2	230 (22.9%)
No history of abortion	810 (80.7%)
Any history of abortion	194 (19.3%)
Umemployed	311 (31.0%)
Informal (casual labourer)	620 (61.8%)
Formal (salaried job)	73 (7.3%)
mean (sd) Gestation age at recruitment (weeks)	20.4 (2.7)
median (IQR) Gestation age at recruitment (weeks)	20.1 (18.6—22.1)
Previous history of preterm birth	85 (12.4%)
No previous history of preterm birth	603 (87.6%)
Personal history of preeclampsia	14 (1.4%)
Not applicable (prime gravida)	316 (31.5%)
No personal history of preeclampsia	674 (67.1%)
Mean (sd) age at menarche (years)	14.4 (1.4)
Median (IQR) age at menarche (years)	14.0 (13.0—15.0)
History of fertility treatment	9 (0.9%)
No history of fertility treatment	995 (99.1%)
Family history of preeclampsia	38 (3.8%)
No family history of preeclampsia	966 (96.2%)
Presence of a chronic illness	90 (9.0%)
No chronic illness	914 (91.0)
Tobacco use in a lifetime	2 (0.2%)
No tobacco use in a lifetime	1,002 (99.8%)
Living with a smoker in one house	104 (10.4%)
No smoker in one house	900 (89.4%)
Alcohol use in pregnancy	56 (5.6%)
No alcohol use in pregnancy	948 (94.4%)

Table 3 Clinical characteristics of the study population at recruitment

Characteristics $n=1,004$	Mean (Sd) / proportion (%)	Median (IQR)
Body mass index	24.7 (3.9)	23.9 (21.8—26.8)
Systolic blood pressure	64.0 (10.4)	63.0 (57.0—70.0)
Diastolic blood pressure	105.7 (12.7)	104.0 (97.0—113.0)
Prenatal hypertension	6 (0.6%)	
No prenatal hypertension	998 (99.4%)	
Singleton pregnancy	980 (97.6%)	
Multiple pregnancy	24 (2.4%)	
No diastolic notch	734 (73.1%)	
Unilateral end diastolic notch	156 (15.5%)	
Bilateral end diastolic notch	114 (11.4%)	
Average Resistive index	0.51 (0.11)	0.50 (0.44—0.58)
Average pulsatility index	0.81 (0.30)	0.75 (0.61—0.96)

Table 4 Laboratory characteristics of the population at recruitment

Characteristics $n=787$	Mean (Sd)	Median (IQR)
Serum ALT	30.4 (27.7)	25.0 (18.0—34.0)
Serum AST	20.1 (23.2)	14.0 (7.0—26.0)
Serum GGT	21.6 (8.5)	20 (15—29)
Serum ALP	153.6 (49.9)	146 (115—179)
Serum bicarbonate	25.4 (2.2)	25 (24—27)
Serum Albumin	4.1 (2.9)	3.9 (3.5—4.1)
Serum Urea	25.3 (26.4)	18 (14—25)
Serum sodium	137.5 (4.0)	137.3 (135.1—139.4)
Serum potassium	4.3 (1.2)	4.2 (3.9—4.5)
Serum chloride	106.3 (4.3)	105.0 (103.5—108.9)
Serum phosphorus	1.3 (0.9)	1.1 (0.9—1.4)
Serum calcium	2.4 (1.2)	2.2 (2.1—2.4)
Serum creatinine	1.0 (0.6)	0.9 (0.8—1.2)
Neutrophil count	3.7 (2.2)	3.5 (2.6—4.6)
Lymphocyte Count	1.8 (0.9)	1.6 (1.3—2.1)
Total White blood cell count	6.3 (2.9)	6.0 (4.9—7.4)
Platelet count	223.9 (69.4)	220 (178—267)
Haemoglobin level	10.7 (2.0)	10.9 (9.5—12.0)
Haematocrit	32.6 (6.7)	33.0 (28.5—33.0)
Mean corpuscular volume	84.3 (7.8)	84.5 (79.9—89.1)
Mean corpuscular haemoglobin concentration	32.9 (2.5)	32.8 (31.4—34.3)

All the variables with unadjusted p-value of ≤ 0.200 were taken for multivariable analysis to produce the models for prediction of stillbirth. Six models were built in R-studio. The variables are removed from the model in a stepwise manner to remain with the least number of variables with a high AUC. Those variables with $p<0.1$ were retained in the model while those with $p<0.05$ were taken as independent risk factors for stillbirth.

Models for prediction of stillbirth

Model 1 examined maternal history and physical examination (details in Table 8). The predictors of stillbirth were parity, age ≥ 35 years, history of abortion and personal history of preeclampsia. Personal history of preeclampsia (aOR = 11.08, 95% CI 1.44—57.34, $p=0.0075$) and history of abortion (aOR = 2.92, 95% CI 1.07—7.57, $p=0.0293$) were independent risk factors for stillbirth.

Table 5 Unadjusted regression analysis for demographic characteristics for prediction of stillbirth

Variable	OR (95% CI)	*p*-value
Maternal age (years) ≥ 35	1.80 (0.63—5.14)	0.271
Married/Cohabiting	0.20 (0.50—0.77)	**0.020**
Nulliparity	1.82 (0.58—5.73)	0.307
Para 1–2	1.38 (0.44—4.29)	0.577
Any history of abortion	2.78 (1.30—6.10)	**0.011**
Informal (casual labourer)	0.67 (0.28—1.57)	0.356
Formal (salaried job)	1.89 (0.60—5.98)	0.277
Previous history of preterm birth	1.09 (0.25—4.76)	0.907
Personal history of preeclampsia	6.15 (1.60—23.62)	**0.008**
age at menarche ≥ 15 years	0.53 (0.16—1.77)	0.305
Family history of preeclampsia	1.06 (0.15—7.63)	0.954
Presence of a chronic illness	0.42 (0.06—3.09)	0.397
Living with a smoker in one house	0.75 (0.18—3.15)	0.697
Alcohol use in pregnancy	1.47 (0.36—6.09)	0.594

Table 6 Unadjusted regression analysis for clinical characteristics for prediction of stillbirth

Variable	OR (95% CI)	*p*-value
Body mass index > 25 kg/m^2	0.76 (0.33—1.74)	0.511
Systolic blood pressure ≥ 140 mmHg	5.94 (0.93—38.05)	**0.060**
Diastolic blood pressure ≥ 90 mmHg	1.70 (0.24—12.08)	0.595
Multiple pregnancy	Too few	
Lateral placental location	1.22 (0.29—5.05)	0.788
Unilateral end diastolic notch	1.01 (0.29—3.47)	0.990
Bilateral end diastolic notch	3.68 (1.58—8.58)	**0.003**
Average Resistive index > 0.65 (90th percentile)	3.75 (1.65—8.49)	**0.002**
Average pulsatility index > 1.19 (90th percentile)	3.82 (1.69—8.66)	**0.001**

Model 2 examined the uterine artery Doppler indices (details in Table 9). The predictor of stillbirth was presence of end diastolic notch on the uterine artery Doppler flow tracing. Bilateral end diastolic notch (aOR = 4.28, 95% CI 1.54—11.19, $p = 0.0035$) was an independent risk factor for stillbirth.

Model 3 examined the combination of maternal history, physical examination and uterine artery Doppler indices (models 1 and 2) (details in Table 10). The predictors of stillbirth were history of abortion and end-diastolic notch on the uterine artery Doppler flow tracing. The history of abortion (aOR = 3.29, 95% CI 1.24—8.41, $p = 0.0134$) and bilateral end-diastolic notch (aOR = 4.49, 95% CI 1.60—11.88), $p = 0.0029$) were independent risk factors for stillbirth.

Model 4 examined maternal laboratory blood tests (details in Table 11). The predictors of stillbirth were platelet neutrophil ratio, neutrophil count and haemoglobin level. The independent risk factors for stillbirth was platelet neutrophil ratio of > 83.95 (aOR = 5.76, 95% CI 1.12—35.90, $p = 0.0437$). Haemoglobin level of 9.5 – 12.1 g/dL (aOR = 0.32, 95% CI 0.11—0.89, $p = 0.0287$) was protective against stillbirth.

Model 5 examined the combination of maternal history and laboratory tests (models 1 and 4) (details in Table 12). The predictors of stillbirth were history of abortion, parity, age ≥ 35 years and haemoglobin level. The independent risk factors for stillbirth was history of abortion (aOR = 3.10, 95% CI 1.11—8.26), $p = 0.0254$). Haemoglobin level of 9.5 – 12.1 g/dL (aOR = 0.33, 95% CI 0.109—0.95, $p = 0.0411$) was protective against stillbirth.

Model 6 examined the combination of maternal history, physical examination, uterine artery Doppler indices and laboratory tests (models 1, 2 and 4) (details in Table 13).The predictors of stillbirth were personal history of preeclampsia, history of abortion, end-diastolic notch and haemoglobin level. The history of abortion (aOR = 3.07, 95% CI 1.11—8.05, $p = 0.0243$) and bilateral end diastolic notch (aOR = 3.51, 95% CI 1.13—9.92, $p = 0.0209$) were independent risk factors for stillbirth while haemoglobin level of 9.5 – 12.1 g/dL (aOR = 0.33, 95% CI 0.11—0.93, $p = 0.0375$) was protective.

Evaluation of the models of stillbirth

The models AUC ranges from 66.8% to 75.0%, with accuracies of 63.9% to 68.1%. Details in Table 14.

Model 1 examined maternal history and physical examination (details in Table 8). The predictors of stillbirth were parity, age ≥ 35 years, history of abortion and personal history of preeclampsia. This predicted stillbirth with 65.8% accuracy, 82.4% sensitivity, 48.4% specificity and 71.9% AUC. The details for the models are found in Table 14.

Discussion

From demographic characteristics of our participants, the predictors of stillbirth were parity, age ≥ 35 years, history of abortion and personal history of preeclampsia. This predicted stillbirth with 65.8% accuracy, 82.4% sensitivity, 48.4% specificity and 71.9% AUC. In Niger state Nigeria, the predictors of stillbirth were maternal comorbidity, rural place of residence, multipara, bleeding during pregnancy, and non-cephalic fetal presentation [8]. Maternal employment was protective of stillbirth [8]. They predicted stillbirth with a C-statistic basic model = 0.80 (95% CI 0.78–0.83), and when ultrasound parameters were added the extended C-statistic model improved slightly to 0.82 (95% CI 0.80–0.83)[8]. In a case–control study in southern Ethiopia, the predictors of stillbirth were women with multiple pregnancy

Table 7 Unadjusted regression analysis for laboratory characteristics for prediction of stillbirth

Variable	OR (95% CI)	*p*-value
Serum ALT 19—25 IU	2.52 (0.79—8.04)	**0.120**
Serum ALT > 25 IU (> 90th percentile)	0.84 (0.24—2.96)	0.792
Serum AST 4—40 IU (10th—90th percentile)	0.81 (0.19—3.49)	0.782
Serum AST > 40 IU (> 90th percentile)	0.95 (0.14—6.55)	0.756
Serum GGT ≤ 30 IU (Normal lab range)	1.34 (0.39—4.54)	0.639
Serum ALP ≤ 98 IU (low lab range)	1.44 (0.20—10.45)	0.717
Serum bicarbonate 24—27 (25th—75th percentile)	4.10 (0.54—30.93)	**0.172**
Serum bicarbonate > 27 (> 75th percentile)	3.77 (0.43—33.36)	0.233
Serum albumin 3.5—4.1 g/dL	0.46 (0.15—1.42)	**0.180**
Serum Albumin < 3.5 g/dL	1.27 (0.43—3.70)	0.667
Serum urea 14—25 mg/dL (25th—75th percentile)	1.50 (0.42—5.40)	0.534
Serum urea > 25 mg/dL (> 75th percentile)	1.85 (0.0.47—7.30)	0.379
serum creatinine 0.61—1.50 mg/dL (10th—90th percentile)	0.62 (0.21—1.86)	0.395
Serum creatinine > 1.50 mg/dL	0.35 (0.40—3.07)	0.343
Neutrophil count 2.63—4.54 cells/microlitre	0.92 (0.31—2.71)	0.881
Neutrophil count > 4.54 cells/microlitre	1.00 (0.29—3.40)	1.000
Lymphocyte Count 0.9—3.9 cells/microlitre	0.33 (0.10—1.12)	**0.075**
Lymphocyte Count > 3.9 cells/microlitre	1.89 (0.34—10.42)	0.465
Total White blood cell count 4000–11,000 cells / microlitre	1.10 (0.26—4.70)	0.900
Total White blood cell count > 11,000 cells / microlitre	2.91 (0.28—30.25)	0.372
platelet count 178—266 cells / microliter (25th—75th percentile)	1.60 (0.45—5.76)	0.470
Platelet count > 266 cells / microliter (> 75th percentile)	1.93 (0.49—7.60)	0.348
Haemoglobin level < 9.5 g/dL (< 25th percentile)	2.78 (0.76—10.12)	**0.120**
Haemoglobin level 9.5—12.1 g/dL (25th—75th percentile)	1.02 (0.27—3.89)	0.981
Haematocrit 30—39.9% (25th—75th percentile)	0.50 (0.20—1.25)	**0.140**
Haematocrit ≥ 40% (> 75th percentile)	0.49 (0.06—3.83)	0.501
Mean corpuscular volume 79.9—89.2 fl (25th—75th percentile)	1.30 (0.42—4.04)	0.647
Mean corpuscular volume < 79.9 fl (< 25th percentile	0.97 (0.25—3.82)	0.965
Mean corpuscular haemoglobin concentration 31.5—34.4 g/dL	1.05 (0.40—2.75)	0.923
Mean corpuscular haemoglobin concentration < 31.5 g/dL	0.18 (0.22—1.47)	**0.110**

Table 8 Model 1 using maternal history for prediction of stillbirth

Variable	OR (95% CI)	*p*-value
Personal history of preeclampsia	11.08 (1.44—57.34)	**0.0075**
History of abortion	2.92 (1.07—7.57)	**0.0293**
Age ≥ 35 years	4.29 (0.72—20.72)	0.0851
nullipara	5.37 (1.10—36.24)	0.0576
para 1—2	2.28 (0.48—13.67)	0.3284
Intercept	0.005 (0.001—0.02)	0.0000

[aOR = 2.98, 95%CI: 1.39–6.36], having preterm birth [aOR = 2.83, 95%CI: 1.58– 508], having cesarean mode of delivery [aOR = 3.19, 95%CI: 1.87–5.44], having no ANC visit [aOR = 4.17, 95%CI: 2.38–7.33], and being hypertensive during pregnancy [aOR = 3.43, 95%CI: 1.93–6.06].

