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Antenatal screening for fetuses at risk of adverse perinatal outcomes: a cohort study of the prevalence of abnormal doppler flow indices in low-risk pregnant women in low- and middle-income countries

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ABSTRACT

Introduction

Few interventions exist to address the high burden of stillbirths in apparently healthy pregnant women in low- and middle-income countries (LMICs). To establish whether a trial on the impact of routine doppler screening in a low-risk obstetric population is warranted, we determined the prevalence of abnormal fetal umbilical artery resistance indices among low-risk pregnant women using a low-cost doppler device in five LMICs.

Methods

We conducted a multicentre, prospective cohort study in Ghana, India, Kenya, Rwanda, and South Africa. Trained nurses or midwives performed a single, continuous-wave doppler screening using the Umbiflow device for low-risk pregnant women (according to local guidelines) between 28- and 34-weeks' gestation. We assessed the prevalence of abnormal (raised) resistance index (RI), including absent end diastolic flow (AEDF), and compared pregnancy and health service utilisation outcomes between women with abnormal RI versus those with normal RI.

Results

Of 7151 women screened, 495 (6·9%) had an abnormal RI, including 14 (0·2%) with AEDF. Caesarean section (40·8% vs 28·1%), labour induction (20·5% vs 9·0%), and low birthweight (<2500g) (15·0% vs 6·8%) were significantly more frequent among women with abnormal RI compared to women with normal RI. Abnormal RI was associated with lower birthweights across all weight centiles. Stillbirth and perinatal mortality rates were similar between women with normal and abnormal RI.

Conclusion

A single doppler screening of low-risk pregnant women in LMICs using the Umbiflow device can detect a large number of fetuses at risk of growth restriction and consequent adverse perinatal outcomes. Many perinatal deaths could potentially be averted with appropriate intervention strategies.

Keywords

LMICs, low-risk, pregnancy, umbilical artery, stillbirth, doppler, Umbiflow

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This the first multi-country study assessing the prevalence of abnormal RI of the fetal umbilical artery in low-risk pregnant women in LMICs.
- All research staff who applied Umbiflow underwent a standardised training, all doppler recordings were independently reviewed for quality assurance and the lost to follow-up in the study was low.
- To reflect usual obstetric practice at each site, the definition of low-risk pregnant women was based on local guidelines, so some conditions (such as a previous caesarean section or HIV) were considered differently across sites.
- The prevalence of AEDF might be under-estimated as, despite our best efforts, 64 women with abnormal RI did not attend their referral visit.

SUMMARY BOX

What is already known?

- Doppler ultrasound screening has been shown to reduce perinatal morbidity and mortality in women with high-risk pregnancies, but there is insufficient evidence on its benefits or harms in low- or unselected-risk pregnancies.
- Few studies from high-income countries reported very low prevalence of abnormal fetal doppler findings in low-risk pregnancies, potentially rendering any intervention strategies to improve perinatal outcomes ineffective.
- Umbiflow is a low-cost, hand-held, continuous-wave doppler device, that can be used at scale by skilled health personnel at all levels of care.
- A cohort analytical study using the Umbiflow device in low-risk pregnant women in South Africa reported a higher-than-expected prevalence of fetal umbilical artery flow abnormalities, and management of these women resulted in a 42% reduction in the risk of perinatal mortality.

What are the new findings?

- To our knowledge, this is the first multi-country study reporting the prevalence of abnormal fetal doppler findings in low-risk pregnant women in LMICs.
- We found a 6·9% prevalence of abnormal resistance index (RI), through a single third-trimester screening with the Umbiflow doppler device.
- Babies of women with an abnormal RI had lower birthweights across all weight centiles.

What do the new findings imply?

- This study shows that doppler screening of low-risk pregnant women in LMICs using the Umbiflow device enabled identification of a large number of fetuses at risk of growth restriction who may be undetected during routine antenatal care.
- This provides an opportunity to mount appropriate intervention strategies to avert perinatal mortality and morbidity, and longer-term health problems in affected babies.
- Randomised trials that embed such intervention strategies are urgently needed to demonstrate impact on priority outcomes and guide future policies and clinical practice.

INTRODUCTION

Nearly 2 million babies are stillborn annually, and 98% of these stillbirths occur in low- and middle-income countries (LMICs).[1] It is estimated that up to 50% of antepartum stillbirths can be attributed to fetal growth restriction (FGR), a pathological inhibition of fetal growth that prevents the fetus from attaining its genetic growth potential.[2] FGR increases the risk of stillbirth by 8-fold, and is associated with neonatal death, perinatal morbidity, and non-communicable diseases into adulthood.[2-7] Placental insufficiency is the leading cause of FGR, and occurs mostly as a consequence of poor uteroplacental blood flow, placental thrombi and infarctions.[8-9]

Despite the adverse fetal and neonatal health outcomes associated with FGR, it is not adequately detected during routine antenatal care. An estimated 74% of babies with a birth weight below the 10th centile are not detected antenatally and in low-risk pregnancies, where there is a lower threshold of suspicion, the detection rate of FGR is even lower.[10-13] There is a five-fold increase in attributable risk for stillbirth if FGR was not detected antenatally.[2] Clinical techniques such as history taking and serial physical assessments for identification of growth restricted fetuses have poor predictive values and have not been shown to reduce stillbirth or perinatal mortality.[14-16] Doppler ultrasound can be used to assess blood flow in fetal umbilical vessels to identify placental insufficiency, and abnormal umbilical artery flow indices (such as a raised resistance index (RI)) are correlated with FGR and adverse fetal and neonatal outcomes.[17-18]

Cochrane review evidence shows that the use of doppler to detect placental insufficiency in high-risk pregnancies, in conjunction with appropriate follow-up and care, reduces perinatal mortality.[19] However, there is insufficient evidence to support the routine use of doppler ultrasound in low- or unselected-risk pregnant women.[20]

In many LMICs, antenatal care for apparently healthy, low-risk women is often delivered in settings without access to doppler ultrasound. Umbiflow, a mobile, continuous-wave doppler ultrasound device which can be used by midwives and nurses is one method to deliver doppler ultrasound service where expertise for conventional ultrasound is lacking (Figure 1).[21] Umbiflow has been validated against pulsed-wave doppler in commercial ultrasound systems for the detection of fetal umbilical flow abnormalities in a South African population.[22]

The prevalence of abnormal umbilical blood flow in low-risk pregnant women in LMICs, and therefore the potential benefit of the use of doppler and detection of FGR, is unknown. A study using Umbiflow in a low-risk population of pregnant women in Mamelodi, Pretoria, South Africa reported a higher-than-expected prevalence of fetal umbilical flow abnormalities – 11·7% of women screened had an abnormal RI and 1·5% of the women had absent end diastolic flow (AEDF).[23] Women with abnormal RI were referred and managed at a referral hospital using a standardized management protocol, which resulted in 42% risk reduction in perinatal mortality. These findings have prompted the need for further observational research into the prevalence of umbilical flow abnormalities in low-risk populations in other LMIC settings.

The World Health Organization (WHO) does not currently recommend the routine use of doppler velocimetry for low-risk antenatal populations.[24] However, the WHO antenatal care guideline panel remarked that the value of routine application of single doppler ultrasound examination of fetal blood vessels in the third trimester needs rigorous research, particularly in LMICs. To address this need, WHO embarked on an international study to determine whether the high prevalence of abnormal fetal doppler findings reported in the South African study is present in similar populations in other LMIC settings, to establish whether a trial on the impact of routine doppler screening in low-risk obstetric population in LMICs is warranted.

The primary objective of this study was to determine the prevalence of abnormal (raised) umbilical artery flow resistance index (RI), including AEDF, in low-risk pregnant women between 28 and 34 weeks' gestation in LMICs, using a single screening with the Umbiflow device. The secondary objectives were to assess the prevalence of abnormal RI by gestational age (GA); determine the pregnancy outcomes of women screened; assess the distribution of RI in women with abnormal results; and assess the effects of doppler screening on health service utilisation outcomes.

METHODS

Study design

We conducted a multi-country, multicentre, facility-based, prospective cohort study in Ghana, India, Kenya, Rwanda, and South Africa. This design was used because it minimised selection and reporting bias to the greatest extent possible and allowed accurate determination of both the point and period prevalence of the primary outcomes of interest (abnormal RI, including AEDF). The design also allowed the follow up of enrolled women to achieve the secondary objectives of the study. The study was reviewed and approved by the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) Research Projects Review Panel (RP2), WHO Ethics Review Committee, and institutional ethics committees in participating countries. All participants in the study gave written informed consent. All activities were conducted conform the Declaration of Helsinki. Findings have been reported in accordance with the STROBE statement.[25] The study was registered in the Clinical Trials Registry of India (CTRI/2018/07/014863).

Setting

Across five participating countries, 11 primary health care facilities were purposively selected to participate (three sites in India, two in the other countries). All facilities normally offer routine antenatal care to low-risk pregnant women (based on local guidelines) provided by midwives. Each facility was provided with an Umbiflow device, a laptop computer (with Umbiflow software pre-installed) and a printer.

Study participants

The population of interest were pregnant women who received antenatal care at participating facilities during the study period. Women were eligible if they were at low risk of pregnancy complications according to local antenatal care guidelines, had an estimated GA between 28 weeks 0 days and 34 weeks 0 days (according to the best obstetric estimate),[26] had a live, singleton pregnancy, were expected to deliver at the recruiting facility or within the catchment area, and were willing and able to give informed consent. During the recruitment period, all women attending the antenatal clinic who were between 28 and 34 weeks' gestation (i.e. potentially eligible women) were approached by research staff and formally screened for eligibility. In higher-volume facilities, where the number of potentially eligible women exceeded capacity of the research team, a random sampling method was used to approach, screen and counsel women for recruitment in order to minimise selection bias. Eligible women were counselled about the study and written informed consent was obtained

prior to recruitment. Women were screened and recruited until the target sample size for the country was reached.

Patient and Public Involvement

Patients were not involved in the development of the protocol. During site visits, participants in the study were informally asked about their experience with the study.

Doppler assessment with Umbiflow

The Umbiflow device consists of a handheld continuous-wave doppler probe with a universal serial bus cable that connects to a Windows-based platform (e.g. laptop computer, tablet or smartphone) on which the doppler analysis software is installed (Figure 1).[22] A trained research nurse or midwife performed a single Umbiflow assessment for all recruited women during their antenatal clinic visit between 28 and 34 weeks' gestation. Training of the research staff was conducted by an expert trainer according to a standardised manual of operations in a 3-day curriculum. Based on a woman's history and estimated due date, the Umbiflow software automatically calculates the GA. During the examination, the Umbiflow software displays the fetal umbilical artery waveform and produces an audible signal. The software automatically calculates the three routinely used and highly correlated indices (RI, pulsatility index, and systolic/diastolic ratio), as well as the fetal heart rate, and plots the obtained RI against the GA as the software has RI centiles built-in.[27-28]

An abnormal RI was defined as RI ≥ 75th centile for the GA of the fetus. This cut-off centile was chosen for Umbiflow based on the best correlation with perinatal mortality in a cohort of South African women with pregnancies classified as high-risk.[21] Women with a normal RI (i.e. < 75th centile for the GA) continued with their usual antenatal care. Women who had an abnormal RI, or when no RI reading could be obtained (after two separate unsuccessful attempts) were immediately referred to a higher-level facility for further obstetric evaluation, including fetal growth and pulsed-wave doppler ultrasound assessment. Women were managed according to local policy, and practice and clinical care was not standardized across sites as the primary objective of the study was solely to determine the prevalence of abnormal doppler. However, due to the nature of the test and its results, there was an intrinsic ethical responsibility to refer and further manage women with abnormal results. Digital recordings of all Umbiflow assessments were all saved electronically and independently reviewed for quality by a clinical expert.

