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COLLEGE OF HEALTH SCIENCES
SCHOOL OF MEDICINE

RESEARCH ETHICS COMMITTEE

March 27, 2026

Assoc. Prof. Nakimuli Annettee Olivia
Department of Obstetrics and Gynecology

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

Dear Assoc. Prof. Nakimuli,

RE: REC REF No. 2022-300

Title: "Enhancing prediction of adverse pregnancy outcomes in Africa through partnerships and innovation"

Renewal Approval Date: 27th March, 2026
Project Expiration Date: 28th March, 2027

On behalf of the committee, I write to inform you that the **proposed extension has been approved.**

The Makerere University School of Medicine Research and Ethics Committee (REC) initially reviewed and approved the above-referenced protocol on 28th March, 2022. Previous approval of this protocol expires on 28th March, 2026.

The review by the committee has found that your renewal is consistent with the continued protection of the rights and welfare of human subjects which protection of human subjects is a partnership between the Research and Ethics Committee (REC) and the investigators. We look forward to working with you as we both fulfill our responsibilities.

Renewals: REC approval is valid until the expiration date given above. If you are continuing your project, you must submit an application for renewal at least six (6) to eight (8) weeks before the lapse date. If the project is completed, please submit an application for permanent closure.

Amendments: The REC must review any changes in the project, prior to initiation of the change. Please submit an Application for Amendments to have your changes reviewed and summarize the proposed change and the rationale for it in a letter to the School of Medicine Research and Ethics Committee. If changes are made at the time of renewal, please include an application for amendments with the renewal application.
In addition, submit three (3) copies of an updated version of your original protocol application- one showing all proposed changes in bold or 'track changes,' and the other without bold or track changes.

Adverse Events: If issues should arise during the conduct of the research, such as unanticipated problems, severe adverse events or any other problem that may increase the risk to the human subjects, notify the REC Chairman promptly. The forms are available to report these issues.

Please use the REC REF number listed above on any forms submitted which relate to this project/study.

Good luck in your research. If we can be of further assistance, please contact us at (+256) 0414 -533541 or via email at research@chs.mak.ac.ug/rresearch9@gmail.com. Thank you for your cooperation.

Yours sincerely,

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Dr. Aloysius Gonzaga Mubuuke
Vice Chairperson School of Medicine Research and Ethics Committee

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Enhancing prediction of adverse pregnancy outcomes in Africa through partnerships and innovation

By

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Makerere University

Calestous Juma Science Leadership Fellow of the Bill and Melinda Gates Foundation

FUNDER:

This research proposal is funded under Calestous Juma Science Leadership Fellowship Programme of the Bill and Melinda Gates Foundation.

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Abbreviations and acronyms

CBC	Complete blood count
DNA	Deoxyribonucleic acid
GOS	Great Obstetrical Syndromes
HELLP	Hemolysis, Elevated Liver enzymes, Low Platelets
HIC	High-income-countries
HLA-C	Human Leukocyte Antigen-C
IRB	Institutional Review Board
KIR	Killer Immunoglobulin-like receptor
LFTs	Liver function tests
LMIC	Low-and-middle-income countries
NK Cells	Natural killer cells
NKR	Natural killer cell receptor
PCR	Polymerase Chain Reaction
PI	Principal Investigator
RFTs	Renal function tests
SGA	Small for gestational age
SSA	Sub-Saharan Africa
SOMREC	School of Medicine Research and Ethics Committee
UNCST	Uganda National Council for Science and Technology
UVRI	Uganda Virus Research Institute
WOA	Weeks of amenorrhoea

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Operational definitions

Pre-eclampsia: Is a hypertensive disorder of pregnancy that is characterised by the onset of hypertension and proteinuria after 20 weeks of gestation.

Nulliparous: A woman who has not carried a pregnancy beyond viability (for Uganda this is 28 weeks of gestation).

Indigenous African: For this study this means a Black African born in Africa and whose parents were also Black Africans born in Africa.

Adverse pregnancy outcomes: are pre-eclampsia, stillbirth, preterm birth and fetal growth restriction.

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Abstract

Background

The burden of maternal and neonatal deaths in Sub Saharan Africa (SSA) remains unacceptably high. The Great Obstetrical Syndromes (GOS) significantly contribute to this burden. These are pregnancy disorders caused by defective placental development and include pre-eclampsia, fetal growth restriction, unexplained stillbirth and spontaneous preterm birth. Attempts to predict and treat these disorders require prospective studies in order to develop better screening tests, but such cohorts are scanty in SSA. The goal of this study is to investigate the clinical, biological and social antecedents of the GOS in a prospective cohort of Ugandan women recruited early in pregnancy.

Methods

Participants will be recruited from the antenatal clinics of Kawempe and Mulago Hospitals. This will be a prospective cohort study of 4,000 nulliparous Ugandan women recruited before 18 weeks of gestation. Eligible participants will be consecutively recruited after giving informed written consent. In addition to a physical examination, we shall perform serial ultrasound scans and blood sampling throughout pregnancy (at recruitment, 20, 28 and 36 weeks of gestation) and blood plus placental sampling at birth. Serum and plasma will be used for analysis of biomarkers and some stored for future studies. The Primary study outcomes are pre-eclampsia, stillbirth, FGR, spontaneous preterm labour.

Data analysis

Analysis of the entire cohort will be done and logistic regression analyses will identify epidemiological, clinical, and laboratory parameters predictive of GOS. Associations will be estimated using risk ratios and 95% confidence intervals (CI). We will also focus on AI techniques to extract and calibrate features, variables and risk factors from the socio-epidemiological data to be collected. The data will then be used in training AI-based model(s) that integrate socio-demographic and clinical/pregnancy outcomes on the one hand, with outcomes on the other to simultaneously ascribe their dynamic effect sizes in varying circumstances.

Utility

This study will facilitate development of predictors of GOS and has potential to shed light on determinants, mechanisms and solutions for the excess burden of maternal and perinatal morbidity and mortality in SSA and for women with African ancestry elsewhere in the world. The biobank will provide an important resource for the future studies.

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Introduction

Background

Despite a significant global reduction in maternal and child deaths over the last decade, several key areas are still woefully neglected. The burden of maternal mortality remains unacceptably high in Sub Saharan Africa (SSA) where 66% of all global maternal deaths occur and the maternal mortality ratio is ~500/100,000 live births (Alkema et al., 2016). Over 80% of preterm births (~12 million) occur in SSA and Asia (Chawanpaiboon et al., 2019) and nearly 3 million neonatal deaths occur globally each year, accounting for more than half all under-five child mortality (Lawn et al., 2014). There is also a silent global epidemic of stillbirths with 2.6 million occurring every year (de Bernis et al., 2016). The risk of perinatal death is approximately 8 times higher in low-and-middle-income countries (LMIC), particularly those of SSA, than in high-income-countries (HIC) (Collaborators, 2017). The Great Obstetrical Syndromes (GOS) collectively are a major contributor to maternal and perinatal morbidity and mortality(Kramer, 2003). GOS are pregnancy disorders caused by defective placental development and include pre-eclampsia, fetal growth restriction (FGR), unexplained stillbirth and spontaneous preterm birth(Brosens, Pijnenborg, Vercruysse, & Romero, 2011). Due to this common mechanistic pathway, these disorders frequently co-exist: FGR is present in ~50% of stillbirths (Smith & Fretts, 2007) and commonly accompanies pre-eclampsia (Weiler, Tong, & Palmer, 2011). Placental maldevelopment in GOS leads to stress later in gestation resulting in a systemic imbalance of soluble fms-like tyrosine kinase 1 (sFLT-1) and Placental growth factor (PlGF). These are potential markers to predict, diagnose and follow disease in GOS (Goel & Rana, 2013; Hurrell et al., 2020).

