Research Paper

The prevalence of abnormal Doppler's of the umbilical artery in a low-risk pregnant population in South Africa

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ARTICLE INFO

ABSTRACT

Background: The assessment of fetal blood flow using Doppler waveform can be used to identify placental insufficiency, and hence is a tool to identify fetuses at risk of stillbirth due to fetal growth restriction (FGR). In South Africa the largest category of perinatal deaths is 'unexplained intrauterine death'. The majority of the mothers are clinically healthy women. This study was performed to determine the prevalence of abnormal umbilical resistance indices (abnormal RI) to see if screening a low-risk pregnant population is worthwhile.
Methods: A descriptive study across 9 sites in 8 provinces of South Africa was performed to determine the prevalence of abnormal RI of the umbilical artery in women classified as having a low-risk pregnancy. The study was conducted from 1st September 2017- February 2020.The pregnant women classified were screened using a continuous wave Doppler ultrasound apparatus (Umbiflow™) between 28 and 34 weeks' gestation. Women with fetuses with an abnormal RI were referred to a high-risk clinic and were managed according to standard protocol. The outcomes of all the deliveries were recorded.
Findings: Umbiflow™ screening of the umbilical artery was performed in 7088 women across nine sites; 919 (13.0%) fetuses had an abnormal RI. Absent end diastolic flow (AEDF) was found in 87 (1.2%) fetuses. The prevalence of small for gestational ages (SGA) babies was 23.1% in the normal RI group and was significantly higher in the abnormal RI group 32.1% ($p<0.0001$). There was a statistical difference in the perinatal mortality rate between the normal RI (9.8/1000) and abnormal RI group (21.4/1000) [RR 0.046; 95% CI -0.06−0.98].
Interpretation: The prevalence of abnormal RI and AEDF in this screened low-risk population was about ten times higher than that previously recorded in high income countries. Continuous wave Doppler ultrasound screening detected previously undiagnosed growth restricted babies. The prevalence of AEDF warrants continuous wave Doppler ultrasound screening of the low-risk pregnant population in South Africa.
Funding: This study was funded by the South African Medical Research Council (SAMRC) and the Council for Scientific and Industrial Research (CSIR)

1. Introduction

The stillbirth rate is a good indicator of care during the third trimester and intrapartum period [1]. Stillbirths remain a global challenge, 2.0 million stillbirths occurred worldwide [2]. Majority occur in low-income and middle-income countries (LMICs) [2]. To put this into a global perspective, three-quarters of stillbirths occur in sub-Saharan Africa and Southern Asia [2,3] Fifty five percent stillbirths occur in rural families from these areas [3].

It is well known that routine clinical methods to detect poor fetal growth (palpation or symphysis fundal growth) are ineffective [4]. Recently a two-stage routine conventional ultrasound in low income countries was shown to have no effect on perinatal or maternal death or on antenatal attendance [5]. Routine fetal movement counting has also been shown to be ineffective and cannot be used as a method to detect fetuses at risk [6]. Detection of the fetuses that are at risk of growth restriction is a challenge due to resource constraints and the subjectivity of the current available antenatal fetal growth monitoring tools in LMIC [4−8].

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Research in Context

Evidence before this study

Doppler ultrasound of the umbilical artery has been shown to reduce the perinatal mortality rate by 38% when used in managing high risk pregnancies. However, there is insufficient evidence for use of routine umbilical artery Doppler ultrasound in low-risk women.

We searched the literature on studies that report on the use of umbilical artery Doppler, prevalence of abnormal Doppler's, absent end diastolic flow and reverse end diastolic flow in low-risk and unselected pregnant populations, with no restriction on date or setting. Evidence suggests that the prevalence of abnormal Doppler's and absent end diastolic flow are rare (0.05−2.1%) in low-risk or unselected pregnancies.

These reports are based on low-risk and unselected populations from high income countries, with low stillbirth numbers and there is insufficient data from low-income and middle-income countries and further research is required.