Primary and secondary outcomes

Primary outcomes included the prevalence of abnormal RI of the fetal umbilical artery as obtained with Umbiflow, including the prevalence of AEDF (confirmed on pulsed-wave doppler ultrasound). Secondary outcomes included pregnancy outcomes, and health service utilisation outcomes following the Umbiflow assessment.

Data collection

All women were followed from time of recruitment until 7 days postpartum or hospital discharge after giving birth (whichever came first). Participant information, including sociodemographic characteristics, nutritional status, behavioural factors, and medical and obstetric history, was obtained at recruitment through interview and medical record review. The findings of the Umbiflow assessment were documented and digital recordings saved in real time. Birth and perinatal outcomes were obtained from medical records. All data were collected using paper-based case report forms and later double-entered into a REDCap database. All data were non-identifiable, using unique, sequential participant numbers.

Sample size

We estimated that 1266 women were needed per country to detect a prevalence of 1·2% of AEDF in fetuses of women undergoing Umbiflow assessment, based on preliminary findings of Nkosi et al in South Africa.[23] With 10% loss to follow-up, about 1407 women per country were required. With five countries, the target study sample size was 7035 women.

Statistical analysis

Analysis was primarily descriptive and based on participants with outcome data available. The Shapiro-Wilk test was used to test for normality. To assess differences between women with abnormal and normal RI, the nonparametric Mann-Whitney U test was used for numerical variables and the Chi squared test was used for categorical variables. The two-proportions z-test was used for cases where only certain categories were compared. The WHO multinational fetal growth charts were used for categorising birth weights according to percentiles, corrected for gestational age and sex.[29] When comparing the cumulative percentage of birthweights according to centiles in neonates of woman with normal and abnormal RI, the two-sample Kolmogorov-Smirnov test was used. All tests were performed at a 5% level of significance.

RESULTS

Recruitment

Between 15 October 2018 and 20 January 2020, 9191 women were screened for eligibility (Figure 2). A total of 7151 women were recruited and underwent an Umbiflow assessment: 6656 women (93·1%) had a normal RI and 495 women (6·9%) had an abnormal RI. The majority of women with abnormal RI (415, 83·8%) attended their referral and underwent further obstetric evaluation, including pulsed-wave doppler ultrasound assessment. A total of 206 recruited women (2·9%) were lost to follow up after Umbiflow assessment (i.e. pregnancy outcomes could not be obtained).

Characteristics of women screened with Umbiflow

The mean maternal age was 27·4 years and one-third of the women were nulliparous (Table 1). Most women (82·2%) were married or cohabitating, and 32·4% were employed at time of recruitment. Most women were on folic acid and iron supplementation; 4·4% had moderate or severe anaemia based on the most recent haemoglobin level. Overall HIV prevalence was 5·7%, largely due to the high HIV prevalence among women recruited in South Africa (20·8%). In 61·5% of the women, last menstrual period was used to estimate the GA at the time of Umbiflow assessment.

Table 1. Characteristics of women assessed with Umbiflow

	N = 7,151
Woman's age (years) mean (SD)	27·4 ± 5·5
Marital status N (%)	
Married/cohabitating	5879 (82·2)
Single/separated/divorced/widowed	1262 (17·6)
Unknown	10 (0·1)
Currently gainfully employed N (%)	2318 (32·4)
Height (cm) N, mean (SD)	5505, 157·9 ± 6·7
Weight at this visit (kg) N, mean (SD)	6427, 66·5 ± 13·8
Mid upper arm circumference (cm) N, mean (SD)	6513, 27·7 ± 4·2
Presence of anaemia in pregnancy based on most recent haemoglobin level N (%)	
Normal haemoglobin level	3365 (58·9)
Mild anaemia	2095 (36·7)
Moderate anaemia	242 (4·2)
Severe anaemia	11 (0·2)
Parity N (%)	
0	2541 (35·5)
1-2	3824 (53·5)
3+	786 (11·0)
Gestational age at time of recruitment N (%)	
28 weeks 0 – 28 weeks 6 days	1083 (15·1)
29 weeks 0 – 29 weeks 6 days	1351 (18·9)
30 weeks 0 – 30 weeks 6 days	1508 (21·1)
31 weeks 0 – 31 weeks 6 days	1112 (15·6)
32 weeks 0 – 32 weeks 6 days	1044 (14·6)
33 weeks 0 - 34 weeks 0 days	1053 (14·7)
Method used to estimate gestational age N (%)	
Certain last menstrual period	4396 (61·5)
First trimester ultrasound (up until 13 weeks 6 days)	775 (10·8)
Second trimester ultrasound (14 and 27 weeks 6 days)	1326 (18·5)
Third trimester ultrasound (28 weeks 0 days and beyond)	597 (8·3)
Symphysis-fundal height measurement	57 (0·8)
HIV status N (%)	
Test negative	6690 (93·6)
Test positive, not on HIV medication	21 (0·3)
Test positive, on HIV medication	386 (5·4)
Test not done	24 (0·3)
Unknown	30 (0·4)

Primary outcome

Of 7151 women who underwent Umbiflow assessment, 495 women had an abnormal RI giving an overall prevalence of 6·9%. The highest country-level prevalence was observed in Ghana (9·9%) and Rwanda (8·3%), and the lowest in Kenya (4·6%) (Table 2). The overall prevalence of AEDF was 0·2% (14 of 7151 women). All countries had a prevalence of AEDF less than 0·2% except South Africa (0·7%). No cases of reversed end diastolic flow were identified.

Table 2: Prevalence of abnormal resistance indices by country

	Abnormal resistance index - N (%, 95% confidence interval (CI))	Absent end-diastolic flow - N (%)
Ghana (N = 1534)	152 (9·91, CI 8·41 - 11·40)	0 (0·00)
India (N = 1408)	79 (5·61, CI 4·41 - 6·81)	1 (0·07)
Kenya (N = 1407)	64 (4·55, CI 3·46 - 5·64)	1 (0·07)
Rwanda (N = 1403)	117 (8·33, CI 6·89 - 9·79)	2 (0·14)
South Africa (N = 1399)	83 (5·93, CI 4·69 - 7·17)	10 (0·71)
All (N = 7151)	**495 (6·92, CI 6·33 - 7·51)**	**14 (0·20)**

Secondary outcomes

Prevalence of abnormal RI by gestational age

The prevalence of abnormal RI by gestational age at time of screening varied between 5·9% and 7·9%, with no clear peak or optimal gestational age for identification of abnormal RI (p=0·36) (Figure 3).

Pregnancy outcomes

Birth outcomes were obtained for 6945 women recruited into the study: 480 women with an abnormal RI and 6465 women with a normal RI (Table 3). A total of 5854 (84·3%) women experienced labour, of whom 9·7% were induced. The overall caesarean section rate was 28·9%. Three women died (all of whom had a normal RI) – two were due to obstetric haemorrhage and for one woman the cause of death was unknown.

Table 3: Birth outcomes following doppler assessment with Umbiflow

	All women assessed N = 6945	Abnormal RI N = 480	Normal RI N = 6465	P-value
Woman experienced labour N (%)	5854 (84·3)	366 (76·2)	5488 (84·9)	<0·01
Mode of onset of labour N (%)				
Spontaneous	5284 (90·3)	291 (79·5)	4993 (91·0)	<0·01†
Induced	569 (9·7)	75 (20·5)	494 (9·0)	
Unknown	1 (0·0)	0 (0·0)	1 (0·0)	··
Final mode of birth N (%)				
Cephalic vaginal birth	4793 (69·0)	274 (57·1)	4519 (69·9)	<0·01†
Breech vaginal birth	38 (0·5)	4 (0·8)	34 (0·5)	··
Vacuum or forceps vaginal birth	104 (1·5)	6 (1·3)	98 (1·5)	
Caesarean section	2010 (28·9)	196 (40·8)	1814 (28·1)	
Experienced maternal complications* N (%)	202 (2·9)	16 (3·3)	186 (2·9)	0·66
Admission to intensive care or special care unit N (%)	26 (0·4)	2 (0·4)	24 (0·4)	··
Maternal death during pregnancy until 7 days postpartum N (%)	3 (0·04)	0 (0·00)	3 (0·05)	··
Gestational age at birth				
Under 34 weeks	118 (1·7)	20 (4·2)	99 (1·5)	<0·01
34 weeks up to 37 weeks	458 (6·6)	21 (4·4)	437 (6·8)	0·05
37 weeks up to 42 weeks	5991 (86·2)	404 (84·2)	5587 (86·4)	0·18
42 weeks and above	375 (5·4)	35 (7·3)	341 (5·3)	0·07
Unknown	1 (0·0)	0 (0·0)	1 (0·0)	··
Stillbirth	65 (0·9)	8 (1·7)	57 (0·9)	0·14
Neonatal sex				
Male	3655 (52·6)	221 (46·1)	3434 (53·1)	<0·01†
Female	3286 (47·3)	259 (54·0)	3027 (46·8)	
Unknown	4 (0·1)	0 (0·0)	4 (0·1)	··
Apgar score below 7 at 5 minutes	166 (2·7)	14 (3·4)	152 (2·7)	0.46
Birth weight (g)				
N, mean (SD)	6901, 3095 ± 491	474, 2913 ± 514	6427, 3108 ± 486	<0·01
< 2500	506 (7·3)	71 (15·0)	435 (6·8)	<0·01†
≥ 2500	6395 (92·7)	403 (85·0)	5992 (93·2)	
Unknown	44 (0·6)	6 (1·3)	38 (0·6)	··
Neonate required resuscitation at birth	586 (8·4)	38 (7·9)	548 (8·5)	0·72
During the first 7 days of life, the neonate was diagnosed with a medical condition	431 (6·2)	41 (8·5)	390 (6·0)	0·02
Neonate admitted to an intensive care unit (ICU) or special care unit (SCU)	377 (5·4)	44 (9·2)	333 (5·2)	<0·01
Neonatal death at 7 days or at discharge	93 (1·3)	9 (1·9)	84 (1·3)	0·43

* Maternal complications after birth included any of the following: postpartum haemorrhage, postpartum preeclampsia/eclampsia, anaemia requiring blood transfusion, postpartum endometritis, infection of caesarean incision site or perineal laceration site, respiratory tract infection, urinary tract infection, mastitis, postpartum psychosis, deep vein thrombosis, pulmonary embolism, peripartum cardiomyopathy; Percentages in parentheses.

† Chi-square p-value for this variable reported over all categories.

The majority of babies were born at term (86·2%), 8·3% were preterm (<37 weeks' gestation), and 5·4% were post-term (>42 weeks). The mean birth weight was 3095 g; 7·3% of babies were <2500 g. There were 93 perinatal deaths: 65 stillbirths, and 28 early neonatal deaths (stillbirth rate of 9·4/1000 births and early neonatal death rate of 4·1/1000 live births).

Comparison of pregnancy outcomes between women with an abnormal and normal RI shows similarities in several outcomes, including frequencies of women with complications after birth, term births, Apgar score <7 at 5 minutes, neonatal resuscitation at birth, stillbirths and perinatal deaths. However, women with an abnormal RI were significantly more likely to give birth via caesarean section (40·8% vs 28·1%, p<0·01), have induced labours (20·5% vs 9·0%, p<0·01) and were more likely to have an early preterm birth <34 weeks' gestation (4·2% vs 1·5%, p<0·01) than women with a normal RI. The leading indications for caesarean section in women with an abnormal RI were suspected or confirmed fetal growth restriction (20·4%) and fetal distress (17·9%) (abnormal RI alone was not an indication for caesarean section across study sites), whereas in women with normal RI the leading indications were previous caesarean section (34·3%) and fetal distress (16·0%) (data not shown).

