Doppler ultrasound to improve prediction of adverse perinatal outcomes in low resource settings

Sam Ali

Doppler ultrasound to improve prediction of adverse perinatal outcomes in low resource settings

Utrecht University, The Netherlands
PhD Thesis, with a Summary in Dutch

Cover, layout and design: Robin Weijland, persoonlijkproefschrift.nl
Cover image derived from https://www.tuasaude.com/hidropsia-fetal/. The image shows a baby inside of the uterus. Darker red lined represent blood vessels of the womb. Blue lines represent ultrasound waves that make up the ultrasound image, after being reflected by e.g. human tissue.
Provided by thesis specialist Ridderprint, ridderprint.nl
Printing: Ridderprint
ISBN: 978-94-6458-851-4

The studies herein described were funded by Grand Challenges Canada (ref. no. R-ST-POC-1808-17 038), the University Medical Center Utrecht (ref. FM/ADB/D-18-015006). The University of Oxford, United Kingdom provided the ultrasound equipment used for data collection. The Open Science Program, Utrecht University (ref. kenmerk OSF22-22) supported the dissemination.

Doppler ultrasound to improve prediction of adverse perinatal outcomes

in low resource settings

Doppler-echografie om perinatale resultaten te verbeteren in lage inkomens-landen

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graag doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. H.R.B.M. Kummeling, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op

donderdag 12 januari 2023 des middags te 2.15 uur

door

Sam Ali

geboren op 16 mei 1989 te Omoro, Uganda

Promotoren:

Prof. dr. D.E. Grobbee

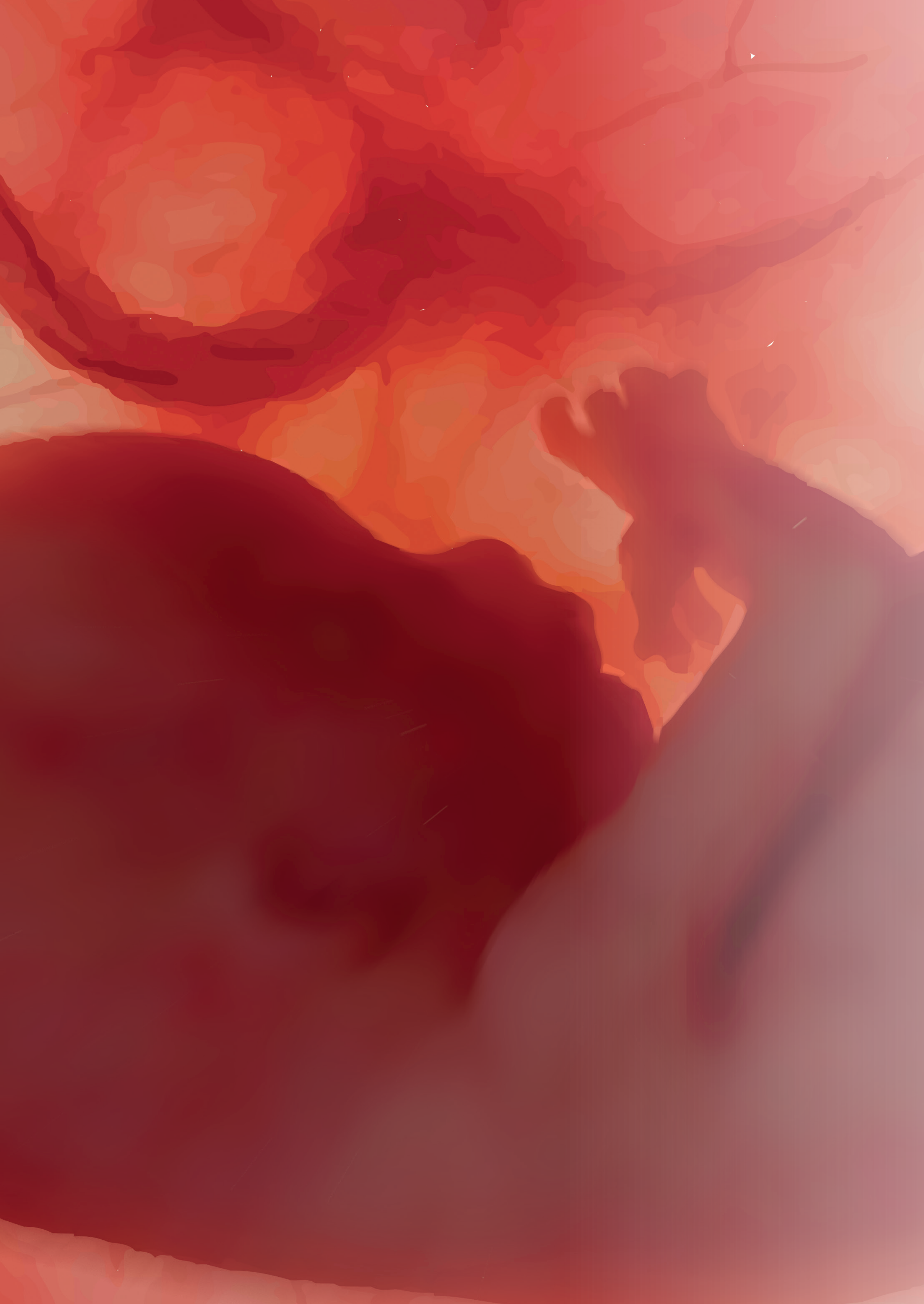
Prof. dr. M. Kawooya

Copromotoren:

Dr. M.J. Rijken

Dr. K. Klipstein-Grobusch

Table of contents



Chapter 1

General Introduction

THE GLOBAL BURDEN OF STILLBIRTHS

Globally, over two million babies are stillborn (at 28 weeks of gestation or more) every year, the vast majority (84%) in low and lower-middle income countries (LMICs).[1,2] The stillbirth rates vary significantly across regions and countries, with up to 22.7 per 1000 total births in the sub-Saharan Africa region compared to 2.9 per 1000 total births in western Europe (Figure 1).[1,2] As of 2019, the stillbirth rate in Uganda stood at 17.8 per 1000 total births,[2] half of them were intrapartum.[3] Stillbirth is traumatizing and associated with short- and long-term psychosocial distress and economic loss to the parents, healthcare providers, and society in general.[4,5]

Stillbirth is a complex outcome of pregnancy whose causes are poorly reported globally, the majority classified as unexplained.[2,6] Commonly reported causes are congenital anomalies, underlying maternal conditions, antepartum hemorrhage, infection and disorders related to fetal growth.[6] Placental conditions account for 14.4% and 13.7% of stillbirths in both high-income countries (HICs) and middle-income countries (MICs), respectively, while the corresponding data for low-income countries (LICs) is unknown.[6] More contributory factors include lack of access to quality health care services, race and ethnicity traits, immunity levels, and genetic differences.[6] Most stillbirths are preventable with access to quality care during pregnancy and childbirth (as recommended by the World Health Organization (WHO)), including antepartum and intrapartum monitoring to identify fetuses at high risk and timely interventions in case of complications.[3] Several screening policies, ranging from the use of a list of known maternal-risk factors to offering selective fetal growth ultrasound assessment based on non-reassuring symphysis-fundal height (SFH) measurements, have been tried but with little success.[7,8] The WHO recommends studies evaluating new approaches, including the potential benefit of a third trimester Doppler scan.[9] Doppler ultrasound enables the depiction of changes in maternal-fetal circulation patterns and thus compromised fetuses whose causes are related to uteroplacental dysfunction and maternal cardiovascular maladaptation to pregnancy can be reliably identified.

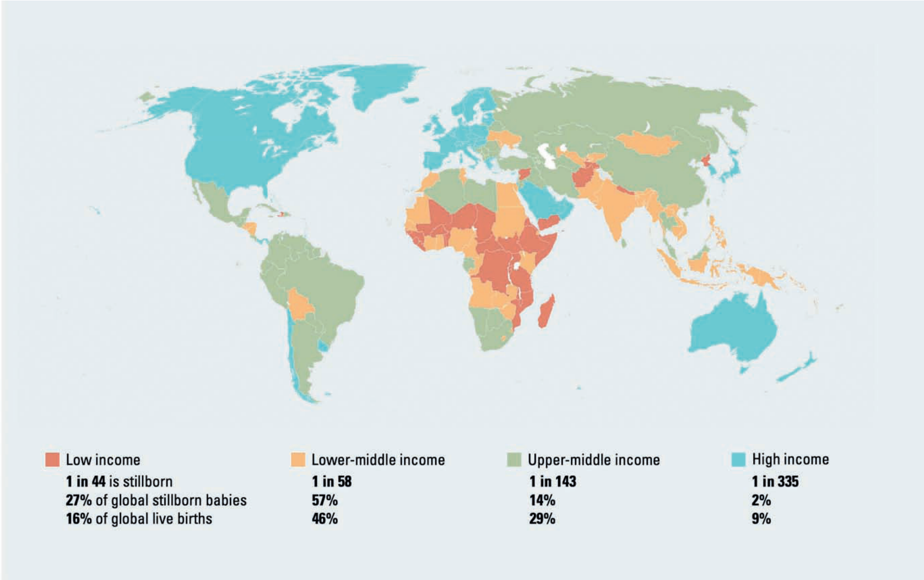


Figure 1 Disparities in the burden of stillbirths across countries. Adopted from UN-IGME, 2020 Report.[2]

Maternal-fetal circulation

Maternal blood flows via the uterine artery (UtA) to the placental membrane (maternal-fetal interface).[10] Nutritional and gaseous exchange takes place at the placenta, through the decidual spiral arteries.[10,11] The umbilical vein (UV) carries nutrient and oxygen-rich blood from the placenta to the fetus, going through the ductus venosus (DV) and inferior vena cava into the right atrium, streaming across foramen ovale to the left atrium and ventricle for distribution to the brain, coronary arteries and the rest of the body.[10,12] Umbilical arteries (UA) return the waste products for excretion at the placenta (Figure 2).[10]

Placental insufficiency is thought to result from the defective trophoblastic invasion of the spiral arteries, consequently leading to maternal vascular mal-perfusion of the placenta, and hypoxemic hypoxia.[11,13] Fetal hypoxemia has been associated with fetal growth restriction (FGR) and high resistance circulation within the UtA and UA.[11,13] Increased impedance to flow is believed to result from the reduced placental surface area available for nutrient and gaseous exchange and increased fetal afterload resistance.[11,14] In the late stages of placental failure, absent end-diastolic flow (AEDF) or reversed end-diastolic flow (REDF) in the UA usually manifests.[11,13] Altered blood flow in the ductus venosus (reversed a-wave) is postulated to result from one or a combination of increased intra-atrial pressure due to high cardiac afterload (increased vascular placental resistance), the direct effect of fetal acidemia on myocardial cell function, or increased flow through the ductus venosus isthmus to compensate for severe hypoxemia.[15,16]

Further, a prolonged hypoxemic insult to the cerebral circuit and vascular beds is thought to stimulate a metabolic and circulatory adaptative response in the fetus: Vasodilation to increase flow and preferentially stream highly oxygenated blood to the vital organs (the brain, heart, and adrenals) while decreasing flow to the other fetal tissues (kidneys, lungs, gut, and liver).[17,18] Fetal muscular activities (fetal tone, gross body movements, and breathing activity) are decreased or absent depending on the severity of the insult, to reduce energy expenditure.[17,18] Abnormal placental morphology and function have been causally related to maternal perception of reduced fetal movements.[19] In addition, decreased fetal movements have been associated with perinatal outcomes like FGR, stillbirth, fetal distress in labor, abnormal 5-min Apgar score, and abnormal umbilical cord gases and/or pH.[20,21]

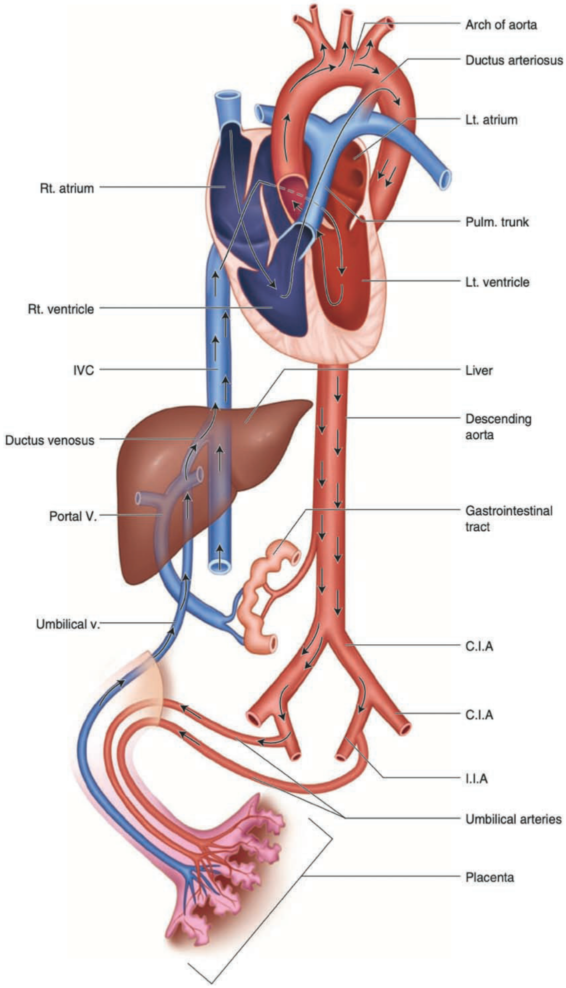


Figure 2 Schematic representation of maternal-fetal circulation. Adopted from Ilina et al[10]

Doppler ultrasound to predict adverse perinatal outcomes

Doppler velocimetry indices are correlated with vascular resistances[22,23] and widely applied in fetal medicine to screen and manage many clinical endpoints in HICs, but not in LMICs where the majority of stillbirths occur. Doppler ultrasound seems to offer modest individual diagnostic values for adverse pregnancy outcomes, but excellent performances when used in combination with other clinical tests. For example, the UtA PI is a useful contributory marker for predicting conditions like pre-eclampsia (PE) and FGR.[24] As a large number of stillbirths are not small for gestational age, especially near term (65% and 30% of the stillbirths had birthweight <10th percentile at <32 weeks and >32 weeks of gestation, respectively, in a HIC. In LMICs, these numbers may differ.),[25] Doppler tests are thought to be useful for differentiating constitutionally small from growth restricted babies, and identifying compromised babies with normal weight.[26–29] The clinical use of UA Doppler was associated with reduced perinatal mortality and obstetric interventions in high-risk pregnancies,[30] while cerebroplacental ratio appeared to be highly predictive of perinatal death[31] and early childhood delayed neurodevelopment in suspected FGR.[32]

Notably, most evidence to guide how Doppler ultrasound should be used in obstetric settings originates from HICs, and its applicability in resource-poor settings may not be appropriate given variations in the population profiles, clinical and health system context across countries and regions.[9,33] Little is known about the feasibility and potential ethical dilemmas related to introducing advanced ultrasound technologies in underserved regions. High-quality studies reporting the predictive value of Doppler ultrasound for adverse perinatal outcomes in LMICs are limited.[34,35] Further, robust externally validated prognostic models for quantifying the risk of perinatal death and stillbirths among women attending antenatal care (ANC) in low-resource settings are acutely lacking.[34–36] Well-designed studies exploring the potential clinical benefits of Doppler ultrasound technology to reduce stillbirth and perinatal death in high-burden settings are urgently required.[9,37]

Thesis objective

This thesis aimed to establish the clinical value of Doppler ultrasound in identifying fetuses whose risk of adverse perinatal outcomes is elevated in a low-resource setting (Uganda). According to ‘The 2021 Lancet Commission on diagnostics’, nearly half of the global population has little to no access to diagnostics, especially the poor, rural, and marginalized communities,[38] yet diagnostics are central and fundamental to quality health care and appropriate access is essential for equity and social justice.[38] Our goal was to contribute novel scientific evidence that could guide the applicability of Doppler ultrasound technology to improve the quality of ANC and perinatal health in Uganda and similar low-resource settings. This project was approached through these specific objectives:

1. To systematically review the available literature on the prognostic accuracy of Doppler ultrasound for adverse perinatal outcomes in low and middle-income countries.
2. To determine the feasibility of embedding antenatal Doppler ultrasound into local health systems and training healthcare providers at the frontline to offer these advanced ultrasound services in Uganda.
3. To explore the views and experiences of women and healthcare providers regarding the use of advanced ultrasound technology to optimize the health of mothers and their babies in a rural community in mid-western Uganda.
4. To determine the prevalence of abnormal umbilical artery (UA), uterine artery (UtA), middle cerebral artery (MCA) and cerebroplacental ratio (CPR) Doppler, and their relationship with adverse perinatal outcomes in women undergoing routine antenatal care in the third trimester in Uganda.
5. To develop and internally validate a multi-variable prediction model combining maternal and Doppler ultrasound parameters to estimate the risk of perinatal death and stillbirth in women near-term in Uganda.
6. To highlight, based on current knowledge and lessons gained from this study, the clinical potential of Doppler ultrasound to improve the quality of ANC and perinatal health in low-resource settings with high burden of stillbirths.

Thesis outline

This thesis comprises a general introduction (chapter 1), three parts (constituting chapters 2-6), and the discussion (Chapter 7). Part 1, including chapter 2, presents current evidence on the prognostic value of Doppler ultrasound for adverse perinatal outcomes in low-resource settings; Part 2 (containing chapters 3 and 4) evaluates the feasibility of introducing Doppler ultrasound services into the local health system in Uganda, and stakeholder views on the value of these services in the care of pregnant women; Part 3 (incorporating chapters 5 and 6) focuses on the value of Doppler ultrasound in predicting adverse perinatal outcomes. In chapter 7, we discuss the potential of Doppler ultrasound to improve the quality of ANC and perinatal health in settings with high burden of stillbirths

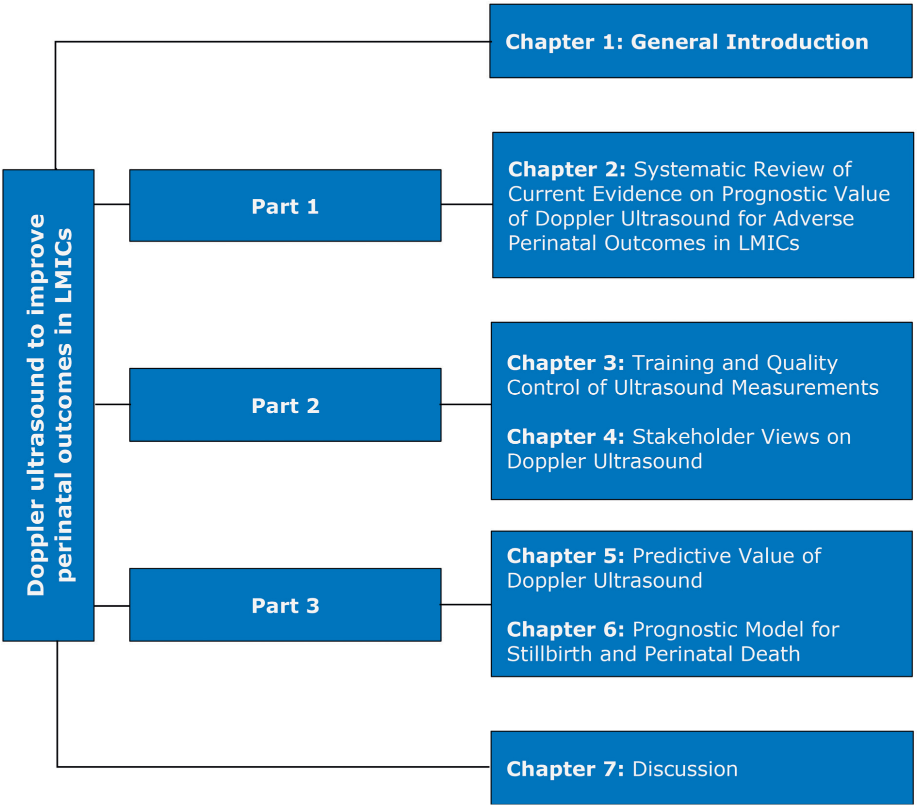


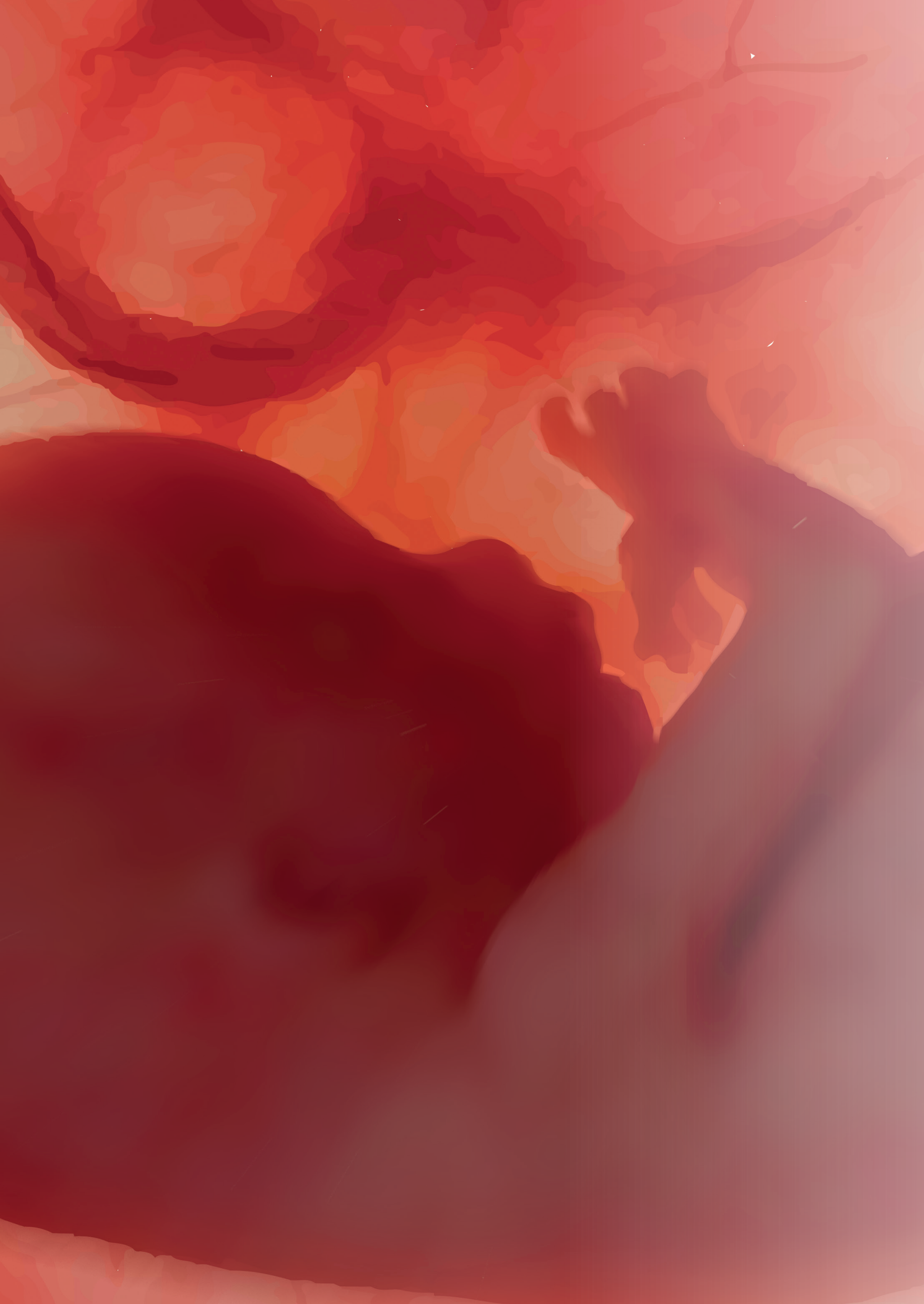
Figure 3 Overview of this thesis

REFERENCES

1. Hug L, You D, Blencowe H, Mishra A, Wang Z, Fix MJ, et al. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. Lancet. 2021 Aug 28;398(10302):772–85.
2. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). A Neglected Tragedy: The global burden of stillbirths [Internet]. New York; 2020. Available from: https://www.who.int/publications/m/item/a-neglected-tragedy-the-global-burden-of-stillbirths
3. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: Rates, risk factors, and acceleration towards 2030. Lancet. 2016;387(10018):587–603.
4. Mills TA, Ayebare E, Mweteise J, Nabisere A, Mukhwana R, Nendela A, et al. 'There is trauma all round': A qualitative study of health workers' experiences of caring for parents after stillbirth in Kenya and Uganda. Women and Birth. 2022;
5. Heazell AEP, Siassakos D, Blencowe H, Burden C, Bhutta ZA, Cacciatore J, et al. Stillbirths: economic and psychosocial consequences. Lancet. 2016;387(10018):604–16.
6. Reinebrant HE, Leisher SH, Coory M, Henry S, Wojcieszek AM, Gardener G, et al. Making stillbirths visible: a systematic review of globally reported causes of stillbirth. BJOG An Int J Obstet Gynaecol. 2018;125(2):212–24.
7. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: A prospective cohort study. Lancet. 2015;386(10008):2089–97.
8. Wanyonyi SZ, Orwa J, Ozelle H, Martinez J, Atsali E, Vinayak S, et al. Routine third-trimester ultrasound for the detection of small-for-gestational age in low-risk pregnancies (ROTTUS) study: a randomized controlled trial. Ultrasound Obstet Gynecol. 2021 Feb 22;
9. WHO. WHO recommendations on antenatal care for a positive pregnancy experience [Internet]. World Health Organization; 2016. Available from: https://www.who.int/publications/i/item/9789241549912
10. Ilina M. Foetal Circulation BT - Clinical Embryology: An Atlas of Congenital Malformations. In: Carachi R, Doss SHE, editors. Cham: Springer International Publishing; 2019. p. 39–43.
11. Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. Am J Obstet Gynecol. 2018 Feb 1;218(2):S745–61.
12. Mavrides E, Moscoso G, Carvalho JS, Campbell S, Thilaganathan B. The anatomy of the umbilical, portal and hepatic venous systems in the human fetus at 14–19 weeks of gestation. Ultrasound Obstet Gynecol. 2001 Dec 1;18(6):598–604.
13. Burton GJ, Woods AW, Jauniaux E, Kingdom JCP. Rheological and Physiological Consequences of Conversion of the Maternal Spiral Arteries for Uteroplacental Blood Flow during Human Pregnancy. Placenta. 2009;30(6):473–82.
14. Levytska K, Higgins M, Keating S, Melamed N, Walker M, Sebire NJ, et al. Placental Pathology in Relation to Uterine Artery Doppler Findings in Pregnancies with Severe Intrauterine Growth Restriction and Abnormal Umbilical Artery Doppler Changes. Am J Perinatol. 2017;34(5).

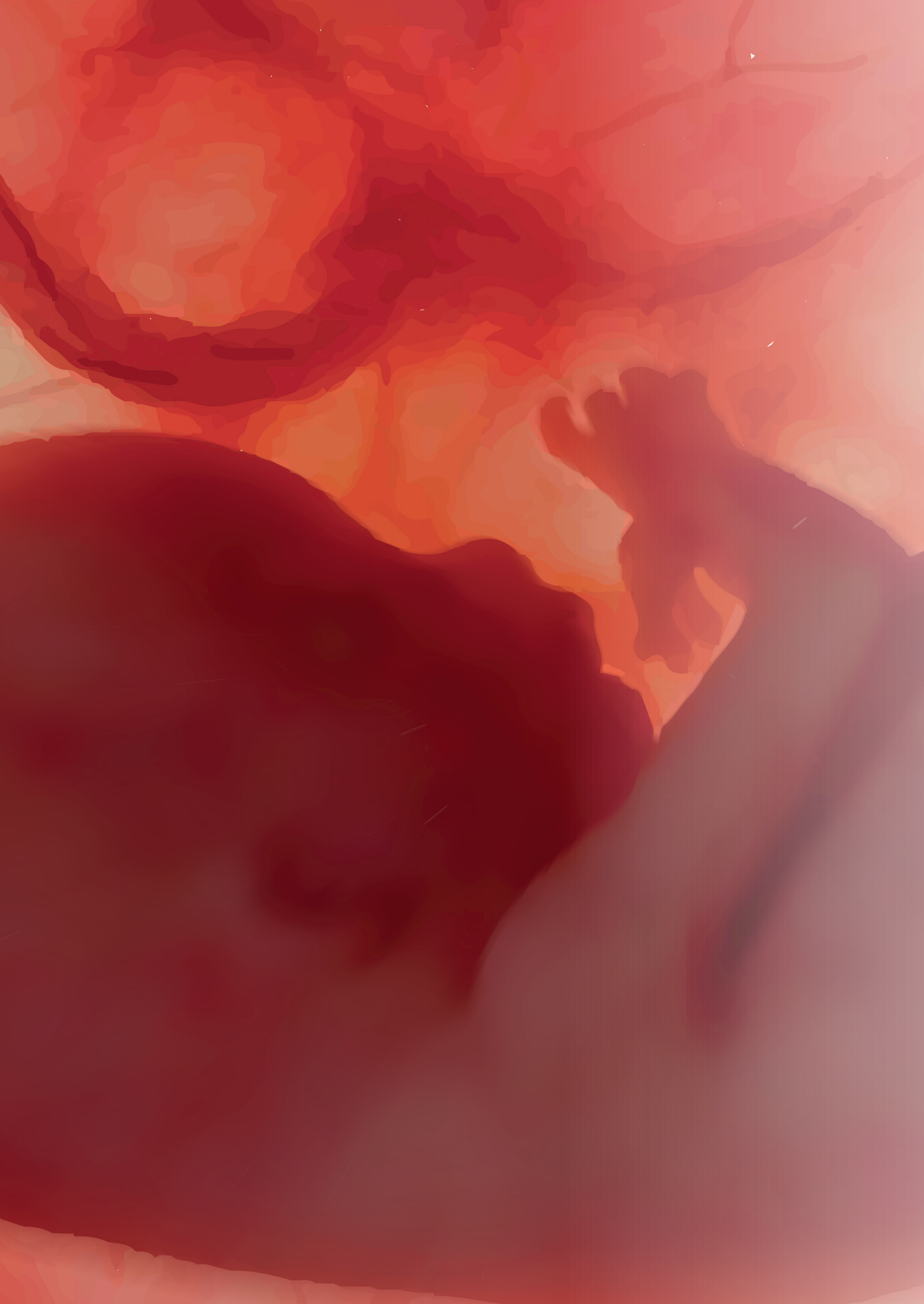
15. Kiserud T, Kessler J, Ebbing C, Rasmussen S. Ductus venosus shunting in growth-restricted fetuses and the effect of umbilical circulatory compromise. Ultrasound Obstet Gynecol. 2006;28(2).
16. Ferrazzi E, Lees C, Acharya G. The controversial role of the ductus venosus in hypoxic human fetuses. Vol. 98, Acta Obstetricia et Gynecologica Scandinavica. 2019.
17. Richardson BS, Bocking AD. Metabolic and circulatory adaptations to chronic hypoxia in the fetus. In: Comparative Biochemistry and Physiology - A Molecular and Integrative Physiology. 1998.
18. Giussani DA. The fetal brain sparing response to hypoxia: physiological mechanisms. Vol. 594. 2016. p. 1215–30.
19. Warrander LK, Batra G, Bernatavicius G, Greenwood SL, Dutton P, Jones RL, et al. Maternal perception of reduced fetal movements is associated with altered placental structure and function. PLoS One. 2012;7(4).
20. Vintzileos AM, Fleming AD, Scorza WE, Wolf EJ, Balducci J, Campbell WA, et al. Relationship between fetal biophysical activities and umbilical cord blood gas values. Am J Obstet Gynecol. 1991;165(3).
21. Hayes DJ, Smyth RM, Heazell AE. Investigating the significance and current state of knowledge and practice of absent or reduced fetal movements in low and lower middle-income countries: a scoping review. J Glob Heal Reports. 2019;3.
22. Ochi H, Suginami H, Matsubara K, Taniguchi H, Yano J, Matsuura S. Micro-bead embolization of uterine spiral arteries and changes in uterine arterial flow velocity waveforms in the pregnant ewe. Ultrasound Obstet Gynecol. 1995;6(4).
23. Valensise H, Novelli GP, Vasapollo B, Borzi M, Arduini D, Galante A, et al. Maternal cardiac systolic and diastolic function: Relationship with uteroplacental resistances. A Doppler and echocardiographic longitudinal study. Ultrasound Obstet Gynecol. 2000;15(6).
24. Sotiriadis A, Hernandez-Andrade E, da Silva Costa F, Ghi T, Glanc P, Khalil A, et al. ISUOG Practice Guidelines: role of ultrasound in screening for and follow-up of pre-eclampsia. Ultrasound Obstet Gynecol. 2019;53(1).
25. Poon LCY, Tan MY, Yerlikaya G, Syngelaki A, Nicolaides KH. Birth weight in live births and stillbirths. Ultrasound Obstet Gynecol. 2016;48(5).
26. Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, et al. Optimizing the definition of intrauterine growth restriction: The multicenter prospective PORTO Study. Am J Obstet Gynecol. 2013;208(4).
27. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48(3):333–9.
28. Lees CC, Stampalija T, Baschat A, da Silva Costa F, Ferrazzi E, Figueras F, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol. 2020;56(2):298–312.
29. Martins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction: (Replaces Clinical Guideline Number 3, April 2012). Am J Obstet Gynecol. 2020 Oct 1;223(4):B2–17.
30. Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev. 2017/06/15. 2017;2017(6):CD007529.

31. Conde-Agudelo A, Villar J, Kennedy SH, Papageorghiou AT. Predictive accuracy of cerebroplacental ratio for adverse perinatal and neurodevelopmental outcomes in suspected fetal growth restriction: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;52(4):430–41.
32. Monteith C, Flood K, Pinnamaneni R, Levine TA, Alderdice FA, Unterscheider J, et al. An abnormal cerebroplacental ratio (CPR) is predictive of early childhood delayed neurodevelopment in the setting of fetal growth restriction. Am J Obstet Gynecol. 2019;221(3).
33. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol. 2018 Feb 1;218(2):S855–68.
34. Heestermans T, Payne B, Kayode GA, Amoakoh-Coleman M, Schuit E, Rijken MJ, et al. Prognostic models for adverse pregnancy outcomes in low-income and middle-income countries: a systematic review. BMJ Glob Heal. 2019 Oct 1;4(5):e001759.
35. Townsend R, Manji A, Allotey J, Heazell AEP, Jorgensen L, Magee LA, et al. Can risk prediction models help us individualise stillbirth prevention? A systematic review and critical appraisal of published risk models. BJOG An Int J Obstet Gynaecol. 2021 Jan 1;128(2):214–24.
36. Allotey J, Whittle R, Snell KIE, Smuk M, Townsend R, von Dadelszen P, et al. External validation of prognostic models to predict stillbirth using International Prediction of Pregnancy Complications (IPPIC) Network database: individual participant data meta-analysis. Ultrasound Obstet Gynecol. 2022 Feb 1;59(2):209–19.
37. Ishak M, Khalil A. Prediction and prevention of stillbirth: dream or reality. Curr Opin Obstet Gynecol. 2021;33(5).
38. Fleming KA, Horton S, Wilson ML, Atun R, DeStigter K, Flanigan J, et al. The Lancet Commission on diagnostics: transforming access to diagnostics. Lancet. 2021 Nov 27;398(10315):1997–2050.



Part 1

Evidence on Doppler ultrasound to predict adverse perinatal outcomes in low-resource settings



Chapter 2

Prognostic accuracy of antenatal Doppler ultrasound for adverse perinatal outcomes in low- and middle-income countries: a systematic review

Sam Ali
Simelina Heuving
Michael G. Kawooya
Josaphat Byamugisha
Diederick E. Grobbee
Aris T. Papageorghiou
Kerstin Klipstein-Grobusch
Marcus J. Rijken

BMJ Open 2021;11: e049799.

ABSTRACT

Objectives

This systematic review examined available literature on the prognostic accuracy of Doppler ultrasound for adverse perinatal outcomes in low-income and middle-income countries (LMIC).

Design

We searched PubMed, Embase, Cochrane Library and Scopus from inception to April 2020.

Setting

Observational or interventional studies from LMICs

Participants

Singleton pregnancies of any risk profile.

Interventions

Umbilical artery (UA), middle cerebral artery (MCA), cerebroplacental ratio (CPR), uterine artery (UtA), fetal descending aorta (FDA), ductus venosus, umbilical vein and inferior vena cava.

Primary and secondary outcome measures.

Perinatal death, stillbirth, neonatal death, expedited delivery for fetal distress, meconium-stained amniotic fluid, low birth weight, fetal growth restriction, admission to neonatal intensive care unit, neonatal acidosis, Apgar scores, preterm birth, fetal anemia, respiratory distress syndrome, length of hospital stay, birth asphyxia and composite adverse perinatal outcomes (CAPO).

Results

We identified 2825 records, and 30 (including 4977 women) from Africa (40.0%, n=12), Asia (56.7%, n=17) and South America (3.3%, n=01) were included. Many individual studies reported associations and promising predictive values of UA Doppler for various adverse perinatal outcomes mostly in high-risk pregnancies, and moderate to high predictive values of MCA, CPR and UtA Dopplers for CAPO. A few studies suggested that the MCA and FDA may be potent predictors of fetal anaemia. No randomized clinical trial (RCT) was found. Most studies were of sub-optimal quality, poorly powered and characterized by wide variations in outcome classifications, the timing for the Doppler tests and study populations.

Conclusion

Local evidence to guide how antenatal Doppler ultrasound should be used in LMIC is lacking. Well-designed studies, preferably RCTs, are required. Standardization of practice and classification of perinatal outcomes across countries, following the international standards, is imperative.

KEYWORDS

Pregnancy, ultrasound, prenatal diagnosis, prenatal care, developing countries, and systematic review.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review used the most optimal database combinations and snowballing technique with no time restrictions to identify the records.
- We comprehensively examined available literature on the prognostic accuracy of Doppler ultrasound for adverse pregnancy outcomes in low-income and middle-income countries.
- Although only English language articles were included, it is unlikely that high impact papers were not identified.
- Pooling and interpreting the data for wider clinical application was not possible due to the large heterogeneity across studies.

PROSPERO REGISTRATION NUMBER

CRD42019128546

INTRODUCTION

Stillbirths remain a major global challenge,[1] with nearly three million cases reported annually.[2] The vast majority of the cases (98%) are contributed by low- and middle-income countries (LMIC).[3] These deaths have profound effects on the families and communities involved, and strategies for reduction are of high societal importance. The risk of adverse perinatal outcomes is higher in compromised fetuses than in normally growing babies, and could be distinguishable using antenatal Doppler ultrasound.[4,5] Prenatal diagnosis of fetuses at risk provides a window for close monitoring and/or expedited delivery of well-developed babies with the prospect of improving survival and long-term well-being.[4]

The predictive performance of Doppler ultrasound for adverse perinatal outcomes has been demonstrated in primary studies, systematic reviews and meta-analysis from high-income countries (HIC), guiding the development of HIC practice guidelines.[6] The use of HIC guidelines for clinical guidance in LMIC without local validation may be inappropriate given the differences in the prevalence of adverse pregnancy outcomes in the two settings. For instance, the stillbirth rates per 1000 total births (95% confidence interval) is 3.4 (3.4 to 3.5) in HIC, 25.5 (22.5 to 29.1) in Southern Asia and 28.7 (25.1 to 34.2) in sub-Saharan Africa.[2] Since the prevalence and severity of a disease influences the diagnostic or prognostic test performance, context-specific guidance is necessary.[7] However, there are still knowledge gaps about the predictive ability of antenatal Doppler for adverse pregnancy outcomes in LMIC.

This systematic review examined existing literature on the prognostic accuracy of Doppler ultrasound for adverse perinatal outcomes in LMIC. The implications for clinical utility of the available local evidence to guide practice in LMIC are highlighted.

MATERIAL AND METHODS

Protocol and registration

This systematic review protocol was registered in the PROSPERO database and reported following the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) Statement.[8]

Eligibility criteria

We included observational (cohort or case-control) studies and randomized clinical trials (RCTs) from LMIC (as per the World Bank country classifications in the year 2020) reporting the prognostic value of Doppler ultrasound for adverse perinatal outcomes in singleton pregnancies of any risk profile. Doppler measurements of interest included umbilical artery (UA), middle cerebral artery (MCA), cerebroplacental ratio (CPR), uterine artery (UtA), fetal descending aorta (FDA), ductus venosus (DV), umbilical vein (UV) and inferior vena cava (IVC). Adverse perinatal outcomes (as defined in the included studies) were perinatal death, stillbirth, neonatal death, expedited delivery for fetal distress, meconium stained amniotic fluid, low birth weight, fetal growth restriction (FGR), admission to neonatal intensive care unit (NICU), neonatal acidosis, Apgar scores, preterm birth, fetal anemia, respiratory distress syndrome (RDS), length of hospital stay, birth asphyxia, and composite adverse perinatal outcomes (CAPO). Conference proceedings/posters that did not appear as full-text papers, case reports and review articles without original data were excluded.

Information sources and search

We conducted a comprehensive literature search in PubMed (Medline), Embase, Cochrane Library and Scopus for articles published from inception to 7 April 2020. The search strategies (supplemental appendix S1) were developed with the support of a librarian at University Medical Center Utrecht. When applicable, pre-defined search (Title/Abstract) and MeSH/Emtree terms were used. No limits were applied to the searches.

Study selection

The records retrieved from the databases were exported to Endnote to eliminate duplicates and then transferred to Rayyan for review and selection. Two reviewers (SA and SH) independently assessed all studies for inclusion based on title and abstract. Studies reporting any Doppler parameter and adverse pregnancy outcome of interest in the title or abstract were further retrieved in full text and assessed by the same two reviewers against full eligibility criteria. Disagreements were resolved by discussion or, if required, we consulted the third review author (MJR).

Data extraction

Using a pre-piloted data extraction sheet, two reviewers (SA and SH) independently extracted data on authors, study title, year of publication, aims of the study, study period, the number of women recruited, gestational age at Doppler ultrasound examination, method of pregnancy dating, pregnancy risk profile, blood vessels studied, pregnancy outcomes (as defined in the primary study) and key results. If any relevant information was missing, the corresponding authors were contacted once by e-mail.

Risk of bias assessment

Two raters (SA and SH) independently evaluated the risk of bias for each study using the quality in prognostic studies (QUIPS) tool.[9] The risk of bias domains included study population, attrition, prognostic factor measurement, outcome measurement, confounding and statistical analysis. All the domains were separately judged by two raters as having a low, moderate or high risk of bias. Any disagreement during this process was resolved by contacting the third rater (MJR).

Prognostic test accuracy measures

Doppler test prognostic performance measures, as reported in the selected studies, are presented in table S1. These included diagnostic test accuracy measures such as sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV); measures of association; proportions and correlations.

Data synthesis and analysis

The results were narratively summarized. The large heterogeneity in the study populations, timing for Doppler tests, outcome definitions and prognostic performance measures in the included studies did not allow for a meta-analysis. If a study reported multiple Doppler indices, the most commonly used (pulsatility index) was selected.

Patient and public involvement

No patient was involved. The public was also not involved in the design, conduct and dissemination of this research.

RESULTS

Study selection

The 2825 records we identified through electronic searches were reduced to 2210 after the removal of duplicates, and 2162 were further excluded based on title and abstract screening, retaining 48 records. After full-text assessment for eligibility, 23 studies were excluded with reasons, and 25 remained (supplemental appendix S2). Five additional records were identified through snowballing (figure 1). Thirty studies, involving a total count of 4977 women and a median (interquartile range) sample size of 100 (30 to 181) were included in the analysis (table 1).

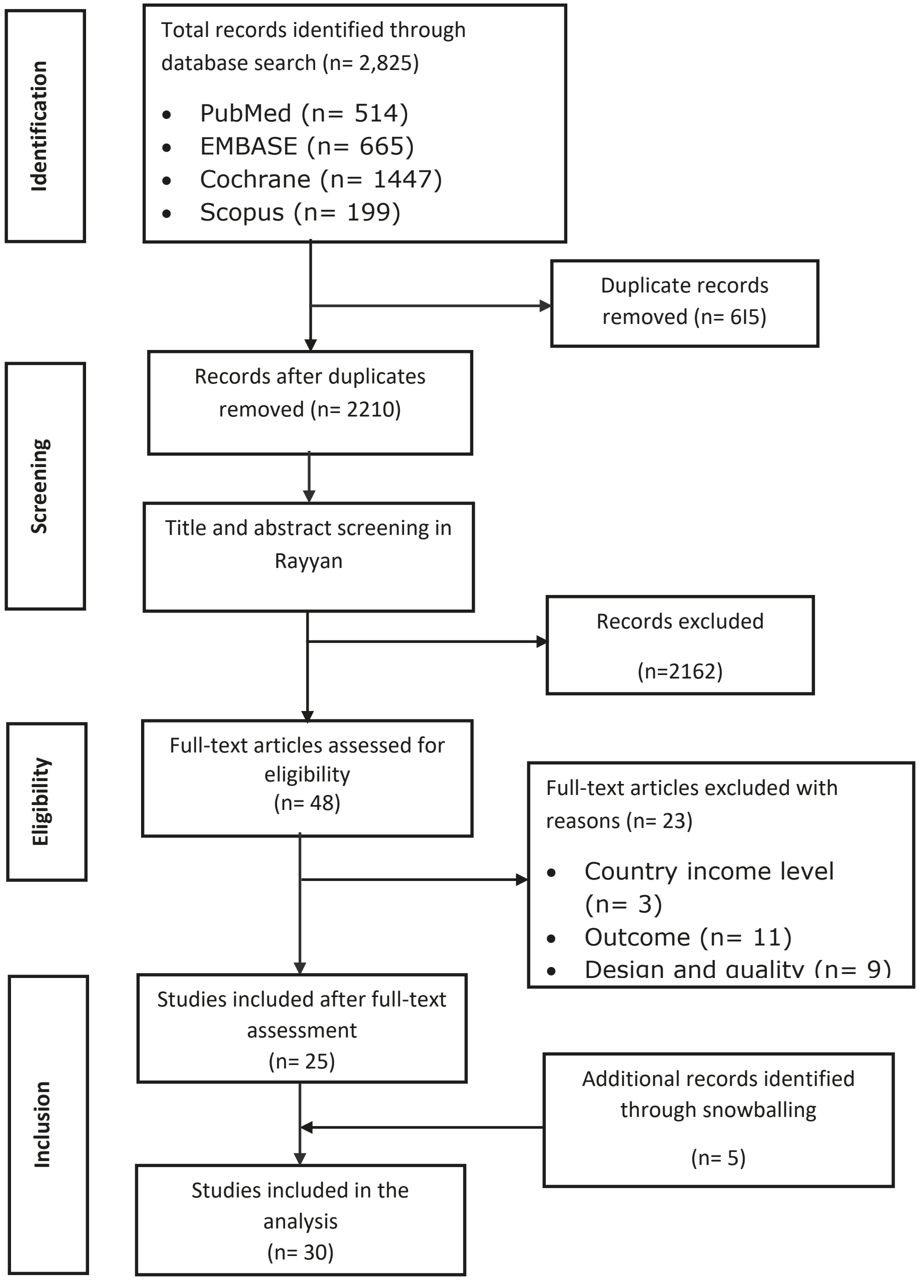


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram

Table 1 Summary of studies included in the systematic review of current evidence on the prognostic value of Doppler ultrasound for predicting adverse pregnancy outcomes in LMIC.

Author, Year	Country	Study Period	Women	Weeks	Study Design	Vessels	Abnormal Doppler Thresholds
Abdallah, 2019.[10]	Egypt	2015-2017	92	>= 37	Cohort	UA	UA (RI, PI and S/D ratio) > 95th centile
Agbaje, 2018.[17]	Nigeria	2014-2015	120	26	Cohort	UA	S/D ratio > 95th percentile, RI > 95th percentile, and AREDF.
Alanwar, 2018.[33]	Egypt	2017	100	30 - 40	Cohort	CPR	CPR PI < 1 or CPR PI < 5th percentile.
Allam, 2013.[30]	Egypt	2007-2010	30	36 - 41	Cohort	MCA, DV	MCA S/D ratio <4.37, DV RI > 0.29, or Decrease in a-, v- and d- waves, or reversed flow in both a- and v-waves.
Anshul, 2010.[18]	India	2005-2007	100	>= 28	Cohort	UA	S/D ratio >= 3 or AREDF.
Bano, 2010.[11]	India	Not stated	90	30 - 41	Cohort	UA, MCA, CPR	MCA < 2SD; UA > 2SD or CPR PI < 1.08
Dhand, 2011.[31]	India	2005-2006	121	28 - 41	Cohort	MCA	Not specified
Dorman, 2002.[35]	Kenya	1996-1997	854	24 - 31	Cohort	UtA	Early diastolic notch or mean/ipsilateral UtA RI >= 0.58
Ebrashy, 2005.[19]	Egypt	2002-2003	80	>= 28	Case-control	UA, MCA, CPR	UA RI > 0.72, MCA RI < 0.69, CPR RI < 1.0
Geerts, 2007.[20]	South Africa	Not stated	113	24 - 34	Cohort	UA, CPR, DV	UA PI >95th centile; UA/MCA >1; DV PI > 95th centile.
Khanduri, 2013.[21]	India	2009-2011	60	23 - 37	Cohort	UA, MCA	UA PI > 1.42 or UA RI > 0.72, MCA PI <1.5, MCA RI < 0.59
Kumari, 2019.[12]	India	2015-2016	30		Cohort	UA, MCA, FDA	MCA PSV > 1.50 MoM, FDA PSV delta > 70.50. Not specified for UA

2

Table 1 Continued

Author, Year	Country	Study Period	Women	Weeks	Study Design	Vessels	Abnormal Doppler Thresholds
Lakhkar, 2006.[13]	India	2001-2002	58	> 30	Cohort	UA, MCA, CPR, FDA	S/D ratio, RI or PI of UA > 2SD; MCA < 5th centile; FDA > 2SD; CPR PI or S/D ratio < 1.0
Lakshmi, 2013.[22]	India	2007-2008	238	< 35	Cohort	UA	Absent and/or reversed end-diastolic flow (AREDF)
Malik, 2013.[23]	India	2010-2011	100	31 - 41	Cohort	UA, MCA, CPR, UtA	Not specified
Masihi, 2019.[34]	Iran	2016-2017	181	38 - 40	Cohort	CPR	CPR PI <1.94
Mullick, 1993.[24]	India	Not stated	73	22 - 26, 30 - 32, > 37	Cohort	UA	S/D ratio >= 4 (26 weeks), 3.5 (30-32 weeks) and 3 (37-40 weeks)
Nagar, 2015.[25]	India	2009 - 2011	500	26 - 30	Cohort	UA, UtA	UA (S/D ratio or RI) > 95th centile or AREDF. UtA S/D ratio > 95th centile
Najam, 2016.[26]	India	Not stated	150	28 - 40	Cohort	UA, MCA, CPR	UA S/D ratio > 2SD, or AREDF, MCA SD ratio < 5th percentile, MCA/UA SD ratio of < 1.0
Nouh, 2011.[36]	Egypt	2009-2011	80	8 - 12, 26	Case-control	UtA	UtA PI> 95th percentile, and/or Unilateral or bilateral notch
Pares, 2008.[32]	Brasil	1997-2005	46	20 - 34	Cohort	MCA, FDA	FDA-MV >= 2SD MCA-PSV >= 1.5 MoM
Pattinson, 1991.[14]	South Africa	1987-1989	53	16 - 28	Cohort	UA, UtA	UA RI > 95th centile UtA RI > 0.58
Pattinson, 1993.[27]	South Africa	1990	496	16 - 24	Cohort	UA	UA RI > 95th centile
Phupong, 2003.[37]	Thailand	2000-2001	322	22 - 28	Cohort	UtA	Unilateral or bilateral early diastolic notch

Table 1 Continued

Author, Year	Country	Study Period	Women	Weeks	Study Design	Vessels	Abnormal Doppler Thresholds
Rani, 2016.[15]	India	2012-2014	223	30 - 36	Cohort	UA, MCA, CPR	UA PI > 1.03, UA RI >0.695; MCA PI < 1.2, MCA RI < 0.75; CPR PI < 1.08 or CPR RI < 1.05.
Rocca, 1995.[16]	Egypt	Not stated	113	>= 28	Cohort	UA	UA S/D ratio >= 3
Verma, 2016.[38]	India	Not stated	165	22 - 24	Cohort	UtA	Bilateral diastolic notches or mean UtA PI > 1.45 (UtA PI > 95th centile).
Waa, 2010.[28]	Kenya	2007	100	>= 28	Cohort	MCA, UA	MCA RI < 0.71, and UA > 0.71.
Yelikar, 2013.[29]	India	Not stated	189	> 32	Cohort	UA	UA S/D ratio > 90th centile or AREDF
Zarean, 2018.[39]	Iran	2015-2016	100	30 - 34	Cohort	UtA	UtA PI > 95th centile

[a]LMP: last menstrual period; UA: umbilical artery; MCA: middle cerebral artery; CPR: cerebroplacental ratio; UtA: uterine artery; FDA: fetal descending aorta; DV: ductus venosus; RI: resistive index; PI: pulsatility index; S/D ratio: systolic diastolic ratio; PSV: peak systolic velocity; MV: mean velocity; AREDF: absent and/or reversed end diastolic flow.

Study characteristics

The selected studies were from Africa (40.0%, n=12), Asia 17 (56.7%, n=17) and South America (3.3%, n=01). Twenty studies (67%) recruited high-risk pregnancies, six (16.7%) both high and low-risk populations, while five (16.7%) studied the low-risk group (supplemental appendix S3). Thirteen (43.3%) studies did not specify a method of pregnancy dating, 13 (43.3%) assessed gestational age using last menstrual period (LMP) combined with ultrasound, three (10.0%) used ultrasound alone, and one (3.3%) study used LMP. No RCTs was identified, and no study provided data on the UV and IVC Dopplers (table 1). The reasons for undertaking the Doppler research varied by individual studies and included the prediction of the risk of FGR, fetal anemia, neonatal acidosis, among others (supplemental appendix S3).

Methodological quality of included studies

The results of the QUIPS assessment are provided in figure 2 and supplemental appendix S4. Overall, the risk of bias was low in 15 (50%), moderate in 10 (33.3%), and high in five (16.7%) studies. In the study population domain, the risk of bias was low in 73.3%, moderate in 23.3%, and high in 3.3% of the studies. Selective reporting remarkably resulted in a moderate to high risk of bias for analysis and reporting in 20 (66.7%) studies. We found a moderate to high risk of bias for outcome measurement in 17 (56.7%) studies, mostly due to inconsistencies in outcome classifications (supplemental table S2).

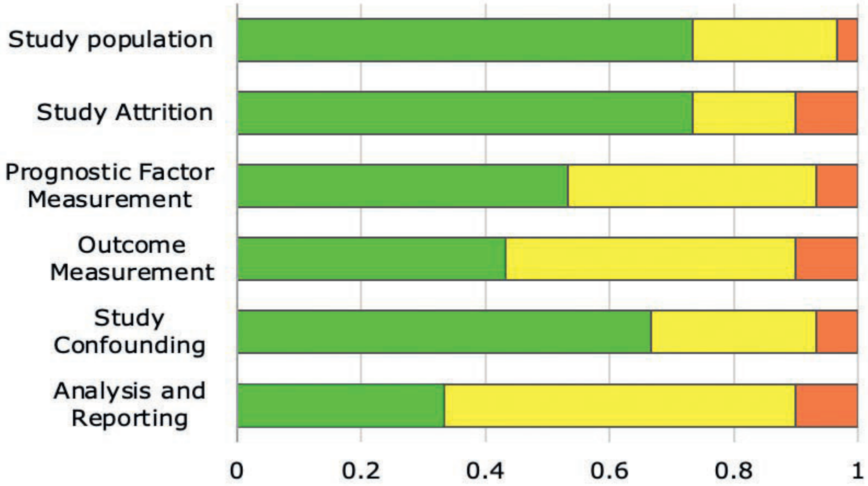
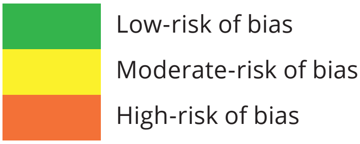


Figure 2 Risk of bias assessment results of the 30 included studies
Figure 2 key



Prognostic accuracy of antenatal Doppler ultrasound for adverse perinatal outcomes

Twenty studies evaluated the umbilical artery,[10–29] and seven reported its predictive values for FGR. The PPV for FGR reported in the individual studies were between 77.40 and 88.5,[11,16,21,24] while the area under the receiver operating characteristic (AU ROC) curve was 0.63,[17] mostly in high-risk pregnancies. The NPV ranged from 55.4 to 95.65.[11,16,21,24] FGR was defined as birth weight or abdominal circumference below the 10th percentile in two studies,[11,17] ponderal index less than 10 in one study,[21] and was not defined in the remaining studies.[16,24,26] Increased flow impedance in the UA had positive predictive values for composite adverse outcomes between 66.60 and 96.6 in high-risk pregnancies.[11,13,19,23] All studies provided individual components of the CAPO except only one.[11] Absent or reversed end-diastolic flow (AREDF) in the UA was associated with poor pregnancy outcomes (perinatal death, odds ratio (OR) 9.8, 95% confidence interval (CI) 2.1 to 46.4; CAPO: OR 2.4, 95% CI 1.1 to 5.0; and RDS: OR 8.4, 95% CI 2.3 to 30.5).[14,22,26]

The MCA was reported in 12 studies.[11,12,13,15,19,21,23,26,28,30,31,32] The PPV for fetal anemia in Rhesus (Rh) isoimmunized pregnancies requiring transfusion were between 83.0 and 90.9 and the AU ROC curve was 0.7.[12,32] Fetal anemia was consistently defined as hemoglobin (Hb) =<0.64 g/dl in the two studies, though they recruited low numbers of women.[12,32] MCA Doppler had a sensitivity of 87.5%, PPV of 74.0% and AU ROC curve of 0.82 for neonatal acidosis.[30] The PPV for CAPO ranged from 80.0 to 100% in high-risk pregnancies,[11,13,19,23,31] but two studies did not provide details of the individual components of the CAPO.[11,31]

Nine studies reported the prognostic value of CPR.[11,13,15,19,20,23,26,33,34] CPR showed promising predictive value for adverse perinatal outcomes in unselected pregnancies in the third trimester. One study reported sensitivity 85.10, specificity 89.72, PPV 80.70 and NPV 92.30 for FGR.[26] Two studies found sensitivity between 80.90 and 90.91%, and specificity between 50.0 and 78.04% for emergency caesarean section for fetal distress though the tests had poor positive predictive values.[26,34] Abnormal CPR had positive predictive values for CAPO between 81.80 and 100% in high-risk pregnancies.[11,13,15,23]

Eight studies reported the prognostic value of UtA Doppler,[14,23,25,35–39] and two showed positive predictive values of over 91.8% for CAPO in high-risk pregnancies.[23,36] The remaining studies had poor predictive values for adverse perinatal outcomes.