Table 9 Model 2 using uterine artery Doppler indices for prediction of stillbirth

Variable	OR (95% CI)	*p*-value
Unilateral	0.40 (0.02—2.09)	0.3843
Bilateral	4.28 (1.54—11.19)	**0.0035**
Intercept	0.02 (0.01—0.03)	0.0000

Table 10 Model 3 using combination of maternal history and uterine artery Doppler indices for prediction of stillbirth

Variable	OR (95% CI)	*p*-value
History of abortion	3.29 (1.24—8.41)	**0.0134**
Unilateral	0.38 (0.02—2.01)	0.3618
Bilateral	4.49 (1.60—11.88)	**0.0029**
Intercept	0.01 (0.006—0.03)	0.0000

Table 11 Model 4 using maternal laboratory tests for prediction of stillbirth

Variable	OR (95% CI)	*p*-value
Platelet neutrophil ratio of 47.04—83.95	1.80 (0.46—9.00)	0.4232
Platelet neutrophil ratio of > 83.95	5.76 (1.12—35.90)	**0.0437**
Neutrophil count of (2.63—4.54) *1000	2.14 (0.60—8.12)	0.2453
Neutrophil count of (> 4.54) *1000	4.16 (0.77—22.81)	0.0958
Haemoglobin level of 9.5—12.1 g/dL	0.32 (0.11—0.89)	**0.0287**
Haemoglobin level of > 12.1 g/dL	0.33 (0.07—1.14)	0.1027
Intercept	0.01 (0.001—0.06)	0.0000

Table 12 Model 5 using combination of maternal history and laboratory tests for prediction of stillbirth

Variable	OR (95% CI)	*p*-value
History of abortion	3.10 (1.11—8.26)	**0.0254**
Age ≥ 35 years	4.87 (0.79—24.57)	0.0677
nullipara	5.09 (1.02—35.71)	0.0715
para 1—2	2.51 (0.52—15.59)	0.2831
Haemoglobin level of 9.5—12.1 g/dL	0.33 (0.109—0.95)	**0.0411**
Haemoglobin level of > 12.1 g/dL	0.27 (0.06—0.99)	0.0656
Intercept	0.01 (0.001—0.005)	0.0000

Table 13 Model 6: Combination of maternal history, uterine artery Doppler indices and laboratory tests for prediction of stillbirth

Variable	OR (95% CI)	*p*-value
Personal history of preeclampsia	5.18 (0.60—30.66)	0.0916
History of abortion	3.07 (1.11—8.05)	**0.0243**
Unilateral	0.37 (0.02—1.98)	0.3507
Bilateral	3.51 (1.13—9.92)	**0.0209**
Haemoglobin level 9.5—12.1 g/dL	0.33 (0.11—0.93)	**0.0375**
Haemoglobin level > 12.1 g/dL	0.30 (0.06—1.07)	0.0850
Intercept	0.03 (0.01—0.07)	0.0000

[22]. However, these women were recruited after they had given birth. In clinical settings in low resource settings one can use the demographic characteristics above as predictors to identify up to two-thirds of mothers at risk of having stillbirth. Despites the model's sensitivity of 82.4%, the model's specificity of 48.4% is low. One will have to put more than twice the number of women identified as at risk of stillbirth in order to get the two thirds of women who will actually get stillbirth.

Combination of uterine artery Doppler indices and maternal history predicted stillbirth by 67.6% accuracy, 75.8% sensitivity and 69.9% AUC. This may be comparable to Akolekar et al.[19] who predicted 55% of all stillbirths, including 75% of those due to impaired placentation and 23% of those that were unexplained or due to other causes, at a false-positive rate of 10% using maternal history and uterine artery Doppler indices. Ultrasound examination is not compulsory in Uganda[23]. It is reserved for a few referral centers, teaching hospitals and private hospitals[24, 25]. Majority of the mothers go through their gestation period without performing a single ultrasound scan.

We predicted stillbirth by 75.0% AUC with 68.1% accuracy, 69.1% sensitivity and 67.1% specificity. This was comparable to the stillbirth-risk calculator [18] validated in Austria at 72% AUC [6]. In the United Kingdom, stillbirth detection rates ranged from 28 to 48% with an AUC of 55.0% to 65.8% even after allowing a 10% false positive rate [7, 19]. In Australia, the detection rate for stillbirth was 45%, with an AUC ranging from 59 to 84% [26]. Similarly, in the United States of America, the detection rate for stillbirth has been 64%—66% AUC [27].

Mastrodima et al. [28] used maternal factors, PAPP-A, Doppler pulsatility index and ductus venosus pulsatility index for veins (DV-PIV), and predicted 40% of all stillbirths and 55% of those due to impaired placentation, at a false-positive rate of 10%. Within the impaired-placentation group, the detection rate of stillbirth < 32 weeks' gestation was higher than that of stillbirth ≥ 37 weeks (64% vs 42%). This makes the study compare favorably to those

Table 14 Evaluation of the models for stillbirth

Model	Accuracy	Sensitivity	Specificity	AUC
Model 1 (Maternal history and exam)	65.8	82.4	48.4	71.9
Model 2 (Uterine artery Doppler indices)	63.9	88.7	37.9	66.8
Model 3 (History and uterine artery Doppler indices)	67.6	75.9	59.0	69.9
Model 4 (lab tests)	65.3	71.6	58.7	69.7
Model 5: (combination of history and laboratory tests)	68.0	67.1	69.0	74.4
Model 6: (combination of maternal history, Doppler indices and laboratory tests)	68.1	69.1	67.1	75.0

conducted in global north. Perhaps the differences seen is due to the differences in the population itself and the technology used for the prediction of stillbirth.

Research implications

These models may be used in several clinics. Future studies may include a larger number of participants from several locations to validate the models to ensure generalizability.

Strengths and limitation

This study was a baseline study in Northern Uganda to find out the predictors of stillbirths and to pave way for more research. There was a high number of mothers lost to follow-up.

Conclusion

In places where ultrasound or laboratory services are not available, the predictors of stillbirths are history of abortion, personal history of preeclampsia, maternal age ≥ 35 years and parity. These variables predict stillbirth by 71.9% AUC with 68.5% accuracy, 82.4% sensitivity and 48.4% specificity.

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Authors' contributions

Silvia Awor is a Ph.D. student who wrote the proposal, collected data and drafted the manuscript. Annettee Nakimuli, Jaspar Ogwal-Okeng and Dan Kabonge Kaye are doctoral supervisors who guided the writing of the manuscript. Rosemary Byanyima, Paul Kiondo and Christopher Garimoi-Orach are doctoral committee members who gave technical advice during the data collection and manuscript writing. Benard Abola, a mathematician, helped develop and validate the model and participated in data analysis. The author(s) read and approved the final manuscript.

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Availability of data and materials

The corresponding author Dr. Silvia Awor or Makerere University Directorate of Research and Graduate training can be contacted to request for the data and other materials.

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval and consent to participate

The study was approved by the Research and Ethics Committee of Makerere University School of Medicine (Reference number 2018–105), Uganda National Council for Science and Technology (Reference number HS258ES), and administrative clearance from St. Mary's hospital Lacor (Reference number LHIREC Adm 009/11/18). Written informed consent was sought from every participant. All methods were carried out according to the "Declaration of Helsinki" guidelines [29].

Consent for publication

Not application.

Conflict of interest

The authors have declared no competing interest.

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RESEARCH Open Access

Prediction of pre-eclampsia at St. Mary's hospital lacor, a low-resource setting in northern Uganda, a prospective cohort study

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Abstract

Background Pre-eclampsia is the second leading cause of maternal death in Uganda. However, mothers report to the hospitals late due to health care challenges. Therefore, we developed and validated the prediction models for prenatal screening for pre-eclampsia.

Methods This was a prospective cohort study at St. Mary's hospital lacor in Gulu city. We included 1,004 pregnant mothers screened at 16–24 weeks (using maternal history, physical examination, uterine artery Doppler indices, and blood tests), followed up, and delivered. We built models in RStudio. Because the incidence of pre-eclampsia was low (4.3%), we generated synthetic balanced data using the ROSE (Random Over and under Sampling Examples) package in RStudio by over-sampling pre-eclampsia and under-sampling non-preeclampsia. As a result, we got 383 (48.8%) and 399 (51.2%) for pre-eclampsia and non-preeclampsia, respectively. Finally, we evaluated the actual model performance against the ROSE-derived synthetic dataset using K-fold cross-validation in RStudio.

Results Maternal history of pre-eclampsia (adjusted odds ratio (aOR) = 32.75, 95% confidence intervals (CI) 6.59—182.05, $p = 0.000$), serum alkaline phosphatase(ALP) < 98 IU/L (aOR = 7.14, 95% CI 1.76—24.45, $p = 0.003$), diastolic hypertension ≥ 90 mmHg (aOR = 4.90, 95% CI 1.15—18.01, $p = 0.022$), bilateral end diastolic notch (aOR = 4.54, 95% CI 1.65—12.20, $p = 0.003$) and body mass index of ≥ 26.56 kg/m^2 (aOR = 3.86, 95% CI 1.25—14.15, $p = 0.027$) were independent risk factors for pre-eclampsia. Maternal age ≥ 35 years (aOR = 3.88, 95% CI 0.94—15.44, $p = 0.056$), nulliparity (aOR = 4.25, 95% CI 1.08—20.18, $p = 0.051$) and white blood cell count ≥ 11,000 (aOR = 8.43, 95% CI 0.92—70.62, $p = 0.050$) may be risk factors for pre-eclampsia, and lymphocyte count of 800 – 4000 cells/microliter (aOR = 0.29, 95% CI 0.08—1.22, $p = 0.074$) may be protective against pre-eclampsia. A combination of all the above variables predicted pre-eclampsia with 77.0% accuracy, 80.4% sensitivity, 73.6% specificity, and 84.9% area under the curve (AUC).

Conclusion The predictors of pre-eclampsia were maternal age ≥ 35 years, nulliparity, maternal history of pre-eclampsia, body mass index, diastolic pressure, white blood cell count, lymphocyte count, serum ALP and end-diastolic notch of the uterine arteries. This prediction model can predict pre-eclampsia in prenatal clinics with 77% accuracy.

Keywords Risk prediction, Uterine artery Doppler indices, Maternal history, Blood tests, Pre-eclampsia, Uganda, Africa

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Introduction

Pre-eclampsia (PE), a pregnancy syndrome, is characterised by hypertension and proteinuria [1, 2]. Approximately 90 per cent of cases present in the late preterm (≥ 34 weeks) period and have good maternal and fetal outcomes [2, 3]. However, 10 per cent of cases who have an early presentation (< 34 weeks) have more severe disease and carry the additional high risks associated with preterm birth [3, 4]. In addition, mothers with a history of pre-eclampsia are at increased risk for developing the cardiovascular and renal disease [2, 3].

Risk factors of PE include low socio-economic status, nulliparity, multiple pregnancies, obesity, chronic hypertension, being a woman of African descent, previous maternal or family history of pre-eclampsia, and maternal age ≥ 35 years [5–7]. In addition, high second-trimester artery Doppler resistive index, pulsatility index, and end-diastolic notch are known risk factors for pre-eclampsia [8, 9]. Early diagnosis and delivery of the fetus is the only known treatment, thus necessitating the need for prediction models of this disorder.

De Kat et al. [10] summarised risk factors and models for predicting pre-eclampsia. Black race stood out as a significant risk factor in all the studies where the communities had a mixed race, insinuating that the predominantly black Ugandan communities are at high risk for pre-eclampsia. Studies by Al-Rubaie et al. [11] achieved the highest area under the curve (AUC) for predicting pre-eclampsia at 76% using maternal history. Gallo et al. [12] screened for PE using maternal history and mean arterial pressure (MAP) at a false-positive rate of 10%; their detection rate of total pre-eclampsia was 49.3%. Jhee et al. [13] used laboratory tests (serum urea, aspartate aminotransferase (AST), alanine transaminase (ALT), creatinine, and haemoglobin levels) to predict pre-eclampsia. They got an area under the curve (AUC) above 57%. Delic et al. added uric acid, urea thrombocytes, hematocrit, AST, and leukocytes to the regression model and correctly classified 83.8% of patients with pre-eclampsia [14]. Yucel et al. [15] predicted pre-eclampsia using mean platelet volume (MPV) with an AUC of 64.1% and plateletcrit (PCT) with an AUC of 71.2%.

Antwi et al. [16] reviewed prediction models for pre-eclampsia between 2000 and 2019 and found diverse prediction accuracy ranging from 45 – 95% in the different regions of the world. After observing the wide variation in prediction rates of pre-eclampsia and consistently having the black race as a risk factor for pre-eclampsia, we developed and validated risk prediction models based on maternal characteristics from northern Uganda.

Methods

The research was a prospective cohort study at St. Mary's Hospital Lacor. This hospital is a private, not-for-profit hospital founded by the Catholic Church. It is located six kilometres west of Gulu city along Juba Road in Gulu district (Longitude 30 – 32 degrees East and Latitude 02 – 04 degrees North). St. Mary's Hospital Lacor is one of the teaching hospitals of Gulu University with a bed capacity of 482. It is staffed by specialists, medical officers, midwives, nurses, laboratory and radiology staff, and support and administrative staff. The hospital receives about three thousand six hundred antenatal mothers and conducts about six thousand deliveries annually [17]. Some mothers go to the hospital for delivery without prenatal care; others are referred from smaller health units. The mothers pay five thousand Uganda shillings (Ugx 5,000/=) ($1.5) as the cost per visit. This cost is often waived for most mothers who cannot afford it. Normal labour and delivery cost fifteen thousand (Ugx 15,000/=) (about $4.50), and Caesarean section costs twenty-five thousand (Ugx 25,000/=) (about $7.5) Uganda shillings.

Using Yamane's 1967 formula [18] for calculating sample size for cohort studies using finite population size: St. Mary's hospital Lacor receives approximately three thousand six hundred antenatal mothers annually. Since my study duration was 24 months, the limited population we could access was about 7,200 mothers.

Yamane 1967 formula: Sample size	$n = N / 1 + Ne^2$
Where N is the finite population size	of 7,200 mothers
The margin of error (e)	05%
Therefore	$n = 7{,}200 / 1 + 7{,}200(0.05)^2$
	$n = 379$

We doubled the sample size to take care of loss to follow-up. We targeted all pregnant women attending antenatal care at St. Mary's Hospital Lacor. In Uganda, the clinical guideline advocates for the first antenatal care to be sought by a pregnant mother up to 20 weeks of gestation [19]. While all expectant mothers attending antenatal care at St. Mary's hospital Lacor were eligible, we included gestational ages of 16 to 24 weeks and those who gave written informed consent to participate in the study. Those whose pregnancies were less than 16 weeks were given a return date for the recruitment, while those above 24 weeks or had molar pregnancies, intrauterine fetal death and anencephaly were excluded.

We used consecutive sampling. We informed the mothers about the study during their morning health education meeting given to all mothers on arrival for prenatal care at the hospital. All the women who satisfied the inclusion criteria were approached and requested to provide informed consent. A research assistant administered

questionnaire to capture their history and performed a physical examination. Some mothers were asked to give blood samples for full haemogram and liver and renal function tests. A few mothers (after the 1000th mother) did not undergo laboratory tests for logistical reasons. An obstetrician performed the uterine artery Doppler sonography.

We recruited 1,285 pregnant mothers at 16–24 weeks from April 2019 to March 2020. All the mothers were of African ancestry at the end of the recruitment period. We followed up with the participants until September 2020. One thousand four (1,004) complete delivery records were obtained at the end of the study period. Seven hundred eighty-two (782) participants had laboratory blood tests (full haemogram, liver and renal function tests) done in addition to blood pressure readings, body mass index calculation and maternal history. Details are in Fig. 1.

The outcome was a combination of a blood pressure $\geq$ 140/90 mmHg and urine protein $\geq +1$ (pre-eclampsia) by delivery time. The data was pre-processed using Stata® version 15 and built models using RStudio version 4.1.3. Model 1 was built from second-trimester maternal history and physical examination findings, model 2 from the ultrasound and uterine artery Doppler indices, model 3 from a combination of maternal history, physical examination and ultrasound findings, model 4 from maternal laboratory tests, model 5 from a combination of laboratory tests with maternal history, and model 6 from the combination of all models.

We included all variables, did a univariate analysis and got unadjusted p-values for every variable collected. Afterwards, we had all variables with p-values ≤ 0.20 or known risk factors for pre-eclampsia in a logistic regression model and removed the non-statistically significant predictors step-wise. Finally, we retained the independent risk factors for pre-eclampsia and used them to build the models of choice, one with the least number of predictors with a higher AUC.