Added value of this study

This study reports on the prevalence of abnormal umbilical artery Doppler flow velocimetry's in a low-risk pregnant population in South Africa. We found the prevalence of abnormal Doppler resistance indices to be 13.0% and AEDF 1.2% in low-risk women screened with a continuous wave Doppler (Umbiflow™) between 28 and 34 weeks gestation. We found a significantly higher number of low birthweights (9.8% vs 20.5%, $p<0.0001$), small for gestational age neonates (23.1% vs 32.1%, $p <0.0001$). There was significant growth differences across all growth percentiles in the normal and abnormal Doppler resistance indices in this screened population.

This study has shown that the prevalence of abnormal Doppler resistance indices and absent end diastolic flow in low-risk 'healthy' pregnant women is higher than reported in high-income countries. It has demonstrated that screening with umbilical artery Doppler ultrasound can detect fetal growth restriction across all birth weight percentiles, identifying all fetuses at risk, not just the small for gestational age fetuses.

Implications of all the available evidence

There is limited evidence on umbilical artery Doppler use in low-risk women and prevalence of abnormal Doppler resistance indices in low-income and middle-income countries, where the burden of stillbirth and fetal growth restriction are high. Umbilical artery Doppler screening will help the South African National Department of Health reach one of their priorities of reducing stillbirths by identifying the fetus with fetal growth restriction antenatally, allowing for suitable interventions to prevent stillbirths.

This could inform further research on the effectiveness of integrating umbilical artery Doppler screening into routine antenatal care particularly in low-income and middle-income countries.

Standard imaging ultrasound is regarded as the gold standard of detecting small for gestational age babies (SGA) as it can assess fetal biometry and fetal growth [8]. Ultrasound Doppler on the other hand is an ultrasound to detect the blood flow waveforms within the umbilical cord vessels of a fetus, and it measures the placental function, and thereby detects placental insufficiency and fetal growth restriction (FGR) [7,8]. Placental insufficiency usually results in a decrease in placental blood flow and is detected by a rise in Doppler indices [7−9]. This rise in Doppler indices (abnormal RI) is associated with adverse outcomes, once absent or reversed end diastolic flow is detected it is associated with poor perinatal outcomes [7]. Doppler ultrasound has the advantage over conventional ultrasound in that it detects placental insufficiency irrespective of the fetal size [7−9]. Conventional ultrasound uses centile charts to detect poor growth and require repeated measurements to detect a fall-off in growth [7−9]. Despite the use of conventional ultrasound, the task of accurately identifying fetuses at risk of stillbirth from placental diseases continues to elude us [8,9]. Doppler ultrasound can detect placental insufficiency with a single reading [7−10].

Doppler ultrasound of the umbilical artery (UA) has been shown to reduce the perinatal mortality rate (PNMR) by 38% when used in the management of high-risk pregnancies [10]. Another systematic review concluded that routine use of umbilical artery Doppler cannot be recommended in low-risk pregnancies [11]. However, these recommendations were based on low-risk populations from high-income countries where the perinatal mortality is very low. They also indicated that further studies are needed to establish whether this intervention could potentially prevent perinatal deaths in LMICs. The WHO guideline development group agreed that the value of routine use of a single Doppler ultrasound assessment of the fetal blood vessels during the third trimester needs more rigorous evaluation, particularly in the LMIC [12].

In South Africa (SA), the largest category of perinatal deaths is unexplained stillbirths, which mostly present as macerated stillbirths [13,14]. One in four of the perinatal deaths were recorded as unexplained stillbirths [15,16]. Research has shown that this group is mainly a mixture of babies that have died due to FGR, post-maturity, congenital abnormalities and intrauterine infections [13−17].

Up to one quarter of the stillbirths are SGA or have FGR [14−16]. Many more stillbirths have placental insufficiency which is not recognised [14−16]. Studies have shown that SGA babies are at an increased risk of stillbirth compared to non-SGA babies in all gestations, and the risk of stillbirth for SGA babies increases with increasing gestation [14,17,18]. Some of the SGAs can be detected and some prevented by proper antenatal care [8,10,18,22,23]. Approximately 25% of children [1,14,17] born in LMICs are SGA. SGA fetuses are at an eight fold higher risk of stillbirth, neonatal death, perinatal morbidity and non-communicable disease[14,17,18] making the detection and clinical management of such infants important [14,15]. However, as many as three quarters of babies with FGR are not recognised as such before delivery [7−9,14−18]. In a low-risk pregnancy with a lower threshold of suspicion the detection rate is even lower, at approximately 15% [8,14]. Early recognition may prevent some of these deaths [8,17,18].