Babies of women with abnormal RI were more likely to be admitted to an intensive care or special care unit (9·2% vs 5·2%, p<0·01) but the duration of admission did not differ between the two groups. The mean birthweight was significantly lower in women with an abnormal RI (2913 g vs 3108 g, p<0·01); low birthweight (<2500 g) was significantly more frequent among women with abnormal RI compared to women with normal RI (15·0% vs 6·8%, p<0·01). Even after correction for gestational age at birth and neonatal sex, abnormal RI was associated with lower birthweights across all weight centiles (p<0·0001) (Figure 4).

RI thresholds for identifying fetuses at increased risk of perinatal mortality

We were unable to identify a specific RI threshold associated with increased risk of perinatal mortality due to few events.

The effect of the screening with the Umbiflow device on utilisation of health service

Women in the abnormal RI group were more likely to have antenatal investigations – such as additional ultrasounds, blood tests or cardiotocography – following Umbiflow screening. 79·5% of these women had 4 or more investigations versus 65·3% of women with a normal RI (p<0·01) (Table 4). The median number of antenatal investigations per woman in the

abnormal RI group was 6 vs 5 in the normal RI group (p<0·01). Women with an abnormal RI had more antenatal visits than women with a normal RI: 3 vs 2 respectively (p<0·01).

Table 4: Health service utilisation outcomes

	All N = 6945	Abnormal RI N = 480	Normal RI N = 6465	P-value
Number of antenatal investigations* per woman after Umbiflow assessment Median (IQR)	5 (3, 7)	6 (4, 9)	5 (3, 7)	<0·01
4 or more antenatal investigations* after Umbiflow assessment N (%)	4494 (66·3)	381 (79·5)	4113 (65·3)	<0·01
Number of antenatal care visits per woman since Umbifow® assessment N, median (IQR)	6746, 2 (1, 3)	472, 3 (2, 4)	6274, 1 (1, 3)	<0·01

* Antenatal investigations included any of the following: full blood count, blood type, haemoglobin electrophoresis, urinalysis, urine culture, rubella test, syphilis test, HIV test, hepatitis B test, hepatitis C test, glucose tolerance test, ultrasound examination, full biophysical profile, amniocentesis, antenatal cardiotocography, labour admission cardiotocography, continuous cardiotocography during labour

DISCUSSION

Key findings

In this multi-country cohort study of low-risk pregnant women in LMICs, we found a 6·9% prevalence of abnormal RI of the fetal umbilical artery, and an overall AEDF prevalence of 0·2%. All countries in this study had a prevalence of AEDF below 0·2%, except South Africa with an AEDF prevalence of 0·7%. The prevalence of abnormal RI was reasonably equally distributed across 28 to 34 weeks' gestation. Women with abnormal RI were more likely to receive obstetric interventions such as caesarean section and labour induction, and had a higher frequency of antenatal investigations and clinic visits. While stillbirth and perinatal mortality rates were similar between women with abnormal and normal RI, we found that abnormal RI was associated with lower birthweights across all weight centiles, after correcting for neonatal sex and GA at birth.

Interpretation

The prevalence of abnormal RI in this study was slightly lower than expected compared to previous South African data as reported by Nkosi et al.[23] Another multi-centre South African Umbiflow study by Hlongwane et al found a 12·5% prevalence of abnormal RI, including AEDF prevalence of 1·2%.[30] The reason for the higher prevalence in South Africa is not yet known, however, it is possible that the higher HIV prevalence in pregnant women in South Africa may play a role.

Even though this study did not find a high prevalence of AEDF, we did detect nearly 500 fetuses with placental insufficiency at risk of FGR and therefore at risk of adverse perinatal outcomes. These fetuses were smaller at birth, irrespective of the GA at which they were born. The leading indications for caesarean section in women with abnormal RI were fetal growth restriction and fetal distress, both of which are suggestive of underlying placental insufficiency. Abnormal RI alone was not an indication for caesarean section across study sites, however women who had an abnormal RI were referred to a higher level of care where they received further intervention such as ultrasound. Thus, it was not surprising there were more investigations and interventions in the group with an abnormal RI, and these interventions might have prevented perinatal deaths.

Using conventional ultrasound, an estimated fetal weight (EFW) below the 10th centile for the GA is generally used to diagnose FGR. This however excludes appropriately grown for GA fetuses who do not reach their genetic growth potential. Furthermore, to diagnose FGR using ultrasound criteria, serial ultrasound examinations may be required, and we need to acknowledge that in LMICs, low-risk healthy pregnant women often do not have access to conventional imaging ultrasound (either single or serial ultrasound examinations).[31] Previous research has also demonstrated that even after making conventional ultrasound available in LMICs, there was no decrease in stillbirth rate or neonatal mortality.[32] These findings suggest that Umbiflow can help detect those fetuses with placental insufficiency at risk of FGR (across all weight centiles) and not just fetuses with an EFW below the 10th centile. It can therefore assist in differentiating between the truly growth restricted and not growth restricted fetus, rather than the "small" and "not-small" fetus. Umbiflow can be implemented at primary health care facilities, and be done by health care workers of all levels as it does not require advanced obstetric ultrasound expertise.

Strengths and limitations

To our knowledge, this is the first multi-country study assessing the prevalence of abnormal RI of the fetal umbilical artery in low-risk pregnant women in LMICs. All research staff who applied Umbiflow underwent a standardised training, and all doppler recordings were independently reviewed for quality assurance. Overall, the lost to follow-up in the study was low (2·9%). Nonetheless, our study has some limitations. Firstly, the definition of low-risk pregnant women was based on local guidelines; we did not mandate a specific risk screening protocol across all sites. While this was done to be pragmatic and reflect usual obstetric practice at each site, some conditions (such as a previous caesarean section or HIV) were considered differently across sites. Secondly, the prevalence of AEDF might be under-estimated as, despite our best efforts, 64 women with abnormal RI did not attend their referral visit. The 75th centile cut-off was chosen as it was the best predictor of perinatal morbidity and mortality in a referral hospital and in a low-risk population this cut-off detected approximately 10% of fetuses.[23] However, secondary analyses are planned to investigate different cut-offs. Lastly, we acknowledge that FGR and doppler abnormalities can arise beyond 34 weeks' gestation. For this study, a single screening was chosen to determine the prevalence and guide further research. The screening time was selected between 28-34 weeks' gestation because there were insufficient neonatal services in the countries to manage neonates under 28 weeks' gestation if delivery was required immediately; and the peak

incidence of small-for-gestational-age stillbirths was 34-37 weeks' gestation, allowing time to intervene prior to a stillbirth.[33]

Implications for policy, practice and research

This study demonstrates that a single doppler screening with Umbiflow between 28 and 34 weeks' gestation in low-risk pregnant women in LMICs can detect a large number of fetuses who are at risk of FGR and adverse perinatal outcomes that may otherwise not have been detected. The Umbiflow device is inexpensive and can be used by health care providers at lower levels of care and thus can be used to screen pregnant populations on a large scale to identify previously undetected FGR. Randomised trials that embed intervention strategies with doppler screening in low-risk women in LMICs are urgently needed to assess impact on priority outcomes, and to inform clinical practice.

CONCLUSION

This study shows that screening a low-risk or unselected pregnant population with Umbiflow detects a large number of fetuses with placental insufficiency at risk of FGR. With large-scale implementation, appropriate referral and intervention, perinatal mortality and morbidity could potentially drastically decrease, especially in LMICs.

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The manuscript reflects views of the named authors only and does not reflect the views of the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) or World Health Organization.

Competing interests

The South African Medical Research Council (SAMRC) / University of Pretoria (UP) Maternal and Infant Health Care Strategies Unit has (VV, RP) has previously received funding from SAMRC and the Council for Scientific and Industrial Research (CSIR) for Umbiflow research done by Nkosi et al and Hlongwane et al. The CSIR provided the Umbiflow doppler probes and Umbiflow software used in this study. As a satellite research unit, the SAMRC Maternal and Infant Health Care Strategies Unit receives research funding from the SAMRC.

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Authors' contributions

This study was conceived by OTO. OTO and JPV coordinated the writing of the study protocol, with input from the country principal investigators. VV prepared the statistical analysis plan and led statistical analysis with TC. All country principal investigators were part of the Umbiflow International Study steering group and led the study with support from the co-investigators in each country. The Umbiflow International Study steering group reviewed and interpreted the final data at a workshop convened by WHO. The first draft of the manuscript was prepared by VV, with substantial input from JPV, RP, and OTO. All authors reviewed and revised the manuscript draft critically for intellectual content and approved the final manuscript for publication. The manuscript represents the views of the named authors only.

Data sharing

Request for access to these data can be made to the World Health Organization through srhmph@who.int. Data sharing with any individual or organization will be subject to WHO data sharing policy.

Figure 1: The Umbiflow device

Credit: CSIR / SAMRC

Figure 2: Recruitment flowchart

Figure 3: Prevalence of abnormal RI by gestational age

Figure 4: Cumulative percentage of birthweights according to centiles in neonates of women with normal and abnormal RI

REFERENCES

1. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). A neglected tragedy: the global burden of stillbirths. United Nations Children's Fund, New York, 2020.
2. Gardosi J, Madurasinghe V, Williams M, et al. Maternal and fetal risk factors for stillbirth: population based study. *BMJ* 2013;**346**:f108. https://doi.org/10.1136/bmj.f108
3. Katz J, Lee ACC, Kozuki N, et al. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. *Lancet* 2013;**382**(9890):417–25. https://doi.org/10.1016/s0140-6736(13)60993-9
4. McIntyre S, Blair E, Badawi N, et al. Antecedents of cerebral palsy and perinatal death in term and late preterm singletons. *Obstet Gynecol* 2013;**122**(4):869–77. https://doi.org/10.1097/aog.0b013e3182a265ab
5. Bukowski R, Burgett AD, Gei A, et al. Impairment of fetal growth potential and neonatal encephalopathy. *Am J Obstet Gynecol* 2003;**188**(4):1011–5. https://doi.org/10.1067/mob.2003.233
6. Ross MG, Beall MH. Adult sequelae of intrauterine growth restriction. *Semin Perinatol* 2008;**32**(3):213–8. https://doi.org/10.1053/j.semperi.2007.11.005
7. Gluckman PD, Hanson MA, Cooper C, et al. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 2008;**359**(1):61–73. https://doi.org/10.1056/nejmra0708473
8. Salafia CM, Minior VK, Pezzullo JC, et al. Intrauterine growth restriction in infants of less than thirty-two weeks' gestation: associated placental pathologic features. *Am J Obstet Gynecol* 1995;**173**(4):1049–57. https://doi.org/10.1016/0002-9378(95)91325-4
9. Alberry M, Soothill P. Management of fetal growth restriction. *Arch Dis Child Fetal Neonatal Ed* 2007;**92**(1):F62–7. https://doi.org/10.1136/adc.2005.082297
10. Sovio U, White IR, Dacey A, et al. 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. https://doi.org/10.1016/s0140-6736(15)00131-2
11. Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. *Am J Obstet Gynecol* 2011;**204**(4):288–300. https://doi.org/10.1016/j.ajog.2010.08.055