Because the incidence of pre-eclampsia was low (4.3%) [20], we generated synthetic balanced data using the ROSE package [21, 22] in RStudio by over-sampling pre-eclampsia and under-sampling non-preeclampsia. We got 383 (48.8%) for those diagnosed with pre-eclampsia and 399 (51.2%) for non-pre-eclampsia. Then, we evaluated the actual model performance against the ROSE-derived synthetic dataset using K-fold cross-validation in RStudio to obtain the AUC's accuracy, sensitivity,

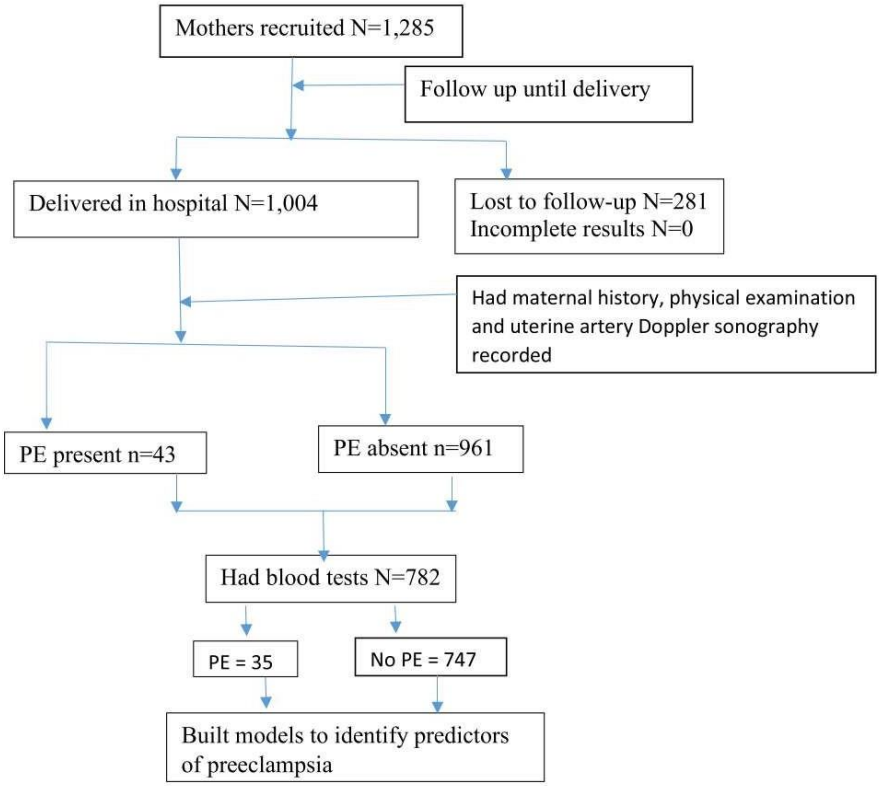

Fig. 1 Flow chart of participants throughout the study

specificity and McFadden's pseudo R^2. The variables were said to be independent risk factors for pre-eclampsia if their p-value < 0.05 in the model. The models, too, had a good fit if McFadden's value was between 0.2 – 0.4.

Results

One thousand four (1,004) participants were used in a regression model to obtain the unadjusted relationship between the maternal history, clinical characteristics and pre-eclampsia. Seven hundred eighty-two (782) participants had additional laboratory blood tests (full haemogram, liver and renal function tests) and complete delivery records. So they were used to build the prediction models.

Unadjusted relationship between the characteristics of pre-eclampsia

All variables with unadjusted p-values ≤ 0.20 or known risk factors are shown in Tables 1 and 2. All the variables with unadjusted p-values < 0.05 in the logistic regression model were independent risk factors for pre-eclampsia. In Table 1, the independent risk factors for pre-eclampsia were maternal history of pre-eclampsia, systolic hypertension, diastolic hypertension, prenatal hypertension, presence of an end-diastolic notch, pulsatility index > 1.34, and resistive index > 0.69.

In Table 2, the independent risk factors for pre-eclampsia were serum alkaline phosphatase (ALP) < 98 IU, serum albumin < 3.5 g/dL and total white blood cell count > 11,000 cells/µl. In addition, the lymphocyte count of 800 – 4,000 cells/µl was protective against pre-eclampsia.

Risk factors and Prediction models for pre-eclampsia

In model 1 (Table 3), the predictors of pre-eclampsia were maternal age, parity, personal history of pre-eclampsia, body mass index, diastolic pressure, and multiple pregnancies. In addition, personal history of pre-eclampsia (aOR = 53.01, 95% CI 12.8—163.7, p = 0.000), nulliparity (aOR = 6.13, 95% CI 1.68—26.05, p = 0.009), diastolic hypertension ≥ 90 mmHg (aOR = 5.66, 95% CI 1.47—18.26, P = 0.006), multiple pregnancies (aOR = 5.16, 95% CI 1.07—18.45, P = 0.020), maternal age > 34 years (aOR = 4.69, 95% CI 1.28—16.36, p = 0.020), and body mass index ≥ 26.56 kg/m2 (aOR = 3.70, 95% CI 1.31—12.54, p = 0.021) were independent risk factors for pre-eclampsia.

In model 2 (Table 4), the predictors of pre-eclampsia were end-diastolic notch and average pulsatility index. Bilateral end-diastolic notch (aOR = 3.71, 95% CI 1.30—9.81, p = 0.010) and average pulsatility index of ≥ 1.34 (aOR = 3.41, 95% CI 1.22—9.48, p = 0.018) were independent risk factors for pre-eclampsia.

In model 3 (Table 5), the predictors of pre-eclampsia were maternal age, parity, personal history of pre-eclampsia, body mass index, diastolic pressure, multiple pregnancies and end-diastolic notch. In addition, personal history of pre-eclampsia (aOR = 36.88, 95% CI 8.40—178.40, p = 0.000), multiple pregnancies (aOR = 6.22, 95% CI 1.29—18.27, p = 0.015), maternal age > 34 years (aOR = 4.93, 95% CI 1.29—18.27, p = 0.017), bilateral end-diastolic notch (aOR = 4.40, 95% CI 1.68—11.29, p = 0.002), nulliparity (aOR = 4.39, 95% CI 1.19—19.54, p = 0.036), diastolic hypertension ≥ 90 mmHg (aOR = 4.39, 95% CI 1.06—15.21,

Table 1 Unadjusted relative risk of maternal history and clinical characteristics with pre-eclampsia

Variable (N = 1,004)	IRR (95% CI)	p-value
Maternal age ≥ 35 (years)	1.53 (0.66—3.54)	0.3170
Para 1—2	1.51 (0.61—3.75)	0.3780
Nulliparity	2.30 (0.93—5.68)	**0.070**
Maternal history of pre-eclampsia	13.75 (7.44—25.42)	**< 0.001**
Age at menarche 13—16 years (years)	0.61 (0.33—1.16)	**0.1310**
Age at menarche > 16 years	0.47 (0.19—1.18)	**0.1070**
Body mass index 21.92—26.56 kg/m^2	0.64 (0.27—1.49)	0.2990
Body mass index ≥ 26.56 kg/m^2 (4th quadrant)	2.11 (0.99—4.48)	**0.054**
Systolic blood pressure Bp ≥ 140 mmHg	10.65 (4.29—26.41)	**< 0.001**
Diastolic blood pressure Bp ≥ 90 mmHg	5.36 (2.31—12.41)	**< 0.001**
hypertension at recruitment Bp ≥ 140/90 mmHg	12.48 (5.30—29.37)	**< 0.001**
Multiple pregnancies	4.95 (2.12—11.55)	**< 0.001**
Unilateral End diastolic notch	2.49 (1.13—5.49)	**0.0230**
Bilateral End diastolic notch	6.44 (3.38—12.25)	**< 0.001**
Average pulsatility index ≥ 1.34 (95th percentile)	6.43 (3.49—11.84)	**< 0.001**
Average Resistive index ≥ 0.69 (4th quadrant)	7.88 (4.33—14.35)	**< 0.001**

Table 2 Unadjusted relative risk of maternal laboratory tests with pre-eclampsia

Variable (*N* = 782)	IRR (95% CI)	*p*-value
Serum GGT (Gamma Glutamyl Transferase)0—30 iu	2.68 (0.83—8.64)	**0.0990**
Serum ALP (Alkaline phosphatase) < 98 iu	4.33 (1.81—10.35)	**0.0010**
Serum Albumin 3.5—4.1 g/dL	1.58 (0.59—4.22)	0.3610
Serum Albumin < 3.5 g/dL	2.82 (1.03—7.76)	**0.0450**
Serum Urea 11.0—44.0 mg/dL	3.64 (0.50—23.39)	0.2010
Serum Urea < 11.0 mg/dL	6.23 (0.72—54.29)	**0.0980**
Serum sodium 135.1—139.4 mmol/L (2nd—3rd quadrant)	0.97 (0.47—2.02)	0.9400
Serum sodium > 139.4 mmol/L (4th quadrant)	0.41 (0.13—1.30)	**0.1310**
Serum phosphorus 0.9—1.4 mg/dL (2nd—3rd quadrant)	2.22 (0.85—5.77)	**0.1030**
Serum phosphorus > 1.4 mg/dL (4th quadrant)	1.67 (0.56—5.03)	0.3590
Serum creatinine 0.8—1.2 µmol/L (2nd—3rd quadrant)	0.94 (0.45—1.94)	0.8600
Serum creatinine > 1.2 µmol/L (4th quadrant)	0.37 (0.10—1.31)	**0.1230**
Lymphocyte Count (0.8—4.0)*1000 cells/µl	0.37 (0.15—0.92)	**0.0330**
Lymphocyte Count (> 4.0)*1000 cells/µl	2.27 (0.68—7.53)	0.1820
Total White blood cell count (4.0—11.0)*1000 cells/µl	0.71 (0.28—1.81)	0.4780
Total White blood cell count (> 11.0)*1000 cells/µl	4.65 (1.40—15.50)	**0.0120**
Haematocrit 30.0—39.9%	1.01 (0.48—2.12)	0.9870
Haematocrit ≥ 40%	2.23 (0.79—6.26)	**0.1290**
Mean corpuscular volume (MCV) 80.0—100.0 fl	0.57 (0.29—1.11)	**0.0990**
Mean corpuscular volume (MCV) ≥ 100.0 fl	1.10 (0.16—7.85)	0.9210

Table 3 Showing model 1 shows the maternal history and physical examination for the prediction of pre-eclampsia

Variable	Adjusted Odds Ratio (95% CI)	*p*-value
Maternal age ≥ 35 years	4.69 (1.28—16.36)	0.020
Para 1—2	2.36 (0.72—8.71)	0.175
Nulliparity	6.13 (1.68—26.05)	0.009
Personal history of pre-eclampsia	53.01 (12.8—163.7)	**< 0.001**
BMI of 21.92—26.56 kg/m^2	1.01 (0.33—3.51)	0.993
BMI of ≥ 26.56 kg/m^2	3.70 (1.31—12.54)	0.021
Diastolic blood pressure ≥ 90 mmHg	5.66 (1.47—18.26)	0.006
Multiple pregnancies	5.16 (1.07—18.45)	0.020
Intercept	0.00 (0.00—0.02)	**< 0.001**

Table 4 Shows model 2 shows uterine artery Doppler indices for the prediction of pre-eclampsia

Variable	Adjusted Odds Ratio (95% CI)	*p*-value
Unilateral end-diastolic notch	2.39 (0.92—5.78)	0.060
Bilateral end-diastolic notch	3.71 (1.30—9.81)	0.010
Average pulsatility index ≥ 1.34	3.41 (1.22—9.48)	0.018
Intercept	0.03 (0.01—0.04)	**< 0.001**

$p = 0.027$), and body mass index ≥ 26.56 kg/m2 (aOR = 3.42, 95% CI 1.17—11.97, $p = 0.034$) were independent risk factors for pre-eclampsia.

In model 4 (Table 6), the predictors of pre-eclampsia were white blood cell count, lymphocyte count, serum alkaline phosphatase, serum albumin, and serum urea. White blood cell count of > 11000cells/dl (aOR = 7.38, 95% CI 1.11—46.17, $p = 0.033$) and serum ALP < 98 IU/L (aOR = 5.84, 95% CI 1.78—16.39, $p = 0.001$) were independent risk factors for pre-eclampsia.

In model 5 (Table 7), the predictors of pre-eclampsia were maternal age, parity, personal history of pre-eclampsia, body mass index, diastolic pressure, white blood cell count, and serum ALP. Personal history of pre-eclampsia (aOR = 48.09, 95% CI 11.11—227.25, $p = 0.000$), serum ALP < 98 IU/L (aOR = 7.77, 95% CI 2.04—25.38,

Table 5 Shows model 3 shows a combination of maternal history and uterine artery Doppler indices for the prediction of pre-eclampsia

Variable	Odds Ratio (95% CI)	*p*-value
Maternal age Over 34 years	4.93 (1.29—18.27)	0.017
Para 1—2	2.13 (0.63—8.17)	0.244
Nulliparity	4.39 (1.19—19.54)	0.036
Personal history of pre-eclampsia	36.88 (8.40—178.40)	**< 0.001**
BMI of 21.92—26.56 kg/m^2	1.03 (0.33—3.71)	0.957
BMI of ≥ 26.56 kg/m^2 (4th quadrant)	3.42 (1.17—11.97)	0.034
Diastolic blood pressure ≥ 90 mmHg	4.39 (1.06—15.21)	0.027
Multiple pregnancies	6.22 (1.29—18.27)	0.015
Unilateral end-diastolic notch	2.39 (0.85—6.30)	0.083
Bilateral end-diastolic notch	4.40 (1.68—11.29)	0.002
Intercept	0.00 (0.00—0.02)	**< 0.001**

Table 6 Model 4 shows maternal laboratory characteristics for the prediction of pre-eclampsia

Variable	Odds Ratio (95% CI)	*p*-value
White cell count of (4.0—11.0)*10^3	1.18 (0.40—4.25)	0.780
White cell count of (> 11.0)*103	7.38 (1.11—46.17)	0.033
Serum ALP (alkaline phosphatase) < 98 iu/L	5.84 (1.78—16.39)	0.001
Serum albumin 3.5–4.1 mg/dl	2.01 (0.74—6.60)	0.247
Serum albumin < 3.5 mg/dl	2.84 (0.97—9.67)	0.080
Serum urea 11.0—44.0 iu/L	4.30 (0.83—80.02)	0.158
Serum urea < 11.0 iu/L	8.00 (1.02—169.30)	0.074
Lymphocyte count of (0.8—4.0)*10^3	0.29 (0.10—1.06)	0.041
Lymphocytes count of > 4.0*10^3	1.30 (0.19—7.91)	0.705
Intercept	0.01 (0.00—0.06)	**< 0.001**

$p = 0.001$), diastolic hypertension ≥ 90 mmHg (aOR = 7.24, 95% CI 1.85—24.32, $p = 0.002$), white blood cell count > 11,000 cells/μl (aOR = 6.40, 95% CI 1.13—33.82, $p = 0.028$), nulliparity (aOR = 6.32, 95% CI 1.69—28.11, $p = 0.010$), body mass index of > 26.56 kg/m^2 (aOR = 4.41, 95% CI 1.49—15.45, $p = 0.012$) and maternal age > 34 years (aOR = 3.88, 95% CI 1.01—14.32, $p = 0.043$) were independent risk factors for pre-eclampsia.