Attempts to identify pregnant women at risk of these adverse outcomes have had little success (Alfirevic, Stampalija, & Medley, 2015). Those described have mainly been identified by opportunistic secondary analyses of data collected for other reasons (Smith et al., 2006). To address this challenge, prospective studies have been conducted mainly in HIC to develop better screening tests (Haas et al., 2016; Myers et al., 2013; Pasupathy et al., 2008). However, pregnancy cohort studies in HIC do not adequately represent the very different biological and socio-economic conditions found in SSA. There are some prospective cohorts in SSA to identify screening tests/predictors for adverse pregnancy outcomes but majority of these are ongoing in and others are inconclusive (Jeffrey N. Bone et al., 2020). The WHO Alliance for Maternal and Newborn Health Improvement (AMANHI) Study is a large cohort of over 10,000

pregnant women and their babies in SSA and South Asia aimed at studying the interactions between genes and a wide range of varying environmental exposures on key pregnancy and birth outcomes (WHO Alliance for Maternal and Newborn Health Improvement Late Pregnancy Dating Study Group, 2020). Prospective pregnancy cohorts in SSA will shed light on determinants, mechanisms and solutions for the excess burden of maternal and perinatal morbidity and mortality. Therefore, our aim is to investigate the clinical, biological and social antecedents of adverse pregnancy outcomes in prospective cohorts of Ugandan women, with a focus on the GOS.

Work which has led up to the project

As an academic obstetrician working at Makerere University, my main research interest has been the enigmatic disorder of pregnancy, pre-eclampsia, which is particularly common in African women (Nakimuli et al., 2013). For my Wellcome-funded PhD project, I undertook a genetic study of immune system genes: "*Killer Immunoglobulin-like receptor (KIR)* and *Human Leucocyte Antigen-C (HLA-C)*: a case-control study of pre-eclampsia". Participants were recruited in Mulago Hospital, the teaching hospital for Makerere University. This was the first genetic case-control study on pre-eclampsia among indigenous Africans despite African ancestry being a predisposing factor to pre-eclampsia (Nakimuli et al., 2015). This study revealed interesting genetic similarities but also differences from comparable studies performed in Europeans. A genetic region marked by the *KIR2DS5*006* gene was associated with protection against pre-eclampsia among Ugandan women; this region is unique to populations in SSA (Hollenbach, Nocedal, Ladner, Single, & Trachtenberg, 2012). Follow-up work has revealed that unique African KIR2DS5 allotypes act as activating receptors for the C2 HLA-C ligand that is expressed by the fetal placenta (Blokhuis et al., 2017). For my post-doctoral work, I recruited ~2000 more pre-eclampsia cases and similar control numbers to continue this genetic study in collaboration with scientists in Cambridge, Denver and Stanford. The analysis is currently ongoing and the genetic and clinical results will contribute to understanding the fundamental mechanisms that underpin pre-eclampsia. Importantly, this work has generated a valuable resource of DNA to study other genetic variants associated with pre-eclampsia in African women in the future.

Despite the insights provided by these studies, their retrospective nature means that there is limited potential to translate knowledge gained into clinically useful predictive tests. Through my ongoing Future Leaders–African Independent Research (FLAIR) fellowship,

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awarded by the Royal Society and African Academy of Sciences, I am beginning to address this challenge by prospectively collecting data and biological samples from a cohort of 1,500 pregnant women from early pregnancy at Kawempe Hospital. The main aim is to determine whether women who go on to experience pre-eclampsia can be identified early in pregnancy. My mentor on this project, Professor Gordon Smith, has successfully performed a similar study in Cambridge and I am aligning my protocols with his Pregnancy Outcome Prediction Study (POPS) (Pasupathy et al., 2008). This approach has the advantage of allowing direct comparisons between the two very different clinical settings and study populations.

Although the ongoing pregnancy cohort study has brought a new dimension to my research program, some challenges remain. Firstly, due to limited resources the study only focuses on pre-eclampsia and not the other GOS with which pre-eclampsia frequently coexists due to the common underlying aetiology of defective placentation (Smith & Fretts, 2007). Studying all these conditions together provides leverage in identifying the determinants, mechanisms and solutions for the excessive maternal and perinatal morbidity and mortality and stillbirths in SSA. Secondly, similar prospective pregnancy cohorts recruited in early pregnancy are rare in SSA despite the excessive maternal and neonatal morbidity and mortality here (J. N. Bone et al., 2020). Thirdly, this is a personal fellowship so opportunities for training and mentoring younger scientists are limited.

The proposed project will address these challenges by prospectively collecting data and biological samples from a larger cohort of pregnant women from early pregnancy at Kawempe and Mulago Hospitals. The aim is to determine whether women who go on to experience these complications (pre-eclampsia, stillbirth, FGR, preterm birth) can be identified early in pregnancy. The advantage of performing this study in these two hospitals is the large numbers of patients delivering there with severe complications (death, HELLP syndrome, eclampsia, peripartum cardiomyopathy, renal failure, intracranial haemorrhage, pulmonary oedema). We will also incorporate multidisciplinary training and mentoring opportunities as well as focussing on the regional and global partnerships we have already established in maternal and newborn health. An innovative aspect will be the use of artificial intelligence in data analysis. While genetic and obstetric/clinical factors can be bioinformatically and experimentally determined, socio-demographic factors are less tractable and may require elaborate data models to quantify. AI and machine learning techniques present a great opportunity to both identify and calibrate socio-demographic parameters important in the aetiology of GOS (Sufriyana, Wu, & Su, 2020). Using AI techniques, we will seek to calibrate the intersection between socio-epidemiological and clinical/biological predictors of GOS.

Our intermediate goal is to develop better methods of screening in SSA with the aim of targeting interventions for women at high risk of pre-eclampsia and other GOS. Characterising the diagnostic effectiveness of candidate screening tests is an essential prerequisite for a randomised clinical trial (RCT) of screening and intervention. Hence, we see the proposed study as an essential first step for our ultimate goal: to determine targets for therapeutic interventions (biological or sociodemographic) which we will then test with an RCT.

Statement of the problem

Pre-eclampsia, as well as other GOS, is a major cause of to maternal and perinatal morbidity and mortality, especially in SSA (Firoz, Sanghvi, Merialdi, & von Dadelszen, 2011; Nakimuli et al., 2014). The cause of the GOS is still unclear which makes prevention difficult and so mainstay of treatment is early diagnosis and management in order to minimize complications to the mother and her newborn. However, early diagnosis and treatment is difficult in SSA partly because of late presentation and health system inadequacies which cause delay in provision of treatment. There is therefore need to identify women at high risk of developing the GOS so that these are prioritized for close follow up in the antenatal clinic and in labour in order to improve outcomes for both mother and baby.