12. Hepburn M, Rosenberg K. An audit of the detection and management of small-for-gestational age babies. *Br J Obstet Gynaecol* 1986;**93**(3):212–6. https://doi.org/10.1111/j.1471-0528.1986.tb07895.x
13. Backe B, Nakling J. Effectiveness of antenatal care: a population based study. *Br J Obstet Gynaecol* 1993;**100**:727–32. https://doi.org/10.1111/j.1471-0528.1993.tb14263.x
14. Bais JMJ, Eskes M, Pel M, et al. Effectiveness of detection of intrauterine growth retardation by abdominal palpation as screening test in a low risk population: an observational study. *Eur J Obstet Gynecol Reprod Biol* 2004;**116**(2):164–9. https://doi.org/10.1016/j.ejogrb.2004.01.037
15. Mufenda J, Gebhardt S, van Rooyen R, et al. 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* 2015;**10**(11):e0142743. https://doi.org/10.1371/journal.pone.0142743
16. Robert Peter J, Ho JJ, Valliapan J, et al. Symphysial fundal height (SFH) measurement in pregnancy for detecting abnormal fetal growth. *Cochrane Database Syst Rev* 2015;(9):CD008136. https://doi.org/10.1002/14651858.cd008136.pub3
17. Society for Maternal-Fetal Medicine Publications Committee, Berkley E, Chauhan SP, et al. Doppler assessment of the fetus with intrauterine growth restriction. *Am J Obstet Gynecol* 2012;**206**(4):300–8. https://doi.org/10.1016/j.ajog.2012.01.022
18. Salafia CM, Pezzullo JC, Minior VK, et al. Placental pathology of absent and reversed end-diastolic flow in growth-restricted fetuses. *Obstet Gynecol* 1997;**90**(5):830–6. https://doi.org/10.1016/s0029-7844(97)00473-0
19. Alfirevic Z, Stampalija T, Gyte GM. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev* 2013;(11):CD007529. https://doi.org/10.1002/14651858.cd007529
20. Alfirevic Z, Stampalija T, Medley N. Fetal and umbilical Doppler ultrasound in normal pregnancy. *Cochrane Database Syst Rev* 2015;(4):CD001450. https://doi.org/10.1002/14651858.cd001450.pub4
21. Hugo EJC, Odendaal HJ, Grove D. Evaluation of the use of umbilical artery Doppler flow studies and outcome of pregnancies at a secondary hospital. *J Matern Fetal Neonatal Med* 2007;**20**(3):233–39. https://doi.org/10.1080/14767050601134926

22. Theron GB, Theron AM, Odendaal HJ, et al. Comparison between a newly developed PC-based Doppler umbilical artery waveform analyser and a commercial unit. *S Afr Med J* 2005;**95**(1):62–4.
23. Nkosi S, Makin J, Hlongwane T, et al. Screening and managing a low-risk pregnant population using continuous-wave Doppler ultrasound in a low-income population: A cohort analytical study. *S Afr Med J* 2019;**109**(5):347–52. https://doi.org/10.7196/samj.2019.v109i5.13611
24. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva. 2016.
25. Von Elm E, Altman DG, Egger M, et al; STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE)statement: guidelines for reporting observational studies. *Bull World Health Organ* 2007;**85**(11):867–72. https://doi.org/10.2471/blt.07.045120
26. Committee on Obstetric Practice, the American Institute of Ultrasound in Medicine, and the Society for Maternal-Fetal Medicine. Committee Opinion No 700: methods for estimating the due date. *Obstet Gynecol* 2017;129(5):e150–e154. https://doi.org/10.1097/AOG.0000000000002046
27. Bhide A, Acharya G, Bilardo CM, et al. ISUOG Practice Guidelines: use of Doppler ultrasonography in obstetrics. *Ultrasound Obstet Gynecol* 2013;**41**:233–239. https://doi.org/10.1002/uog.12371
28. Pattinson RC, Theron GB, Thompson ML, et al. Doppler ultrasonography of the feto-placental circulation – normal reference values. *S Afr Med J* 1989;**76**:623–625.
29. Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. *PLoS Med* 2017;**14**(1):e1002220. doi: 10.1371/journal.pmed.1002220
30. Hlongwane TMAG, Cronjé T, Nkosi BSS, et al. The prevalence of abnormal Doppler's of the umbilical artery in a low-risk pregnant population in South Africa. 2020. Accepted for publication. *EClinicalMedicine* 2021;100792. https://doi.org/10.1016/j.eclinm.2021.100792
31. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consesus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol* 2016;**48**(3):333–9. https://doi.org/10.1002/uog.15884

32. Goldenberg R, Nathan RO, Swanson D, et al. Routine antenatal ultrasound in low- and middle-income countries: first look - a cluster randomised trial. *BJOG* 2018;**125**(12):1591–99. https://doi.org/10.1111/1471-0528.15287

33. Lavin T, Preen DB, Pattinson R. Timing and cause of perinatal mortality for small-for-gestational-age babies in South Africa: critical periods and challenges with detection. *Matern Health Neonatol Perinatol* 2016;**2**(1):11. https://doi.org/10.1186/s40748-016-0039-4

Figure 1: The Umbiflow deviceCredit: CSIR / SAMRC

159x105mm (72 x 72 DPI)

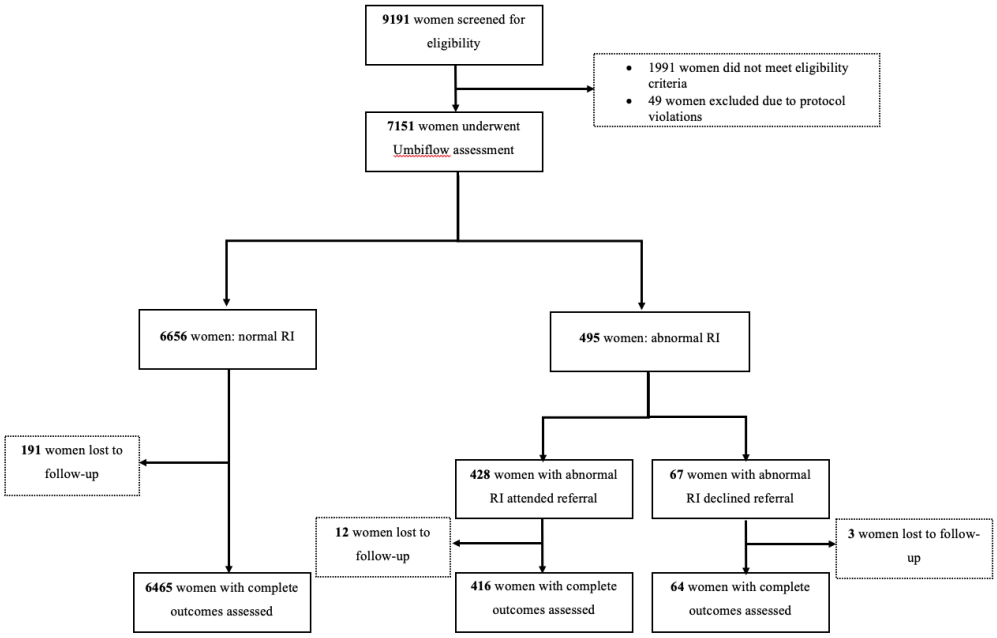

Figure 2: Recruitment flowchart

446x294mm (72 x 72 DPI)

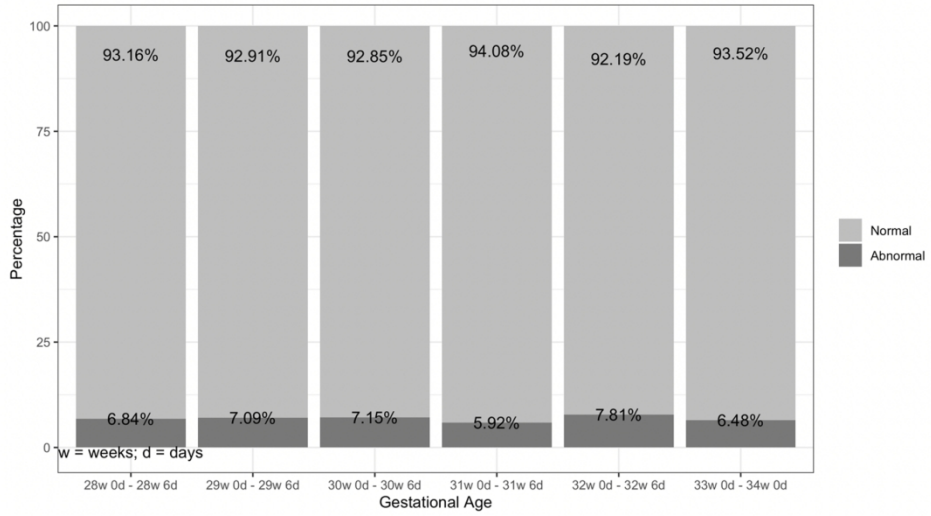

Figure 3: Prevalence of abnormal RI by gestational age

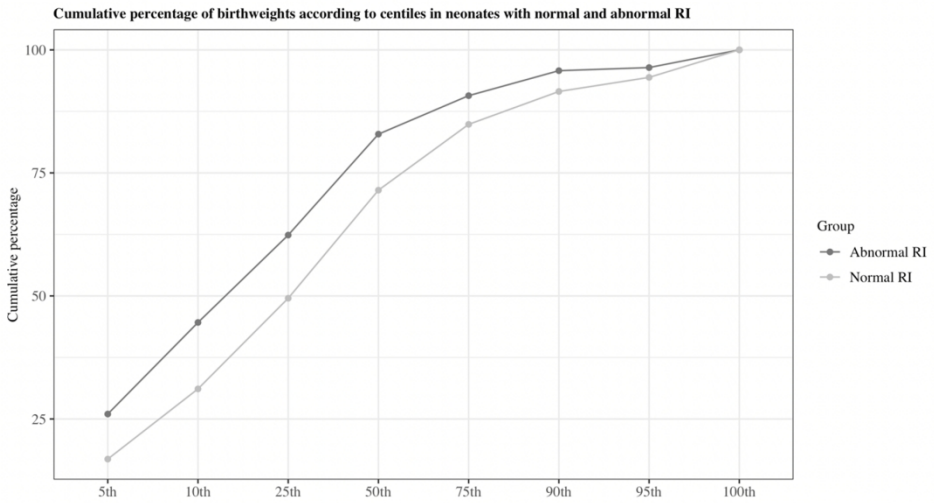

Figure 4: Cumulative percentage of birthweights according to centiles in neonates of women with normal and abnormal RI

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	10
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-Fig2
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	Fig2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	T1
		(b) Indicate number of participants with missing data for each variable of interest	T1
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	T2-4

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	T2 T3-4 NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	T3-4
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	4,19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Antenatal doppler screening for fetuses at risk of adverse outcomes: a multi-country cohort study of the prevalence of abnormal resistance index in low-risk pregnant women

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Keywords:	PRIMARY CARE, PUBLIC HEALTH, OBSTETRICS

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Antenatal doppler screening for fetuses at risk of adverse outcomes: a multi-country cohort study of the prevalence of abnormal resistance index in low-risk pregnant women

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ABSTRACT

Introduction

Few interventions exist to address the high burden of stillbirths in apparently healthy pregnant women in low- and middle-income countries (LMICs). To establish whether a trial on the impact of routine doppler screening in a low-risk obstetric population is warranted, we determined the prevalence of abnormal fetal umbilical artery resistance indices among low-risk pregnant women using a low-cost doppler device in five LMICs.

Methods

We conducted a multicentre, prospective cohort study in Ghana, India, Kenya, Rwanda, and South Africa. Trained nurses or midwives performed a single, continuous-wave doppler screening using the Umbiflow device for low-risk pregnant women (according to local guidelines) between 28- and 34-weeks' gestation. We assessed the prevalence of abnormal (raised) resistance index (RI), including absent end diastolic flow (AEDF), and compared pregnancy and health service utilisation outcomes between women with abnormal RI versus those with normal RI.

Results

Of 7151 women screened, 495 (6·9%) had an abnormal RI, including 14 (0·2%) with AEDF. Caesarean section (40·8% vs 28·1%), labour induction (20·5% vs 9·0%), and low birthweight (<2500g) (15·0% vs 6·8%) were significantly more frequent among women with abnormal RI compared to women with normal RI. Abnormal RI was associated with lower birthweights across all weight centiles. Stillbirth and perinatal mortality rates were similar between women with normal and abnormal RI.

Conclusion

A single doppler screening of low-risk pregnant women in LMICs using the Umbiflow device can detect a large number of fetuses at risk of growth restriction and consequent adverse perinatal outcomes. Many perinatal deaths could potentially be averted with appropriate intervention strategies.