Three studies evaluated the prognostic accuracy of FDA Doppler.[12,13,32] The FDA sensitivity for fetal anemia in Rh isoimmunized pregnancies ranged from 87.0% to 95.7% when used in isolation.[12,32] The sensitivity varied between 86.0% and 98.4% and PPV ranged from 86.0 to 100% when combined with the MCA.[12,32]

The DV was sampled in two studies undertaken in high-risk pregnancies.[20,30] Abnormal DV had a sensitivity of 100, PPV of 72.0 and AU ROC curve of 0.88 for the prediction of neonatal acidosis, though this study included only 30 women between 36 and 41 weeks of gestation.[30] The second study found a borderline significance and positive predictive value of 92.0% for the prediction of composite adverse perinatal outcomes at 24-34 weeks of gestation.[20]

DISCUSSION

Summary of findings

Many individual studies showed that abnormal UA Doppler was associated with poor perinatal outcomes, mostly in high-risk pregnancies, and that abnormal UA, MCA, CPR and UtA Dopplers had moderate to high predictive values for composite adverse perinatal outcomes. A few studies suggested that abnormal MCA Doppler had high individual predictive value for fetal anemia, but performed better when combined with the FDA. However, the majority of the available evidence was of sub-optimal quality, based on a few poorly powered studies and had no RCTs. Further, wide variations in the populations studied, definitions of adverse perinatal outcomes and prognostic accuracy measures across studies was present. Thus, pooling and interpreting the evidence for wider clinical application was not possible.

Implications for practice

Evidence from HIC suggests that adding Doppler studies into clinical diagnostic or prognostic rules improves pregnancy risk assessment,[6] and are increasingly becoming integrated into their pregnancy management guidelines.[4,6] The use of guidance based entirely on HIC data in daily practice in LMIC could be inappropriate considering the differences in the adverse pregnancy outcome rates in the two settings. The stillbirth rates in LMIC is approximately 10 times that of HIC,[2] a large variation likely to influence the predictive performance of diagnostic or prognostic tests.[7] Thus, a proper understanding of existing literature from LMIC is important. This paper reports the findings of a systematic review of primary evidence on the prognostic value of antenatal Doppler ultrasound for adverse perinatal outcomes in LMIC.

Abnormal blood flow patterns in the UA had moderate to high predictive values for FGR and was associated with poor outcomes in high-risk pregnancies. Similarly, a recent Cochrane review of RCTs from HIC suggests that using UA Doppler in high-risk pregnancies could reduce perinatal deaths by 30% (risk ratio 0.71, 95% CI 0.52 to 0.98), and lead to fewer obstetric interventions.[40] Despite some similarities with our findings, the definitions of adverse outcomes, including FGR were inconsistent (or not even defined in many studies included in this review) with recommended international standards,[4,41] and with no clear distinction between early and late FGR. Scanty data from this review indicate that abnormal CPR, UA, MCA and UtA Doppler could be predictive of CAPO. However, in a previous systematic review from HIC, CPR had low predictive accuracy (pooled sensitivity: 57%, specificity: 77%, and summary positive likelihood ratio (LR): 2.5, and negative LR: 0.60) for CAPO in pregnancies with suspected FGR antenatally.[42] In another review, CPR was significantly better than UA and MCA Doppler in predicting CAPO ($P < 0.001$) and emergency delivery for fetal distress in singleton pregnancies of all risk profiles,[43] but the primary studies reviewed had numerous methodological limitations.[43] Further, first-trimester UtA Doppler had very low sensitivity 25.8% (95% CI 15.5 to 39.7) for CAPO in a systematic review of 18 studies (involving 55974 women).[44] More data from HIC indicate that MCA-PSV reliably predicts fetal anemia in untransfused fetuses.[45] The area under the hierarchical summary ROC curve for moderate-severe anemia in untransfused fetuses was 87%, pooled sensitivity 86% (95% CI 75 to 93%) and specificity 71% (95% CI 49 to 87%).[45] Similarly, in our study, MCA alone or when combined with FDA had high predictive values for fetal anemia in Rh isoimmunized pregnancies, but this was based on only three studies. Overall, this review found that high-quality studies on the predictive accuracy of Doppler ultrasound for adverse perinatal outcomes in LMIC were scarce. The large heterogeneity across studies precluded a meta-analysis and between-study comparisons.

Implications for research

Future studies need to specify the methods and timing for pregnancy dating. Accurate dating is crucial for timing the Doppler tests and interventions to expedite delivery in compromised fetuses. The interpretation and comparison of Doppler studies could be improved by using standard outcome definitions and completeness in reporting.[46] Most primary studies in this review studied the predictive ability of a single variable (Doppler test) for the outcome(s) of interest, without considering existing characteristics of clinical importance to estimate pregnancy risk. The predictive accuracies of new determinants need to be assessed individually and by multivariable analysis to facilitate the clinical applicability of the findings. The clinical applicability of Doppler ultrasound also depends on the clinical judgement of the Doppler measurements and the feasibilities of local healthcare systems to interpret and respond to the results of the Doppler scan. Along the same line, our recently concluded prospective cohort study in a rural sub-Saharan African setting will soon highlight the prognostic value of Doppler ultrasound in the late third trimester and the feasibilities of integrating such advanced technologies into routine antenatal care in LMIC.

Strengths and limitations

A strength of this systematic review is that it was conducted according to a registered protocol, using the most optimal database combinations and snowballing with no time restrictions. However, it is possible that some studies performed in low-resource settings, may not have been indexed in the searched databases. Although we only included English language articles, it is unlikely that high impact papers were not identified. Further, this review primarily aimed to thoroughly examine the current evidence on the predictive value of Doppler ultrasound for adverse perinatal outcomes in LMIC using a meta-analysis. However, due to the inherent limitations in the included studies such as large heterogeneity in the study populations, inconsistencies in the definition of pregnancy outcomes, differences in the gestational age at the Doppler study and prognostic accuracy measures reported, we were only able to present our findings narratively. A future updated systematic review and meta-analysis of high-quality evidence is recommended.

CONCLUSION

This review demonstrated that a scientific basis to provide evidence for how antenatal Doppler should be used in LMIC is lacking. Well-designed studies, preferably randomized clinical trials, testing application models of antenatal Doppler while respecting the local conditions are needed. Moreover, local practice and classification of perinatal outcomes need to be standardized, utilizing approaches consistent with international consensus.

ACKNOWLEDGEMENTS

We thank the University Medical Center Utrecht librarians Paulien Wiersma and Felix. We thank the team from Makerere University College of Health Sciences and ECUREI that supported us to undertake this review. We thank Fosca Tumushabe for the English language review.

CONTRIBUTORS

SA, SH, KKG, and MJR drafted the protocol and conducted the review. MGK, JB, DEG, and ATP critically reviewed the work for important intellectual content. All the authors approved the final manuscript.

FUNDING

This research was supported by the UMC Utrecht Global Health Support Program (Ref: FM/ADB/D-18-015006), University Medical Center Utrecht,

Utrecht, The Netherlands, and Grand Challenges Canada (Grant Number: R-ST-POC-1808-17038).

COMPETING INTERESTS

None

DATA SHARING STATEMENT

No data are available. No additional data are available.

ETHICS STATEMENTS

PATIENT CONSENT FOR PUBLICATION

Not applicable

ETHICS APPROVAL

Given this is a systematic review, ethics approval is not required.

SUPPLEMENTARY MATERIALS

Supplemental appendix S1. Search strings for the databases used to retrieve articles.
Supplemental appendix S2. List of full-text articles excluded with reasons.
Supplemental appendix S3. The aims of the selected studies and risk profiles of the women recruited
Supplemental appendix S4. Risk of bias assessment results of the 30 studies included in the analysis.
Supplemental table S1. Statistical measures of prognostic performance of Doppler ultrasound reported in the selected studies.
Supplemental table S2. Definitions of adverse perinatal outcomes reported in the selected studies

REFERENCES

1. de Bernis L, Kinney M V, Stones W, ten Hoope-Bender P, Vivio D, Leisher SH, et al. Stillbirths: ending preventable deaths by 2030. Lancet. 2016;387(10019):703–16.
2. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: Rates, risk factors, and acceleration towards 2030. Lancet. 2016;387(10018):587–603.
3. Reinebrant HE, Leisher SH, Coory M, Henry S, Wojcieszek AM, Gardener G, et al. Making stillbirths visible: a systematic review of globally reported causes of stillbirth. BJOG An Int J Obstet Gynaecol. 2018 Jan 1;125(2):212–24.
4. Lees CC, Stampalija T, Baschat A, da Silva Costa F, Ferrazzi E, Figueras F, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol. 2020;56(2):298–312.
5. Figueras F, Caradeux J, Crispi F, Eixarch E, Peguero A, Gratacos E. Diagnosis and surveillance of late-onset fetal growth restriction. Am J Obstet Gynecol. 2018 Feb 1;218(2):S790-S802.e1.
6. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol. 2018 Feb 1;218(2):S855–68.
7. Grobbee DE, Hoes AW. Clinical Epidemiology: Principles, Methods, and Applications for Clinical Research. Jones & Bartlett Publishers; 2014. 472 p.
8. McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, and the P-DTAG. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018;319(4):388–96.
9. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing Bias in Studies of Prognostic Factors. Ann Intern Med. 2013;158(4):280–6.
10. Abdallah A, Eldorf A, Sallam S, Ahmed S, Shawky M, Nawara M, et al. Nuchal cord: impact of umbilical artery Doppler indices on intrapartum and neonatal outcomes: a prospective cohort study. J Matern Neonatal Med. 2019;32(20):3367–78.
11. Bano S, Chaudhary V, Pande S, Mehta V, Sharma A. Color doppler evaluation of cerebral-umbilical pulsatility ratio and its usefulness in the diagnosis of intrauterine growth retardation and prediction of adverse perinatal outcome. Indian J Radiol Imaging. 2010;20(1):20–5.
12. Kumari S, Deka D, Dadhwal V, Perumal V. Correlation of fetal blood vessel Doppler measurements with fetal anemia among Rhesus isoimmunized pregnancies after two intrauterine transfusions. Int J Gynecol Obstet. 2019;146(2):218–22.
13. Lakhkar BN, Rajagopal K V, Gourisankar PT. Doppler prediction of adverse perinatal outcome in PIH and IUGR. Indian J Radiol Imaging. 2006;16(1):109.
14. Pattinson RC, Brink AL, De Wet PE, Odendaal HJ. Early detection of poor fetal prognosis by serial Doppler velocimetry in high-risk pregnancies. South African Med J. 1991/11/02. 1991;80(9):428–31.
15. Rani S, Huria A, Kaur R. Prediction of perinatal outcome in preeclampsia using middle cerebral artery and umbilical artery pulsatility and resistance indices. Hypertens Pregnancy. 2016;35(2):210–6.

16. Rocca MM, Said MS, Khamis MY, Ghanem IA, Karkour TA. The Value of Doppler Study of the Umbilical Artery in Predicting Perinatal Outcome in Pre-Eclamptic Patients. J Obstet Gynaecol (Lahore). 1995;21(5):427–31.
17. Agbaje OA, Adeyomoye AAO, Omidiji OAT, Oboke OS, Afolabi BB. Evaluation of Umbilical Artery Doppler Indices in Pregnant Women With Sickle Cell Anemia Disease at a Nigerian Tertiary Hospital. J Diagnostic Med Sonogr. 2018;34(6):466–78.
18. Anshul D, Neelu S, Suneeta G. Significance of umbilical artery Doppler velocimetry in the perinatal outcome of the growth restricted fetuses. J Obstet Gynecol India. 2010;60(1):38–43.
19. Ebrashy A, Azmy O, Ibrahim M, Waly M, Edris A. Middle cerebral/umbilical artery resistance index ratio as sensitive parameter for fetal well-being and neonatal outcome in patients with preeclampsia: case-control study. Croat Med J. 2005;46(5).
20. Geerts L, Odendaal HJ. Severe early onset pre-eclampsia: prognostic value of ultrasound and Doppler assessment. J Perinatol. 2007;27(6):335–42.
21. Khanduri S, Parashari UC, Bashir S, Bhadury S, Bansal A. Comparison of diagnostic efficacy of umbilical artery and middle cerebral artery waveform with color Doppler study for detection of intrauterine growth restriction. J Obstet Gynaecol India. 2013/03/12. 2013;63(4):249–55.
22. Lakshmi CVS, Pramod G, Geeta K, Subramaniam S, Rao MB, Kallapur SG, et al. Outcome of very low birth weight infants with abnormal antenatal doppler flow patterns: A prospective cohort study. Indian Pediatr. 2013;50(9):847–52.
23. Malik R, Saxena A. Role of Colour Doppler Indices in the Diagnosis of Intrauterine Growth Retardation in High-Risk Pregnancies. J Obstet Gynecol India. 2013;63(1):37–44.
24. Mullick S, Kushtagi P, Swain UK, Rao K, Muralidhar BG. Doppler waveform patterns of the umbilical artery — screening test for high risk pregnancies. Int J Gynecol Obstet. 1993 Feb 1;40(2):115–8.
25. Nagar T, Sharma D, Choudhary M, Khoiwal S, Nagar RP, Pandita A. The Role of Uterine and Umbilical Arterial Doppler in High-risk Pregnancy: A Prospective Observational Study from India. Clin Med Insights Reprod Heal. 2015;9:CMRH.S24048.
26. Najam R, Gupta S, Shalini. Predictive Value of Cerebroplacental Ratio in Detection of Perinatal Outcome in High-Risk Pregnancies. J Obstet Gynecol India. 2016;66(4):244–7.
27. Pattinson RC, Norman K, Odendaal HJ. The use of Doppler velocimetry of the umbilical artery before 24 weeks' gestation to screen for high-risk pregnancies. South African Med J. 1993;83(10):734–6.
28. Waa S, Vinayak S. Comparision of doppler studies in obstetrics with foetal outcome. East Afr Med J. 2010;87(12):502–8.
29. Yelikar KA, Prabhu A, Thakre GG. Role of Fetal Doppler and Non-Stress Test in Preeclampsia and Intrauterine Growth Restriction. J Obstet Gynecol India. 2013;63(3):168–72.
30. Allam IS, Abuelghar W, Fathy H, Enin LA, Sayed M. Prediction of neonatal acidosis by ductus venosus Doppler pattern in high risk pregnancies. Middle East Fertil Soc J. 2013;18(1):47–52.
31. Dhand H, Kansal HK, Dave A. Middle cerebral artery Doppler indices better predictor for fetal outcome in IUGR. J Obstet Gynecol India. 2011;61(2):166–71.

32. Pares D, Chinen PA, Camano L, Moron AF, Torloni MR. Prediction of fetal anemia by Doppler of the middle cerebral artery and descending thoracic aorta. Arch Gynecol Obstet. 2008;278(1):27–31.
33. Alanwar A, El Nour AA, El Mandooh M, Abdelazim IA, Abbas L, Abbas AM, et al. Prognostic accuracy of cerebroplacental ratio for adverse perinatal outcomes in pregnancies complicated with severe pre-eclampsia; a prospective cohort study. Pregnancy Hypertens. 2018;14:86–9.
34. Masihi S, Nikbakht R, Barati M, Momen Gharibvand M, Jadidi A. Association Between Fetal Middle Cerebral Artery and Umbilical Artery Doppler Ratio with Fetal Distress in 38–40 Weeks of Gestation. J Obstet Gynecol India. 2019;69(6):509–13.
35. Dorman EK, Shulman CE, Kingdom J, Bulmer JN, Mwendwa J, Peshu N, et al. Impaired uteroplacental blood flow in pregnancies complicated by falciparum malaria. Ultrasound Obstet Gynecol. 2002;19(2):165–70.
36. Nouh AA, Shalaby SM. The predictive value of uterine blood flow in detecting the risk of adverse pregnancy outcome in patients with polycystic ovary syndrome. Middle East Fertil Soc J. 2011;16(4):284–90.
37. Phupong V, Dejthevaporn T, Tanawattanacharoen S, Manotaya S, Tannirandorn Y, Charoenvidhya D. Predicting the risk of preeclampsia and small for gestational age infants by uterine artery Doppler in low-risk women. Arch Gynecol Obstet. 2003;268(3):158–61.
38. Verma D, Gupta S. Prediction of adverse pregnancy outcomes using uterine artery Doppler imaging at 22-24 weeks of pregnancy: A North Indian experience. Turkish J Obstet Gynecol. 2016/06/15. 2016;13(2):80–4.
39. Zarean E, Shabaninia S. The Assessment of Association between Uterine Artery Pulsatility Index at 30-34 Week's Gestation and Adverse Perinatal Outcome. Adv Biomed Res. 2018;7:111.
40. Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev. 2017/06/15. 2017;2017(6):CD007529.
41. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48(3):333–9.
42. Conde-Agudelo A, Villar J, Kennedy SH, Papageorghiou AT. Predictive accuracy of cerebroplacental ratio for adverse perinatal and neurodevelopmental outcomes in suspected fetal growth restriction: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;52(4):430–41.
43. Vollgraff Heidweiller-Schreurs CA, De Boer MA, Heymans MW, Schoonmade LJ, Bossuyt PMM, Mol BWJ, et al. Prognostic accuracy of cerebroplacental ratio and middle cerebral artery Doppler for adverse perinatal outcome: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;51(3):313–22.
44. Velauthar L, Plana MN, Kalidindi M, Zamora J, Thilaganathan B, Illanes SE, et al. First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55 974 women. Ultrasound Obstet Gynecol. 2014 May 1;43(5):500–7.
45. Martinez-Portilla RJ, Lopez-Felix J, Hawkins-Villareal A, Villafan-Bernal JR, Paz y Miño F, Figueras F, et al. Performance of fetal middle cerebral artery peak systolic velocity for prediction of anemia in untransfused and transfused fetuses: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2019;54(6):722–31.

46. Duffy JMN, Rolph R, Gale C, Hirsch M, Khan KS, Ziebland S, et al. Core outcome sets in women's and newborn health: a systematic review. BJOG An Int J Obstet Gynaecol. 2017 Sep 1;124(10):1481–9.

Supplemental appendix S1. Search strings for the databases used to retrieve articles

EMBASE

(‘developing countr*’:ti,ab,kw OR ‘developing nation*’:ti,ab,kw OR ‘developing population*’:ti,ab,kw OR ‘developing econom*’:ti,ab,kw OR ‘undeveloped countr*’:ti,ab,kw OR ‘undeveloped nation*’:ti,ab,kw OR ‘undeveloped economy’:ti,ab,kw OR ‘undeveloped economies’:ti,ab,kw OR ‘least developed countr*’:ti,ab,kw OR ‘least developed nation*’:ti,ab,kw OR ‘least developed economy’:ti,ab,kw OR ‘least developed economies’:ti,ab,kw OR ‘less-developed countr*’:ti,ab,kw OR ‘less-developed nation*’:ti,ab,kw OR ‘less-developed population’:ti,ab,kw OR ‘less-developed populations’:ti,ab,kw OR ‘less-developed econom*’:ti,ab,kw OR ‘lesser developed countr*’:ti,ab,kw OR ‘lesser developed nation*’:ti,ab,kw OR ‘lesser developed population’:ti,ab,kw OR ‘lesser developed populations’:ti,ab,kw OR ‘lesser developed economy’:ti,ab,kw OR ‘lesser developed economies’:ti,ab,kw OR ‘under-developed countr*’:ti,ab,kw OR ‘under-developed nation*’:ti,ab,kw OR ‘underdeveloped countr*’:ti,ab,kw OR ‘underdeveloped nation*’:ti,ab,kw OR ‘underdeveloped population*’:ti,ab,kw OR ‘underdeveloped econom*’:ti,ab,kw OR ‘low income countr*’:ti,ab,kw OR ‘middle income countr*’:ti,ab,kw OR ‘low income nation*’:ti,ab,kw OR ‘middle income nation*’:ti,ab,kw OR ‘low income population*’:ti,ab,kw OR ‘middle income population*’:ti,ab,kw OR ‘low income econom*’:ti,ab,kw OR ‘middle income econom*’:ti,ab,kw OR ‘lower income countr*’:ti,ab,kw OR ‘lower income nation*’:ti,ab,kw OR ‘lower income population*’:ti,ab,kw OR ‘lower income economy’:ti,ab,kw OR ‘lower income economies’:ti,ab,kw OR ‘resource limited’:ti,ab,kw OR ‘low resource countr*’:ti,ab,kw OR ‘lower resource countr*’:ti,ab,kw OR ‘low resource nation*’:ti,ab,kw OR ‘low resource population*’:ti,ab,kw OR ‘low resource economy’:ti,ab,kw OR ‘low resource economies’:ti,ab,kw OR ‘underserved countr*’:ti,ab,kw OR ‘underserved nation*’:ti,ab,kw OR ‘underserved population*’:ti,ab,kw OR ‘underserved economy’:ti,ab,kw OR ‘underserved economies’:ti,ab,kw OR ‘under-served country’:ti,ab,kw OR ‘under-served countries’:ti,ab,kw OR ‘under-served nation':ti,ab,kw OR 'under-served nations':ti,ab,kw OR 'under-served population':ti,ab,kw OR 'under-served populations':ti,ab,kw OR 'underserved economy':ti,ab,kw OR 'underserved economies':ti,ab,kw OR 'derived countr*':ti,ab,kw OR 'deprived nation':ti,ab,kw OR 'deprived nations':ti,ab,kw OR 'derived population*':ti,ab,kw OR 'deprived economy':ti,ab,kw OR 'deprived economies':ti,ab,kw OR 'poor countr*':ti,ab,kw OR 'poor nation*':ti,ab,kw OR 'poor population*':ti,ab,kw OR 'poor econom*':ti,ab,kw OR 'poorer countr*':ti,ab,kw OR 'poorer nation*':ti,ab,kw OR 'poorer population*':ti,ab,kw OR 'poorer econom*':ti,ab,kw OR 'lmic':ti,ab,kw OR 'lmics':ti,ab,kw OR 'lami':ti,ab,kw OR 'transitional countr*':ti,ab,kw OR 'transitional nation':ti,ab,kw OR 'transitional nations':ti,ab,kw OR 'transitional econom*':ti,ab,kw OR 'transition countr*':ti,ab,kw OR 'transition nation*':ti,ab,kw OR 'transition econom*':ti,ab,kw OR low 'resource setting*':ti,ab,kw OR 'lower resource setting*':ti,ab,kw OR 'middle resource setting*':ti,ab,kw OR 'Third World*':ti,ab,kw OR 'south east asia*':ti,ab,kw OR 'middle east*':ti,ab,kw OR 'Afghan*':ti,ab,kw OR 'Angola*':ti,ab,kw OR 'Angolese*':ti,ab,kw OR 'Angolian*':ti,ab,kw OR 'Armenia*':ti,ab,kw OR 'Bangladesh*':ti,ab,kw OR 'Benin*':ti,ab,kw OR 'Bhutan*':ti,ab,kw OR 'Birma*':ti,ab,kw OR 'Burma*':ti,ab,kw OR 'Birmese*':ti,ab,kw OR 'Burmese*':ti,ab,kw OR 'Boliv*':ti,ab,kw OR 'Botswan*':ti,ab,kw OR 'burkina Faso*':ti,ab,kw OR 'Burundi*':ti,ab,kw OR 'Cabo Verde*':ti,ab,kw OR 'Cambod*':ti,ab,kw OR 'Cameroon*':ti,ab,kw OR 'Cape Verd*':ti,ab,kw OR 'Central Africa*':ti,ab,kw OR 'Chad':ti,ab,kw OR 'Comoro*':ti,ab,kw OR 'Congo*':ti,ab,kw OR 'Cote d/Ivoire*':ti,ab,kw OR 'Djibouti*':ti,ab,kw OR 'East Africa*':ti,ab,kw OR 'Eastern Africa*':ti,ab,kw OR 'Egypt*':ti,ab,kw OR 'El Salvador*':ti,ab,kw OR 'Equatorial Guinea*':ti,ab,kw OR 'Eritre*':ti,ab,kw OR 'Ethiopia*':ti,ab,kw OR 'Gabon*':ti,ab,kw OR 'Gambia*':ti,ab,kw OR 'Gaza*':ti,ab,kw OR 'Georgia Republic'/exp OR 'Ghan*':ti,ab,kw OR 'Guatemal*':ti,ab,kw OR 'Guinea':ti,ab,kw OR 'Haiti*':ti,ab,kw OR 'Hondur*':ti,ab,kw OR 'India*':ti,ab,kw OR 'Indones*':ti,ab,kw OR 'Ivory Coast*':ti,ab,kw OR 'Kenya*':ti,ab,kw OR 'Kiribati*':ti,ab,kw OR 'Kosovo*':ti,ab,kw OR 'Kyrgyz*':ti,ab,kw OR 'Lao PDR*':ti,ab,kw OR 'Laos*':ti,ab,kw OR 'Lesotho*':ti,ab,kw OR 'Liberia*':ti,ab,kw OR 'Madagascar*':ti,ab,kw OR 'Malaw*':ti,ab,kw OR 'Mali':ti,ab,kw OR

'Mauritan*':ti,ab,kw OR 'Mauriti*':ti,ab,kw OR 'Micronesi*':ti,ab,kw OR 'Mocambiqu*':ti,ab,kw OR 'Moldov*':ti,ab,kw OR 'Mongolia*':ti,ab,kw OR 'Morocc*':ti,ab,kw OR 'Mozambiqu*':ti,ab,kw OR 'Myanmar*':ti,ab,kw OR 'Namibia*':ti,ab,kw OR 'Nepal*':ti,ab,kw OR 'Nicaragua*':ti,ab,kw OR 'Niger*':ti,ab,kw OR 'North Korea*':ti,ab,kw OR 'Northern Korea*':ti,ab,kw OR 'Democratic People/s Republic of Korea':ti,ab,kw OR 'Pakistan*':ti,ab,kw OR 'Papua New Guinea*':ti,ab,kw OR 'Philippine*':ti,ab,kw OR 'Principe':ti,ab,kw OR 'Rhodesia*':ti,ab,kw OR 'Rwanda*':ti,ab,kw OR 'Samoa*':ti,ab,kw OR 'Sao Tome*':ti,ab,kw OR 'Senegal*':ti,ab,kw OR 'Sierra Leone*':ti,ab,kw OR 'Solomon Islands*':ti,ab,kw OR 'Somalia*':ti,ab,kw OR 'South Africa*':ti,ab,kw OR 'South Sudan*':ti,ab,kw OR 'Southern Africa*':ti,ab,kw OR 'Sri Lanka*':ti,ab,kw OR 'Sub Saharan Africa*':ti,ab,kw OR 'Subsaharan Africa*':ti,ab,kw OR 'Sudan*':ti,ab,kw OR 'Swaziland*':ti,ab,kw OR 'Syria*':ti,ab,kw OR 'Tajikist*':ti,ab,kw OR 'Tanzan*':ti,ab,kw OR 'Timor*':ti,ab,kw OR 'Togo*':ti,ab,kw OR 'Tonga*':ti,ab,kw OR 'Tunis*':ti,ab,kw OR 'Ugand*':ti,ab,kw OR 'Ukrain*':ti,ab,kw OR 'Uzbekistan*':ti,ab,kw OR 'Vanuatu*':ti,ab,kw OR 'Vietnam*':ti,ab,kw OR 'West Africa*':ti,ab,kw OR 'West Bank*':ti,ab,kw OR 'Western Africa*':ti,ab,kw OR 'Yemen*':ti,ab,kw OR 'Zaire*':ti,ab,kw OR 'Zambia*':ti,ab,kw OR 'Zimbabw*':ti,ab,kw)

AND

('Umbilical Arter*'/exp OR 'Uterine Artery'/exp OR 'Middle Cerebral Artery'/exp OR 'Ductus Venosus'/exp OR 'Umbilical Vein*'/exp OR 'Inferior Cava Vein'/exp OR 'Umbilical Arter*':ti,ab,kw OR 'Uterine Arter*':ti,ab,kw OR 'Middle Cerebral Arter*':ti,ab,kw OR 'Patent Ductus Venosus':ti,ab,kw OR 'Umbilical Vein*':ti,ab,kw OR 'Inferior Vena Cava':ti,ab,kw OR 'Cerebroplacental Ratio':ti,ab,kw OR 'CPR':ti,ab,kw OR 'Fetal Descending Aorta':ti,ab,kw OR 'FDA':ti,ab,kw OR 'Doppler Ultrasonography'/exp OR 'Doppler Ultrasound*':ti,ab,kw OR 'Doppler Ultrasonography':ti,ab,kw OR 'Uterine Artery Doppler':ti,ab,kw)

AND

(‘Stillbirth’:ti,ab,kw OR ‘Perinatal Death’:ti,ab,kw OR ‘Cesarean Section*’:ti,ab,kw OR ‘Caesarean Section*’:ti,ab,kw OR ‘Acidosis’:ti,ab,kw OR ‘Premature Birth’:ti,ab,kw OR ‘Neonatal Intensive Care’:ti,ab,kw OR ‘Fetal Growth Retard*’:ti,ab,kw OR ‘Newborn Respiratory Distress Syndrome*’:ti,ab,kw OR ‘Gestational Age’:ti,ab,kw OR ‘Birth Weight’:ti,ab,kw OR ‘Asphyxia Neonatorum’:ti,ab,kw OR ‘Apgar Score*’:ti,ab,kw OR ‘Length of Stay’:ti,ab,kw OR ‘Stillbirth’/exp OR ‘Perinatal Death’/exp OR ‘Perinatal Mortality’/exp OR ‘Cesarean Section’/exp OR ‘Acidosis’/exp OR ‘Prematurity’/exp OR ‘Newborn Intensive Care’/exp OR ‘Intrauterine Growth Retardation’/exp OR ‘Neonatal Respiratory Distress Syndrome’/exp OR ‘Gestational Age’/exp OR ‘Birth Weight’/exp OR ‘Newborn Hypoxia’/exp OR ‘Apgar Score’/exp OR ‘Length of Stay’/exp OR ‘Pregnancy’:ti,ab,kw OR ‘Pregnancies’:ti,ab,kw OR ‘Gestation’:ti,ab,kw OR ‘Pregnant’:ti,ab,kw OR ‘Pregnancy’/exp)

PUBMED (MEDLINE)

(“Developing Countries”[Mesh] OR developing countr*[tiab] OR developing nation*[tiab] OR developing population*[tiab] OR developing econom*[tiab] OR undeveloped countr*[tiab] OR undeveloped nation*[tiab] OR “undeveloped economy”[tiab] OR “undeveloped economies”[tiab] OR least developed countr*[tiab] OR least developed nation*[tiab] OR “least developed economy”[tiab] OR “least developed economies”[tiab] OR less-developed countr*[tiab] OR less-developed nation*[tiab] OR “less-developed population”[tiab] OR “less-developed populations”[tiab] OR less-developed econom*[tiab] OR lesser developed countr*[tiab] OR lesser developed nation*[tiab] OR “lesser developed population”[tiab] OR “lesser developed populations”[tiab] OR “lesser developed economy”[tiab] OR “lesser developed economies”[tiab] OR under-developed countr*[tiab] OR under-developed nation*[tiab] OR underdeveloped countr*[tiab] OR underdeveloped nation*[tiab] OR underdeveloped population*[tiab] OR underdeveloped econom*[tiab] OR low income countr*[tiab] OR middle income countr*[tiab] OR low income nation*[tiab] OR middle income nation*[tiab] OR low income population*[tiab] OR middle income population*[tiab] OR low income econom*[tiab] OR middle income econom*[tiab] OR lower income countr*[tiab] OR lower income nation*[tiab]

OR lower income population*[tiab] OR “lower income economy”[tiab] OR “lower income economies”[tiab] OR resource limited[tiab] OR low resource countr*[tiab] OR lower resource countr*[tiab] OR low resource nation*[tiab] OR low resource population*[tiab] OR “low resource economy”[tiab] OR “low resource economies”[tiab] OR underserved countr*[tiab] OR underserved nation*[tiab] OR underserved population*[tiab] OR “underserved economy”[tiab] OR “underserved economies”[tiab] OR “under-served country”[tiab] OR “under-served countries”[tiab] OR “under-served nation”[tiab] OR “under-served nations”[tiab] OR “under-served population”[tiab] OR “under-served populations”[tiab] OR “underserved economy”[tiab] OR “underserved economies”[tiab] OR derived countr*[tiab] OR “deprived nation”[tiab] OR “deprived nations”[tiab] OR derived population*[tiab] OR “deprived economy”[tiab] OR “deprived economies”[tiab] OR poor countr*[tiab] OR poor nation*[tiab] OR poor population*[tiab] OR poor econom*[tiab] OR poorer countr*[tiab] OR poorer nation*[tiab] OR poorer population*[tiab] OR poorer econom*[tiab] OR lmic[tiab] OR lmics[tiab] OR lami[tiab] OR transitional countr*[tiab] OR “transitional nation”[tiab] OR “transitional nations”[tiab] OR transitional econom*[tiab] OR transition countr*[tiab] OR transition nation*[tiab] OR transition econom*[tiab] OR low resource setting*[tiab] OR lower resource setting*[tiab] OR middle resource setting*[tiab] OR Third World*[tiab] OR south east asia*[tw] OR middle east*[tw] OR Afghan*[tw] OR Angola*[tw] OR Angolese*[tw] OR Angolian*[tw] OR Armenia*[tw] OR Bangladesh*[tw] OR Benin*[tw] OR Bhutan*[tw] OR Birma*[tw] OR Burma*[tw] OR Birmese*[tw] OR Burmese*[tw] OR Boliv*[tw] OR Botswan*[tw] OR burkina Faso*[tw] OR Burundi*[tw] OR Cabo Verde*[tw] OR Cambod*[tw] OR Cameroon*[tw] OR Cape Verd*[tw] OR Central Africa*[tw] OR Chad[tw] OR Comoro*[tw] OR Congo*[tw] OR Cote d’Ivoire*[tw] OR Djibouti*[tw] OR East Africa*[tw] OR Eastern Africa*[tw] OR Egypt*[tw] OR El Salvador*[tw] OR Equatorial Guinea*[tw] OR Eritre*[tw] OR Ethiopia*[tw] OR Gabon*[tw] OR Gambia*[tw] OR Gaza*[tw] OR “Georgia Republic”[Mesh] OR Ghan*[tw] OR Guatemal*[tw] OR Guinea[tw] OR Haiti*[tw] OR Hondur*[tw] OR India*[tw] OR Indones*[tw] OR Ivory Coast*[tw] OR Kenya*[tw] OR Kiribati*[tw] OR Kosovo*[tw] OR Kyrgyz*[tw] OR Lao PDR*[tw] OR Laos*[tw] OR Lesotho*[tw] OR Liberia*[tw]

OR Madagascar*[tw] OR Malaw*[tw] OR Mali[tw] OR Mauritan*[tw] OR Mauriti*[tw] OR Micronesi*[tw] OR Mocambiqu*[tw] OR Moldov*[tw] OR Mongolia*[tw] OR Morocc*[tw] OR Mozambiqu*[tw] OR Myanmar*[tw] OR Namibia*[tw] OR Nepal*[tw] OR Nicaragua*[tw] OR Niger*[tw] OR North Korea*[tw] OR Northern Korea*[tw] OR "Democratic People s Republic of Korea"[tiab] OR "Democratic People's Republic of Korea"[Mesh] OR Pakistan*[tw] OR Papua New Guinea*[tw] OR Philippine*[tw] OR Principe[tw] OR Rhodesia*[tw] OR Rwanda*[tw] OR Samoa*[tw] OR Sao Tome*[tw] OR Senegal*[tw] OR Sierra Leone*[tw] OR Solomon Islands*[tw] OR Somalia*[tw] OR South Africa*[tw] OR South Sudan*[tw] OR Southern Africa*[tw] OR Sri Lanka*[tw] OR Sub Saharan Africa*[tw] OR Subsaharan Africa*[tw] OR Sudan*[tw] OR Swaziland*[tw] OR Syria*[tw] OR Tajikist*[tw] OR Tanzan*[tw] OR Timor*[tw] OR Togo*[tw] OR Tonga*[tw] OR Tunis*[tw] OR Ugand*[tw] OR Ukrain*[tw] OR Uzbekistan*[tw] OR Vanuatu*[tw] OR Vietnam*[tw] OR West Africa*[tw] OR West Bank*[tw] OR Western Africa*[tw] OR Yemen*[tw] OR Zaire*[tw] OR Zambia*[tw] OR Zimbabw*[tw])

2

AND

("Umbilical Arteries"[Mesh] OR "Uterine Artery"[Mesh] OR "Middle Cerebral Artery"[Mesh] OR "Ductus Venosus" [Supplementary Concept] OR "Umbilical Veins"[Mesh] OR "Vena Cava, Inferior"[Mesh] OR Umbilical Arter*[tiab] OR Uterine Arter*[tiab] OR Middle Cerebral Arter*[tiab] OR Patent Ductus Venosus[tiab] OR Umbilical Vein*[tiab] OR Inferior Vena Cava[tiab] OR Cerebroplacental Ratio[tiab] OR CPR[tiab] OR Fetal Descending Aorta[tiab] OR FDA[tiab] OR "Ultrasonography, Doppler"[Mesh] OR Doppler Ultrasound*[Title/Abstract] OR Doppler Ultrasonography[Title/Abstract] OR Uterine Artery Doppler[Title/Abstract])

AND

("Stillbirth"[tiab] OR "Perinatal Death"[tiab] OR "Cesarean Section*"[tiab] OR "Caesarean Section*"[tiab] OR Acidosis[tiab] OR Premature Birth[tiab] OR Neonatal Intensive Care"[tiab] OR Fetal Growth Retard*[tiab] OR Newborn

Respiratory Distress Syndrome*[tiab] OR Gestational Age[tiab] OR Birth Weight[tiab] OR Asphyxia Neonatorum[tiab] OR Apgar Score*[tiab] OR Length of Stay"[tiab] OR "Stillbirth"[Mesh] OR "Perinatal Death"[Mesh] OR "Cesarean Section"[Mesh] OR "Acidosis"[Mesh] OR "Premature Birth"[Mesh] OR "Intensive Care, Neonatal"[Mesh] OR "Fetal Growth Retardation"[Mesh] OR "Respiratory Distress Syndrome, Newborn"[Mesh] OR "Gestational Age"[Mesh] OR "Birth Weight"[Mesh] OR "Asphyxia Neonatorum"[Mesh] OR "Apgar Score"[Mesh] OR "Length of Stay"[Mesh] OR Pregnancy[Title/Abstract] OR Pregnancies[Title/Abstract] OR Gestation[Title/Abstract] OR Pregnant[Title/Abstract] OR "Pregnancy"[Mesh])

COCHRANE

'developing countr*' OR 'developing nation*' OR 'developing population*' OR 'developing econom*' OR 'undeveloped countr*' OR 'undeveloped nation*' OR 'undeveloped economy' OR 'undeveloped economies' OR 'least developed countr*' OR 'least developed nation*' OR 'least developed economy' OR 'least developed economies' OR 'less-developed countr*' OR 'less-developed nation*' OR 'less-developed population' OR 'less-developed populations' OR 'less-developed econom*' OR 'lesser developed countr*' OR 'lesser developed nation*' OR 'lesser developed population' OR 'lesser developed populations' OR 'lesser developed economy' OR 'lesser developed economies' OR 'under-developed countr*' OR 'under-developed nation*' OR 'underdeveloped countr*'OR 'underdeveloped nation*' OR 'underdeveloped population*' OR 'underdeveloped econom*' OR 'low income countr*' OR 'middle income countr*' OR 'low income nation*' OR 'middle income nation*' OR 'low income population*' OR 'middle income population*' OR 'low income econom*' OR 'middle income econom*' OR 'lower income countr*' OR 'lower income nation*' OR 'lower income population*' OR 'lower income economy' OR 'lower income economies' OR 'resource limited' OR 'low resource countr*' OR 'lower resource countr*' OR 'low resource nation*' OR 'low resource population*' OR 'low resource economy' OR 'low resource economies' OR 'underserved countr*' OR 'underserved nation*' OR 'underserved population*' OR 'underserved economy' OR 'underserved economies' OR 'under-served country' OR 'under-served countries' OR 'under-served nation'

OR ‘under-served nations’ OR ‘under-served population’ OR ‘under-served populations’ OR ‘underserved economy’ OR ‘underserved economies’ OR ‘derived countr*’ OR ‘deprived nation’ OR ‘deprived nations’ OR ‘derived population*’ OR ‘deprived economy’ OR ‘deprived economies’ OR ‘poor countr*’ OR ‘poor nation*’ OR ‘poor population*’ OR ‘poor econom*’ OR ‘poorer countr*’ OR ‘poorer nation*’ OR ‘poorer population*’ OR ‘poorer econom*’ OR ‘lmic’ OR ‘lmics’ OR ‘lami’ OR ‘transitional countr*’ OR ‘transitional nation’ OR ‘transitional nations’ OR ‘transitional econom*’ OR ‘transition countr*’ OR ‘transition nation*’ OR ‘transition econom*’ OR low ‘resource setting*’ OR ‘lower resource setting*’ OR ‘middle resource setting*’ OR ‘Third World*’ OR ‘south east asia*’ OR ‘middle east*’ OR ‘Afghan*’ OR ‘Angola*’ OR ‘Angolese*’ OR ‘Angolian*’ OR ‘Armenia*’ OR ‘Bangladesh*’ OR ‘Benin*’ OR ‘Bhutan*’ OR ‘Birma*’ OR ‘Burma*’ OR ‘Birmese*’ OR ‘Burmese*’ OR ‘Boliv*’ OR ‘Botswan*’ OR ‘burkina Faso*’ OR ‘Burundi*’ OR ‘Cabo Verde*’ OR ‘Cambod*’ OR ‘Cameroon*’ OR ‘Cape Verd*’ OR ‘Central Africa*’ OR ‘Chad’ OR ‘Comoro*’ OR ‘Congo*’ OR ‘Cote d’Ivoire*’ OR ‘Djibouti*’ OR ‘East Africa*’ OR ‘Eastern Africa*’ OR ‘Egypt*’ OR ‘El Salvador*’ OR ‘Equatorial Guinea*’ OR ‘Eritre*’ OR ‘Ethiopia*’ OR ‘Gabon*’ OR ‘Gambia*’ OR ‘Gaza*’ OR ‘Georgia Republic’ OR ‘Ghan*’ OR ‘Guatemal*’ OR ‘Guinea’ OR ‘Haiti*’ OR ‘Hondur*’ OR ‘India*’ OR ‘Indones*’ OR ‘Ivory Coast*’ OR ‘Kenya*’ OR ‘Kiribati*’ OR ‘Kosovo*’ OR ‘Kyrgyz*’ OR ‘Lao PDR*’ OR ‘Laos*’ OR ‘Lesotho*’ OR ‘Liberia*’ OR ‘Madagascar*’ OR ‘Malaw*’ OR ‘Mali’ OR ‘Mauritan*’ OR ‘Mauriti*’ OR ‘Micronesi*’ OR ‘Mocambiqu*’ OR ‘Moldov*’ OR ‘Mongolia*’ OR ‘Morocc*’ OR ‘Mozambiqu*’ OR ‘Myanmar*’ OR ‘Namibia*’ OR ‘Nepal*’ OR ‘Nicaragua*’ OR ‘Niger*’ OR ‘North Korea*’ OR ‘Northern Korea*’ OR ‘Democratic People’s Republic of Korea’ OR ‘Pakistan*’ OR ‘Papua New Guinea*’ OR ‘Philippine*’ OR ‘Principe’ OR ‘Rhodesia*’ OR ‘Rwanda*’ OR ‘Samoa*’ OR ‘Sao Tome*’ OR ‘Senegal*’ OR ‘Sierra Leone*’ OR ‘Solomon Islands*’ OR ‘Somalia*’ OR ‘South Africa*’ OR ‘South Sudan*’ OR ‘Southern Africa*’ OR ‘Sri Lanka*’ OR ‘Sub Saharan Africa*’ OR ‘Subsaharan Africa*’ OR ‘Sudan*’ OR ‘Swaziland*’ OR ‘Syria*’ OR ‘Tajikist*’ OR ‘Tanzan*’ OR ‘Timor*’ OR ‘Togo*’ OR ‘Tonga*’ OR ‘Tunis*’ OR ‘Ugand*’ OR ‘Ukrain*’ OR ‘Uzbekistan*’ OR ‘Vanuatu*’ OR ‘Vietnam*’ OR ‘West Africa*’ OR ‘West Bank*’ OR ‘Western Africa*’ OR ‘Yemen*’ OR ‘Zaire*’ OR ‘Zambia*’ OR ‘Zimbabw*’

AND

‘Umbilical Arter*’ OR ‘Uterine Artery’ OR ‘Middle Cerebral Artery’ OR ‘Ductus Venosus’ OR ‘Umbilical Vein*’ OR ‘Inferior Cava Vein’ OR ‘Uterine Arter*’ OR ‘Middle Cerebral Arter*’ OR ‘Patent Ductus Venosus’ OR ‘Inferior Vena Cava’ OR ‘Cerebroplacental Ratio’ OR ‘CPR’ OR ‘Fetal Descending Aorta’ OR ‘FDA’ OR ‘Doppler Ultrasonography’ OR ‘Doppler Ultrasound*’ OR ‘Doppler Ultrasonography’ OR ‘Uterine Artery Doppler’

AND

‘Stillbirth’ OR ‘Perinatal Death’ OR ‘Cesarean Section*’ OR ‘Caesarean Section*’ OR ‘Acidosis’ OR ‘Premature Birth’ OR ‘Neonatal Intensive Care’ OR ‘Fetal Growth Retard*’ OR ‘Newborn Respiratory Distress Syndrome*’ OR ‘Gestational Age’ OR ‘Birth Weight’ OR ‘Asphyxia Neonatorum’ OR ‘Apgar Score*’ OR ‘Perinatal Mortality’ OR ‘Cesarean Section’ OR ‘Prematurity’ OR ‘Newborn Intensive Care’ OR ‘Intrauterine Growth Retardation’ OR ‘Neonatal Respiratory Distress Syndrome’ OR ‘Gestational Age’ OR ‘Birth Weight’ OR ‘Newborn Hypoxia’ OR ‘Length of Stay’ OR ‘Pregnancy’ OR ‘Pregnancies’ OR ‘Gestation’ OR ‘Pregnant’

SCOPUS

TITLE-ABS-KEY(“developing countr*” OR “developing nation*” OR “developing population*” OR “developing econom*” OR “undeveloped countr*” OR “undeveloped nation*” OR “undeveloped economy” OR “undeveloped economies” OR “least developed countr*” OR “least developed nation*” OR “least developed economy” OR “least developed economies” OR “less-developed countr*” OR “less-developed nation*” OR “less-developed population” OR “less-developed populations” OR “less-developed econom*” OR “lesser developed countr*” OR “lesser developed nation*” OR “lesser developed population” OR “lesser developed populations” OR “lesser developed economy” OR “lesser developed economies” OR “under-developed countr*” OR “under-developed nation*” OR “underdeveloped countr*” OR “underdeveloped nation*” OR “underdeveloped population*” OR “underdeveloped econom*” OR “low income countr*” OR “middle income countr*” OR “low income nation*” OR “middle income nation*” OR “low income population*” OR “middle income population*” OR “low income econom*” OR “middle income econom*” OR “lower income countr*” OR “lower income nation*” OR “lower income population*” OR “lower income economy” OR “lower income economies” OR “resource limited” OR “low resource countr*” OR “lower resource countr*” OR “low resource nation*” OR “low resource population*” OR “low resource economy” OR “low resource economies” OR “underserved countr*” OR “underserved nation*” OR “underserved population*” OR “underserved economy” OR “underserved economies” OR “under-served country” OR “under-served countries” OR “under-served nation” OR “under-served nations” OR “under-served population” OR “under-served populations” OR “underserved economy” OR “underserved economies” OR “derived countr*” OR “deprived nation” OR “deprived nations” OR “derived population*” OR “deprived economy” OR “deprived economies” OR “poor countr*” OR “poor nation*” OR “poor population*” OR “poor econom*” OR “poorer countr*” OR “poorer nation*” OR “poorer population*” OR “poorer econom*” OR “lmic” OR “lmics” OR “lami” OR “transitional countr*” OR “transitional nation” OR “transitional nations” OR “transitional econom*” OR “transition countr*” OR “transition nation*” OR “transition econom*” OR low “resource setting*” OR “lower resource setting*” OR “middle resource setting*” OR “Third World*” OR “south east asia*” OR “middle east*” OR “Afghan*” OR “Angola*” OR “Angolese*” OR “Angolian*” OR “Armenia*” OR “Bangladesh*” OR “Benin*” OR “Bhutan*” OR “Birma*” OR “Burma*” OR “Birmese*” OR “Burmese*” OR “Boliv*” OR “Botswan*” OR “burkina Faso*” OR “Burundi*” OR “Cabo Verde*” OR “Cambod*” OR “Cameroon*” OR “Cape Verd*” OR “Central Africa*” OR “Chad” OR “Comoro*” OR “Congo*” OR “Cote d/Ivoire*” OR “Djibouti*” OR “East Africa*” OR “Eastern Africa*” OR “Egypt*” OR “El Salvador*” OR “Equatorial Guinea*” OR “Eritre*” OR “Ethiopia*” OR “Gabon*” OR “Gambia*” OR “Gaza*” OR “Georgia Republic” OR “Ghan*” OR “Guatemal*” OR “Guinea” OR “Haiti*” OR “Hondur*” OR “India*” OR “Indones*” OR “Ivory Coast*” OR “Kenya*” OR “Kiribati*” OR “Kosovo*” OR “Kyrgyz*” OR “Lao PDR*” OR “Laos*” OR “Lesotho*” OR “Liberia*” OR “Madagascar*” OR “Malaw*” OR “Mali” OR “Mauritan*” OR “Mauriti*” OR “Micronesi*” OR “Mocambiqu*” OR “Moldov*” OR “Mongolia*” OR “Morocc*” OR “Mozambiqu*”

OR “Myanmar*” OR “Namibia*” OR “Nepal*” OR “Nicaragua*” OR “Niger*” OR “North Korea*” OR “Northern Korea*” OR “Democratic People/s Republic of Korea” OR “Pakistan*” OR “Papua New Guinea*” OR “Philippine*” OR “Principe” OR “Rhodesia*” OR “Rwanda*” OR “Samoa*” OR “Sao Tome*” OR “Senegal*” OR “Sierra Leone*” OR “Solomon Islands*” OR “Somalia*” OR “South Africa*” OR “South Sudan*” OR “Southern Africa*” OR “Sri Lanka*” OR “Sub Saharan Africa*” OR “Subsaharan Africa*” OR “Sudan*” OR “Swaziland*” OR “Syria*” OR “Tajikist*” OR “Tanzan*” OR “Timor*” OR “Togo*” OR “Tonga*” OR “Tunis*” OR “Ugand*” OR “Ukrain*” OR “Uzbekistan*” OR “Vanuatu*” OR “Vietnam*” OR “West Africa*” OR “West Bank*” OR “Western Africa*” OR “Yemen*” OR “Zaire*” OR “Zambia*” OR “Zimbabw*”)

AND

TITLE-ABS-KEY(“Stillbirth” OR “Perinatal Death” OR “Cesarean Section*” OR “Caesarean Section*” OR “Acidosis” OR “Premature Birth” OR “Neonatal Intensive Care” OR “Fetal Growth Retard*” OR “Newborn Respiratory Distress Syndrome*” OR “Gestational Age” OR “Birth Weight” OR “Asphyxia Neonatorum” OR “Apgar Score*” OR “Length of Stay” OR “Stillbirth” OR “Perinatal Death” OR “Cesarean Section” OR “Acidosis” OR “Premature Birth” OR “Intensive Care, Neonatal” OR “Fetal Growth Retardation” OR “Respiratory Distress Syndrome, Newborn” OR “Gestational Age” OR “Birth Weight” OR “Asphyxia Neonatorum” OR “Apgar Score” OR “Length of Stay” OR “Pregnancy” OR “Pregnancies” OR “Gestation” OR “Pregnant” OR “Pregnancy”)

AND

TITLE-ABS-KEY(“Umbilical Arteries” OR “Uterine Artery” OR “Middle Cerebral Artery” OR “Ductus Venosus” OR “Umbilical Veins” OR “Vena Cava, Inferior” OR “Umbilical Arter*” OR “Uterine Arter*” OR “Middle Cerebral Arter*” OR “Patent Ductus Venosus” OR “Umbilical Vein*” OR “Inferior Vena Cava” OR “Cerebroplacental Ratio” OR “CPR” OR “Fetal Descending Aorta” OR “FDA” OR “Ultrasonography, Doppler” OR “Doppler Ultrasound*”OR” Doppler Ultrasonography” OR “Uterine Artery Doppler”)

Supplemental appendix S2. List of full-text articles excluded with reasons

a) Country income level: 3 studies

1. El Shourbagy, S., Elsakhawy, M. (2012). Prediction of fetal anemia by middle cerebral artery Doppler. *Middle East Fertility Society Journal, 17(4), 275-282.*
2. Haley, J., Tuffnell, D. J., Johnson, N. (1997). Randomized controlled trial of cardiotocography versus umbilical artery Doppler in the management of small for gestational age fetuses. *British Journal of Obstetrics and Gynaecology, 104(4), 431-435).*
3. Morales-Rosello, J., Dias, T., Khalil, A., Fornes-Ferrer, V., Ciammella, R., Gimenez-Roca, L., Perales-Marin, A., Thilaganathan, B. (2018). Birth-weight differences at term are explained by placental dysfunction and not by maternal ethnicity. *Ultrasound Obstet Gynecol, 52(4), 488-493.*

b) Design and quality: 9 studies

1. Abidoye, I. A., Ayoola, O. O., Idowu, B., Aderibigbe, A. S., Loto, O. M. (2017). Uterine artery Doppler velocimetry in hypertensive disorder of pregnancy in Nigeria. *J Ultrason, 17(71)) 253-258.*
2. Agarwal, R., Tiwari, A., Wadhwa, N., Radhakrishnan, G., Bhatt, S., Batra, P. (2017). Abnormal umbilical artery Doppler velocimetry and placental histopathological correlation in fetal growth restriction. *South African Journal of Obstetrics and Gynaecology, 23(1), 12-16.*
3. Ali, A., Ara, I., Sultana, R., Akram, F., Zaib, M. J. (2014). Comparison of perinatal outcome of growth restricted fetuses with normal and abnormal umbilical artery Doppler waveforms. *Journal of Ayub Medical College, Abottabad: JAMC, 26(3), 344-348.*
4. Kumar, S., Datta, S., Mittal, S., Roy, K. K. (2002). Doppler flow studies in middle cerebral and umbilical arteries in growth retarded and normal pregnancies. *JK Science, 4(0), 185-189*
5. Mufenda, J., Gebhardt, S., van Rooyen, R., Theron, G. (2015). Introducing a Mobile-Connected Umbilical Doppler Device (UmbiFlow) into a Primary Care Maternity Setting: Does This Reduce Unnecessary

Referrals to Specialised Care? Results of a Pilot Study in Kraaifontein, South Africa. *PLoS One, 10(11) e0142743.*

6. Nguku, S. W., Wanyoike-Gichuhi, J., Aywak, A. A. (2006). Biophysical profile scores and resistance indices of the umbilical artery as seen in patients with pregnancy induced hypertension. *East African Medical Journal, 83(3), 96-101*
7. Nkosi, S., Makin, J., Hlongwane, T. M. A. G., & Pattinson, R. C. (2019). Screening and managing a low-risk pregnant population using continuous-wave Doppler ultrasound in a low-income population: A cohort analytical study. *SAMJ: South African Medical Journal*, *109*(5), 347-352.
8. Siddiqui, T. S., Asim, A., Ali, S., Tariq, A. (2014). Comparison of perinatal outcome in growth restricted fetuses retaining normal umbilical artery Doppler flow to those with diminished end-diastolic flow. *Journal of Ayub Medical College, Abbottabad: JAMC, 26(2), 221-224.*
9. Kachewar, S. G., Gandage, S. G., Pawar, H. J. (2012). An Indian study of novel non-invasive method of screening for foetal anaemia. *Journal of Clinical and Diagnostic Research, 6(4), 688-691.*

c) Outcomes: 11 studies

1. Adekanmi, A. J., Roberts, A., Akinmoladun, J. A., & Adeyinka, A. O. (2019). Uterine and umbilical artery doppler in women with pre-eclampsia and their pregnancy outcomes. *Nigerian Postgraduate Medical Journal*, *26*(2), 106.
2. El Behery, M. M., Siam, S., Seksaka, M. A., Mansou, S. M. (2013). Uterine artery Doppler and urinary hyperglycosylated HCG as predictors of threatened abortion outcome. *Middle East Fertility Society Journal, 19(1), 42-46.*
3. El-Mashad, A. I., Mohamed, M. A., Elahadi Farag, M. A., Ahmad, M. K., Ismail, Y. (2011). Role of uterine artery Doppler velocimetry indices and plasma adrenomedullin level in women with unexplained recurrent pregnancy loss. *Journal of Obstetrics and Gynaecology Research, 37(1), 51-57.*

4. Geerts, L., Van der Merwe, E., Theron, A., Rademan, K. (2016). Placental insufficiency among high-risk pregnancies with a normal umbilical artery resistance index after 32 weeks. *Int J Gynaecol Obstet, 135(1), 38-42.*
5. Kumar, B. S., Sarmila, K., Prasad, K. S. (2012). Prediction of preeclampsia by midtrimester uterine artery doppler velocimetry in high-risk and low-risk women. *Journal of Obstetrics and Gynecology of India, 62(3), 297-300.*
6. Maged. A. M., Elnassery, N., Fouad, M., Abdelhafiz, A., Al Mostafa, W. (2015). Third-trimester uterine artery Doppler measurement and maternal postpartum outcome among patients with severe pre-eclampsia. *International Journal of Gynecology and Obstetrics, 131(1), 49-53.*
7. Prajapati, S. R., Maitra, N. (2013). Prediction of pre-eclampsia by a combination of history, uterine artery doppler, and mean arterial pressure (A Prospective Study of 200 Cases). *Journal of Obstetrics and Gynecology of India, 63(1), 32-36.*
8. Sebastian, A., Raj, T. S., Yenuberi, H., Job, V., Varuhghese, S., & Regi, A. (2019). Angiogenic factors and uterine artery Doppler in predicting preeclampsia and associated adverse outcomes in a tertiary hospital in south India. *Pregnancy hypertension*, *16*, 26.
9. Shehata, N. A. A., Ali, H. A. A., Hassan, A., Katta, M. A., Ali, A. S. F. (2018). Doppler and biochemical assessment for the prediction of early pregnancy outcome in patients experiencing threatened spontaneous abortion. *Int J Gynaecol Obstet, 143(2), 150-155.*
10. Yusuf, M., Galadanci, H., Ismail, A., Aliyu, L. D., Danbatta, A. H. (2017). Uterine artery doppler velocimetry for the prediction of preeclampsia among high-risk pregnancies in low-resource setting: Our experience at aminu Kano teaching hospital, Kano, Nigeria. *Donald School Journal of Ultrasound in Obstetrics and Gynecology, 11(3), 197-202*
11. Puri, M. S., Deshpande, H., Kohli, S., Sharma, K., Singhania, S. (2013). A study of uterine artery colour doppler at 20-24 weeks gestation as a predictor of pregnancy induced hypertension and intra uterine growth restriction from industrial town in Western India. *Research Journal of Pharmaceutical, Biological and Chemical Sciences, 4(1), 698-705.*

Supplemental appendix S3. The aims of the selected studies and risk profiles of the women recruited

First Author	Aim of study	Dating method	Risk Profile	Participant risk profile details in the article
Abdallah et al., 2019	To study the value of umbilical artery Doppler indices in predicting the risk of intrapartum and neonatal outcomes in pregnancies with and without nuchal cord.	LMP or first trimester ultrasound	Low risk	Primigravida >=37 weeks admitted in labor to the delivery unit. Women with BMI >30 kg/m2, multiple pregnancy, fetal malpresentation, fetal demise, chorioamnionitis, meconium-stained liquor, associated medical disorder (hypertension, diabetes, autoimmune disease, etc.), perinatal complication (e.g. placental abruption), fetal malformation or abnormal fetal growth were excluded from the study.
Agbaje et al., 2018	To assess umbilical artery Doppler findings in women with sickle cell anemia in the local environment at the onset of the third trimester and compare with obstetric outcomes.	LMP and/or early dating sonograms	High-risk	Sickle cell anemia.