While Doppler assessment is beneficial for women with high-risk pregnancies, there is insufficient evidence on the benefits and harms of using Doppler in low-risk pregnancies [10,19,20]. The prevalence of abnormal RI or absent end-diastolic flow (AEDF) or reversed end-diastolic flow (REDF) in low-risk women is not well documented especially in LMIC [19,20]. Nkosi et al.[21] demonstrated a high prevalence of AEDF in a low-risk antenatal population in Mamelodi Township in South Africa. This study was undertaken to ascertain if the findings of Nkosi et al.[21] could be repeated in other areas in South Africa and to establish the true prevalence of abnormal RI and AEDF.

2. Methods

2.1. Study design

A descriptive study investigated the prevalence of abnormal RI and AEDF of the umbilical artery detected by screening in women classified as having low-risk pregnancies attending primary health

antenatal care at their local clinics. The population of low-risk women, were defined as pregnant woman attending non-specialist antenatal care clinics and classified as "low-risk" according to local clinical guidelines at the time of recruitment [12], based on their obstetric and clinical assessment, as guided by the SA basic antenatal care plus program following the WHO recommendations for a positive pregnancy experience [12,22]. The risk classification is updated and revised after each antenatal contact based on the pregnancy progress and assessment [12,22]. Basic antenatal care plus, pregnant women have a minimum of eight antenatal contacts, including the booking contact prior to 12 weeks, and 20 weeks dating ultrasound (This is recommended, but not available and or accessible at all facilities in the country. Routine ultrasounds are not done in primary health care clinics and ultrasound is performed on indication [e.g. symphysis fundal height greater than dates, multiple pregnancy, or fetal heart activity not heard]. The woman needs to be referred to hospital to have an ultrasound). A pragmatic approach incorporating information such as the last menstrual period, symphysis fundal height and early ultrasound if it available is used. Women are then seen four weekly till 32; followed by 2 weekly contacts until 38 weeks, then weekly contact till delivery [12,15,22,23]. At the booking contact women are fully assessed, medical and previous obstetric history considered, appropriate physical examinations done and side room investigations are done for; haemoglobin, rhesus blood group, rapid plasma reagin and human immunodeficiency virus (HIV) testing after informed consent has been obtained. HIV reactive women are only classified as high risk if they develop complications associated with HIV infection or have other secondary pregnancy or medical complications. Pregnant women are issued with patient-held maternity case record [22]. They are referred to the higher level of care if they develop pregnancy related complications or have pre-existing medical conditions [2].

The recruitment sites consisted of primary care clinics in the catchment areas of nine regional hospitals across South Africa; namely Pholosong Hospital, Mafikeng Hospital, Dr Harry Surtie Hospital, Tshilidzini Hospital, Themba Hospital, Bongani Hospital, Stanger Hospital, Klerksdorp Hospital and Dora Nginza Hospital. The sites were purposively selected, and had a study health care worker screening eligible women on specific days of the week. Each site had an established referral route to refer women with abnormal RI findings for further assessment and management by a hospital team at the appropriate level of care. The next level of care had a maternal and neonatal unit, with access to theatre, blood products and ability to care for neonates of 1000 g or more. Facilities had access to emergency medical services for ease of patient transportation when necessary and were familiar with the Perinatal Problem Identification Program [13] (PPIP) data system.

The study started with recruitment and screening in September 2017, the different sites started at different times to allow for adequate training and quality control at all of the nine sites across SA.

2.2. Ethics

Ethics approval was obtained from the University of Pretoria faculty of Health Sciences (473/2014), and the study was registered with the South African National Research database. Written, informed consent was obtained from all women prior to conducting the Umbiflow™ screening.