Keywords

LMICs, low-risk, pregnancy, umbilical artery, stillbirth, doppler, Umbiflow

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This the first multi-country study assessing the prevalence of abnormal RI of the fetal umbilical artery in low-risk pregnant women in LMICs.
- All research staff who applied Umbiflow underwent a standardised training, all doppler recordings were independently reviewed for quality assurance and the lost to follow-up in the study was low.
- To reflect usual obstetric practice at each site, the definition of low-risk pregnant women was based on local guidelines, so some conditions (such as a previous caesarean section or HIV) were considered differently across sites.

  The prevalence of AEDF might be under-estimated as, despite our best efforts, 64 women with abnormal RI did not attend their referral visit.

INTRODUCTION

Nearly 2 million babies are stillborn annually, and 98% of these stillbirths occur in low- and middle-income countries (LMICs).[1] It is estimated that up to 50% of antepartum stillbirths can be attributed to fetal growth restriction (FGR), a pathological inhibition of fetal growth that prevents the fetus from attaining its genetic growth potential.[2] FGR increases the risk of stillbirth by 8-fold, and is associated with neonatal death, perinatal morbidity, and non-communicable diseases into adulthood.[2-7] Placental insufficiency is the leading cause of FGR, and occurs mostly as a consequence of poor uteroplacental blood flow, placental thrombi and infarctions.[8-9]

Despite the adverse fetal and neonatal health outcomes associated with FGR, it is not adequately detected during routine antenatal care. An estimated 74% of babies with a birth weight below the 10th centile are not detected antenatally and in low-risk pregnancies, where there is a lower threshold of suspicion, the detection rate of FGR is even lower.[10-13] There is a five-fold increase in attributable risk for stillbirth if FGR was not detected antenatally.[2] Clinical techniques such as history taking and serial physical assessments for identification of growth restricted fetuses have poor predictive values and have not been shown to reduce stillbirth or perinatal mortality.[14-16] Doppler ultrasound can be used to assess blood flow in fetal umbilical vessels to identify placental insufficiency, and abnormal umbilical artery flow indices (such as a raised resistance index (RI)) are correlated with FGR and adverse fetal and neonatal outcomes.[17-18]

Cochrane review evidence shows that the use of doppler to detect placental insufficiency in high-risk pregnancies, in conjunction with appropriate follow-up and care, reduces perinatal mortality.[19] However, there is insufficient evidence to support the routine use of doppler ultrasound in low- or unselected-risk pregnant women.[20]

In many LMICs, antenatal care for apparently healthy, low-risk women is often delivered in settings without access to doppler ultrasound. Umbiflow, a mobile, continuous-wave doppler ultrasound device which can be used by midwives and nurses is one method to deliver doppler ultrasound service where expertise for conventional ultrasound is lacking (Figure 1).[21] Umbiflow has been validated against pulsed-wave doppler in commercial ultrasound systems for the detection of fetal umbilical flow abnormalities in a South African population.[22]

The prevalence of abnormal umbilical blood flow in low-risk pregnant women in LMICs, and therefore the potential benefit of the use of doppler and detection of FGR, is unknown. A study using Umbiflow in a low-risk population of pregnant women in Mamelodi, Pretoria, South Africa reported a higher-than-expected prevalence of fetal umbilical flow abnormalities – 11·7% of women screened had an abnormal RI and 1·5% of the women had absent end diastolic flow (AEDF).[23] Women with abnormal RI were referred and managed at a referral hospital using a standardized management protocol, which resulted in 42% risk reduction in perinatal mortality. These findings have prompted the need for further observational research into the prevalence of umbilical flow abnormalities in low-risk populations in other LMIC settings.

The World Health Organization (WHO) does not currently recommend the routine use of doppler velocimetry for low-risk antenatal populations.[24] However, the WHO antenatal care guideline panel remarked that the value of routine application of single doppler ultrasound examination of fetal blood vessels in the third trimester needs rigorous research, particularly in LMICs. To address this need, WHO embarked on an international study to determine whether the high prevalence of abnormal fetal doppler findings reported in the South African study is present in similar populations in other LMIC settings, to establish whether a trial on the impact of routine doppler screening in low-risk obstetric population in LMICs is warranted.

The primary objective of this study was to determine the prevalence of abnormal (raised) umbilical artery RI, including AEDF, in low-risk pregnant women between 28 and 34 weeks' gestation in LMICs, using a single screening with the Umbiflow device. The secondary objectives were to assess the prevalence of abnormal RI by gestational age (GA); determine the pregnancy outcomes of women screened; assess the distribution of RI in women with abnormal results; and assess the effects of doppler screening on health service utilisation outcomes.

METHODS

Study design

We conducted a multi-country, multicentre, facility-based, prospective cohort study using pre-defined eligibility criteria in Ghana, India, Kenya, Rwanda, and South Africa. This design was used because it minimised selection and reporting bias to the greatest extent possible, allowed accurate determination of both the point and period prevalence of the primary outcomes of interest (abnormal RI, including AEDF) and involved diverse women and antenatal care settings. The design also allowed the follow up of enrolled women to achieve the secondary objectives of the study. The study was reviewed and approved by the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) Research Projects Review Panel (RP2) and the WHO Ethics Review Committee. The study was further approved by the following institutional ethics committees in participating countries: Ghana Health Service Ethics Review Committee, KLE Academy of Higher Education and Research Institutional Ethics Committee, Indian Council of Medical Research (Health Ministry's Screening Committee), Kenyatta National Hospital – University of Nairobi Ethics and Research Committee, Rwanda National Ethics Committee and University of Pretoria Faculty of Health Sciences Research Ethics Committee. All participants in the study gave written informed consent. All activities were conducted conform the Declaration of Helsinki. Findings have been reported in accordance with the STROBE statement.[25] The study was registered in the Clinical Trials Registry of India (CTRI/2018/07/014863).

Setting

Across five participating countries, 11 primary health care facilities were purposively selected to participate (three sites in India, two sites in each of the other countries). All facilities normally offer routine antenatal care to low-risk pregnant women provided by midwives. All countries used an 8-visit antenatal care model, except for Kenya which used a 4-visit antenatal care model. Each facility was provided with an Umbiflow device, a laptop computer (with Umbiflow software pre-installed) and a printer.

Study participants

The population of interest were pregnant women who received antenatal care at participating facilities during the study period. Women were eligible if they were at low risk of pregnancy complications according to local antenatal care guidelines, had an estimated GA between 28 weeks 0 days and 34 weeks 0 days (according to the best obstetric estimate),[26] had a live, singleton pregnancy, were expected to deliver at the recruiting facility or within the

catchment area, and were willing and able to give informed consent. Local antenatal care guidelines were very similar across all study sites: women with pre-existing medical conditions (e.g. type 1 or type 2 diabetes mellitus, hypertension, renal disease or other such conditions), poor obstetric history, pregnancy complications (e.g. vaginal bleeding, infection, severe anaemia) or a fetus with a known congenital anomaly (chromosomal or structural) were considered high-risk and were not eligible. Pregnant women with advanced maternal age or teenagers are considered high-risk across all study sites, though age definitions vary slightly. Antenatal care guidelines in India are more stringent than the other four countries – a pregnant woman who is rhesus negative, HIV-infected or who had a previous caesarean section was considered high-risk in India, whereas in the other four countries a woman with any one of these is considered low-risk.

During the recruitment period, all women attending participating antenatal clinics who were between 28 and 34 weeks' gestation (i.e. potentially eligible women) were approached by research staff and formally screened for eligibility. In higher-volume facilities, where the number of potentially eligible women exceeded capacity of the research team, a random sampling method was used to approach, screen and counsel women for recruitment in order to minimise selection bias. Eligible women were counselled about the study and written informed consent was obtained prior to recruitment. Women were screened and recruited until the target sample size for the country was reached.

Patient and Public Involvement

Patients were not involved in the development of the protocol. During site visits, participants in the study were informally asked about their experience with the study.

Doppler assessment with Umbiflow

The Umbiflow device consists of a handheld continuous-wave doppler probe with a universal serial bus cable that connects to a Windows-based platform (e.g. laptop computer, tablet or smartphone) on which the doppler analysis software is installed (Figure 1).[22] A trained research nurse or midwife performed a single Umbiflow assessment for all recruited women during their antenatal clinic visit between 28 and 34 weeks' gestation. Training of the research staff was conducted by an expert trainer according to a standardised manual of operations in a 3-day curriculum. Based on a woman's history and estimated due date, the Umbiflow software automatically calculates the GA. During the examination, the Umbiflow software displays the fetal umbilical artery waveform and produces an audible signal. The

software automatically calculates the three routinely used and highly correlated indices (RI, pulsatility index, and systolic/diastolic ratio), as well as the fetal heart rate, and plots the obtained RI against the GA as the software has RI centiles built-in.[27-28]

An abnormal RI was defined as RI ≥ 75th centile for the GA of the fetus. This cut-off centile was chosen for Umbiflow based on the best correlation with perinatal mortality in a cohort of South African women with pregnancies classified as high-risk.[21] Women with a normal RI (i.e. < 75th centile for the GA) continued with their usual antenatal care. Women who had an abnormal RI, or where a RI reading could not be obtained after two separate unsuccessful attempts, were immediately referred to a higher-level facility for further obstetric evaluation, including fetal growth and pulsed-wave doppler ultrasound assessment. Women were managed according to local antenatal care policies; clinical care was not standardized across sites as the primary objective of the study was solely to determine the prevalence of abnormal doppler. However, due to the nature of the test and its results, there was an intrinsic ethical responsibility to refer and further manage women with abnormal results. Digital recordings of all Umbiflow assessments were saved electronically and independently reviewed for quality by a clinical expert.

Primary and secondary outcomes

Primary outcomes included the prevalence of abnormal RI of the fetal umbilical artery as obtained with Umbiflow, including the prevalence of AEDF (confirmed on pulsed-wave doppler ultrasound). Secondary outcomes included pregnancy outcomes, and health service utilisation outcomes following the Umbiflow assessment.

Data collection

All women were followed from time of recruitment until 7 days postpartum or hospital discharge after giving birth (whichever came first). Participant information, including sociodemographic characteristics, nutritional status, behavioural factors, and medical and obstetric history, was obtained at recruitment through interview and medical record review. The findings of the Umbiflow assessment were documented and digital recordings saved in real time. Birth and perinatal outcomes were obtained from medical records. All data were collected using paper-based case report forms and later double-entered into a REDCap database. All data were non-identifiable, using unique, sequential participant numbers.

Sample size

We estimated that 1266 women were needed per country to detect a prevalence of 1·2% of AEDF in fetuses of women undergoing Umbiflow assessment, based on preliminary findings of Nkosi et al in South Africa.[23] With 10% loss to follow-up, about 1407 women per country were required. With five countries, the target study sample size was 7035 women.

Statistical analysis

Analysis was primarily descriptive and based on participants with outcome data available. The Shapiro-Wilk test was used to test for normality. To assess differences between women with abnormal and normal RI, the nonparametric Mann-Whitney U test was used for numerical variables and the Chi squared test was used for categorical variables. The two-proportions z-test was used for cases where only certain categories were compared. The WHO multinational fetal growth charts were used for categorising birth weights according to percentiles, corrected for gestational age and sex.[29] When comparing the cumulative percentage of birthweights according to centiles in neonates of woman with normal and abnormal RI, the two-sample Kolmogorov-Smirnov test was used. All tests were performed at a 5% level of significance.

RESULTS

Recruitment

Between 15 October 2018 and 20 January 2020, 9191 women were screened for eligibility (Figure 2). A total of 7151 women were recruited and underwent an Umbiflow assessment: 6656 women (93·1%) had a normal RI and 495 women (6·9%) had an abnormal RI. The majority of women with abnormal RI (415, 83·8%) attended their referral and underwent further obstetric evaluation, including pulsed-wave doppler ultrasound assessment. A total of 206 recruited women (2·9%) were lost to follow up after Umbiflow assessment (i.e. pregnancy outcomes could not be obtained).