In model 6 (Table 8), the predictors of pre-eclampsia were maternal age, parity, personal history of pre-eclampsia, body mass index, diastolic pressure, white blood cell count, lymphocyte count, serum ALP and end-diastolic notch of the uterine arteries. Personal history of pre-eclampsia (aOR = 32.75, 95% CI 6.59—182.05, $p = 0.000$), serum ALP < 98 IU/L (aOR = 7.14, 95% CI 1.76—24.45, $p = 0.003$), diastolic hypertension ≥ 90 mmHg (aOR = 4.90, 95% CI 1.15—18.01, $p = 0.022$), bilateral end diastolic notch (aOR = 4.54, 95% CI 1.65—12.20, $p = 0.003$) and body mass index of ≥ 26.56 kg/m2 (aOR = 3.86, 95% CI 1.25—14.15, $p = 0.027$) were independent risk factors for pre-eclampsia.

Evaluation of the models' performance

We evaluated the models using K (10) -fold cross-validation to obtain the accuracy, specificity, sensitivity, AUC and McFadden's pseudo R^2. Details are in Table 9.

Discussion

In this research, maternal history predictors of pre-eclampsia were maternal age, parity, personal history of pre-eclampsia, body mass index, diastolic pressure, and multiple pregnancies. They predicted pre-eclampsia with 66.6% accuracy, 82.7% sensitivity, and 78.4% AUC with a McFadden's pseudo R^2 of 0.21. It can identify four out of five participants destined to develop pre-eclampsia. The low specificity of the model of close to 50% reduces the model's accuracy to 66%. This model is of good fit and can be used independently in prenatal clinics to screen for pre-eclampsia. In Ghana [23], predictors of pre-eclampsia were diastolic blood pressure, family history

Table 7 Model 5 shows the maternal history and laboratory tests for the prediction of pre-eclampsia

Variable	Adjusted Odds Ratio (95% CI)	*p*-value
Maternal age Over 34 years	3.88 (1.01—14.32)	0.043
Para 1—2	2.62 (0.77—10.15)	0.140
Nulliparity	6.32 (1.69—28.11)	0.010
Personal history of pre-eclampsia	48.09 (11.11—227.25)	**< 0.001**
BMI of 21.92—26.56 kg/m^2	1.06 (0.34—3.74)	0.923
BMI of ≥ 26.56 kg/m^2	4.41 (1.49—15.45)	0.012
Diastolic blood pressure ≥ 90 mmHg	7.24 (1.85—24.32)	0.002
White cell count of (4.0—11.0)*10^3	0.52 (0.18—1.74)	0.241
White cell count of > 11.0*10^3	6.40 (1.13—33.82)	0.028
Serum ALP < 98.0 iu/L	7.77 (2.04—25.38)	0.001
Intercept	0.01 (0.001—0.03)	**< 0.001**

Table 8 Model 6 shows maternal history, uterine artery Doppler indices, and laboratory tests for the prediction of pre-eclampsia

Variable	Adjusted Odds Ratio (95% CI)	*p*-value
Maternal age Over 34 years	3.88 (0.94—15.44)	0.056
Para 1—2	2.56 (0.73—10.62)	0.144
Nulliparity	4.25 (1.08—20.18)	0.051
Maternal history of pre-eclampsia	32.75 (6.59—182.05)	**< 0.001**
BMI of 21.92—26.56 kg/m^2	1.09 (0.34—3.98)	0.888
BMI of ≥ 26.56 kg/m^2	3.86 (1.25—14.15)	0.027
Diastolic blood pressure ≥ 90 mmHg	4.90 (1.15—18.01)	0.022
Unilateral end-diastolic notch	2.36 (0.81—6.39)	0.100
Bilateral end-diastolic notch	4.54 (1.65—12.20)	0.003
White cell count of (4.0—11.0) *10^3 cells /μl	0.85 (0.24—3.49)	0.807
White cell count of > 11.0 *10^3	8.43 (0.92—70.62)	0.050
Serum ALP < 98 iu/L	7.14 (1.76—24.45)	0.003
Lymphocyte count of (0.8—4.0) *10^3	0.29 (0.08—1.22)	0.074
Lymphocytes count of > 4.0*10^3	0.84 (0.09—6.96)	0.876
Intercept	0.01 (0.00—0.06)	**< 0.001**

Table 9 Shows model performance evaluation using K-fold cross-validation

Model	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC (%)	McFadden's
Model 1 (History and physical exam)	66.6	82.7	49.9	78.4	**0.21**
Model 2 (Uterine artery Doppler indices)	68.8	73.7	63.7	71.4	0.09
Model 3 (Combination of models 1 and 2)	76.0	78.2	73.6	80.4	**0.25**
Model 4 (Maternal blood tests)	67.1	76.9	56.9	75.6	0.11
Model 5 (combination of models 1 and 4)	72.7	84.0	61.1	82.2	**0.26**
Model 6 (Combination of models 3 and 4)	77.0	80.2	73.6	84.9	**0.30**

Models 1, 3, 5 and 6 had a good fit with McFadden's pseudo-R-square between 0.2 and 0.4. Therefore they are helpful for the screening of pre-eclampsia in prenatal clinics

of hypertension in parents, history of pre-eclampsia in a previous pregnancy, nulliparity and obesity, with an AUC of the original model being 70% and 68% in the validation cohort. Gallo et al. [12] screened by maternal characteristics and mean arterial pressure (MAP) at a false-positive rate of 10%; their detection rate of total pre-eclampsia was 49.3%. In a systematic review by Al-Rubaie et al. [11], their detection rate was 76%.

With uterine artery Doppler indices, we predicted pre-eclampsia with over 68% accuracy and 71.4% AUC. Unfortunately, the model had a McFadden's pseudo R^2 of 0.09 and was not a good fit. Therefore, this model cannot be used independently in prenatal clinics to screen for pre-eclampsia. That was way below Trudinger et al. [9], who predicted up to 90% of pre-eclampsia in Australia using an end-diastolic notch. Using a combination of maternal history, physical examination and uterine artery Doppler indices, we got an AUC of 80.4% with 76.0% accuracy. That is comparable to Pedroso et al. [24], who found a combination of uterine artery Doppler indices and maternal history predicted 75% of PE.

With laboratory blood tests, we predicted pre-eclampsia with 67.1% accuracy and 75.6% AUC with McFadden's pseudo R^2 of 0.11. However, this model cannot be used independently in prenatal clinics to screen for pre-eclampsia. Jhee et al. [13] used a combination of serum urea, aspartate aminotransferase (AST), ALT, creatinine, and haemoglobin levels to predict pre-eclampsia with AUC above 57%. Yucel et al. [15] predicted pre-eclampsia using mean platelet volume (MPV) and plateletcrit (PCT) with AUC of 64.1% and 71.2%, respectively.

When we combined laboratory blood tests with maternal history, the accuracy improved to 72.7% with an AUC of 82.2% with a McFadden's pseudo R^2 of 0.26. The combination of maternal history and uterine artery Doppler indices improved the accuracy to 76% with 80.4% AUC with a McFadden's pseudo R^2 of 0.25. Combining maternal history, blood tests, and uterine artery Doppler indices (model 6) slightly improved the prediction accuracy to 77.0% and 80.2% sensitivity with an AUC of 84.9% with a McFadden's pseudo R^2 of 0.30. All the combined

models were of good fit and could be used independently in prenatal clinics to screen for pre-eclampsia.

Delic et al. [14] added uric acid, urea thrombocytes, hematocrit, AST and leukocytes into the logistic regression model and correctly classified 83.8% of patients with pre-eclampsia. That had a better detection rate than 57% in the UK [25]. A low level of serum ALP may signify a reduced viable mass of placental tissue in pregnancy [26, 27], which means a decreased surface area for the transfer of nutrients from mother to baby. This reduced surface area of the functional placenta may increase the number of placental infarcts and, eventually, placental debris released into the maternal circulation. In addition, increased levels of placental tissue in maternal circulation lead to maternal systemic inflammation [28]. That may result in endothelial injury, vasoconstriction and hypertension [29].

Duckit et al. [6], in a systematic review, found controlled cohort studies showing the risk of pre-eclampsia increased in women with a previous history of pre-eclampsia, multiple (twin) pregnancy, nulliparity, family history, raised blood pressure (diastolic $\geq$ 80 mm Hg) at booking, increased body mass index before pregnancy at booking, or maternal age $\geq$ 40. Antwi et al. [16] reviewed prediction models for pre-eclampsia between 2000 and 2019 and found diverse prediction accuracy ranging from 45 – 95% in the different regions of the world. The other prediction rates could explain the differences in the populations studied or the test techniques and the ultrasound machines used. Our models seem within acceptable accuracy, although the whole study population was at high risk. These models will ease the identification of high-risk mothers and referral to specialists' healthcare providers. That may, in turn, contribute to reducing maternal mortality and morbidity in the community.

Strength of the study

This is a baseline study in northern Uganda and could open ways for further research on pre-eclampsia in this community.

Weakness of the study

There were many losses to follow-ups, which could have skewed the results differently. The data collection period (April 2019 to September 2020) coincided with part of the covid -19 lockdowns in Uganda. Many mothers could not come to the hospital and may have delivered from home or in smaller health units near their homes. Patients were not motivated by transport refunds or covering hospital bills. The government hospital (Gulu regional referral hospital) was only 6 km away, offering free prenatal and delivery services. That could have affected the return of those who could not afford the hospital bills. Future studies could find ways of motivating mothers to deliver in hospitals.

What is already known about this topic

It is known that women of African descent are more at risk of pre-eclampsia than other communities [5–7]. It is also known that in prenatal clinics where pre-eclampsia is predicted, early diagnosis and appropriate treatment are made to save lives [30–32].

What new knowledge the study adds

The new knowledge added through this study is that the incidence of pre-eclampsia in this black community is comparable to global estimates of pre-eclampsia [33]. The predictors of pre-eclampsia are also similar to other communities. We also predicted pre-eclampsia using a full haemogram, liver and renal function tests, uterine artery Doppler sonography, and maternal history. However, the Doppler indices percentiles differ when compared to the global north.

Implication for practice

The prediction models can be adapted for use in prenatal clinics to screen mothers for the prediction of pre-eclampsia. In addition, data from such clinics can be used to validate the models.

Conclusions

Predictors of pre-eclampsia in the low resource setting of northern Uganda are maternal age $\geq$ 35 years, nulliparity, maternal history of pre-eclampsia, body mass index, diastolic pressure, white blood cell count, lymphocyte count, serum alkaline phosphatase and end-diastolic notch of the uterine arteries. Prenatal clinics without any ultrasound scans or laboratory can adequately predict pre-eclampsia with up to 66.6% accuracy and 78.4% AUC. However, clinics with Doppler ultrasound and laboratory tests can use maternal history either with ultrasound or laboratory blood tests or both. That will improve the prediction AUC to over 80%.

Recommendation

We built the models based on data from one health facility, and most of the respondents lived in one region of Uganda. Therefore, we recommend that the models be further validated with datasets from other areas of the country to scale up the use.

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Authors' contribution
Silvia Awor is a PhD student who wrote the proposal, collected data and drafted the manuscript. Benard Abola built the models and cross-validated the models. Rosemary Byanyima, Paul Kiondo and Christopher Garimoi Orach provided expert opinions and guided me in writing the manuscript. Annettee Nakimuli, Jasper Ogwal-Okeng and Dan Kabonge Kaye are doctoral supervisors who guided me through the concept and writing of the manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials
Dr Silvia Awor or Makerere University Directorate of Research and Graduate training has the dataset.

Declarations

Ethics approval and consent to participate
We got study approval from the Research and Ethics Committee of Makerere University School of Medicine (reference number 2018–105), Uganda National Council for Science and Technology (Reference number HS258ES), and administrative clearance from St. Mary's Hospital Lacor (Reference number LHIREC Adm 009/11/18). In addition, the research team sought written informed consent from every participant. Finally, all methods carried out were according to the declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Publisher's Note

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INCIDENCE OF PREECLAMPSIA AND RETENTION TO PRENATAL CARE IN NORTHERN UGANDA
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INCIDENCE OF PREECLAMPSIA AND RETENTION TO PRENATAL CARE IN NORTHERN UGANDA

S. Awor, R. Byanyima, B. Abola, A. Nakimuli, C. G. Orach, P. Kiondo, J. Ogwal-Okeng and D. Kaye

ABSTRACT

Background: **Known risk factors for preeclampsia include women of African descent and low socioeconomic status. This means all the mothers in Northern Uganda are at risk. In Uganda preeclampsia causes 12 – 19% of maternal deaths. However, data on its burden is limited.**

Objective: **To determine prenatal care retention and preeclampsia incidence in northern Uganda.**

Setting: **St. Mary's hospital Lacor, northern Uganda.**

Design: **Prospective cohort study.**

Participants**: Recruited 1,285 mothers at 16-24 weeks of gestation. Their history, physical findings, blood tests, and uterine artery Doppler indices were taken at baseline, and the women were followed up until delivery.**

Outcome: **A combination of hypertension with proteinuria was taken as preeclampsia.**

Statistical analysis: **Means, medians, and proportions were used to describe the population. The incidence per 10^4 women weeks of follow-up computed for different gestation ages.**

Results**: Seventy-eight percent of the women delivered at the health facility. Women who were not retained through to delivery were younger ($p<0.0001$), had low BMI ($p=0.0001$) and more likely to be unemployed ($p<0.0001$). Overall, 43 women developed preeclampsia giving a prevalence of 4.3% (95% CI 3.1% - 5.7%), and an incidence of 11 per 10^4 women weeks. The incidence of preeclampsia was 68 per 10^4 women weeks' for women delivered at < 34**

completed weeks of pregnancy, and 6.0 per 10^4 women weeks for those delivered at ≥ 37 weeks.

Conclusion: **Retention to prenatal care is 78% while the incidence of preeclampsia is 4.3% in Northern Uganda. This incidence is higher at lower gestation ages.**

INTRODUCTION

Preeclampsia (PE) is any new-onset hypertension (Blood pressure of ≥140/90 mmHg) and proteinuria (≥ + urine dipstick or 0.3 grams per 24-hour urine) after 20 weeks of gestation in a previously normotensive woman[1]. The exact cause of PE is not known[2], however, many risk factors have been associated with it. These include low socioeconomic status, nulliparity, obesity, chronic hypertension, women of African descent, previous personal or family history of PE, delivery of male babies, maternal age ≥35 years, new partner fathering the pregnancy, Kidney disease, diabetes mellitus, pregnancy at high altitude, antiphospholipid antibodies, systemic lupus erythematosus, Molar, and twin pregnancies[3-6]. Primary smoking on the other hand is known to be protective[7, 8]. And yet we do not know whether secondary smoking is also protective.

PE affects 2-10% of pregnancies globally with incidence ranging from 3 to 10% in nulliparous and 1 to 3% in multiparous women[9, 10]. It is a major cause of maternal death in Sub-Saharan Africa. In Uganda, it causes 10 to 19 percent of maternal deaths every year[11]. There is limited data on both its incidence and burden in Sub-Saharan Africa. PE is associated with many adverse maternal and fetal outcomes including intrauterine growth restriction, low Apgar score, perinatal death, maternal morbidity, and mortality[12]. Early diagnosis and timely delivery of the baby improve pregnancy outcomes[12]. This can only be done by regular prenatal screening and visits to ensure early diagnosis.

In Northern Uganda, over 93% of pregnant women come into contact with a skilled health care provider at least once over the prenatal period[13]. However, health facility delivery has been low (about 55%), only rising occasionally whenever there is motivation of the mothers by the provision of free delivery incentives[13]. This is contrary to 98.4% retention to prenatal care in the developed world where mothers have health insurance to cover prenatal care and delivery costs[14]. So we set out to determine the incidence of preeclampsia and retention to prenatal care in Northern Uganda.