Supplemental appendix S3. Continued

First Author	Aim of study	Dating method	Risk Profile	Participant risk profile details in the article
Alanwar et al., 2018	To assess the efficacy of fetal middle cerebral artery/umbilical artery pulsatility index ratio (cerebroplacental ratio CPR) in predicting the occurrence of adverse perinatal outcomes in pregnancies complicated with severe pre-eclampsia.	Not specified	High-risk	Pregnancies complicated with severe pre-eclampsia.
Allam et al., 2013	To investigate, in high-risk pregnancies, the prediction of neonatal acidosis using DV, MCA and UA Doppler studies and subsequently to determine the best parameters and cutoff values.	Not specified	High-risk	Suspected IUGR, oligohydramnios, preeclampsia, or placental vascular dysfunction documented by abnormal umbilical artery pulsatility index by local reference ranges.
Anshul et al., 2010	To evaluate the role of umbilical artery Doppler in growth-restricted fetuses.	LMP and first trimester dating scan	High-risk	SGA foetuses, some mothers had hypertensive disorder, anemia, bad obstetric history
Bano et al., 2010	To evaluate the usefulness of the pulsatility index (PI) of the umbilical artery (UA) and that of the middle cerebral artery (MCA), as well as the ratio of the MCA PI to the UA PI (C/U ratio), in the diagnosis of small-for-gestational-age (SGA) fetuses and the prediction of adverse perinatal outcome.	Not specified	High risk	Clinical suspicion of FGR

2

Supplemental appendix S3. Continued

First Author	Aim of study	Dating method	Risk Profile	Participant risk profile details in the article
Dhand et al., 2011	To compare the role of the middle cerebral artery and umbilical artery Doppler pulsatility indices in predicting the fetal outcome in intrauterine growth restriction.	LMP and fetal biometry <22weeks	High risk	SGA fetuses
Dorman et al., 2002	To determine whether impaired uteroplacental blood flow might account for the low infant birth weight associated with maternal falciparum malaria infection.	LMP and fetal biometry	High-risk	Maternal falciparum malaria infection.
Ebrashy et al., 2005	To evaluate the accuracy of middle cerebral/ umbilical artery resistance index (C/U RI) ratio in predicting acidemia and low Apgar score at 5 minutes after birth in the infants of women with preeclampsia.	Fetal biometry (BPD, AC and FL)	High-risk	Pre-eclampsia women
Geerts et al., 2007	To assess the prognostic value of ultrasound findings and fetoplacental Doppler indices in severe preterm preeclampsia in identifying fetuses at high risk of death, major morbidity or long-term compromise.	LMP and fetal biometry	High-risk	Women with severe pre-eclampsia

Supplemental appendix S3. Continued

First Author	Aim of study	Dating method	Risk Profile	Participant risk profile details in the article
Khanduri et al., 2013	To measure the pulsatility index (PI) and resistive index (RI) of the middle cerebral artery (MCA) and umbilical artery (UA) in predicting fetal growth restriction.	LMP and first or second trimester ultrasound	High-risk	Clinical suspicion of FGR
Kumari et al., 2019	To assess the correlation between fetal blood vessel Doppler measurements and fetal anemia among Rhesus isoimmunized pregnancies after two intrauterine transfusions as a potential guide to therapy.	Not specified	High risk	Rhesus isoimmunized complicated pregnancies
Lakhkar et al., 2006	To determine and compare the diagnostic performance of Doppler sonography of fetal middle cerebral artery (MCA), descending abdominal aorta (DAA), umbilical artery (UA), umbilical vein (UV) and inferior vena cava (IVC) for prediction of adverse perinatal outcome in suspected intrauterine growth retardation (IUGR) and pre-eclampsia (PET).	LMP, clinical gestational age, 1st or 2nd trimester biometry	High risk	Preeclampsia and suspicion of growth-restricted fetuses
Lakshmi et al., 2013	To determine outcomes of preterm infants with history of absent/reversed end-diastolic umbilical artery Doppler flow (AREDF) vs. infants with forward end-diastolic flow (FEDF).	LMP or first trimester ultrasound	High-risk	FGR, pregnancy induced hypertension, h/o previous intrauterine death

Supplemental appendix S3. Continued

First Author	Aim of study	Dating method	Risk Profile	Participant risk profile details in the article
Malik et al., 2013	To determine the role of ultrasonography in screening high-risk mothers for detection of IUGR, to find out the impact of fetal parameters on the extent of IUGR, correlation between the sonographic pattern of IUGR and the birth weight, and to find out the sensitivities of various fetal parameters and their evaluation against each other and against the birth weight.	LMP	High-risk	FGR; hypertensive disorder; pre-eclampsia
Masihi et al.2019	To determine the relationship between the fetal middle cerebral artery and the umbilical artery ratio on color Doppler sonography with fetal distress at 38-40 weeks of gestation.	First trimester ultrasound	Low risk	Women that had uncomplicated pregnancies
Mullick et al., 1993	To explore whether measurement of umbilical artery blood velocity waveform between 22 and 26 weeks might predict pregnancies destined to become complicated by pregnancy could induce hypertension (PIH) and/or fetal growth restriction (IUGR).	Not specified	Low and high-risk	Women attending routine antenatal (any risk profile).

Supplemental appendix S3. Continued

First Author	Aim of study	Dating method	Risk Profile	Participant risk profile details in the article
Nagar et al., 2015	To evaluate the predictive values of Uterine and Umbilical artery Doppler indices in high-risk pregnancies.	LMP and ultrasound before 21 weeks	High risk	History of preeclampsia or eclampsia in previous pregnancy pre-existing medical disorders like: Diabetes, Renal disease, Epilepsy, Autoimmune disease, Thrombophilia, and Hypertension, History of IUGR or still birth, history of abruptio placentae, preeclampsia or pregnancy-induced hypertension current, Nulliparity, Extremes of age (<20 years and >35 years).
Najam et al., 2016	To assess the predictive value of the cerebroplacental ratio in the detection of perinatal outcome in high-risk pregnancies in comparison to its components.	Not specified	Low and high-risk	Pregnancies undergoing routine antenatal (any risk profile).
Nouh et al., 2011	To assess the value of uterine artery Doppler screening during pregnancy in predicting adverse pregnancy outcomes in women with polycystic ovary syndrome (PCOS).	LMP and first trimester ultrasound	High-risk	Primigravida with ovulatory polycystic ovary syndrome (PCOS)

2

Supplemental appendix S3. Continued

First Author	Aim of study	Dating method	Risk Profile	Participant risk profile details in the article
Pares et al., 2008	To evaluate the accuracy of middle cerebral artery peak systolic velocity (MCA-PSV) associated with descending thoracic aorta mean velocity (DTA-MV) in the prediction of fetal anemia.	Sonographic exam at <= 20 weeks	High-risk	Fetuses at risk for anemia because of maternal alloimmunization to red-cell antigens
Pattinson et al., 1991	To investigate whether abnormalities in Doppler waveform can predict the outcome of pregnancy accurately before other clinical signs develop	LMP and biometry: 16-20 weeks	High risk	SGA, preeclampsia and pregnancy wastage
Pattinson et al., 1993	To describe the prevalence and natural history of absent end-diastolic velocities (AEDV) in the umbilical artery of the fetus between 16 and 24 weeks gestation, and to evaluate its role as a screening test for identifying high-risk pregnancies.	Not specified	Low and high-risk	Pregnancies undergoing routine antenatal (any risk profile).
Phupong et al., 2003	To assess the value of uterine artery notching as a screening test for preeclampsia and fetal growth restriction in a low-risk population of healthy pregnant women.	LMP and first trimester ultrasound	Low-risk	Healthy pregnant women

Supplemental appendix S3. Continued

First Author	Aim of study	Dating method	Risk Profile	Participant risk profile details in the article
Rani et al., 2016	To assess the accuracy of the middle cerebral artery (MCA) and umbilical artery (UmA), pulsatility index (PI) and resistance index (RI) in predicting perinatal outcome in pregnancies complicated by preeclampsia with or without intrauterine growth restriction (IUGR).	Not specified	Low and high-risk	Women attending routine antenatal (any risk profile).
Rocca et al., 1995	To test the value of routine Doppler study of the umbilical artery to predict the perinatal outcome in pre-eclamptic patients.	Not specified	High risk	Pre-eclampsia women
Verma et al., 2016	To assess the predictive value of uterine artery Doppler imaging at 22-24 weeks of gestation for adverse pregnancy outcomes.	Not specified	Low-risk	Women with uncomplicated pregnancies
Waa et al., 2010	To assess the value of umbilical and middle cerebral artery doppler ultrasound values in predicting foetal outcome in high and low-risk pregnancies.	Not specified	Low and high-risk	Women undergoing routine antenatal (any risk profile).
Yelikar et al., 2013	To study the efficacy of fetal Doppler and Non-Stress Test (NST) in predicting fetal compromise in preeclampsia and growth-restricted fetuses.	Not specified	High-risk	Preeclampsia and growth-restricted fetuses

2

Supplemental appendix S3. Continued

First Author	Aim of study	Dating method	Risk Profile	Participant risk profile details in the article
Zarean et al., 2018	To assess the diagnostic value of UtA-PI in the prediction of the adverse perinatal outcome at 30–34 week's gestation.	Not specified	Low-risk	Women that had uncomplicated pregnancies

[a]FGR: fetal growth restriction; LBW: low birth weight; NICU: neonatal intensive care unit. High risk: pregnancies with any underlying condition that threatens the health or life of the mother or her foetus. Any risk profile: unselected pregnancies (pregnancies undergoing routine antenatal). Low risk: Uncomplicated pregnancies or healthy pregnant women

Supplemntal appendix S4. Risk of bias assessment results of the 30 studies included in the analysis

Study	Study population	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Analysis and Reporting	Overall Assessment
Agbaje et al., 2018	moderate	low	low	moderate	moderate	moderate	moderate
Abdallah et al., 2018	low	moderate	low	moderate	low	moderate	moderate
Alanwar et al., 2018	low	low	low	low	low	low	low
Allam et al., 2013	low	low	low	low	moderate	moderate	low
Bano et al., 2010	moderate	low	moderate	high	high	moderate	high
Deshmukh et al, 2010	low	high	moderate	high	low	high	high
Dhand et al., 2011	low	moderate	high	high	low	high	high
Dorman et al., 2002	low	low	low	low	low	low	low
Ebrashy et al., 2005	low	low	low	low	low	moderate	low
Geerts et al., 2007	low	low	low	moderate	moderate	low	low
Khanduri et al., 2013	low	low	low	moderate	low	moderate	low

2

Supplemntal appendix S4. Continued

Study	Study population	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Analysis and Reporting	Overall Assessment
Kumari et al., 2019	moderate	moderate	low	moderate	low	low	moderate
Lakhkar et al., 2006	moderate	low	moderate	low	low	moderate	moderate
Lakshmi et al., 2013	low	low	low	low	low	moderate	low
Malik et al., 2013	low	high	high	moderate	moderate	moderate	high
Masihi et al., 2019	low	moderate	moderate	low	low	low	low
Mullick et al., 1993	low	low	moderate	moderate	moderate	moderate	moderate
Nagar et al., 2015	low	low	moderate	moderate	low	moderate	moderate
Najam et al., 2016	high	high	moderate	moderate	high	high	high
Nouh et al., 2011	low	low	low	low	low	moderate	low
Pares et al., 2008	low	low	moderate	low	low	low	low
Pattinson et al., 1991	low	low	low	moderate	low	moderate	low
Pattinson et al., 1993	low	low	moderate	low	low	low	low

Supplemntal appendix S4. Continued

Study	Study population	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Analysis and Reporting	Overall Assessment
Phupong et al., 2003	low	low	low	low	low	low	low
Rani et al., 2016	moderate	low	moderate	low	moderate	moderate	moderate
Rocca et al., 1995	moderate	low	moderate	moderate	moderate	moderate	moderate
Verma et al., 2016	low	low	low	low	low	low	low
Waa et al., 2010	low	low	low	moderate	moderate	moderate	moderate
Yelikar et al., 2013	low	moderate	moderate	moderate	low	moderate	moderate
Zarean et al., 2018	moderate	low	low	moderate	low	low	low

2

Supplemental table S1. Statistical measures of prognostic performance of Doppler ultrasound reported in the selected studies

Prognostic determinant	Outcome	Studies	Sn	Sp	PPV	NPV	AUC	DA	OR [95% CI]	RR [95% CI]	COR	Normal Doppler n (%)	ABN Doppler n (%)
UA flow impedance	FGR	Agbaje et al., 2018	67.00	53.00			0.63						
		Mullick et al., 1993	85.00	89.00	88.50								
		Najam et al., 2016	48.15	80.67	53.06	77.40							
		Rocca et al., 1995	92.30	91.90	77.40	97.60		92.0					
		Khanduri et al., 2013	73.80	75.90	87.70	55.40		75.0					
		Bano et al., 2010	46.70	93.30	87.50	63.60		70.0					
		Nagar et al., 2015	42.86	94.62	37.50	95.65							
	NICU Admission	Anshul et al., 2010										13 (24.1)	36 (78.2)
		Najam et al., 2016	50.00	80.30	48.90	80.95							

Supplemental table S1. Continued

Prognostic determinant	Outcome	Studies	Sn	Sp	PPV	NPV	AUC	DA	OR [95% CI]	RR [95% CI]	COR	Normal Doppler n (%)	ABN Doppler n (%)
UA flow impedance	Fetal Distress	Anshul et al., 2010										18 (33)	35 (76)
		Rocca et al., 1995										2 (2.5)	12 (39)
		Najam et al., 2016	66.67	78.04	74.89	89.72							
		Yelikar et al., 2013	42.10	65.90	12.10	91.10							
	Stillbirth	Anshul et al., 2010										0 (0)	4 (9.5)
		Najam et al., 2016										0 (0)	5 (8.2)
	Perinatal death	Rocca et al., 1995										0 (0)	2 (6.5)
		Anshul et al., 2010										0 (0)	9 (60)
	LBW	Anshul et al., 2010										15 (27.0)	35 (77.8)

Supplemental table S1. Continued

Prognostic determinant	Outcome	Studies	Sn	Sp	PPV	NPV	AUC	DA	OR [95% CI]	RR [95% CI]	COR	Normal Doppler n (%)	ABN Doppler n (%)
UA flow impedance	Apgar Score	Rocca et al., 1995	80.00	82.40	41.00	96.00		83.00					
		Anshul et al., 2010										2 (3.7)	14 (82.35)
		Najam et al., 2016										3 (60.0)	6 (85.71)
		Agbaje et al., 2018									0.38		
	Fetal Anemia	Kumari et al., 2019									0.21		
	HIE	Najam et al., 2016										1 (1.3)	8 (16.31)
	MAS	Najam et al., 2016										1 (1.3)	16 (32.65)

Supplemental table S1. Continued

Prognostic determinant	Outcome	Studies	Sn	Sp	PPV	NPV	AUC	DA	OR [95% CI]	RR [95% CI]	COR	Normal Doppler n (%)	ABN Doppler n (%)
UA flow impedance	CAPO	Bano et al., 2010	79.20	92.40	79.20	92.20		88.90					
		Lakhkar et al 2006	50.00	59.00	66.60	41.90							
		Rani et al., 2016	17.80	95.80	80.70	50.50	0.57						
		Geerts et al., 2007	75.00			95.00			0.6 (0.1, 4.1)				
		Malik et al., 2013	64.40	80.00	96.60	20.00							
		Pattinson et al., 1993	12.50	91.80	22.70	84.50							
		Ebrashy et al., 2005	53.30	36.40	81.10	30.80							
		Waa et al., 2010	8.00	100.00	0.00	26.00							

Supplemental table S1. Continued

Prognostic determinant	Outcome	Studies	Sn	Sp	PPV	NPV	AUC	DA	OR [95% CI]	RR [95% CI]	COR	Normal Doppler n (%)	ABN Doppler n (%)
UA AREDF	Perinatal death	Lakshmi et al., 2013							9.8 (2.1, 46.4)				
		Najam et al., 2016										2 (2.6)	4 (33.33)
	RDS	Lakshmi et al., 2013							2.4 (1.1, 5.0)				
	CAPO	Pattinson et al., 1991	75.00	90.00	69.00								
		Lakshmi et al., 2013							8.4 (2.3, 30.5)				
MCA flow impedance	FGR	Najam et al., 2016	59.25	88.89	72.72	81.35							
		Bano et al., 2010	8.90	100.0	100.0	52.30		54.40					
		Khanduri et al., 2013	26.20	92.60	89.20	35.00		46.10					
	Fetal Anemia	Pares et al., 2008	100.00	65.00	90.90	100.0		92.20					
		Kumari et al., 2019	68.00	57.00	83.00	33.00	0.70				-0.43		
	NICU Admission	Najam et al., 2016	64.58	88.69	70.45	85.71							

Supplemental table S1. Continued

Prognostic determinant	Outcome	Studies	Sn	Sp	PPV	NPV	AUC	DA	OR [95% CI]	RR [95% CI]	COR	Normal Doppler n (%)	ABN Doppler n (%)
MCA flow impedance	Neonatal Acidosis	Allam et al., 2013	87.50	64.00	74.00	82.00	0.82						
	Fetal Distress	Najam et al., 2016	72.73	78.05	54.55	91.53							
	Stillbirth	Najam et al., 2016										0 (0)	2 (4.5)
	Apgar Score	Najam et al., 2016										1 (1.3)	17 (38.6)
	HIE	Najam et al., 2016										1 (1.3)	10 (22.7)
	MAS	Najam et al., 2016										1 (1.3)	20 (45.5)

Supplemental table S1. Continued

Prognostic determinant	Outcome	Studies	Sn	Sp	PPV	NPV	AUC	DA	OR [95% CI]	RR [95% CI]	COR	Normal Doppler n (%)	ABN Doppler n (%)
		Bano et al., 2010	16.70	100.0	100.0	76.70		77.80					
		Lakhkar et al 2006	41.60	90.90	88.20	48.70							
		Rani et al., 2016	18.60	90.30	68.70	49.40	0.58						
MCA flow impedance	CAPO	Dhand et al., 2011	71.00	92.00	94.00	65.00							
		Malik et al., 2013	7.70	90.00	87.50	9.80							
		Ebrashy et al., 2005	41.00	63.60	80.00	23.30							
		Waa et al., 2010	23.0	68.00	76.00	33.00							
		Najam et al., 2016	85.10	89.72	80.70	92.30							
	FGR	Bano et al., 2010						72.20					
CPR		Najam et al., 2016	75.00	82.92	63.15	89.47							
	NICU Admission	Alanwar et al., 2018	62.50	71.42	29.40	90.90							

Supplemental table S1. Continued

Prognostic determinant	Outcome	Studies	Sn	Sp	PPV	NPV	AUC	DA	OR [95% CI]	RR [95% CI]	COR	Normal Doppler n (%)	ABN Doppler n (%)
CPR	Foetal Distress	Najam et al., 2016	90.91	78.04	52.63	96.97							
		Masihi et al.2019	80.95	50.00	17.50	95.20							
	Stillbirth	Najam et al., 2016										0 (0)	4 (7.1)
	Apgar Score	Najam et al., 2016										1 (1.3)	19 (33.3)
		Alanwar et al., 2018	50.0	88.10	44.40	90.20							
	Neonatal Acidosis	Ebrashy et al., 2005	64.10	72.70	89.30	36.40				1.4 (1.2, 1.7)			
		Alanwar et al., 2018	43.75	69.05	21.21	86.57							
	HIE	Najam et al., 2016										1 (1.3)	12 (21.1)
	MAS	Najam et al., 2016	96.15			99.20						1 (1.29)	25 (43.9)

Supplemental table S1. Continued

Prognostic determinant	Outcome	Studies	Sn	Sp	PPV	NPV	AUC	DA	OR [95% CI]	RR [95% CI]	COR	Normal Doppler n (%)	ABN Doppler n (%)
		Bano et al., 2010	83.30	100.0	100.00	94.30		95.60					
		Lakhkar et al 2006	47.20	86.30	85.00	50.00							
CPR	CAPO	Rani et al., 2016	7.60	98.00	81.80	48.30	0.60						
		Malik et al., 2013	68.80	100.00	100.0	26.30							
		Geerts et al., 2007			57.0				1.1 (0.1, 14.6)				
		Verma et al., 2016	45.0	84.10	28.10	91.70							
	FGR	Phupong et al., 2003	67.0	82.90	6.90	99.20				9.1 (1.7, 48.5)			
		Nagar et al., 2015	25.0	94.56	28.57	93.55							
UtA flow impedance	Perinatal Death	Dorman et al., 2002								2.37 (1.3, 4.3)			
	LBW	Verma et al., 2016	45.40	84.60	31.30	90.90							
		Dorman et al., 2002								2.52 (1.5, 4.2)			

Supplemental table S1. Continued

Prognostic determinant	Outcome	Studies	Sn	Sp	PPV	NPV	AUC	DA	OR [95% CI]	RR [95% CI]	COR	Normal Doppler n (%)	ABN Doppler n (%)
UtA flow impedance	Preterm Birth	Verma et al., 2016	57.10	63.20	18.50	91.00							
		Dorman et al., 2002								1.53 (0.9, 2.4)			
	CAPO	Verma et al., 2016	48.20	95.40	84.40	78.20							
		Nouh et al., 2011	84.60	96.30	91.70	92.90							
		Malik et al., 2013	37.70	70.00	91.80	11.00							
		Zarean et al., 2018	37.50	73.30	48.40	63.70	0.55						
FDA flow impedance	Fetal anemia	Pares et al., 2008	95.70	100.0	100.0	86.90		96.70					
		Kumari et al., 2019	87.00	57.00			0.80				-0.54		
	CAPO	Lakhkar et al 2006	44.40	59.00	64.00	56.50							
FDA & MCA	Fetal anemia	Pares et al., 2008	98.40	100.0	100.0	91.70		98.60					
		Kumari et al., 2019	86.00	67.00	86.00	67.00							

Supplemental table S1. Continued

Prognostic determinant	Outcome	Studies	Sn	Sp	PPV	NPV	AUC	DA	OR [95% CI]	RR [95% CI]	COR	Normal Doppler n (%)	ABN Doppler n (%)
DV flow impedance	Neonatal Acidosis	Allam et al., 2013	100.0	57.00	72.0	100.0	0.88	80.00					
	CAPO	Geerts et al., 2007		92.0	33.0				0.3 (0.03, 4.6)				

[a]UA: umbilical artery; MCA: middle cerebral artery; CPR: cerebroplacental ratio; UtA: uterine artery; FDA: fetal descending aorta; DV: ductus venosus; RI: resistive index; PI: pulsatility index; S/D ratio: systolic diastolic ratio; PSV: peak systolic velocity; MV: mean velocity; AREDF: absent and/or reversed end diastolic flow; FGR: fetal growth restriction; LBW: low birth weight; HIE: hypoxic ischemic encephalopathy; MAS: meconium aspiration syndrome; RDS: respiratory distress syndrome; NICU: neonatal intensive care unit; CAPO: composite adverse perinatal outcomes; Sn: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; AUC: area under curve; DA:diagnostic accuracy; OR: odds ratio; RR: relative risk; COR: correlation; ABN: abnormal; and n (%): frequency (percentage).

Supplemental table S2. Definitions of adverse perinatal outcomes reported in the selected studies

First Author	Outcomes	Definition (detailed description in the article)
Abdallah et al., 2019	LBW	Not defined
	NICU admission	Not defined
	Stillbirth	Not defined
	Perinatal mortality	Not defined
	Low APGAR score at 1 and 5 minutes	Not defined
Agbaje et al., 2018	FGR	Abnormal birth weight: defined as estimated foetal weight below the 10th percentile for gestational age and abdominal circumference below the 10th percentile for gestational age.
	Low APGAR score at 5 minutes	APGAR score less than 6
Alanwar et al., 2018	Acidosis	Neonatal academia of pH < 7.2
	NICU admission	New-born was admitted to the neonatal intensive care unit
	Low APGAR score at 5 minutes	APGAR score < 7 at 5 min
Allam et al., 2013	Neonatal acidosis	Cord blood pH <7.25
Anshul et al., 2010	Stillbirth	Not defined
	Neonatal death	Not defined
	NICU admission	Admission required
	Foetal distress	Delivered by emergency caesarean section for suspected foetal distress
	LBW	Not defined
	Low APGAR score at birth.	APGAR score <7 at birth

2

Supplemental table S2. Continued

First Author	Outcomes	Definition (detailed description in the article)
Bano et al., 2010	Perinatal death	Not defined
	Foetal distress	Caesarean section for foetal distress (FD not defined)
	NICU admission	Not defined
	Low APGAR score at 5min	APGAR score <7 at 5 min
	FGR	Birth weight less than 10th percentile for gestational age
	Composite adverse perinatal outcome	Not defined
Dhand et al., 2011	Composite adverse perinatal outcome	Abnormal foetal outcome (details not provided)
Dorman et al., 2002	Perinatal death	Not defined
	Preterm delivery	Delivery < 37 weeks
	LBW	Birth weight <2.5kg
Ebrashy et al., 2005	Acidosis	Neonatal acidaemia of pH<7.2 were present
	Composite adverse neonatal outcome	Neonatal morbidity (neonatal academia pH<7.2, 5-minute APGAR score <6, and/or admission to NICU)
Geerts et al., 2007	Composite adverse perinatal outcome	Poor outcome (perinatal demise or clinical/ultrasound signs of neurological compromise in the infant at the time of discharge from the tertiary institution)
Khanduri et al., 2013	FGR	Ponderal index was calculated as birth weight (in gm) per length (in cm3). Ponderal index of <10 indicates growth restriction.
Kumari et al., 2019	Foetal anaemia	Haematocrit of the umbilical cord blood was used as the reference test to diagnose foetal anaemia (defined as haemoglobin <0.65 times the median for gestational age).

Supplemental table S2. Continued

First Author	**Outcomes**	**Definition (detailed description in the article)**
Lakhkar et al., 2006	Composite adverse perinatal outcome	Adverse perinatal outcome (Major and Minor). Major adverse outcomes were perinatal deaths including intrauterine and early neonatal deaths. Major complications like hypoxic ischemic encephalopathy, intraventricular haemorrhage, periventricular leukomalacia, pulmonary haemorrhage and necrotizing enterocolitis. Minor outcomes include-caesarean delivery for foetal distress, APGAR score below 7 at 5 minutes, admission to NICU (neonatal intensive care unit) for treatment.
Lakshmi et al., 2013	Neonatal death	Not defined
	Respiratory distress syndrome	Not defined
	Composite adverse perinatal outcome	Composite outcome of death or major neuro-morbidity at 12-18 months of corrected age, defined as presence of cerebral palsy or visual or hearing impairment.
Malik et al., 2013	Composite adverse perinatal outcome	Abnormal foetal outcome (IUGR, IUFD and perinatal mortality)
Masihi et al.2019	Intrapartum foetal distress	Emergency caesarean section for foetal distress
Mullick et al., 1993	FGR	Not defined
Nagar et al., 2015	FGR	Not defined

2

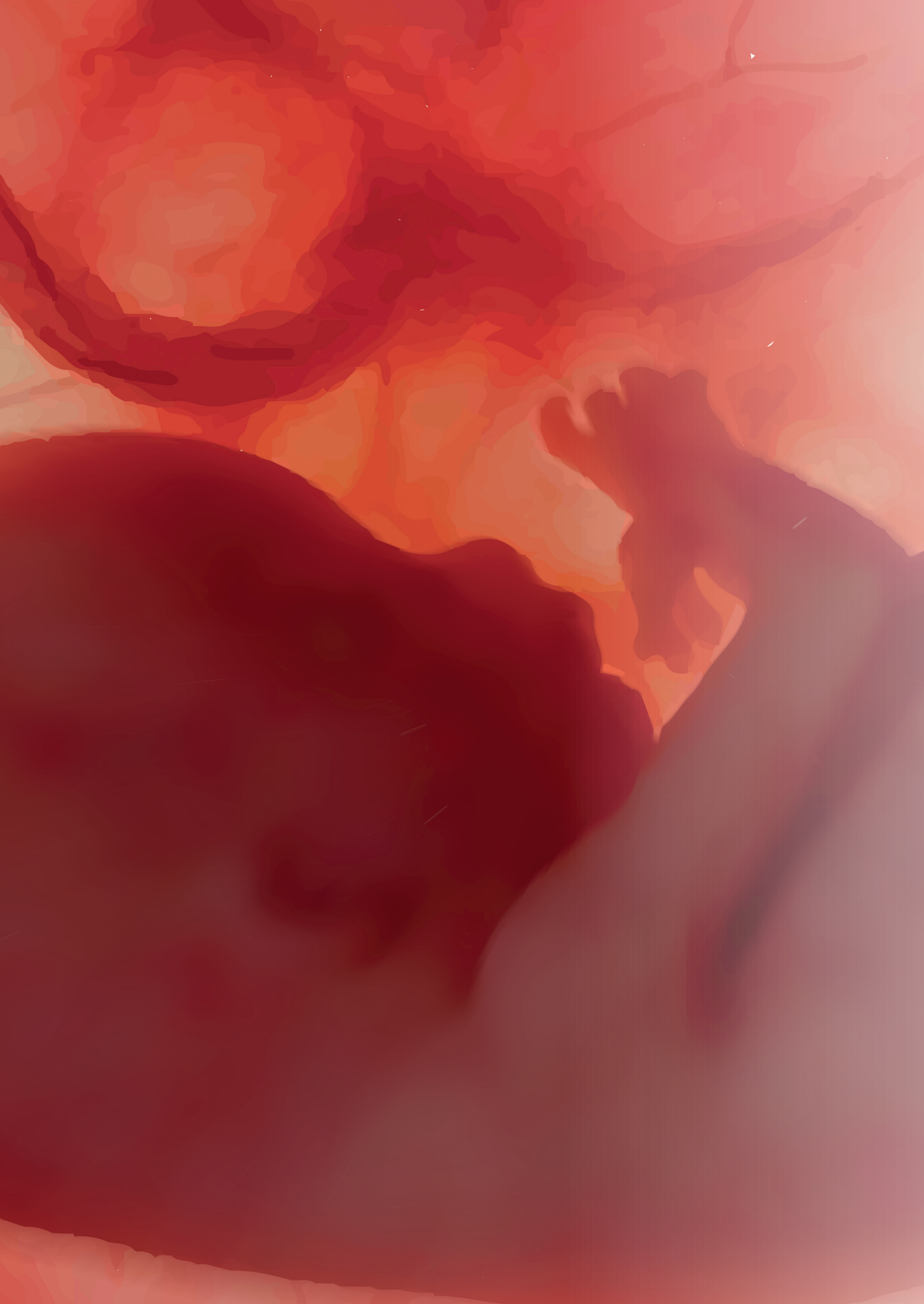
Supplemental table S2. Continued

First Author	Outcomes	Definition (detailed description in the article)
Najam et al., 2016	FGR	Not defined
	NICU admission	Not defined
	Foetal distress	Not defined
	Stillbirth	Not defined
	Neonatal death	Not defined
	Low APGAR score	Not defined
	Hypoxic ischemic encephalopathy	Not defined
	Meconium aspiration syndrome	Not defined.
Nouh et al., 2011	Composite adverse perinatal outcome	The presence of one or more of the following; miscarriage, gestational DM, PIH, PE, antepartum haemorrhage, intrauterine growth retardation, instrumental, caesarean delivery and preterm labour.
Pares et al., 2008	Foetal anaemia	Anaemia was considered moderate to severe when foetal haemoglobin concentrations were < or =0.64 multiples of the median for gestational age.
Pattinson et al., 1991	Composite adverse perinatal outcome	Poor foetal outcome (details not provided).
Pattinson et al., 1993	Composite adverse perinatal outcome	Complications of pregnancy, namely intra-uterine growth retardation and proteinuric hypertension.
Phupong et al., 2003	FGR	Birth weight less than 10 percentile for gestational age.
Rani et al., 2016	Composite adverse perinatal outcome	Adverse perinatal outcome was defined as any of these: small for gestational age, still birth, APGAR score <5 at 5 minutes, need of bag and mask ventilation for >10 minutes or hypoxic ischemic encephalopathy, admission to neonatal intensive care unit (NICU), and caesarean section due to non-reassuring foetal heart rate.

Supplemental table S2. Continued

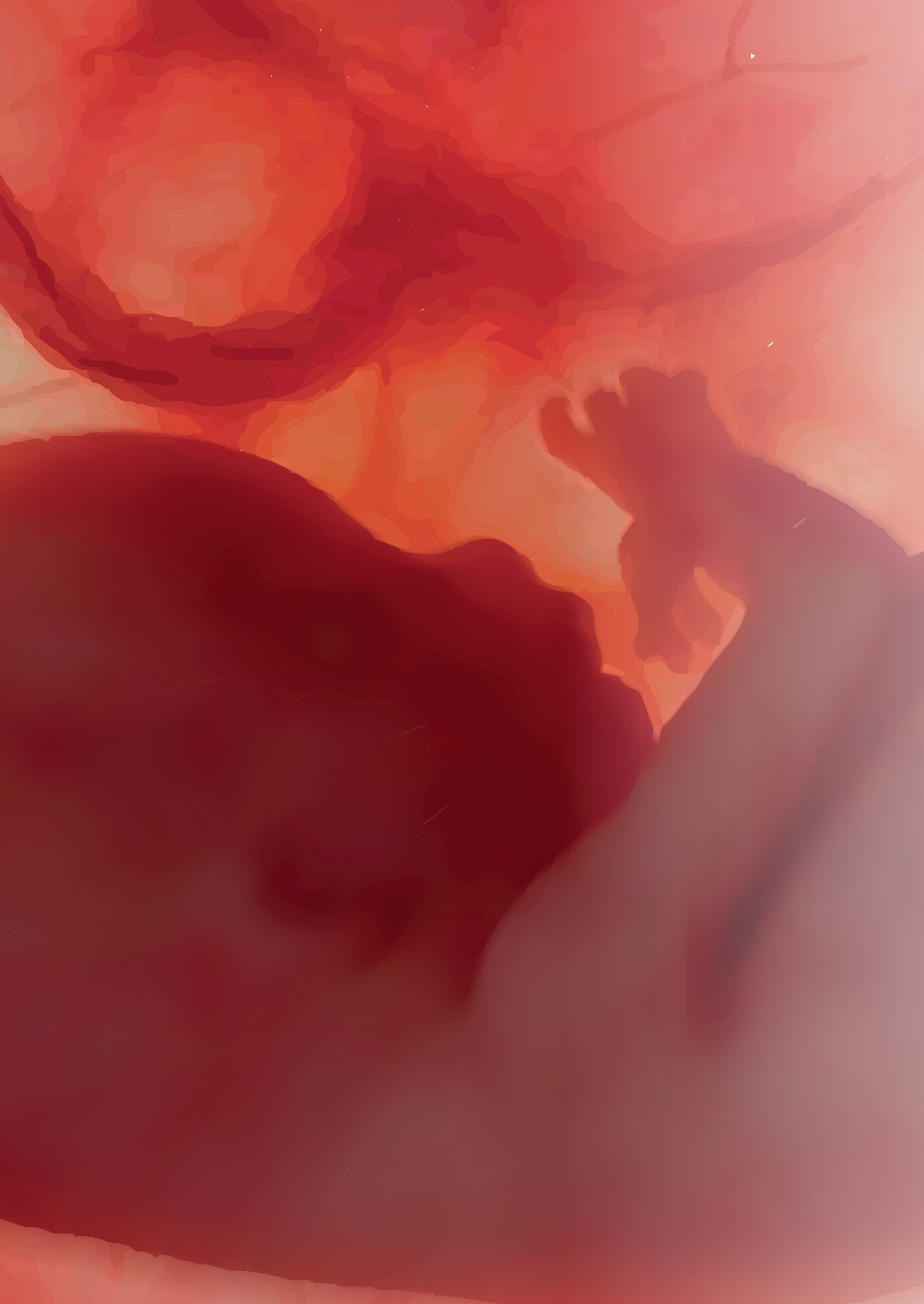
First Author	Outcomes	Definition (detailed description in the article)
Rocca et al., 1995	FGR	Not defined.
	Low APGAR score 5mins	APGAR score <7 at 5 minutes.
	Perinatal death	Not defined.
	Foetal distress	Emergency operative delivery for foetal distress.
Verma et al., 2016	FGR	Not defined.
	LBW	Birth weight <2500 gm.
	Preterm delivery	Spontaneous delivery <37 weeks.
	Composite adverse perinatal outcome	At least one adverse outcome (preeclampsia, FGR, low birth weight, spontaneous preterm delivery, oligohydramnios, foetal loss).
Waa et al., 2010	Composite adverse perinatal outcome	Poor outcome was defined by foetal mortality or appearance, pulse rate, grimace, activity, respiration (APGAR) score less than eight at five minutes or weight less than 10^{th} percentile for gestation 20 or head circumference and length below 10^{th} percentile for gestation.
Yelikar et al., 2013	Intrapartum foetal distress	Delivered by emergency caesarean section for suspected foetal distress.
Zarean et al., 2018	Composite adverse perinatal outcome	Adverse perinatal outcome, including preterm labour, intrauterine foetal death, PE, low 5-min APGAR score (<7), low umbilical arterial cord blood pH, admitted to Intensive Care Unit in the first 3 days of birth, low birth weight, infant with low weight, death of new-borns, caesarean section for respiratory distress, and meconial amniotic fluid.

[a]FGR: fetal growth restriction; FGR: intrauterine growth restriction; LBW: low birth weight; NICU: neonatal intensive care unit.



Part 2

Deploying Doppler ultrasound services in low-resource settings



Chapter 3

Standardization and quality control of Doppler and fetal biometry ultrasound measurements in low-income setting

Sam Ali
Josaphat Byamugisha
Michael G. Kawooya
Isaac M. Kakibogo
Immaculate Ainembabazi
Esther A. Biira
Adia N. Kagimu
Aminah Migisa
Melodie Munyakazi
Samson Kuniha
Connie Scheele
Aris T. Papageorghiou
Kerstin Klipstein-Grobusch
Marcus J. Rijken

Ultrasound Obstet Gynecol. 2022 Aug 17

ABSTRACT

Objectives

We aimed to determine the quality of fetal biometry and pulse-wave Doppler ultrasound measurements in a prospective cohort study in Uganda.

Methods

This was an ancillary study in the Ending Preventable Stillbirths by Improving Diagnosis of Babies at Risk (EPID) project where women enrolled in early pregnancy were subjected to Doppler and fetal biometry ultrasound assessments between 32 and 40 weeks of gestation. A total of 125 images for each of the umbilical (UA), middle cerebral (MCA), uterine (UtA) arteries, head circumference (HC), abdominal circumference (AC) and femur length (FL) were arbitrarily selected from the EPID study database and independently evaluated by two experts in a blinded fashion using an objective scoring criterion. Inter-rater agreement was assessed using modified Fleiss' Kappa for nominal variables and systematic errors were explored using Q-Q plots.

Results

Over 96.8% of the UA images, 84.8% of the MCA images and 93.6% of the UtA images were classified as of acceptable quality by both reviewers. For fetal biometry measurements, 96.0% of the HC images, 96.0% of the AC images and 88.0% of the FL images were acceptable. The Kappa values for inter-rater reliability of quality assessment were 0.94 (95% CI, 0.87–0.99), 0.71 (95% CI, 0.58–0.82), and 0.87 (95% CI, 0.78–0.95), for the UA, MCA, and UtA, respectively. The inter-rater agreement HC was 0.94 (95% CI, 0.87–0.98) for the HC, 0.93 (95% CI, 0.87–0.98) for the AC and 0.78 (95% CI, 0.66–0.88) for the FL measurements.The Q-Q plots indicated no influence of systematic biases in the measurements.

Conclusion

Training local healthcare providers to perform Doppler ultrasound, and implementation of quality control systems and audits of measurements using objective scoring tools in clinical and research settings of low- and

middle-income countries is feasible. Although we did not assess the impact of in-service re-training offered to practitioners deviating from prescribed standards in this study, such interventions could possibly enhance the quality of the ultrasound measurements and should be investigated in future studies.

SHORT TITLE

Quality of antenatal ultrasound measurements

KEYWORDS

Doppler ultrasound; developing countries; antenatal; reliability; training; quality assurance

CONTRIBUTION

What are the novel findings of this work?
This is the first study from a low-resource setting to demonstrate that the quality of pulse-wave Doppler and fetal biometry ultrasound measurements can be reliably assessed using freely available objective evaluation tools.

What are the clinical implications of this work?
Well-trained healthcare providers in underserved regions can perform Doppler and fetal biometry scans with consistency. Although we did not measure the impact of the re-training exercise, we believe it could have enhanced the quality of our measurements. The impact of such interventions on the quality of scans should be evaluated in future studies.

INTRODUCTION

Stillbirths and the associated psychosocial effects and economic loss are critical global health problems disproportionately affecting the parents, healthcare providers, and communities in low- and middle-income countries (LMICs).[1–3] Over 50% of stillbirths in sub-Saharan Africa are antepartum and the majority are strongly linked to placental failure.[4] Placental dysfunction leads to impaired exchange of oxygen and nutrients at the maternal-fetal interface and manifestation of acute or chronic fetal hypoxia which is known to be associated with increased impedance to flow in the umbilical and uterine arteries.[5] This stresses the clinical importance of examining the placental and fetal circulation (commonly using Doppler ultrasound), in addition to the fetal biometry assessments, to identify endangered fetuses. Given the essential role of Doppler and fetal biometry ultrasound assessment in clinical practice, these measurements must be accurate and reproducible. Slight variations in the measurements may be unavoidable, but significant systematic errors can lead to inappropriate interpretations, intervention and harmful effects on the pregnant women.[6] In the context of research, erroneous findings could prompt misleading public health policies. Thus, the measurements must be undertaken and interpreted by well-trained healthcare providers, using adequate equipment and following standardized procedures. In addition, regular departmental audits are necessary to identify ultrasonographers who may require tailored feedback and retraining to ensure that the desired examination standards are upheld.[7,8]

Audit tools for 2D fetal biometry,[9] crown-rump length (CRL),[10] and pulse-wave Doppler ultrasound measurements are already published.[7,8] The tools are based on an objective equally weighted scoring criteria and have been found very reproducible than the subjective evaluation approach in high-income countries (HICs).[7–9] However, studies documenting quality assurance procedures and the clinical applicability of obstetric ultrasound quality control tools in routine practice and research settings of LMICs are limited, yet being a fertile ground for high research activity and future application of the Doppler ultrasound technology to avert the high burden of stillbirths and perinatal complications. In this work, we report the quality of fetal biometry and pulse-wave Doppler ultrasound measurements and the quality control strategies employed in a large prospective cohort study implemented in a rural community in Uganda.

METHODS

Design and participants

This ultrasound image quality assessment study was designed and reported in accordance with the Guidelines for Reporting Reliability and Agreement Studies (GRRAS).[11] In this study, we report the ultrasound measurement quality control procedures used in the Ending Preventable Stillbirths By Improving Diagnosis of Babies at Risk (EPID) project, a prospective cohort study implemented between 2018 and 2020 in an obstetric care setting of a rural Hospital in western Uganda. The primary aim of the EPID study was to determine the predictive performance of Doppler ultrasound for adverse perinatal outcomes in a low- resource setting. We enrolled pregnant women attending Kagadi Hospital in early pregnancy at <23 weeks, and then followed them up to the third trimester (between 32 and 40 weeks of gestation) when they were offered fetal growth and Doppler assessment scans. Perinatal and maternal outcomes were assessed at the time of birth and up to 28 days of the postnatal period. Additional information on the EPID study is published elsewhere.[12–14] All the women recruited in the main prospective cohort study provided informed and written consent, with the illiterate participants signing using a thumbprint. This study was approved by the Makerere University School of Medicine Research and Ethics Committee (SOMREC): Ref. 2018-090; and the Uganda National Council for Science and Technology (UNCST): Ref. HS 2459. We obtained permission to work within the Kagadi region from the Kagadi District Health Team and local authorities.

Setting

The EPID study was implemented in Kagadi Hospital, a secondary care level health facility handling about 4000 births annually and serving women in the rural communities of the greater Kibaale region in mid-western

Uganda, approximately 215 km from the national capital, Kampala. The Uganda Demographic and Health Survey (2016) found the total population for Kibaale at 788,714, with 389,278 (49.36%) males and 399,436 (50.64%) females.[15]

Data collection

The EPID project adapted the strategies for standardization and quality control of ultrasound measurements from the methodological recommendations by the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) Consortium.[16] The training and quality control program was led and coordinated by a maternal-fetal ultrasound specialist and research scientist (SA). We created a training and quality control (TQC) team (SA, EAB, ANK, AM, MM, SK, CS and MRJ) that supported the training of sonographers and continuous assessment of the quality and consistency of the ultrasound measurements obtained during the study.

The training components included but were not limited to, pregnancy dating using ultrasound; common fetal anomalies; Doppler ultrasound principles and safety, and interpretation of results; scanning techniques; as well as general data collection procedures. To ensure sustainability of the service, the trainees included two residential sonographers on-site (Kagadi Hospital) at the time of study implementation. Before commencing training, we evaluated their knowledge and skills using pre and post-training theoretical and practical assessments. Even though the trainee sonographers had been practising basic obstetric ultrasound between 11-15 years as of 2018, they barely had any experience performing Doppler scans. Also, their pre-assessment results informed the need for thorough training. Thus their pre-study implementation training exercise lasted six weeks (a week was dedicated to the review of theoretical materials, three weeks of hands-on practice at training centers, and two weeks at the study site).

Pre-implementation training took place at Ernest Cook Ultrasound Research and Education Institute (ECUREI), Mengo Hospital, Kampala, Uganda, and The Woman's Place, Kampala, Uganda. ECUREI a local tertiary teaching institution, nominated center of excellence for the World Federation for

Ultrasound in Medicine and Biology in Uganda in 2007 and has previously participated in ultrasound capacity-building projects. The Woman's Place, Kampala, Uganda, is a local maternal-fetal ultrasound clinic equipped with futuristic ultrasound systems for specialized obstetric and gynecological imaging.

Before starting participant enrolment, we conducted additional training on-site for the sonographers to become familiar with the study equipment and data collection procedures. We further undertook spot reviews of a few randomly selected images on three occasions during implementation (once in the initial phases of participant enrolment, and twice at the start of follow up examinations for the biometry and Doppler measurements in the third trimester), whose results guided areas for further re-training on-site. During implementation, we had monthly site visits to address any implementation issues such as equipment servicing, assessing adherence to study protocols, refrehers training for the entire study team, and among others.

All fetal biometry and Doppler scans in the EPID study were recorded by two Kagadi Hospital resident ultrasonographers, and the first author (SA) following prescribed standards,[17,18] and using two different machines, a Voluson™ e (GE Healthcare, Chicago, IL, USA) or Philips HD-9 (Philips, Amsterdam, The Netherlands). The head circumference (HC) was acquired in the transthalamic plane with calipers placed on the outer border of the skull. Abdominal circumference (AC) was measured in an axial plane, with the umbilical vein in the anterior third of the fetal abdomen (at the level of the portal sinus) and the stomach bubble visible. The femur length (FL) of the limb closest to the transducer was obtained with the calipers placed on the outer borders of the diaphysis of the femoral bone (Figure S1).

The umbilical artery (UA) was examined in a free loop of the umbilical cord, with measurements taken in the absence of fetal movement, while keeping the insonation angle at <30°. The middle cerebral artery (MCA) was examined at its proximal third, close to its origin in the internal carotid artery, with the angle of insonation kept as close as possible to 0°. The uterine arteries (UtA) were recorded trans-abdominally, with the angle of insonation maintained at <30° (Figure S2).

For image quality assessment, the ultrasound measurements were scored according to a set of published criteria[7–9] by two independent raters (A and B) blinded to each other's rating results. Each criterion was assigned a score of one point when satisfied and zero when not satisfied, had equal weight towards the total score, and the sum of the points was the final image score. A maximum score of four points, was possible for the FL and six points for the HC, AC, UA, MCA, and UtA (Appendix S1 and Appendix S2). Women for whom fetal biometry and all Doppler measurements had been obtained were randomly selected for inclusion in this study. Based on previous studies, a minimum of 125 images would be sufficient to detect a 10% difference (inter-rater agreement) between two raters with 90% power, assuming an inter-rater agreement rate of 80%.[7,8] We, therefore, randomly selected up to 125 images per ultrasound examination for this analysis, using the function set.seed to ensure that our random sample was replicable.

Statistical analysis

The final image scores of each reviewer were dichotomized into acceptable and non-acceptable. For the FL, images with a score of ≥≥ 3 points were classified as acceptable while those with a score of << 2 points as unacceptable. A threshold of ≥≥ 4 points was considered acceptable and those with image scores << 3 points as unacceptable for the HC, AC, UA, MCA, and UtA ultrasound images. We adopted the classification schemes from published studies and recommendations by the quality scoring tool developers.[7,8,19] Descriptive statistics of the fetal biometry and pulse-wave Doppler image quality scores were reported using frequencies, proportions, and graphically using bar graphs.

To determine the inter-rater agreement, we used the s* statistic, a modified Fleiss' Kappa for nominal variables not affected by the paradoxes of Cohen's and Fleiss Kappa.[20] Then calculated the 95^{th} percentile bootstrap confidence intervals (CI) of the s* statistic using Monte Carlo simulations with 1000 iterations. The p-values were also approximated using the Monte Carlo procedure at a 5% level of significance. For interpretation of Kappa, we used the following cut-offs: 0.00- 0.20, slight; 0.21-0.40, fair; 0.41-0.6, moderate; 0.61-0.8, good; and, above 0.8, very good.[11]

Analysis of the z-score distribution is also a recommended approach for quality assessment.[21] The z-score distributions are expected to follow properties of a standard normal distribution; their means and standard deviations should be approximately zero and one, respectively. We, therefore, first transformed the HC, AC, FL, and UA PI measurements to gestational-specific z-scores using the INTERGROWTH-21st fetal growth standards[22] embedded in the R package 'healthy birth, growth, & development (hbgd)',[23] and INTERGROWTH-21st Doppler charts.[24] Then constructed normal quantile-quantile (Q-Q) plots for the HC, AC, FL and UA PI z-scores to allow for visual assessments of their distributions. The z-score means and standard deviations were compared with the expected standard normal distribution. We also used Shapiro-Wilk test to assess normality at a 5% level of significance. SA carried out data management in STATA 14.0 (StataCorp. 2015) and analysis using the package 'raters' in R 4.0.4 (15 February 2021).

RESULTS

Image quality

The EPID study ultrasound measurement quality control team had between eight to 15 years of experience in obstetric ultrasound as of 2020. A total of 875 ultrasound images (125 each for the HC, AC, FL, UA, MCA, and the two UtA) scored by two reviewers were considered for this analysis. The image score assessment results for pulsed-wave Doppler and fetal biometry ultrasound measurements by reviewers A and B are reported in Table 1, Figure S3 and Figure S4.

For the MCA pulse-wave Doppler images, 119/125 (95.2%) of the images were classified as acceptable by reviewer A, 111/125 (88.8%) by reviewer B, and 106/125 (84.8%) by both reviewers A and B. For the UA, 125/125 (100%) of the images were classified as acceptable by reviewer A, 121/125 (96.8%) by reviewer B and 121/125 (96.8%) by both reviewers (Table 1). For biometry measurements, 124/25 (99.2%), 120/125 (96.0%), and 120/120 (96.0%) of the AC images were classified as acceptable by reviewer A, reviewer B and both reviewers, respectively. For the FL, reviewer A scored 114/125 (91.2%) as acceptable, review B 120/125 (96.0%), and both reviewers 110/125 (88.0%). Additional quality score assessment results for each element of the fetal biometry and Doppler measurement scoring criterion are reported in Tables S1 and Table S2.

Table 1 Proportion of fetal biometry and pulsed-wave Doppler measurements classifies as acceptable, according raters A and B

Parameter	Rater A	Rater B	Both Raters
Biometry			
HC	120 (96.0)	124 (99.2)	120 (96.0)
AC	124 (99.2)	120 (96.0)	120 (96.0)
FL	114 (91.2)	120 (96.0)	110 (88.0)
Doppler			
UA	125 (100.0)	121 (96.8)	121 (96.8)
MCA	119 (95.2)	111 (88.8)	106 (84.8)
RUtA	124 (99.2)	118 (94.4)	117 (93.6)
LUtA	123 (98.4)	116 (92.8)	114 (91.2)

*N= 125; data reported as: acceptable, n (%); HC: head circumference; AC: abdominal circumference; FL: femur length; UA: umbilical Doppler; MCA: middle cerebral artery; RUtA: right uterine artery; LUtA: left uterine artery; acceptable score cutoff point for HC, AC, UA, MCA and UtA is >= 4; acceptable score cutoff point for FL is >=3

Rater agreement

The overall inter-observer percent agreement for objective evaluation of the UA Doppler images was 96.8% (modified Kappa, 0.94 (95% CI, 0.87–0.99); P <0.001). For the MCA, the inter-observer agreement was 85.6% (modified Kappa, 0.71 (95% CI, 0.58–0.82); P <0.001), while for the uterine artery, the inter-observer agreement was 93.6% (modified Kappa, 0.87 (95% CI, 0.78–0.95); P <0.001) and 91.2% (modified Kappa, 0.82 (95% CI, 0.71–0.92); P <0.001), for the right and left sides, respectively. The inter-observer percent agreement for objective evaluation of the AC measurements was 96.8% (modified Kappa, 0.93 (95% CI, 0.87–0.98), P <0.001); and for the

HC measurement was 96.8% (modified Kappa, 0.94 (95% CI, 0.87–0.98), P <0.001), (Table 2).