Most studies conducted in sub-Saharan Africa (SSA) to investigate the risk of adverse pregnancy outcomes have been case-control in nature. There are very few cohorts recruited from early in pregnancy in a SSA population, who are most at risk of maternal and newborn mortality and severe morbidity. Despite the insights provided by case-control studies, these fail to provide insights into events and biomarkers present in early pregnancy that determine and predict GOS– when preventive interventions could best be implemented. To address this challenge, prospective studies have been conducted in HIC to develop screening tests that perform better (Haas et al., 2016; Pasupathy et al., 2008). However, pregnancy cohort studies in HIC do not adequately represent biological and socio-economic conditions found in SSA.

Therefore, in this project I aim to investigate the clinical, biological and social antecedents of pre-eclampsia and other GOS in a prospective cohort of Ugandan women. Data generated from this prospective pregnancy cohort in SSA would have the potential to shed light on determinants, mechanisms and solutions for the excess burden of maternal and perinatal morbidity and mortality in the region.

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Research Questions

1. What exposures (epidemiological, social, demographic, clinical, laboratory) linked to the different adverse pregnancy outcomes - pre-eclampsia, stillbirth, preterm birth and fetal growth restriction?
2. What is the positive predictive value of screening using biomarkers (soluble Flt-1 and placental growth factor) and serial ultrasound for the different adverse pregnancy outcomes in (1)?
3. What is the intersection between socio-epidemiological, clinical and laboratory parameters of the GOS using artificial intelligence?

General aim of the research

To enhance prediction of adverse pregnancy outcomes in Africa through partnerships and innovation

Specific objectives

1. To determine the exposures (epidemiological, social, demographic, clinical, laboratory) linked to the different outcomes - pre-eclampsia, stillbirth, preterm birth and fetal growth restriction.
2. To determine the positive predictive value of screening using biomarkers (soluble Flt-1 and placental growth factor) and serial ultrasound for the different adverse pregnancy outcomes in (1) above.
3. To generate a resource of data and biological samples to facilitate hypothesis driven and discovery based approaches to identifying novel predictors and/or mechanisms of pre-eclampsia and the other GOS.
4. Calibrate the intersection between socio-epidemiological, clinical and laboratory parameters of the GOS using artificial intelligence.

Significance of the Study and impact

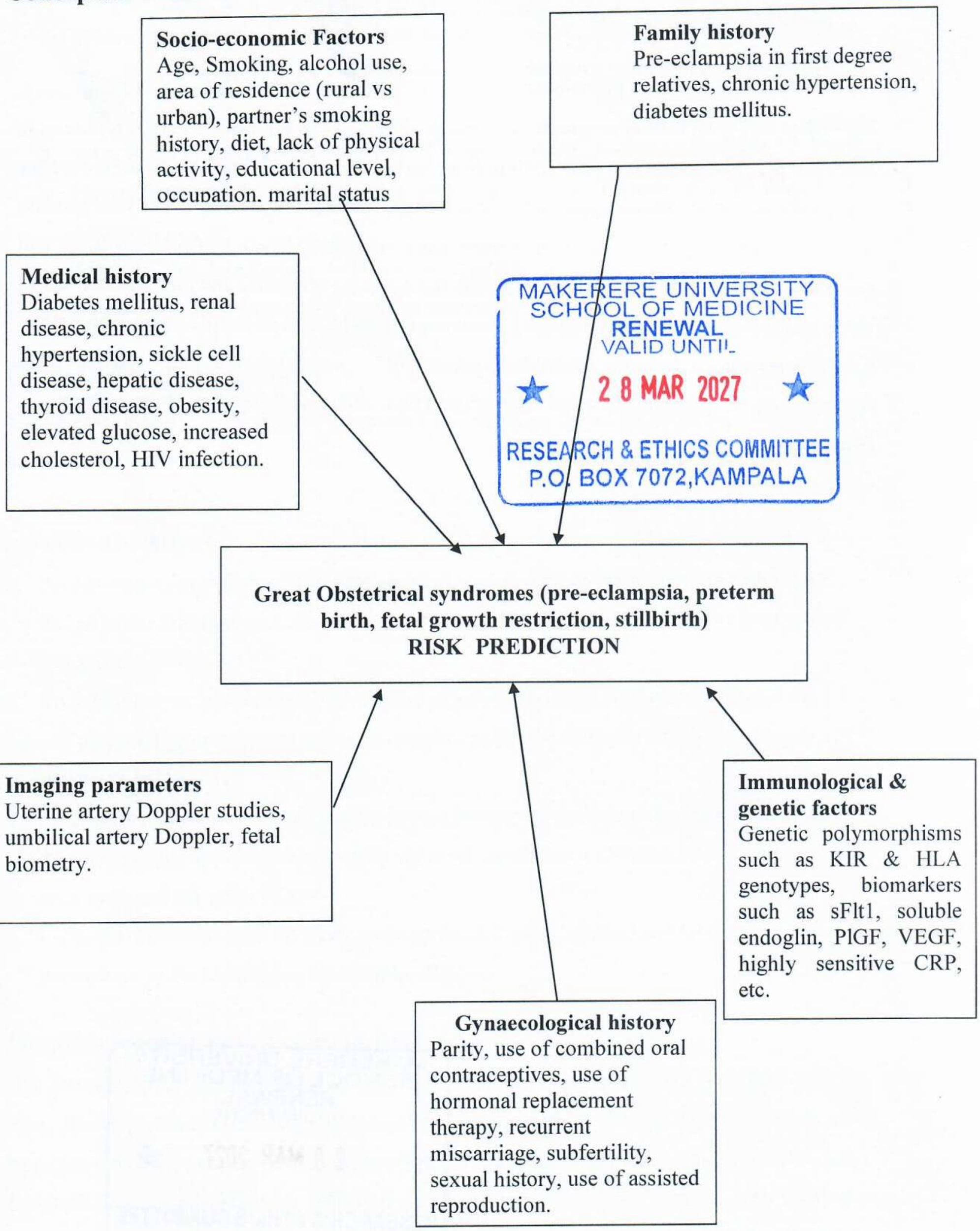
We will update the clinical-epidemiological risk factors for pre-eclampsia and other GOS in SSA, allowing women at risk to be selected for close pre-natal follow up. The biomarkers will be translated into point of care diagnostics. The high numbers of pathological pregnancies will facilitate rapid development of high-performance algorithms (based on clinical-epidemiological risk factors) and tests (based on biomarker identification and validation) through RCTs of screening/interventions. Importantly, although the performance of tests will

be context-specific to SSA, the results will inform approaches for HIC. Indeed, our clinical setting allows study of adverse pregnancy outcomes that are rare in HIC and yet of global health importance, such as stillbirth and complications of severe pre-eclampsia. Indeed, these occur more commonly in women with recent African ancestry in USA and elsewhere.

This study will establish a much-needed resource describing in detail, from early pregnancy, the course and outcomes of pregnancy in women of SSA. We are aware of very few studies in SSA that provide meticulous phenotyping from early pregnancy to term. To achieve this, our study will use serial ultrasonography to allow accurate dating and assessment of fetal growth, complemented by rigorous collection of biochemical and clinical data. Biological samples will provide a resource to identify African-specific mechanisms of disease and may identify useful novel biomarkers for adverse pregnancy outcomes caused by underlying placental dysfunction. Longer-term studies from the established cohort will be planned for the future such as those for predictors of future health of the mothers and their offspring following adverse pregnancy outcomes.