METHODS

Setting: St. Mary's Hospital Lacor.

Study design: This was a prospective cohort study

Participants

We recruited 1,285 pregnant mothers at 16-24 weeks of gestation from April 2019 to March 2020 and followed up until September 2020 when the last one was delivered. No transport refund or incentive was given to participants for being recruited into the study. Excluded those with preeclampsia or lethal congenital anomalies.

Study procedure: The mothers were informed about the study during the morning health education talk in the antenatal clinic. Those who satisfied the inclusion criteria were approached and requested for written informed consent. The mothers were given questionnaire about their personal history administered by a research assistant (midwife). Their weight and height (to calculate body mass index BMI); and blood pressure were taken.

The mothers were requested to give blood samples, and these were collected in the EDTA and sterile containers. The serum from the sterile containers were analyzed for liver and renal function tests using humalyzer serum chemistry machine (Humastar 200, Wiesbaden, Germany) The blood samples in the EDTA container were for full haemogram, analyzed using a coulter counter machine (HumaCount, Wiesbaden, Germany) at St. Mary's hospital Lacor. They also gave urine samples for urine proteins.

The mothers were requested to empty their urinary bladder and lie supine on the examination couch. Obstetric ultrasound with uterine artery Doppler sonography was done according to guidelines from the international society of ultrasound in obstetrics and gynecology (ISUOG) from April 2019 to March 2020 using GE Logiq V2 ultrasound (GE healthcare China, distributed by Computech limited in Uganda). The appearance of the Doppler flow tracing is shown in figure 1. A depression at the end of diastole in the cardiac cycle on the waveform tracing is taken as an end-diastolic notch (abnormal). Since uterine artery Doppler pulsatility (PI) and resistive (RI) indices values for the study population were not yet known, we got all the Doppler indices of participants and grouped them into percentiles. The indices above the 90th percentile or the presence of an end-diastolic notch in the uterine artery Doppler waveform was taken as abnormal.

Figure 1a: Normal uterine artery Doppler flow tracing

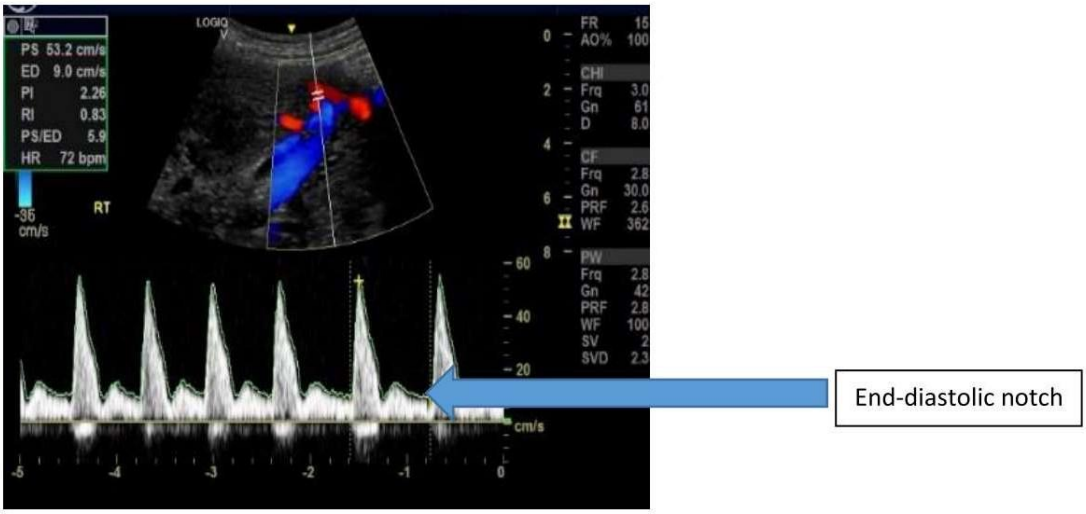

Figure 1: Abnormal uterine artery Doppler flow tracing

Outcomes: A combination of a blood pressure ≥140/90mmHg and urine protein ≥ +1 was preeclampsia at the time of delivery, and those who delivered in the hospital were taken as retained to prenatal care.

Statistical analysis: Given the known risk factors of preeclampsia from literature (body mass index, nulliparity, personal history of preeclampsia, family history of preeclampsia, antenatal blood pressure, menarche and cigarette smoking, pulsatility index, resistive index, end-diastolic notch) and global prevalence of preeclampsia estimated at 4.6%[10], we used an online software for calculating sample size since the incidence of preeclampsia was not known in our community. The sample size was estimated to be at least 750 mothers, however, we added about 20% to the calculated sample size to reduce the effect of low response rate, loss to follow-up, or withdrawal from the study.

We applied t-test and Mann-Whitney tests to compare means and medians, respectively, and Pearson's chi-square to compare proportions for categorical variables, of those who were retained in the study and those who were lost. We also calculated the proportions of women who got preeclampsia at the different gestation ages (in weeks) and per 10,000 women weeks of follow-up.

Ethical consideration: The study was approved by Makerere University School of Medicine Research and Ethics Committee (Reference number 2018-105), Uganda National Council for Science and Technology (Reference number HS25,8ES), and administrative clearance to conduct the research at St. Mary's hospital Lacor was also obtained (Reference number LHIREC Adm 009/11/18). Written informed consent was obtained from every participant.

RESULTS

Maternal characteristics in the second trimester

One thousand two hundred eighty-five (1,285) pregnant mothers were recruited. Of the mothers recruited, the median maternal age was 25 years with an interquartile range of 22 to 30 years. The average parity was 1.5 with a range of 0 – 2. The majority of women (777, 60.5%) were employed in the informal sector while 429 (33.4%) reported being unemployed. At recruitment only 15 (1.2%) of women reported previous experience with pre-eclampsia, 412 (32.1%) were prime gravida and for 856 (66.7%) women, previous pregnancies were free of pre-eclampsia. A total of 253 (19.7%) had experienced a miscarriage and 113 (8.8%) had a chronic illness. Very few women, < 0.2% reported

ever smoking but 136 (10.6%) lived with a smoker and so exposed to side-stream smoking, and 71 (5.5%) were using alcohol during the current pregnancy. The mean gestation age at recruitment was 20.4 weeks with an interquartile range of 18.6 to 22.1 weeks. Details are in Table 1a below.

Table 1a

Social demographic characteristics of the study population at recruitment

Characteristics		**Total population recruited = 1,285**
Demographic characteristics		
Maternal age (years)	mean (sd)	26.0 (5.4)
	median (IQR)	25 (22-30)
Marital Status	Single	22 (1.7)
	Married / cohabiting	1,263 (98.3%)
Parity	mean (sd)	1.5 (1.6)
	median (IQR)	1 (0 - 2)
Employment	Unemployed	429 (33.4%)
	Informal	777 (60.5%)
	Formal (salaried job)	79 (6.2%)
Gestation age at recruitment (weeks)	mean (sd)	20.4 (2.8)
	median (IQR)	20.3 (18.6 - 22.1)
Past obstetric history		
Personal history of preeclampsia	Not applicable (prime gravida)	412 (32.1%)
	No	856 (66.7%)
	Yes	15 (1.2%)
Past Gynaecological history		
Age at menarche (years)	Mean (sd)	14.4 (1.5)
	median (IQR)	14 (13-15)
History of miscarriage	no	1,032 (81.3%)
	yes	253 (19.7%)
History of fertility treatment	no	1,275 (99.2%)
	yes	10 (0.8%)
Past medical history		
Family history of preeclampsia	no	1,239 (96.4%)
	yes	46 (3.6%)
Presence of a chronic illness	no	1,172 (91.2%)
	yes	113 (8.8%)
Tobacco use in a lifetime	no	1,283 (99.8%)
	yes	2 (0.2)
Living with a smoker in one house	no	1,149 (89.4%)
	yes	136 (10.6%)
Alcohol use in pregnancy	no	1,214 (94.5%)
	yes	71 (5.5%)

Prenatal hypertension was present in 0.5% of participants. About 2.6% had diastolic hypertension, and 9.3% of the mothers were obese. Overall, 141 (11.0%) of the mothers had a bilateral end-diastolic notch. Details in Table 1b below.

Table 1b

Clinical and uterine artery Doppler characteristics of the study population

Characteristics		**Total population recruited = 1,285**
Clinical findings		
Body mass index	mean (sd)	24.5 (3.8)
	Median (IQR)	23.7 (21.7 - 26.6)
Systolic blood pressure	mean (sd)	105.9 (12.0)
	median (IQR)	105.0 (97 - 113)
Diastolic blood pressure	mean (sd)	63.9 (10.5)
	median (IQR)	63.0 (57 - 70)
Prenatal hypertension	no (Bp<140/90mmHg)	1,278 (99.5%)
	yes (Bp≥140/90mmHg)	7 (0.5%)
Singleton	No	28 (2.18%)
	Yes	1257 (97.82%)
Uterine artery Doppler indices		
End diastolic notch	No notch	953 (74.16%)
	Unilateral notch	191 (14.86%)
	Bilateral notch	141 (10.97%)
Average pulsatility index	mean (sd)	0.80 (0.29)
	median (IQR)	0.75 (0.61 - 0.94)
Average Resistive index	mean (sd)	0.51 (0.11)
	median (IQR)	0.50 (0.44 - 0.58)

At baseline, the median haemoglobin level was 10.8g/dL (9.5 – 12.1) and 405 (40.5%) of the women were anaemic with a haemoglobin level of < 10.5g/dL. The median mean corpuscular volume was 84.7fL (IQR 79.9 – 89.2). Only a few women 23 (2.3%) had white blood cell count above 11000 per microliter. Overall 226 (22.6%) of the women had serum Albumin <3.5 g/dL).

There were many women with abnormal liver function tests: 166 (16.6%) with serum ALT > 40 U/L and 201 (20.1%) with serum GGT >30 U/L. The details of these findings are in table 1c.

Table 1c

Maternal laboratory characteristics of the study population

Characteristics	**Total population recruited = 1,000**	
	Median (IQR)	Mean (sd)
Serum ALT	24.0 (18 - 34)	30.0 (26.8)
Serum AST	14.0 (6.0 -26.0)	19.9 (23.3)
Serum GGT	20.0 (14 - 29)	21.6 (8.5)
Serum ALP	147.0 (115 - 179)	153.4 (48.8)
Serum bicarbonate	25.0 (24 - 27)	25.4 (2.3)
Serum Albumin	3.9 (3.5 - 4.1)	4.1 (3.1)
Serum Urea	18.0 (14 - 25)	25.8 (28.0)
Serum sodium	137.3 (135.1 - 139.4)	137.5 (3.8)
Serum potassium	4.2 (3.9 - 4.5)	4.2 (1.1)
Serum chloride	105.9 (103.7 - 108.9)	106.4 (4.3)
Serum phosphorus	1.1 (0.9 - 1.4)	1.3 (0.8)
Serum calcium	2.2 (2.1 - 2.4)	2.4 (1.1)
Serum creatinine	0.9 (0.8 - 1.2)	1.1 (0.8)
Neutrophil count	3.5 (2.6 - 4.5)	3.7 (2.1)
Lymphocyte Count	1.7 (1.3 - 2.1)	1.8 (1.1)
Total White blood cell count	6.0 (4.8 - 7.5)	6.3 (2.9)
Platelet count	219 (178 - 266)	224 (73)
Haemoglobin level	10.8 (9.5 - 12.1)	10.7 (1.9)
Haematocrit	32.9 (28.5 - 36.0)	32.5 (6.5)
Mean corpuscular volume	84.7 (79.9 - 89.2)	84.5 (7.7)
Mean corpuscular haemoglobin concentration	32.8 (31.5 - 34.4)	32.9 (2.5)

Sd = standard deviation, IQR= Interquartile range

Maternal retention to prenatal care

One thousand four (78.1%) mothers had complete delivery records. The two hundred eighty-one (21.9%) mothers had missing delivery records and so could not be used to calculate the incidence of preeclampsia.

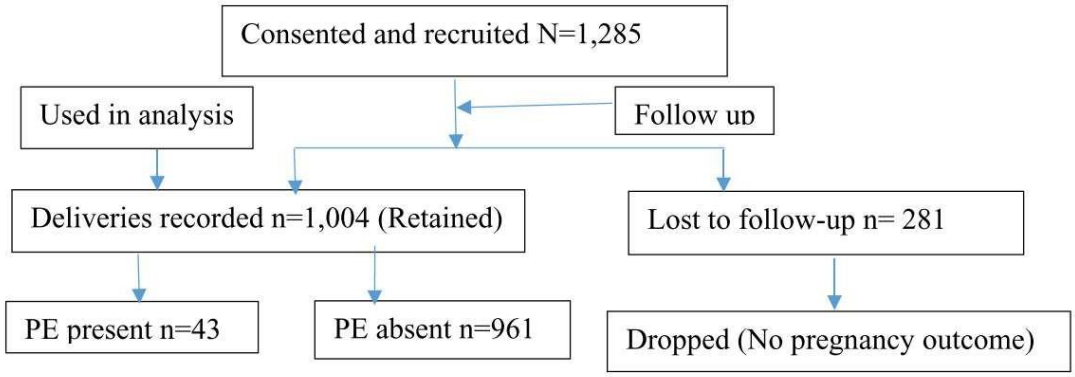

Fig.2: Flow chart showing retention of participants in the study

The mean age of women retained in the study was significantly higher than those lost to follow-up (26.3 versus 24.7 years, p= 0.0000). Similarly, women who were retained had a significantly higher BMI compared to those who were lost to follow-p (24.7Kg/m^2 (sd 3.9) versus 23.7Kg/m^2 (sd 3.1), p=0.0001). The prevalence of singleton foeti was marginally lower than multiple foeti in the women who were retained compared to those who were lost to follow-up (77.8% versus 92.9% p=0.057). The two groups of women were similar in all other variables included in table 1a, 1b and 1c above. Other details are shown in Table 2 below.

Table 2

Comparison of the baseline characteristics of individuals retained in the study versus those who were lost to follow-up

Characteristics	**population retained = 1004**	**population lost =281**	***p*-value**
Maternal age (years)			
mean (sd)	26.3 (5.5)	24.7 (5.3)	0.0000
median (IQR)	26.0 (22 - 30)	24 (20 - 28)	0.0000
Employment category			
Unemployed	311 (72.5%)	118 (27.5%)	0.0000
Informal	620 (79.8%)	157 (20.2%)	
Formal	73 (92.4%)	6 (7.6%)	
Body mass index			
mean (sd)	24.7 (3.9)	23.7 (3.1)	0.0001
Median (IQR)	23.9 (21.8 - 26.8)	23.2 (21.4 - 25.2)	0.0003
Diastolic blood pressure			
mean (sd)	64.0 (10.4)	63.0 (10.8)	0.1791
median (IQR)	63 (57 - 70)	62 (56 - 68)	0.0847
Singleton pregnancy			
Yes	978 (77.8%)	279 (22.2%)	0.0570
No	26 (92.9%)	2 (7.1%)	
Maternal Laboratory tests	population retained = 782	population lost =218	*p*-value
Serum ALT (Alanine Aminotransferase)			
mean (sd)	30.6 (27.7)	27.9 (23.9)	0.1743
median (IQR)	25 (18.0 - 34.5)	23 (16.0 - 34.0)	0.0378
Lymphocyte Count			
mean (sd)	1.8 (0.9)	1.9 (1.5)	0.0954
median (IQR)	1.6 (1.3 - 2.1)	1.8 (1.3 - 2.2)	0.0789

Incidence of preeclampsia

Preeclampsia developed in 43 out of 1004 who returned to deliver in hospital. Seven mothers had early-onset preeclampsia that is onset at ≤ 34 weeks gestation while 36 had late-onset preeclampsia as shown in figure 3. Table 3 shows the incidence of pre-eclampsia according to the FIGO classification of preeclampsia[1].