2.3. Study participants

A sub-set of women classified as having low-risk pregnancies, between 28 and 34 week's gestations or a symphysis fundal height of more than 26 cm if gestational age was unknown were recruited by health care workers for an Umbiflow™ screening examination. Gestational age staging was determined by the best available clinical obstetric assessment using the last normal menstrual period, early dating ultrasound, or both and or antenatal symphysis fundal height measurement if gestational age was unknown. Dating ultrasound services are not available at all facilities offering antenatal care [23]
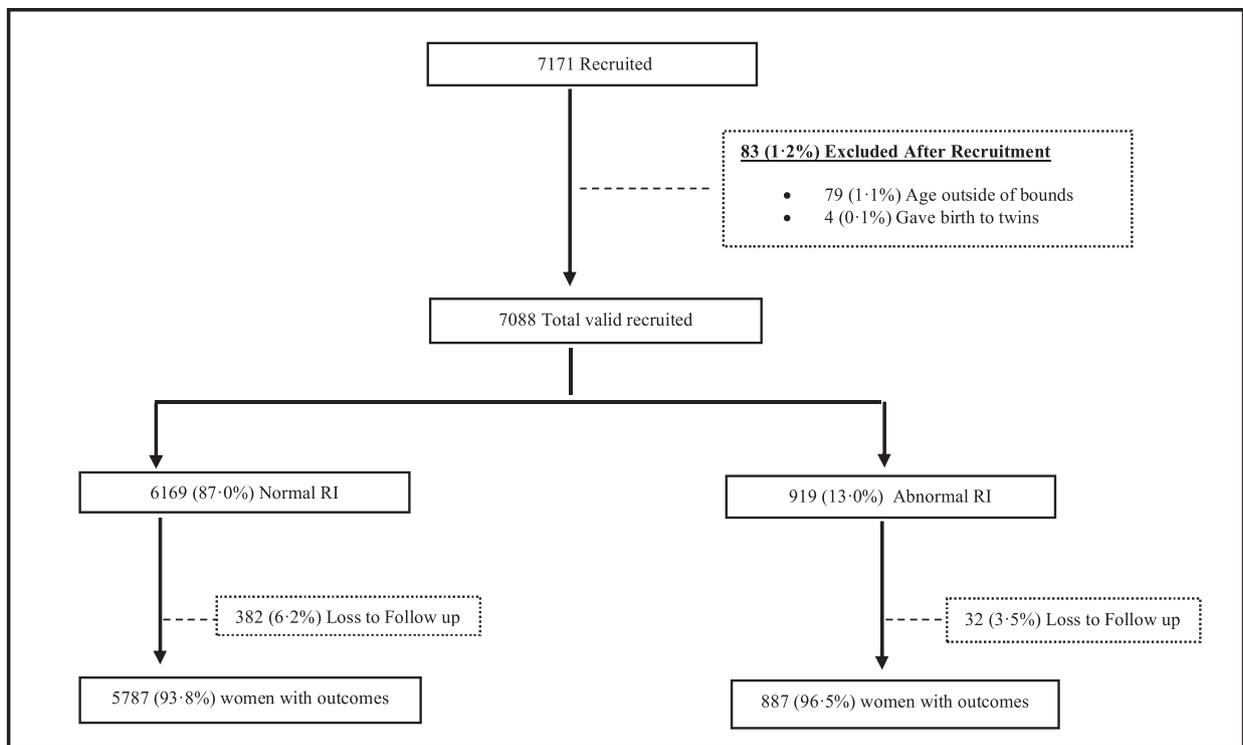
Flow diagram of participants screened with Umbiflow. RI=Resistance index

Fig. 1. . Flow diagram of participants in the Umbiflow study
Flow diagram of participants screened with Umbiflow. RI=Resistance index.

and only 25·5% of the Umbiflow screened women had a dating sonar before 22 weeks gestation [not shown]. Women screened had a printout of the Umbiflow™ examination for transparency and quality of the Doppler waveform of the umbilical artery could be assessed.

Women with multiple pregnancies (multiple pregnancies are considered as high-risk, and were not eligible) and those women with a gestational age below 28 weeks or symphysis fundal height below 26 cm, or aged below 18 years were excluded. Screening was done at or after 28 weeks' gestation, so most fetuses would have weighed more than 1000 g at enrolment into the study. Fig. 1 illustrates the flow diagram of women recruited in the study.