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Conceptual frame work



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The conceptual framework for the study

Narrative for conceptual framework

GOS are pregnancy disorders caused by defective placental development and include pre-eclampsia, fetal growth restriction (FGR), unexplained stillbirth and spontaneous preterm birth(Brosens et al., 2011). Due to this common mechanistic pathway, potential predictors for these disorders can be commonly investigated. In this conceptual framework, maternal factors (socio-economic, family history, medical history, gynaecological history, immunological and genetic factors) may lead to defective placentation. Placental maldevelopment in GOS leads to stress later in gestation resulting in a systemic imbalance of biomarkers like soluble fms-like tyrosine kinase 1 (sFLT-1) and Placental growth factor (PlGF). These are potential markers to predict, diagnose and follow disease in GOS (Goel & Rana, 2013; Hurrell et al., 2020). Also noteworthy, is that defective placentation may impede blood flow in the uterine arteries and this makes ultrasound Doppler studies potentially useful as predictors of GOS.

The scope of these study will include investigating the predictive ability for GOS of all the socio-factors shown in the conceptual frame work, except the genetic variants. Soluble fms-like tyrosine kinase 1 (sFLT-1) and Placental growth factor (PlGF) will be the only serum biomarkers investigated but others will be assessed in future studies when more resources are acquired and stored samples will be utilized for this.

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Research design and methods

Study setting

The study will be conducted at Kawempe National Referral Hospital (KNRH) and Mulago Specialised Women and Neonatal Hospital (MSWNH), some of the main teaching hospitals for Makerere University. The two hospitals are located in Kawempe Division of Kampala district and together have over 28,000 deliveries a year (60-100 deliveries per day). KNRH offers outpatient antenatal care services from Tuesday to Thursday to women with both high risk and low risk pregnancies. On average 200 women are seen per antenatal clinic day and of these 100 women are first-time attendees and ~50% of women present at a gestational age of less than 18 weeks. Approximately 25 nulliparous women attend the clinic in the first trimester on an antenatal clinic day. MSWNH offers outpatient antenatal care services from Monday to Friday to women with both high risk and low risk pregnancies. On average 50 women are seen per antenatal clinic day and of these 30 women are first-time attendees and ~50% of women present at a gestational age of less than 18 weeks. Approximately 10 nulliparous women attend the clinic in the first trimester on an antenatal clinic day. This setting allows getting sufficient numbers of pre-eclampsia adverse outcomes that are rare in HIC, including eclampsia and stillbirth.

At both hospitals, all women found to have hypertension are sent to the labour ward for further care which may include delivery. After delivery all women, including normotensives, are admitted to the postnatal ward from where they are subsequently discharged. Upon discharge women are advised to return to the postnatal clinic at 6 weeks or earlier in case of any concerns or complications. Women who have had complications such as pre-eclampsia, postpartum haemorrhage and obstructed labour are usually advised to return to the postnatal clinic after a week. Most of the services at the KNRH are free but some of the paid for services are ultrasound scan, CT scan and X-ray. Most of the services at the MSWNH are paid including ultrasound scan, but for the study related procedures these costs will be incurred by the project.

The research tests (biomarkers) will be done at the Translational Lab at Mulago (which is a collaboration between the Department of Obstetrics and Gynaecology and Infectious Diseases Institute). The baseline (routine) lab tests will be carried out by a commercial lab that will be selected through the Makerere University procurement process.

Study design:

This will be a prospective cohort study.

Study endpoints

The study outcomes are:

Primary: pre-eclampsia, stillbirth, FGR, spontaneous preterm labour

Secondary: Conditions associated with severe pre-eclampsia: eclampsia, HELLP syndrome, renal failure, pulmonary edema, intracranial haemorrhage, peripartum cardiomyopathy, maternal death, neonatal death prior to discharge, postpartum haemorrhage.

Case definition for pre-eclampsia

This will be according to the international definition (Cunningham et al., 2005).

1. New onset hypertension of 140/90 mmHg or more, on more than one occasion at least 4 hours apart
2. At 20 weeks of gestation or more assessed by ultrasound scan
3. Proteinuria of +1 or more by dipstick on at least one occasion

Case definition for spontaneous preterm labour

This will be according to the international definition (Cunningham et al., 2005).

Preterm labour will be defined as labor or delivery that occurs before 37 completed weeks of gestation but after viability (28 weeks of gestation for our study). Spontaneous preterm labour will refer to preterm labour which is not induced due to medical indications or otherwise.

Case definition for fetal growth restriction (FGR)

This will be according to the international definition (Cunningham et al., 2005).

FGR will be defined as babies with birthweights less than the 10th percentile for gestational age.

Case definition for stillbirth

A stillbirth is the death or loss of a baby before or during delivery.

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Sample size determination

This will be a prospective cohort study conducted at Mulago and Kawempe Hospitals, with >25,000 deliveries/year. Daily antenatal clinics see ~150 new patients/day allowing recruitment of significant numbers of severe GOS outcomes rare in HIC, including eclampsia, cardiomyopathy and stillbirth. The study is strategically designed as a prospective cohort providing opportunities to investigate multiple potential exposures and outcomes. A sample size of 4,000 gives sufficiently precise confidence intervals for all adverse events up to an incidence of 0.1%.

Table 1 – Pilot Data from PROGRESS study (unpublished) – Prevalence of outcomes in a cohort of women recruited at delivery in Kawempe Hospital

		Number	%
Outcomes	Premature Birth/ Livebirths	363/4142	8.8
	Stillbirth / Total Births	27/4169	0.6
	Low birthweight / Total Births	437/4169	10.5
	Early neonatal death (in labour room) / Livebirths	41/4142	0.98
	Maternal deaths between birth and 3 months post-partum	7/4169	0.17

Table 1 is an estimate of the proportion of women and infants experiencing key adverse outcomes at Kawempe Hospital. These have been used to inform sample size calculations for the cohort study. For a rare outcome such as stillbirth that is estimated to affect 0.6% of births, it will be possible to achieve acceptably narrow confidence intervals around point estimates with a sample size of 4000 mother-infant dyads (see Table 2).

Table 2 – Confidence intervals around point estimates based on a sample size of 4,000

Proportion affected by the outcome	Lower Limit of the 95% CI	Upper Limit of the 95% CI
0.1%	0.03	0.26
1%	0.72	1.36
2%	1.59	2.48
3%	2.49	3.58
4%	3.41	4.65
5%	4.35	5.72
10%	9.09	10.97
15%	13.91	16.14

Based on analysis of electronic medical records (EMR) data over a 12 month period, the numbers of subjects with the outcomes of interest (based on estimates from PROGRESS study

in Table 1 and Table 3; 21,000 deliveries/year at Kawempe Hospital (unpublished denominator data from PREPARE study).

Table 3 – Estimated subjects with outcomes of interest based on pilot data of the PREPARE Cohort at Kawempe Hospital.

Outcomes	Premature Birth	8.8%	1848
	Stillbirth	0.6%	126
	Neonatal death (in labour room)	0.98%	206
	Maternal deaths between birth and 3 months post-partum	0.17%	36
	Hypertensive Disorders of Pregnancy	5%	1050

Study participants

Study population

Nulliparous pregnant women attending the antenatal clinics at Kawempe and Mulago Hospitals.