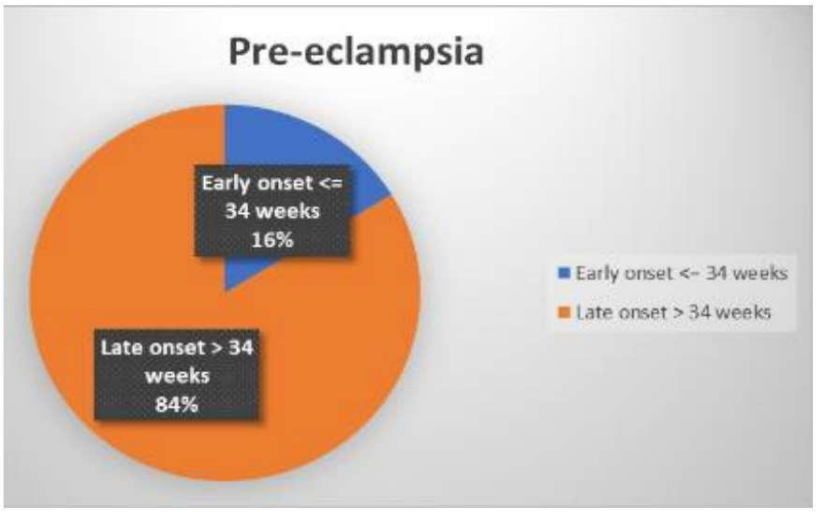

Fig 3: Pie chart showing the proportion of early and late-onset preeclampsia

Table 4

Incidence of preeclampsia

Variables	**N**	**Diseased**	**[% (95% CI)]**	**Incidence of preeclampsia per 10^4 women weeks**
Overall preeclampsia				
No preeclampsia	961	0	[95.7% (94.3% - 96.9%)]	0
Number with preeclampsia	43	43	[4.3% (3.1% - 5.7%)]	11 (8 - 15)
Early and late onset preeclampsia				
Early onset preeclampsia <34 weeks	35	7	[20% (8.4% - 36.9%)]	68 (29 - 126)
Late onset preeclampsia (Delivery at ≥34 weeks)	969	36	[3.7% (2.6% - 5.1%)]	9 (7 - 13)
Preterm and term preeclampsia				
Preterm preeclampsia (Delivery at <37 weeks)	128	21	[16.4% (10.5% - 24.0%)]	48 (31 - 71)
Term preeclampsia (Delivery at ≥ 37 weeks)	876	22	[2.5% (1.6% - 3.8%)]	6 (4 - 10)

Overall, 43 women developed preeclampsia giving a prevalence of 4.3% (95% CI 3.1% - 5.7%) and an incidence of 11 per 10^4 women weeks of follow-up. Out of the thirty-five mothers who delivered before 34 weeks of gestation, 7 [20% (95% CI 8.4% - 36.9%)] had preeclampsia. That translates to an incidence of 0.0068 preeclampsia per woman week (68 preeclampsia per 10^4 women weeks'). However, for those who delivered at ≥34 weeks of gestation, 3.7% had preeclampsia, translating to 0.0009 preeclampsia per woman week [9 per 10^4 woman weeks]. The incidence of preeclampsia is higher at lower gestation ages.

DISCUSSION

The prevalence of preeclampsia was 4.3%, similar to published data. The global estimates for preeclampsia are 4.6%[10] with a lot of variation between regions. Khalil et al[3] found women of Afro-Caribbean racial origin and South Asian racial origin were most at risk of preeclampsia in the global north. The incidence of preeclampsia among women of Afro-Caribbean racial origin was 2.9% within the global north[3] while it was 5.8% in South Africa[5]. The incidence of preeclampsia is 3.8% in india[15] and 3.0% in Pakistan[15]. The incidence of preeclampsia is higher in Latin American countries with 4.4% in Uruguay, 5.5% in Mexico, and almost 10% in Argentina[10, 16]. Considering the majority of women in Argentina are Caucasians, it may not necessarily make Afro-Caribbean racial origin a risk factor for preeclampsia.

The incidence of preeclampsia was higher at early gestation age compared to term pregnancies, with 20.0% at <34 weeks compared to 2.5% at ≥37 weeks. This trend is comparable to the 8.7% to 30.0% for preterm and 2.0% term preeclampsia in low-risk populations[1, 17]. Fourteen (15%) of 93 deliveries of women with gestation age of 34.0-<37 weeks had preeclampsia compared to the 22 (2.5% among 876 women who delivered with ≥37 weeks pregnancy gestation. Most of the births for early-onset preeclampsia are iatrogenic (induced)[17], therefore, adding to the complications of preterm birth.

However, this incidence of preeclampsia could be inaccurate because of the high number of losses to follow-up of up to 22%. These women were younger, and unemployed with lower body mass index compared to those who were retained. This was probably an indicator of low socioeconomic status. Low socioeconomic status is a known risk factor for preeclampsia[18].

The laboratory tests revealed a high prevalence of liver dysfunction with one in five women having elevated liver enzymes, and a similar proportion having low serum albumin which points towards protein-energy malnutrition. In Riyadh, liver enzymes AST, ALT and ALP were found to be increased in women at high risk of preeclampsia compared to the low risk group[19]. A substantive number of the study participants had features of HELLP syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelet count). These could have been pre-clinical manifestations of preeclampsia. There is a need for further studies to determine what proportion of women are at risk, how many actually develop the full-blown HELLP condition in our population, and what are the other causes of these abnormalities. Our findings point to a need to further studies to document the prevalence and pattern of chronic illness among pregnant women in this region.

In Uganda healthcare is free, with massive shortages of supplies and drugs. Most poor mothers prefer to deliver from home because they are unable to purchase the supplies needed to access the free hospital births[18]. This study never covered any bills for the mothers, and got 78% retention. In contrast, in the developed world where most mothers have health insurance to cover delivery costs, hospital delivery rates are over 98%[14]. Therefore, many of the mothers who were lost to follow-up could have got preeclampsia and its adverse effects.

CONCLUSION

The incidence of preeclampsia was 4.3%, with higher values at lower gestation ages. While the retention to prenatal care in Northern Uganda was 78%, many of the mothers who were lost to follow-up were probably of lower socioeconomic status, who could have got preeclampsia but were missed.

Strength of our study

This was a baseline study in Northern Uganda and our result could be used to determine the nature of subsequent studies in the community and probably the country/region.

Weakness of our study

We discharged mothers from the study at the delivery of the baby. Therefore, mothers who developed preeclampsia after delivery were not captured. We did not look for mothers who were lost to follow-up into the community to find out how they were in the puerperium.

RECOMMENDATION

We hope future studies will do serial measurements at intervals during the prenatal period, and endeavor to motivate more mothers to deliver in hospital by awarding incentives and covering the costs of hospital births.

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Article 6

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Research

Prediction of low birth weight at term in low resource setting of Gulu city, Uganda: a prospective cohort study

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Prediction of low birth weight at term in low resource setting of Gulu city, Uganda: a prospective cohort study

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Abstract

Introduction: *despite the widespread poverty in Northern Uganda resulting in undernutrition, not all mothers deliver low birth weight babies. Therefore, we developed and validated the risk prediction models for low birth weight at term in Northern Uganda from a prospective cohort study.* ***Methods:*** *one thousand mothers were recruited from 16 - 24 weeks of gestation and followed up until delivery. Six hundred and eighty-seven mothers delivered at term. The others were either lost to follow-up or delivered preterm. Used proportions to compute incidence of low birth weight at term, build models for prediction of low birth weight at term in RStudio. Since there were few low birth weight at term, were generated synthetic data using ROSE-package in RStudio by over-sampling low birth weights and under-sampling normal birth weights, and evaluated the model performance against the synthetic data using K (10) - fold cross-validation.* ***Results:*** *mean age was 26.3 years with an average parity of 1.5. Their mean body mass index was 24.7 and 7.1% (49 of 687) had lateral placenta. The incidence of low birth weight was 5.7% (39 of 687). Predictors of low birth weight were gravidity, level of education, serum alanine aminotransferase (ALT), serum gamma-glutamyl transferase (GGT), lymphocyte count, placental location, and end-diastolic notch in the uterine arteries. This predicted low birth weight at term by 81.9% area under the curve (AUC), 76.1% accuracy, 72.9% specificity, and 79.1% sensitivity.* ***Conclusion:*** *a combination of gravidity, level of education, serum ALT, serum GGT, lymphocyte count, placental location, and end-diastolic notch in the uterine arteries can be used for screening for low birth weight in prenatal clinics for screening low birth weight at term.*

Introduction

Low birth weight at term (≥37 weeks of gestation) is diagnosed when the baby weighs less than 2.5Kg at birth [1,2]. It affects 5 - 10% of babies born in the global north [3], and slightly higher number in the global south [4-6]. The causes are multifactorial including prenatal undernutrition, maternal race, and low socioeconomic status [7-9]. There is a known black racial predisposition to low birth weight in multiracial communities [9]. However, inadequate maternal nutrition is the hallmark of sub-Saharan Africa [10]. In northern Uganda, over 60% of the population eats less than three meals a day [11]. This may worsen the pregnancy outcomes associated with nutritional problems [7].

Complications of low birth weight at term include low APGAR score at five minutes of birth, neonatal asphyxia, foetal distress, respiratory distress, neurodevelopmental deficits, impaired renal development, and neonatal death [12-15]. These may require advanced paediatric care available at tertiary level hospitals to manage neonates with low birth weight. Knowledge of the predictors of low birth weight may help prepare better to refer these mothers to tertiary health centers. Despite the widespread poverty and predominantly black population in Northern Uganda, not all mothers deliver low birth weight babies. Therefore, we set out to develop and validate the risk prediction models for low birth weight in Northern Uganda.

Methods

Study design and Study setting: this was a prospective cohort study at St. Mary´s Hospital Lacor. It is a private, not-for-profit hospital, founded by the Catholic Church. It is located six kilometers west of Gulu city along Juba Road in Gulu district (Longitude 30 - 32 degrees East and Latitude 02 - 04 degrees North). St. Mary´s Hospital Lacor is one of the teaching hospitals of Gulu University with a bed capacity of 482. It is staffed by specialists, medical officers, midwives, nurses, laboratory and radiology staff, as well as support and administrative staff. The hospital receives over nine thousand antenatal mothers and conducts about seven thousand deliveries per year [16].

Study population: we recruited 1,000 pregnant mothers 16 - 24 weeks from April 2019 to March 2020, gave them unique identifiers (study numbers). Excluded all participants with lethal congenital anomalies.

Sample size estimation: using Yamane 1967 formula [17] for calculating sample size for cohort studies using finite population size, St. Mary´s hospital Lacor delivers approximately seven thousand mothers per year. Since my study duration is 12 months for recruitment of the mothers, the finite population I can access is about 7,000 mothers. Yamane 1967 formula: Sample size:

$$n = \frac{N}{1 + N(e)^2}$$

Where N is the finite population size= 7,000 mothers; margin of error (e)= 5%; therefore, n = 7,000/1+7,000(0.05)^2; n = 379. The required sample size was 379 mothers. We doubled the number (to >758) to cater for loss to follow up, preterm delivery and clients opting out of the study during the follow-up period. We expected over 50% loss to follow-up since rate of hospital delivery in this region is low [18], and some people may deliver from the free government hospitals nearby.

Data collection: a questionnaire was filled with the help of a midwife (research assistant), blood samples taken for complete blood count, liver and renal function tests, and uterine artery Doppler sonography done. The laboratory and sonographers only used the study numbers to identify the participants. The mothers were followed up until September 2020 when the last one was delivered. The delivery team had no access to the questionnaire, laboratory and ultrasound results.

Outcomes: birth weight of the baby <2.5Kg at ≥37 weeks was taken as low birth weight.

Definitions: from maternal history, grouping was based on known classification e.g. level of education in Uganda is grouped as primary, secondary and tertiary education levels. Gravidity was grouped as prime gravida for first pregnancies, multigravida for 2-4 and grand multigravida >4. Laboratory tests were grouped according to the reference ranges given by the laboratory while ultrasound pulsatility and resistive indices were grouped using percentiles. End diastolic notch of the uterine arteries was either present or absent; if present it was either unilateral or bilateral. The participants with incomplete results were dropped from the final analysis.

Statistical analysis: six hundred eighty-seven (687) mothers delivered at term. Data were pre-processed using Stata® 15.0 and built models in RStudio (R version 4.1.1 (2021-08-10)). Used proportions to compute incidence of low birth weight at term. Univariable analysis was done, and all variables with p-values ≤0.20 or were known risk factors for low birth weight were included in a logistic regression model. Built models for prediction of low birth weight at term in RStudio. The predictors with p-value <0.05 in the logistic regression model were taken as independent risk factors for low birth weight. Since there were few low birth weight at term, we used all the participants for the development of the models. For the validation cohort, we generated synthetic data using ROSE-package in RStudio by over-sampling low birth weights and under-sampling normal birth weights to balance the data. We obtained 349 (51.2%) and 332 (48.8%) normal and low birth weights respectively. We evaluated (validated) the model performance against the synthetic data using K (10) - fold cross-validation. The original model was put into a confusion matrix against the ROSE-derived data to calculate the accuracy, sensitivity, and specificity of the model in RStudio.

Ethical consideration: the study was approved by Makerere University School of Medicine Research and Ethics Committee (Reference number 2018-

105), Uganda National Council for Science and Technology (Reference number HS258ES), and administrative clearance to conduct the research at St. Mary´s Hospital Lacor was also obtained (Reference number LHIREC Adm 009/11/18). The participants were informed about the study during the morning health education by the midwives when they arrived in the hospital. Those who satisfied the inclusion criteria were approached and requested to join the study. Written informed consent was sought from every participant in either English or Acholi language.

Results

One thousand pregnant mothers were recruited. Six hundred and eighty-seven (687) mothers delivered at term. Three hundred and thirteen (313) mothers were lost to follow-up or delivered preterm, dropped and not used in the data analysis. The prevalence of birth weight < 2.5Kg at term was 5.7% (39 out of 687) (Figure 1).

General characteristics of the study population: mean maternal age was about 26 years, with majority being informally employed. Only one in five of the mothers had a tertiary level of education (Table 1). Average body mass index was 24.7Kg^2 while prevalence of prenatal hypertension of 0.7%. About 7.1% had lateral placental location and 10.2% had bilateral end diastolic notch [19] (Table 2). Average maternal haemoglobin level was 10.8g/dL with a haematocrit of 32.5%. Mean serum alkaline phosphatase (ALP), GGT, aspartate aminotransferase (AST) and ALT were 154.3IU, 21.7IU, 20.2IU and 30.7IU respectively (Table 2). The mothers were followed up for an average of 19.1 weeks over one and half years (April 3rd 2019 to September 30th 2020)

Unadjusted estimates of the variables against low birth weight: all continuous variables were categorized using the laboratory reference ranges and interquartile ranges for the participants. Both ranges were analyzed and the best-fitted range for the models was chosen by the researcher. All variables with unadjusted p-value of ≤0.20 at univariable analysis were taken for multivariable level to build the models (Table 3, Table 4). A model was chosen based on one with fewer variables producing higher accuracy, sensitivity, specificity and AUC.