Characteristics of women screened with Umbiflow

The mean maternal age was 27·4 years and one-third of the women were nulliparous (Table 1). Most women (82·2%) were married or cohabitating, and 32·4% were employed at time of recruitment. Most women were on folic acid and iron supplementation; 4·4% had moderate or severe anaemia based on the most recent haemoglobin level. Overall HIV prevalence was

5·7%, largely due to the high HIV prevalence among women recruited in South Africa (20·8%). In 61·5% of the women, last menstrual period was used to estimate the GA at the time of Umbiflow assessment.

Table 1. Characteristics of women assessed with Umbiflow

	N = 7,151
Woman's age (years) mean (SD)	27·4 ± 5·5
Marital status N (%)	
Married/cohabitating	5879 (82·2)
Single/separated/divorced/widowed	1262 (17·6)
Unknown	10 (0·1)
Currently gainfully employed N (%)	2318 (32·4)
Height (cm) N, mean (SD)	5505, 157·9 ± 6·7
Weight at this visit (kg) N, mean (SD)	6427, 66·5 ± 13·8
Mid upper arm circumference (cm) N, mean (SD)	6513, 27·7 ± 4·2
Presence of anaemia in pregnancy based on most recent haemoglobin level N (%)	
Normal haemoglobin level	3365 (58·9)
Mild anaemia	2095 (36·7)
Moderate anaemia	242 (4·2)
Severe anaemia	11 (0·2)
Parity N (%)	
0	2541 (35·5)
1-2	3824 (53·5)
3+	786 (11·0)
Gestational age at time of recruitment N (%)	
28 weeks 0 – 28 weeks 6 days	1083 (15·1)
29 weeks 0 – 29 weeks 6 days	1351 (18·9)
30 weeks 0 – 30 weeks 6 days	1508 (21·1)
31 weeks 0 – 31 weeks 6 days	1112 (15·6)
32 weeks 0 – 32 weeks 6 days	1044 (14·6)
33 weeks 0 - 34 weeks 0 days	1053 (14·7)
Method used to estimate gestational age N (%)	
Certain last menstrual period	4396 (61·5)
First trimester ultrasound (up until 13 weeks 6 days)	775 (10·8)
Second trimester ultrasound (14 and 27 weeks 6 days)	1326 (18·5)
Third trimester ultrasound (28 weeks 0 days and beyond)	597 (8·3)
Symphysis-fundal height measurement	57 (0·8)
HIV status N (%)	
Test negative	6690 (93·6)
Test positive, not on HIV medication	21 (0·3)
Test positive, on HIV medication	386 (5·4)
Test not done	24 (0·3)
Unknown	30 (0·4)

Primary outcome

Of 7151 women who underwent Umbiflow assessment, 495 women had an abnormal RI giving an overall prevalence of 6·9%. The highest country-level prevalence was observed in Ghana (9·9%) and Rwanda (8·3%), and the lowest in Kenya (4·6%) (Table 2). The overall prevalence of AEDF was 0·2% (14 of 7151 women). All countries had a prevalence of AEDF less than 0·2% except South Africa (0·7%). No cases of reversed end diastolic flow were identified.

Table 2: Prevalence of abnormal resistance indices by country

	Abnormal resistance index - N (%, 95% confidence interval (CI))	Absent end-diastolic flow - N (%)
Ghana (N = 1534)	152 (9·91, CI 8·41 - 11·40)	0 (0·00)
India (N = 1408)	79 (5·61, CI 4·41 - 6·81)	1 (0·07)
Kenya (N = 1407)	64 (4·55, CI 3·46 - 5·64)	1 (0·07)
Rwanda (N = 1403)	117 (8·33, CI 6·89 - 9·79)	2 (0·14)
South Africa (N = 1399)	83 (5·93, CI 4·69 - 7·17)	10 (0·71)
All (N = 7151)	**495 (6·92, CI 6·33 - 7·51)**	**14 (0·20)**

Secondary outcomes

Prevalence of abnormal RI by gestational age

The prevalence of abnormal RI by gestational age at time of screening varied between 5·9% and 7·9%, with no clear peak or optimal gestational age for identification of abnormal RI (p=0·36) (Figure 3).

Pregnancy outcomes

Birth outcomes were obtained for 6945 women recruited into the study: 480 women with an abnormal RI and 6465 women with a normal RI (Table 3). A total of 5854 (84·3%) women experienced labour, of whom the majority had a spontaneous onset (5284, 90·3%) and 569 (9·7%) were induced. The overall caesarean section rate was 28·9%. Three women died (all of whom had a normal RI) – two were due to obstetric haemorrhage and for one woman the cause of death was unknown.

Table 3: Birth outcomes following doppler assessment with Umbiflow

	All women assessed N = 6945	Abnormal RI N = 480	Normal RI N = 6465	P-value
Woman experienced labour N (%)	5854 (84·3)	366 (76·2)	5488 (84·9)	<0·01
Mode of onset of labour N (%)				
Spontaneous	5284 (90·3)	291 (79·5)	4993 (91·0)	<0·01†
Induced	569 (9·7)	75 (20·5)	494 (9·0)	
Unknown	1 (0·0)	0 (0·0)	1 (0·0)	··
Final mode of birth N (%)				
Cephalic vaginal birth	4793 (69·0)	274 (57·1)	4519 (69·9)	<0·01†
Breech vaginal birth	38 (0·5)	4 (0·8)	34 (0·5)	··
Vacuum or forceps vaginal birth	104 (1·5)	6 (1·3)	98 (1·5)	
Caesarean section	2010 (28·9)	196 (40·8)	1814 (28·1)	
Experienced maternal complications* N (%)	202 (2·9)	16 (3·3)	186 (2·9)	0·66
Admission to intensive care or special care unit N (%)	26 (0·4)	2 (0·4)	24 (0·4)	··
Maternal death during pregnancy until 7 days postpartum N (%)	3 (0·04)	0 (0·00)	3 (0·05)	··
Gestational age at birth				
Under 34 weeks	118 (1·7)	20 (4·2)	99 (1·5)	<0·01
34 weeks up to 37 weeks	458 (6·6)	21 (4·4)	437 (6·8)	0·05
37 weeks up to 42 weeks	5991 (86·2)	404 (84·2)	5587 (86·4)	0·18
42 weeks and above	375 (5·4)	35 (7·3)	341 (5·3)	0·07
Unknown	1 (0·0)	0 (0·0)	1 (0·0)	··
Stillbirth	65 (0·9)	8 (1·7)	57 (0·9)	0·14
Neonatal sex				
Male	3655 (52·6)	221 (46·1)	3434 (53·1)	<0·01†
Female	3286 (47·3)	259 (54·0)	3027 (46·8)	
Unknown	4 (0·1)	0 (0·0)	4 (0·1)	··
Apgar score below 7 at 5 minutes	166 (2·7)	14 (3·4)	152 (2·7)	0.46
Birth weight (g)				
N, mean (SD)	6901, 3095 ± 491	474, 2913 ± 514	6427, 3108 ± 486	<0·01
< 2500	506 (7·3)	71 (15·0)	435 (6·8)	<0·01†
≥ 2500	6395 (92·7)	403 (85·0)	5992 (93·2)	
Unknown	44 (0·6)	6 (1·3)	38 (0·6)	··
Neonate required resuscitation at birth	586 (8·4)	38 (7·9)	548 (8·5)	0·72
During the first 7 days of life, the neonate was diagnosed with a medical condition	431 (6·2)	41 (8·5)	390 (6·0)	0·02
Congenital abnormality	30 (0·4)	4 (0·8)	26 (0·4)	··
Neonate admitted to an intensive care unit (ICU) or special care unit (SCU)	377 (5·4)	44 (9·2)	333 (5·2)	<0·01
Neonatal death at 7 days or at discharge	93 (1·3)	9 (1·9)	84 (1·3)	0·43

* Maternal complications after birth included any of the following: postpartum haemorrhage, postpartum preeclampsia/eclampsia, anaemia requiring blood transfusion, postpartum endometritis, infection of caesarean incision site or perineal laceration site, respiratory tract infection, urinary tract infection, mastitis, postpartum psychosis, deep vein thrombosis, pulmonary embolism, peripartum cardiomyopathy; Percentages in parentheses.

† Chi-square p-value for this variable reported over all categories.

The majority of babies were born at term (86·2%), 8·3% were preterm (<37 weeks' gestation), and 5·4% were post-term (>42 weeks). The mean birth weight was 3095 g; 7·3% of babies were <2500 g. There were 93 perinatal deaths: 65 stillbirths, and 28 early neonatal deaths (stillbirth rate of 9·4/1000 births and early neonatal death rate of 4·1/1000 live births).

Comparison of pregnancy outcomes between women with an abnormal and normal RI shows similarities in several outcomes, including frequencies of women with complications after birth, term births, Apgar score <7 at 5 minutes, neonatal resuscitation at birth, stillbirths and perinatal deaths. However, women with an abnormal RI were significantly more likely to give birth via caesarean section (40·8% vs 28·1%, p<0·01), have induced labours (20·5% vs 9·0%, p<0·01) and were more likely to have an early preterm birth <34 weeks' gestation (4·2% vs 1·5%, p<0·01) than women with a normal RI. The leading indications for caesarean section in women with an abnormal RI were suspected or confirmed fetal growth restriction (20·4%) and fetal distress (17·9%) (abnormal RI alone was not an indication for caesarean section across study sites), whereas in women with normal RI the leading indications were previous caesarean section (34·3%) and fetal distress (16·0%) (data not shown).

Babies of women with abnormal RI were more likely to be admitted to an intensive care or special care unit (9·2% vs 5·2%, p<0·01) but the duration of admission did not differ between the two groups. The mean birthweight was significantly lower in women with an abnormal RI (2913 g vs 3108 g, p<0·01); low birthweight (<2500 g) was significantly more frequent among women with abnormal RI compared to women with normal RI (15·0% vs 6·8%, p<0·01). Even after correction for gestational age at birth and neonatal sex, abnormal RI was associated with lower birthweights across all weight centiles (p<0·0001) (Figure 4).

RI thresholds for identifying fetuses at increased risk of perinatal mortality

We were unable to identify a specific RI threshold associated with increased risk of perinatal mortality due to few events.

The effect of the screening with the Umbiflow device on utilisation of health service

Women in the abnormal RI group were more likely to have antenatal investigations – such as additional ultrasounds, blood tests or cardiotocography – following Umbiflow screening. 79·5% of these women had 4 or more investigations versus 65·3% of women with a normal RI (p<0·01) (Table 4). The median number of antenatal investigations per woman in the

abnormal RI group was 6 vs 5 in the normal RI group (p<0·01). Women with an abnormal RI had more antenatal visits than women with a normal RI: 3 vs 2 respectively (p<0·01).

Table 4: Health service utilisation outcomes

	All N = 6945	Abnormal RI N = 480	Normal RI N = 6465	P-value
Number of antenatal investigations* per woman after Umbiflow assessment Median (IQR)	5 (3, 7)	6 (4, 9)	5 (3, 7)	<0·01
4 or more antenatal investigations* after Umbiflow assessment N (%)	4494 (66·3)	381 (79·5)	4113 (65·3)	<0·01
Number of antenatal care visits per woman since Umbifow® assessment N, median (IQR)	6746, 2 (1, 3)	472, 3 (2, 4)	6274, 1 (1, 3)	<0·01

* Antenatal investigations included any of the following: full blood count, blood type, haemoglobin electrophoresis, urinalysis, urine culture, rubella test, syphilis test, HIV test, hepatitis B test, hepatitis C test, glucose tolerance test, ultrasound examination, full biophysical profile, amniocentesis, antenatal cardiotocography, labour admission cardiotocography, continuous cardiotocography during labour

DISCUSSION

Key findings

In this multi-country prospective cohort study of low-risk pregnant women in five LMICs, we found a 6·9% prevalence of abnormal RI of the fetal umbilical artery, and an overall AEDF prevalence of 0·2%. All countries in this study had a prevalence of AEDF below 0·2%, except South Africa with an AEDF prevalence of 0·7%. The prevalence of abnormal RI was reasonably equally distributed across 28 to 34 weeks' gestation. Women with abnormal RI were more likely to receive obstetric interventions such as caesarean section and labour induction, and had a higher frequency of antenatal investigations and clinic visits. While stillbirth and perinatal mortality rates were similar between women with abnormal and normal RI, we found that abnormal RI was associated with lower birthweights across all weight centiles, after correcting for neonatal sex and GA at birth.