Table 2 Percentage of agreement and Modified Fleiss' Kappa between raters A and B for fetal biometry and pulse-wave Doppler measurements in EPID study

Parameter	Agreement (%)	Modified Fleiss' Kappa (95% CI)	P-value
Biometry			
HC	96.8	0.94 (0.87 – 0.98)	<0.001
AC	96.8	0.93 (0.87 – 0.98)	<0.001
FL	88.8	0.78 (0.66 – 0.88)	<0.001
Doppler			
UA	96.8	0.94 (0.87 – 0.99)	<0.001
MCA	85.6	0.71 (0.58 – 0.82)	<0.001
RUtA	93.6	0.87 (0.78 – 0.95)	<0.001
LUtA	91.2	0.82 (0.71 – 0.92)	<0.001

*N= 125; HC: head circumference; AC: abdominal circumference; FL: femur length; UA: umbilical Doppler; MCA: middle cerebral artery; RUtA: right uterine artery; LUtA: left uterine artery; CI: confidence interval; level of significance = 0.05.

Z-score distributions

The Q-Q plots in Figure 1 (a-d) demonstrate normal distributions of the HC, AC, FL, and UA pulsatility index gestational specific z-scores. In addition, the mean (standard deviation, SD) was -0.02 (1.00) for the HC z-scores, 0.03 (0.92) for the AC z-scores, 0.53 (0.82) for the FL z-scores, and -0.27 (1.05) for the UA PI z-scores in the sample. The corresponding Shapiro- Wilk test P-values for the HC z-scores, AC z-scores, FL z-scores and UA PI z-scores were 0.955, 0.409, 0.416 and 0.286, respectively.

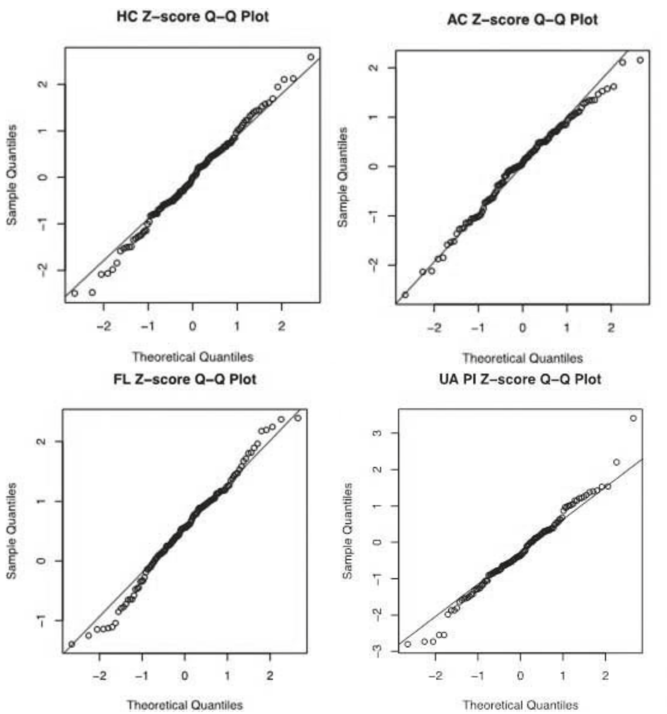


Figure 1 Normal Q-Q plots for head circumference (a), abdominal circumference (b), femur length (c), and UA PI (d) measurement z-scores in EPID study

DISCUSSION

Summary of key findings

The quality scores of ultrasound measurements obtained in the EPID study were high, with over 84.8% of the pulse-wave Doppler images and 88.0% of the fetal biometry images scored as acceptable by both reviewers. The inter-rater agreement was very good for Doppler and biometry images, with adjusted Kappa of up to 0.94 (95% CI, 0.87–0.99) for the umbilical artery and 0.94 (95% CI, 0.87–0.98) for the HC measurements. All fetal biometry and UA PI z-scores had normal distributions, implying negligible influence of systematic errors in our measurements.

Strength and limitations

Ultrasound measurements in the EPID study were acquired following standard techniques, the sonographers had a longer pre-implementation training period (up to six weeks) than in most published studies and underwent audits and refresher trainings. Though we did not measure the impact of the retraining exercise, it could have enhanced the quality of our measurements. The quality assessments were undertaken by experienced reviewers who were blinded to each other's ratings and without access to the study sonographers' findings. Further, they were not involved in data collection and re-training, allowing for independence in their reviews.

Although we used arbitrary thresholds to classify images as acceptable or unacceptable, this is recommended by the audit tool developers to allow for simplicity in interpreting the findings.[7–9] According to the International society of Ultrasound in Obstetrics and Gynecology (ISUOG) clinical standards committee, a comprehensive quality control strategy should also involve assessment of caliper placement bias and the limits of agreement of the actual measurements. These are not reported as we did not obtain multiple measurements in a repeated fashion from each woman, for feasibility reasons. However, we used z-score distribution method to checked for systematic biases in our measurements.

The training exercise was resource-intensive. However, basing on our experience implementing ultrasound studies in low-resource contexts, similar results are achievable within a shorter period. Future studies should also include ultrasound naïve practitioners.

Interpretation

This study shows that it is possible to train ultrasonographers in under-priviledged regions to undertake Doppler scans with consistency. Fetal biometry and Doppler ultrasound measurements quality can be reliably assessed using freely available objective evaluation tools.[7–9] In our study, more than 85% of the Doppler images were acceptable. Similar findings were reported a multi-center Doppler study in a HIC where 89.2% of the MCA images and 85.0% of the UA images were of acceptable quality.[25] For fetal biometry, nearly 90% of our images were of acceptable quality. In comparison, over 98% of the biometry images were of very high quality in a large multi-center international project.[19]

The inter-rater agreement in our study was very good for all images, with an agreement rate of up to 96.8% (modified kappa, 0.94) for the UA and 85.6% (modified kappa, 0.71) for the MCA. Previous studies from HICs have demonstrated that inter-observer agreement for Doppler image assessment is very good when using an objective scoring system compared to subjective assessment in both clinical and multi-center research settings.[7,8,25] The INTERGROWTH-21st group reported overall agreement of 85% (adjusted Kappa, 0.70) when using an objective scale compared to 70% (adjusted Kappa, 0.47) for subjective assessment.[8] The objective assessment with a six-point scoring system had a greater inter-observer agreement (91.9%; Kappa, 0.839) than subjective agreement (75.8%; Kappa, 0.516) for MCA images.[7] In a multi-center randomized controlled trial, Kappa values for inter-rater values were 0.85 (95% CI, 0.81–0.89) and 0.84 (95% CI, 0.80–0.89) for the MCA and UA, respectively.[25] Further, a high level of inter-rater agreement was reported for the HC (Kappa, 0.99, 95% CI, 0.98–0.99), AC (Kappa, 0.98, 95% CI, 0.97–0.99) and FL (Kappa, 0.96, 95% CI, 0.95–0.98) measurements in the INTERGROWTH-21st study sites adhering to strict quality control measures.[19] Similarly, the inter-rater agreement for all the fetal biometry measurements obtained in our study was excellent.

It is not surprising that most of our findings were comparable to those from HICs. Acceptable and accurate Doppler scans are achievable when performed by adequately trained ultrasonographers observing strict examination protocols.[6] We have previously demonstrated similar results for CRL measurements in a Ugandan clinical setting,[26] and fetal biometry by local healthcare workers in a refugee camp on the Thai–Burmese border.[27] Standardization of obstetric ultrasound practice is important for clinical settings of LMICs, and multi-center studies in which a broad range of settings, women and practitioners are involved. Although there was no evidence of systematic errors in our measurements, differences in reviewer scores for individual elements, like UA image clarity, emphasize the need to adequately orient practitioners using any clinical tools to ensure its uniform interpretations.

As the World Health Organization (WHO) now recommends the use of UA Doppler to manage high-risk pregnancies,[28] it is imperative that quality

control systems are established and adhered to in obstetric ultrasound units of LMICs. Co-created local guidelines for the management of suspected growth-restricted fetuses developed following a bottom-up approach are needed and should emphasize the use of similar and context-appropriate reference standards constructed using robust methodologies such as the INTERGROWTH 21st range of charts, to confer appropriate care to the women.[29,30]
Increasing access and promoting the efficient use of ultrasound technology in LMICs will require commitments by governments, funding agencies, and international communities to improve the quality of ANC. A structured training program in obstetric ultrasound taking into account the local context and available cadres at the frontline seems a more beneficial strategy.[27,31] With the advent of artificial intelligence, there is hope for future commercial products with the ability to support practitioners to undertake and interpret complex ultrasound procedures with high precision.[32]
Such modern clinical decision support tools are an urgent obstetric need in high-burden settings where highly skilled care providers (fetal medicine specialists) counts are still very limited.

CONCLUSION

Training healthcare providers in underserved regions to undertake Doppler ultrasound examinations with consistency was feasible. Implementation of quality control systems and freely available objective ultrasound image scoring tools in clinical and research settings of low-resource settings is strongly recommended. Future studies evaluating the impact of regular in-servce audits and re-training will be very valuable.

ACKNOWLEDGEMENTS

We thank the study participants, Kagadi District Health Team, The Woman's Place, ECUREI and Makerere University College of Health Sciences for supporting the implementation of the EPID project. The University of Oxford, Oxford, United Kingdom is immensely appreciated for contributing the ultrasound equipment for data collection. Further, our gratitude goes to Fosca Tumushabe who assisted with the English language review. We thank the INTERGROWTH-21st consortium for assistance and for providing freely available training materials and protocols (https://intergrowth21.tghn.org/); Lior Drukker for his help in calculation of UA Doppler centiles. This project was funded by Grand Challenges Canada (Grant Number: R-ST-POC-1808-17038) through a generous grant to Makerere University College of Health Sciences. SA is supported by the UMC Utrecht Global Health Support Program (Ref: FM/ADB/D- 18-015006), University Medical Center Utrecht, Utrecht, The Netherlands. ATP is funded by the Oxford Partnership Comprehensive Biomedical Research Centre with funding from the NIHR Biomedical Research Centre (BRC) funding scheme.

SUPPORTING INFORMATION

Table S1 Proportion of individual elements of the fetal biometry ultrasound measurements meeting the quality score criterion, according to raters

Table S2 Proportion of individual elements of the pulse-wave Doppler ultrasound measurements meeting the quality score criterion, according to raters.

Figure S1 Color and pulsed-wave Doppler images with correct measurement of umbilical artery (a), middle cerebral artery (b) and uterine artery (c).

Figure S2 Fetal biometry images with correct measurement of head circumference (a), abdominal circumference (b) and femur length (c).

Figure S3 Distribution of the total scores of umbilical artery (a), middle cerebral artery (b), right uterine artery (c), and left uterine artery (d) pulsed-wave Doppler images, by reviewers A and B.

Figure S4 Distribution of the total scores of head circumference (a), abdominal circumference (b), and femur length (c) ultrasound images, by reviewers A and B.

Appendix S1 Image-scoring criteria for umbilical, middle cerebral and uterine artery pulse-wave Doppler ultrasound measurements.

Appendix S2 Image scoring criteria for head circumference, abdominal circumference and femoral length ultrasound measurements.

REFERENCES

1. Mills TA, Ayebare E, Mweteise J, Nabisere A, Mukhwana R, Nendela A, et al. 'There is trauma all round': A qualitative study of health workers' experiences of caring for parents after stillbirth in Kenya and Uganda. Women and Birth. 2022;
2. Heazell AEP, Siassakos D, Blencowe H, Burden C, Bhutta ZA, Cacciatore J, et al. Stillbirths: economic and psychosocial consequences. Lancet. 2016;387(10018):604–16.
3. Hug L, You D, Blencowe H, Mishra A, Wang Z, Fix MJ, et al. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. Lancet. 2021 Aug 28;398(10302):772–85.
4. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: Rates, risk factors, and acceleration towards 2030. Lancet. 2016;387(10018):587–603.
5. Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. Am J Obstet Gynecol. 2018 Feb 1;218(2):S745–61.
6. Rolnik DL, da Silva Costa F, Sahota D, Hyett J, McLennan A. Quality assessment of uterine artery Doppler measurement in first-trimester combined screening for pre-eclampsia. Ultrasound Obstet Gynecol. 2019 Feb 1;53(2):245–50.
7. Ruiz-Martinez S, Volpe G, Vannuccini S, Cavallaro A, Impey L, Ioannou C. An objective scoring method to evaluate image quality of middle cerebral artery Doppler. J Matern Neonatal Med. 2020 Feb 1;33(3):421–6.
8. Molloholli M, Napolitano R, Ohuma EO, Ash S, Wanyonyi SZ, Cavallaro A, et al. Image-scoring system for umbilical and uterine artery pulsed-wave Doppler ultrasound measurement. Ultrasound Obstet Gynecol. 2019 Feb 1;53(2):251–5.
9. Salomon LJ, Bernard JP, Duyme M, Doris B, Mas N, Ville Y. Feasibility and reproducibility of an image-scoring method for quality control of fetal biometry in the second trimester. Ultrasound Obstet Gynecol. 2006 Jan 1;27(1):34–40.
10. Wanyonyi SZ, Napolitano R, Ohuma EO, Salomon LJ, Papageorghiou AT. Image-scoring system for crown–rump length measurement. Ultrasound Obstet Gynecol. 2014 Dec 1;44(6):649–54.
11. Kottner J, Audigé L, Brorson S, Donner A, Gajewski BJ, Hróbjartsson A, et al. Guidelines for Reporting Reliability and Agreement Studies (GRRAS) were proposed. J Clin Epidemiol. 2011 Jan 1;64(1):96–106.
12. Ali S, Kawooya MG, Byamugisha J, Kakibogo IM, Biira EA, Kagimu AN, et al. Middle cerebral arterial flow redistribution is an indicator for intrauterine fetal compromise in late pregnancy in low-resource settings: a prospective cohort study. BJOG An Int J Obstet Gynaecol. 2022 Feb 4;129:1712– 1720.
13. Ali S, Kabajaasi O, Kawooya MG, Byamugisha J, Zakus D, Papageorghiou AT, et al. Antenatal Doppler ultrasound implementation in a rural sub-Saharan African setting: exploring the perspectives of women and healthcare providers. Reprod Health. 2021;18(1):199.
14. Ali S, Heuving S, Kawooya MG, Byamugisha J, Grobbee DE, Papageorghiou AT, et al. Prognostic accuracy of antenatal Doppler ultrasound for adverse perinatal outcomes in low-income and middle-income countries: a systematic review. BMJ Open. 2021 Dec 1;11(12):e049799.
15. UBOS and ICF. Uganda Demographic and Health Survey 2016. Kampala, Uganda and Rockville, Maryland, USA; 2018.

16. Sarris I, Ioannou C, Ohuma EO, Altman DG, Hoch L, Cosgrove C, et al. Standardisation and quality control of ultrasound measurements taken in the INTERGROWTH-21st Project. BJOG An Int J Obstet Gynaecol. 2013 Sep 1;120(s2):33–7.
17. Salomon LJ, Alfirevic Z, Da Silva Costa F, Deter RL, Figueras F, Ghi T, et al. ISUOG Practice Guidelines: ultrasound assessment of fetal biometry and growth. Ultrasound Obstet Gynecol. 2019 Jun 1;53(6):715–23.
18. Bhide A, Acharya G, Baschat A, Bilardo CM, Brezinka C, Cafici D, et al. ISUOG Practice Guidelines (updated): use of Doppler velocimetry in obstetrics. Ultrasound Obstet Gynecol. 2021 Aug 1;58(2):331–9.
19. Cavallaro A, Ash ST, Napolitano R, Wanyonyi S, Ohuma EO, Molloholli M, et al. Quality control of ultrasound for fetal biometry: results from the INTERGROWTH-21st Project. Ultrasound Obstet Gynecol. 2018 Sep 1;52(3):332–9.
20. Marasini D, Quatto P, Ripamonti E. Assessing the inter-rater agreement for ordinal data through weighted indexes. Stat Methods Med Res. 2014 Apr 16;25(6):2611–33.
21. Salomon LJ, Bernard JP, Ville Y. Analysis of Z-score distribution for the quality control of fetal ultrasound measurements at 20–24 weeks. Ultrasound Obstet Gynecol. 2005 Dec 1;26(7):750–4.
22. Papageorghiou AT, Ohuma EO, Altman DG, Todros T, Ismail LC, Lambert A, et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet. 2014 Sep 6;384(9946):869–79.
23. Hafen R, Anderson C, Schloerke B. hbgd: Healthy birth, growth & development [Internet]. 2016 [cited 2021 Sep 23]. Available from: https://github.com/HBGDki/hbgd
24. Drukker L, Staines-Urias E, Villar J, Barros FC, Carvalho M, Munim S, et al. International gestational age-specific centiles for umbilical artery Doppler indices: a longitudinal prospective cohort study of the INTERGROWTH-21st Project. Am J Obstet Gynecol. 2020 Jun 1;222(6):602.e1-602.e15.
25. Rial-Crestelo M, Morales-Roselló J, Hernández-Andrade E, Prefumo F, Oros D, Caffici D, et al. Quality assessment of fetal middle cerebral and umbilical artery Doppler images using an objective scale within an international randomized controlled trial. Ultrasound Obstet Gynecol. 2020 Aug 1;56(2):182–6.
26. Ali S, Byanyima RK, Ononge S, Ictho J, Nyamwiza J, Loro ELE, et al. Measurement error of mean sac diameter and crown-rump length among pregnant women at Mulago hospital, Uganda. BMC Pregnancy Childbirth. 2018;18(1):129.
27. Rijken MJ, Lee SJ, Boel ME, Papageorghiou AT, Visser GHA, Dwell SLM, et al. Obstetric ultrasound scanning by local health workers in a refugee camp on the Thai–Burmese border. Ultrasound Obstet Gynecol. 2009 Oct 1;34(4):395–403.
28. WHO. WHO recommendations on antenatal care for a positive pregnancy experience [Internet]. World Health Organization; 2016. Available from: https://www.who.int/publications/i/item/9789241549912
29. Papageorghiou AT, Kennedy SH, Salomon LJ, Altman DG, Ohuma EO, Stones W, et al. The INTERGROWTH-21st fetal growth standards: toward the global integration of pregnancy and pediatric care. Am J Obstet Gynecol. 2018;218(2, Supplement):S630–40.
30. Drukker L, Staines-Urias E, Papageorghiou AT. The INTERGROWTH-21st Doppler centile charts: complementing tools for monitoring of growth and development from pregnancy to childhood. Am J Obstet Gynecol. 2021 Feb 1;224(2):249–50.

31. Kawooya MG. Training for Rural Radiology and Imaging in Sub-Saharan Africa: Addressing the Mismatch Between Services and Population. J Clin Imaging Sci. 2012;2:37.
32. Drukker L, Noble JA, Papageorghiou AT. Introduction to artificial intelligence in ultrasound imaging in obstetrics and gynecology. Ultrasound Obstet Gynecol. 2020 Oct 1;56(4):498–505.

SUPPLEMENTARY MATERIALS

Table S1 Proportion of individual elements of the fetal biometry ultrasound measurements meeting the quality score criterion, according to raters.

Parameter	Rater A	Rater B	Both Raters
HC			
Symmetrical plane	121 (96.8)	123 (98.4)	120 (96.0)
Thalami visible	115 (92.0)	123 (98.4)	115 (92.0)
Cavum septum pellucidum visible	107 (85.6)	112 (89.6)	100 (80.0)
Cerebellum not visible	120 (96.0)	123 (98.4)	119 (95.2)
Head occupy >30% of image	124 (99.2)	125 (100)	124 (99.2)
Correct caliper placement	124 (99.2)	109 (87.2)	108 (86.4)
AC			
Symmetrical plane	120 (96.0)	120 (96.0)	115 (92.0)
Stomach bubble	103 (82.4)	109 (87.2)	99 (79.2)
Portal sinus	97 (77.6)	110 (88.0)	90 (72.0)
Kidneys not visible	118 (94.4)	111 (88.8)	107 (85.6)
Abdomen occupy >30% of image	125 (100)	125 (100)	125 (100)
Correct caliper placement	119 (95.2)	116 (92.8)	112 (89.6)
FL			
Both ends clearly visible	115 (92.0)	118 (94.4)	111 (88.8)
Femur <45^0 angle to the horizontal	124 (99.2)	125 (100)	124 (99.2)
Femur occupy >30% of image	121 (96.8)	114 (91.2)	110 (88.0)
Correct caliper placement	112 (89.6)	121 (96.8)	112 (89.6)

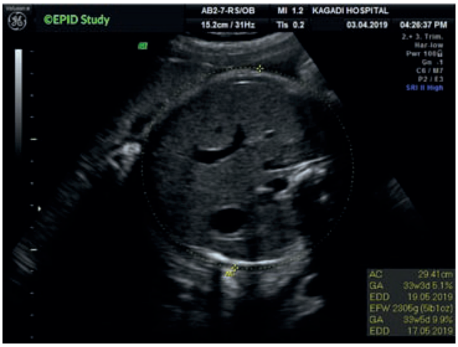
*N= 125; data reported as n (%); HC: head circumference; AC: abdominal circumference; FL: femur length.

Table S2 Proportion of individual elements of the pulse-wave Doppler ultrasound measurements meeting the quality score criterion, according to raters.

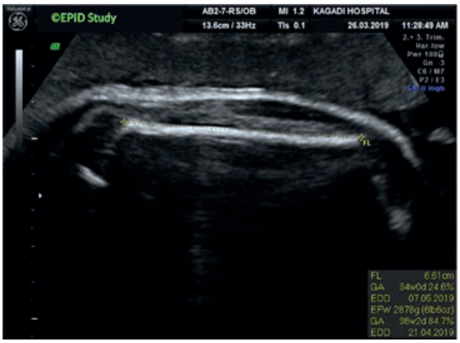
Parameter	Rater A	Rater B	Both Raters
UA			
Magnification	122 (97.6)	120 (96.0)	118 (94.4)
Angle of insonation	125 (100)	117 (93.6)	117 (93.6)
Sweep speed	121 (96.8)	118 (94.4)	115 (92.0)
Image clarity	117 (93.6)	64 (51.2)	61 (48.8)
Anatomical site	123 (98.4)	125 (100)	123 (98.4)
Velocity scale	116 (92.8)	97 (77.6)	92 (73.6)
MCA			
Magnification	115 (92.0)	122 (97.6)	112 (89.6)
Angle of insonation	123 (98.4)	95 (76.0)	93 (74.4)
Sweep speed	118 (94.4)	122 (97.6)	116 (92.8)
Image clarity	108 (86.4)	113 (90.4)	101 (80.8)
Anatomical site	115 (92.0)	96 (76.8)	87 (70.0)
Velocity scale	112 (89.6)	58 (46.4)	56 (44.8)
RUtA			
Magnification	124 (99.2)	110 (88.0)	110 (88.0)
Angle of insonation	125 (100)	101 (80.8)	101 (80.8)
Sweep speed	125 (100)	124 (99.2)	124 (99.2)
Image clarity	121 (96.8)	98 (78.4)	95 (76.0)
Anatomical site	119 (95.2)	106 (84.8)	100 (80.0)
Velocity scale	120 (96.0)	103 (82.4)	99 (79.2)
LUtA			
Magnification	122 (97.6)	102 (81.6)	99 (79.2)
Angle of insonation	123 (98.4)	107 (85.6)	105 (84.0)
Sweep speed	125 (100)	125 (100)	125 (100)
Image clarity	113 (90.4)	108 (86.4)	101 (80.8)
Anatomical site	116 (92.8)	115 (92.0)	107 (85.6)
Velocity scale	120 (96.0)	106 (84.8)	102 (81.6)

*N= 125; data reported as n (%); UA: umbilical artery; MCA: middle cerebral artery; RUtA: right uterine artery; LUtA: left uterine artery

a)

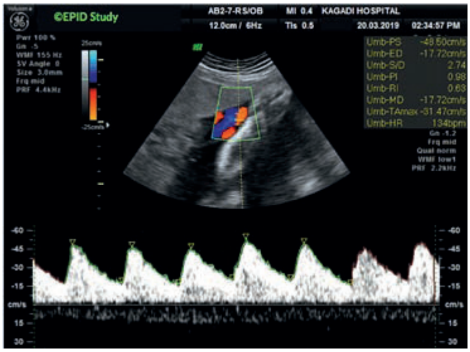


b)



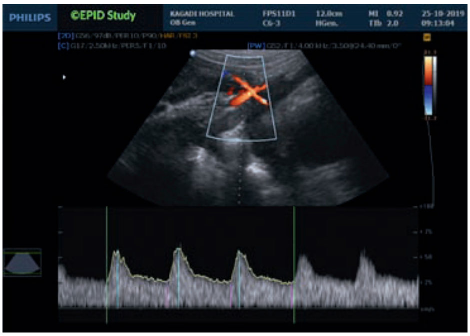
c)

Figure S1 Fetal biometry images with correct measurement of head circumference (a), abdominal circumference (b) and femur length (c).



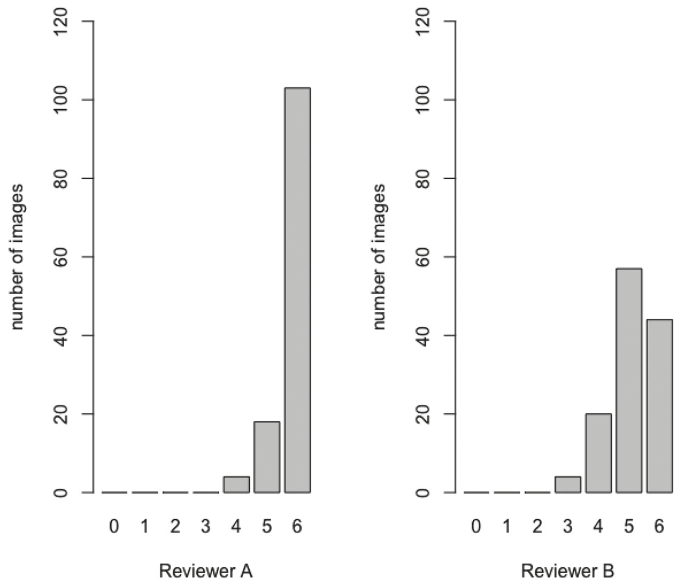
a)

b)

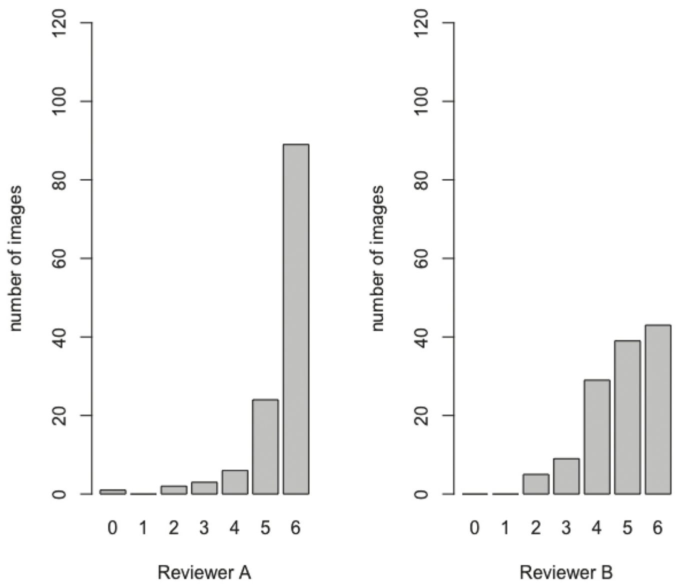


c)

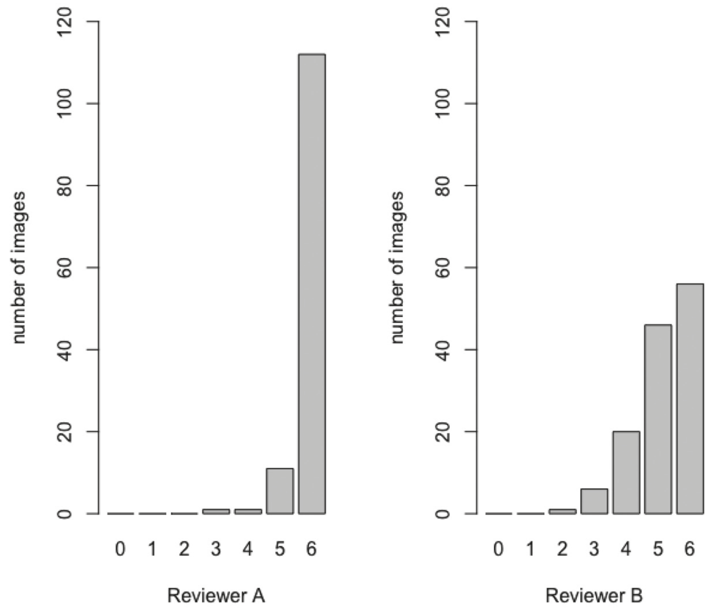
Figure S2 Color and pulsed-wave Doppler images with correct measurement of umbilical artery (a), middle cerebral artery (b) and uterine artery (c).



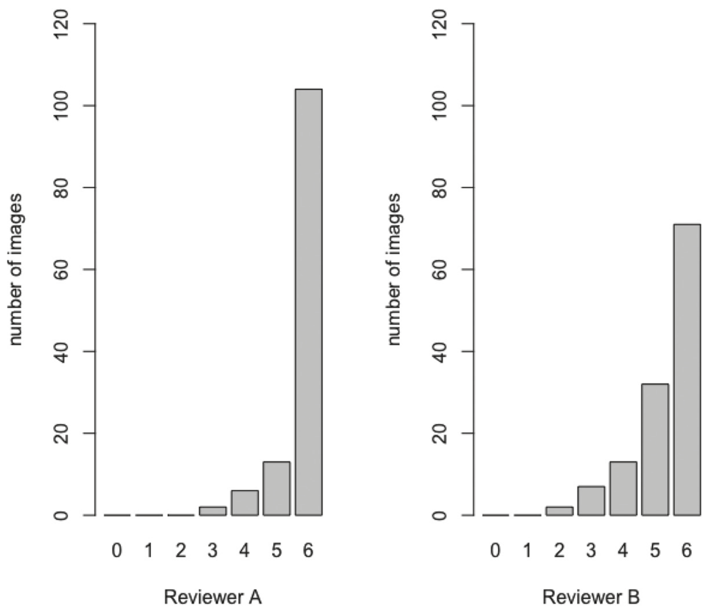
a) Umbilical artery



b) Middle cerebral artery

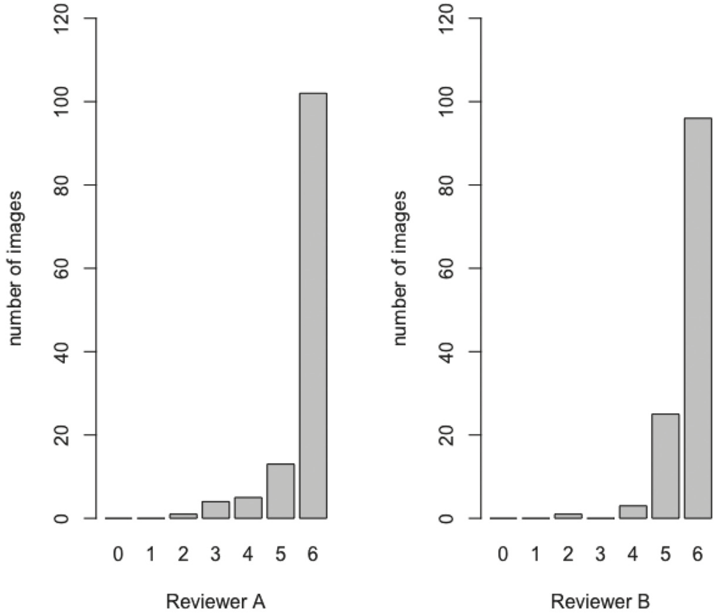


c) Right uterine artery

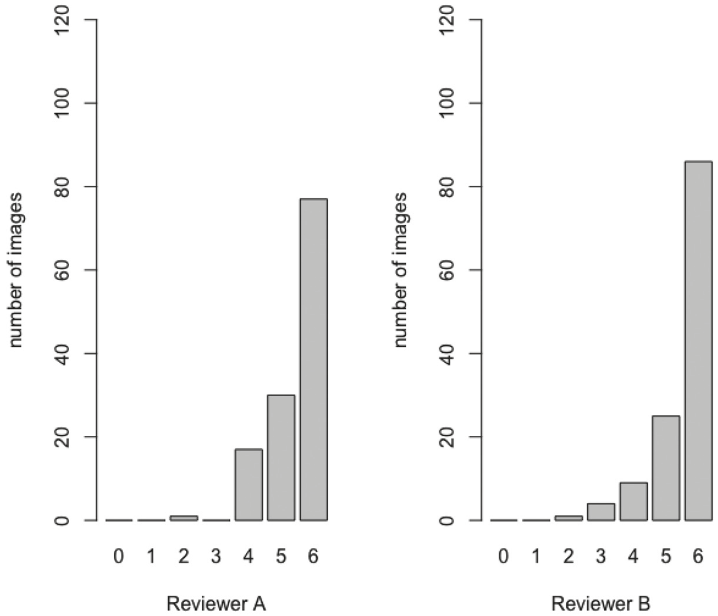


d) Left uterine artery

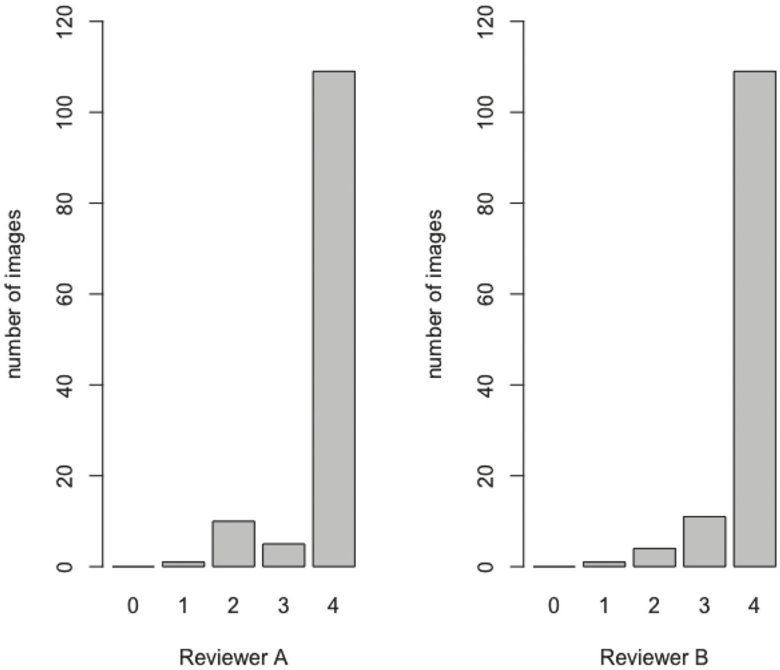
Figure S3 Distribution of the total scores of umbilical artery (a), middle cerebral artery (b), right uterine artery (c), and left uterine artery (d) pulsed-wave Doppler images by reviewers A and B



a) Head circumference



b) Abdominal circumference



c) Femur length

Figure S4 Distribution of the total scores of head circumference (a), abdominal circumference (b), and femur length (c) ultrasound images by reviewers A and B

Appendix S1 Image-scoring criteria for umbilical, middle cerebral and uterine artery Doppler measurements

a) Umbilical artery

#	Criterion	Description	Score
1.	Magnification	Area of interest fills 50% of screen, with zoom box and sample gate in center of vessel	
2.	Angle of insonation	Less than 30^0	
3.	Sweep speed	Four to six waveforms with consistent and similar signals	
5.	Image clarity	Pulse rate frequency and color gain correction (avoid venous signal)	
5.	Anatomical site	Free loop	
6.	Velocity scale	75% of peak systolic velocity	

b) Middle cerebral artery

#	Criterion	Description	Score
1.	Magnification	Area of interest fills 50% of screen, with zoom box and sample gate in center of vessel	
2.	Angle of insonation	Near 0^0 (angel correction if $>20^0$)	
3.	Sweep speed	Four to six waveforms with consistent and similar signals	
5.	Image clarity	Pulse rate frequency and color gain correction (avoid venous signal)	
5.	Anatomical site	Before bifurcation above the iliac vessels	
6.	Velocity scale	75% of peak systolic velocity	

c) Uterine artery

#	Criterion	Description	Score
1.	Magnification	Area of interest fills 50% of screen, with zoom box and sample gate in center of vessel	
2.	Angle of insonation	Less than 30^0	
3.	Sweep speed	Four to six waveforms with consistent and similar signals	
5.	Image clarity	Pulse rate frequency and color gain correction (avoid venous signal)	
5.	Anatomical site	Before bifurcation above the iliac vessels	
6.	Velocity scale	75% of peak systolic velocity	

3

Appendix S2 Image scoring criteria for head circumference, abdominal circumference and femoral length measurements

a) Head circumference

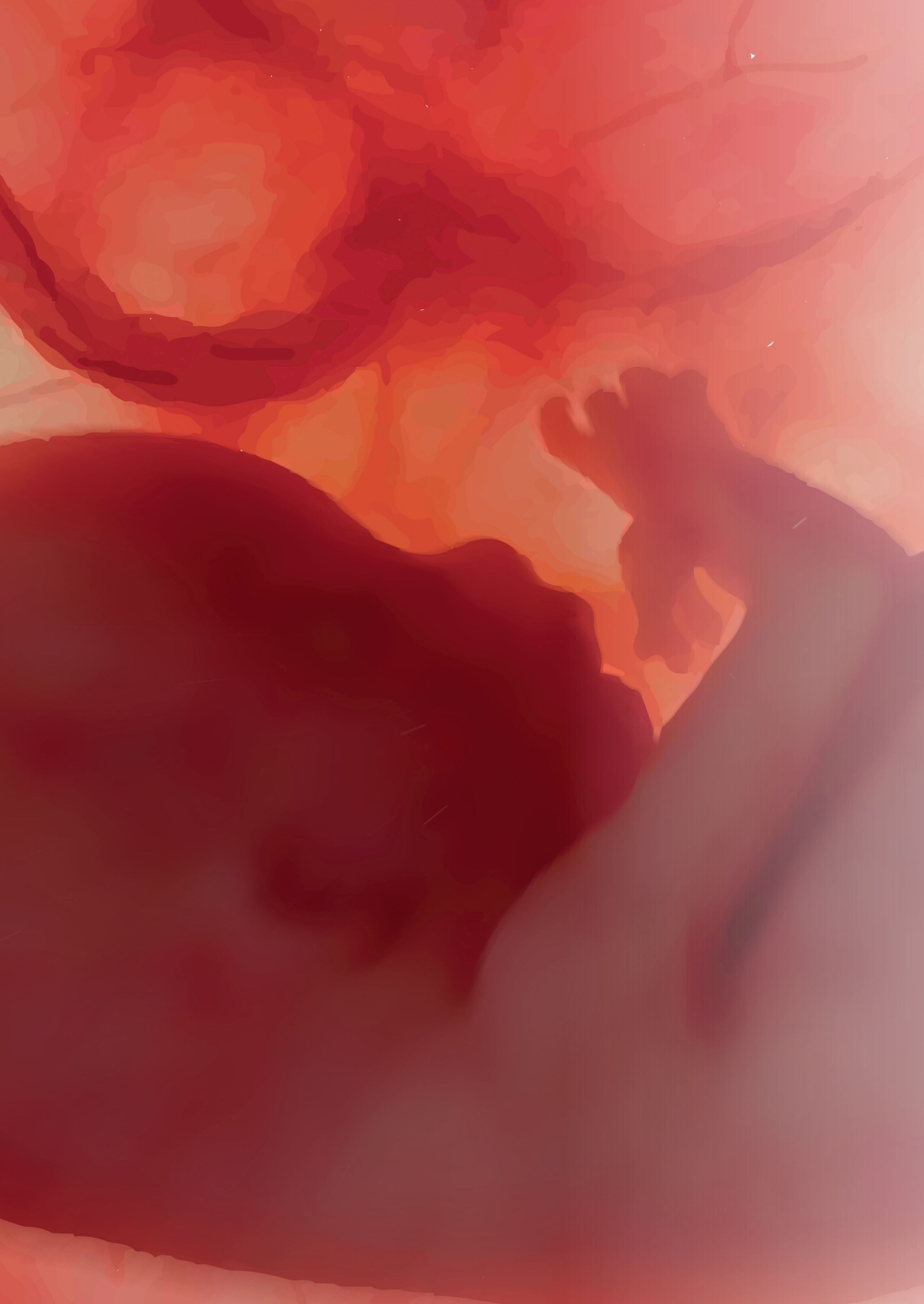
#	Criterion	Description	Score
1.	Symmetry	Symmetrical plane	
2.	Thalami	Visible	
3.	Cavum septum pellucidum	Visible	
5.	Cerebellum	Not visible	
5.	Magnification	Head occupying at least 30% of image	
6.	Calipers/ellipse	Placed correctly	

b) Abdominal circumference

#	Criterion	Description	Score
1.	Symmetry	Symmetrical plane	
2.	Stomach bubble	Stomach bubble visible	
3.	Portal sinus	Portal sinus visible	
5.	Kidneys	Kidneys not visible	
5.	Magnification	Abdomen occupying at least 30% of image	
6.	Calipers/ellipse	Placed correctly	

c) Femoral length

#	Criterion	Description	Score
1.	Bone ends	Clearly visible	
2.	Angle	Femur $<45^{0}$ angle to the horizontal	
3.	Magnification	Femur occupying at least 30% of image	
5.	Caliper	Placed correctly	



Chapter 4

Antenatal Doppler ultrasound implementation in a rural sub-Saharan African setting: exploring the perspectives of women and healthcare providers

Sam Ali
Olive Kabajaasi
Michael G. Kawooya
Josaphat Byamugisha
David Zakus
Aris T. Papageorghiou
Kerstin Klipstein-Grobusch
Marcus J. Rijken

Reprod Health. 2021;18(1):199.

ABSTRACT

Background

The World Health Organization recommends research to evaluate the effects of a single third trimester Doppler ultrasound examination on preventable deaths in unselected-risk pregnancies, particularly in low- and middle-income countries (LMICs) where the evidence base is scarce. While evaluating such technologies, researchers often ignore women and health care provider perspectives. This study explored the views and experiences of women and healthcare providers regarding the use of advanced ultrasound technology to optimize the health of mothers and their babies in a rural community in mid-western Uganda.

Methods

We enrolled 53 mothers and 10 healthcare providers, and captured data on their perceptions, barriers, and facilitators to the use of Doppler ultrasound technology using focus group discussions, semi-structured interviews and observations. Using qualitative content analysis, we inductively coded the transcripts in ATLAS.ti 8.0, detecting emerging themes.

Results

Women were afraid that ultrasound would harm them or their fetuses and many of them had never seen an ultrasound scan. The majority of the women found their partners supportive to attend antenatal care and use ultrasound services. Healthcare providers in Kagadi Hospital were unfamiliar with Doppler technology and using it to guide clinical decisions. Other barriers to the implementation of Doppler ultrasound included shortage of trained local staff, insufficient equipment, long distance to and from the hospital, and frequent power cuts.

Conclusion

We found limited exposure to Doppler ultrasound technology among women and healthcare providers in mid-western Uganda. Engaging male partners may potentially influence the likelihood of accepting and using it

to improve the health of women and their fetuses while wide spread myths and misconceptions about it may be changed by community engagement. Healthcare workers experienced difficulties in offering follow-up care to mothers detected with complications and Doppler ultrasound required a high level of training. While introducing advanced ultrasound machines to weak health systems, it is important to adequately train healthcare providers to avoid inappropriate interventions based on misinterpretation of the findings, consider where it is likely to be most beneficial, and embed it with realistic clinical practice guidelines.

PLAIN ENGLISH SUMMARY

Globally, nearly three million babies are stillborn every year, but most especially in low- and middle-income countries like Uganda. One of the factors contributing to a high number of stillbirths in low-income countries is the difficulty in identifying complications and accessing high quality care during pregnancy. Although antenatal Doppler scans are being widely used to diagnose complications in high-risk pregnancies in developed countries, studies evaluating it in LMICs are needed before it is implemented on a wide scale. We engaged 53 mothers, eight health workers from a hospital and two healthcare managers from a local government in Uganda to attain their opinions about Doppler ultrasound. We found that spousal involvement may promote acceptance and use of ultrasound services. However, the health workers did not have adequate knowledge about Doppler technology and using it for the benefit of mothers and the mothers feared that ultrasound procedures might harm them or their unborn babies. Making matters worse, the hospital faced frequent power cuts that affected the use of the equipment. Further, mothers must cover a long distance to access the hospital and its services. To reduce the number of babies dying during pregnancy or a few days after birth in Uganda and similar low-resource settings using Doppler technology, it is essential to strengthen the health systems. Starting with the training of healthcare providers to equipping and stabilizing power supply in health facilities, and educating the public about critical health procedures to break myths and misconceptions.

KEYWORDS

Pregnancy, Antenatal care, Healthcare workers, Doppler ultrasound, Low- and middle-income countries, Qualitative.

BACKGROUND

In most low- and middle-income countries (LMICs), perinatal mortality rates are very high, about 10 times that of high-income countries (HICs).[1,2] In Uganda, the stillbirth rate is 17.8 per 1000 live births.[2] The causes of perinatal mortality in LMICs are complex, ranging from high rates of home deliveries to poor quality of intrapartum care, and undetected pregnancy complications such as growth-restricted fetuses, among others. Significant mortality reductions will require a multi-sectoral effort, including strengthening health facility surveillance systems to accurately detect all fetuses truly at risk of adverse outcomes combined with timely effective medical interventions where the maternal and fetal benefits and risks of such interventions were carefully evaluated. Doppler ultrasound is a potentially valuable surveillance tool and its role in high-risk pregnancies is already established in HIC.[3,4] In low-risk or unselected obstetric populations, there is still no evidence to indicate that its use improves perinatal outcomes in both LMICs and HICs.[4] In fact, there is a potential risk of inappropriate interventions such as cesarean sections and adverse effects.[5] Its use remains reserved for the fear of high false positive diagnosis and iatrogenic morbidity or even mortality.[6] Studies evaluating the effects of introducing Doppler ultrasound into antenatal care on perinatal mortality are needed, especially in low-resource settings where evidence about the effects of this intervention is acutely lacking. While evaluating such technologies, researchers often ignore women and healthcare provider perspectives. Stakeholder perspectives are vital to guide its integration into routine antenatal care to optimize the health of pregnant women and their fetuses.

Previous studies in LMICs have reported experiences and views of local stakeholders on the implementation of obstetric ultrasound.[7–13] In general, pregnant women had mixed views regarding antenatal ultrasound: the majority saw it as beneficial, while some feared it.[9–11,14] For example, studies in Uganda and Thailand showed that some respondents believed ultrasound could be dangerous.[11,15] Healthcare providers, meanwhile, perceived it as a useful tool in pregnancy.[8,10,11] Furthermore, both healthcare providers and local women reported lack of equipment, personnel capacity, equipment cost and maintenance as major challenges to regular use of ultrasound.[12–14] These findings mostly relate to the use of basic ultrasound equipment. To date, we know little about potential dilemmas in implementing more advanced ultrasound technologies with Doppler and color flow capabilities in LMICs.

This study explored the views and experiences of mothers, healthcare workers, and health system managers regarding the use of Doppler ultrasound in pregnancy in a rural community in mid-western Uganda. We highlight operational and practical issues regarding its clinical application in Uganda and examine the factors that could influence its introduction into similar LMICs.

METHODS

Design and setting

This explorative qualitative study was conducted and reported per the consolidated criteria for reporting qualitative research (COREQ).[16] It was part of the EPID project, a larger cohort study involving over 1239 pregnant women prospectively enrolled between 2018 and 2020 in Uganda to evaluate the prognostic accuracy of Doppler ultrasound for adverse perinatal outcomes. The EPID study women underwent pregnancy dating ultrasound scans at <24 weeks, followed by biometry and Doppler ultrasound examinations in the late third trimester. They were scanned at Kagadi Hospital; a 150-bed facility located in the greater Kibaale region in mid-western Uganda approximately 215 kilometers from the national capital, Kampala. According to the Uganda Demographic and Health Survey report 2016, the total population for Kibaale stands at 788,714, with 389,278 (49.36%) males and 399,436 (50.64%) females.[17] The district had 168,358 households, giving an average size of 4.7 persons per household. The District Health Information Systems shows that Kagadi hospital had about 4,449 deliveries in 2020, and about 1,483 women achieved four or more ANC contacts while only 13 achieved eight contacts.

Sample and recruitment

We recruited women prospectively to a point of saturation of the themes both from the overall EPID study cohort and from the routine antenatal clinic setting in order to ensure that women whom we did not enroll in the EPID study were also represented. Women attending routine antenatal care appointments were recruited in an unselected fashion by convenience sampling: with a quota of one daily. We purposively sampled women recruited from the overall EPID study cohort and healthcare providers.

All participants including emancipated minors and adults 18 years and above provided informed written consent before enrollment. The illiterate participants provided a thumbprint and their interviews were conducted in the local language. The research team assured participants of confidentiality and privacy and promised to act in the spirit of the informed consent received. The study received ethical clearance from Makerere University School of Medicine Research and Ethics Committee (SOMREC): approval number #REC REF 2018-090; and from the Uganda National Council for Science and Technology (UNCST): approval number HS 2459. Further, we obtained written permission from Kagadi district and hospital authorities to implement the study in their territory.

To determine sample size, we looked at previous studies assessing perceptions of key stakeholders on antenatal ultrasound and estimated that approximately 45 participants should be sufficient.[10,11] However, we recruited the study sample beyond the estimated mark. The study team recruited nearly half of the estimated participants, undertook a preliminary analysis and based on the initial analytic ideas further enrolled more women to a point where no new sub-themes, themes or insights to the research questions emerged.

Interviews

Data collection methods included focus group discussions (FGDs), semi-structured interviews, observations using a daily activity log, and field notes. We conducted nine FGDs with women (one with women who declined an ultrasound examination, three with pregnant women attending ANC, two with mothers who gave birth at home, and three with those who completed the EPID study follow-up and gave birth in a health facility). Seven individual semi-structured interviews were conducted with women who had been pregnant (three had experienced perinatal death, and four had complications such as ectopic pregnancy, spinal defect, and premature delivery). Ten individual semi-structured interviews were held with eight healthcare workers (two sonographers, five midwives, and one records clerk), and two healthcare managers (administrators of Kagadi hospital and the district health offices) (Table 1).

Table 1: Type of interview and participants recruited

Participant categories	Semi-structured interviews	FGD	Number of Participants
Women			
Women attending ANC		3	18
Women who declined the ultrasound scan examination		1	3
Mothers from EPID study who delivered at home [a]		2	9
Mothers from EPID study who delivered in a health facility [a]		3	16
Mothers who experienced stillbirth or neonatal death [a]	3		3
Mothers who had complications (ectopic pregnancy, spinal defect, preterm deliveries) [a]	4		4
Healthcare workers			
Sonographers	2		2
Nurses and midwives	6		6
District Health Team	2		2
Total	**17**	**9**	**63**

[a]32 participants enrolled from the list of EPID study

We used the interview guides with open-ended questions focused on four main topics: perceptions of women, experiences of women and providers, barriers and facilitators of Doppler ultrasound use in pregnancy to conduct the discussions (Additional files 1, 2, 3 and 4: interview and focus group discussion guides). Each interview began with an explanation of the EPID study, the consent process, and the assignment of unique numbers to FGD participants to assure anonymity. For the women recruited from the EPID study database, we scheduled the interviews at their homes or Kagadi Hospital depending on one's preference, while all women recruited at the ANC clinic were interviewed at the health facility. We interviewed all healthcare providers at Kagadi Hospital, except for one at the district health offices. The FGDs lasted about 45 minutes and the semi-structured interviews between 20 to 30 minutes. A social scientist (OK) with over 10 years of experience in qualitative research and training in mixed methods research led all the interviews. OK was assisted by two experienced midwives purposively selected from the pool of research assistants serving in the project. They conducted the interviews in English and the local language (Runyoro) between September and December 2019. All interviews were audio-recorded.

Data analysis

Two study team members (OK and a research assistant) transcribed the audio recordings verbatim and translated them into English. They read the transcripts and listened to the audio recordings simultaneously, to check for accuracy and consistency, resolving disagreements by discussion. The principal investigator (SA) reviewed all the transcripts to ensure reliability before analysis.

Using qualitative content analysis, we inductively coded the transcripts in ATLAS.ti 8. This inductive approach allows for the unexpected and permits more socially-located responses from interviewees that may include matters of cultural beliefs or links to other important events in their lives, such as grief, which cannot be predicted by the researcher in advance.[18] The data analyst (OK) carefully read the transcripts, applying labels (codes) to expressions related to the research question. To identify the codes, categories or themes from the transcripts, we used line-by-line scrutiny (repetitions, similarities and differences, indigenous typologies, and transitions) and processing (cutting and sorting, word list and key words in context, and word co-occurrence) techniques. SA went through the coded transcripts and cut out all the quotes that pertained to each of the major categories.

After the initial analysis, a larger research team (SA, OK, KKG, and MJR) discussed and agreed on the working analytical framework based on the codes and categories emerging from the data. The working thematic framework was then applied by indexing all the subsequent transcripts with the categories and codes, taking care to note any new codes or impressions not in the initial set.[18] We then revised the analytical framework to include new and refined codes, and agreed on the groupings of conceptually related codes. We repeated this process until no new codes, themes or insights emerged from the data. The main themes were generated by reviewing the final matrix, defined and illustrated using direct quotations from the participants. We reported the results in a semi-quantitative format using qualifiers: very few (<10%), some (10–24%), about half (25–49%), majority (50–75%), most (76–89%) and almost all (> 90%), adopted from a previous study by Das et al [19].

RESULTS

We recruited 53 women, 32 from the overall cohort of women participating in the EPID project and 21 from the routine antenatal clinic setting. Forty-six women attended FGDs with an average of six individuals per group while seven consented for IDIs. Their median age (range) was 28 (15-42) years, 17 (32.1%) were primigravida and 36 (67.9%) were married (Table 2). All healthcare providers (two males and eight females) participated in the individual interviews. Their median age (range) was 44 (27, 54), nine were married and only one was single. Three main themes emerged from the data, including safety, resource availability (service availability, technicalities in performing the Doppler exam and follow-up), and partner involvement (Table 3).

Table 2: Background characteristics of women interviewed

Variables	**Results**	
	Women (N= 53)	**Health workers (N= 10)**
Age (years)		
Median (range)	28 (15, 42)	44 (27, 54)
Gender		
Male	0 (0)	2 (20.0)
Female	53 (100)	8 (80.0)
Gravidity		
1	17 (32.1)	
2	14 (26.4)	
3	10 (18.9)	
>=4	12 (22.6)	
Marital status		
Married	36 (67.9)	9 (9.0)
Separated	3 (5.7)	0 (0)
Single	14 (26.4)	1 (10.0)
Education level		
None	2 (3.8)	0 (0)
Primary	30 (56.6)	0 (0)
Secondary	16 (30.2)	0 (0)
Tertiary	5 (9.4)	10 (100)

[a] Results presented as: n (%)

Table 3: Themes or categories of interest obtained from the final analytical framework with constituent codes, descriptions of codes, and illustrative quotes

Codes	Description of the codes	Examples of illustrative quotes
Resource availability		
Ultrasound service availability	Text or phrases related access to the pregnancy dating and Doppler ultrasound services when needed by the women.	*"When I came back, there was no power, so I returned without going to the scan. Since then, I have been coming and finding no power. I don't know if I will get a chance of getting scanned today"* [**R5: FGD 1 with mothers undergoing routine ANC**]. *"But the way I see, people really like the scan, they like coming here, even today, mothers came for Doppler and we told them we are sorry that our machine went for service"* [**IDI with Sonographer 2**]. *"Yes, they told me to go back on 10th of July 2019 but when I went there, they told me that the scan is dead and we came back"* [**IDI with mother who suffered a neonatal death**].
Doppler exam technicalities	Text describing the Doppler ultrasound examination procedure, including the ease or complexity of performing it and technical limitations of the procedure.	*"I'm not technical in these things of the scan, but what I have seen when they are doing a Doppler, they take a lot of time…dating is okay but when they are doing Doppler, it takes a lot of time"* [**IDI with midwife 5**]. *"Sometimes also, it takes time to get the vessels, as you are getting there, a mother says am tired, you wait and I change, like that. Though others are fast and they don't take a lot of time"* [**IDI with Sonographer 1**].