Risk prediction models for low birth weight: six risk prediction models were built from maternal history and physical examination, obstetric ultrasound parameters and uterine artery Doppler indices, maternal laboratory lab tests and the combinations of maternal history with either laboratory tests or ultrasound parameters or all the variables (Table 5, Table 6). In model 6, (combination of all the variables) (details in Table 6), the predictors of low birth weight were gravidity, level of education, serum ALT, serum GGT, lymphocyte count, placental location and end-diastolic notch in the uterine arteries. Being a prime gravida (aOR = 5.89, 95% CI 1.42 -41.94, p=0.032), having a laterally (one-sided) located placenta (aOR = 3.42, 95% CI 1.23 - 9.45, p=0.018) and presence of end-diastolic notch (aOR = 2.59, 95% CI 1.07 - 6.28, p=0.035) were independent risk factors, while having a tertiary level of education (aOR = 0.16, 95% CI 0.04 - 0.69, p=0.013), normal lymphocyte count (aOR = 0.30, 95% CI 0.10 - 0.91, p=0.033) and serum ALT (aOR = 0.22, 95% CI 0.09 - 0.56, p=0.001) were protective against low birth weight.

Evaluation of the performance of the models 1-6 for the prediction of low birth weight: the models´ performance was evaluated using K (10) - fold cross validation against synthetic data derived from the ROSE package in RStudio, and listed in (Table 2). Model accuracies ranged from 59.3% - 76.1%, while AUC from 62.6% - 81.9%. In the absence of ultrasound scan and laboratory tests, model 1 can predict low birth weight with 62.3% accuracy, 37.3% sensitivity, 88.3% specificity and 65.3% AUC.

Discussion

We developed and validated risk prediction models for low birth weight at term in Northern Uganda from a prospective cohort study. From maternal history, the predictors of low birth weight were education level and gravidity. This predicted low birth weight at term by 65.3% AUC, 62.3% accuracy, 88.3% specificity, and 37.3% sensitivity. In Ethiopia, similar demographic characteristics were used to predict low birth weight. At a 26% false positive rate, they predicted low birth weight with 83%, AUC with 82% specificity and 71% sensitivity [20]. While in India, Singh *et al.* [21] found the prediction model AUC of 79% with 72% sensitivity and 56% specificity. In the USA, maternal history predicted low birth weight with 75.3% accuracy [22]. Considering the uterine artery Doppler indices, the predictors of low birth weight were placental location and end-diastolic notch in the uterine arteries. This predicted low birth weight at term by 62.6% AUC, 59.3% accuracy, 42.5% specificity, and 75.4% sensitivity. In Denmark, uterine artery pulsatility index predicted low birth weight with 74% AUC [23], while in Saudi Arabia, placental thickness of <2cm and diameter of <18cm predicted low birth weight with 88.6% AUC [24]. This probably outline the differences in population and techniques used in the data analysis. When the maternal history is combined with uterine artery Doppler indices, the predictors of low birth weight were education level, gravidity, placental location, and end-diastolic notch. This predicted low birth weight at term by 71.6% AUC, 62.3% accuracy, 64.8% specificity and 61.8% sensitivity. In India, a combination of uterine artery Doppler indices and maternal history predicted low birth weight with 65.9% AUC, 45.4% sensitivity and 84.6% specificity [25].

While we found the predictors of low birth weight to be serum GGT, serum ALT and lymphocyte count to have predicted low birth weight at term by 66.9% AUC, 59.3% accuracy, 35.8% specificity and 81.7% sensitivity, there is limited data on the prediction of low birth weight using maternal full haemagram, liver and renal function tests. There is no evidence that maternal blood levels of alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), or pregnancy-associated plasma protein A (PAPP-A) used as a single predictor are useful to predict low-birth-weight newborns [26]. When the laboratory blood tests were combined with maternal history, the predictors of low birth weight were gravidity, level of education, serum ALT, serum GGT and lymphocyte count. This predicted low birth weight at term by 66.9% AUC, 66.7% accuracy, 59.6% specificity and 73.4% sensitivity. The addition of blood glucose levels to maternal history in Mexico predicted low birth weight with 72% AUC [27]. After combining all the variables from maternal history, laboratory tests, and uterine artery Doppler indices, the predictors of low birth weight were gravidity, level of education, serum ALT, serum GGT, lymphocyte count, placental location, and end-diastolic notch in the uterine arteries. These predicted low birth weight at term by 81.9% AUC, 76.1% accuracy, 72.9% specificity and 79.1% sensitivity. Considering the few predictors, this model can be used for screening low birth weights in prenatal clinics. This makes our model favorably compared to the other models. This is a baseline study in Northern Uganda. We hope it will open doors to a wide range of research in sub-Saharan Africa. There were many losses to follow-up or preterm birth. This could have skewed the models in other ways. Future research should be done in several other locations for external validation of these models to ensure generalizability.

Conclusion

In places with no laboratory tests and ultrasound scan, the predictors of low birth weight from maternal history alone are level of education and number of pregnancies (gravidity). These predicted low birth weight by 65.3% AUC with 62.3% accuracy.

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What is known about this topic

- *Black women are more at risk of low birth weight in multiracial communities;*
- *Malnutrition is a predictor of low birth weight;*
- *Low birth weight is known to be associated with increased risks of early neonatal death.*

What this study adds

- *Being a prime gravida, and having laterally located placenta are risk factors for low birth weight while tertiary level of education is protective;*
- *The prevalence of low birth weight in Gulu city, Northern Uganda is comparable to those in multiracial communities.*

Competing interests

The authors declare no competing interests.

Authors' contributions

Silvia Awor, wrote the proposal, collected data and drafted the manuscript. Benard Abola built the models and cross-validated the models. Rosemary Byanyima, Paul Kiondo and Christopher Garimoi-Orach are doctoral committee members who provided expert opinion and guided to write the manuscript. Jaspar Ogwal-Okeng, Annettee Nakimuli and Dan Kabonge Kaye are doctoral supervisors who guided through the concept and writing of the manuscript. All the authors have read and agreed to the final manuscript.

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Tables and figure

Table 1: social demographic characteristics of mothers who delivered at term

Table 2: clinical and laboratory characteristics of mothers who delivered at term

Table 3: unadjusted risk ratio of social demographic characteristics and low birth weight

Table 4: unadjusted risk ratio of clinical and laboratory characteristics with low birth weight

Table 5: model 1 - 4 for the prediction of low birth weight

Table 6: model 5 - 6 for the prediction of low birth weight

Table 7: model performance evaluation using K-fold cross-validation

Figure 1: participant flow through the study

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Table 1: social demographic characteristics of the mothers delivered at term		
Characteristics (n=687)	**Mean (SD) or proportions (%)**	**Median (IQR)**
Maternal age (years)	26.3 (5.4)	26 (22 - 30)
Age at menarche (years)	14.4 (1.5)	14 (14 - 15)
Parity	1.5 (1.5)	1 (0 - 2)
Marital status (single)	11 (1.6)	
Marital status (married/cohabiting)	676 (98.4)	
Primary level of education	244 (35.5)	
Secondary level of education	317 (46.1)	
Tertiary level of education	126 (18.4)	
Unemployed	214 (31.2)	
Informal (non-salaried) employment	416 (60.5)	
Formal (salaried) employment	57 (8.3)	
Personal history of preeclampsia present	4 (0.6)	
No personal history of preeclampsia	683 (99.4)	
No history of miscarriage	557 (81.1)	
History of miscarriage	130 (18.9)	
No family history of preeclampsia	656 (95.5)	
Family history of preeclampsia	31 (4.5)	
No chronic illness	625 (91.0)	
Presence of a chronic illness	62 (9.0)	
Not living with a smoker	604 (87.9)	
Living with a smoker in one house	83 (12.1)	
No Alcohol use in pregnancy	642 (93.4)	
Alcohol use in pregnancy	45 (6.6)	

Table 2: clinical and laboratory characteristics of mothers who delivered at term		
Characteristics (n=687)	**Mean (SD) or proportions (%)**	**Median (IQR)**
Body mass index	24.7 (3.9)	23.9 (22.0 - 27.0)
Systolic blood pressure	105.8 (12.4)	104 (97 - 103)
Diastolic blood pressure	63.7 (10.4)	63 (57 -70)
Gestation age at recruitment (weeks)	20.4 (2.6)	20.3 (18.5 - 22.1)
Gestation age at delivery (weeks)	39.5 (1.6)	39.6 (38.0 - 40.6)
Average duration for follow up (weeks)	19.1	
No hypertension	682 (99.3)	
Prenatal hypertension	5 (0.7)	
Multiple pregnancy	7 (1.0)	
Singleton	680 (99.0)	
Lateral placental location	49 (7.1)	
Central placenta location	638 (92.9)	
No end-diastolic notch	501 (72.9)	
Unilateral end-diastolic notch	116 (16.9)	
Bilateral end diastolic notch	70 (10.2)	
Average pulsatility index	0.80 (0.29)	0.75 (0.61 - 0.95)
Average resistive index	0.51 (0.11)	0.50 (0.44 - 0.58)
Serum ALT	30.7 (27.5)	25 (18 - 35)
Serum AST	20.2 (23.3)	14 (7 - 26)
Serum GGT	21.7 (8.6)	20 (15-29)
Serum ALP	154.3 (50.1)	149 (115 - 180)
Serum bicarbonate	35.2 (2.3)	25 (24 - 27)
Serum albumin	4.1 (3.0)	3.9 (3.5 - 4.1)
Serum urea	25.6 (27.0)	18 (14 - 25)
Serum sodium	137.6 (4.0)	137.4 (135.2 - 139.4)
Serum potassium	4.2 (1.3)	4.2 (3.9 - 4.5)
Serum chloride	106.4 (4.3)	105.8 (103.6 - 108.9)
Serum phosphorus	1.3 (0.8)	1.1 (0.9 - 1.4)
Serum calcium	2.4 (1.1)	2.2 (2.1 - 2.4)
Serum creatinine	1.0 (0.6)	0.9 (0.8 - 1.2)
Neutrophil count	3.7 (2.2)	3.5 (2.6 - 4.5)
Lymphocyte count	1.8 (0.9)	1.6 (1.3 - 2.1)
Total white blood cell count	6.3 (3.0)	6.0 (4.9 - 7.6)
Platelet count	233.8 (69.4)	220 (179 - 267)
Haemoglobin level	10.8 (2.0)	10.9 (9.5 - 12.1)
Haematocrit	32.5 (6.6)	32.8 (28.7 - 36.0)
Mean corpuscular volume	82.4 (7.8)	82.3 (79.7 - 89.1)
Mean corpuscular haemoglobin concentration	32.9 (2.6)	32.9 (31.4 - 34.5)
ALT: Alanine transaminase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma glutamyl transferase		

Table 3: unadjusted risk ratio of social demographic characteristics and low birth weight		
Variable	**IRR (95% CI)**	**P-value**
Age at menarche ≤15 (years)	1	
Age at menarche >15 (years)	0.75 (0.34 - 1.66)	0.477
Prime gravida	4.82 (1.13 - 20.49)	0.033
Gravida 2-4	2.91 (0.69 - 12.19)	0.144
Gravida >4	1	
Nullipara	2.71 (1.04 - 7.12)	0.042
Para 1 - 2	1.67 (0.63 - 4.45)	0.303
Para >2	1	
Marital status (single)	1	
Marital status (married / cohabiting)	0.65 (0.10 - 4.32)	0.657
Primary level of education	1	
Secondary level of education	1.01 (0.54 - 1.90)	0.975
Tertiary level of education	0.48 (0.17 - 1.42)	0.186
Unemployed	1	
Informal (non-salaried) employment	1.22 (0.61 - 2.41)	0.576
Formal (salaried) employment	1.37 (0.45 - 4.13)	0.582
No history of miscarriage	1	
History of miscarriage	1.04 (0.49 - 2.20)	0.921
No chronic illness	1	
Presence of a chronic illness	1.40 (0.57 - 3.44)	0.463
Not living with a smoker	1	
Living with a smoker in one house	1.50 (0.69 - 3.27)	0.310
No alcohol use in pregnancy	1	
Alcohol use in pregnancy	0.73 (0.18 - 2.94)	0.659

Table 4: unadjusted risk ratio of clinical and laboratory characteristics with low birth weight		
Variable	**IRR (95% CI)**	**P-value**
Body mass index <25 Kg	1	
Body mass index ≥25 Kg	0.57 (0.29 - 1.11)	0.098
Normal diastolic blood pressure <90mmHg	1	
Diastolic hypertension ≥90mmHg	2.15 (0.57 - 8.15)	0.260
Uterine artery Doppler indices		
Lateral placental location	3.66 (1.85 - 7.23)	0.000
Central placenta location	1	
No end-diastolic notch	1	
Unilateral end-diastolic notch	2.47 (1.25 - 4.87)	0.009
Bilateral end diastolic notch	2.73 (1.26 - 5.92)	0.011
Average pulsatility index ≤1.235	1	
Average pulsatility index >1.235	2.00 (0.93 - 4.34)	0.078
Average resistive index ≤0.655	1	
Average resistive index >0.655	2.00 (0.93 - 4.34)	0.078
Serum GGT ≤30IU	3.07 (0.96 - 9.82)	0.059
Serum GGT >30IU	1	
Serum bicarbonate <24 mEq/L	1	
Serum bicarbonate 24 - 27 mEq/L	1.98 (0.71 - 5.56)	0.194
Serum bicarbonate >27 mEq/L	2.39 (0.77 - 7.42)	0.133
Serum calcium <2.09mg/dL	1	
Serum calcium 2.09 - 2.41mg/dL	1.66 (0.77 - 3.59)	0.199
Serum calcium >2.41mg/dL	0.89 (0.33 - 2.39)	0.810
Neutrophil count of < 2630 cells/µl	1	
Neutrophil count of 2630 - 4540 cells/µl	0.66 (0.35 - 1.27)	0.214
Neutrophil count >4540 cells/µl	0.39 (0.15 - 0.97)	0.044
Lymphocyte count of 900 cells/µl	1	
Lymphocyte count of 900 - 3900 cells/µl	0.38 (0.16 - 0.93)	0.033
Lymphocyte count >3900 cells/µl	2.17 (0.68 - 6.96)	0.192
Platelet count of <178 cells/µl	1	
Platelet count of 178 - 266 cells/µl	1.02 (0.51 - 2.04)	0.951
Platelet count > 266 cells/µl	0.34 (0.11 - 1.06)	0.063
Mean corpuscular haemoglobin concentration <31.5g/dL	1	
Mean corpuscular haemoglobin concentration 31.5 - 34.4g/dL	0.60 (0.30 - 1.20)	0.150
Mean corpuscular haemoglobin concentration >34.4g/dL	0.80 (0.38 - 1.72)	0.574
ALT: Alanine transaminase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma glutamyl transferase		