2.4. Measurements

Umbiflow device is a low-cost continuous wave Doppler device, it has been developed by the Council for Scientific and Industrial Research (CSIR) and SAMRC in SA [24]. Umbiflow™ is a mobile-connected Doppler device that uses a continuous-wave waveform to detect blood flow within the fetal umbilical cord [24,25]. It consists of a handheld proprietary Doppler probe (transducer) with a universal serial bus (USB) cable that connects to any windows-based notebook on which the necessary software is installed [24,25]. Umbiflow™ measures the RI in the umbilical cord and plots it against the estimated gestational age to identify the fetus at risk for growth restriction [24–26]. The accuracy of the Umbiflow system in measuring the RI in the fetal umbilical artery has already been proven to be comparable to the commercial standard unit "gold standard" [24,25].

The Umbiflow™ of the umbilical artery screening was classified as either normal or abnormal RI depending on the RI value in relation to gestational age, which was plotted on a graphic representation using the 75th centile as a cut off [26,27]. Screened women with a RI findings below the 75th centile for their gestational age were considered normal RI, and continued their routine antenatal care at their local primary health care clinics. Those with RI findings above the 75th centile for gestational age were considered as having an abnormal RI and were referred to a high-risk clinic at their local regional hospitals for further assessment and management.

At the high-risk clinic a detailed ultrasound examination and pulsed wave Doppler were performed. Women identified as having abnormal RIs were managed according to a standard protocol. Women with AEDF at the high risk visit were admitted, given corticosteroids (unless gestational age was more than 34 weeks) and the fetus was monitored using a cardiotocograph. Women with an abnormal RI were followed-up biweekly at the clinic and received a Doppler ultrasound at each visit and a growth scan every two weeks. Delivery was performed if the pregnancy reached 34 weeks' gestation and had AEDF or 38 weeks' gestation based on risk; or if cardiotocograph became pathological; no fetal growth or if the maternal condition deteriorated. We estimated that 1000 women were needed per site to detect a prevalence of 1.5% of AEDF in women screened with the Umbiflow™ device, based on the findings from Nkosi et al [21].

2.5. Data collection

Participant information including sociodemographic, behavioural factors, medical and obstetric history was obtained at enrolment through an interview and medical record review. The Umbiflow™ findings were documented. The details of all the women delivering at the antenatal clinics and the referral hospitals was recorded in the electronic birth registers. The outcome of all Umbiflow™ screened was recorded, and the normal RI and abnormal RI groups compared, with focus on demographics and delivery outcomes. Outcome data was obtained from the electronic birth register at the various delivery sites. An outcome was regarded as missing if there was no record of delivery at the relevant hospitals or clinics and after three attempts were made to contact the participants telephonically at different times of the day using the contact details recorded at the start of the study.

2.6. Statistical analysis

Analysis of the prevalence of abnormal Doppler's was limited to all screened women, analysis of delivery outcomes was limited to woman-infant dyad that had available delivery outcomes; including the mode of delivery, neonates' sex, and birth weight.

Maternal clinical information was collected at the time of enrolment in the study. Variables reported in this manuscript include maternal age in years, parity, HIV status, birth weight in grams (g), low birth weight (defined by birth weight below 2500 g), neonatal admission to neonatal unit post-delivery, mode of delivery, and stillbirths (defined as an infant with no signs of life at 1 min and 5 min [APGAR of zero]) and neonatal deaths (defined as death of neonate in the first 28 days of life). Neonatal clinical outcomes were abstracted from the maternity case records, this included birth weight, sex, APGAR at one and five minutes, neonatal admission and neonatal complications. The maternal demographics are reported as frequency and the prevalence of normal RI and abnormal RI are reported in percentage. Categorical characteristics were investigated using chi square tests to express differences between the normal RI and abnormal RI groups and the two-proportion z tests for cases where only certain categories were compared. The WHO multinational fetal growth charts were used for categorizing birth weight according to percentiles, and corrected for gestational age at delivery and neonatal sex [27]. All tests were performed at a 5% level of significance. The relative risk was calculated using the incidence proportions of total stillbirth rate, fresh and macerated stillbirth rate and the overall perinatal mortality rate between the normal RI and abnormal RI groups. All statistical analyses were done with R Core Team (2020) https://www.R-project.org/.