Table 3: Continued

Codes	Description of the codes	Examples of illustrative quotes
Follow-up of pregnant women	Phrases describing different aspects of the follow-up antenatal care, including follow-up Doppler ultrasound services for pregnant women after initiation of the antenatal care visits.	*"Some mothers have no contact" [**IDI with mid-wife 5**].* *"Another thing, may be, is that these mothers complain of distance if you tell them to come back for Doppler" [**IDI with midwife 1**].* *"Those who don't have phones and their husbands don't have, we ask for the chairman's phone who can deliver reminder information and we tell her that we need you on this date"* [**IDI with midwife 3]**
Partner Involvement		
Male partner participation	Male partner accompanying his wife or female partner to antenatal care, providing social economic support and ensuring that all recommendations made at the antenatal care are observed to safeguard the wellbeing of the couple and the baby.	*"Like me, I was with my husband and they told me to go for scan. He also accepted and I came"* [**R5: FGD 1 with mothers who delivered in the hospital**]. *"Me, when I heard about the service, I told him and we started from there to come together* [**R0: FGD 3 with mothers who delivered in the hospital**]. *"I came with my husband and I told him immediately after the scan about the baby. And when we reached home, we explained to my mother-in-law about all the results they gave us"* [**R3: FGD 2 with mothers who delivered from home**]. *"You find you think about going to the hospital, even me I wouldn't have wished to go to scan late but because you find you are with a man and you don't agree with each other"* [**IDI with mothers who suffered a stillbirth**].

Table 3: Continued

Codes	Description of the codes	Examples of illustrative quotes
Safety		
Safety of ultrasound	Potential harm to the mother or fetus resulting from exposure to the ultrasound during fetal life, as perceived by the pregnant women	*"I fear the scan, if I don't have a very serious disease, I can never go for a scan. Because they say that the scan reduces peoples' years"* [**R3: FGD 2 with mothers attending routine ANC**]. *"Sometimes they tell you, it reduces our age"* [**Interview: Sonographer 1**]. *"The truth is, I know very well that when you put your child in the scan, the child won't be delivered like a clever child. There is a way that electricity affects the child's brains and he or she becomes dull. So, I said to myself, instead of delivering of a dull child, I would rather not go for the scan"* [**R1: FGD with mothers who declined an ultrasound examination**]. *"Most people here associate the scan with reducing years (life expectancy)"* [**Interview: midwife 5**]. *"Most women in the villages dislike this scan. They think that the scan chops their years"* [**Interview with midwife 1**]. *"I had a lot of thoughts but when they educated me about them, I stopped"* **[Interview with a mother whose baby was diagnosed with a spinal defect].** *"I normally hear people say that the scan reduces your years, that if you keep on going to the scan, your years keep on reducing but me I don't believe in that"* **[Interview with a mother who had a scan but experienced a stillbirth]**. *"What they are saying, I think they are lies because when I got out, I have never got any problem"* **[R4: FGD 1 with mothers attending ANC clinic].**

4

Views and experience of mothers

Safety

Mothers had mixed views about the safety of the ultrasound scan technology. While some of them had positive feelings about it, nearly half believed that it could harm them or their unborn baby. Women across the consultations (FGDs and individual interviews) repeatedly raised community rumors that the scan reduces their lifespan. Due to these rumors, some women declined the ultrasound examination. Of the women that undertook the scan, some were afraid before enrollment but felt safer after receiving educational talks about it.

"The truth is I know very well that when you put your child in the scan, the child won't be delivered like a clever child. There is a way that electricity affects the child's brains and he or she becomes dull. So, I said to myself, instead of delivering of a dull child, I would rather not go for the scan" [**R1: FGD with mothers who declined ultrasound examination**].

"I fear the scan, if I don't have a very serious disease, I can never go for a scan. Because they say that the scan reduces peoples' years (life expectancy)" [**R3: FGD 2 with mothers attending routine ANC**].

"I had a lot of thoughts but when they educated me about them (safety of ultrasound), I stopped" [**Interview with a mother whose baby was diagnosed with a spinal defect**].

"I normally hear people say that the scan reduces your years (life expectancy), that if you keep on going to the scan, your years keep on reducing but me I don't believe in that" **[Interview with a mother who had a scan but experienced a stillbirth]**.

Resource availability

Ultrasound service availability

Some mothers attending FGDs said they frequently failed to access the ultrasound services at Kagadi Hospital due to power outages or machine breakdown. The power outages during the study period sometimes lasted for nearly two weeks, and twice damaged the project equipment. This halted ultrasound services for several weeks and many women missed their follow-up Doppler examinations. One of the mothers who suffered a neonatal death said she was unable to access a follow-up ultrasound to check the status of her pregnancy.

"When I came back, there was no power, so I returned (home) without going to the scan. Since then, I have been coming and finding no power. I don't know if I will get a chance of getting scanned today" [**R5: FGD 1 with mothers undergoing routine ANC**].

"Yes, they told me to go back on 10th of July 2019 but when I went there, they told me that the scan is dead and we came back (home)" [**interview with mother who suffered a neonatal death**].

Partner involvement

Partner involvement emerged as a key issue during the discussions, and we further probed mothers about their spousal involvement in antenatal care and access to ultrasound services. The majority of the women who underwent ultrasound examinations saw their spouses as very supportive. In addition, our team observed many men accompany their spouses to the scan appointments.

"Like me, I was with my husband and they told me to go for a scan. He also accepted and I came" [**R5: FGD 1 with mothers who delivered in the hospital**].

"When I heard about the service, I told him and we started from there to come together [**R0: FGD 3 with mothers who delivered in the hospital**].

"I came with my husband and I told him immediately after the scan about the baby. And when we reached home, we explained to my mother-in-law about all the results they gave us" [**R3: FGD2 of mothers who delivered at home**].

Views and experiences of providers

Safety

Most of the healthcare workers said mothers believed ultrasound examinations would reduce their lifespan. This misconception was common and thought to be due to a lack of differentiation between ultrasound and x-ray. Before recruitment into the EPID study, all mothers attending the antenatal care clinic received educational talks about obstetric ultrasound to alleviate their fears.

"Most people here associate the scan with reducing years (life expectancy)" [**Interview: midwife 5**].

"Sometimes they tell you, it reduces our age" [**Interview: Sonographer 1**].

"Most women in the villages dislike this scan. They think that the scan chops their years" [**Interview with midwife 1**].

Resource availability

Ultrasound service availability

The majority of the healthcare workers said power blackouts and sudden breakdowns of the ultrasound equipment due to electricity excesses were serious impediments to the continuity of the scan services at the hospital.

"We had a challenge, a serious one, and mothers would wait, we would all be waiting for power; when it comes, it comes and it goes" [**Interview with midwife 5**].

"But the way I see, people really like the scan, they like coming here, even today, mothers came for Doppler and we told them we are sorry that our machine went for service" [**Interview with Sonographer 2**].

Generally, such advanced ultrasound equipment is not readily available in remote health facilities in rural Uganda due to the high costs, and this was the first of its kind
in Kagadi Hospital. An administrator in Kagadi Hospital said that many healthcare workers were unfamiliar with Doppler ultrasound technology, image analysis and using diagnostic test results to inform clinical decisions.

It is a huge advancement, which, of course, very many people are not aware of, especially the Doppler aspect of it. You know people only know scan, scan, but this advanced scan, many people are not aware of it and of course we were not expecting it, given the finances involved [**Interview with an administrator 1**].

Technicalities aspect of Doppler exams

The majority of the healthcare workers expressed concerns over the complexity and duration of the Doppler ultrasound examinations. The sonographers reported that the mother's habitus, health condition and level of fetal activity influenced the duration of the exam. Longer procedures caused delays in the ultrasound scan unit.

"I'm not technical in these things of the scan, but what I have seen when they are doing a Doppler, they take a lot of time…dating is okay but when they are doing Doppler, it takes a lot of time" [**Individual interview with midwife 5**].

"Sometimes also, it takes time to get the vessels, as you are getting there, a mother says I'm tired; you wait and I change, like that. Though others are fast and they don't take a lot of time" [**Individual interview with Sonographer 1**].

Follow-up of pregnant women

Most of the healthcare workers found it challenging to follow-up pregnant women until delivery. Some mothers lacked mobile phones, while others resided too far away and lacked funds and/or means of transport to and from the hospital. Therefore, necessary close monitoring of high-risk pregnancies using follow-up Doppler assessments was impractical for some mothers in the study setting.

"Some mothers have no contact" [**Interview with mid-wife 5**].

"Another thing, may be, is that these mothers complain of distance if you tell them to come back for Doppler" [**Interview with mid-wife 1**].

"The midwife can write that I have referred this mother; I have identified a transverse lie. And reaching Kagadi in ultrasound, giving the results to the mother that your baby is okay and that's not the transverse lie, the mother can say if ultrasound is saying my baby is in good position, I can stop coming" **[Interview with an administrator 2].**

DISCUSSION

This study assessed the views and experiences of women, healthcare workers, and health system managers regarding the use of modern ultrasound equipment with Doppler and color flow capabilities in an obstetric department in a rural Ugandan hospital. Many women had never seen or undergone an ultrasound scan and the majority of them were afraid it would harm them or their fetuses. On a positive note, the majority of the women found their husbands supportive of antenatal care attendance including the use ultrasound services. Healthcare providers were unfamiliar with

Doppler technology and using it to guide clinical decisions. Other barriers to its implementation were a shortage of trained local staff, insufficient equipment, long distance to and from the hospital, and frequent power cuts. Mothers felt that an ultrasound exam would reduce their lifespan and/or harm their fetuses. Nearly every healthcare worker we interviewed had heard this. The literature reports mixed perceptions of women regarding ultrasound safety.[14] Women in selected health facilities in Uganda have previously reported fears and misconceptions about imaging.[15] Similarly, in Thailand, 5.1% of respondents reported that they believed ultrasound could be dangerous, while the majority viewed it as a safe and useful tool in pregnancy.[11] In Kenya, 30% (10/34) of the women interviewed before receiving an ultrasound were worried it could harm them or their fetus.[10] That proportion dropped to 8% (n= 2/25) at their second or subsequent ANC visit,[10] demonstrating that with exposure and proper health education, perceptions can transform. In a high-income setting, women generally held positive views about getting a third trimester ultrasound.[20] Even though some women in this study were afraid that the procedure could cause harm, the service demand remained high probably due to the larger number of patients Kagadi hospital receives yet they had only a single machine donated by the EPID project.

Negative views may be attributable to lack of exposure and common myths. Such misconceptions regarding the safety of ultrasound in pregnancy could preclude future adoption and large-scale implementation of this technology in vulnerable, poor communities. However, it is also possible that widespread implementation and continued public engagement on the safety and role of obstetric ultrasound, stressing the importance of early initiation of antenatal care and adequate pregnancy dating can lead to its greater acceptance over time.

Pregnant women had challenges accessing screening and follow-up scans due to the unreliable electricity supply characterized by frequent blackouts, equipment breakdown attributed to power supply, insufficient equipment, shortage of trained local staff and long distance to and from Kagadi Hospital. Empowering community-level heath workers to support expectant mothers and engaging them with the health system could improve follow-up care.

Uganda's skilled birth attendance policy previously implemented by the Ministry of Health to improve access to obstetric care through training more health workers, expanding infrastructure, equipment, and distribution of supplies could be enhanced.[21] We recommend context-specific strategies to improve access to follow-up care in other LMICs.

In addition, the majority of the women had never seen or undergone an ultrasound examination. These findings are in line with the results of previous studies undertaken in similar low-resource settings,[7,8,12–14] implying inequitable distribution of ultrasound services and its benefits to vulnerable poor women in rural communities. This is contrary to the WHO recommendations that every woman should receive at least one scan before 24 weeks gestation to estimate gestational age and improve detection and referral for the care of pregnancy complications.[4] Accurate gestational age estimation and early identification of complications guide the timing for delivery and appropriate management of a mother and fetus at risk.[4] Doppler ultrasound is indicated for close monitoring and management of high-risk pregnancies.[4]

However, the healthcare staffs' interpretation and application often limit the usefulness of a diagnostic tool such as Doppler ultrasound. Healthcare staff in Kagadi Hospital were unfamiliar with antenatal Doppler ultrasound technology and using it to manage high-risk pregnancies, but received training about it and a Doppler ultrasound machine from EPID project. There is a need for training activities beyond Kagadi Hospital. Our study highlights the need for continued education and targeted interventions on the interpretation of Doppler ultrasound findings as an important component of introducing modern ultrasound technology for clinical practice in Uganda and beyond. Likewise, two studies from Uganda and Tanzania observed that frequent training may be necessary when introducing new obstetric tools into ANC settings of LMICs to improve healthcare providers' knowledge and ensure their acceptability and correct usage, despite differences in the technologies studied [22,23]. Furthermore, local staff and stakeholders should be involved in developing realistic clinical practice guidelines (for example "bottom-up guidelines" in Suriname) so that the new interventions are well suited and accepted in the local setting (for example the Partoma project in Tanzania).[24,25] It is key to note that in many LMICs, babies still die due to poor transportation, lack of skilled health care workers, poor quality of care provided to pregnant and laboring women, and high rates of home deliveries among other reasons. Therefore, while introducing advanced ultrasound machines to weak health systems, we must carefully consider where it is likely to be beneficial. Its introduction into antenatal care requires a health system strong enough to manage an increase in the number of detected high-risk pregnancies including the surgical capacity to manage a potential increase in caesarean sections.

In the current study, the majority of the women reported that their husbands supported them to attend ANC and use ultrasound services. Male involvement in sexual and reproductive health has recently been recognized as a strategy for enhancing ANC attendance and utilization of antenatal care interventions.[26,27] Engaging male partners and other stakeholders to support women and children to access care promote men's positive involvement as husbands, fathers, and birth companions.[26–28] Men in Uganda have most of the access to economic resources and decision-making power, and their optimal involvement could facilitate the implementation and uptake of ultrasound. However, key actors such as international organizations and the Ministry of Health inadequately address male involvement strategies in Uganda, and gaps between policy and practice exist.[29] Strategies that accommodate men, such as making the obstetric services more father-friendly by improving ultrasound room spaces, and male recruitment into healthcare services are required.

Strengths of this study included the large number of interviews conducted with a heterogeneous sample including women, healthcare workers and health system managers, yielding broader understandings of Doppler ultrasound implementation issues in a low resource setting from the perspectives of major actors in maternal, newborn, and child health. Additionally, a multi-disciplinary and team approach in developing a working analytical framework, selecting emerging codes and themes, and data interpretation allowed multiple stakeholders to engage with the data and offer their perspectives during analysis. This systematic and rigorous data analysis approach in addition to triangulation of results from different methods and sources enhanced the credibility and trustworthiness of our findings.

The study had some limitations. We had one main coder (OK) though she was very experienced in qualitative research and the codes were continuously reviewed and discussed by a larger research team to ensure that no important perspectives were left out. Although interviews at different time points (first contact, follow-up Doppler exam, and after delivery) and multiple facilities, and sustained engagement with respondents to capture their views on our interpretations might have provided additional insights, this is one of the first studies of its kind. Further, we did not conduct any IDI of healthy women but many women of this category were included in FGDs. While practitioners should extrapolate the findings to other geographical regions with caution, we remain confident that they are representative of similar low resource settings. Important dimensions outside the scope of the current study such as views of men could be considered in future research.

CONCLUSION

This study found limited exposure to Doppler ultrasound technology among women and healthcare providers in mid-western Uganda. Partner involvement may potentially promote its acceptance and use to improve the health of women and their unborn babies. Some implementation challenges included difficulty in offering follow-up care to mothers detected with complications and Doppler ultrasound required a high level of training.

It is critical to seek family and community engagement to break the associated myths and misconceptions, and to strengthen the healthcare system to improve access to necessary interventions and follow-up care for complications detected at the ultrasound exam. Lastly, while introducing advanced ultrasound machines to weak health systems, adequate training of healthcare professionals is important to avoid the risk of unnecessary interventions based on misinterpretation of the findings and carefully consider where it is likely to be beneficial. It should be embedded in the local setting with realistic clinical practice guidelines.

ABBREVIATIONS

ANC: Antenatal care LMICs: Low- and middle-income countries; HICs: High-income countries; WHO: World Health Organization; COREQ: Consolidated criteria for reporting qualitative research; FGDs: Focus group discussions; R: Respondent.

ACKNOWLEDGEMENTS

The authors thank the research participants and a team from Kagadi district, ECUREI and Makerere University College of Health Sciences for supporting the implementation of the EPID study. The University of Oxford, Oxford, United Kingdom contributed the ultrasound equipment for data collection. Linda McPhee guided the authors in developing the manuscript. We thank Fosca Tumushabe for additional editorial support. We immensely thank the study funders (Grand Challenges Canada and the UMC Utrecht Global Health Support Program). ATP is supported by the Oxford Partnership Comprehensive Biomedical Research Centre with funding from the NIHR Biomedical Research Centre (BRC) funding scheme.

AUTHOR CONTRIBUTIONS

SA, KKG, MJR, MGK, JB, DZ and ATP contributed to study conception and design. SA and OK designed the data collection methods and tools. OK carried out the interviews and led the focus group discussions. SA and OK carried out data analysis and drafted the manuscript with regular inputs from KKG and MJR. ATP, MGK, JB and DZ critically reviewed the work for important intellectual content. All the authors approved the final manuscript.

FUNDING

Grand Challenges Canada (Grant Number: R-ST-POC-1808-17038) funded the EPID study through a grant to Makerere University College of Health Sciences. SA is supported by the UMC Utrecht Global Health Support

Program (Ref: FM/ADB/D- 18-015006), University Medical Center Utrecht, Utrecht, The Netherlands.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study obtained ethical clearance from Makerere University School of Medicine Research and Ethics Committee (SOMREC): approval number #REC REF 2018-090; and from the Uganda National Council for Science and Technology (UNCST): approval number HS 2459. Further, we obtained permission to operate the EPID study in Kagadi territory from the district and hospital authorities. All participants provided written informed consent to participate in this study. The illiterate participants provided a thumbprint and their interviews were conducted in the local language.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

SUPPLEMENTARY INFORMATION

Additional File 1 FGD Guide for Women
Additional File 2 Interview Guide for Women
Additional File 3 Interview Guide for Healthcare Workers
Additional File 4 Interview Guide for Healthcare Managers

REFERENCES

1. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: Rates, risk factors, and acceleration towards 2030. Lancet. 2016;387(10018):587–603.
2. UNIGME. United Nations Inter-agency Group for Child Mortality Estimation [Internet]. UN Inter-agency Group. 2022 [cited 2022 Jun 8]. Available from: https://childmortality.org/data/World
3. Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev. 2017/06/15. 2017;2017(6):CD007529.
4. WHO. WHO recommendations on antenatal care for a positive pregnancy experience [Internet]. World Health Organization; 2016. Available from: https://www.who.int/publications/i/item/9789241549912
5. Sobhy S, Arroyo-Manzano D, Murugesu N, Karthikeyan G, Kumar V, Kaur I, et al. Maternal and perinatal mortality and complications associated with caesarean section in low-income and middle-income countries: a systematic review and meta-analysis. Lancet. 2019 May 11;393(10184):1973–82.
6. Martins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction: (Replaces Clinical Guideline Number 3, April 2012). Am J Obstet Gynecol. 2020 Oct 1;223(4):B2–17.
7. Holmlund S, Ntaganira J, Edvardsson K, Lan PT, Sengoma JPS, Åhman A, et al. Improved maternity care if midwives learn to perform ultrasound: A qualitative study of Rwandan midwives' experiences and views of obstetric ultrasound. Glob Health Action. 2017;10(1):1350451.
8. Holmlund S, Ntaganira J, Edvardsson K, Lan PT, Sengoma JPS, Kidanto HL, et al. Health professionals' experiences and views on obstetric ultrasound in Rwanda: A cross-sectional study. PLoS One. 2018;13(12):e0208387.
9. Mensah YB, Nkyekyer K, Mensah K. The Ghanaian woman's experience and perception of ultrasound use in antenatal care. Ghana Med J. 2014;48(1):31–8.
10. Oluoch DA, Mwangome N, Kemp B, Seale AC, Koech A, Papageorghiou AT, et al. "You cannot know if it's a baby or not a baby": Uptake, provision and perceptions of antenatal care and routine antenatal ultrasound scanning in rural Kenya. BMC Pregnancy Childbirth. 2015;15(1):127.
11. Rijken MJ, Gilder ME, Thwin MM, Kajeechewa HML, Wiladphaingern J, Lwin KM, et al. Refugee and migrant women's views of antenatal ultrasound on the thai burmese border: A mixed methods study. PLoS One. 2012/04/13. 2012;7(4):e34018–e34018.
12. Shah S, Bellows BA, Adedipe AA, Totten JE, Backlund BH, Sajed D. Perceived barriers in the use of ultrasound in developing countries. Crit Ultrasound J. 2015;7(1):11.
13. Swanson D, Lokangaka A, Bauserman M, Swanson J, Nathan RO, Tshefu A, et al. Challenges of implementing antenatal ultrasound screening in a rural study site: A case study from the democratic republic of the congo. Glob Heal Sci Pract. 2017;5(2):315–24.
14. Kim ET, Singh K, Moran A, Armbruster D, Kozuki N. Obstetric ultrasound use in low and middle income countries: A narrative review. Reprod Health. 2018;15(1):129.

15. Kawooya M, Pariyo G, Malwadde E, Byanyima R, Kisembo H. Assessing the diagnostic imaging needs for five selected hospitals in Uganda. J Clin Imaging Sci. 2011;1(1):53.
16. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): A 32-item checklist for interviews and focus groups. Int J Qual Heal Care. 2007;19(6):349–57.
17. UBOS and ICF. Uganda Demographic and Health Survey 2016. Kampala, Uganda and Rockville, Maryland, USA; 2018.
18. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol. 2013;13(1):117.
19. Das MK, Arora NK, Kaur G, Malik P, Kumari M, Joshi S, et al. Perceptions of family, community and religious leaders and acceptability for minimal invasive tissue sampling to identify the cause of death in under-five deaths and stillbirths in North India: a qualitative study. Reprod Health. 2021;18(1):168.
20. Westerneng M, Diepeveen M, Witteveen AB, Westerman MJ, Van Der Horst HE, Van Baar AL, et al. Experiences of pregnant women with a third trimester routine ultrasound - A qualitative study. BMC Pregnancy Childbirth. 2019;19(1):319.
21. Munabi-Babigumira S, Nabudere H, Asiimwe D, Fretheim A, Sandberg K. Implementing the skilled birth attendance strategy in Uganda: a policy analysis. BMC Health Serv Res. 2019;19(1):655.
22. Mugyenyi GR, Atukunda EC, Ngonzi J, Boatin A, Wylie BJ, Haberer JE. Functionality and acceptability of a wireless fetal heart rate monitoring device in term pregnant women in rural Southwestern Uganda. BMC Pregnancy Childbirth. 2017;17(1):178.
23. Rivenes Lafontan S, Sundby J, Kidanto HL, Mbekenga CK, Ersdal HL. Acquiring Knowledge about the Use of a Newly Developed Electronic Fetal Heart Rate Monitor: A Qualitative Study Among Birth Attendants in Tanzania. Vol. 15, International Journal of Environmental Research and Public Health . 2018.
24. Verschueren KJC, Kodan LR, Brinkman TK, Paidin RR, Henar SS, Kanhai HHH, et al. Bottom-up development of national obstetric guidelines in middle-income country Suriname. BMC Health Serv Res. 2019;19(1):651.
25. Maaløe N, Ørtved AMR, Sørensen JB, Sequeira Dmello B, van den Akker T, Kujabi ML, et al. The injustice of unfit clinical practice guidelines in low-resource realities. Lancet Glob Heal. 2021 Jun 1;9(6):e875–9.
26. Davis J, Vyankandondera J, Luchters S, Simon D, Holmes W. Male involvement in reproductive, maternal and child health: A qualitative study of policymaker and practitioner perspectives in the Pacific. Reprod Health. 2016;13(1):81.
27. WHO. WHO recommendations on health promotion interventions for maternal and newborn health [Internet]. Geneva, Switzerland: World Health Organization; 2015. Available from: https://apps.who.int/iris/bitstream/handle/10665/172427/9789241508742_report_eng.pdf?sequence=1%0Awww.who.int
28. Tokhi M, Comrie-Thomson L, Davis J, Portela A, Chersich M, Luchters S. Involving men to improve maternal and newborn health: A systematic review of the effectiveness of interventions. PLoS One. 2018;13(1):e0191620.
29. Gopal P, Fisher D, Seruwagi G, Taddese HB. Male involvement in reproductive, maternal, newborn, and child health: evaluating gaps between policy and practice in Uganda. Reprod Health. 2020;17(1):114.

Additional File 1 FGD Guide for Women

Focus Group Discussion Guide for Women (English Version)

[*Pregnant women seeking ANC services, women who deliver from home, and women who maintain all ANC contacts and deliver from the hospital*]

Study Title: <u>Understanding women's and healthcare workers' experiences and perceptions regarding the use of Doppler Ultrasound Examination for Pregnant Women in Western Uganda</u>

- Age of study participants
- Marital status of participants
- Education level of participants
- Number of previous pregnancies, including the current one.
- Age of pregnancy at first scan (months)

Opening question

1) How do people in the community describe pregnant women?

Questions on awareness

2) How would you describe ultrasound scan to a person who doesn't know anything about it?
   - What you were told about the role of ultrasound scan in pregnant women

3) How did you learn about ultrasound?
   - Sources of information about ultrasound scan?
   - Had you heard about scan before it was offered at Kagadi hospital?
   - Did you previously know that Ultrasound Scan was available at the Kagadi hospital before it was offered?

Perceptions and feelings about USS

4) How did you feel when you learnt that there was ultrasound scan while you were already at the hospital?
   - Were you happy, sad, scared, not prepared, not sure, etc.?

- Explain your imaginations and expectations before you underwent the scan
- Were you given the opportunity to decide whether to use ultrasound scan or not?
- If yes, how much time were you given to decide to do a scan?
- Probe if they needed to consult their male counterparts, elders, etc.
- Find out if ultrasound scan was compulsory for pregnant women

5) Describe the process of undergoing an ultrasound scan examination
   - Who did the scan (Would you have preferred a man/woman to do ultrasound scan)?
   - Did you feel comfortable if it was a man? And why?
   - What exactly happened during the scan
   - How did it feel to undergo a scan? Did you enjoy it, get scared, felt pain etc.?

6) Describe the aspects of ultrasound scan that you enjoyed during your examination
   - What aspects did you enjoy and why?
   - Which aspects didn't you like and why?
   - Explain how the aspects that you didn't enjoy can be improved?

7) How would you describe what happened in relation to what you had imagined or expected?

8) Describe how this process changed the way you perceived your antenatal visits and ultrasound scan in general?

Communication/Relationships with HCWs

9) Explain what the HCW discussed before and after the scan
   - Safety of the ultrasound scan
   - Health of the baby
   - Expected date of delivery, do you think/ was it accurate at the time of delivery

10) How did it feel to learnt about your baby's delivery date? feelings about the baby…happy sad, anxious, did they feel the baby wasn't safe etc.).
    - Who did you discuss your feelings with (HCW, family member, traditional healer)
    - How did they react to your fears? Were they helpful and why?

11) How would you describe the staff and place where the scan was conducted (friendliness, warm HCWs, ultrasound machine etc.)?

Barriers and enablers to completing ANC Visits

12) How do people in the community describe an ultrasound scan for pregnant women?
    - Why do they think about USS like that? Where do they get this information?
    - Do you always agree with what they think? If yes/no, why?

13) In other communities, some mothers perceive ultrasound scan to be harmful to their health and the health of their babies and therefore feared to complete their ANC visits.
    - Explain your thoughts in relation to this
    - Give other reasons for non-completion of ANC visits/ not delivering at the hospital?
    - Probe for reasons for the answers given
    - Why do other women come complete their ANC visits and deliver at the hospital after ultrasound scan?

14) If you came across a pregnant woman, would you recommend her to undergo an ultrasound scan?
    - Why would you volunteer to do that?
    - Can you give me a scenario of what you would tell this person?

Thank you for your time!

Focus Group Discussion Guide for Women (Runyoro Version)

Ebikaguzo ebirakozesibwa mukuhanuura okwahamu (Abakazi abaine enda abaizire kutunga obuhereza bw'okukeberwa, abakazi abazaaliire muka, abakazi abasoboire kwija emrundi y'okukeberwa yoona kandi bazaarra omwirwarro)

Study Title: Okwetegereza Eby'abakazi Hamu N'abajanjabi Arabamu Kandi N'ebitekerezo Ebirukukwata Ha Kukozesa Akativi Okukebere Abakazi Abaine Enda Omubugwa Izooba Bwa Uganda

- Emyaka y'omweteranizi
- Embeera y'omweteranizi muby'obuswezi
- Eby'okusoma by'omweteranizi
- Omuhendo gw'abaana otaireho nenda eyahati
- Emyezi y'enda nambere wakeberiirwe akativi omurundi gw'okubanza

4

Ekikaguzo eky'okukinguraho

15) Abantu bomubyaaro abakazi benda babeeta rundu babazaaho bata?

Ebikaguzo hakumanya

16) Okusobora ota okusoborra akativi hali omuntu ataine ekyakamanyireho?
    - Inywe mukagambirwaaki hamugaso gwaka tivi hali abakazi benda?

17) Mukaija muta okumanya hakativi
    - Amakuru agakwata hakativi nambere garuga
    - Mukaba muhuliire ha kativi obu baali batakandikire kukakozesa hairwarro lya Kagadi?
    - Mukaba mukimanyire ngu akativi karoho hairwarro lyakagadi obubali batakakibagambiire hanu?

Ebitekerezo hamu n'okwehurra hakativi

18) Mukehurra muta obu mwamanyire ngu hairwarro hanu nibakozesa akativi kandi obu mumazire kuhikaho?

- Mukasemererwa, mukabihirwa, mukatiina, mukahurra timwetegekere, mukaba mutakugumya kurungi?
- Munsoborre ebimwaali nimutebereza kandi nimunihira mutakagenzire mukativi
- Mukaheebwa omugisa okucwamu okukuzesa akativi rundi nangwa?
- Obu kiraba ngu ego, mukaheebwa bwiire oburukwingana nkaha okusobora okucwaamu?
- Kaguliriza obu baraba bayetagisize okwehanuzaaho nabasaija baabo, abakuru, nabandi
- Zoora akativi obu karaaba kaali kabuli muntu wena anyakwiine enda.

19) Munsoboroorre emitwaarre ey'okugenda n'okukorwaaho akativi okekeberwa enda
   - Nooha ayabakozireho mukativi (mwakugondeze omukazi rundi omusaija okukebeza akativi?
   - Obu muraaba mwakozirweho omusaija, mukehuurra kurungi? Kandi habwaaki?
   - Kiki kyenyini ekyabaireho obumwaali mukativi akakebere enda?
   - Mukehurra muta kukeberwa nakativi? Mukakegondezaamu? Mukatiina, mukahuurra obusaasi

20) Munsoborre ebicweka ebyakativi ebimwakizire kwegondezaamu obubaali nibabakebera
   - Bicweka ki ebyabasemiize kandi habwaaki?
   - Bicweka ki ebitarakusemiize kandi habwaaki?
   - Munsobororre nkuku tusobora kusemeza ebiceka ebyo ebitarabasemiize

21) Musobora kunsoboroorra muta ebyabaireho okusigikiirra hali ebimwaali nimunihira?

22) Munsobororre nkoku okukeberwa kunu kwahingisizeemu omulingo waroziremu kandi watekerezaamu okwija mwirwarro kukeberwa kandi nokukozesa akativi okutwarra hamu?

Okubaza hamu n'enkwatagana nabajanjabi

23) Munsobororre biki abajanjabi ebibabagambiire mutakagenzire mukativi kandi nobu mwali murugireyo?
    - Safety of the ultra sound scan
    - Akativi okuba katakuleeta kizibu kyoona
    - Obwomeezi bwomwaana ali munda
    - Ebiro ebikuteberezibwa kuzaraamu, bikaba nibyo hakiro wazaliremu?

24) Mukahurra muta okumanya Ebiro abaana banyu baali nibagenda kuzalirwamu? Mukahaurra muta hali omwana, kusemererwa, kubihirwa, kweralikirra, mukehurra muta ngu omwana tali kurungi?
    - Nibaha abamwagaibe nabo nkoku mwali nimwehurra (abajannjabi, omuntu womuka, omufumu)
    - Bakahurra/ bakagarukamu bata hali okutiina kwawe? Bakaba bomugaso? Kandi habwaki?

25) Ekikaro nambere okukeberwa akativi kwakoliirwe hamu nabajanjabi ababakebiire musobora kubansooborra muta? (bagonza abantu, abajanjabi nibakwata kurungi, akativi nebindi)?

Ebitukutangira nokuyamba kumaliriza emirund eyokukeberwa

26) Abantu b'omubyaro akativi k'okukebera abakazi benda bakasoborra bata?
    - Habwaki batekereza bati ha kativi? Amakuru ago bagaiha nkaha?
    - Do you always agree with what they think? If yes/no, why?
    - Nainywe mwikirizanganiza nabo hali ebibatekereza? Obukiraaba ego/ nangwa, habwaki?

27) Mubyaro ebindi, abakazi batekereza akativi kasobora kubakobuzibu hali mama n'omwana alimunda nahabweeki batiina kwija kukeberwa emirundi yoona.
    - Munsoborre ebitekerezo byanyu hali ekintu kinu
    - Mumpeyo ensonga ezindi ezireta okutamaliriza okukeberwa enda nokutazaarra omwirwarro

- Weyongere okukaguza habigarukwamu ebibahaireyo
- Habwaki kandi abakazi abandi bamarayo okukeberwa kandi bazaarra omwirwarro hanyuma yokukeberwa nakativi

28) Kakusangwa otangaana omukazi aine enda, okusobora kumuha amagezi agende mu kativi
    - Habwaki mukusobora kukikora?
    - Mukusobora nkumpayo ekyokurorraaho eky'ebyo enimusobora kumugamba?

Webale obwiire bwaawe!

Additional File 2 Interview Guide for Women

Interview Guide for Women (English Version)

Study Title: <u>Understanding Women's and Healthcare Worker's Experiences and Perceptions Regarding the Use of Doppler Ultrasound Examination for Pregnant Women in Western Uganda</u>

SECTION A: Interview Guide for Women (Refused to undergo ultrasound Examination)

- Age of study participants
- Marital status of participants
- Education level of participants
- Number of previous pregnancies, including the current one.
- Age of pregnancy at first scan (months)

1) Tell me what it is like being pregnant?
   - How does it feel?
   - How do people in the community describe or think about a pregnant woman?

2) Describe the services that you were offered during your (antenatal care) ANC visit
   - Health education, HIV testing and counselling, ultrasound scan services, call or home visits (later after the visit)
   - How did staff treat you during your ANC? (friendliness, warm HCWs, kind, sympathetic)

3) Tell me more about ultrasound scan. How did you learn about it?
   - Had you heard about an ultrasound scan before it was offered at the hospital?

   If yes, from where?

- Did you previously know that ultrasound scan was available at the hospital before it was offered to you?
- What did HCWs say the role of ultrasound scan was?
- Were you given the opportunity to decide or it was compulsory?

4) How did you feel when you learnt that ultrasound scan was available and free at the hospital?

5) How did you feel after the HCW explained the process of undergoing an ultrasound scan?

6) What did you decide? Why did you decline to undergo the ultrasound scan even after the HCW explained that it was safe? Did you have enough time to ask questions? What discussion did you have with the healthcare workers after you had declined? How much time did you need to decide?

7) Explain what happened after you had declined the scan (feelings, who did you discuss your experience with? Did you tell other people about it) did you continue to come for ANC? In your opinion what could have been the benefits if you had undergone the ultrasound scan?

8) If there was another chance of undergoing the scan, what would be your reaction?

SECTION B: Interview Guide for Women (Pregnancy complications/ Lost their babies 4 weeks after delivery)

- Age of study participants
- Marital status of participants
- Education level of participants
- Number of previous pregnancies, including the current one.
- Age of pregnancy at first scan (months)

1) Tell me what it is like being pregnant?

- How does it feel?
- How do people in the community describe or think about a pregnant woman?

2) Describe the services that you were offered during your ANC visit
   - Health education, HIV testing and counselling, scan services, call or home visits (later after the visit)
   - How did staff treat you during your ANC? (Friendliness, warm HCWs, kind, sympathetic)

3) Tell me more about ultrasound scan. How did you learn about it?
   - Had you heard about scan before it was offered at the hospital? If yes, from where?
   - Did you previously know that ultrasound scan was available at the hospital before it was offered to you?
   - What did HCWs say the role of ultrasound scan was?
   - Were you given the opportunity to decide or it was compulsory?

4) How did you feel when you learnt that ultrasound scan was available and free at the hospital?
   - Did you decide to undergo a scan or it was mandatory for all pregnant woman?
   - If not mandatory how much time did it take you to make a decision to undertake a scan?
   - What were your expectations before you underwent the scan?

5) Tell me about the actual day you underwent the ultrasound scan examination
   - Who did the scan (Would you have preferred a man/woman to do ultra sound scan?)
   - Did you feel comfortable if it was a man doing scan? And why?
   - How did you feel when you underwent the actual ultrasound scan? Did you enjoy it, get scared, felt pain?

6) Describe the aspects of ultrasound scan that you enjoyed during your examination
   - What aspects did you enjoy and why? Which aspects didn't you like and why?
   - Explain how the aspects that you didn't enjoy can be improved?
   - As you underwent the scan, did it meet your earlier expectations in relation to the role of the scan as earlier told by the HCW?
   - How did you feel after the scan?

7) Describe the outcome of the scan that was communicated to you
   - The baby had complications
   - The baby was dead
   - The baby was okay

8) For those who lost babies within 4 weeks after birth: How did you feel about the results from the scan?
   - How did it feel to learnt about your baby's delivery date? feelings about the baby…happy sad, anxious, did they feel the baby wasn't safe etc.)
   - What do you think was not done well that could have caused the baby to die after?

9) For those who had complications: How did you feel after getting the news about the complication?
   - Who did you share the outcomes with?
   - How did they react to your fears? Were they helpful and why?
   - What ideas do you have about what could have caused the complications?
   - In your opinion, explain what could have caused the pregnancy complications that you had/have?

10) If still pregnant, what is currently being done about your condition?
   - How confident are you about the current interventions to ensure that you and the baby continue to live?

- Is there anything that you think the project could do to improve this pregnancy outcome? If the baby died, what would the hospital have done to ensure that your baby survived?
- How did your experience of the ultrasound scan shape the way you perceived your antenatal visits now or in the future?

11) How do people in the community describe a scan for pregnant women?
    - Why do they think about ultrasound scan like that? Where do they get this information?
    - Do you always agree with what they think? If yes/no, why?

12) Some of the women I interviewed earlier told me that they stopped going for ultrasound scan because they felt the scan would be harmful to their health and the health of their babies
    - What do you think about this idea? Why?
    - What are some of the reasons why women would not complete their ANC visits or deliver at the hospital?

13) If you came across a pregnant woman, would you recommend her to undergo an ultrasound scan?
    - Why would you volunteer to do that given the outcome of your pregnancy?
    - What aspects of ultrasound scan would you emphasize?

14) Apart from the ultrasound scan, explain what you think the hospital can do to ensure that pregnancy complications are detected early and ensure babies survive.

Thank you for your time!

Interview Guide for Women (Runyoro Version)

Study Title: Okwetegereza Eby'abakazi Hamu N'abajanjabi Arabamu Kandi N'ebitekerezo Ebirukukwata Ha Kukozesa Akativi Okukebere Abakazi Abaine Enda Omubugwa Izooba Bwa Uganda

EKICWEKA A: Ebikaguzo ebirakozesibwa hakukaguza abakazi (Abakazi abayangire kukozesa akativi)

- Emyaka y'omweteranizi
- Embeera y'omweteranizi muby'obuswezi
- Eby'okusoma by'omweteranizi
- Omuhendo gw'abaana otaireho nenda eyahati
- Emyezi y'enda nambere wakeberiirwe akativi omurundi gw'okubanza

9) Ngambira, nikisisana ki okuba nenda?
   - Kihulirwa kita?
   - Abantu b'omukyaro batekerezaaki rundi bagambaki habakazi benda?

10) Nsobororra obuhereza obu wahairwe obuwaizire hairwarro kukeberwa
   - Okusomesebwa, okukeberwa akahuka ka silimu, kukeberwa akativi, obuhereza bwesimu, kubungirwa nebindi)
   - Abajanjabi bakakurabya bata obuwaizire kukeberwa? (bagonza abantu, nibatangiirra, baine ekisa)

11) Weyongere okungambira ha kativi. Okakamanyira nkaha?
   - Okaba okahuliireho obubaali batakakugambiire hanu hairwarro? Obu kiraba ego, nkaha?
   - Okaba okimanyire ngu kativi kali hairwarro obubaali batakakugambiire?
   - Abajanjabi bakabagambira akativi kaine mugaso ki?
   - Okaheebwa omugisa kwecweramu rundi buli mukazi aine enda akabaine okukagendamu?

12) Okehurra ota obuwahuliire ngu haliyo akativi kandi kabusa?

13) Okehurra ota obu abajanjabi bamazire kukusoboroorra emitwalize ey'okugenda mukativi?

14) Iwe okasaraho ki? Habwaki wayangire okukeberwa akativi nahanyum y'omujanjabi okukusoboroorra ngu tikaine kizibu? Okaheebwa obwiire okukaguza ebikaguzo? Kuhanuuraki okuwabairenakwo hanyuma y'okwanga? Okaba noyenda obwiire obukwingana nkaha okusobora okucwamu?

15) Nsobororra ekyabaireho hanyuma y'okwanga okugenda mukativi (okwehuurra, nooha owu wagabaineho nebyo ebiwarabiremu? Oine owu wakigambiireho? Okeyongera kwija kukeberwa okuruga obwiire obu? Mukutekereza kwawe, birungi ki ebiwakutungire kakuba wali iokiriize kukeberwa akativi?

16) Kakuba otunga omugisa ogundi okukeberwa akativi, nosobora kugarukamu ota?

EKICWEKA B: Ebikaguzo ebirakozesibwa hakukaguza abakazi (Enda zikaba n'ebizibu/ bakafeerwa abaana sabiiti ina hanyuma yokuzaara

- Emyaka y'omweteranizi
- Embeera y'omweteranizi muby'obuswezi
- Eby'okusoma by'omweteranizi
- Omuhendo gw'abaana otaireho nenda eyahati
- Emyezi y'enda namebere wakeberiirwe akativi omurundi gw'okubanza

1) Ngambira, nikisisana ki okuba nenda?
   - Kihiirwa kita?
   - Abantu bomukyaro abatekerezaaki rundi bagambaki habakazi benda?

2) Nsobororra obuhereza obu wahairwe obuwaizire hairwarro kukeberwa
   - Okusomesebwa, okukeberwa akahuka ka silimu, kukeberwa akativi, obuhereza bwesimu, kubungirwa nebindi)
   - Abajanjabi bakakurabya bata obuwaizire kukeberwa? (bagonza abantu, nibatangiirra, baine ekisa)

3) Weyongere okungambira ha kativi. Okakamanyira nkaha?
   - Okaba okahuliireho obubaali batakakugambiire hanu hairwarro? Obu kiraba ego, nkaha?
   - Okaba okimanyire ngu kativi kali hairwarro obubaali batakakugambiire?
   - Abajanjabi bakabagimbira akativi kaine mugaso ki?
   - Okaheebwa omugisa kwecweramu rundi buli mukazi aine enda akaba aine okukagendamu?

4) Okehurra ota obuwamanyire ngu hairwarro haroho akativi?
   - Obukaraaba kakaba kataine kugendwamu bulimukazi weena, okatwara bwireki okucwamu okugenda mukativi?
   - Biki eby'okaba nonihira otakagenzire mukativi?

5) Ngambira hakiro kyenyini obuwagenzire mukativi
   - Nooha ayakukozireho omukativi? (wakugondeze omusaija rundi omukazi okukukebera nakativi)
   - Wakwehuliire kurungi kakuba ayakukozireho yali musaija, kandi habwaki?
   - Okehurra ota obugenzire mukativi? Kakakusemeza, kakutinisa, kakusaasa?

6) Nsobororra ebicweka byakativi ebyakizire kukusemeza obu baali nibekukebera
   - Bicwekaki ebiwagondeze kandi habwaki, bicwekaki eby'otaragondeze kandi habwaki?
   - Nsobororra nkoku ebicweka eby'otaragondeze bisobora kusemezibwamu
   - Obuwali omukativi, kakuyamba okuhikiriza ebintu ebiwali nonihira otakakagenziremu ebikwataine nomugaso gwakativi omujanjabi ebiyali akugambireho?
   - Okehurra ota hanyuma yakativi

7) Ninkusaba ongambire biki ebyakugambiirwe ebyarugire omukukeberwa akativi
   - Omwana akaba aine obuzibu
   - Omwana akaba afire
   - Omwana akaba ali kurungi

8) Baferiirwe abaana hanyuma yasabiiti ina: Okehurra ota hanyuma y'okutunga amakuru agarugire omukativi?
   - Kikakuhuliza kita okumanya ebiro by'okuzalirwamu kwomwana wawe? Kwehurra hali omwana,...nkasemererwa, kweralikirra, okehurra ota omwana obu araba yali atali kurungi)
   - Notekereza kiki ekitarakozirwe kurungi ekisobora kuba kyarugiireho omwana kufa hanyuma?

9) Abaine enda baitu abaana baine ekizibu: Okehurra ota hanyuma y'okutunga amakuru ngu omwana aine ekizibu?
   - Amakuru ago okagabaganaho nooha?
   - Bakagarukamu bata hakutiina kwawe, bakasobora kukuyamba kandi bata?
     Oine bitekerezo ki ebikukwata ha kiki ekisobora kuba kyaleteriize obuzibu buno omwana obu aine/yali aine?

10) Obu araba akyaine enda, kiki ekiriyo nikukorwa handa yaawe? Nogumya ota ngu ebiriyo nibikorwa hati okurora ngu omwana yayongere kwomeera?
   - Haroho ekintu kyoona okyokutekereza ngu entegeka enu nesobora kukora okusemeza ebiraruga munda yaawe? Omwana obu araba yafiire, kiki irwarro ekiryakukozire okurora ngu omwana wawe akomeera?
   - Hanyuma yokukozesa akativi, kikahindura kita entekereza yawe hakugenda kukeberwe hato rundi omumaiso?

11) Abantu b'omukyaro basoborra bata hakativi akakebera abakazi abaine enda?
    - Akativi bakatekerezaho ki? Amakuru ganu bagaiha nkaha?
    - Oikiranganiza nabo hali ebibakutekereza? Obukiraba ego/ nangwa,habwaki?

12) Abamu habakazi abanakagwiizeeho kara bakangambira ngu bkaleka kugenda mukativi habwokuba bakabe nibatekereza nikasobora kuletera mama n'omwana obuzibu.
    - Iwe kinu nokitekerezaaho ki? Kandi habwaki?
    - Nsonga ki ezimu ezisobora kuletera abakazi okutamarayo emirundi eyokukeberwa rundi kuzaarra hairwarro?

13) Kakusangwa otangaana omukazi aine enda, okusobora kumuha amagezi okugenda mukativi?
    - Habwaki okusobora kukikora okusigikirra biki ebyakurugiiremu mukutwara enda?
    - Bicweka ki ebyakativi ebosobora kutekaho amaani kumusoboroorra?

14) Oihireho akativi, nsobororra kiki ekyorukutekereza irwarro ekirisobora kukora okurora ngu enda eziroho obuzibu zakeberwa kandi zamanywa kara okurora ngu abaana bayomeera?

Webale obwiire bwawe!

Additional File 3 Interview Guide for Healthcare Workers

Interview Guide for Healthcare Workers (English Version)

Study Title: Understanding Women's and Healthcare Workers' Experiences and Perceptions Regarding the Use of Doppler Ultrasound Examination for Pregnant Women in Western Uganda

- Age of Key Informant
- Job title/position held
- Education level
- Years in current position

You are being invited to participate in the above study. We selected you to participate because of your role and expertise in the area of child and maternal health. The information you will give us will contribute to improved maternal and child health services in Kagadi hospital. We will be asking you questions related to the use of ultrasound examination for pregnant women in Kagadi and the district in general, the barriers to accessing ANC services and ways to improve maternal and child health in the district. Feel free not to answer any questions that you are not comfortable with.

1) What does your role in the EPID project involve?

2) How do women come to learn about ultrasound scan services that you offer in this hospital?
   - Do women come when they already know that ultrasound scan is offered at the facility?
   - How do they learn about such? Probe for sources of information about the scan

3) Describe the process of providing ultrasound examination to pregnant women in this hospital
   - Probe for health education aspects
   - The discussions and activities that take place in the scan room, discussions about the scan
   - How do they react or respond? What is your experience with those that refuse to use the scan?
   - How do you address these concerns?

4) Explain the different outcomes of undergoing a scan. How do you communicate results especially when the mother has complications or the baby is dead?
   - How do these mothers respond? Does this affect the subsequent visits to use the scan and complete the ANC visits?
   - How does the outcome of the scan meet the expectations of the mothers?

5) What is it like providing ultrasound scan services to pregnant women (feelings, discomforts)?

6) In your opinions what are the potential appeals and benefits of ultrasound scan for pregnant women?
   - What aspects are less appealing about the scan?
   - Explain the concerns that you may have about ultrasound scan and why?

7) In your opinion what are some of the potential barriers and challenges to:
   - Acceptance of Doppler ultrasound scan,
   - Completion of ANC visits,
   - Delivery at the hospital
   - Probe for reasons for their views

8) What are your thoughts about the idea of using Doppler ultrasound scan for pregnant women to identify mothers who may be vulnerable to stillbirth?

9) From your perspective what role could ultrasound play in addressing some of these pregnancy challenges? Probe for how and why

10) What would you recommend as the next steps for improving the use of ultrasound and the EPID project for pregnant women?

Thank you for your time!

Additional File 4 Interview Guide for Healthcare Managers

Interview Guide for Healthcare Managers (English Version)

Study Title: Understanding Women's and Healthcare Workers' Experiences and Perceptions Regarding the Use of Doppler Ultrasound Examination for Pregnant Women in Western Uganda

Key Informants Interview Guide

- Age of Key Informant
- Job title/position held
- Education level
- Years in current position/district
- Institution represented
- Job responsibilities relating to Maternal and Child Health

11) What does your role in maternal and child health involve?

12) Describe the projects related to maternal and child health being run in your district

13) What are your thoughts about the idea of using Doppler ultrasound scan for pregnant women to identify mothers who may be vulnerable to stillbirth and streamline a path for early intervention in the shortest time possible?
    - Probe for reasons for their views
    - What additional information could you have regarding the use of ultrasounds scan and follow-up of pregnant mothers?

14) In your opinions what are the potential appeals and benefits of ultrasound scan for pregnant women?
    - What aspects are less appealing about the scan?
    - Explain the concerns that you may have about ultrasound scan and why?
    - One of the concerns is that ultrasound scan affects the health of the mother and baby? Any thoughts?

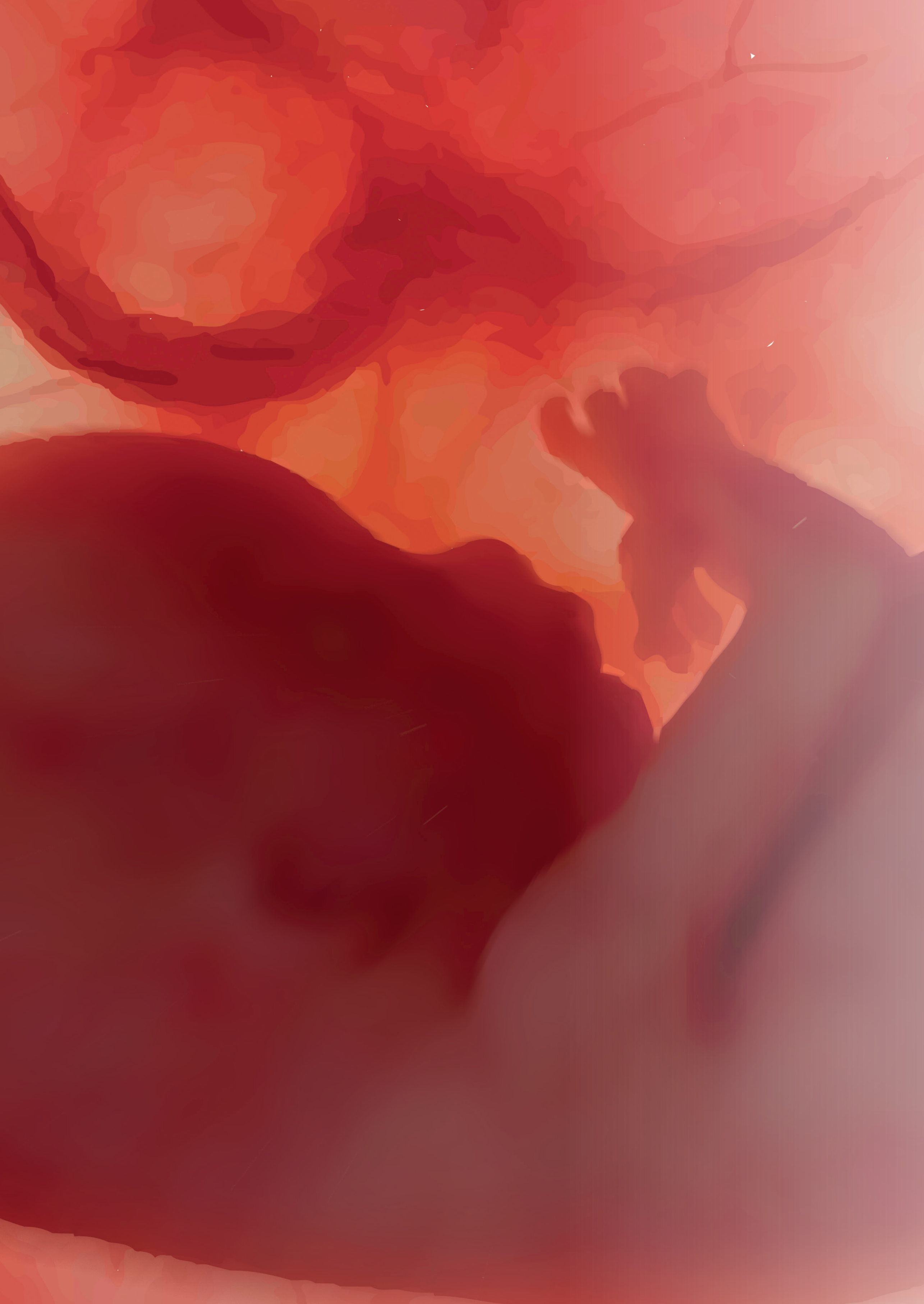
15) In your opinion what are some of the potential barriers and challenges to:
    - Acceptance of Doppler ultrasound scan
    - Completion of ANC visits
    - Delivery at the hospital
    - Probe for reasons for their views

16) From your perspective, what role could ultrasound play in addressing some of these health challenges? (Probe for how and why)

17) What would you recommend as the next steps for improving the EPID project for pregnant women?

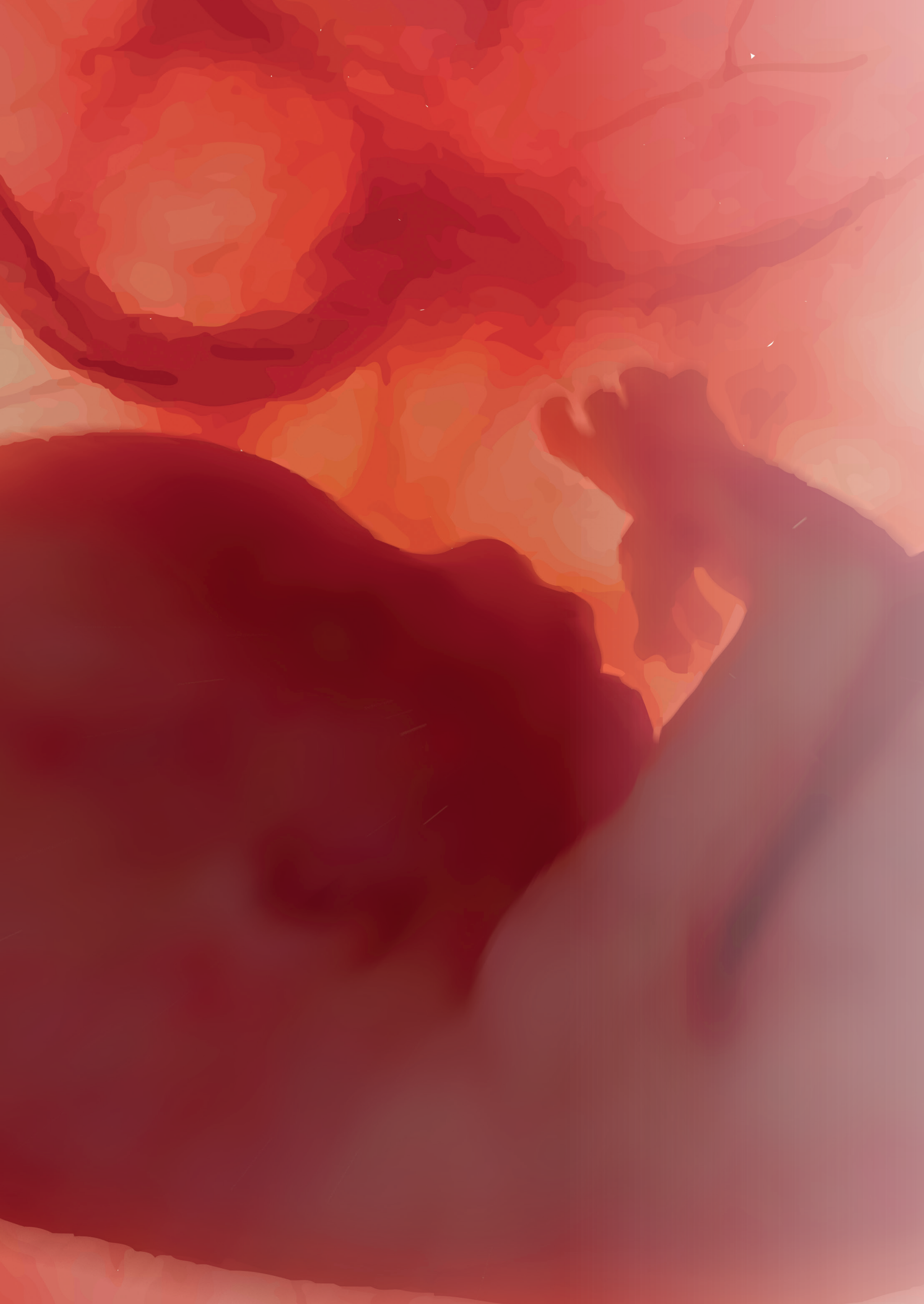
18) Is there anything that you would like to tell me that I have not asked?