Table 5: model 1 - 4 for the prediction of low birth weight		
Variable	**OR (95% CI)**	**p-value**
Model 1: maternal history and physical examination		
Secondary education	0.92 (0.46 - 1.88)	0.819
Tertiary level education	0.31 (0.07 - 0.97)	0.070
Gravida 2 - 4	3.30 (0.93 - 21.02)	0.113
Prime gravida	5.58 (1.51 - 36.10)	0.025
Intercept	0.02 (0.003 - 0.07)	0.000
Model 2: obstetric ultrasound and uterine artery Doppler indices		
Lateral placental location	2.86 (1.10 - 6.95)	0.025
Unilateral end-diastolic notch	1.79 (0.75 - 4.00)	0.171
Bilateral end-diastolic	2.20 (0.82 - 5.26)	0.093
Intercept	0.04 (0.03 - 0.06)	0.000
Model 3: combination of maternal history, ultrasound and uterine artery Doppler indices		
Secondary education	0.97 (0.48 - 2.00)	0.931
Tertiary level education	0.23 (0.05 - 0.75)	0.028
Gravida 2 - 4	3.56 (0.99 - 22.87)	0.095
Prime gravida	4.97 (1.32 - 32.53)	0.039
Lateral placental location	3.29 (1.20 - 8.35)	0.015
Unilateral end-diastolic notch	1.98 (0.83 - 4.46)	0.101
Bilateral end-diastolic	2.01 (0.73 - 4.88)	0.141
Intercept	0.01 (0.002 - 0.05)	0.000
Model 4: maternal laboratory tests		
Serum GGT of 0.0 - 30.0 IU	2.91 (1.01 - 12.27)	0.082
Lymphocyte count of 900 - 3900 cells/µl (normal)	0.30 (0.12 - 0.95)	0.024
Lymphocyte count > 3900 cells/µl (high)	2.28 (0.46 - 10.88)	0.295
Serum ALT of 12 - 49 IU	0.33 (0.15 - 0.84)	0.013
Serum ALT <12 IU	0.60 (0.17 - 1.98)	0.408
Intercept	0.16 (0.03 - 0.71)	0.026
ALT: Alanine transaminase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma glutamyl transferase		

Table 6: model 5 - 6 for the prediction of low birth weight		
Model 5: maternal history and laboratory tests		
Secondary education	0.91 (0.44 - 1.92)	0.798
Tertiary level education	0.26 (0.06 - 0.86)	0.045
Gravida 2 - 4	3.34 (0.90 - 21.87)	0.119
Prime gravida	6.35 (1.63 - 42.51)	0.020
Serum GGT of 0.0 - 30.0 IU	3.22 (1.11 - 13.74)	0.059
Lymphocyte count of 900 - 3900 cells/µl (normal)	0.37 (0.14 - 1.21)	0.070
Lymphocyte count > 3900 cells/µl (high)	3.59 (0.67 - 19.04)	0.128
Serum ALT of 12 - 49 IU	0.31 (0.13 - 0.80)	0.010
Serum ALT <12 IU	0.60 (0.16 - 2.06)	0.427
Intercept	0.04 (0.004 - 0.32)	0.005
Model 6: combination of maternal history, laboratory tests, ultrasound and uterine artery Doppler indices		
Gravida 2 - 4	3.91 (0.99 - 27.09)	0.091
Prime gravida	5.89 (1.42 -41.94)	0.032
Secondary education	1.06 (0.51 - 2.29)	0.876
Tertiary level education	0.16 (0.03 - 0.60)	0.013
Serum GGT of 0.0 - 30.0 IU	3.25 (1.11 - 13.96)	0.059
Lymphocyte count of 900 - 3900 cells/µl (normal)	0.30 (0.11 - 1.00)	0.033
Lymphocyte count > 3900 cells/µl (high)	2.40 (0.43 - 13.22)	0.310
Serum ALT of 12 - 49 IU	0.22 (0.09 - 0.58)	0.001
Serum ALT <12 IU	0.45 (0.12 - 1.59)	0.224
Lateral placental location	3.42 (1.18 - 9.19)	0.018
Unilateral end-diastolic notch	2.59 (1.03 - 6.18)	0.035
Bilateral end-diastolic	2.58 (0.91 - 6.60)	0.057
Intercept	0.04 (0.003 - 0.31)	0.005
ALT: Alanine transaminase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma glutamyl transferase		

Table 7: model performance evaluation using K-fold cross-validation				
Model	**Accuracy (%)**	**Sensitivity (%)**	**Specificity (%)**	**AUC (%)**
Model 1 (history and physical exam)	62.3	37.3	88.3	65.3
Model 2 (uterine artery Doppler indices)	59.3	75.4	42.5	62.6
Model 3 (combination of model 1 and 2)	62.3	61.8	64.8	71.6
Model 4 (maternal blood tests)	59.3	81.7	35.8	66.9
Model 5 (combination of model 1 and 4)	66.7	73.4	59.6	66.9
Model 6 (combination of models 3 and 4)	76.1	79.1	72.9	81.9

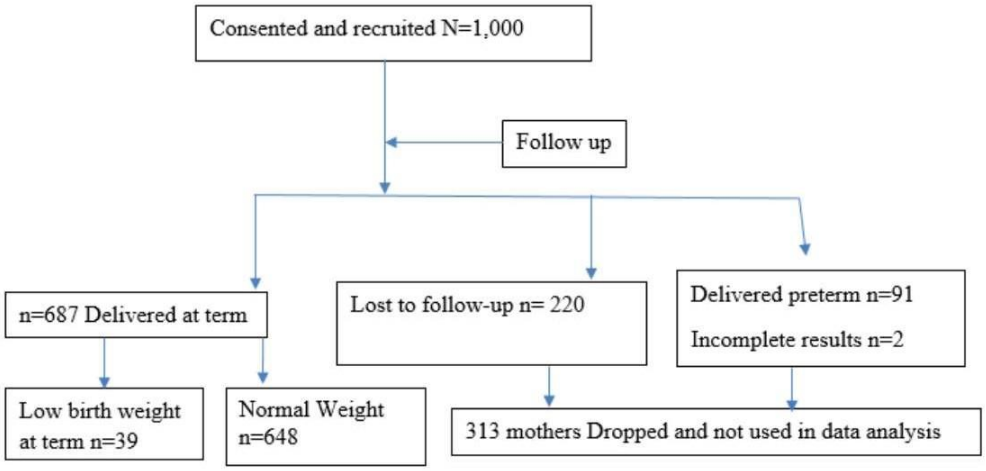

Figure 1: participant flow through the study

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COLLEGE OF HEALTH SCIENCES
SCHOOL OF MEDICINE

RESEARCH ETHICS COMMITTEE

December 17, 2018

The Director
Directorate of Research and Graduate Training
Makerere University

Dear Sir,

RE: Approval of Dr. Silvia Awor's proposal

The Higher Degrees Research Ethics committee during its 102nd meeting held on 28th June 2018 considered the proposal of Dr. Silvia Awor –Department of Obstetrics and Gynecology entitled **"Using ultrasonography and maternal characteristics to predict preeclampsia and adverse pregnancy outcomes at St. Mary's Hospital, Lacor"**

The proposal was reviewed and some amendments suggested for incorporation, in order to improve on the science and ethics of the study. She has revised the proposal to the satisfaction of the committee.

Approved supervisors

1. Assoc. Prof. Daniel Kabonge Kaye –Supervisor, Department of Obstetrics and Gynecology, School of Medicine, Makerere University College of Health Sciences.
2. Dr. Annet Nakimuli-Supervisor, Head of Department, Obstetrics and Gynecology, School of Medicine Research and Ethics Committee, Makerere University College of Health Sciences
3. Prof. Jasper Ogwal-Okeng- Supervisor, Principal, Gulu University.

Approved Doctoral Committee

1. Assoc. Prof. Daniel Kabonge Kaye –Supervisor, Department of Obstetrics and Gynecology, School of Medicine, Makerere University College of Health Sciences.
2. Dr. Annet Nakimuli-Supervisor, Head of Department, Obstetrics and Gynecology, School of Medicine Research and Ethics Committee, Makerere University College of Health Sciences
3. Prof. Jasper Ogwal-Okeng- Supervisor, Principal, Gulu University.
4. Assoc. Prof. Paul Kiondo- Assoc. Prof. of Obstetrics and Gynecology- School of Medicine Research and Ethics Committee, Makerere University College of Health Sciences
5. Prof. Christopher Garimoi Orach-Member- School of Public Health, Makerere University College of Health Sciences.

6. Dr.Rosemary Byanyima -Member ,Senior consultant, Radiologist and Clinical Head of Diagnostics at Mulago National Referral hospital

On behalf of the committee, I do confirm that she has gone through all the required formalities. You may now consider her for full registration.

Yours sincerely,

Assoc. Prof. Ponsiano Ocama
Chairperson School of Medicine Research Ethics Committee/Higher Degrees Committee

Cc **Deputy Principal College of Health Sciences**
Academic Registrar College of Health Sciences
Supervisors

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18th February 2019

To

Dr. Sylvia Awor

Makerere University

P.O Box 7072 Kampala

Re: LHIREC Adm. 009/11/18. Study Title: "Using Ultrasonography and Maternal Characteristics to predict pre-eclampsia and adverse pregnancy outcomes at Gulu Regional Referral Hospital"

Lacor Hospital Institutional Research and Ethics Committee (LHIREC) has reviewed the study referenced above and noted that it was granted an ethical approval by Makerere University School of Medicine Research Ethics Committee. LHIREC therefore grants an Administrative clearance for the study to be conducted in St. Mary's Hospital Lacor.

Please note that your study Protocol number with LHIREC is 009/11/18, always reference it in any correspondence with LHIREC. If it is necessary to continue with the research beyond the expiry date, a request for continuation should only be made in writing to the Secretary Makerere University School of Medicine Research Ethics Committee and a copy to LHIREC

Yours

Dr. Martin David Ogwang

Chairman LHIREC

ST. MARY'S HOSPITAL LACOR
P. O. Box 180, Gulu - Uganda
St. Mary's Hospital LACOR
Date: 18/02/2019
Institutional Research and Ethics Committee

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COLLEGE OF HEALTH SCIENCES
SCHOOL OF MEDICINE

RESEARCH ETHICS COMMITTEE

December 18, 2018

Dr. Awor Silvia
Department of Obstetrics and Gynaecology

Category of review
[ ] Initial review
[ ] Continuing review
[X] Amendment
[ ] Termination of study
[ ] SAEs

Dear Dr. Awor,

Re: REC REF 2018-105
Title: "Using Ultrasonography and maternal characteristics to predict pre-eclampsia and adverse Pregnancy outcomes at St. Mary's Hospital Lacor"

Your proposal entitled **"Using Ultrasonography and maternal characteristics to predict pre-eclampsia and adverse Pregnancy outcomes at St. Mary's Hospital Lacor"** was initially reviewed and approved by the School of Medicine Research and Ethics committee on November 16th, 2018

On December 13th, 2018, you requested for permission to make some modifications in the study: to change the study site from Gulu Regional Referral hospital to St. Mary's Hospital Lacor, to rephrase the consent form in a way that reflects the researcher being the one talking to the participant, to clarify reference No.41, addressed formatting issues, this is because Gulu National referral hospital laboratory equipment are down, the CBC, RFT, and LFT are not done, the Ultra Sound Machine is unable to provide the Doppler readings.

The committee considered these changes on 18th December 2018. On behalf of the committee, I am glad to inform you that these changes have been approved. You may now proceed with the study. But forward regular reports on your study to the committee.

Yours sincerely,

Assoc. Prof. Ponsiano Ocama
Chairman School of Medicine Research & Ethics Committee

MAKERERE UNIVERSITY
SCHOOL OF MEDICINE
APPROVED
★ 18 DEC 2018 ★
RESEARCH & ETHICS COMMITTEE
P.O.BOX 7072, KAMPALA

Uganda National Council for Science and Technology

(Established by Act of Parliament of the Republic of Uganda)

Our Ref: HS258ES **24th June 2019**

Dr. Sylvia Awor
Principal Investigator
Gulu University
Gulu

Dear Dr. Awor,

I am pleased to inform you that on **24/06/2019**, the Uganda National Council for Science and Technology (UNCST) approved your study titled, **Using Ultrasonography and Maternal Characteristics to Predict Preeclampsia and Adverse Pregnancy Outcomes at St. Mary's Hospital Lacor.** The Approval is valid for the period of **24/06/2019** to **24/06/2021.**

Your study reference number is **HS258ES**. Please, cite this number in all your future correspondences with UNCST in respect of the above study.

Please, note that as Principal Investigator, you are responsible for:

1. Keeping all co-investigators informed about the status of the study.
2. Submitting any changes, amendments, and addenda to the study protocol or the consent form, where applicable, to the designated local Research Ethics Committee (REC) or Lead Agency, where applicable, for re-review and approval prior to the activation of the changes.
3. Notifying UNCST about the REC or lead agency approved changes, where applicable, within five working days.
4. For clinical trials, reporting all serious adverse events promptly to the designated local REC for review with copies to the National Drug Authority.
5. Promptly reporting any unanticipated problems involving risks to study subjects/participants to the UNCST.
6. Providing any new information which could change the risk/benefit ratio of the study to the UNCST for final registration and clearance.
7. Submitting annual progress reports electronically to UNCST. Failure to do so may result in termination of the research project.

Please, note that this approval includes all study related tools submitted as part of the application.

Yours sincerely,

Hellen Opolot
For: Executive Secretary
UGANDA NATIONAL COUNCIL FOR SCIENCE AND TECHNOLOGY

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DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

December 06, 2023 The Deputy

Principal
College of Health Sciences Makerere University

Dear Sir

Ref: **Using ultrasonography, laboratory blood tests and maternal characteristics to predict pre-eclampsia and adverse pregnancy outcomes at st. Mary's Hospital Lacor, Northern Uganda**

I have reviewed the corrections made on the dissertation by Dr. Sylvia Awori. She has made the corrections as recommended by the examiners; Associate Professor Joseph Ngonzi (External examiner) from Mbarara University of Science and Technology, Dr Gonzaga Roy Mubuke (Internal examiner) from Makerere University School Medicine, Dr Sam Ononge (Internal examiner) from Makerere University School of medicine and Prof. Geofrey Bugasa Buga (Opponent), Department of Gynaecology and Obstetrics, Walter Sisulu University,

South Africa

.

She may proceed and submit his dissertation to your office

Yours Sincerely

Dr. Sam Ononge PhD
Senior Lecturer (Obs/Gyn)

CC. Director, Directorate of Graduate Training and Research Dean,
School of Medicine

MAKERERE UNIVERSITY

COLLEGE OF HEALTH SCIENCES

The Dean, School of Medicine

Makerere University College of Health Sciences invites you to a scheduled

PUBLIC PhD DEFENSE

PhD CANDIDATE

DR. SILVIA AWOR

THURS, 30TH NOVEMBER, 2023 | TIME: 09:00 AM

VENUE: MakCHS, Conference Room

Thesis Title:

Using ultrasonography, laboratory blood tests and maternal characteristics to predict Pre-eclampsia and adverse pregnancy outcomes at St. Mary's Hospital Lacor, Northern Uganda

JOIN US LIVE:

Zoom link: https://shorturl.at/kySX8

Meeting ID: 941 2354 2945

Passcode: 339013

Scan QR to join Defense

SUPERVISORS:

1. Prof. Dan Kaye - School of Medicine, MakCHS
2. Prof. Jasper Ogwal-Okeng - Vice Chancellor, Lira University
3. Prof. Annettee Olivia Nakimuli - School of Medicine, MakCHS

INTERNAL EXAMINERS:

1. Dr. Aloysius Gonzaga Mubuuke - Senior Lecturer, College of Health Sciences, MakCHS
2. Dr. Sam Ononge - Senior Lecturer, College of Health Sciences, MakCHS

OPPONENT:

Prof. Geoffrey Bugasi Buga - Walter Sisulu University South Africa

EXTERNAL EXAMINER:

Dr. Joseph Ngonzi - Department of Obstetrics & Gynecology, Faculty of Medicine, Mbarara University of Science and Technology

DEFENSE CHAIR:

Dean, School of Medicine, MakCHS

You're All most Welcome Virtual & Physical