2.7. Role of funding source

The funding source played no role in the study design, screening, data collection and analyses, preparation of manuscript or approval of the manuscript. The funder was provided the opportunity to hear the preliminary findings of this study, but the authors were solely responsible for the final content and interpretation of the manuscript. The authors had access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

Umbiflow screening was performed in 7171 women across nine sites in SA. Eighty three women were excluded from the analysis; 79 (1·1%) were below 18 years of age, and four women (0·1%) had multiple pregnancies. We analysed 7088 women and normal RIs were found in 6169 (87·0%) women; 919 (13·0%) fetuses abnormal RIs. AEDF was found in 87 (1·2%) of fetuses. Table 1 illustrates all the recruitment sites.

Of the 7088 women screened, 6674 (94·2%) had delivery outcomes. The demographics and outcomes of the Umbiflow population describing the normal RI and abnormal RI groups are given in Table 2.

There was no statistical difference in age (20 years−34 years: 77·1% vs 75·1%, p 0·056) and parity (parity 1−4: 65·0% vs 66·8%, p 0·309) between the abnormal RI group and the normal RI group. The abnormal RI group had significantly more HIV reactive women (29·9% vs 33·2%, p 0·048). The abnormal RI group had more low birth weight neonates (9·8%. vs 20·5%, p <0·0001), SGA neonates (23·1% vs 32·1%, p <0·0001) and more admissions to the neonatal care unit (6·5% vs 12·0%, p <0·0001). The abnormal RI group also had more caesarean section deliveries than the normal RI group (28·3% vs 38·3%, p <0·0001).

Table 1
Prevalence of abnormal Doppler's across 9 sites in South Africa.

Sites	Recruited (N = 7088)	Normal RI (n = 6169)	Abnormal RI (n = 919)	AEDF (n = 87)
Pholosong	1111	883 (79·5%)	228 (20·5%)	10 (0·9%)
Dr Harry Surtie	509	467 (91·7%)	42 (8·3%)	6 (1·2%)
Mafikeng	476	449 (94·3%)	27 (5·7%)	4 (0·8%)
Tshilidzini	673	616 (91·5%)	57 (8·5%)	7 (1·0%)
Bongani	629	520 (82·7%)	109 (17·3%)	9 (1·4%)
Stanger	1097	972 (88·6%)	125 (11·4%)	10 (0·9%)
Klerksdorp	982	919 (93·6%)	63 (6·4%)	14 (1·4%)
Themba	749	582 (77·7%)	167 (22·3%)	18 (2·4%)
Dora Nginza	862	761 (88·3%)	101 (11·7%)	9 (1·0%)
Average Prevalence* (%) (95% CI)		87·0% (83·8%; 92.3%)	13·0% (7.7%; 17.2%)	1·2% (0.87%; 1.61%)

The Prevalence of normal and abnormal Doppler's across 9 sites. Data n/N (%), RI= resistance index, AEDF= absent end diastolic flow, CI= confidence interval. * The overall average prevalence across all 9 sites with the 95% CI included.

Table 2
Demographic and outcome information on the Umbiflow™ population.