Selection criteria for study participants

(a) Inclusion criteria

i. Viable singleton pregnancy at the time of the dating ultrasound scan
ii. At less than 18 weeks of gestation by ultrasound scan
iii. Nulliparous
iv. Women who are indigenous Africans (defined as Black Africans born in Africa, whose parents were also Black Africans born in Africa);
v. Those 18 years and above
vi. Consent to participate in the study by the participant

(b) Exclusion criteria

i. Those who reside more 30km than from Kawempe Hospital or Mulago Hospital

Note: To maximise the generalisability of the findings, no other exclusions will be applied. For example, we will not exclude women with pre-existing medical conditions (e.g. sickle cell anaemia, HIV, diabetes). Hence, the sample will be unselected rather than low risk.

Sampling procedure and data collection:

All women identified as nulliparous from the antenatal register or antenatal charts will be approached and then screened for eligibility using a checklist. Recruitment into the study will

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take place 5 days a week and study participants will be consecutively recruited. Specifically, participation in the study will involve the following:

1. The screening for potential study participants will be done by my research assistants and for those willing to participate in the study an obstetric ultrasound scan will be performed to determine the gestational age of the pregnancy and the viability of the fetus. To be eligible the gestational age should be below18 weeks and the fetus has to be alive. It is feasible to recruit 30 participants per week.
2. Information about the study will be given to all eligible participants and those who agree to participate will sign a consent form. After obtaining written informed consent a study number will be allocated to the enrolled participant and then demographic data (age, marital status, religion, your ethnicity and that of your parents, the ethnicity of your spouse and his parents, address, and educational level) and clinical history will be collected using an interviewer-administered questionnaire. In addition, a physical examination will be performed on the participants and also recorded in the questionnaire. Data will be entered electronically.
3. At enrolment 15ml of blood will be taken from the participant. Seven (7) mls will be used to carry out tests that should be routinely done for all pregnant women and these include; complete blood count, renal function tests, liver function tests, malaria, HIV test and syphilis test. Eight (8) mls will be used to test for biomarkers (soluble Flt-1 and PlGF). In addition, 10 mls of urine will be taken for proteins, cells, casts and glucose.
4. We plan to follow up participants at three time points in pregnancy (at 20, 28 and 36 weeks of gestation) and at the time of delivery. The visit windows are as follows (in weeks); 20 (19-22), 28 (26-30) and 36 (34-38). We shall try to make these visits to coincide with regular antenatal care visits for participant's convenience. Participants will still be expected to attend any other visits scheduled by the hospital team that cares for them, outside the research related visits.
5. At each antenatal follow up visit, more clinical information and a physical examination will be performed (in particular blood pressure and urine protein measurement). Participants will also have further scans and blood sample collection of 10 mls which will be used to get serum and plasma to be used for analysis of biomarkers (soluble Flt-1 and PlGF) that predict pre-eclampsia. At the 20 weeks visit an additional 3mls of blood will be taken off and stored for DNA extraction in future. Separate consent will be sought for storage of this whole blood and the remaining serum and plasma (after the initial analysis), such that it can be used for future studies. For example, plasma

can be subsequently processed for the analysis of micro particles, cell free DNA and cell free RNA.

6. The scan at 20 weeks will take place as normally and is routinely done to assess the fetal anatomy. Any findings from that scan will result in the same care as for non-study participants. We will obtain some further measurements at the time of the scan (fetal biometry, Doppler flow velocimetry and amniotic fluid volume) but this will not affect the participants' care.
7. Participants will have research scans at 28 and 36 weeks. These scans are not normally part of routine care. We will mask the results of scan measurements (fetal biometry, Doppler flow velocimetry and amniotic fluid volume) to clinicians and participants. Masking is justified as there is no evidence, even in high income settings, that revealing these results from non-clinically indicated scans is effective in reducing the risk of perinatal complications. However, we will reveal five scan diagnoses which will lead directly to changes in clinical management: (1) placenta praevia, (2) fetal anomaly, (3) severe oligohydramnios and (4) breech presentation at 36 weeks and (5) intrauterine fetal death (IUFD). In case of fetal anomaly or IUFD, the standard of care will be followed in delivering the news and managing the patient thereafter. This requires that the team of doctors and midwives managing the patient delivers the news and then offer counseling thereafter. In case of congenital anomalies that are not compatible with extrauterine life (eg anencephaly), the mother will be advised about termination of the pregnancy. Otherwise, she is counselled to carry the pregnancy till delivery. In situations of these adverse outcomes our research team will work with the hospital team to beef up the ongoing counseling to the patient.
8. At delivery, research midwives will record details of labour, delivery and pregnancy outcome including data on duration of labour, mode of delivery and intrapartum complications. Routine data from the baby (weight, sex, Apgar score) will also be collected. They will take samples of the umbilical cord for DNA (a 2cm piece), 10mls of maternal blood for serum and plasma samples for a viral screen and samples of the placenta to make formalin-fixed blocks for histology of placentas and membranes. 10 mls of cord blood will be taken for isolation of serum. All samples taken off at the time of delivery will be used for future studies and additional consent will be sought from participants.
9. Study participants and their babies will be reviewed 6 weeks after delivery as a routine and not for research purposes.

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There will be training on the study processes and measurements before the study begins and then monthly for the first 3 months and on quarterly basis thereafter. All devices will be calibrated and maintained as per local/manufacturers' requirements before the study begins and during the course of the study. To ensure reliability of measurements, clearly written down standard operating procedures (SOPs) will be developed. The SOPs will be signed off before the first participant is recruited. In case any abnormality is detected in the blood and urine tests during any of the study visits, participants will be referred for appropriate care.

To minimise loss to follow-up for study participants, we shall mainly rely on regular phone calls to the participants.

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Study Flow chart

Women eligible to participate in study: N=4,000

Recruitment : at 18 weeks gestation or less
-Conducted at the time of dating scan
-Informed written consent
-History & demographic data
-Samples: blood (infections, biomarkers, renal & liver function tests, complete blood count), urine (proteins, cells, casts)

Study visit 1: at 20 weeks gestation
- Ultrasound (uterine & umbilical artery, fetal biometry, cervical length)
- Fill questionnaire
- Samples: blood (biomarkers, serum, plasma), urine (proteins)

Study visit 2: at 28 weeks gestation
- Ultrasound (uterine & umbilical artery, fetal biometry, cervical length)
- Fill questionnaire
- Samples: blood (biomarkers, serum, plasma), urine (proteins)

Study visit 3: at 36 weeks gestation
- Ultrasound (uterine & umbilical artery, fetal biometry)
- Fill questionnaire
- Samples: blood (biomarkers, serum, plasma), urine (proteins)

Study visit 4: at delivery
- Collect baby's details & other outcome data
-Placental sampling
-Other samples for future studies: umbilical cord for DNA, cord blood (serum)

Routine visit at six weeks after delivery
- Assess mother's condition
-Assess baby's condition
-Routine Samples: urine (proteins)

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Ethical considerations:

Before the start of the research project, approval to conduct the study will be sought from the School of Medicine Research and Ethics Committee at Makerere University and finally the Uganda National Council for Science and Technology (UNCST). Permission to conduct the study will be sought from management of Kawempe National Referral Hospital and Mulago Specialized Women and Neonatal Hospital. The participants will give written informed consent to participate in the study. Participants will give additional written informed consent to sample storage for future studies and for re-contact during future studies. We shall ask for participants' mobile phone numbers and those of their next of kin or friend and this is for purposes of easily contacting them in case there is need. These phone contacts will be only known to the researchers closely working on this study. Women diagnosed with pre-eclampsia or any other pregnancy complication will be managed according to the Kawempe and Mulago Hospital protocols.