Interpretation

The prevalence of abnormal RI in this study was slightly lower than expected compared to previous South African data as reported by Nkosi et al.[23] Another study using Umbiflow in 9 centres in South Africa by Hlongwane et al found a 12·5% prevalence of abnormal RI, including AEDF prevalence of 1·2%.[30] The reason for the higher prevalence in pregnant women in South Africa is not yet known, however, it is possible that the higher HIV prevalence in this setting may play a role.

Even though this study did not find a high prevalence of AEDF, we did detect nearly 500 fetuses with placental insufficiency at risk of FGR and therefore at risk of adverse perinatal outcomes. These fetuses were smaller at birth, irrespective of the GA at which they were born. The leading indications for caesarean section in women with abnormal RI were fetal growth restriction and fetal distress, both of which are suggestive of underlying placental insufficiency. Abnormal RI alone was not an indication for caesarean section across study sites, however women who had an abnormal RI were referred to a higher level of care where they received further intervention such as ultrasound. Thus, it was not surprising there were more investigations and interventions in the group with an abnormal RI, and these interventions might have prevented perinatal deaths.

Using conventional ultrasound, an estimated fetal weight below the 10th centile for the GA is generally used to diagnose FGR. However, this approach does not identify fetuses who are appropriate for gestational age, but did not reach their genetic growth potential. Furthermore, to diagnose FGR using ultrasound criteria, serial ultrasound examinations may be required, and we need to acknowledge that in LMICs, low-risk healthy pregnant women often do not have access to conventional imaging ultrasound (either single or serial ultrasound examinations).[31] Previous research has also demonstrated that even when conventional ultrasound is made available in LMICs, stillbirth or neonatal mortality rates will not necessarily improve.[32] These findings suggest that Umbiflow can help detect those fetuses with placental insufficiency at risk of FGR (across all weight centiles) and not just fetuses with an EFW below the 10th centile. It can therefore assist in differentiating between the truly growth restricted and not growth restricted fetus, rather than the "small" and "not-small" fetus. Umbiflow can be implemented at primary health care facilities, and be done by health care workers of all levels as it does not require advanced obstetric ultrasound expertise.

Strengths and limitations

To our knowledge, this is the first multi-country study assessing the prevalence of abnormal RI of the fetal umbilical artery in low-risk pregnant women in LMICs. All research staff who applied Umbiflow underwent a standardised training, and all doppler recordings were independently reviewed for quality assurance. Overall, the lost to follow-up in the study was low (2·9%). Nonetheless, our study has some limitations. Firstly, the definition of low-risk pregnant women was based on local guidelines; we did not mandate a specific risk screening protocol across all sites. While this was done to be pragmatic and reflect usual obstetric practice at each site, some conditions (such as a previous caesarean section or HIV) were considered differently across sites. Secondly, the prevalence of AEDF might be under-estimated as, despite our best efforts, 64 women with abnormal RI did not attend their referral visit. The 75th centile cut-off was chosen as it was the best predictor of perinatal morbidity and mortality in a referral hospital and in a low-risk population this cut-off detected approximately 10% of fetuses.[23] However, secondary analyses are planned to investigate different cut-offs. Lastly, we acknowledge that FGR and doppler abnormalities can arise beyond 34 weeks' gestation. For this study, a single screening was chosen to determine the prevalence and guide further research. The screening time was selected between 28-34 weeks' gestation because there were insufficient neonatal services in the countries to manage neonates under 28 weeks' gestation if delivery was required immediately; and the peak

incidence of small-for-gestational-age stillbirths was 34-37 weeks' gestation, allowing time to intervene prior to a stillbirth.[33]

Implications for policy, practice and research

This study demonstrates that a single doppler screening with Umbiflow between 28 and 34 weeks' gestation in low-risk pregnant women in LMICs can detect a large number of fetuses who are at risk of FGR and adverse perinatal outcomes that may otherwise not have been detected. The Umbiflow device is inexpensive and can be used by health care providers at lower levels of care and thus can be used to screen pregnant populations on a large scale to identify previously undetected FGR. Randomised trials that embed intervention strategies with doppler screening in low-risk women in LMICs are urgently needed to assess impact on priority outcomes, and to inform clinical practice.

CONCLUSION

This study shows that screening a low-risk pregnant population with Umbiflow detects a large number of fetuses with placental insufficiency and who were at risk of FGR. This high prevalence warrants further research into large-scale implementation so, with appropriate referral and intervention, perinatal mortality and morbidity could potentially drastically be decreased, especially in LMICs.

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The manuscript reflects views of the named authors only and does not reflect the views of the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) or World Health Organization.

Competing interests

The South African Medical Research Council (SAMRC) / University of Pretoria (UP) Maternal and Infant Health Care Strategies Unit has (VV, RP) has previously received funding from SAMRC and the Council for Scientific and Industrial Research (CSIR) for Umbiflow research done by Nkosi et al and Hlongwane et al. The CSIR provided the Umbiflow doppler probes and Umbiflow software used in this study. As a satellite research unit, the SAMRC Maternal and Infant Health Care Strategies Unit receives research funding from the SAMRC.

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Authors' contributions

This study was conceived by OTO. OTO and JPV coordinated the writing of the study protocol, with input from the country principal investigators. VV prepared the statistical analysis plan and led statistical analysis with TC. All country principal investigators (RA, EM, SSG, YP, AK, UC, ZQ, AO, GG, SR, RP, VV) were part of the Umbiflow International Study steering group and led the study with support from the co-investigators in each country. The Umbiflow International Study steering group reviewed and interpreted the final data at a workshop convened by WHO. The first draft of the manuscript was prepared by VV, with substantial input from JPV, RP, and OTO. All authors reviewed and revised the manuscript draft critically

for intellectual content and approved the final manuscript for publication. The manuscript represents the views of the named authors only.

Data sharing

Request for access to these data can be made to the World Health Organization through srhmph@who.int. Data sharing with any individual or organization will be subject to WHO data sharing policy.

Figure 1: The Umbiflow device

Credit: CSIR / SAMRC

Figure 2: Recruitment flowchart

Figure 3: Prevalence of abnormal RI by gestational age

Figure 4: Cumulative percentage of birthweights according to centiles in neonates of women with normal and abnormal RI

REFERENCES

1. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). A neglected tragedy: the global burden of stillbirths. United Nations Children's Fund, New York, 2020.
2. Gardosi J, Madurasinghe V, Williams M, et al. Maternal and fetal risk factors for stillbirth: population based study. *BMJ* 2013;**346**:f108. https://doi.org/10.1136/bmj.f108
3. Katz J, Lee ACC, Kozuki N, et al. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. *Lancet* 2013;**382**(9890):417–25. https://doi.org/10.1016/s0140-6736(13)60993-9
4. McIntyre S, Blair E, Badawi N, et al. Antecedents of cerebral palsy and perinatal death in term and late preterm singletons. *Obstet Gynecol* 2013;**122**(4):869–77. https://doi.org/10.1097/aog.0b013e3182a265ab
5. Bukowski R, Burgett AD, Gei A, et al. Impairment of fetal growth potential and neonatal encephalopathy. *Am J Obstet Gynecol* 2003;**188**(4):1011–5. https://doi.org/10.1067/mob.2003.233
6. Ross MG, Beall MH. Adult sequelae of intrauterine growth restriction. *Semin Perinatol* 2008;**32**(3):213–8. https://doi.org/10.1053/j.semperi.2007.11.005
7. Gluckman PD, Hanson MA, Cooper C, et al. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 2008;**359**(1):61–73. https://doi.org/10.1056/nejmra0708473
8. Salafia CM, Minior VK, Pezzullo JC, et al. Intrauterine growth restriction in infants of less than thirty-two weeks' gestation: associated placental pathologic features. *Am J Obstet Gynecol* 1995;**173**(4):1049–57. https://doi.org/10.1016/0002-9378(95)91325-4
9. Alberry M, Soothill P. Management of fetal growth restriction. *Arch Dis Child Fetal Neonatal Ed* 2007;**92**(1):F62–7. https://doi.org/10.1136/adc.2005.082297
10. Sovio U, White IR, Dacey A, et al. 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. https://doi.org/10.1016/s0140-6736(15)00131-2
11. Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. *Am J Obstet Gynecol* 2011;**204**(4):288–300. https://doi.org/10.1016/j.ajog.2010.08.055

12. Hepburn M, Rosenberg K. An audit of the detection and management of small-for-gestational age babies. *Br J Obstet Gynaecol* 1986;**93**(3):212–6. https://doi.org/10.1111/j.1471-0528.1986.tb07895.x
13. Backe B, Nakling J. Effectiveness of antenatal care: a population based study. *Br J Obstet Gynaecol* 1993;**100**:727–32. https://doi.org/10.1111/j.1471-0528.1993.tb14263.x
14. Bais JMJ, Eskes M, Pel M, et al. Effectiveness of detection of intrauterine growth retardation by abdominal palpation as screening test in a low risk population: an observational study. *Eur J Obstet Gynecol Reprod Biol* 2004;**116**(2):164–9. https://doi.org/10.1016/j.ejogrb.2004.01.037
15. Mufenda J, Gebhardt S, van Rooyen R, et al. 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* 2015;**10**(11):e0142743. https://doi.org/10.1371/journal.pone.0142743
16. Robert Peter J, Ho JJ, Valliapan J, et al. Symphysial fundal height (SFH) measurement in pregnancy for detecting abnormal fetal growth. *Cochrane Database Syst Rev* 2015;(9):CD008136. https://doi.org/10.1002/14651858.cd008136.pub3
17. Society for Maternal-Fetal Medicine Publications Committee, Berkley E, Chauhan SP, et al. Doppler assessment of the fetus with intrauterine growth restriction. *Am J Obstet Gynecol* 2012;**206**(4):300–8. https://doi.org/10.1016/j.ajog.2012.01.022
18. Salafia CM, Pezzullo JC, Minior VK, et al. Placental pathology of absent and reversed end-diastolic flow in growth-restricted fetuses. *Obstet Gynecol* 1997;**90**(5):830–6. https://doi.org/10.1016/s0029-7844(97)00473-0
19. Alfirevic Z, Stampalija T, Gyte GM. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev* 2013;(11):CD007529. https://doi.org/10.1002/14651858.cd007529
20. Alfirevic Z, Stampalija T, Medley N. Fetal and umbilical Doppler ultrasound in normal pregnancy. *Cochrane Database Syst Rev* 2015;(4):CD001450. https://doi.org/10.1002/14651858.cd001450.pub4
21. Hugo EJC, Odendaal HJ, Grove D. Evaluation of the use of umbilical artery Doppler flow studies and outcome of pregnancies at a secondary hospital. *J Matern Fetal Neonatal Med* 2007;**20**(3):233–39. https://doi.org/10.1080/14767050601134926