Thank you for your time!



Part 3

Predicting adverse perinatal outcomes in low-resource settings



Chapter 5

Middle cerebral arterial flow redistribution is an indicator for intrauterine fetal compromise in late pregnancy in low-resource settings: a prospective cohort study

Sam Ali
Michael G. Kawooya
Josaphat Byamugisha
Isaac M. Kakibogo
Esther A. Biira
Adia N. Kagimu
Diederick E. Grobbee
David Zakus
Aris T. Papageorghiou
Kerstin Klipstein-Grobusch
Marcus J. Rijken

BJOG. 2022; 129: 1712–1720.

ABSTRACT

Objective

We aimed to determine the prevalence of abnormal umbilical artery (UA), uterine artery (UtA), middle cerebral artery (MCA), and cerebroplacental ratio (CPR) Doppler, and their relationship with adverse perinatal outcomes in women undergoing routine antenatal care in the third trimester.

Design

Prospective cohort.

Setting

Kagadi Hospital, Uganda.

Population

Non-anomalous singleton pregnancies.

Methods

Women underwent an early dating ultrasound and a third trimester Doppler scan between 32 and 40 weeks, from 2018 to 2020. We handled missing data using multiple imputation and analyzed the data using descriptive methods and a binary logistic regression model.

Main outcome measures

Composite adverse perinatal outcome (CAPO), perinatal death, and stillbirth.

Results

We included 995 women. The mean gestational age at Doppler scan was 36.9 weeks (SD, 1.02 weeks) and 88.9% of the women gave birth in a health facility. About 4.4% and 5.6% of the UA pulsatility index (PI) and UtA PI were above the 95th percentile, whereas 16.4% and 10.4% of the MCA PI and CPR were below the fifth percentile, respectively. Low CPR was strongly associated with stillbirth (OR 4.82, 95% CI 1.09 – 21.30). CPR and MCA PI below the fifth percentile were independently associated with CAPO; the association with MCA PI was stronger in small for gestational age neonates, (OR 3.75, 95% CI 1.18 – 11.88).

Conclusion

In late gestation, abnormal UA PI was rare. Fetuses with cerebral blood flow redistribution were at increased risk of stillbirth and perinatal complications. Further studies examining the predictive accuracy and effectiveness of antenatal Doppler ultrasound in reducing the risk of perinatal deaths in low- and middle-income countries are warranted.

KEYWORDS

Cerebroplacental ratio, developing countries, Doppler ultrasound, perinatal death, prediction, prenatal care, screening, stillbirth

5

TWEETABLE ABSTRACT

Blood f low redistribution to the fetal brain is strongly associated with stillbirths in low-resource settings.

FUNDING INFORMATION

The study received funding from Grand Challenges Canada (ref. no. R-ST-POC-1808-17 038) and the University Medical Center Utrecht (ref. no. FM/ADB/D- 18-015006). The funders had no role in the study design, data collection, data analysis or writing of the article.

This article includes Author Insights, a video abstract available at https://vimeo.com/bjogabstracts/authorinsights17115

INTRODUCTION

Of the nearly 7000 stillbirths daily worldwide, three-quarters occur in South Asia and sub-Saharan Africa.[1] About half are antepartum stillbirths, frequently associated with fetal growth restriction (FGR) secondary to placental insufficiency.[1] In low- and middle-income countries (LMICs), one in five infants is born small for gestational age (SGA) and 22% of neonatal deaths are among such infants.[2]

Growth-restricted fetuses are not only at high risk of perinatal death but are also at risk of short- and long-term complications, making detection and management crucial.[2–4] However, their prenatal detection rates are low, particularly at late gestation.[2] According to data from high-income countries (HICs), late-onset FGR is usually mild in presentation and often associated with normal umbilical and uterine arterial Doppler indices.[5–8] Nevertheless, abnormal fetal cerebral Doppler flow is a frequent finding in such fetuses.[7,8] There is still limited evidence on the clinical value of a third trimester Doppler ultrasound for fetal surveillance in low-risk pregnancies or women undergoing routine antenatal care (ANC), particularly in LMICs.[9] The World Health Organization (WHO) recommends well-conducted studies to provide concrete evidence for its use in ANC.[9]

Some studies, mostly from HICs, show significant correlations between abnormal umbilical and middle cerebral artery Doppler measurements and perinatal complications in fetuses that appear appropriately grown upon ultrasound.[10–15] This suggests a potential role for Doppler ultrasound in preventing stillbirths amongst women with low-risk pregnancies or undergoing routine ANC. Although its effectiveness as a screening tool has not been established in these HIC settings, it is clear that test performance depends on the underlying prevalence of perinatal complications or abnormal Doppler in the general population.[16] This is of relevance to LMIC settings where stillbirths are 10 times more common than in HICs.[1] It should also be noted that a recent systematic review was unable to establish, due to a lack of studies, the prevalence in LMIC settings of absent or reversed end-diastolic flow (AEDF or REDF) in the umbilical artery (UA) among low-risk pregnancies or women undergoing routine ANC.[17] The finding was rare

(0-2%) in HICs.[17] Therefore, this study aimed to investigate the prevalence of abnormal antenatal Doppler ultrasound findings and their relationship with adverse perinatal outcomes in a cohort of women undergoing routine ANC during the third trimester in Uganda.

METHODS

Study design

This prospective cohort study was implemented between September 2018 and December 2020 at Kagadi Hospital, a secondary healthcare level facility serving as a referral center for the neighboring districts in the greater Kibaale region in mid-western Uganda. According to the District Health Information Systems (DHIS), less than 10% of the women present to Kagadi Hospital for their first antenatal care (ANC) contact in the first trimester annually. In 2020, 264/3080 women presented for their first ANC in the first trimester, 1483 achieved four or more ANC contacts, and only 13 achieved the recommended eight ANC contacts. The Hospital handles over 4000 births a year. This study recruited women from the ANC clinic, maternity unit, and ultrasound department.

Eligibility criteria

We included pregnant women with singletons who enrolled in early pregnancy (< 24 weeks), with no obvious fetal abnormalities on the scan. The exclusion criteria included women with missed miscarriage or intrauterine fetal demise, and birth before the Doppler scan (i.e., those who gave birth before 33+0 weeks of gestation). Gestational age (GA) was confirmed by a first-trimester ultrasound between 9 $^{+0}$ and 13 $^{+6}$ weeks of gestations using the crown-rump length (CRL)[18] or head circumference combined with femoral length measurements taken before 24 weeks of gestation.[19]

Data collection

The first author (SA) and two resident sonographers at Kagadi Hospital carried out all the ultrasound examinations. The sonographers had

experience performing obstetric ultrasound and they received additional training on fetal Doppler ultrasound at Ernest Cook Ultrasound Research and Education Institute (ECUREI), Kampala, Uganda, and The Women's Place, Kampala, Uganda before beginning study implementation. Ultrasound examinations were performed using a Voluson™ e (GE Healthcare, Chicago, IL, USA) with a 2–8 MHz convex probe or Philips HD-9 (Philips, Amsterdam, the Netherlands) equipped with C5-2 and C6-3 convex probes.
We performed all ultrasound scans according to standard protocols.[20] Doppler scans were done between 32 and 40 weeks of gestation. The UA was examined in a free loop of the umbilical cord, and measured in the absence of fetal movement while keeping the insonation angle at $<30^0$. The middle cerebral artery (MCA) was examined at its proximal third, close to its origin in the internal carotid artery, with the angle of insonation kept as close as possible to 0^0. We recorded the uterine artery (UtA) Doppler trans-abdominally, with the angle of insonation maintained at $<30^0$. The mean value of the left and right UtA pulsatility index (PI) was calculated. All Doppler waveform velocities were recorded as the average of three similar consecutive waveforms. At the time of the study, there were no local guidelines for the management of suspected SGA fetuses, and Dopplers were not routinely used to manage pregnancies in the study setting. Therefore, clinicians were blinded to the Doppler results except when AEDF or REDF in the UA was detected. Any woman with an abnormal ultrasound finding was referred to the clinicians for management as per the standard of care that the clinician deemed suitable. All women enrolled in the study were followed up until 28 days postnatally. Given COVID-19 lockdowns, we remotely captured some follow-up data by phone calls, such as reports on neonatal death.

Maternal and pregnancy characteristics

The characteristics recorded included maternal age, weight and height, parity, malaria in pregnancy, urinary tract infection, syphilis, HIV status, previous stillbirth, chronic hypertension, alcohol use during pregnancy, maternal smoking, and gestational age at Doppler scan and birth. Ultrasound measurements included estimated fetal weight (EFW), abdominal circumference (AC), UA PI, MCA PI, cerebroplacental ratio (CPR), and mean UtA PI.

Outcome measures

The primary outcomes included a composite adverse perinatal outcome (CAPO), perinatal death, and stillbirth. A CAPO was defined as the occurrence of one or more of the following: stillbirths (intrauterine fetal death after 28 weeks gestation), neonatal death within 28 days of the postnatal period, admission to the neonatal intensive care unit (NICU) >24 hours, APGAR score <7 at 5 minutes, emergency cesarean birth for fetal distress (based on abnormal fetal heart rate monitoring), and respiratory distress syndrome (RDS). Perinatal death was defined as the occurrence of either stillbirth or neonatal death within 28 days of the postnatal period. We defined SGA as birthweight <10th percentile and AGA as birthweight ≥10th percentile using the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) newborn birth weight standards.[21]

Statistical analysis

We computed EFW using Hadlock equation 3 and converted it to gestational-specific z-scores using the INTERGROWTH-21st charts.[22,23] We also converted fetal biometry and birthweight to gestational-specific z-scores and percentiles using the INTERGROWTH-21st fetal growth standards,[24] and newborn birthweight standards after adjustment for sex.[21] CPR was calculated as a ratio of the MCA PI divided by the UA PI. We transformed UA PI to gestational age-specific z-scores and percentiles using the INTERGROWTH-21st Doppler charts,[25] and dichotomized it at the 95th percentile to estimate prevalence. The cutoff points of UtA PI >95th percentile, and MCA PI and CPR <5th percentiles commonly used in clinical practice were considered abnormal using reference ranges by Rizzo et al.[26]

We inspected the distributions of continuous variables using Shapiro-Wilk test, histogram, and Kernel density plots, then checked for missing data mechanism using the Student's t-test and chi-square test of records with and without complete information, and graphical methods. We assumed variables were missing at random and imputed 100 datasets over 20 iterations using multiple imputation via fully conditional specification with the MICE package in R.[27] To ensure congeniality, we included all transformed variables in the imputation model, and imputed them passively. Missing fetal biometry and newborn measurement z-scores and percentiles were imputed via the INTERGROWTH formulas embedded in the R package "HBGD".[28] We checked the final imputation for completeness and plausibility using density plots, box-and-whisker plots, summary statistics, and comparison of the observed and imputed data before analysis.

Women's characteristics were summarized using mean (standard deviation, SD) or median (interquartile range, IQR) values, frequencies and percentages. Using the imputed data, we then examined the differences in the women's characteristics in the outcome groups using a two-sample Student's t-test, and pooled chi-square statistics, based on Rubin's procedure,[29] and pooled estimates of the binomial proportions based on Wilson's confidence interval method.[30] We corrected Pearson's Chi-squared p-values by applying Monte Carlo simulations with 2000 replicates. Significant differences between the pooled estimates of the binomial proportions were assessed using Newcombe's confidence interval method.[31] We conducted univariable and multivariable binary logistic regression analyses on the 100 multiply imputed data sets and pooled estimates using Rubin's rules[29] to identify the Doppler indices significantly associated with the primary outcomes. Variables for multivariable analysis were selected based on either univariate analysis p-value of ≤ 0.27 or clinical importance. We included parity and malaria based on clinical importance. The multivariable model was fitted assuming a two-sided significance level of 0.05. We checked for confounding by examining the significant variable for a difference in the crude and adjusted coefficient estimate of 15% or more. SA carried out the analysis in R version 4.0.4 (2021-02-15).

Ethical statement

We obtained ethical clearance from Makerere University School of Medicine Research and Ethics Committee (ref. 2018-090) and Uganda National Council for Science and Technology (ref. HS 2459), and permission to implement the Ending Preventable Stillbirths by Improving Diagnosis of Babies at Risk (EPID) study in Kagadi territory from both the district and Hospital authorities. All participants were counselled and provided written informed consent. Illiterate participants used a thumbprint. Patients were not involved in the development of this study.

RESULTS

Participant characteristics

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies. We enrolled 1239 pregnant women, 175 of them between 9 $^{+0}$ and 13 $^{+6}$ weeks. We lost 216 women to follow-up mostly due to COVID-19 lockdown and temporary breakdown of the ultrasound equipment. Morever, 22 had miscarriages, five gave birth before 33 $^{+0}$ weeks, and one woman had a Doppler scan before 32 weeks, leaving 995 women for analysis **(Figure S1).** The cohort characteristics and the extent of missing values are reported in **Table S1**. The mean gestational age at Doppler scan and birth was 36.9 weeks (SD, 1.02 weeks) and 39.8 weeks (SD, 1.39 weeks), respectively, whereas the median gestational age at pregnancy dating was 18.4 weeks (range, 9 – 23 weeks). The median maternal age was 25 years (IQR, 22 – 30 years), and 188 (18.9%) of the women were nulliparous. Most women (88.9%, n= 885) gave birth in a health facility, whereas the remainder gave birth from traditional birth attendants, at home or on their way to hospital. The incidence of stillbirths, neonatal deaths, and CAPO was 1.8% (n= 18), 1.3% (n= 13) and 13.7% (n= 136), respectively. Follow-up fetal biometry and Doppler scans were obtained from 544 mothers. Birth weight was missing in 13.8% of the neonates while the right uterine artery PI had a high proportion (55.8%) of missing values.

Prevalence of abnormal Doppler

The prevalence of UA PI and UtA PI >95th percentile was 4.4% (95% CI 3.2 – 6.1) and 5.6% (95% CI 4.3 – 7.4), respectively. About 16.4% (95% CI 13.9 –

19.2) of the MCA PI and 10.4% (95% CI 8.4 – 12.8) of the CPR values were <5th percentile. One pregnancy had absent end-diastolic flow in the UA.

Predictors of composite adverse perinatal outcome

We compared the characteristics of pregnancies with and without adverse perinatal outcomes (**Table 1)**. The proportion of women with MCA PI and CPR <5th percentile or UtA PI >95th percentile was significantly higher in women who experienced adverse outcomes than women without adverse outcomes. In multivariable logistic regression analysis, MCA PI <5th percentile (OR 2.08, 95% CI 1.17 – 3.70, p= 0.013), CPR <5th percentile (OR 2.22, 95% CI 1.13 – 4.37, p= 0.020), and UtA PI >95th percentiles were significantly associated with CAPO (**Table 2**). On the other hand, CPR <5th percentile was strongly associated with stillbirth (OR 4.82, 95% CI 1.09 – 21.30, p= 0.038) (**Table 3**), but had weak relations with perinatal death (**Table S4**). In contrast, the UA PI >95th percentile had no significant relations with CAPO, perinatal death or stillbirth. Other important risk factors for adverse perinatal outcomes were syphilis, fetal sex, gestational age at birth, and previous stillbirth.

Table 1: Maternal and pregnancy characteristics in pregnancies with adverse perinatal outcome compared with those that did not experience an adverse outcome

Characteristic	No adverse perinatal outcome group (n= 859)	Adverse perinatal outcome group (n= 136)	P-value
Body mass index, (kg/m2), mean (SD)	24.5 (3.89)	25.1 (4.12)	**0.145**
Log.age, mean (SD)	3.23 (0.24)	3.24 (0.24)	0.636
Nulliparous, yes, %	24.2	28.3	0.367
Malaria, yes, %	40.4	37.6	0.597
Syphilis, yes, %	6.8	12.8	**0.040***
Previous stillbirth, yes, %	2.4	4.6	0.197
Chronic hypertension, yes, %	1.5	5.3	0.084
Alcohol use in pregnancy, yes, %	14.9	12.2	0.440
Urinary tract infection, yes, %	15.4	19.8	0.259
HIV, positive, %	9.9	12.5	0.437
Sex of baby, male, %	46.8	58.8	**0.009***
EFW z scores, mean (SD)	0.07 (1.45)	0.02 (1.48)	0.660
AC z-scores, mean (SD)	0.06 (1.63)	-0.10 (1.56)	0.212
UA PI >95th percentile, %	4.2	5.4	0.598
UtA PI >95th percentile, %	4.6	11.5	**0.017***
MCA PI <5th percentile, %	14.8	26.2	**0.014***
CPR PI <5th percentile, %	9.1	18.2	**0.022***
Gestational age at Doppler (weeks), mean (SD)	36.8 (1.41)	36.8 (1.34)	0.874
Gestational age at birth, full term	63.9	47.1	**0.001***
Preterm	3.1	10.3	
Early term	15.1	17.6	
Late term	14.6	19.9	
Post-term	3.3	5.1	

Note: Percentages are pooled proportions estimated from Wilson's confidence interval method: N = 995; m = 100 imputed data sets.
* Significant (in bold) at p < 0.05; p-value from multiple imputation two-sample Student's t-test and pooling chi-square statistics using Rubin's procedure; SD, pooled standard deviation; GA, gestational age at birth: preterm, <37 weeks; early term, 37–38 weeks; full term, 39–40 weeks; late term, 41 weeks; post-term, ≥42 weeks.

5

Table 2: Univariable and multivariable logistic regression analysis of composite adverse perinatal outcome prediction from the maternal and pregnancy characteristics in women undergoing routine antenatal care.

	Univariate		Multivariate			
			Model A		Model B	
	Crude OR		Adjusted OR		Adjusted OR	
Characteristic	(95% CI)	P-value	(95% CI)	P-value	(95% CI)	P-value
Body mass index	1.03 (0.98 – 1.08)	0.145	1.04 (0.99 – 1.09)	0.082	1.05 (1.00 – 1.10)	0.051
Syphilis, yes	1.98 (1.04 – 3.79)	0.037	2.12 (1.05 – 4.30)	0.035*	2.07 (1.02 – 4.18)	0.042*
Previous stillbirth, yes	1.93 (0.71 – 5.26)	0.196	2.13 (0.73 – 6.22)	0.162	2.29 (0.79 – 6.62)	0.123
Chronic hypertension, yes	3.51 (0.93 – 13.27)	0.063	2.89 (0.69 – 12.11)	0.145	2.74 (0.65 – 11.58)	0.170
Sex of baby, male	1.62 (1.12 – 2.34)	0.009	1.66 (1.12 – 2.47)	0.011*	1.69 (1.14 – 2.50)	0.009*
AC z-scores	0.86 (0.68 – 1.08)	0.214	0.83 (0.66 – 1.05)	0.128	0.84 (0.66 – 1.07)	0.155
Nulliparous, yes	1.23 (0.78 – 1.93)	0.368	1.31 (0.81 – 2.13)	0.262	1.30 (0.80 – 2.11)	0.284
Malaria, yes	0.88 (0.58 – 1.34)	0.581	0.80 (0.51 – 1.25)	0.334	0.80 (0.51 – 1.26)	0.336
GA at birth, full-term	Ref.		Ref.		Ref.	
Preterm	4.45 (2.21 – 8.92)	0.001	4.98 (2.26 – 10.99)	0.001*	4.84 (2.20 – 10.66)	0.001*
Early term	1.58 (0.95 – 2.63)	0.075	1.43 (0.84 – 2.45)	0.184	1.47 (0.86 – 2.51)	0.159
Late term	1.85 (1.13 – 3.03)	0.013	1.87 (1.11 – 3.14)	0.018*	1.87 (1.11 – 3.13)	0.017*
Postterm	2.14 (0.90 – 5.11)	0.085	2.22 (0.89 – 5.49)	0.085	2.09 (0.84 – 5.19)	0.112
UtA PI>95th percentile	2.64 (1.21 – 5.70)	0.014	2.36 (1.03 – 5.39)	0.041*	2.39 (1.05 – 5.44)	0.038*
MCA PI<5th percentile	2.04 (1.17 – 3.54)	0.012	2.08 (1.17 – 3.70)	0.013*		
CPR PI <5th percentile	2.20 (1.15 – 4.20)	0.017			2.22 (1.13 – 4.37)	0.020*

*Significant at $p < 0.05$; OR, odds ratio after pooling estimates using Rubin's rule; N = 995; m = 100 imputed data sets; model A includes MCA PI; model B includes CPR; GA, gestational age at birth: preterm, <37 weeks; early term, 37–38 weeks; full term, 39–40 weeks; late term, 41 weeks; post-term, ≥42 weeks.

Table 3: Univariable and multivariable logistic regression analysis of stillbirth prediction from the maternal and pregnancy characteristics in women undergoing routine antenatal care.

	Univariate		Multivariate			
			Model A		Model B	
Characteristic	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Body mass index	1.06 (0.96 – 1.18)	0.231	1.05 (0.95 – 1.17)	0.336	1.07 (0.96 – 1.19)	0.197
Syphilis, yes	2.61 (0.62 – 10.9)	0.188	2.56 (0.57 – 11.64)	0.221	2.40 (0.52 – 11.14)	0.263
Previous stillbirth, yes	5.42 (1.15 – 25.6)	0.032	5.58 (1.06 – 29.27)	0.042*	6.98 (1.28 – 37.91)	0.024*
GA at birth, full-term	Ref.		Ref.		Ref.	
Preterm	4.44 (0.89 – 22.13)	0.068	5.25 (0.96 – 28.81)	0.056	5.06 (0.90 – 28.51)	0.065
Early term	2.31 (0.67 – 8.00)	0.186	2.00 (0.51 – 6.98)	0.335	2.00 (0.53 – 7.45)	0.303
Late term	1.74 (0.44 – 6.83)	0.424	1.78 (0.44 – 7.22)	0.415	1.76 (0.43 – 7.21)	0.433
Postterm	5.25 (1.05 – 26.30)	0.043	6.02 (1.14 – 31.91)	0.034*	5.57 (1.04 – 29.76)	0.044*
MCA PI<5th percentile	2.76 (0.60 – 12.79)	0.193	2.75 (0.56 – 13.52)	0.211		
CPR PI <5th percentile	4.28 (1.07 – 17.14)	0.040			4.82 (1.09 – 21.30)	0.038*

*Significant at p-value <0.05; OR: odds ratio after pooling estimates using Rubin's rule; N= 995; m= 100 imputed datasets; Model A includes MCA PI; Model B includes CPR; GA: gestational age at birth; preterm: <37 weeks; early term: 37-38 weeks; full term: 39-40 weeks; late term: 41 weeks; postterm: ≥42 weeks.

5

Sub-group analysis in pregnancies with and without SGA neonates

The incidence of SGA at birth was 15.4% (95% CI 13.5 – 17.5). Adverse perinatal outcome rates were remarkably higher in SGA births than in non-SGA births (**Figure 1**). For instance, the incidence of CAPO was 25% (95% CI 23.0 – 36.1) in SGA newborns compared to 11.5% (95% CI 9.6 – 13.5) in AGA births.

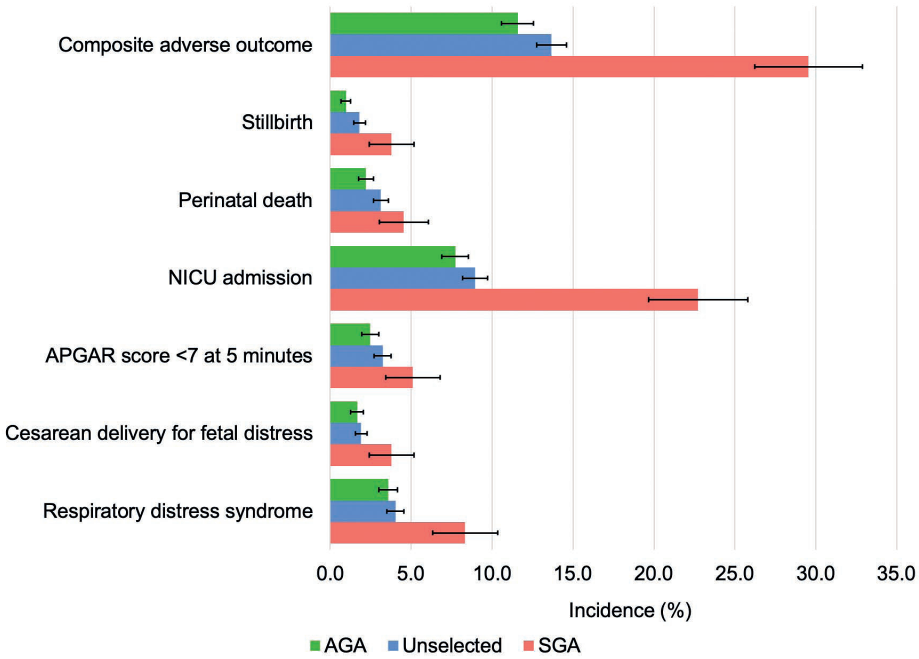


Figure 1 Comparison of the incidence of adverse perinatal outcomes in AGA pregnancies, women undergoing routine antenatal care, and SGA pregnancies at Kagadi Hospital, Uganda.

In the SGA sub-group, the proportion of MCA PI <5^{th} percentile was 21.2% (95% CI 14.8 – 29.5) while that of CPR <5^{th} percentile was 13.9% (95% CI 8.8 – 21.2). The proportions of UA PI and UtA PI >95^{th} percentiles were low, about 6.2% (95% CI 3.2 – 11.5) and 6.5% (95% CI 3.4 – 12.4), respectively. In multivariable logistic regression analysis, MCA PI <5^{th} percentile was associated with a composite adverse outcome (OR 3.75, 95% CI 1.18 – 11.88, p= 0.025), (**Table S2**). Gestational age at birth, fetal sex, chronic hypertension, and body mass index were also associated with CAPO in multivariable analysis (**Table S3**).

DISCUSSION

Main findings

The proportion of abnormal MCA PI and CPR was quite high, whereas abnormal UA PI was rare. The occurrence of CPR <5th percentile was strongly associated with stillbirth whereas MCA PI and CPR <5th percentile, and UtA PI >95th percentiles were independently associated with CAPO. In the SGA subgroup, the association between MCA PI <5th percentile and CAPO was stronger than in women undergoing routine ANC. The incidence of adverse perinatal outcomes was remarkably higher in SGA pregnancies than in AGA pregnancies.

Strengths and limitations

This is one of the few studies with robust methodology from a LMIC setting to investigate the relationship between antenatal Doppler ultrasound in the third trimester and adverse perinatal outcomes. We blinded the Doppler ultrasound results from the attending clinicians who would have used them to manage patients and alter their prognosis. Many variables known to be associated with adverse pregnancy outcomes were included in the analysis and adjusted for as important confounders. The sonographers were well trained and met a predefined quality criterion. We handled missing data using multiple imputation, increasing the precision and validity of our findings.

Although 17.4% (n= 216) of the women dropped out mostly as a result of the COVID-19 lockdown and temporary breakdown of the ultrasound equipment, this remains one of the largest Doppler studies from a low-income setting. We examined the women using two different brands of ultrasound machines. It is, however, unlikely that this introduced significant differences in the findings since we used the same equations and reference ranges for biometry and Doppler computations. This reflects the practice in a realistic clinical setting facilitating the generalizability of our findings. Only a few women (n= 175) had a dating scan in the first trimester, but the study utilized an alternative optimal dating method for women presenting later than 13 weeks of gestation. Since we offered all women a single third trimester Doppler scan, placental insufficiency may have occurred after the scan but few women were examined as early as 32 weeks. This being a single-center primary study, caution is urged when extrapolating the findings to other clinical settings.

Interpretation

There is limited evidence on the clinical role of antenatal Doppler in low-resource settings, where the burden of stillbirths is highest. In this study, abnormal UA PI was rare. The results are comparable to the prevalence of AEDF or REDF (0% - 2.13%) reported in low-risk pregnancies in HICs.[17] Interestingly, a study from South Africa reported a prevalence of abnormal UA RI (and AREDF) in low-risk pregnancies of 13.0% (1.2%).[32] The large difference with our observations could be explained by the classical differences in the pathophysiology of early and late FGR: Hlongwane et al[32] enrolled women between 28 - 34 weeks, a gestation at which abnormal UA commonly manifests.

In our study, the proportion of abnormal MCA PI and CPR was quite high, but studies for comparisons were limited. The MCA blood flow redistribution was associated with a twice increased risk of a composite adverse perinatal outcome. Similar results were reported in an HIC study.[15]

Studies from HICs indicate that CPR may be a useful indicator for intrauterine fetal compromise.[33] Its predictive value for perinatal death was high (area under the summary ROC curve (AUC) of 0.83, 95% CI 0.74 – 0.92),[33] and low for CAPO (AUC 0.71- 0.74).[33] Similarly, our study found that fetuses with CPR <5th percentile were four times more likely to experience stillbirths and twice as likely to experience a CAPO compared to fetuses with CPR ≥5th percentile. However, it only had borderline significance for perinatal death (p= 0.069). Some neonatal deaths may have resulted from causes unrelated to pregnancy complications, like FGR due to placental insufficiency.

The UtA PI had significant relations with CAPO in women undergoing routine ANC. Among the SGA subgroup, the cases were too few (n= 153) to allow us to reliably study it, though studies from HICs suggest its potential clinical role in suspected SGA pregnancies in late gestation.[34]

Subgroup analysis in SGA pregnancies showed a low prevalence of UA PI >95th percentile. Studies from HICs indicate that less than 10% of UA PI may be abnormal in SGA pregnancies in late gestation.[5–8] In contrast, of the SGA fetuses >35 weeks of gestaion with normal UA, 16 (34%) had MCA redistribution.[7] In another study involving 171 SGA fetuses examined after 36 weeks of gestaion, the proportion of abnormal UA PI was significantly lower than that of abnormal MCA PI (2.9 versus 13.5%; $P < 0.01$) and CPR (2.9 veersus 22.8%; $P < 0.001$) before birth,[8] as observed in our study. In multivariable logistic regression analysis, the risk of CAPO in fetuses with MCA PI <5th percentile was three times as high as that observed in fetuses with MCA PI ≥5th percentile.

Further, like in our study, syphilis, gestational age at birth, fetal sex, previous stillbirth, and chronic hypertension are known risk factors for adverse perinatal outcomes.[1,35] We have enhanced our existing knowledge on key predictors for developing risk prediction models for adverse perinatal outcomes in LMICs.[35]

Our study affirms that fetal cerebral blood flow redistribution is an indicator for intrauterine fetal compromise in the third trimester, a finding particularly important in LMICs where rigorous evidence on the role of Doppler ultrasound in preventing stillbirths is acutely lacking yet having the highest burden of disease.[9,36] Stillbirth rates in sub-Saharan African settings remain substantially high and interventions to reduce their occurrence need to be prioritized.[37] In the current study, the adverse perinatal outcome rates were higher in SGA neonates than in non-SGA neonates, in keeping with previous studies from HICs.[2–4] Prenatal screening for suspected SGA fetuses in whom Doppler ultrasound is thought to be more beneficial seems reasonable.[38,39]

In women undergoing routine ANC, stillbirths were strongly associated with low CPR indicating that this could help identify fetuses at high risk of dying and requiring close clinical attention. Many stillbirths in our cohort were attributed to poor monitoring of mothers at high risk and delayed access to cesarean section birth. Adoption of practice guidelines can greatly improve the quality of care during pregnancy and reduce the rate of stillbirths. Obstetric guidelines help to ensure that women are put on the appropriate care pathway. However, like in many low-resource settings, there are no local guidelines for screening and management of suspected growth-restricted fetuses in the study setting. Thus, it is important that Doppler ultrasound is embedded into LMICs for use in recommended obstetric populations with context-tailored evidence-informed clinical guidelines.[40] In addition, clinicians must be adequately trained in using Doppler and interpreting the results for managing patients to avoid inappropriate interventions. There is a need to use uniform Doppler reference standards to avoid differences in clinical management arising from using one chart rather than another.[41]

CONCLUSION

In women undergoing routine ANC in the third trimester, abnormal UA PI was uncommon. Fetal cerebral blood flow redistribution was strongly and independently associated with stillbirth and perinatal complications. We recommend further studies examining its predictive performance and trials evaluating its effectiveness in reducing the risk of perinatal morbidity and mortality in low- and middle-income settings.

ACKNOWLEDGEMENTS

We are grateful to the women and teams from Kagadi district, ECUREI and Makerere University College of Health Sciences, who supported the EPID study. The University of Oxford, Oxford, UK, provided the ultrasound equipment used for data collection. We further thank Fosca Tumushabe for her support with the English language review. We extend immense gratitude to the study funders (Grand Challenges Canada and the UMC Utrecht Global Health Support Program). ATP is supported by the Oxford Partnership Comprehensive Biomedical Research Centre, with funding from the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) funding scheme.

DISCLOSURE OF INTERESTSS

SA reports grants from Grand Challenges Canada and University Medical Center Utrecht, Utrecht, The Netherlands, and ultrasound equipment support from the University of Oxford, Oxford, United Kingdom. ATP reports research grants from UK, European and USA research councils and charities: the NIHR / HTA, NIHR Oxford Biomedical Research Centre, EPSRC, GCRF, ERC, NIH and Bill and Melinda Gates Foundation; personal fees and support from Capital Medical University, Beijing; Ministry of Health, Cyprus; from GE Healthcare; and Samsung Medison. ATP holds a patent entitled "A system and method are provided to automatically categorize biological and medical images" US10762630B2, and is a senior advisor for Intelligent Ultrasound. The remaining authors have no disclosures. Completed disclosure of interests form available to view online as supporting information.

AUTHOR CONTRIBUTIONS

SA, MGK, JB, DEG, DZ, ATP, KKG and MJR contributed to the study conception and design. SA and IMK carried out data collection. SA, EAB and ANK conducted ultrasound training and quality control. SA analysed the data and drafted the article, with regular inputs from KKG and MJR. MGK, JB, DEG, DZ and ATP critically reviewed the work for important intellectual content. All authors approved the final version for publication.

DETAILS OF ETHICS APPROVAL

This study obtained ethical clearance from Makerere University School of Medicine Research and Ethics Committee (SOMREC) (ref. 2018–090) and from the Uganda National Council for Science and Technology (UNCST) (ref. HS 2459). Further, we obtained permission to operate the EPID study in Kagadi territory from both the district and hospital authorities. All participants provided written and informed consent to participate in this study. Participants who were illiterate provided a thumbprint and were interviewed in the local language.

DATA AVAIL ABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

SUPPORTING INFORMATION

Figure S1 Flow diagram of women screened, recruited and included in the analysis of the EPID study, Kagadi Hospital, Uganda.
Table S1: Overall maternal and pregnancy characteristics of the study cohort and the percentage of missing information
Table S2: Univariable and multivariable logistic regression analysis in prediction of composite adverse perinatal outcome from maternal and pregnancy characteristics in a subgroup of SGA births.
Table S3: Univariable and multivariable logistic regression analysis of composite adverse perinatal outcome prediction from maternal and pregnancy characteristics in a subgroup of AGA births.

REFERENCES

1. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: Rates, risk factors, and acceleration towards 2030. Lancet. 2016;387(10018):587–603.
2. Lee ACC, Kozuki N, Cousens S, Stevens GA, Blencowe H, Silveira MF, et al. Estimates of burden and consequences of infants born small for gestational age in low- and middle-income countries with INTERGROWTH-21st standard: analysis of CHERG datasets. BMJ. 2017 Aug 17;358:j3677.
3. Pilliod RA, Cheng YW, Snowden JM, Doss AE, Caughey AB. The risk of intrauterine fetal death in the small-for-gestational-age fetus. Am J Obstet Gynecol. 2012 Oct 1;207(4):318.e1-318.e6.
4. Madden J V, Flatley CJ, Kumar S. Term small-for-gestational-age infants from low-risk women are at significantly greater risk of adverse neonatal outcomes. Am J Obstet Gynecol. 2018 May 1;218(5):525.e1-525.e9.
5. Figueras F, Gratacós E. Update on the Diagnosis and Classification of Fetal Growth Restriction and Proposal of a Stage-Based Management Protocol. Fetal Diagn Ther. 2014;36(2):86–98.
6. Figueras F, Caradeux J, Crispi F, Eixarch E, Peguero A, Gratacos E. Diagnosis and surveillance of late-onset fetal growth restriction. Am J Obstet Gynecol. 2018 Feb 1;218(2):S790-S802.e1.
7. Hershkovitz R, Kingdom JCP, Geary M, Rodeck CH. Fetal cerebral blood flow redistribution in late gestation: identification of compromise in small fetuses with normal umbilical artery Doppler. Ultrasound Obstet Gynecol. 2000 Mar 1;15(3):209–12.
8. Oros D, Figueras F, Cruz-Martinez R, Meler E, Munmany M, Gratacos E. Longitudinal changes in uterine, umbilical and fetal cerebral Doppler indices in late-onset small-for-gestational-age fetuses. Ultrasound Obstet Gynecol. 2011 Feb 1;37(2):191–5.
9. WHO. WHO recommendations on antenatal care for a positive pregnancy experience [Internet]. World Health Organization; 2016. Available from: https://www.who.int/publications/i/item/9789241549912
10. Al Hamayel NA, Baghlaf H, Blakemore K, Crino JP, Burd I. Significance of abnormal umbilical artery Doppler studies in normally grown fetuses. Matern Heal Neonatol Perinatol. 2020;6(1):1.
11. Filmar G, Panagopoulos G, Minior V, Barnhard Y, Divon MY. Elevated umbilical artery systolic/diastolic ratio in the absence of fetal growth restriction. Vol. 288. 2013. p. 279–85.
12. Bolz N, Kalache KD, Proquitte H, Slowinski T, Hartung JP, Henrich W. Value of Doppler sonography near term: can umbilical and uterine artery indices in low-risk pregnancies predict perinatal outcome? Vol. 41. 2013. p. 165–70.
13. Group DFS. A randomised controlled trial of Doppler ultrasound velocimetry of the umbilical artery in low-risk pregnancies. BJOG An Int J Obstet Gynaecol. 1997 Apr 1;104(4):419–24.
14. Roza SJ, Steegers EAP, Verburg BO, Jaddoe VW V, Moll HA, Hofman A, et al. What Is Spared by Fetal Brain-Sparing? Fetal Circulatory Redistribution and Behavioral Problems in the General Population. Am J Epidemiol. 2008 Nov 15;168(10):1145–52.

15. Morales-Roselló J, Khalil A, Morlando M, Papageorghiou A, Bhide A, Thilaganathan B. Changes in fetal Doppler indices as a marker of failure to reach growth potential at term. Ultrasound Obstet Gynecol. 2014;43(3):303–10.
16. Grobbee DE, Hoes AW. Clinical Epidemiology: Principles, Methods, and Applications for Clinical Research. Jones & Bartlett Publishers; 2014. 472 p.
17. Vogel JP, Vannevel V, Robbers G, Gwako G, Lavin T, Adanikin A, et al. Prevalence of abnormal umbilical arterial flow on Doppler ultrasound in low-risk and unselected pregnant women: a systematic review. Reprod Health. 2021;18(1):38.
18. Papageorghiou AT, Kennedy SH, Salomon LJ, Ohuma EO, Cheikh Ismail L, Barros FC, et al. International standards for early fetal size and pregnancy dating based on ultrasound measurement of crown–rump length in the first trimester of pregnancy. Ultrasound Obstet Gynecol. 2014 Dec 1;44(6):641–8.
19. Papageorghiou AT, Kemp B, Stones W, Ohuma EO, Kennedy SH, Purwar M, et al. Ultrasound-based gestational-age estimation in late pregnancy. Ultrasound Obstet Gynecol. 2016 Dec 1;48(6):719–26.
20. Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, et al. ISUOG practice guidelines: Use of Doppler ultrasonography in obstetrics. Ultrasound Obstet Gynecol. 2013;41(2):233–9.
21. Villar J, Ismail LC, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014 Sep 6;384(9946):857–68.
22. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements—A prospective study. Am J Obstet Gynecol. 1985 Feb 1;151(3):333–7.
23. Stirnemann J, Salomon LJ, Papageorghiou AT. INTERGROWTH-21st standards for Hadlock's estimation of fetal weight. Ultrasound Obstet Gynecol. 2020 Dec 1;56(6):946–8.
24. Papageorghiou AT, Ohuma EO, Altman DG, Todros T, Ismail LC, Lambert A, et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet. 2014 Sep 6;384(9946):869–79.
25. Drukker L, Staines-Urias E, Villar J, Barros FC, Carvalho M, Munim S, et al. International gestational age-specific centiles for umbilical artery Doppler indices: a longitudinal prospective cohort study of the INTERGROWTH-21st Project. Am J Obstet Gynecol. 2020 Jun 1;222(6):602.e1-602.e15.
26. Rizzo G, Pietrolucci ME, Mappa I, Bitsadze V, Khizroeva J, Makatsariya A, et al. Modeling Pulsatility Index nomograms from different maternal and fetal vessels by quantile regression at 24–40 weeks of gestation: a prospective cross-sectional study. J Matern Neonatal Med. 2020 May 25;1–9.
27. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J Stat Softw. 2011 Dec 12;45(3 SE-Articles):1–67.
28. Hafen R, Anderson C, Schloerke B. hbgd: Healthy birth, growth & development [Internet]. 2016 [cited 2021 Sep 23]. Available from: https://github.com/HBGDki/hbgd
29. Rubin DB. Multiple imputation for nonresponse in surveys. Vol. 81. John Wiley & Sons; 2004.
30. Lott A, Reiter JP. Wilson Confidence Intervals for Binomial Proportions With Multiple Imputation for Missing Data. Am Stat. 2020 Apr 2;74(2):109–15.

31. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998 Apr 30;17(8):873–90.
32. Hlongwane T, Cronje T, Nkosi BSS, Pattinson RC. The prevalence of abnormal Doppler's of the umbilical artery in a low-risk pregnant population in South Africa. EClinicalMedicine. 2021 Apr 1;34.
33. Conde-Agudelo A, Villar J, Kennedy SH, Papageorghiou AT. Predictive accuracy of cerebroplacental ratio for adverse perinatal and neurodevelopmental outcomes in suspected fetal growth restriction: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;52(4):430–41.
34. Martinez-Portilla RJ, Caradeux J, Meler E, Lip-Sosa DL, Sotiriadis A, Figueras F. Third-trimester uterine artery Doppler for prediction of adverse outcome in late small-for-gestational-age fetuses: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2020 May 1;55(5):575–85.
35. Townsend R, Sileo FG, Allotey J, Dodds J, Heazell A, Jorgensen L, et al. Prediction of stillbirth: an umbrella review of evaluation of prognostic variables. BJOG An Int J Obstet Gynaecol. 2021 Jan 1;128(2):238–50.
36. Ali S, Heuving S, Kawooya MG, Byamugisha J, Grobbee DE, Papageorghiou AT, et al. Prognostic accuracy of antenatal Doppler ultrasound for adverse perinatal outcomes in low-income and middle-income countries: a systematic review. BMJ Open. 2021 Dec 1;11(12):e049799.
37. Ishak M, Khalil A. Prediction and prevention of stillbirth: dream or reality. Curr Opin Obstet Gynecol. 2021;33(5).
38. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol. 2018 Feb 1;218(2):S855–68.
39. Lees CC, Stampalija T, Baschat A, da Silva Costa F, Ferrazzi E, Figueras F, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol. 2020;56(2):298–312.
40. Ali S, Kabajaasi O, Kawooya MG, Byamugisha J, Zakus D, Papageorghiou AT, et al. Antenatal Doppler ultrasound implementation in a rural sub-Saharan African setting: exploring the perspectives of women and healthcare providers. Reprod Health. 2021;18(1):199.
41. Oros D, Ruiz-Martinez S, Staines-Urias E, Conde-Agudelo A, Villar J, Fabre E, et al. Reference ranges for Doppler indices of umbilical and fetal middle cerebral arteries and cerebroplacental ratio: systematic review. Ultrasound Obstet Gynecol. 2019 Apr 1;53(4):454–64.

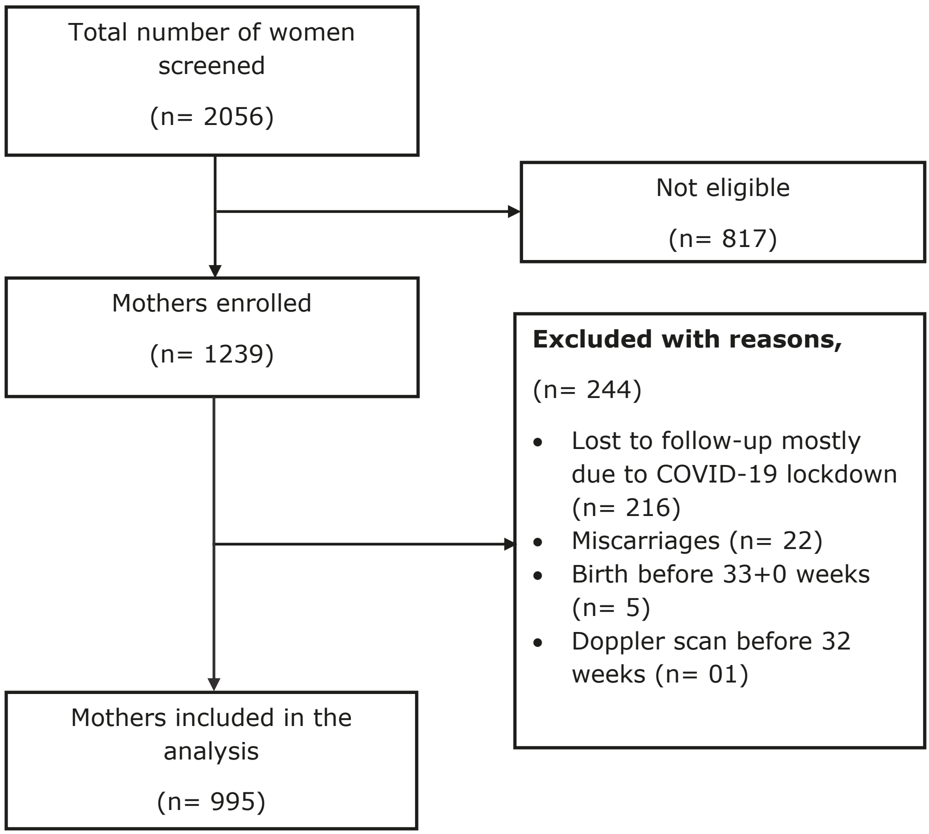


Figure S1 Flow diagram of women screened, recruited and included in the analysis of the EPID study, Kagadi Hospital, Uganda.

Table S1: Overall maternal and pregnancy characteristics of the study cohort and the percentage of missing information

Characteristic	Overall (N= 995)	Missing (%)
Maternal height (cm), mean (SD)	157.1 (6.11)	0.0
Weight (kg), median (IQR)	60.0 (54.0 – 68.0)	0.0
Maternal BMI (kg/m^2), mean (SD)	24.6 (3.93)	0.0
Maternal age (years), median (IQR)	25.0 (22.0 – 30.0)	24.4
Nulliparous, yes, n (%)	188 (18.9)	24.4
Malaria, yes, n (%)	299 (30.1)	24.4
Urinary tract infection, yes, n (%)	113 (11.4)	24.4
Syphilis, yes, n (%)	52 (5.2)	24.4
HIV, positive, n (%)	69 (6.9)	24.5

Table S1: Continued

Characteristic	Overall (N= 995)	Missing (%)
Previous stillbirth, yes, n (%)	21 (2.1)	24.4
Chronic hypertension, yes, n (%)	9 (0.9)	24.4
Alcohol use in pregnancy, yes, n (%)	99 (9.9)	24.4
Smoking, yes, n (%)	5 (0.5)	27.2
Stillbirth, yes, n (%)	18 (1.8)	0.0
Neonatal death, yes, n (%)	13 (1.3)	0.0
NICU admission, yes, n (%)	89 (8.9)	0.0
APGAR score <7 at 5 minutes, yes, n (%)	26 (2.6)	53.0
EMCS for fetal distress, yes, n (%)	19 (1.9)	0.0
Respiratory distress syndrome, yes, n (%)	40 (4.0)	0.0
Composite adverse outcome, yes, n (%)	136 (13.7)	0.0
Birth weight, mean (SD)	3.18 (0.46)	13.8
Birth weight z-scores, mean (SD)	-0.28 (1.07)	13.8
Birth weight centiles, mean (SD)	41.66 (29.31)	13.8
Mode of birth		
Vaginal birth, n (%)	866 (87.0)	0.0
Cesarean birth, n (%)	129 (13.0)	
Place of birth		
Health unit, n (%)	885 (88.9)	0.0
Traditional birth attendant (TBA), n (%)	44 (4.4)	
Home, n (%)	58 (5.8)	
Way to hospital, n (%)	8 (0.8)	
Sex of baby, male, n (%)	482 (48.4)	0.0
GA at dating scan (weeks), median (IQR)	18.4 (15.7 – 21.0)	0.0
GA at Doppler (weeks), mean (SD)	36.90 (1.02)	45.3
GA at birth (weeks), mean (SD)	39.80 (1.39)	0.0
GA at birth (weeks)		
Preterm, n (%)	41 (4.1)	0.0
Early term, n (%)	154 (15.5)	0.0
Full term, n (%)	613 (61.6)	0.0
Late term, n (%)	152 (15.3)	0.0
Postterm, n (%)	35 (3.5)	0.0
EFW (g), mean (SD)	2829.3 (374.7)	45.3
EFW z scores, mean (SD)	0.08 (0.94)	45.3

5

Table S1: Continued

Characteristic	Overall (N= 995)	Missing (%)
AC (cm), mean (SD)	32.19 (1.93)	45.3
AC z-scores, mean (SD)	0.04 (0.97)	45.3
AC percentiles, mean (SD)	51.57 (28.06)	45.3
UA PI, median (IQR)	0.82 (0.73 – 0.92)	46.1
UA PI z-scores, mean (SD)	-0.23 (1.04)	46.1
UA PI percentiles, mean (SD)	42.75 (28.78)	46.1
MCA PI, mean (SD)	1.66 (0.30)	47.4
CPR PI, median (IQR)	2.0 (1.70 – 2.32)	48.1
Right UtA PI, median (IQR)	0.70 (0.60 – 0.81)	55.8
Left UtA PI, median (IQR)	0.73 (0.61 – 0.88)	51.7
UtA PI, median (IQR)	0.73 (0.63 – 0.84)	59.5

*SD: standard deviation; IQR: interquartile range; BMI: body mass index; EMCS: Emergency cesarean section; EFW: estimated fetal weight; AC: abdominal circumference: UA: umbilical artery; MCA: middle cerebral artery; CPR: cerebroplacental ratio; UtA: uterine artery; UtA: mean uterine artery; GA: gestational age; preterm: <37 weeks; early term: 37-38 weeks; full term: 39-40 weeks; late term: 41 weeks; postterm: ≥42 weeks.

Table S2: Univariable and multivariable logistic regression analysis in prediction of composite adverse perinatal outcome from maternal and pregnancy characteristics in a subgroup of SGA births.

	Univariate		**Multivariate**			
			Model A		**Model B**	
Characteristic	**Crude OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Syphilis, yes	3.42 (0.95 – 12.32)	0.059	4.29 (0.95 – 19.45)	0.058	3.69 (0.87 – 15.64)	0.075
Nulliparous, yes	1.02 (0.44 – 2.30)	0.965	1.05 (0.40 – 2.75)	0.918	1.07 (0.42 – 2.70)	0.891
Malaria, yes	0.59 (0.25 – 1.35)	0.215	0.48 (0.18 – 1.26)	0.133	0.52 (0.20 – 1.33)	0.172
GA at birth, full-term	Ref.		Ref.		Ref.	
Preterm	9.21 (1.01 – 83.86)	0.048	9.59 (0.82 – 112.28)	0.071	8.59 (0.78 – 94.72)	0.078
Early term	1.56 (0.51 – 4.83)	0.432	1.15 (0.32 – 4.21)	0.827	1.22 (0.35 – 4.24)	0.756
Late term	1.48 (0.60 – 3.62)	0.392	1.39 (0.51 – 3.78)	0.511	1.44 (0.54 – 3.83)	0.459
Postterm	2.91 (0.56 -15.13)	0.202	3.37 (0.54 – 20.97)	0.191	3.05 (0.48 – 19.12)	0.230
MCA PI <5th centile	2.96 (1.04 – 8.48)	0.042	3.75 (1.18 – 11.88)	0.025*		
CPR PI <5th centile	2.39 (0.70 – 8.14)	0.159			2.58 (0.69 – 9.61)	0.154

*Significant at p-value <0.05; OR: odds ratio after pooling estimates using Rubin's rule; N= 995; m= 100 imputed datasets; Model A includes MCA PI; Model B includes CPR; GA: gestational age at birth; preterm: <37 weeks; early term: 37-38 weeks; full term: 39-40 weeks; late term: 41 weeks; postterm: ≥42 weeks.

5

Table S3: Univariable and multivariable logistic regression analysis of composite adverse perinatal outcome prediction from maternal and pregnancy characteristics in a subgroup of AGA births.