Consent forms will be securely kept by the PI and separate from the data collection tools. Withdrawal from the study will not jeopardize health care and this will be provided free to all women. Participants will receive 8.33 USD (30,000 Ug Shs) as a modest transport refund at each follow up visit and 1.375 USD (5,000 Ug Shs) as compensation for their time at each follow-up visit. The compensation will be in kind as refreshments for participants.

Reporting of adverse events and disease related events

When a maternal death occurs in the study it will be considered as a serious adverse event (SAE) and will be reported to the School of Medicine IRB within 7 days as is stipulated in the guidelines. The IRB form for recording, evaluating, and assessing causality of SAEs is provided in the appendices.

Data management

Data will be entered electronically by the research assistants using tablets. Data cleaning will be carried out by the PI assisted by the study coordinator. The cleaned soft data will then be duplicated and stored in safe custody while the duplicate copy will be used for further analysis using STATA software and R. A confidential register of the details for each participant will be made, only accessible to the research assistants and the PI. It is only the study numbers that will appear on the participants' study documents except the consent forms. Consent forms will be securely kept by the PI and separate from the other data collection tools.

Data analysis:

The use of a prospective cohort study design allows multiple subsequent analytic approaches. The three main methods of analysis will be (1) **analysis of the entire cohort**, (2) **analysis as case cohort studies**, (3) **analysis as nested case control studies**. As examples, for exposures (objective 1) or biomarkers/ultrasound findings (objective 2) available for all participants, analysis of the entire cohort will be used and logistic regression analyses will identify epidemiological, clinical, and laboratory parameters predictive of pre-eclampsia or other GOS. Associations will be estimated using risk ratios and 95% confidence intervals (CI).

In a case cohort design, all women experiencing the outcome of interest will be identified and a random sample of the cohort also obtained (Sharp, Poulaliou, Thompson, White, & Wood, 2014). All women who develop pre-eclampsia or any GOS will be compared to a random sample of the cohort who will have not developed that outcome of interest by the time of delivery. We shall assess the relationship between the sFLT1:PlGF ratio with and without serial ultrasound data, and the risk of GOS. Analysis will be performed using logistic regression as for objective 1, but the data from the comparison group will be statistically weighted by the inverse of the sampling fraction to allow calculation of screening statistics, such as positive predictive value, sensitivity and specificity.

The nested case control approach will be used where assays are expensive or laborious, such as in studies comparing the placenta in cases of stillbirth, and when using DNA sequencing-based approaches to detect pathogens (viral, bacterial or eukaryotic).

We will focus on AI techniques to extract and calibrate features, variables and risk factors from the socio-epidemiological data to be collected [5]. The data will then be used in training AI-based model(s) that integrate socio-demographic and clinical/pregnancy outcomes on the one hand, with GOS outcomes on the other to simultaneously ascribe their dynamic effect sizes in varying circumstances. That calibration could inform early interventions through helping optimize service delivery models to improve the prevention, tracking, management and treatment of women with GOS. This would not only help quantify the relative contributions of biological versus socio-demographic factors to GOS but also bolster the implementation of the problematic last mile in the mitigation of the GOS.

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Quality control

Given the extensive experience of the PI in such studies, she will train and supervise the research assistants (midwives and lab technicians) to make sure that the study samples are collected within the stipulated time as indicated in the proposal. Standard operating procedures will be developed (SOPs) for the processes involved in the study such as blood pressure measurement, drawing of blood, placental sampling. Only accredited laboratories will be used to perform the desired tests.

Dissemination plan

At the end of the study, a report will be compiled and sent to Kawempe Hospital, Mulago Hospital, Ministry of Health, SOMREC, UNCST and the Bill & Melinda Gates Foundation. Manuscripts will be prepared and submitted to journals for peer review and publication. This work will also be presented in national and international meetings.

Summary of milestones/time scales

Ethical approvals are expected to take 3 months and research site preparations 2 months. Recruitment and follow up of participants will take 3 years and there will be 1 extra year of only follow up of the participants. Writing of manuscripts will start in the fourth year of the fellowship. The final project report will be written at the end of the fellowship.



Time frames and mile stones

	Months 1 - 6	Months 7 - 12	Months 13 - 24	Months 25 - 36	Months 37 - 48	Months 49 - 60
Obtaining research and ethics approval from the research and ethics committees (School of Medicine and Uganda National Council for Science & Technology)						
Research site preparations: procurement of supplies and services; training research assistants in the study protocols, standard operating procedures and Good clinical practices (GCP)						
Recruitment of healthy pregnant women (participants) into the study between 12 -18 weeks of gestation						
Follow-up of study participants (20 weeks, 28 weeks, 36 weeks and at delivery)						
Attend short courses						
Data analysis and writing manuscripts						
Writing up additonal grants						
Writing final project report						

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Budget Estimates for the 5 years

Is attached as an appendix.

Budget justification

All currency listed is in US Dollars.

Personnel

Annettee Nakimuli (PI): will have primary responsibility for the overall conduct of the project. She will work with the study coordinator to perform all preliminary steps before recruitment of participants starts: seeking research approvals, procurement of supplies and services and developing standard operating procedures (SOPs). All other research staff will commence work 2 weeks before recruitment to allow for training in relevant protocols and SOPs and until all participants have been followed up (3 years).
She will commit 6 calendar months (50% FTE) to this project each year translating into $132,000 for the five-year project period.

7 part-time (PT) midwives/nurses: will be recruit participants, document clinical data on the tablets, sample participants, schedule appointments and collect outcome data at delivery.
They will commit 6 calendar months (50% FTE) to this project for year 1, year 2 and year 3 translating into $ 118,800 for the five-year project period.

2 sonographers: will perform the obstetric scans at 12, 20, 28 and 36 weeks of gestation (WGA).
They will commit 6 calendar months (50% FTE) to this project for year 1, year 2 and year 3 translating into $ 39,600 for the five-year project period.

1 PT lab technologist: will perform all the laboratory work and I will occasionally assist him/her. They will perform the biomarker assays (PlGF and sFLT), separate the cells from cord blood, arrange samples in the lab freezer, transport samples to the biorepository and plan lab procurements.
S/he will commit 5.4 calendar months (45% FTE) to this project for year 1, year 2 and year 3 translating into $ 21,384 for the five-year project period.

1 data manager: will manage the databases and sample archives.
S/he will commit 3.6 calendar months (30% FTE) to this project for year 1, year 2 and year 3 translating into $8,910 for the five-year project period.

Tayebwa Mordecai: will be the Grants Manager. He will assist in the monitoring of expenditure, managing records and receipts and reconciling daily, monthly and yearly transactions and processing invoices.

He will commit 2.4 calendar months (20% FTE) to this project each year, translating into $33,000 for the five-year project period.

Study Coordinator: will be responsible for the day to day running of the program to ensure smooth project implementation.
S/he will commit 12 calendar months (100% FTE) to this project each year, translating into $99,000 for the five-year project period.

Travel

Domestic travel: An estimated total cost of $7,200 for the five-year period is requested to cover local travel fuel contribution that will be used to carry out project activities such as transportation of samples from hospitals to the laboratories. A total of $1200 will be used in year 1, $2,400 in year 2, $1200 in year 3, $1200 in year 4 and $1200 in year 5.