22. Theron GB, Theron AM, Odendaal HJ, et al. Comparison between a newly developed PC-based Doppler umbilical artery waveform analyser and a commercial unit. *S Afr Med J* 2005;**95**(1):62–4.
23. Nkosi S, Makin J, Hlongwane T, et al. Screening and managing a low-risk pregnant population using continuous-wave Doppler ultrasound in a low-income population: A cohort analytical study. *S Afr Med J* 2019;**109**(5):347–52. https://doi.org/10.7196/samj.2019.v109i5.13611
24. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva. 2016.
25. Von Elm E, Altman DG, Egger M, et al; STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE)statement: guidelines for reporting observational studies. *Bull World Health Organ* 2007;**85**(11):867–72. https://doi.org/10.2471/blt.07.045120
26. Committee on Obstetric Practice, the American Institute of Ultrasound in Medicine, and the Society for Maternal-Fetal Medicine. Committee Opinion No 700: methods for estimating the due date. *Obstet Gynecol* 2017;129(5):e150–e154. https://doi.org/10.1097/AOG.0000000000002046
27. Bhide A, Acharya G, Bilardo CM, et al. ISUOG Practice Guidelines: use of Doppler ultrasonography in obstetrics. *Ultrasound Obstet Gynecol* 2013;**41**:233–239. https://doi.org/10.1002/uog.12371
28. Pattinson RC, Theron GB, Thompson ML, et al. Doppler ultrasonography of the feto-placental circulation – normal reference values. *S Afr Med J* 1989;**76**:623–625.
29. Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. *PLoS Med* 2017;**14**(1):e1002220. doi: 10.1371/journal.pmed.1002220
30. Hlongwane TMAG, Cronjé T, Nkosi BSS, et al. The prevalence of abnormal Doppler's of the umbilical artery in a low-risk pregnant population in South Africa. 2020. Accepted for publication. *EClinicalMedicine* 2021;100792. https://doi.org/10.1016/j.eclinm.2021.100792
31. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consesus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol* 2016;**48**(3):333–9. https://doi.org/10.1002/uog.15884

32. Goldenberg R, Nathan RO, Swanson D, et al. Routine antenatal ultrasound in low- and middle-income countries: first look - a cluster randomised trial. *BJOG* 2018;**125**(12):1591–99. https://doi.org/10.1111/1471-0528.15287

33. Lavin T, Preen DB, Pattinson R. Timing and cause of perinatal mortality for small-for-gestational-age babies in South Africa: critical periods and challenges with detection. *Matern Health Neonatol Perinatol* 2016;**2**(1):11. https://doi.org/10.1186/s40748-016-0039-4

Figure 1: The Umbiflow device"Credit: CSIR / SAMRC

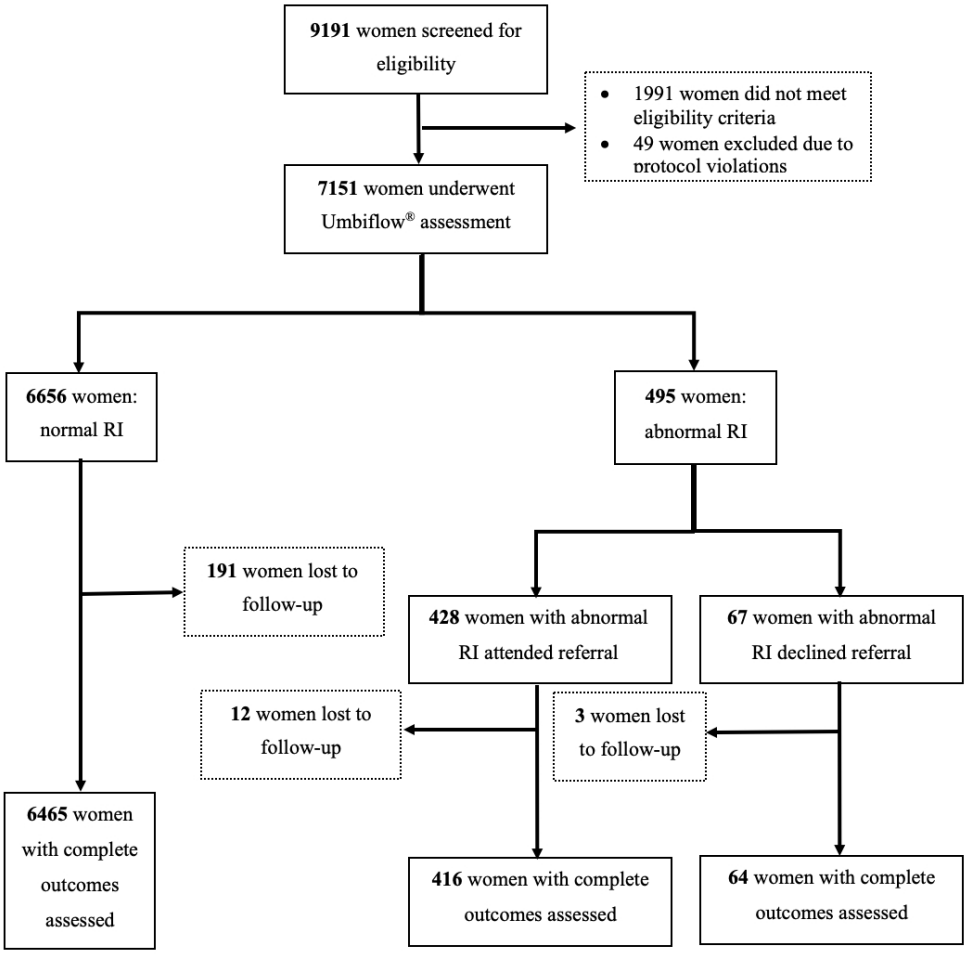

Figure 2: Recruitment flowchart

190x190mm (144 x 144 DPI)

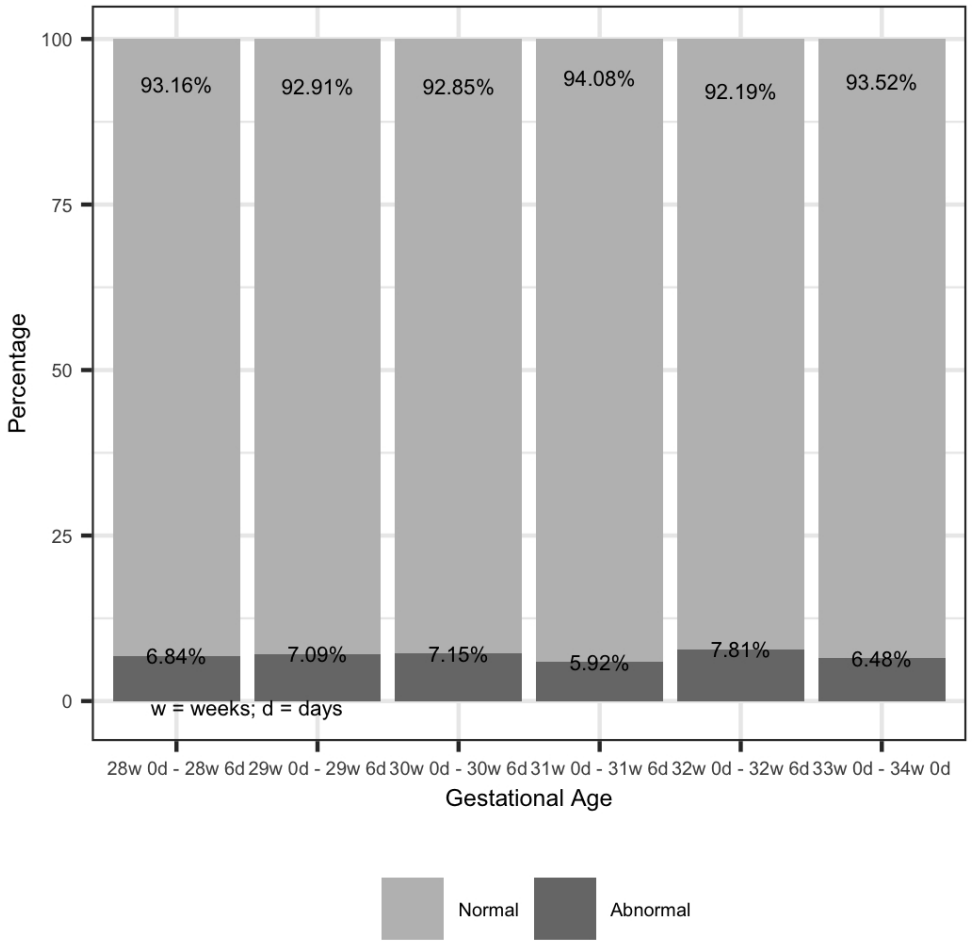

Figure 3: Prevalence of abnormal RI by gestational age

374x374mm (72 x 72 DPI)

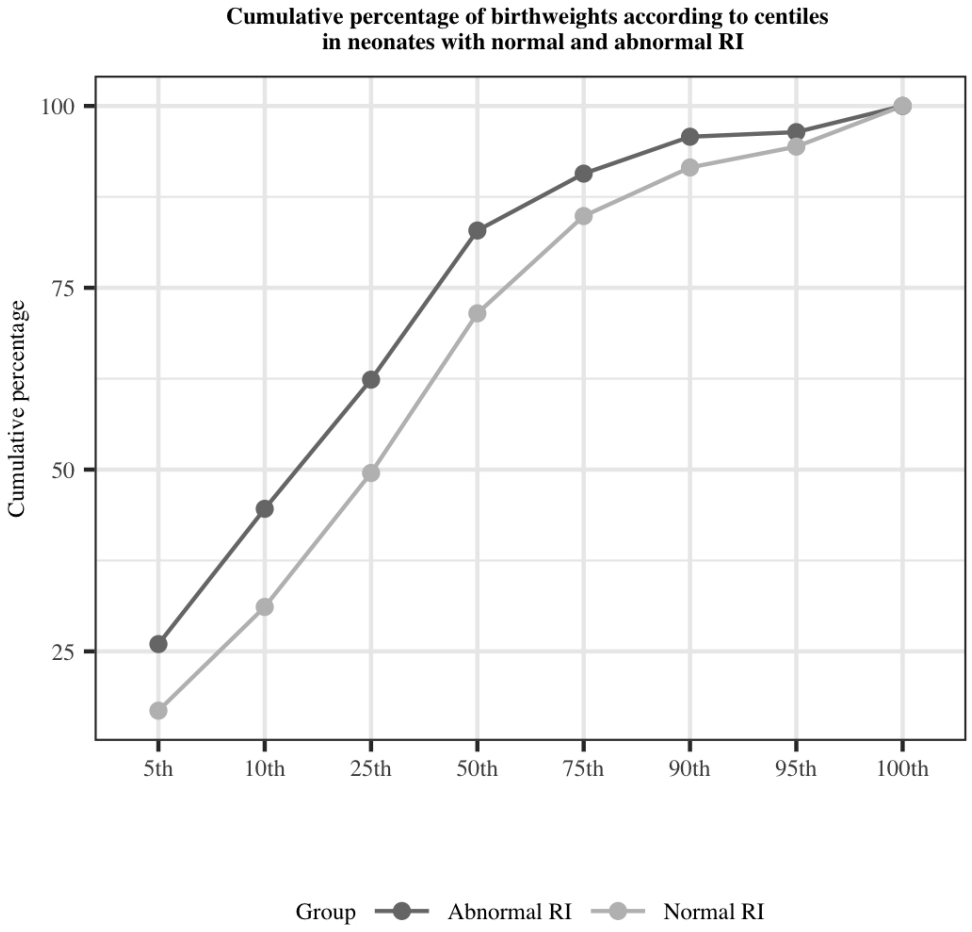

Figure 4: Cumulative percentage of birthweights according to centiles in neonates of women with normal and abnormal RI

374x374mm (72 x 72 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) If applicable, explain how loss to follow-up was addressed	10
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-Fig2
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	Fig2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	T1
		(b) Indicate number of participants with missing data for each variable of interest	T1
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	T2-4

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	T2 T3-4 NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	T3-4
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	4,19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.