	Univariate		**Multivariate**			
			Model A		**Model B**	
Characteristic	**Crude OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Body mass index, (kg/m2)	1.04 (0.99 – 1.10)	0.080	1.05 (0.99 – 1.11)	0.070	1.05 (1.001 – 1.12)	0.048*
Chronic hypertension, yes	4.73 (1.22 – 18.38)	0.024	4.25 (1.02 – 17.67)	0.046*	4.02 (0.96 – 16.8)	0.056
Sex of baby, male	1.59 (1.03 – 2.47)	0.038	1.58 (1.00 – 2.49)	0.052	1.59 (1.01 – 2.52)	0.047*
Nulliparous, yes	1.15 (0.66 – 2.02)	0.603	1.28 (0.71 – 2.30)	0.410	1.27 (0.70 – 2.29)	0.424
Malaria, yes	1.02 (0.62 – 1.68)	0.929	1.02 (0.61 – 1.71)	0.937	1.01 (0.60 – 1.70)	0.955
GA at birth, full-term	Ref.		Ref.		Ref.	
Preterm	4.10 (1.82 – 9.22)	0.001	4.27 (1.76 – 10.35)	0.001*	4.18 (1.72 – 10.15)	0.001*
Early term	1.60 (0.89 – 2.88)	0.112	1.56 (0.85 – 2.87)	0.152	1.57 (0.85 – 2.89)	0.145
Late term	1.65 (0.88 – 3.09)	0.117	1.66 (0.87 – 3.19)	0.125	1.63 (0.85 – 3.14)	0.141
Post term	1.62 (0.50 – 5.20)	0.411	1.65 (0.50 – 5.44)	0.413	1.59 (0.48 – 5.25)	0.444
UtA PI >95th centile	2.79 (1.13 - 6.84)	0.024	2.54 (0.99 – 6.56)	0.052*	2.51 (0.97 - 6.49)	0.057*
MCA PI <5th centile	1.65 (0.83 - 3.29)	0.151	1.56 (0.76 – 3.21)	0.228		
CPR PI <5th centile	2.01 (0.91 - 4.44)	0.084			1.90 (0.82, 4.39)	0.133

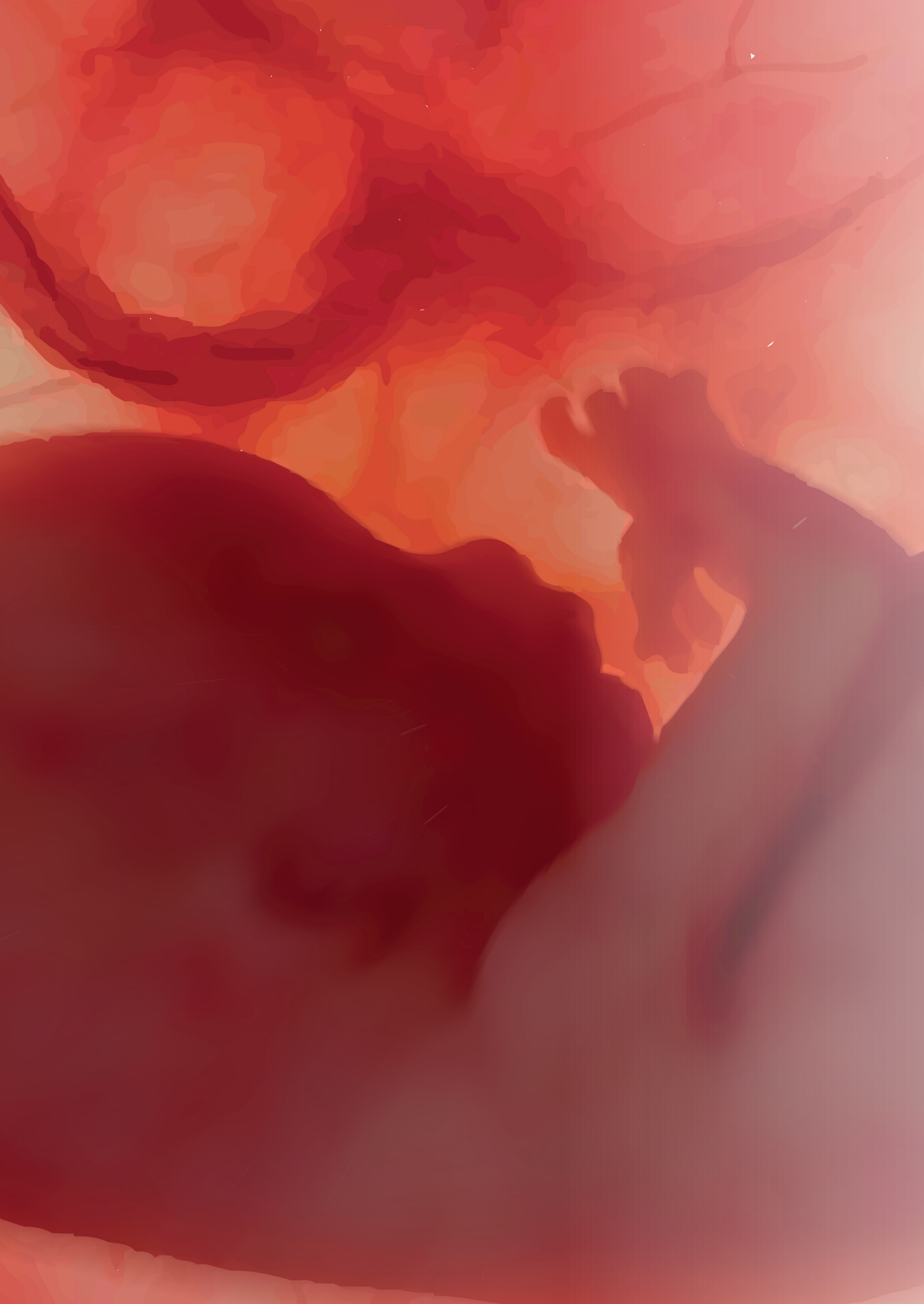
*Significant at p-value <0.05; OR: odds ratio after pooling estimates using Rubin's rule; N= 995; m= 100 imputed datasets; Model A includes MCA PI; Model B includes CPR; GA: gestational age at birth; preterm: <37 weeks; early term: 37-38 weeks; full term: 39-40 weeks; late term: 41 weeks; postterm: ≥42 weeks.

Table S4: Univariable and multivariable logistic regression analysis of perinatal death prediction from the maternal and pregnancy characteristics in women undergoing routine antenatal care.

	Univariate		**Multivariate**			
			Model A		**Model B**	
Characteristic	**Crude OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Syphilis, yes	2.47 (0.74 – 8.29)	0.142	2.48 (0.69 – 8.94)	0.165	2.34 (0.65 – 8.50)	0.192
Previous stillbirth, yes	5.69 (1.57 – 20.59)	0.008	6.33 (1.57 – 25.46)	0.009*	7.45 (1.82 – 30.41)	0.005*
Sex of baby, male	1.71 (0.82 – 3.57)	0.151	1.73 (0.80 – 3.76)	0.163	1.78 (0.81 – 3.88)	0.148
GA at birth, full-term	Ref.		Ref.		Ref.	
Preterm	6.95 (2.32 – 20.84)	0.001	7.68 (2.32 – 25.48)	0.001*	7.38 (2.20 – 24.77)	0.001*
Early term	2.74 (1.10 – 6.94)	0.030	2.41 (0.92 – 6.29)	0.071	2.52 (0.96 – 6.61)	0.060
Late term	1.01 (0.28 – 3.62)	0.989	1.03 (0.28 – 3.81)	0.969	1.05 (0.28 – 3.93)	0.938
Postterm	4.70 (1.25 – 17.50)	0.021	4.79 (1.21 – 19.01)	0.025	4.58 (1.15 – 18.24)	0.030*
UtA PI >95th centile	2.39 (0.49 – 11.54)	0.274	2.19 (0.44 – 10.83)	0.336	2.22 (0.44 - 11.28)	0.332
MCA PI <5th centile	2.08 (0.62 – 6.98)	0.236	2.08 (0.59 – 7.28)	0.248		
CPR PI <5th centile	2.97 (0.90 – 9.78)	0.072			3.17 (0.91 – 11.09)	0.070

*Significant at p-value <0.05; OR: odds ratio after pooling estimates using Rubin's rule; N= 995; m= 100 imputed datasets; Model A includes MCA PI; Model B includes CPR; GA: gestational age at birth; preterm: < 37 weeks; early term: 37-38 weeks; full term: 39-40 weeks; late term: 41 weeks; postterm ≥ 42 weeks.

5



Chapter 6

A clinical prediction model to estimate the risk of perinatal death in women near-term in low-resource settings

Sam Ali
Josaphat Byamugisha
Michael G. Kawooya
Isaac M. Kakibogo
Nasali Tusiime
Diederick E. Grobbee
David Zakus
Aris T. Papageorghiou
Marcus J. Rijken
Kerstin Klipstein-Grobusch

Submitted

ABSTRACT

Background

At present, there is no effective screening strategy to detect growth restricted fetuses at risk of poor birth outcomes, especially in stillbirth high-burden settings. We examined the performance of a multivariable model combining maternal and third-trimester Doppler ultrasound parameters in predicting the risk of perinatal death in women undergoing routine antenatal care in a low-resource setting.

Methods

This prospective cohort study enrolled non-anomalous singleton pregnant women attending a rural Hospital in Uganda between 2018 and 2020. Women underwent an early dating ultrasound and a single third-trimester Doppler ultrasound scan between 32 and 40 weeks. Missing data were imputed and multivariable binary logistic regression used to develop the prediction models using the available predictors and outcomes. We reported the model's predictive performance using measures of discrimination (area under the receiver-operating characteristics curve (AUC)) and calibration (slope and intercept).

Results

This analysis included 995 pregnancies, 31 (3.1%) perinatal deaths and 18 (1.8%) stillbirths. In a model combining maternal characteristics with middle cerebral artery pulsatility index (MCA PI) or cerebroplacental ratio (CPR), the AUCs for predicting perinatal death were 0.78 (95% CI: 0.67–0.87) and 0.78 (95% CI: 0.65–0.87), respectively, in the development data set. The bootstrap corrected AUC was 0.71, with a slope of 0.70. The uterine artery and umbilical artery PIs had minimal impact on the prediction of perinatal death.

Conclusion

The predictive performance for perinatal death and stillbirth of a model incorporating maternal characteristics combined with fetal cerebral Doppler in a general obstetric population near-term was only moderate and below clinically relevant threshold. Models including promising markers such as biochemical and maternal cardiovascular function parameters need to be investigated in future studies, and innovative ways to ensure that these new tests are available and affordable in low-resource settings will be required.

KEYWORDS

Placental dysfunction; stillbirth; middle cerebral artery; cerebroplacental ratio; prediction; developing countries

SHORT TITLE

Clinical prediction model for perinatal death and stillbirth

6

INTRODUCTION

Although there has been recognizable progress in reducing stillbirths globally, little has changed in the sub-Saharan African region. As of 2019, the stillbirth rate in sub-Saharan Africa stood at 21.7 per 1000 total births compared to 3.0 per 1000 total births in high income countries (HICs).[1] A high proportion of stillbirths are associated with placental dysfunction,[2–4] and are preventable through effective screening strategies and timely referral of pregnancies, in case of complications, for appropriate care. Prognostic models are important tools with great potential to reliably quantify a woman's individual risk of perinatal death, permitting close monitoring and expedited birth of fetuses at risk to improve their survival and long-term outcomes.

A recent review from low- and middle- income countries (LMICs) identified 21 prognostic models for adverse pregnancy outcomes, 17 models for predicting maternal outcomes and only two for perinatal death and stillbirth.[5] Two other reviews of primary studies on prognostic models for stillbirth from both LMICs and HICs found a few third trimester multivariable prediction models, none from a LMIC.[6,7] In Tanzania, a model for use in the labor ward to predict the risk of intrapartum related stillbirths and early neonatal deaths has recently been developed.[8] In addition, a few studies, many of sub-optimal quality, report the predictive accuracy of antenatal Doppler ultrasound for adverse perinatal outcomes in resource-poor settings.[9]

Third-trimester prognostic models are lacking, yet much needed in LMICs where the burden of stillbirths is still unacceptably high.[10,11] Although we recently found a strong association between fetal cerebral arterial blood flow redistribution and stillbirth,[12] it remains unknown whether there is a clinical benefit of a late third-trimester Doppler ultrasound scan to reduce perinatal death or stillbirth. The World Health Organization (WHO) calls for studies to close this knowledge gap.[11] This study prospectively investigated the added value of a single third-trimester Doppler ultrasound to maternal characteristics to predict the risk of perinatal death and stillbirth in women undergoing routine antenatal care in Kagadi Hospital, Uganda.

MATERIALS AND METHODS

Design and setting

This prospective cohort study was implemented between September 2018 and December 2020 at Kagadi Hospital, a secondary healthcare care facility serving as a referral center for the neighboring districts in the greater Kibaale region in mid-western Uganda. According to the District Health Information System (DHIS2), 264/3080 women presented for their 1st antenatal care (ANC) in the first trimester, 1483 achieved ≥ 4 ANC contacts and 13 achieved 8 ANC contacts, in 2020. The Hospital handles over 4000 deliveries a year. This study recruited women from the ANC clinic, maternity unit and ultrasound department.

Eligibility criteria

We included singleton pregnant women who enrolled in early pregnancy (<24 weeks), with no obvious fetal abnormalities on scan. Exclusion criteria included women with missed miscarriage or intrauterine fetal demise, and birth before the Doppler scan (i.e., those who gave birth before 33+0 weeks). Gestational age was confirmed by a first trimester ultrasound between 9+0 – 13+6 weeks using the crown rump length (CRL)[13] or the head circumference combined with femoral length measurements taken below 24 weeks.[14]

Ethics approval and consent to participate

All women enrolled provided written and informed consent. The illiterate participants provided a thumbprint and were interviewed in the local language. The study received ethical clearance from Makerere University School of Medicine Research and Ethics Committee (SOMREC): approval number #REC REF 2018-090; and from the Uganda National Council for Science and Technology (UNCST): approval number HS 2459. We also obtained permission from Kagadi Hospital, Kagadi District Health Team and local administrative authorities to undertake the Ending Preventable Stillbirths by Improving Diagnosis of Babies at Risk (EPID) study in Kagadi region.

Data collection

The first author (SA) and two resident sonographers at Kagadi Hospital carried out all the ultrasound scans. The sonographers were experienced in performing obstetric ultrasound and received a pre-study implementation training on fetal Doppler ultrasound at Ernest Cook Ultrasound Research and Education Institute (ECUREI), Kampala, Uganda including extensive hands-on practical sessions at The Women's Place, Kampala, Uganda. Ultrasound examinations were performed using two systems: Voluson e (GE Medical Systems, Zipf, Austria) with a 2-8 MHz convex probe or Phillips HD-9 (Philips Ultrasound, Bothell, WA, USA) equipped with C5-2 and C6-3 convex probes. We performed all ultrasound scans according to standard protocols.[15,16] Doppler scans were done between 32 and 40 weeks of gestation. The umbilical artery (UA) was examined in a free loop of the umbilical cord, and measured in the absence of fetal movement while keeping the insonation angle at less than 30^0. The middle cerebral artery (MCA) was examined at its proximal third, close to its origin in the internal carotid artery, with the angle of insonation kept as close as possible to 0^0. We also recorded the uterine artery (UtA) Doppler trans-abdominally. Using color flow mapping, we identified the UtA at the point it appears to cross the external iliac artery and then applied pulsed wave Doppler at 1cm medial to the crossover point, with the angle of insonation maintained at less than 30^0. The mean value of the left and right UtA pulsatility index (PI) was calculated. All Doppler waveform velocities were recorded as the average of three similar consecutive waveforms.

At the time of the study, Doppler measurements were not routinely used to manage pregnancies in the study setting. Therefore, clinicians were blinded to the Doppler results except when absent end-diastolic flow (AEDF) or reversed end-diastolic flow (REDF) in the UA was detected. In addition, there were no local guidelines for management of suspected fetal growth restriction (FGR). Therefore, any woman with an abnormal finding detected on ultrasound was referred to the attending clinicians for management as per the standard of care which was variable from clinician to clinician. All women enrolled in the study were followed up until 28 days postnatally.

Given COVID-19 lockdowns, we remotely captured some follow-up data by phone calls, for instance, a report on neonatal death.

Maternal and pregnancy characteristics

The characteristics recorded included maternal age, weight, height, body mass index, parity, malaria in pregnancy, urinary tract infection, syphilis, HIV status, previous stillbirth, chronic hypertension, alcohol use during pregnancy, maternal smoking, and gestational age at Doppler scan and birth. Ultrasound measurements included estimated fetal weight (EFW), abdominal circumference (AC), UA PI, MCA PI, cerebroplacental ratio (CPR), and UtA PI.

Outcome measures

The primary outcomes included perinatal death and stillbirth. Stillbirth was defined as intrauterine fetal death after 28 weeks' gestation as per the WHO definition, neonatal death as death within 28 days of the postnatal period, while perinatal death was defined as the occurrence of either stillbirth or neonatal death. We defined small for gestational age (SGA) as birthweight <10^{th} percentile and appropriate for gestational age (AGA) as birthweight ≥10^{th} percentile using the International Fetal and Newborn Growth Consortium for the 21^{st} Century (INTERGROWTH-21^{st}) new-born birth weight standards.[17]

6

Statistical analysis

Variable transformations

EFW was determined using Hadlock formula 3 and converted to gestational specific z-scores using the INTERGROWTH-21^{st} charts.[18,19] We converted fetal biometry to gestational specific z-scores using the INTERGROWTH-21^{st} fetal growth standards.[20] CPR was calculated as a ratio of the MCA PI divided by the UA PI. We inspected the distributions of continuous variables using Shapiro-Wilk test, histogram and Kernel density plots. Maternal characteristics and the extent of missing data were expressed as mean (standard deviation (SD)) or median (interquartile range (IQR)), frequencies and percentages.

Imputation model

Statistical assessment for missingness using the student's t-test and the chi-square test of records with and without complete data, and by graphical methods indicated that data was missing at random. We then imputed 100 datasets over 20 iterations using multiple imputation via fully conditional specification by use of the multivariate imputation by chained equations (mice) package in R.[21] Binary logistic regression model was used to impute incomplete dichotomous variables and predictive mean matching to impute continuous variables. To ensure congeniality, variable transformations were imputed by passive imputation. Missing fetal biometry and new-born measurement z-scores and percentiles were imputed via the INTERGROWTH 21st formulas embedded in the R package "hbgd".[22] The final imputations were checked for completeness and plausibility using density plots, summary statistics, and comparison of the observed and imputed data. We compared women's characteristics in the outcome groups using a two-sample t-test, pooled chi-square statistics based on Rubin's procedure,[23] and pooled estimates of the binomial proportions based on Wilson's confidence interval method.[24]

Model development and internal validation

We first fitted a model with maternal characteristics alone; then extended it to include the Doppler indices, to assess whether adding Doppler ultrasound tests improved model performance. The prognostic variables for model development were selected based on prior knowledge of important predictors and using a univariable analysis p-value of <0.2. We checked for a linear relationship between the continuous predictor variables and the outcomes using fractional polynomials and restricted cubic spline plots, before modelling. The Doppler indices showed a non-linear relationship and were modelled as continuous variables by applying restricted cubic splines with 03 knots. Non-contributing predictors were excluded by applying automatic backward stepwise variable selection using the Likelihood ratio tests (D3),[25] at a p-value of 0.157 recommended in the TRIPOD reporting standards.[26]

After model development, we internally validated the reduced models using the "MI_boot method" which combines multiple imputation with bootstrapping technique.[27,28] Using the 100 imputed datasets, 200 bootstrap samples were randomly drawn with replacement from each imputed dataset, giving us a total number of 20000 datasets for validation. The difference between the training and test data performance was used to estimate the optimism in the models developed. We, therefore, reported the development and bootstrap corrected pooled performance measures. The predictive performance and accuracy of the models were reported using discrimination and calibration respectively. Discriminative ability of the model was determined using the area under the receiver-operating-characteristics curve (AUC), which indicates the ability of the model to distinguish between women with and without the outcomes (perinatal death and stillbirth). An AUC value of 1 indicates a perfect discrimination and 0.5 indicates no discrimination beyond chance. Calibration assesses whether the predicted probabilities agree with observed probabilities, and was quantified using an estimate of slope shrinkage and the corresponding intercept. An intercept close to 0 and a slope close to 1 indicates good calibration. SA conducted the analysis with inputs from KKG, by the use of the psfmi" package in R version 4.0.4 (2021-02-15).[29]

Patient and public involvement

There was no patient and public involvement in the design, conduct, analysis and reporting of this research.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Participants

This study was reported as per the TRIPOD statement.[26] A total of 1,239 women were recruited in early pregnancy (<24 weeks; 175 of them between 9+0–13+6 weeks). We excluded 244 women, leaving 995 for the analysis (Figure 1). In Table 1, the characteristics of women included in the analysis are shown. The incidence of stillbirth and perinatal death in the cohort was 1.8% (n=18) and 3.1% (n=31), respectively. The median maternal age was 25 (IQR, 22–30) years and 18.9% (n=188) of the women were nulliparous. The median gestational age at a dating scan was 18.4 (Range, 9–23) weeks, whereas the mean gestational age at Doppler scan and birth was 36.9 (SD, 1.02) and 39.8 (SD, 1.39) weeks, respectively. The overall cohort characteristics and the percentage of missing data are shown in supporting information S1 Table. Fetal biometry and Doppler ultrasound indices had the highest percentages of missing data ranging between 45.3–51.5%, mostly due to COVID-19 lockdown and temporary breakdown of the study equipment during the follow-up period.

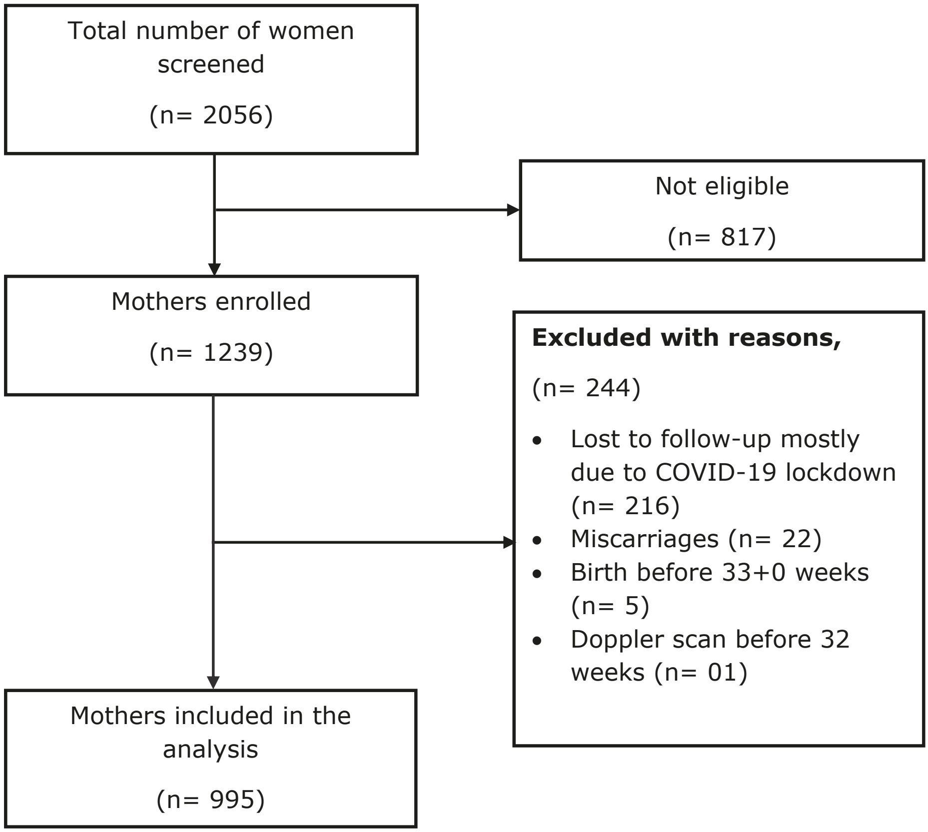


Figure 1 Flow diagram of women screened, recruited and included in the analysis of the EPID study, Kagadi Hospital, Uganda.

6

Tables

Table 1 Comparison of maternal and pregnancy characteristics between women who experienced perinatal death and those who had live babies in EPID study at Kagadi Hospital, Uganda.

Characteristic	No perinatal death (n= 964)	Perinatal death (n= 31)	P-value
Body mass index, (kg/m2), mean (SD)	24.7 (3.92)	25.1 (4.34)	0.528
Nulliparous, %	24.8	26.6	0.747
Malaria, yes, %	39.9	45.3	0.637
Syphilis, yes, %	7.4	16.9	0.164
Previous stillbirth, yes, %	2.4	12.5	0.013*
Sex of baby, male, %	48.0	61.3	0.145
EFW z scores, mean (SD)	0.07 (1.45)	0.02 (1.82)	0.884
AC z-scores, mean (SD)	0.04 (1.63)	−0.10 (1.92)	0.633
UA PI z-scores, mean (SD)	−0.22 (1.55)	0.15 (1.66)	0.204
UtA PI >95th percentile, %	5.4	12.9	0.227
MCA PI <5th percentile, %	16.0	29.1	0.219
CPR PI <5th percentile, %	9.9	25.2	0.098
Gestational age at Doppler (weeks), mean (SD)	36.8 (1.40)	36.8 (1.47)	0.997
Gestational age at birth (weeks), mean (SD)	39.8 (1.34)	38.9 (2.23)	0.001*

*Significant at p-value <0.05; p-value from multiple imputation two sample t-test and pooling chi-square statistics using Rubin's procedure; SD: pooled standard deviation; %: pooled proportions estimated from Wilson's confidence interval method; N=995; m= 100 imputed datasets.

Model development and specification

Univariable and multivariable associations between the predictors and the outcomes were reported elsewhere.[12] The baseline model for predicting perinatal death and stillbirth included maternal body mass index (BMI), history of previous stillbirth, syphilis, and gestational age at birth. The extended models included MCA PI, CPR, UA PI and UtA PI, singly and in combinations of two Doppler tests. The strongest predictors for perinatal death (Table 2 and Table 3) and stillbirth were a history previous stillbirths and gestational age at birth (S2 to S5 Tables).

Table 2 Multivariable prognostic model for estimating the risk of perinatal death in women undergoing routine antenatal care from maternal characteristics and MCA PI.

Intercept and Predictors	β coefficient	Odds ratio (95% CI)	P value	β† Coefficient
Intercept	–6.37			–5.39
Body mass index	0.03	1.03 (0.94 – 1.12)	0.573	0.02
Syphilis, yes	0.87	2.78 (0.65 – 8.82)	0.190	0.61
Previous stillbirth,	1.93	6.87 (1.67 – 28.22)	0.007	1.35
Gestational age at birth				
Full-term	0.00	1.00 (reference)		0.00
Preterm	2.19	8.92 (2.7 – 29.52)	0.001	1.53
Early term	1.01	2.74 (1.04 – 7.20)	0.040	0.71
Late term	0.08	1.08 (0.29 – 4.01)	0.903	0.06
Postterm	1.72	5.62 (1.43 – 22.07)	0.013	1.21
MCA PI spline 1	–0.70	0.49 (0.01 – 19.07)	0.706	–0.49
MCA PI spline 2	–1.06	0.35 (0.01 – 56.72)	0.682	–0.74

*β: Regression coefficient; OR: odds ratio after pooling estimates using Rubin's rule; N= 995; m= 100 imputed datasets; MCA: middle cerebral artery.
*$\beta^{\dagger}$ Regression coefficient multiplied with a shrinkage factor (obtained from the bootstrapping procedure) of 0.70; CI: confidence interval.
*Preterm: <37 weeks; early term: 37-38 weeks; full term: 39-40 weeks; late term: 41 weeks; postterm: ≥42 weeks.
*The probability of perinatal death can be calculated as: P (perinatal death) = 1/ (1 + exp (–(–5.3934 + 0.0180*body mass index + 0.6094*syphilis + 1.3491*previous stillbirth + 1.5324*preterm + 0.7055*early term + 0.0564*late term + 1.2081*postterm – 0.4887*MCA PI spline 1 – 0.7427*MCA PI spline 2))).

6

Table 3 Multivariable prognostic model for estimating the risk of perinatal death in women undergoing routine antenatal care from maternal characteristics and CPR.

Intercept and Predictors	β coefficient	Odds ratio (95% CI)	P value	β† Coefficient
Intercept	–5.37			–4.61
Body mass index	0.03	1.04 (0.95 – 1.13)	0.451	0.02
Syphilis, yes	0.84	2.31 (0.62 – 8.65)	0.212	0.56
Previous stillbirth,	1.97	7.20 (1.78 – 29.06)	0.006*	1.32
Gestational age at birth				
Full-term	0.00	1.00 (reference)		0.00
Preterm	2.17	8.78 (2.57 – 30.03)	0.001*	1.46
Early term	1.03	2.79 (1.05 – 7.38)	0.038*	0.69
Late term	0.11	1.12 (0.30 – 4.20)	0.865	0.08
Postterm	1.74	5.73 (1.42 – 23.01)	0.014*	1.17
MCA PI spline 1	–1.34	0.26 (0.03 – 2.23)	0.218	0.90
MCA PI spline 2	0.20	1.12 (0.06 – 25.68)	0.897	0.13

*β: Regression coefficient; odds ratio after pooling estimates using Rubin's rule; N= 995; m= 100 imputed datasets; CPR: cerebroplacental ratio.
*β† Regression coefficient multiplied with a shrinkage factor (obtained from the bootstrapping procedure) of 0.67; CI: confidence interval.
*Preterm: <37 weeks; early term: 37-38 weeks; full term: 39-40 weeks; late term: 41 weeks; postterm: ≥42 weeks.
*The probability of perinatal death can be calculated as: P (perinatal death) = 1/ (1 + exp (–(–4.6146 + 0.0232*body mass index + 0.5613*syphilis + 1.323*previous stillbirth + 1.4558*preterm + 0.6873*early term + 0.0763*late term + 1.1691*postterm – 0.9006*CPR spline 1 + 0.1343*CPR spline 2))).

Model performance

The predictive performance for perinatal death and stillbirth is shown in Table 4. The AUC for perinatal death of the baseline model was 0.74 (95% CI: 0.63 – 0.83) in the development data, and 0.68 after adjustment for overfitting. Adding MCA PI or CPR to the baseline model improved the discrimination performance for perinatal death but the difference was not statistically significant. The AUCs of the development model containing MCA PI and CPR were 0.78 (95% CI: 0.67 – 0.87) and 0.78 (95% CI: 0.65 – 0.87), respectively. In the model incorporating MCA PI, the bootstrap corrected AUC was 0.71.

The AUC for stillbirth in a model containing maternal factors alone was 0.72 (95% CI: 0.58 – 0.82) in the development set while the optimism corrected AUC was 0.60. Adding MCA PI or CPR to the baseline model improved the discrimination performance for stillbirth, giving AUCs of 0.79 (95% CI: 0.64 – 0.89) and 0.78 (95% CI: 0.61 – 0.89), respectively, in the development set. The bootstrap corrected AUCs for models including MCA PI and CPR were 0.67 and 0.64. Extending the baseline model comprising of maternal factors by adding the MCA PI or CPR marginally improved the discrimination for stillbirth. Adding UtA PI and UA PI to maternal and pregnancy characteristics had a negligible impact on the predictive performance for perinatal death or stillbirth.

Table 4 Predictive performance for perinatal death and stillbirth in women undergoing routine antenatal care in Kagadi Hospital, Uganda

	AUC			
Prognostic model	**Development (95% CI)**	**Bootstrap corrected**	**Slope**	**Intercept**
Perinatal death (n= 31)				
Baseline model	0.74 (0.63 – 0.83)	0.68	0.68	–1.0092
Baseline model + MCA PI	0.78 (0.67 – 0.87)	0.71	0.70	–0.8835
Baseline model + CPR	0.78 (0.65 – 0.87)	0.71	0.67	–0.9602
Baseline model + UtA PI	0.75 (0.64 – 0.85)	0.68	0.70	–0.9550
Baseline model + UA PI	0.75 (0.63 – 0.85)	0.68	0.67	–1.0134
Baseline model + MCA PI + UtA PI	0.79 (0.68 – 0.87)	0.71	0.67	–1.0138
Baseline model + CPR + UtA PI	0.79 (0.67 – 0.88)	0.71	0.67	– 0.9522
Stillbirth (n= 18)				
Baseline model	0.72 (0.58 – 0.82)	0.60	0.41	–2.3572
Baseline model + MCA PI	0.79 (0.64 – 0.89)	0.67	0.44	–2.1225
Baseline model + CPR	0.78 (0.61 – 0.89)	0.64	0.38	–2.3858
Baseline model + UtA PI	0.77 (0.62 – 0.88)	0.64	0.39	–2.4082
Baseline model + UA PI	0.74 (0.60 – 0.85)	0.58	0.34	–2.5940
Baseline model + MCA PI + UtA PI	0.83 (0.68 – 0.91)	0.68	0.40	–2.2635
Baseline model + CPR + UtA PI	0.82 (0.66 – 0.91)	0.67	0.40	–2.2718

*MCA: middle cerebral artery; CPR: cerebroplacental ratio; UtA: uterine artery; UA: umbilical artery; AUC: pooled area under receiver operating characteristics curve; CI: confidence interval; N= 995; m= 100 imputed datasets.

DISCUSSION

Main findings

A multivariable model of maternal factors alone had a moderate predictive performance for perinatal death and stillbirth. The model incorporating maternal factors in combination with MCA PI or CPR had a higher predictive performance for perinatal death and stillbirth than the one with maternal factors alone, but the performance remained below clinically acceptable thresholds. Adding UtA PI and UA PI to maternal characteristics had minimal impact on the predictive value for perinatal death and stillbirth.

Strengths and limitations

This is the first original study to investigate the added value of a third trimester Doppler ultrasound to maternal characteristics in predicting adverse perinatal outcomes in a general obstetric population in LMICs. Doppler ultrasound results were not made available to the attending clinicians, preventing them from managing pregnant women based on the tests under investigation. We handled missing data using multiple imputation technique which ensured that random variation between and within the completed datasets are persevered, and enhanced the power and validity of our findings.

The sample and number of events were relatively low due to the short time duration for data collection, limited funding and the rarity of stillbirths. Consequently, it could have possibly led to overfitted predictions. Although only a few women (n= 175) were recruited in the first trimester between 9+0–13+6 weeks of gestation, the study utilized recommended late dating methods as an alternative. About 17.5% (n= 216/1239) of the women were lost to follow-up mostly due to Covid-19 lockdown restrictions, equipment breakdown during the follow-up period and some challenges in the health system such as power cuts. However, there was no significant difference in the profile of patients lost to follow-up compared to those included in the analysis. Further, this was a single-center study and caution is urged when extrapolating the findings to other geographical regions.

Interpretation

Three studies have previously developed prediction models to quantify the risk of perinatal death in LMICs.[5,7,8] The miniPIERS study developed a prognostic model to identify women with hypertension who were at increased risk of perinatal death.[30] Their model containing maternal age, a count of symptoms, and dipstick proteinuria had an AUC of 0.75 (95% CI: 0.71 – 0.80).[30] A new prognostic model from Tanzania to triage women at the time of admission in the labor ward for the risk of perinatal death had a promising performance with AUC and slope of 0.78 and 0.94, respectively, but it is not applicable in the antepartum period.[8] A stillbirth prediction model from Nigeria had a high discriminative ability for stillbirth in the development study, (AUC 0.80 (95% CI: 0.78 – 0.83)),[31] but exhibited a poor discrimination on external validation in Zanzibar (Tanzania), with an AUC of 0.57 (95% CI: 0.56-0.58).[8] Further, the Nigerian model was developed for use in the second-trimester and did not include important predictors such as previous stillbirth, gestational age at birth and antenatal Dopplers tests. In comparison, our model was developed for clinical application at a routine third-trimester antenatal care visit. The performance of a model combining MCA PI or CPR with maternal factors for predicting perinatal death was good, with an AUC of 0.78 in the development data and 0.71 after correcting for overfitting. However, due to the relatively small number of perinatal deaths (n=31) and sample (n=995) in our cohort, our model could have had slightly overfitted predictions. The slope was 0.70 compared to an acceptable value of ≥0.90.[32,33] The model incorporating maternal factors, MCA PI and UtA PI had a high discrimination for stillbirth in the development data (AUC 0.83 (95% CI: 0.68 – 0.91)), although due to the low number of stillbirths, predictions may have also been overfitted. We limited the number of variables for model development to a minimal set possible with the sample we had, although our model has the potential to achieve higher predictive performance with a few more important predictors added to it.

Implications for clinical practice and research

The stillbirth rates in LMICs have barely dropped in the last two decades.[1] The majority of the stillbirths result from preventable causes,[2–4] and no reductions in the rates imply inefficiencies in existing strategies to combat it. The current routine screening policy (standard of care) in which ultrasound is only offered to pregnant women with suspicion of fetal growth restriction based on serial symphysis-fundus height measurements is ineffective. Both the Routine Third-trimester Ultrasound (ROTTUS) and the Pregnancy Outcome Prediction (POP) studies compared the diagnostic effectiveness of screening for FGR/SGA by a universal third trimester ultrasound versus selective ultrasound based on serial symphysis–fundus height (SFH) measurements in singleton pregnancies in Kenya and United Kingdom, respectively. The detection rate for growth restricted fetuses was only 7.7% in the ROTTUS study,[34] and 20% (95% CI: 15 – 24) in the POP study.[35] Novel approaches, for instance, multivariable prediction models to estimate a woman's individual risk of poor birth outcomes and facilitate their allocation to the appropriate care pathway has been proposed,[36,37] but such clinical decision support tools for use in the antepartum period are lacking, especially in LMIC settings.

Despite some limitations in our study, our model offers an opportunity to arrange two targeted ultrasound scans, the first one in early pregnancy at <24 weeks of gestation as per the WHO 2016 ANC model and a second one between 36^{+0}– 37^{+6} weeks of gestation to reliably assess fetal growth and wellbeing, identify and inform the frequency of monitoring of high-risk pregnancies and to time obstetric interventions to improve perinatal outcomes at an individualized and person-centered level. This would be a cost-friendly approach most importantly in LMICs where the resources and services like ultrasound may be limited. Although the World Health Organization (WHO) guidelines do not yet recommend a routine third trimester ultrasound,[11,38] there is considerable evidence that the best detection rates for fetuses at risk of adverse perinatal outcomes due to late FGR can be achieved when an ultrasound is offered in the late third trimester at around 36 weeks of gestation,[39] and that fetal cerebral blood flow redistribution could be a useful test for diagnosis of fetuses at risk of perinatal death in pregnancies with suspected FGR.[40]

Further considerations to facilitate the use of our model for estimating the risk of perinatal death in a clinical setting was its development based on a minimal set of easily accessible and precisely measurable variables. Recent trends demonstrate that ultrasound services are becoming more available in LMICs,[41] and we have ably demonstrated the feasibility of training healthcare providers in rural settings of LMICs to undertake Doppler ultrasound scans with consistency.[42] In addition, gestational age at birth was a strong predictor in our model, although accurate gestational age estimation is a challenge in LMICs: very few women, for instance, 15% in our cohort, present for their first ANC contact by 14 weeks of gestation. The majority of women begin ANC after 20 weeks of gestation. Notably, a single set of biometry ultrasound measurements combining HC and FL could be suitable for pregnancy dating with reasonable accuracy (95% prediction interval was within 8–9 days) in the second trimester.[14] Alternatively, the transcerebellar diameter (TCD) could be used, and it seems to be the most accurate method for late dating at any gestational age.[43] Although there are approaches offering a window for reliable late pregnancy dating that can be employed in underserved populations, efforts to ensure early initiation of ANC for all pregnant women globally, including first trimester ultrasound dating, will have far-reaching benefits.[14]

It is however important to note that the success of such a surveillance program in low resource settings would be challenged by the already existing health systems constraints. Therefore, initiatives to strengthen health systems, including but not limited to training healthcare professionals to offer ANC and ultrasound services, increasing availability and access of ultrasound equipment and services to all pregnant women preferably hand-held devices with solar power capabilities for deployment in remote settings, access to affordable follow-up care to women detected with complications, and development of a good and strict management protocol for fetuses at risk, are required. Such a management protocol should include a careful consideration of the potential fetal risks and the dangers of expediting labor or performing a caesarean section, since maternal and perinatal deaths following caesarean sections are disproportionately high in LMICs.[44] According to the WHO 2016 ANC model development group, "there is likely to be little impact on lives saved or improved without substantial investment in improving the quality of ANC services provided in LMICs".[11]

In HIC studies, prognostic models including biochemical markers seem to have the best predictive performance for stillbirth.[7] There is a need to explore the incremental predictive value of promising biochemical and maternal cardiovascular function markers to the current model. Innovative approaches to ensure that these new tests are accessible non-invasively, and affordable to the deprived populations that need them the most will be required. We recommend that clinicians in LMICs are well-trained in interpreting new markers, including Doppler ultrasound, and that similar reference standards are adopted alongside context-specific management guidelines for compromised fetuses, to avoid differences in clinical management and iatrogenic deaths.[45]

CONCLUSION

This study reveals that a multivariable model containing maternal risk factors in combination with fetal cerebral Doppler measurements near term has moderate predictive performance for perinatal death and stillbirth in a general obstetric population in low-resource settings. The model performance is slightly below clinically relevant thresholds to sufficiently identify fetuses at the greatest risk of poor birth outcomes. Further studies investigating the added value of novel markers like biochemical and maternal cardiovascular function indicators are strongly recommended.

ACKNOWLEDGEMENTS

We thank the study participants, and the teams from Kagadi district, ECUREI, The Women's Place, and Makerere University College of Health Sciences for the administrative and implementation support. We are grateful to the University of Oxford, Oxford, United Kingdom for providing the ultrasound equipment used for data collection. We would like to acknowledge the INTERGROWTH-21ST consortium for assistance and for providing freely available training materials and protocols (https://intergrowth21.tghn.org/); Lior Drukker for his help in calculation of Doppler centiles; and Maria-Clara Restrepo Mendez for help with the imputation model. We also thank Fosca

Tumushabe for her support with the English language review. We extend immense gratitude to the study funders (Grand Challenges Canada and the UMC Utrecht Global Health Support Program). ATP is supported by the Oxford Partnership Comprehensive Biomedical Research Centre with funding from the NIHR Biomedical Research Centre (BRC) funding scheme.

SUPPORTING INFORMATION

S1 Table: Overall maternal and pregnancy characteristics of the study cohort and the percentage of missing information.
S2 Table: Multivariable prognostic model for estimating the risk of perinatal death from maternal characteristics alone in women undergoing routine antenatal care.
S3 Table: Multivariable prognostic model for estimating the risk of stillbirth from maternal characteristics alone in women undergoing routine antenatal care.
S4 Table: Multivariable prognostic model for estimating the risk of stillbirth from maternal characteristics and MCA PI in women undergoing routine antenatal care.
S5 Table: Multivariable prognostic model for estimating the risk of stillbirth from maternal characteristics and CPR in women undergoing routine antenatal care.

REFERENCES

1. Hug L, You D, Blencowe H, Mishra A, Wang Z, Fix MJ, et al. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. Lancet. 2021 Aug 28;398(10302):772–85.
2. Melamed N, Baschat A, Yinon Y, Athanasiadis A, Mecacci F, Figueras F, et al. FIGO (International Federation of Gynecology and Obstetrics) initiative on fetal growth: Best practice advice for screening, diagnosis, and management of fetal growth restriction. Int J Gynecol Obstet. 2021 Mar 1;152(S1):3–57.
3. Lees CC, Stampalija T, Baschat A, da Silva Costa F, Ferrazzi E, Figueras F, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol. 2020;56(2):298–312.
4. Reinebrant HE, Leisher SH, Coory M, Henry S, Wojcieszek AM, Gardener G, et al. Making stillbirths visible: a systematic review of globally reported causes of stillbirth. BJOG An Int J Obstet Gynaecol. 2018;125(2):212–24.
5. Heestermans T, Payne B, Kayode GA, Amoakoh-Coleman M, Schuit E, Rijken MJ, et al. Prognostic models for adverse pregnancy outcomes in low-income and middle-income countries: a systematic review. BMJ Glob Heal. 2019 Oct 1;4(5):e001759.
6. Allotey J, Whittle R, Snell KIE, Smuk M, Townsend R, von Dadelszen P, et al. External validation of prognostic models to predict stillbirth using International Prediction of Pregnancy Complications (IPPIC) Network database: individual participant data meta-analysis. Ultrasound Obstet Gynecol. 2022 Feb 1;59(2):209–19.
7. Townsend R, Manji A, Allotey J, Heazell AEP, Jorgensen L, Magee LA, et al. Can risk prediction models help us individualise stillbirth prevention? A systematic review and critical appraisal of published risk models. BJOG An Int J Obstet Gynaecol. 2021 Jan 1;128(2):214–24.
8. Housseine N, Rijken MJ, Weller K, Nassor NH, Gbenga K, Dodd C, et al. Development of a clinical prediction model for perinatal deaths in low resource settings. eClinicalMedicine. 2022 Feb 1;44.
9. Ali S, Heuving S, Kawooya MG, Byamugisha J, Grobbee DE, Papageorghiou AT, et al. Prognostic accuracy of antenatal Doppler ultrasound for adverse perinatal outcomes in low-income and middle-income countries: a systematic review. BMJ Open. 2021 Dec 1;11(12):e049799.
10. Ishak M, Khalil A. Prediction and prevention of stillbirth: dream or reality. Curr Opin Obstet Gynecol. 2021;33(5).
11. WHO. WHO recommendations on antenatal care for a positive pregnancy experience [Internet]. World Health Organization; 2016. Available from: https://www.who.int/publications/i/item/9789241549912
12. Ali S, Kawooya MG, Byamugisha J, Kakibogo IM, Biira EA, Kagimu AN, et al. Middle cerebral arterial flow redistribution is an indicator for intrauterine fetal compromise in late pregnancy in low-resource settings: a prospective cohort study. BJOG An Int J Obstet Gynaecol. 2022 Feb 4;129:1712– 1720.
13. Papageorghiou AT, Kennedy SH, Salomon LJ, Ohuma EO, Cheikh Ismail L, Barros FC, et al. International standards for early fetal size and pregnancy dating based on ultrasound measurement of crown–rump length in the first trimester of pregnancy. Ultrasound Obstet Gynecol. 2014 Dec 1;44(6):641–8.

14. Papageorghiou AT, Kemp B, Stones W, Ohuma EO, Kennedy SH, Purwar M, et al. Ultrasound-based gestational-age estimation in late pregnancy. Ultrasound Obstet Gynecol. 2016 Dec 1;48(6):719–26.
15. Salomon LJ, Alfirevic Z, Da Silva Costa F, Deter RL, Figueras F, Ghi T, et al. ISUOG Practice Guidelines: ultrasound assessment of fetal biometry and growth. Ultrasound Obstet Gynecol. 2019 Jun 1;53(6):715–23.
16. Bhide A, Acharya G, Baschat A, Bilardo CM, Brezinka C, Cafici D, et al. ISUOG Practice Guidelines (updated): use of Doppler velocimetry in obstetrics. Ultrasound Obstet Gynecol. 2021 Aug 1;58(2):331–9.
17. Villar J, Ismail LC, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014 Sep 6;384(9946):857–68.
18. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements- a prospective study. Am J Obstet Gynecol. 1985 Feb 1;151(3):333–7.
19. Stirnemann J, Salomon LJ, Papageorghiou AT. INTERGROWTH-21st standards for Hadlock's estimation of fetal weight. Ultrasound Obstet Gynecol. 2020 Dec 1;56(6):946–8.
20. Papageorghiou AT, Ohuma EO, Altman DG, Todros T, Ismail LC, Lambert A, et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet. 2014 Sep 6;384(9946):869–79.
21. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J Stat Softw. 2011 Dec 12;45(3 SE-Articles):1–67.
22. Hafen R, Anderson C, Schloerke B. hbgd: Healthy birth, growth & development [Internet]. 2016 [cited 2021 Sep 23]. Available from: https://github.com/HBGDki/hbgd
23. Rubin DB. Multiple imputation for nonresponse in surveys. Vol. 81. John Wiley & Sons; 2004.
24. Lott A, Reiter JP. Wilson Confidence Intervals for Binomial Proportions With Multiple Imputation for Missing Data. Am Stat. 2020 Apr 2;74(2):109–15.
25. van Buuren S. Flexible Imputation of Missing Data. 2nd Editio. Boca Raton: Chapman and Hall/CRC; 2018. 444 p.
26. Moons KGM, Altman DG, Reitsma JB, Ioannidis JPA, Macaskill P, Steyerberg EW, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): Explanation and Elaboration. Ann Intern Med. 2015 Jan 6;162(1):W1–73.
27. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Med Res Methodol. 2009;9(1):57.
28. Heymans MW, van Buuren S, Knol DL, van Mechelen W, de Vet HCW. Variable selection under multiple imputation using the bootstrap in a prognostic study. BMC Med Res Methodol. 2007;7(1):33.
29. Heymans MW. psfmi: Prediction Model Pooling, Selection and Performance Evaluation Across Multiply Imputed Datasets [Internet]. 2021. Available from: https://mwheymans.github.io/psfmi/

30. Payne BA, Groen H, Ukah UV, Ansermino JM, Bhutta Z, Grobman W, et al. Development and internal validation of a multivariable model to predict perinatal death in pregnancy hypertension. Pregnancy Hypertens An Int J Women's Cardiovasc Heal. 2015;5(4):315–21.
31. Kayode GA, Grobbee DE, Amoakoh-Coleman M, Adeleke IT, Ansah E, de Groot JAH, et al. Predicting stillbirth in a low resource setting. BMC Pregnancy Childbirth. 2016;16(1):274.
32. Riley RD, Snell KIE, Ensor J, Burke DL, Harrell Jr FE, Moons KGM, et al. Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes. Stat Med. 2019 Mar 30;38(7):1276–96.
33. Riley RD, Ensor J, Snell KIE, Harrell FE, Martin GP, Reitsma JB, et al. Calculating the sample size required for developing a clinical prediction model. BMJ. 2020 Mar 18;368:m441.
34. Wanyonyi SZ, Orwa J, Ozelle H, Martinez J, Atsali E, Vinayak S, et al. Routine third-trimester ultrasound for the detection of small-for-gestational age in low-risk pregnancies (ROTTUS) study: a randomized controlled trial. Ultrasound Obstet Gynecol. 2021 Feb 22;
35. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: A prospective cohort study. Lancet. 2015;386(10008):2089–97.
36. Coutinho CM, Melchiorre K, Thilaganathan B. Stillbirth at term: Does size really matter? Int J Gynecol Obstet. 2020 Sep 1;150(3):299–305.
37. Vollgraff Heidweiller-Schreurs CA, van Osch IR, Heymans MW, Ganzevoort W, Schoonmade LJ, Bax CJ, et al. Cerebroplacental ratio in predicting adverse perinatal outcome: a meta-analysis of individual participant data. BJOG An Int J Obstet Gynaecol. 2021 Jan 1;128(2):226–35.
38. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol. 2018 Feb 1;218(2):S855–68.
39. Caradeux J, Martinez-Portilla RJ, Peguero A, Sotiriadis A, Figueras F. Diagnostic performance of third-trimester ultrasound for the prediction of late-onset fetal growth restriction: a systematic review and meta-analysis. Am J Obstet Gynecol. 2019 May 1;220(5):449-459.e19.
40. Conde-Agudelo A, Villar J, Kennedy SH, Papageorghiou AT. Predictive accuracy of cerebroplacental ratio for adverse perinatal and neurodevelopmental outcomes in suspected fetal growth restriction: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;52(4):430–41.
41. Stewart KA, Navarro SM, Kambala S, Tan G, Poondla R, Lederman S, et al. Trends in Ultrasound Use in Low and Middle Income Countries: A Systematic Review. Int J MCH AIDS. 2020;9(1):103–20.
42. Ali S, Byamugisha J, Kawooya MG, Kakibogo IM, Ainembabazi I, Biira EA, et al. Standardization and quality control of Doppler and fetal biometry ultrasound measurements in low-income setting. Ultrasound Obstet Gynecol. 2022 Aug 17;
43. Self A, Daher L, Schlussel M, Roberts N, Ioannou C, Papageorghiou AT. Second and third trimester estimation of gestational age using ultrasound or maternal symphysis-fundal height measurements: A systematic review. BJOG An Int J Obstet Gynaecol. 2022 Feb 14;

44. Sobhy S, Arroyo-Manzano D, Murugesu N, Karthikeyan G, Kumar V, Kaur I, et al. Maternal and perinatal mortality and complications associated with caesarean section in low-income and middle-income countries: a systematic review and meta-analysis. Lancet. 2019 May 11;393(10184):1973–82.
45. Oros D, Ruiz-Martinez S, Staines-Urias E, Conde-Agudelo A, Villar J, Fabre E, et al. Reference ranges for Doppler indices of umbilical and fetal middle cerebral arteries and cerebroplacental ratio: systematic review. Ultrasound Obstet Gynecol. 2019 Apr 1;53(4):454–64.

6

S1 Table: Overall maternal and pregnancy characteristics of the study cohort and the percentage of missing information

Characteristic	Overall (N= 995)	Missing (%)
Maternal height (cm), mean (SD)	157.1 (6.11)	0.0
Weight (kg), median (IQR)	60.0 (54.0 – 68.0)	0.0
Maternal BMI (kg/m^2), mean (SD)	24.6 (3.93)	0.0
Maternal age (years), median (IQR)	25.0 (22.0 – 30.0)	24.4
Nulliparous, yes, n (%)	188 (18.9)	24.4
Malaria, yes, n (%)	299 (30.1)	24.4
Urinary tract infection, yes, n (%)	113 (11.4)	24.4
Syphilis, yes, n (%)	52 (5.2)	24.4
HIV, positive, n (%)	69 (6.9)	24.5
Previous stillbirth, yes, n (%)	21 (2.1)	24.4
Chronic hypertension, yes, n (%)	9 (0.9)	24.4
Alcohol use in pregnancy, yes, n (%)	99 (9.9)	24.4
Smoking, yes, n (%)	5 (0.5)	27.2
Stillbirth, yes, n (%)	18 (1.8)	0.0
Neonatal death, yes, n (%)	13 (1.3)	0.0
NICU admission, yes, n (%)	89 (8.9)	0.0
APGAR score <7 at 5 minutes, yes, n (%)	26 (2.6)	53.0
EMCS for fetal distress, yes, n (%)	19 (1.9)	0.0
Respiratory distress syndrome, yes, n (%)	40 (4.0)	0.0
Composite adverse outcome, yes, n (%)	136 (13.7)	0.0
Birth weight, mean (SD)	3.18 (0.46)	13.8
Birth weight z-scores, mean (SD)	-0.28 (1.07)	13.8
Birth weight centiles, mean (SD)	41.66 (29.31)	13.8
Mode of birth		
Vaginal birth, n (%)	866 (87.0)	0.0
Cesarean birth, n (%)	129 (13.0)	
Place of birth		
Health unit, n (%)	885 (88.9)	0.0
Traditional birth attendant (TBA), n (%)	44 (4.4)	
Home, n (%)	58 (5.8)	
Way to hospital, n (%)	8 (0.8)	
Sex of baby, male, n (%)	482 (48.4)	0.0
GA at dating scan (weeks), median (IQR)	18.4 (15.7 – 21.0)	0.0

S1 Table: Overall maternal and pregnancy characteristics of the study cohort and the percentage of missing information

Characteristic	Overall (N= 995)	Missing (%)
GA at Doppler (weeks), mean (SD)	36.90 (1.02)	45.3
GA at birth (weeks), mean (SD)	39.80 (1.39)	0.0
GA at birth (weeks)		
Preterm, n (%)	41 (4.1)	0.0
Early term, n (%)	154 (15.5)	0.0
Full term, n (%)	613 (61.6)	0.0
Late term, n (%)	152 (15.3)	0.0
Postterm, n (%)	35 (3.5)	0.0
EFW (g), mean (SD)	2829.3 (374.7)	45.3
EFW z scores, mean (SD)	0.08 (0.94)	45.3
AC (cm), mean (SD)	32.19 (1.93)	45.3
AC z-scores, mean (SD)	0.04 (0.97)	45.3
AC percentiles, mean (SD)	51.57 (28.06)	45.3
UA PI, median (IQR)	0.82 (0.73 – 0.92)	46.1
UA PI z-scores, mean (SD)	-0.23 (1.04)	46.1
UA PI percentiles, mean (SD)	42.75 (28.78)	46.1
MCA PI, mean (SD)	1.66 (0.30)	47.4
CPR PI, median (IQR)	2.0 (1.70 – 2.32)	48.1
Right UtA PI, median (IQR)	0.70 (0.60 – 0.81)	55.8
Left UtA PI, median (IQR)	0.73 (0.61 – 0.88)	51.7
UtA PI, median (IQR)	0.73 (0.63 – 0.84)	59.5

*SD: standard deviation; IQR: interquartile range; BMI: body mass index; EMCS: Emergency cesarean section; EFW: estimated fetal weight; AC: abdominal circumference: UA: umbilical artery; MCA: middle cerebral artery; CPR: cerebroplacental ratio; UtA: uterine artery; UtA: mean uterine artery; GA: gestational age; preterm: <37 weeks; early term: 37-38 weeks; full term: 39-40 weeks; late term: 41 weeks; postterm: ≥42 weeks.

6

S2 Table: Multivariable prognostic model for estimating the risk of perinatal death from maternal characteristics alone in women undergoing routine antenatal care

Intercept and Predictors	β coefficient	Odds ratio (95% CI)	P value	β† Coefficient
Intercept	–7.67			–6.24
Body mass index	0.04	1.03 (0.95 – 1.13)	0.429	0.02
Syphilis, yes	0.82	2.28 (0.63 – 8.21)	0.206	0.56
Previous stillbirth,	1.83	6.23 (1.61 – 24.19)	0.008	1.24
Gestational age at birth				
Full-term	0.00	1.00 (reference)		0.00
Preterm	2.11	8.27 (2.62 – 26.02)	0.001	1.44
Early term	0.94	2.56 (1.00 – 6.57)	0.051	0.64
Late term	0.05	1.05 (0.29 – 3.85)	0.938	0.03
Postterm	1.61	4.98 (1.30 – 19.08)	0.019	1.09

*β: Regression coefficient; odds ratio after pooling estimates using Rubin's rule; N= 995; m= 100 imputed datasets; CI: confidence interval.

*β† Regression coefficient multiplied with a shrinkage factor (obtained from the bootstrapping procedure) of 0.68.

*Preterm: <37 weeks; early term: 37-38 weeks; full term: 39-40 weeks; late term: 41 weeks; postterm: ≥42 weeks.

*The probability of perinatal death can be calculated as: P (perinatal death) = 1/ (1 + exp (– (–6.2418 + 0.0238*body mass index + 0.5609*syphilis + 1.2450*previous stillbirth + 1.4362*preterm + 0.6385*early term + 0.0346*late term + 1.0916*postterm))).

S3 Table: Multivariable prognostic model for estimating the risk of stillbirth from maternal characteristics alone in women undergoing routine antenatal care

Intercept and Predictors	β coefficient	Odds ratio (95% CI)	P value	β† Coefficient
Intercept	–8.89			–5.93
Body mass index	0.06	1.06 (0.96 – 1.18)	0.251	0.03
Syphilis, yes	0.91	2.48 (0.56 – 10.97)	0.230	0.37
Previous stillbirth,	1.75	5.76 (1.14 – 29.13)	0.034	0.72
Gestational age at birth				
Full-term	0.00	1.00 (reference)		0.00
Preterm	1.68	5.41 (1.03 – 28.39)	0.045	0.69
Early term	0.73	2.08 (0.58 – 7.44)	0.258	0.30
Late term	0.57	1.77 (0.44 – 7.12)	0.417	0.24
Postterm	1.70	5.47 (1.06 – 28.20)	0.042	0.70

*β: Regression coefficient; odds ratio after pooling estimates using Rubin's rule; N= 995; m= 100 imputed datasets; CI: confidence interval.