Demographic information on the Umbiflow screened population			
Indicator	Normal RI (N = 6169, 87·0)n (%)	Abnormal RI (N = 919, 13·0%)n (%)	Total (N = 7088)n (%)	p-value
Age in years (y)				
unknown	8	0	8	
18−19	446 (7·2%)	58 (6·3%)	504 (7·1%)	0·056
20−34	4751 (77·1%)	690 (75·1%)	5441 (76·9%)	
35+	964 (15·6%)	171 (18·6%)	1135 (16·0%)	
Parity (before current pregnancy)				
0 to 0	2097 (34·0%)	292 (31·8%)	2389 (33·7%)	0·309
1 to 4	4004 (65·0%)	613 (66·8%)	4617 (65·2%)	
5+	61 (1·0%)	12 (1·3%)	73 (1·0%)	
unknown	7 (0·1%)	2 (0·2%)	9 (0·1%)	
HIV				
positive	1842 (29·9%)	304 (33·2%)	2146 (30·3%)	0·048
negative	4324 (70·1%)	613 (66·8%)	4937 (69·7%)	
unknown	3 (0·0%)	2 (0·2%)	5 (0·1%)	
Outcomes information of the Umbiflow screened population				
Indicator	Normal RI (N = 5787) n (%)	Abnormal RI (N = 887) n (%)	Total (N = 6674) n (%)	p-value
Birth Weight in grams (g) Categories at Delivery				
1000 g- 1499 g	11 (0·2%)	21 (2·4%)	32 (0·5%)	<0·0001
1500 g - 1999 g	83 (1·4%)	42 (4·8%)	125 (1·9%)	
2000 g −2499 g	472 (8·2%)	118 (13·4%)	590 (8·9%)	
>2500 g	5189 (90·2%)	701 (79·5%)	5890 (88·7%)	
missing	32 (0·6%)	5 (0·6%)	37 (0·6%)	
LBW <2500 g	566 (9·8%)	181 (20·5%)	747 (11·3%)	<0·0001
SGA*	1335 (23·1%)	285 (32·1%)	1620 (24·3%)	<0·0001
Admission Nursery**	350 (6·5%)	104 (12·0%)	454 (7·3%)	<0·0001
Delivery Mode				
Caesarean Section	1603 (28·2%)	339 (38·3%)	1942 (29·5%)	<0·0001
Vaginal Delivery	4086 (71·8%)	546 (61·7%)	4632 (70·5%)	
missing	98 (1·7%)	2 (0·2%)	100 (1·5%)	
Impact on the Umbiflow screened population				
Indicator	Normal (N = 5787)	Abnormal RI (N = 887)	Total (N = 6674)	
Impact				RR (95% CI)
SBR (/1000)	54 (9·3)	13 (14·6)	67 (10·0)	0·64 (0·03; 1·25)
MSB (/1000)	34 (5·9)	9 (10·1)	43 (6·4)	0·58 (−0·16; 0·132)
FSB (/1000)	20 (3·5)	4 (4·5)	24 (3·6)	0·77 (−0·31; 0·84)
NND (/1000)	3 (0·5)	6 (6·8)	9 (1·3)	0·08 (−1·31; 1·46)
PNMR(/1000)	57 (9·8)	19 (21·4)	76 (11·4)	0·046 (−0·06; 0·98)

Data are n/N (%),) LBW= low birth weight, RR= Risk ratio, CI= confidence interval, SB= stillbirth, SBR= Stillbirth rate, MSB= macerated stillbirth, FSB= fresh stillbirth, NND= neonatal death, PNMR= perinatal mortality rate.
*SGA determined using the WHO growth charts (Total 6580; 94 missing values due to variables needed for growth charts).
**Neonatal admission includes all newborns admitted to the neonatal unit for observation or treatment after delivery.

The perinatal mortality rate was higher in the abnormal RI group (9·8/1000 vs 21·4/1000, RR 0·046, 95% CI −0·06−0·98) where there were nine macerated and four fresh stillbirths and six neonatal deaths. Of the 13 stillbirths, six had AEDF (three were stillbirths which occurred after the mother declined admission or treatment. The other three were admitted; but two had fresh stillbirth, and one

had no fetal heart activity at the time of admission to the ward). The six neonatal deaths in the abnormal RI group, one had AEDF; the mother was admitted at 29 weeks, received steroids and later developed a pathological CTG, and was delivered by a caesarean section. The neonate weighed 1150 g, and demised in the neonatal unit due to complications of prematurity. Two were admitted with severe

Table 3
Primary Obstetric causes of stillbirths in the screened population.

Primary Obstetrics causes of stillbirths in the screened population	Normal RI ($n = 54$)	Abnormal RI ($n = 13$)	All screened SB ($N = 67$)
Idiopathic preterm labour	4	0	4
Unexplained intrauterine death	19	5	24
Intrapartum care related asphyxia	12	3	15
Infection Amniotic fluid infection	1	0	1
Congenital abnormalities	3	2	5
Idiopathic intrauterine growth restriction	0	3	3
Postdates	9	0	9
Hypertensive disorders in pregnancy	5	0	5
Antepartum haemorrhage	1	0	1

RI=resistance index.