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International Travel:

A forecasted total of $12,000 for the five-year period is requested to cover travel costs (air tickets, perdiem and accommodation) of the Principal Investigator to attend international conferences to disseminate study findings and also develop networks. She will spend up to one week every time she travels. An estimated total of $4,000 each year for year 3, 4 and 5 will be used.

Materials and consumables

General consumables (gloves, needles & syringes, etc.). A total of $8,000 over the entire project period is requested to cover general consumable costs at $2,000 once a year for years 1,2 and 3. These will be used to sample 4000 participants at 5 time points (12, 20, 28 and 36 WGA) and at birth). Each participant will require $2 to purchase the consumables needed.

Specimen containers (blood, urine, swabs). A total of $32,000 over the entire project period is requested to cover specimen container costs at $8,000 once a year for years 1,2 and 3. These will be used to collect and store samples from 4,000 participants at the 5 time-points. We anticipate a total of 80,000 samples (20 per participant for 4,000 participants). Each sampling time point will generate 4 samples (whole blood, serum, plasma, urine) and at birth (cord blood, placenta, swabs), hence we have quoted 8USD to purchase all the containers needed for 1 participant during 5 time-points.

ELISA kits for PlGF and S-FLt1 assays for 1000 participants; 200 pre-eclampsia, 200 FGR and 600 controls. We shall use the case-cohort design for this analysis and estimate 5% of the population (200) will develop pre-eclampsia and another 5% FGR (200). We shall select 600 common controls. The ELISAs will be performed at 5 time points (12, 20, 28 and 36 WGA and at birth). We have quoted $42 to purchase all the ELISAs required for 1 participant. A total of $42,000 over the entire project period is requested to cover specimen container costs at $14,000 once a year for years 1,2 and 3

Outsourcing: We shall outsource services for routine baseline tests to be performed recruitment (urine protein, complete blood count, syphilis, malaria). Each of the 4000 participants will need $15 to have these tests done. HIV tests are free. We therefore budgeted a total of $20,000 per year (once a year) for year 1,2 and 3 translating into $60,000 for the entire-year project period.

Consumables to process blood samples from 4,000 participants at 5 time-points (12, 20, 28 and 36 WGA, at birth). The blood will be separated into serum and plasma. Each of the 4000 participants will need approximately $10.78 for the consumables. We therefore budgeted a total of $14,375 for years 1,2 and 3 translating into $43,125 for the entire project period.

Consumables to process cord blood and placentae from 4,000 participants at delivery. The cord blood will be separated into serum and plasma. One sample of the placenta will be fixed with formalin and another put in RNA later. Each of the 4000 participants will need $2.4 for the consumables. We therefore budgeted a total of $3,200 per year (once a year) for year 1,2 and 3 translating into $9,600 for the entire project period.

Other Direct Costs.

Ultrasound Machine Maintenance Costs: We will perform serial ultrasound scans at 4 time-points (12, 20, 28 and 36 weeks of gestation). Over the past 3 years the hospitals have bought state-of-the-art ultrasound machines, one of which can be used for the project. We shall however need to contribute towards maintenance costs and consumables used. Hence, we budgeted a total of $4,000 per year (once a year) for year 1,2,3 and 4 translating into $16,000 for the 5-year project period.

Office Supplies and Small Consumables
2 laptops for PI and data manager for an estimated total cost of $3,000 at $1,500 each is requested for project work.

The project will also purchase 8 tablets to enter participants' electronic data and this are estimated at $350 per tablet totaling to $2800.

2 filing cabinets will be purchased for storage of records eg consent forms at $201 each totaling to $402 to be added to the 2 that we already have.

2 barcode printer for printing sample labels and 2 barcode scanners for scanning barcodes on samples will be purchased at $200 per barcode printer and $100 per barcode scanner totaling to $400 and $200 respectively. Labels will be purchased under general consumables.

Office Stationery: An estimated total of $6,900 is requested to cater for costs of office stationery to enable administrative work on the project over the 5 project year period.
This will be at a rate of $150 10 times in year 1,2 and 3 and $150 8 times in year 4 and 5.

Participant reimbursement costs
Time compensation & refreshments for study participants as required by the IRB (4 visits for 4000 participants) and for each participant $1.375 per visit. The total for 16,000 person-visits will be $22,000.

Transport refund for study participants as required by the IRB (3 visits for 4000 participants) and for each participant approximately $8.33 per visit. The total for 12,000 person-visits will be $100,000. No refund for recruitment and delivery contacts.

Miscellaneous (Other)
We estimate to store complete number of samples for 3000 participants in the biorepository. Each participant will generate 16 samples for storage (1 whole blood, 5 serum, 5 plasma, 1 placenta sample, 1 cord, 1 serum for cord blood, 2 swabs). So we anticipate a total of 48,000 samples. hence, we have quoted $24,000 to store these samples during the project duration and for another 2 years after the project. This cost is highly subsidized by the Biorepository for faculty like PI.
Institutional ethics committees reviews fees (initial & continuation): A total of $950 over five years is requested to cover the fees for the ethical approval from different government bodies: Uganda National council for Science and technology and Makerere Ethics Committee.

Statistical support: An estimated total of $2000 is requested for database design and analysis over the 5-year project period.

Meetings: An estimated total of $2000 at $1000 for year 1 and year 2 is requested to cater for Protocol training meetings, monthly and dissemination meeting costs.
Public engagement meetings with the communities around Mulago and Kawempe Hospitals will be organised once a year at a rate of $1000 for each meeting every year for the 5-year project period.
Internet and communication costs: Airtime for mobile phones is needed to be able to call back study participants and for communication among study staff at a rate of 2400 for year1,4 and 5 and $2000 for 10 months in year 2 and 3.
Dissemination and Publications: An estimated total of $6,000 is requested to cover costs for dissemination and costs to publish the results of the study in peer review journals in year 4 and 5 at a rate of $3000 per year.

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References

Alfirevic, Z., Stampalija, T., & Medley, N. (2015). Fetal and umbilical Doppler ultrasound in normal pregnancy. *Cochrane Database Syst Rev*(4), CD001450. doi:10.1002/14651858.CD001450.pub4

Alkema, L., Chou, D., Hogan, D., Zhang, S., Moller, A. B., Gemmill, A., . . . technical advisory, g. (2016). Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. *Lancet, 387*(10017), 462-474. doi:10.1016/S0140-6736(15)00838-7

Blokhuis, J. H., Hilton, H. G., Guethlein, L. A., Norman, P. J., Nemat-Gorgani, N., Nakimuli, A., . . . Parham, P. (2017). KIR2DS5 allotypes that recognize the C2 epitope of HLA-C are common among Africans and absent from Europeans. *Immun Inflamm Dis, 5*(4), 461-468. doi:10.1002/iid3.178

Bone, J. N., Pickerill, K., Woo Kinshella, M.-L., Vidler, M., Craik, R., Poston, L., . . . Network, P. (2020). Pregnancy cohorts and biobanking in sub-Saharan Africa: a systematic review. *BMJ Glob Health, 5*(11), e003716. doi:10.1136/bmjgh-2020-003716

Bone, J. N., Pickerill, K., Woo Kinshella, M. L., Vidler, M., Craik, R., Poston, L., . . . Magee, L. A. (2020). Pregnancy cohorts and biobanking in sub-Saharan Africa: a systematic review. *BMJ Glob Health, 5*(11). doi:10.1136/bmjgh-2020-003716