*$\beta^{\dagger}$ Regression coefficient multiplied with a shrinkage factor (obtained from the bootstrapping procedure) of 0.60.

*Preterm: <37 weeks; early term: 37-38 weeks; full term: 39-40 weeks; late term: 41 weeks; postterm: ≥42 weeks.

*The probability of stillbirth can be calculated as: P (stillbirth) = 1/ (1 + exp (– (–5.9300 + 0.02513*body mass index + 0.3727*syphilis + 0.7182*previous stillbirth + 0.6922*preterm + 0.3009*early term + 0.2353*late term + 0.6970*postterm))).

S4 Table: Multivariable prognostic model for estimating the risk of stillbirth from maternal characteristics and MCA PI in women undergoing routine antenatal care

Intercept and Predictors	β coefficient	Odds ratio (95% CI)	P value	β† Coefficient
Intercept	–6.38			–4.90
Body mass index	0.05	1.05 (0.94 – 1.17)	0.376	0.02
Syphilis, yes	0.96	2.61 (0.56 – 12.08)	0.217	0.42
Previous stillbirth,	1.83	6.23 (1.13 – 34.53)	0.036	0.81
Gestational age at birth				
Full-term	0.00	1.00 (reference)		0.00
Preterm	1.79	5.98 (1.06 – 33.84)	0.042	0.79
Early term	0.78	2.19 (0.59 – 8.12)	0.239	0.35
Late term	0.63	1.87 (0.46 – 7.66)	0.383	0.28
Postterm	1.88	6.59 (1.21 – 35.87)	0.029	0.83
MCA PI spline 1	–1.45	0.24 (0.01 – 18.45)	0.513	–0.64
MCA PI spline 2	–1.35	0.26 (0.01 – 426.75)	0.720	–0.59

*β: Regression coefficient; OR: odds ratio after pooling estimates using Rubin's rule; N= 995; m= 100 imputed datasets;

*$\beta^{\dagger}$ Regression coefficient multiplied with a shrinkage factor (obtained from the bootstrapping procedure) of 0.44.

*MCA: middle cerebral artery. CI: confidence interval; preterm: <37 weeks; early term: 37-38 weeks; full term: 39-40 weeks; late term: 41 weeks; postterm: ≥42 weeks.

*The probability of stillbirth can be calculated as: P (stillbirth) = 1/ (1 + exp (– (–4.9041 + 0.0217*body mass index + 0.4228*syphilis + 0.8052*previous stillbirth + 0.7872*preterm + 0.3453*early term + 0.2759*late term + 0.8293*postterm – 0.6370*MCA PI spline 1 – 0.5931*MCA PI spline 2))).

S5 Table: Multivariable prognostic model for estimating the risk of stillbirth from maternal characteristics and CPR in women undergoing routine antenatal care

Intercept and Predictors	β coefficient	Odds ratio (95% CI)	P value	β† Coefficient
Intercept	–5.74			–4.5
Body mass index	0.07	1.07 (0.96 – 1.19)	0.238	0.03
Syphilis, yes	0.87	2.39 (0.51 – 11.19)	0.265	0.33
Previous stillbirth,	1.85	6.37 (1.18 – 34.27)	0.031	0.70
Gestational age at birth				
Full-term	0.00	1.00 (reference)		0.00
Preterm	1.71	5.53 (0.96 – 31.74)	0.055	0.65
Early term	0.79	2.19 (0.59 – 8.18)	0.242	0.30
Late term	0.63	1.87 (0.45 – 7.72)	0.385	0.24
Postterm	1.78	5.92 (1.08 – 32.38)	0.040	0.68
MCA PI spline 1	–1.93	0.15 (0.01 – 2.17)	0.162	0.73
MCA PI spline 2	1.32	3.74 (0.11 – 125.60)	0.459	0.50

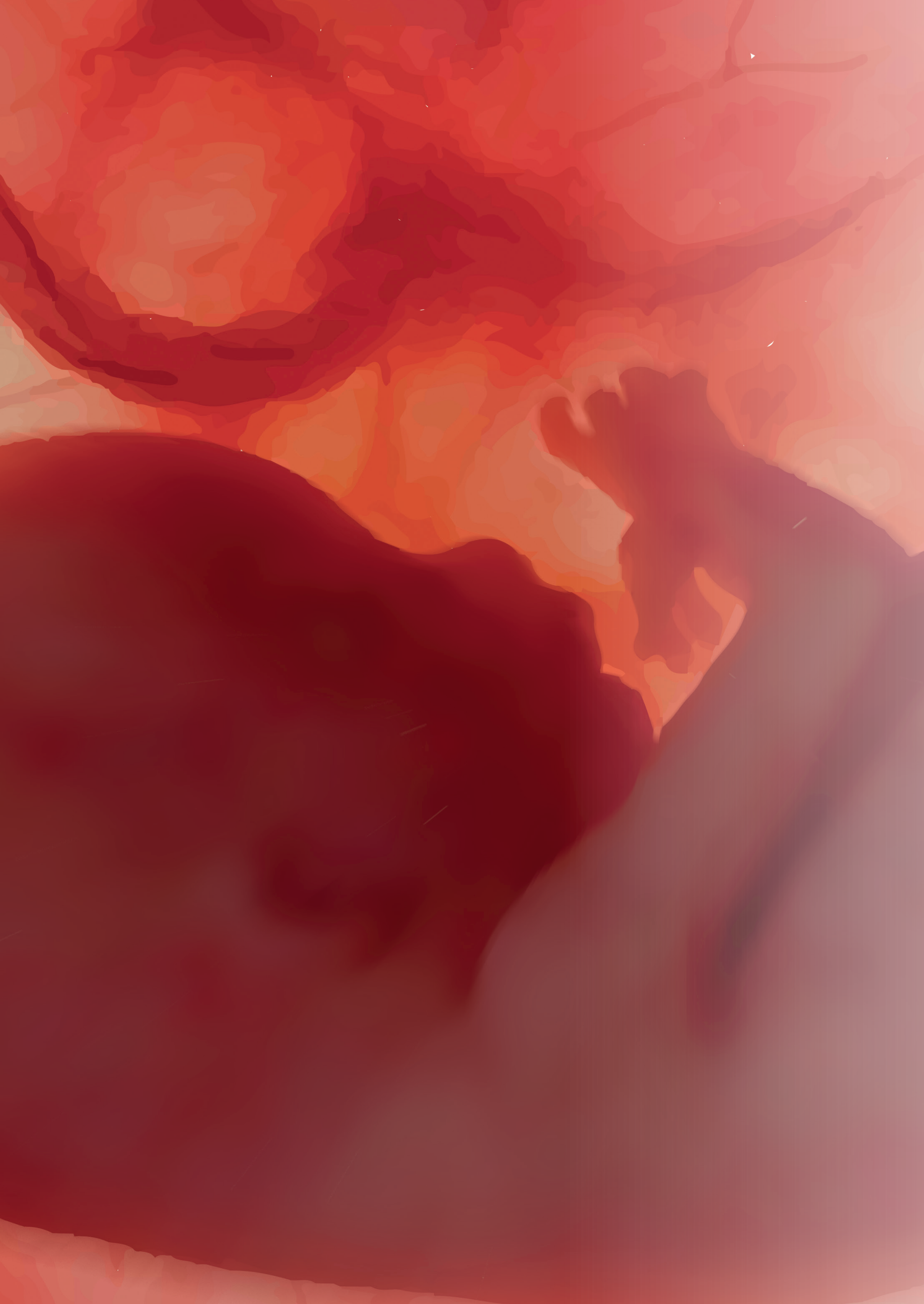
*β: Regression coefficient; odds ratio after pooling estimates using Rubin's rule; N= 995; m= 100 imputed datasets;

*β† Regression coefficient multiplied with a shrinkage factor (obtained from the bootstrapping procedure) of 0.38.

*CPR: cerebroplacental ratio; CI: confidence interval; preterm: <37 weeks; early term: 37-38 weeks; full term: 39-40 weeks; late term: 41 weeks; postterm: ≥42 weeks.

*The probability of stillbirth can be calculated as: P (stillbirth) = 1/ (1 + exp (– (–4.5382 + 0.0250*body mass index + 0.3323*syphilis + 0.7036*previous stillbirth + 0.6498*preterm + 0.2985*early term + 0.23848*late term + 0.6760*postterm – 0.7323*CPR spline 1 + 0.5022*CPR spline 2))).

6



Chapter 7

Discussion

The potential of advanced (Doppler) ultrasound technology to improve perinatal health in settings with high burden of stillbirth

According to the 2021 Lancet Commission on diagnostics, 47% of the global population has little to no access to diagnostics; a problem disproportionately affecting the poor, rural, and marginalised communities.[1] The commission further notes that diagnostics are central and fundamental to quality health care, and appropriate access is essential for equity and social justice.[1] Great strides have been reached in advancing obstetric diagnostic tools, ranging from new Doppler ultrasound modalities to artificial intelligence embedded systems.[2] However, the possible reasons for the lack of significant reductions in stillbirth, especially in low- and middle-income countries (LMICs), are unclear. The World Health Organization (WHO) is committed to improving ANC globally and recommends an investigation into the potential benefits of antenatal Doppler ultrasound.[3] In pregnancy, Doppler ultrasound plays a critical role in the diagnosis and guiding management decisions for several conditions such as fetal growth restriction (FGR), congenital anomalies, and placental pathologies, among others. In fact, it has become an indispensable clinical tool for screening high-risk pregnancies to combat perinatal death and stillbirth in high income countries (HICs).[4] In this thesis, we report and discuss findings of our recently concluded studies on Doppler ultrasound in LMICs between October 2018 and December 2020 (before the onset and during the COVID-19 pandemic). We then provide practical reflections for researchers, policymakers, and stakeholders considering embedding advanced (Doppler) ultrasound services into routine healthcare for the benefit of women in underserved regions.

First, we conducted a systematic review which revealed scarce robust Doppler ultrasound studies in LMICs,[5] implying the lack of local evidence to inform Doppler ultrasound practice guidelines and policies in such settings. Obstetric guidelines help healthcare providers to put women on the appropriate care pathway. Based on our review results, it is not surprising that many LMICs, including Uganda lack local guidelines for screening and management of women with suspected FGR with/without abnormal Dopplers. Nearly all current guidance is based on evidence from HICs,[3,6] which are not directly transferable to LMICs given differences in population risk profiles and contextual variations. For instance, the risk of stillbirth in sub-Saharan African settings is eight times higher than in HICs.[7,8] It is highly plausible that Doppler ultrasound may have significant impact on perinatal outcomes when embedded into low-resource setting health systems with context-tailored evidence informed clinical guidelines. Thus, more high-quality primary studies are needed. As a meta-analysis was impossible in our review due to large heterogeneity across studies, an updated systematic review or aggregation of data for individual patient data (IPD) meta-analysis (the strongest evidence level) will be required to inform the guidelines. There are just a few IPD meta-analyses for obstetric interventions,[9,10] with no attempts from low-resource settings.

Second, we then deployed Doppler ultrasound services in a remote setting in western Uganda and investigated the feasibility of training local healthcare providers to offer the services, assessing the impact of our training exercises using freely available objective scoring tools.[11–13] Ultrasound measurements obtained in our study were of high quality, with over 85% of the Doppler images and 90% of the fetal biometry images scored as acceptable, comparable to other findings from HICs.[14,15] This study found it feasible to train ultrasound practitioners in under-privileged regions to perform Doppler scans with consistency, and it is the first of its kind to report the use of an objective scoring system for quality assessment of Doppler and fetal biometry ultrasound measurements in a low-resource setting. Standardisation and quality control systems are important to ensure that the ultrasound measurements are accurate and reproducible, as significant systematic errors can lead to wrong interpretations, interventions and harmful effects on the pregnant women.[16] In addition, erroneous research findings can lead to misleading public health policies and/or practice guidelines. We believe our findings are transferable to similar low-resource settings and recommend that capacity building initiatives for the ultrasound practitioners must be tailored to the context, focusing on healthcare providers on the frontline (training both medical and non-medical doctors) for the ultrasound technology to have a realistic impact on perinatal health in low-resource settings. Important areas such as the impact of regular audits and in-service re-training on the quality of ultrasound scans should be further studied.

Third, while we have ably demonstrated the feasibilities of integrating advanced (Doppler) ultrasound technologies into routine ANC of LMICs, we must highlight the potential hindrances and facilitators for its success. To obtain such insights, we designed and executed an ancillary qualitative study exploring stakeholder perspectives and experiences using Doppler ultrasound.[17] Some studies had previously reported stakeholder views, but regarding the use of basic ultrasound technology.[18–21] The potential dilemmas in implementing more advanced (novel) ultrasound technologies in low-resource settings were unknown. On a positive note, we found that spousal involvement may promote acceptance and uptake of ultrasound services, a strategy recently endorsed by key stakeholders to promote attendance and utilization of ANC interventions.[22,23] Some of the challenges included: Doppler ultrasound required a high level of training for sonographers, and healthcare providers did not know how to interpret and use the measurements to manage mothers.[17] As the clinical applicability of Doppler ultrasound services will depend on the abilities of local healthcare systems to interpret and respond to the results of the Doppler examinations, it is essential that proper guidance is included in local practice guidelines and to extend the Doppler ultrasound training initiatives beyond the ultrasonographers.

Over 85% of the women in our cohort begun their first ANC visit after 14 weeks of gestation,[24] a common observation in many LMICs.[25] For women presenting late for their first ANC contact, optimal pregnancy dating is challenging and the risk of perinatal morbidity and mortality due to iatrogenic preterm delivery (provider-initiated preterm birth) is high. Although we used late dating methods (HC+FL at <24 weeks of gestation) in our study,[26,27] encouraging all women to initiate ANC in the first trimester will have more tangible benefits. Further, women were afraid that ultrasound procedures would harm them or their fetuses. These thoughts are mostly attributed to common myths, leave alone the lack of ultrasound services within their reach.[17] To ensure good health systems performance to allow embedding

Doppler ultrasound into routine healthcare in low-resource settings, we must establish health services closer to the community, equip and stabilize power supply in the health facilities, and educate the public about critical health procedures to break the associated myths and misconceptions. The views of key stakeholders outside the scope of this study, such as religious leaders, should be addressed in future research.

Fourth, the primary aim of our project was to establish the predictive value of Doppler ultrasound for adverse perinatal outcomes. Using prospectively collected data, we first modelled the independent relationship between Doppler ultrasound and adverse perinatal outcomes.[24] Fetuses with abnormal middle cerebral artery pulsatility index (MCA PI) or cerebroplacental ratio (CPR) in the late third trimester were at increased risk of stillbirth (OR 4.82, 95% CI 1.09–21.30) and perinatal complications, re-affirming findings from HICs.[28,29] These studies found CPR highly predictive of perinatal death and early childhood delayed neurodevelopment.[28,29] We found a higher rate of adverse perinatal outcomes in SGA neonates than in non-SGA neonates, as in previous HICs studies.[30–32] Our findings are extremely important for LMICs where evidence on the clinical role of antenatal Doppler is acutely lacking, but shouldering the highest burden of stillbirths.[3,5,33,34] It implies that Doppler ultrasound could help identify fetuses at high risk of stillbirth who require close clinical attention. These findings are akin to current guidance from HICs indicating that Doppler ultrasound tests could be an adjunct to differentiating constitutionally small babies from those deprived in utero.[35–38] Whereas the role of Doppler in a general obstetric population is not yet clearly defined to date, its use in high-risk women is associated with lower risk of perinatal mortality and obstetric interventions.[4] The next leap is to develop a clinical decision guide about what to do with abnormal Doppler (ultrasound) findings, and for counselling patients around the risk of stillbirth and the need for close follow-up management in Uganda and similar low-resource settings. Abnormal Doppler ultrasound results is a useful tool to identify a fetus at risk, but the risk of the fetus in the subsequent days is unknown. Potential additional diagnostics may be required. Thus, further studies investigating follow-up frequency and management of pregnant women with abnormal

Doppler ultrasound findings are warranted. The only available intervention (expedited birth by induction of labour or caesarean section) for deprived fetuses reduces the risk of stillbirth but it is associated with grave risks for the mothers and neonates.[39,40] It must be acknowledged that a large part of our study was implemented in the COVID-19 pandemic times. Enrolment and follow-up of participants was heavily impacted by lockdown measures, affecting the study sample and completeness of our data. However, this remains one of the largest and robust Doppler studies from a low-resource setting to date. Additional strengths are that Doppler results were blinded from the attending clinicians, preventing them from using the results to manage patients and alter their prognosis, and multiple imputation was used to handle missing information.

Fifth, we then developed and internally validated a prognostic model (using maternal and Doppler factors) to quantify the risk of stillbirth and perinatal death in a general obstetric population in the late third-trimester. Even though our model had a significant performance, its predictive value was below clinically acceptable thresholds, denoting that those models incorporating only maternal and Doppler parameters are unlikely to achieve a diagnostic yield sufficient enough to accurately detect compromised fetuses in a general obstetric population. We anticipated a higher predictive value for perinatal outcomes in such a setting with a high number of stillbirths, but our model performance may have been limited by the sample, number of events and variables used for its development. Novel ultrasound technologies like micro-vascular flow might provide additional clinical information beyond that obtained from the conventional Doppler ultrasound scans.[2] However, their clinical usefulness, reliability and safety warrant further investigation. In studies which evaluated prediction models for stillbirth in HICs, models including biochemical markers had the highest predictive performance.[34] We, therefore, recommend to include such markers, ideally those broadly available in LMICs, in future studies developing and/or validating prediction models. A precise model is required to minimise unnecessary potentially harmful interventions to rather very healthy pregnancies.

Finally, the stillbirth rates in sub-Saharan African settings remain substantially high.[7,8] Given the current trends, considerable efforts are required to achieve the Every Newborn Action Plan target of 12 stillbirths or fewer per 1,000 total births by 2030 in Uganda and similar high burden settings.[41] Interventions to reduce their occurrence must be prioritised. Numerous efficacious obstetric interventions and essential diagnostic tools like Doppler ultrasound technologies exist, but their potential in low-resource settings is largely untapped.[3] We further recommend that stakeholders considering embedding promising obstetric innovations in LMICs should not focus solely on breakthroughs, but also on follow-throughs to analyse the barriers and facilitators of implementation. The penetration, adoption and sustainability of the interventions should be questioned, investigated and necessary actions taken accordingly to reduce the evidence-practice gaps,[42] for us to realise significant and widespread impact of the innovations on perinatal health in LMICs.

Conclusion

We have demonstrated that Doppler ultrasound has great clinical potential and is feasible to embed into routine practice in low-resource settings. Doppler tests could help identify fetuses with elevated risk of stillbirth who require close monitoring and clinical attention. However, there is still dire need for rigorously conducted Doppler studies in LMICs to inform practice and clinical guidelines. Doppler services must be embedded into local healthcare systems with a clinical decision guide about what to do with abnormal findings, and clinicians must be adequately trained in using the results to manage patients to avoid harmful interventions. Doppler ultrasound services must be made more accessible to the marginalized and most affected populations if we are to realize the precipitous drop in the global burden of stillbirths. Spousal involvement could promote the use of ultrasound services. Further studies investigating follow-up frequency and management of women with abnormal Doppler ultrasound findings are warranted.

Key messages

- There is limited robust evidence to guide how antenatal Doppler ultrasound should be used in low-resource settings
- Advanced (Doppler) ultrasound services are lacking in sub-Saharan African settings but it is feasible to embed them into local healthcare systems and train healthcare providers to reliably offer these services
- Abnormal fetal cerebral Doppler is a strong indicator for intrauterine fetal compromise and elevated risk of stillbirth in late gestation
- Local clinical guidance about how to perform, interpret and use abnormal Doppler findings to manage pregnant women is required
- To date, there is no prognostic model to accurately predict with high precision fetuses at risk of perinatal death and stillbirth in a general obstetric population in LMICs

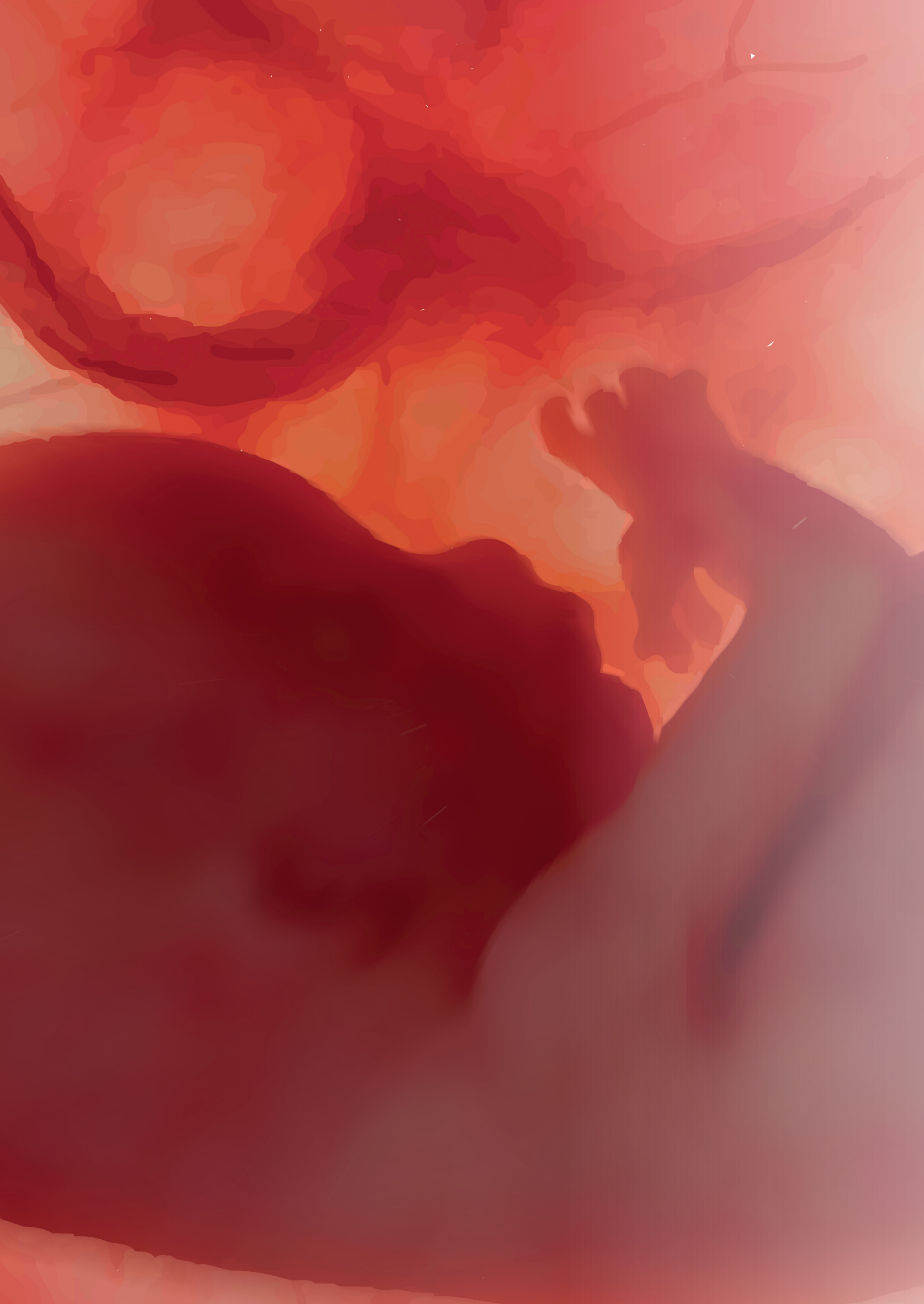
References

1. Fleming KA, Horton S, Wilson ML, Atun R, DeStigter K, Flanigan J, et al. The Lancet Commission on diagnostics: transforming access to diagnostics. Lancet. 2021 Nov 27;398(10315):1997–2050.
2. Drukker L, Droste R, Ioannou C, Impey L, Noble JA, Papageorghiou AT. Function and Safety of SlowflowHD Ultrasound Doppler in Obstetrics. Ultrasound Med Biol. 2022 Jun 1;48(6):1157–62.
3. WHO. WHO recommendations on antenatal care for a positive pregnancy experience [Internet]. World Health Organization; 2016. Available from: https://www.who.int/publications/i/item/9789241549912
4. Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev. 2017/06/15. 2017;2017(6):CD007529.
5. Ali S, Heuving S, Kawooya MG, Byamugisha J, Grobbee DE, Papageorghiou AT, et al. Prognostic accuracy of antenatal Doppler ultrasound for adverse perinatal outcomes in low-income and middle-income countries: a systematic review. BMJ Open. 2021 Dec 1;11(12):e049799.
6. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol. 2018 Feb 1;218(2):S855–68.
7. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). A Neglected Tragedy: The global burden of stillbirths [Internet]. New York; 2020. Available from: https://www.who.int/publications/m/item/a-neglected-tragedy-the-global-burden-of-stillbirths
8. Hug L, You D, Blencowe H, Mishra A, Wang Z, Fix MJ, et al. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. Lancet. 2021 Aug 28;398(10302):772–85.
9. Vollgraff Heidweiller-Schreurs CA, van Osch IR, Heymans MW, Ganzevoort W, Schoonmade LJ, Bax CJ, et al. Cerebroplacental ratio in predicting adverse perinatal outcome: a meta-analysis of individual participant data. BJOG An Int J Obstet Gynaecol. 2021 Jan 1;128(2):226–35.
10. Allotey J, Whittle R, Snell KIE, Smuk M, Townsend R, von Dadelszen P, et al. External validation of prognostic models to predict stillbirth using International Prediction of Pregnancy Complications (IPPIC) Network database: individual participant data meta-analysis. Ultrasound Obstet Gynecol. 2022 Feb 1;59(2):209–19.
11. Salomon LJ, Winer N, Bernard JP, Ville Y. A score-based method for quality control of fetal images at routine second-trimester ultrasound examination. Prenat Diagn. 2008 Sep 1;28(9):822–7.
12. Molloholli M, Napolitano R, Ohuma EO, Ash S, Wanyonyi SZ, Cavallaro A, et al. Image-scoring system for umbilical and uterine artery pulsed-wave Doppler ultrasound measurement. Ultrasound Obstet Gynecol. 2019 Feb 1;53(2):251–5.
13. Ruiz-Martinez S, Volpe G, Vannuccini S, Cavallaro A, Impey L, Ioannou C. An objective scoring method to evaluate image quality of middle cerebral artery Doppler. J Matern Neonatal Med. 2020 Feb 1;33(3):421–6.

14. Rial-Crestelo M, Morales-Roselló J, Hernández-Andrade E, Prefumo F, Oros D, Caffici D, et al. Quality assessment of fetal middle cerebral and umbilical artery Doppler images using an objective scale within an international randomized controlled trial. Ultrasound Obstet Gynecol. 2020 Aug 1;56(2):182–6.
15. Cavallaro A, Ash ST, Napolitano R, Wanyonyi S, Ohuma EO, Molloholli M, et al. Quality control of ultrasound for fetal biometry: results from the INTERGROWTH-21st Project. Ultrasound Obstet Gynecol. 2018 Sep 1;52(3):332–9.
16. Rolnik DL, da Silva Costa F, Sahota D, Hyett J, McLennan A. Quality assessment of uterine artery Doppler measurement in first-trimester combined screening for pre-eclampsia. Ultrasound Obstet Gynecol. 2019 Feb 1;53(2):245–50.
17. Ali S, Kabajaasi O, Kawooya MG, Byamugisha J, Zakus D, Papageorghiou AT, et al. Antenatal Doppler ultrasound implementation in a rural sub-Saharan African setting: exploring the perspectives of women and healthcare providers. Reprod Health. 2021;18(1):199.
18. Rijken MJ, Gilder ME, Thwin MM, Kajeechewa HML, Wiladphaingern J, Lwin KM, et al. Refugee and migrant women's views of antenatal ultrasound on the thai burmese border: A mixed methods study. PLoS One. 2012/04/13. 2012;7(4):e34018–e34018.
19. Shah S, Bellows BA, Adedipe AA, Totten JE, Backlund BH, Sajed D. Perceived barriers in the use of ultrasound in developing countries. Crit Ultrasound J. 2015;7(1):11.
20. Swanson D, Lokangaka A, Bauserman M, Swanson J, Nathan RO, Tshefu A, et al. Challenges of implementing antenatal ultrasound screening in a rural study site: A case study from the democratic republic of the congo. Glob Heal Sci Pract. 2017;5(2):315–24.
21. Kim ET, Singh K, Moran A, Armbruster D, Kozuki N. Obstetric ultrasound use in low and middle income countries: A narrative review. Reprod Health. 2018;15(1):129.
22. Davis J, Vyankandondera J, Luchters S, Simon D, Holmes W. Male involvement in reproductive, maternal and child health: A qualitative study of policymaker and practitioner perspectives in the Pacific. Reprod Health. 2016;13(1):81.
23. WHO. WHO recommendations on health promotion interventions for maternal and newborn health [Internet]. Geneva, Switzerland: World Health Organization; 2015. Available from: https://apps.who.int/iris/bitstream/handle/10665/172427/9789241508742_report_eng.pdf?sequence=1%0Awww.who.int
24. Ali S, Kawooya MG, Byamugisha J, Kakibogo IM, Biira EA, Kagimu AN, et al. Middle cerebral arterial flow redistribution is an indicator for intrauterine fetal compromise in late pregnancy in low-resource settings: a prospective cohort study. BJOG An Int J Obstet Gynaecol. 2022 Feb 4;129:1712– 1720.
25. Kaswa R, Rupesinghe GFD, Longo-Mbenza B. Exploring the pregnant women's perspective of late booking of antenatal care services at Mbekweni Health Centre in Eastern Cape, South Africa. African J Prim Heal Care & Fam Med Vol 10, No 1 (2018)DO - 104102/phcfm.v10i11300. 2018 Jul 2;
26. Papageorghiou AT, Kemp B, Stones W, Ohuma EO, Kennedy SH, Purwar M, et al. Ultrasound-based gestational-age estimation in late pregnancy. Ultrasound Obstet Gynecol. 2016 Dec 1;48(6):719–26.
27. Self A, Daher L, Schlussel M, Roberts N, Ioannou C, Papageorghiou AT. Second and third trimester estimation of gestational age using ultrasound or maternal symphysis-fundal height measurements: A systematic review. BJOG An Int J Obstet Gynaecol. 2022 Feb 14;

28. Conde-Agudelo A, Villar J, Kennedy SH, Papageorghiou AT. Predictive accuracy of cerebroplacental ratio for adverse perinatal and neurodevelopmental outcomes in suspected fetal growth restriction: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;52(4):430–41.
29. Monteith C, Flood K, Pinnamaneni R, Levine TA, Alderdice FA, Unterscheider J, et al. An abnormal cerebroplacental ratio (CPR) is predictive of early childhood delayed neurodevelopment in the setting of fetal growth restriction. Am J Obstet Gynecol. 2019;221(3).
30. Lee ACC, Kozuki N, Cousens S, Stevens GA, Blencowe H, Silveira MF, et al. Estimates of burden and consequences of infants born small for gestational age in low and middle income countries with INTERGROWTH-21st standard: analysis of CHERG datasets. BMJ. 2017 Aug 17;358:j3677.
31. Pilliod RA, Cheng YW, Snowden JM, Doss AE, Caughey AB. The risk of intrauterine fetal death in the small-for-gestational-age fetus. Am J Obstet Gynecol. 2012 Oct 1;207(4):318.e1-318.e6.
32. Madden J V, Flatley CJ, Kumar S. Term small-for-gestational-age infants from low-risk women are at significantly greater risk of adverse neonatal outcomes. Am J Obstet Gynecol. 2018 May 1;218(5):525.e1-525.e9.
33. Heestermans T, Payne B, Kayode GA, Amoakoh-Coleman M, Schuit E, Rijken MJ, et al. Prognostic models for adverse pregnancy outcomes in low-income and middle-income countries: a systematic review. BMJ Glob Heal. 2019 Oct 1;4(5):e001759.
34. Townsend R, Manji A, Allotey J, Heazell AEP, Jorgensen L, Magee LA, et al. Can risk prediction models help us individualise stillbirth prevention? A systematic review and critical appraisal of published risk models. BJOG An Int J Obstet Gynaecol. 2021 Jan 1;128(2):214–24.
35. Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, et al. Optimizing the definition of intrauterine growth restriction: The multicenter prospective PORTO Study. Am J Obstet Gynecol. 2013;208(4).
36. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48(3):333–9.
37. Lees CC, Stampalija T, Baschat A, da Silva Costa F, Ferrazzi E, Figueras F, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol. 2020;56(2):298–312.
38. Martins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction: (Replaces Clinical Guideline Number 3, April 2012). Am J Obstet Gynecol. 2020 Oct 1;223(4):B2–17.
39. Sobhy S, Arroyo-Manzano D, Murugesu N, Karthikeyan G, Kumar V, Kaur I, et al. Maternal and perinatal mortality and complications associated with caesarean section in low-income and middle-income countries: a systematic review and meta-analysis. Lancet. 2019 May 11;393(10184):1973–82.
40. GRIT Study Group. A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. BJOG An Int J Obstet Gynaecol. 2003 Jan 1;110(1):27–32.

41. World Health Organization and United Nations Children's Fund. Every Newborn: An action plan to end preventable deaths [Internet]. Geneva; 2014. Available from: https://www.healthynewbornnetwork.org/hnn-content/uploads/Every_Newborn_Action_Plan-ENGLISH_updated_July2014.pdf
42. Hamm RF, Iriye BK, Srinivas SK. Implementation Science is Imperative to the Optimization of Obstetric Care. Am J Perinatol. 2021;38(7).



Chapter 8

Summary

While significant reductions in stillbirth rates have been registered in high- income countries, particularly in western Europe, in the past two decades, the stillbirth numbers are instead increasing in sub-Saharan Africa. There have been advances in diagnostic technologies, including Doppler ultrasound, whose clinical potential in obstetric field is yet to be exploited in low-resource settings.

Chapter 1 provides the general background for the thesis, providing an overview of the global burden and trends of stillbirths. While most stillbirths result from preventable causes, the possible reasons behind the lack of their substantial drop remain unclear. We highlight the potential of Doppler ultrasound to improve perinatal outcomes.

Part 1 of the thesis examines the current evidence base on the diagnostic value of Doppler ultrasound in low- and middle- income countries (LMICs).

In **Chapter 2**, we reviewed available literature on the prognostic accuracy of Doppler ultrasound for adverse perinatal outcomes in LMICs. We identified 2825 records, and 30 studies (including 4977 women) from Africa (40.0%, n=12), Asia (56.7%, n=17) and South America (3.3%, n=01) were included. Most studies were of suboptimal quality. Evidence to guide how Doppler ultrasound should be used in LMICs was lacking. We recommend well-designed primary studies, and standardisation of practice and definitions of adverse perinatal outcomes across settings as per the International Classification of Diseases-10 Perinatal Mortality.

Part 2 of the thesis presents our experience and lessons for key stakeholders considering deploying Doppler ultrasound services in remote regions.

In **Chapter 3**, we aimed to determine the quality of fetal biometry and pulse-wave Doppler ultrasound measurements in our study. The quality scores of our ultrasound measurements were high, with over 84.8% of the pulse-wave Doppler images and 88.0% of the biometry images scored as acceptable. The inter-rater agreement was very good for Doppler and biometry images, with adjusted Kappa coefficient of up to 0.94 (95% CI, 0.87–0.99) for the umbilical artery and 0.94 (95% CI, 0.87–0.98) for the HC measurements. Training local healthcare providers to perform Doppler ultrasound and implementing of quality control systems in our clinical and research settings was feasible.

In **Chapter 4**, we explored the views of women and healthcare providers regarding the use of advanced ultrasound technology in pregnancy. We found that spousal involvement may promote acceptance and use of ultrasound services. However, the health workers did not have adequate knowledge about Doppler technology and using it for the benefit of mothers and the mothers feared that ultrasound procedures might harm them or their unborn babies.

In **Part 3**, the predictive performance of Doppler ultrasound for adverse perinatal outcomes is presented.

Chapter 5 evaluates the prevalence of abnormal Doppler ultrasound and the association with adverse perinatal outcomes. Low cerebroplacental ratio (CPR) was strongly associated with stillbirth (OR 4.82, 95% CI 1.09–21.30). CPR and middle cerebral artery (MCA) PI below the fifth percentile were independently associated with a composite perinatal outcome (defined as the occurrence of one or more of the following: stillbirths (intrauterine fetal death after 28 weeks of gestation, neonatal death within 28 days of the postnatal period, admission to neonatal intensive care unit (NICU) for >24 hours, Apgar score of <7 at 5 minutes, emergency caesarean birth for fetal distress (based on abnormal fetal heart rate monitoring) and respiratory distress syndrome (RDS)); the association with MCA PI was stronger in small-for-gestational-age neonates (OR 3.75, 95% CI 1.18–11.88). Fetuses with abnormal MCA PI or CPR near-term were at increased risk of stillbirth and perinatal complications.

In **Chapter 6** we develop and internally validate a multivariable prediction model to estimate the risk of perinatal death and stillbirth in women near-term in Uganda. In a model combining maternal characteristics with MCA

PI or CPR, the AUCs for predicting perinatal death were 0.78 (95% CI: 0.67 – 0.87) and 0.78 (95% CI: 0.65 – 0.87), respectively, in the development set. The bootstrap corrected AUC was 0.71, with a slope of 0.70. The predictive performance of our model was only moderate and below clinically relevant threshold. Its performance could be enhanced by addition of other important clinical tests like biomarkers and maternal cardiac function indicators.

Finally, **Chapter 7** comprehensively discusses, based on what we have learnt from the current study and beyond, the potential for Doppler ultrasound to improve the quality of ANC and perinatal health in settings with high burden of stillbirths.

Samenvatting

Terwijl het aantal doodgeboren kinderen de afgelopen twee decennia aanzienlijk is gedaald in rijke landen, met name in West-Europa, neemt dit aantal in Afrikaanse landen ten zuiden van de Sahara juist toe. Hoewel er vooruitgang is geboekt in diagnostisch technologische mogelijkheden, waaronder Doppler echografie, moet de klinische toepassing van doppler echografie in lage-inkomenslanden op verloskundig gebied nog worden onderzocht.

Hoofdstuk 1 vormt de algemene achtergrond van het proefschrift en geeft een overzicht van de omvang en trends in het aantal doodgeboren kinderen wereldwijd. Hoewel de meeste doodgeboorten te voorkomen zijn, blijft het aantal hoog en waarom een substantiële daling uitblijft, is onduidelijk. In dit proefschrift belichten we het potentieel van Doppler echografie om perinatale uitkomsten te verbeteren.
In deel 1 van het proefschrift onderzoeken we de huidige medische kennis over de diagnostische waarde van Doppler echografie in lage- en middeninkomenslanden (LMICs).

In hoofdstuk 2 hebben we de beschikbare literatuur over de prognostische nauwkeurigheid van Doppler echografie voor ongunstige perinatale uitkomsten in LMICs beoordeeld. We identificeerden 2825 manuscripten, en 30 studies (met daarin 4977 vrouwen) uit Afrika (40,0%, n=12), Azië (56,7%, n=17) en Zuid- Amerika (3,3%, n=01) werden geïncludeerd. De meeste studies waren van suboptimale kwaliteit. Bewijsmateriaal om aan te geven hoe Doppler echografie moet worden gebruikt in LMICs ontbrak. Wij suggereren dat goed opgezette primaire studies nodig zijn, waarbij de studiemethodes zoveel mogelijk gestandaardiseerd zijn en perinatale uitkomsten worden gedefinieerd volgens de International Classification of Diseases-10 Perinatal Mortality.

In deel 2 van het proefschrift presenteren we onze ervaringen en lessen voor alle stakeholders die overwegen Doppler echografie in te zetten in lage inkomens landen of afgelegen gebieden.

In hoofdstuk 3 hebben we de kwaliteit van foetale biometrie en Doppler echografie metingen in onze studie samengevat. De kwaliteitsscores van onze ultrasound metingen waren hoog, waarbij meer dan 84.8% van de Doppler beelden en 88.0% van de biometrie beelden als acceptabel werden gescoord. De overeenstemming tussen beoordelaars was zeer goed voor Doppler- en biometriebeelden, met aangepaste Kappa waarde van maximaal 0,94 (95% CI, 0,87-0,99) voor de foetale navelstrengslagader en 0,94 (95% CI, 0,87-0,98) voor de foetale hoofdomtrek (HC)-metingen. Het trainen van lokale zorgverleners in het uitvoeren van Doppler echografie, en het implementeren van kwaliteitscontrole systemen in onze klinische en onderzoeks-omgeving was haalbaar in Uganda.

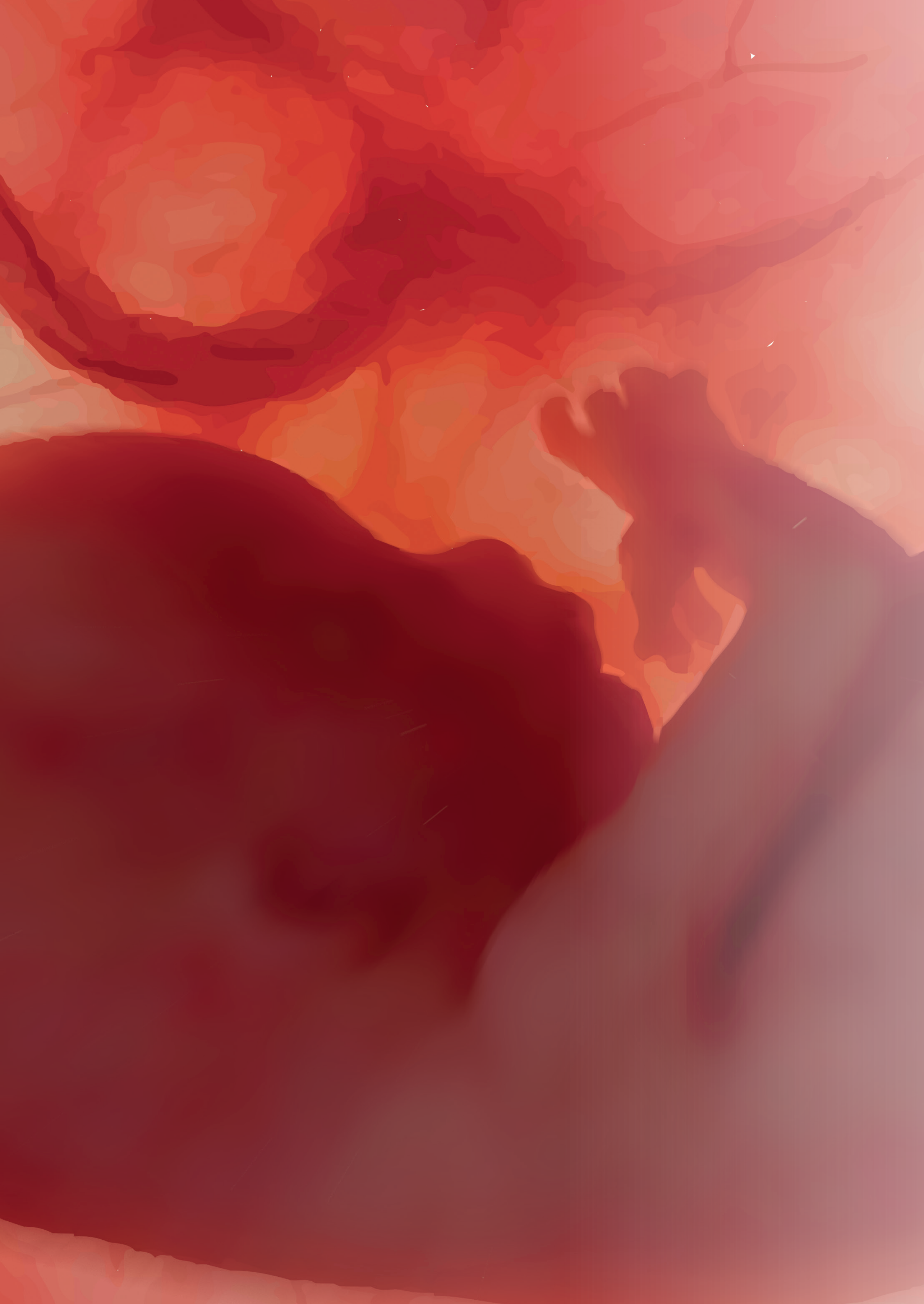
In hoofdstuk 4 onderzochten we de mening van vrouwen en zorgverleners over het gebruik van geavanceerde echografie technologie tijdens de zwangerschap. We vonden dat het betrekken van de partner bij de voorlichting de acceptatie en het gebruik van echografie in de zwangerschap kan bevorderen. De gezondheidswerkers hadden onvoldoende kennis over Doppler technologie en het mogelijkheden van echografie ten behoeve van de zwangere vrouwen. De moeders vreesden dat echoscopische procedures henzelf of hun ongeboren baby's zouden kunnen schaden.

In deel 3 wordt de voorspellende waarde van Doppler echografie voor ongunstige perinatale uitkomsten gepresenteerd.

In hoofdstuk 5 evalueren we de prevalentie van abnormale Doppler echografie en de associatie met ongunstige perinatale uitkomsten. Lage cerebroplacentale ratio (CPR) was sterk geassocieerd met doodgeboorte (OR 4,82, 95% CI 1,09-21,30). CPR en pulsatility index (PI) van de middelste cerebrale slagader (MCA) onder het vijfde percentiel waren onafhankelijk geassocieerd met de samengestelde perinatale uitkomst; de associatie met PI van de MCA was sterker bij pasgeborenen met een kortere zwangerschapsduur (OR 3,75, 95% CI 1,18-11,88). Foetussen met een herverdeling van de cerebrale bloedstroom hadden een verhoogd risico op doodgeboorte.

In hoofdstuk 6 bespreken we ons multivariabel voorspelmodel, en doen we een interne validatie om het risico op perinatale sterfte en doodgeboorte te schatten bij zwangere vrouwen die a-terme zijn. In een model dat maternale kenmerken combineert met MCA PI of CPR, waren de AUCs voor het voorspellen van perinataal overlijden respectievelijk 0.78 (95% CI: 0.67 - 0.87) en 0.78 (95% CI: 0.65 - 0.87), in de database. De bootstrap gecorrigeerde AUC was 0,71, met een helling van 0,70. De voorspellende waarde van ons model was slechts matig en onder de klinisch relevante drempelwaarde. De prestatie van het voorspelmodel zou verbeterd kunnen worden door toevoeging van biomarkers en hartfunctie-indicatoren van de moeder.

Tenslotte worden in hoofdstuk 7 alle bevindingen uitgebreid besproken. Op basis van wat we hebben geleerd van de huidige studies worden aanbevelingen gedaan om met de mogelijkheden die Doppler echografie biedt de kwaliteit van zwangerschapszorg en perinatale gezondheid te verbeteren in landen met een hoog aantal doodgeboortes.



Chapter 9

Appendices

Acknowledgements

With bent knees, I thank God for the blessings, grace, wisdom, and courage to commit to and complete this PhD within the planned academic calendar. Glory to Him, always.

I am extremely grateful to my dear family for the love, prayers, sacrifices, and unwavering support they have extended to me during this PhD research journey. I am forever indebted to you! I dedicate this work to my lovely wife Asiimire Caroline, and my two children Shawn Ali and Clarisse Asher Lalam.

Prof. Dr. Diederick E. Grobbee; thank you for endorsing my application for the Global Health Support Program to cover my PhD studies at the UMC Utrecht, and for providing methodological guidance in this project. I have learnt a lot from you during my PhD tenure and look forward to a long-lasting mutually beneficial relationship.

Prof. Dr. Michael G. Kawooya; I am grateful to have had such a lovely and supportive mentor as you. Thank you for introducing me to new research collaborations and networks. Your experience as a professor of radiology, educationist, and researcher from a low-resource setting immensely contributed to my success on this PhD journey. In my indigenous dialect, we say "apwoyo atek (thank you very much)"

Prof. Kerstin Klipstein-Grobusch was my first contact with UMC Utrecht. I thank you for having faith in and picking an interest in me when I wrote an email requesting you to become my PhD promoter. Thank you for involving me with the rest of the team at UMC Utrecht. As my daily supervisor, you committed your all to ensuring that I kept on track with the PhD milestones and deliverables, allowing me to eventually complete the program on time.

Dr. Marcus J. Rijken; besides being my daily supervisor, you have been a great friend. At the start of my PhD research journey, it seemed an impossible mission to set up this study in a rural community. You never doubted my capacity, and you worked with me to make it a success story. My deepest gratitude for all the new research networks established, starting with Prof. Aris. When I shared with you both difficult academic and non-academic situations, you lent me the strength to keep going. I feel so proud and yet humbled to have you as my mentor.

Prof. Dr. Josaphat Byamugisha; you have always encouraged me to remain focused and keep going even when we encountered barriers along this journey. You always worked relentlessly with me to find solutions to the challenges I encountered. With your stewardship, we won four grants; from Grand Challenges Canada, UMC Global Health Support Program, Utrecht University Open Science Support Fund and recently the Wellcome Leap funding to build on the work we have done as part of my PhD. Thank you indeed for your support and guidance. I believe there is more to achieve as we continue working together. I look forward to many more future projects to improve maternal and child health in Uganda and globally.

Prof. Dr. Aris T. Papageorghiou; your problem-solving skills and intelligent practical solutions to issues are a marvel. In your capacity as Research Director of the Oxford Maternal and Perinatal Health Institute, you have helped me set-up two large projects in Uganda. Through your endorsement, the University of Oxford offered me two high-end ultrasound systems for data collection in the PhD research project. It is intriguing to know that despite your overwhelming commitments, you have always availed your time to me, whenever I have called for your assistance. Prof. Aris, I cannot thank you enough for the new research networks and collaborations that you have helped me establish in the past five years that we have so far worked together. I am profoundly humbled to work with you.

Ms. Simelina Heuving, thank you for your support with the systematic review. You were always available to help with any task related to this PhD work. I can’t thank you enough for also supporting me to put together a successful grant “Utrecht University Open Science Fund” to support the dissemination of this PhD work. I am indebted to you.

Special thanks to the University Medical Center Utrecht librarians Paulien Wiersma and Felix Weijdema for assisting with the development of the systematic search strategies and for your succour in searching the database of records.

Ms. Olive Kabajaasi; thank you for supporting the development of the qualitative study tools, interviewing important stakeholders, and preparing a report of the qualitative findings.

Prof. David Zakus, thank you for being part of the collaboration and visiting the field (Kagadi Hospital) encouraging our team to work towards the project targets. Your visit was indeed a confidence builder for our field team.

My colleagues, the Global Health PhD Fellows (Hannah Amokah, Daniel Boateng, Solomon Nyamye, Natasha Hussein, Fridah Soesanti, Patane Slyvester Shilabye, Anna Marza, Timothy) for the warm treat while in The Netherlands together, thank you.

Herm Lamberink; I will not soon forget your kind reception during my first visit and first class at the UMC Utrecht. Thank you for maintaining this true friendship through which you taught me how to survive and find my way around The Netherlands. I truly enjoyed touring the various cities in Holland. I am deeply indebted to you and hold the hope one day you will visit me in Uganda so I can return the favour.

Connie Scheele; thank you for inviting me to your ultrasound department to observe the obstetric ultrasound procedures; for reviewing and critiquing the ultrasound images together and for contributing to our standardization and quality control manuscript.

Coby van Rijn and the rest of UMC Utrecht staff that I may not have mentioned by individual names, I thank you very much for the hospitality and support throughout my stay in The Netherlands.

Esther A. Biira, we certainly thank you for your kindness, and for offering your time and health unit facilities for training the study sonographers at no fee. Thank you for your contributions to the resulting publications.

Adia N. Kagimu, Aminah Migisa, Samson Kuniha and Melodie Munyakazi), it was amazing to work with you. Thank you for contributing to the training and quality review of the ultrasound images.

The University of Oxford, Oxford, United Kingdom is immensely appreciated for providing the ultrasound equipment for data collection.

I would like to acknowledge the INTERGROWTH-21st consortium for assistance and for providing freely available training materials and protocols (https://intergrowth21.tghn.org/).

Lior Drukker is immensely appreciated for his help with the calculation of the Doppler centiles.

Maria-Clara Restrepo Mendez, thank you for the help with the imputation model.

Linda McPhee; thank you for the manuscript writing lessons and for guiding the development through to publication of the qualitative manuscript.

Fosca Tumushabe; thank you for your passion for improving maternal and child health, and the timely support with the English language review.

My immense gratitude goes to the study funders. This project would not have been possible without funding from Grand Challenges Canada (Grant Number: R-ST-POC-1808-17038) through a generous grant to Makerere University College of Health Sciences. UMC Utrecht Global Health Support Program (Ref: FM/ADB/D- 18-015006), which covered all the courses and PhD travel-related costs.

I must also thank the Open Science Program, Utrecht University, The Netherlands (ref. kenmerk OSF22-22), for their support with the dissemination of this PhD research work.

I am extremely elated by the support received directly or indirectly from the Oxford Partnership Comprehensive Biomedical Research Centre with funding from the NIHR Biomedical Research Centre (BRC) funding scheme, through my mentor Prof. Aris.

My gratitude goes to the women we recruited as research participants.

Isaac M. Kakibogo; thank you for warmly welcoming us to Kagadi and honouring our request to implement this project in Kagadi Hospital.

Kagadi District Health Team, thank you for the logistical support and approval to implement this research in Kagadi region.

I extend my sincere gratitude to the study site team that was based at Kagadi Hospital Dr. Isaac Kakibogoi, Sr.Nazareth Kabgenyi, Sebalamu Shem Azariah; Businge Mary Grance; Musiimenta Lillian; Namukisa Pauline Akiiki; Asiimwe Mary; Ainembabazi Immaculate; Ndagire Fiona, Tusiime Nassali, and Sr. Sabititi.

I would like to thank the administration, finance team, and all staff of Makerere University College of Health Sciences and Ernest Cook Ultrasound and Research Institute for supporting me in so many ways during this PhD Journey.

Robin Weijland, I vastly thank you for designing the cover page and layout of this thesis. I appreciate your patience and meticulous attention to detail.

Contributing authors

Adia N. Kagimu,
Ernest Cook Ultrasound Research and Education Institute (ECUREI), Mengo Hospital, Kampala, Uganda

Aminah Migisa
Ernest Cook Ultrasound Research and Education Institute (ECUREI), Mengo Hospital, Kampala, Uganda

Aris T. Papageorghiou
Nuffield Department of Women's and Reproductive Health, John Radcliffe Hospital, University of Oxford, Oxford, UK

Connie Scheele
Division Woman and Baby, Department of Obstetrics, Birth Center Wilhelmina's Children Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

David Zakus
Division of Clinical Public Health, Dalla Lana School of Public Health, University of Toronto, Toronto, Canada

Diederick E. Grobbee
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

Esther A. Biira
The Woman's Place, Kampala, Uganda

Immaculate Ainembabazi
Antenatal and Maternity Unit, Kagadi Hospital, Kagadi District, Uganda

Isaac M. Kakibogo
Antenatal and Maternity Unit, Kagadi Hospital, Kagadi District, Uganda

Josaphat Byamugisha
Department of Obstetrics and Gynaecology, School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda

Kerstin Klipstein-Grobusch
Julius Global Health, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
Division of Epidemiology and Biostatistics, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg-Braamfontein, South Africa

Marcus J. Rijken
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
Department of Obstetrics and Gynaecology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

Melodie Munyakazi
Ernest Cook Ultrasound Research and Education Institute (ECUREI), Mengo Hospital, Kampala, Uganda

Michael G. Kawooya
Professor Emeritus, Radiology Department, Makerere University College of Health Sciences, Kampala, Uganda
Radiology Department, Ernest Cook Ultrasound Research and Education Institute (ECUREI), Mengo Hospital, Kampala, Uganda.

Nasali Tusiime
Antenatal and Maternity Unit, Kagadi Hospital, Kagadi District, Uganda

Olive Kabajaasi
Training and Social Sciences Unit, Walimu, Kampala, Uganda

Samson Kuniha
Department of Radiology, Mulago Hospital Complex, Kampala, Uganda

Simelina Heuving
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

Curriculum Vitae

Sam Ali was born on 16th May 1989 in Omoro, Lira District, Uganda. He finished his medical training in the field of diagnostic radiology and medical imaging in 2012, and a master of Science in Clinical Epidemiology and Biostatistics in 2016 from Makerere University. He has previously worked as the head and in-charge of the Radiology Department of Kitovu Hospital and Bishop Masereka Christian Foundation, respectively, before joining Kadic Hospital and UMC Victoria Hospital in 2014 and 2016, respectively, all based in Uganda. During the past four years, Sam has pursued a PhD program in Clinical Epidemiology at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands. His PhD research focused on the clinical use of Doppler ultrasound to improve prediction of adverse perinatal outcomes in low resource settings, and was supervised by an excellent team comprised of Prof. Dr. Diederick E. Grobbee (promoter), Prof. Dr. Michael G. Kawooya (promoter), Dr. Marcus J. Rijken (co-promoter), Prof. Kerstin Klipstein-Grobusch (co-promoter), Prof. Dr. Josaphat Byamugisha (mentor), and Prof. Dr. Aris T. Papageorghiou (mentor). Sam's line of research focuses on maternal, fetal and neonatal health, with a bias on diagnostics, utilizing his over-the-top clinical and research skills to contribute novel solutions to diagnostic challenges, especially in the underserved regions of the world.