Brosens, I., Pijnenborg, R., Vercruysse, L., & Romero, R. (2011). The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. *Am J Obstet Gynecol, 204*(3), 193-201. doi:S0002-9378(10)00998-1 [pii]
10.1016/j.ajog.2010.08.009

Chawanpaiboon, S., Vogel, J. P., Moller, A. B., Lumbiganon, P., Petzold, M., Hogan, D., . . . Gülmezoglu, A. M. (2019). Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health, 7*(1), e37-e46. doi:10.1016/s2214-109x(18)30451-0

Collaborators, G. B. D. M. (2017). Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet, 390*(10100), 1084-1150. doi:10.1016/S0140-6736(17)31833-0

Cunningham, F. G., Leveno, K. J., Bloom, S. L., Hauth, J. C., Gilstrap, L., & Wenstron, K. D. (2005). Hypertensive disorders in pregnancy
In F. G. Cunningham, K. J. Leveno, S. L. Bloom, J. C. Hauth, L. Gilstrap, & K. D. Wenstron (Eds.), *Williams OBSTETRICS*
(22nd ed., pp. 761-798): Mc Graw Hill.

de Bernis, L., Kinney, M. V., Stones, W., Ten Hoope-Bender, P., Vivio, D., Leisher, S. H., . . . Lancet Ending Preventable Stillbirths Series Advisory, G. (2016). Stillbirths: ending preventable deaths by 2030. *Lancet, 387*(10019), 703-716. doi:10.1016/S0140-6736(15)00954-X

Firoz, T., Sanghvi, H., Merialdi, M., & von Dadelszen, P. (2011). Pre-eclampsia in low and middle income countries. *Best Pract Res Clin Obstet Gynaecol, 25*(4), 537-548. doi:10.1016/j.bpobgyn.2011.04.002

Goel, A., & Rana, S. (2013). Angiogenic factors in preeclampsia: potential for diagnosis and treatment. *Curr Opin Nephrol Hypertens, 22*(6), 643-650. doi:10.1097/MNH.0b013e328365ad98

Haas, D. M., Ehrenthal, D. B., Koch, M. A., Catov, J. M., Barnes, S. E., Facco, F., . . . Burwen, D. R. (2016). Pregnancy as a Window to Future Cardiovascular Health:

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28 MAR 2027
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Design and Implementation of the nuMoM2b Heart Health Study. *Am J Epidemiol, 183*(6), 519-530. doi:10.1093/aje/kwv309

Hollenbach, J. A., Nocedal, I., Ladner, M. B., Single, R. M., & Trachtenberg, E. A. (2012). Killer cell immunoglobulin-like receptor (KIR) gene content variation in the HGDP-CEPH populations. *Immunogenetics, 64*(10), 719-737. doi:10.1007/s00251-012-0629-x

Hurrell, A., Beardmore-Gray, A., Duhig, K., Webster, L., Chappell, L., & Shennan, A. (2020). Placental Growth Factor in Suspected Preterm Pre-eclampsia: A Review of the Evidence and Practicalities of Implementation. *BJOG*. doi:10.1111/1471-0528.16425

Kramer, M. S. (2003). The epidemiology of adverse pregnancy outcomes: an overview. *J Nutr, 133*(5 Suppl 2), 1592S-1596S. doi:10.1093/jn/133.5.1592S

Lawn, J. E., Blencowe, H., Oza, S., You, D., Lee, A. C., Waiswa, P., . . . Lancet Every Newborn Study, G. (2014). Every Newborn: progress, priorities, and potential beyond survival. *Lancet, 384*(9938), 189-205. doi:10.1016/S0140-6736(14)60496-7

Myers, J. E., Kenny, L. C., McCowan, L. M., Chan, E. H., Dekker, G. A., Poston, L., . . . North, R. A. (2013). Angiogenic factors combined with clinical risk factors to predict preterm pre-eclampsia in nulliparous women: a predictive test accuracy study. *BJOG, 120*(10), 1215-1223. doi:10.1111/1471-0528.12195

Nakimuli, A., Chazara, O., Byamugisha, J., Elliott, A. M., Kaleebu, P., Mirembe, F., & Moffett, A. (2013). Pregnancy, Parturition and Pre-eclampsia in Women of African Ancestry. *Am J Obstet Gynecol*. doi:10.1016/j.ajog.2013.10.879

Nakimuli, A., Chazara, O., Byamugisha, J., Elliott, A. M., Kaleebu, P., Mirembe, F., & Moffett, A. (2014). Pregnancy, parturition and preeclampsia in women of African ancestry. *Am J Obstet Gynecol, 210*(6), 510-520 e511. doi:10.1016/j.ajog.2013.10.879

Nakimuli, A., Chazara, O., Hiby, S. E., Farrell, L., Tukwasibwe, S., Jayaraman, J., . . . Moffett, A. (2015). A KIR B centromeric region present in Africans but not Europeans protects pregnant women from pre-eclampsia. *Proc Natl Acad Sci U S A, 112*(3), 845-850. doi:10.1073/pnas.1413453112

Pasupathy, D., Dacey, A., Cook, E., Charnock-Jones, D. S., White, I. R., & Smith, G. C. (2008). Study protocol. A prospective cohort study of unselected primiparous women: the pregnancy outcome prediction study. *BMC Pregnancy Childbirth, 8*, 51. doi:10.1186/1471-2393-8-51

Sharp, S. J., Poulaliou, M., Thompson, S. G., White, I. R., & Wood, A. M. (2014). A review of published analyses of case-cohort studies and recommendations for future reporting. *PLoS One, 9*(6), e101176. doi:10.1371/journal.pone.0101176

Smith, G. C., & Fretts, R. C. (2007). Stillbirth. *Lancet, 370*(9600), 1715-1725. doi:10.1016/s0140-6736(07)61723-1

Smith, G. C., Shah, I., Crossley, J. A., Aitken, D. A., Pell, J. P., Nelson, S. M., . . . Dobbie, R. (2006). Pregnancy-associated plasma protein A and alpha-fetoprotein and prediction of adverse perinatal outcome. *Obstet Gynecol, 107*(1), 161-166. doi:10.1097/01.AOG.0000191302.79560.d8

Sufriyana, H., Wu, Y. W., & Su, E. C. (2020). Artificial intelligence-assisted prediction of preeclampsia: Development and external validation of a nationwide health insurance dataset of the BPJS Kesehatan in Indonesia. *EBioMedicine, 54*, 102710. doi:10.1016/j.ebiom.2020.102710

Weiler, J., Tong, S., & Palmer, K. R. (2011). Is fetal growth restriction associated with a more severe maternal phenotype in the setting of early onset pre-eclampsia? A retrospective study. *PLoS One, 6*(10), e26937. doi:10.1371/journal.pone.0026937

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WHO Alliance for Maternal and Newborn Health Improvement Late Pregnancy Dating Study Group. (2020). Performance of late pregnancy biometry for gestational age dating in low-income and middle-income countries: a prospective, multicountry, population-based cohort study from the WHO Alliance for Maternal and Newborn Health Improvement (AMANHI) Study Group. *Lancet Glob Health, 8*(4), e545-e554. doi:10.1016/s2214-109x(20)30034-6