Table 4
Primary causes of neonatal morality in the screened population.

| Primary causes of neonatal deaths in the screened population	Normal RI ($N = 3$)	Abnormal RI ($N = 6$)	Screened ($N = 9$)
Proteinuric hypertension	0	2	2
Labour related intrapartum asphyxia	1	0	1
Abnormality of multiple systems	1	0	1
Cardiovascular system abnormality	0	1	1
Immaturity related (prematurity)	0	1	1
No obstetric cause / not applicable	1	2	3

RI= resistance index.

preeclampsia and developed fetal distress and delivered a 1390 g infant and 1600 g respectively, the 1390 g infant demised in NICU on day eight of life and the 1660 g infant demised on day five of life. The other two abnormal RI group neonatal deaths, delivered and both mothers and neonates were discharged home, and had adverse outcomes whilst at home. One other had congenital abnormalities of multiple systems involving the respiratory and cardiovascular system. There were 57 perinatal deaths in the normal RI group, 54 stillbirths and three neonatal deaths. Table 3 and 4 demonstrates the causes of perinatal deaths in the screened population.

Figs. 2 and 3 show the patterns of growth in the normal and abnormal RI groups. Even after correction for gestational age at birth, neonatal sex, an abnormal RI was associated with a lower birthweight across all weight percentiles ($p<0.0001–p\ 0.0304$). These patterns are significantly different between the 2 groups (below 5th percentile to 75th percentile $p<0.0001$ across all percentile categories, between 75th and 90th percentile p 0.0082). This indicates the abnormal RI group had more growth restricted babies across all growth centiles.
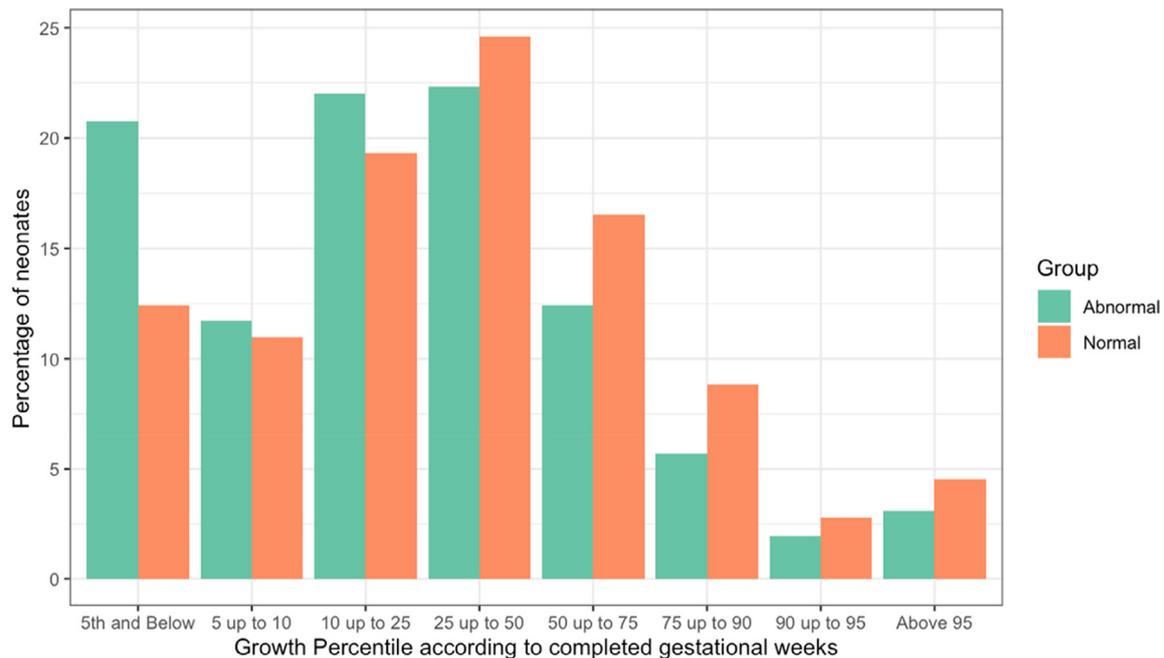
Data are n/N (%). Testing to see if differences exist between normal and abnormal points

Fig. 2. Distribution of growth in the normal RI and abnormal RI groups
Data are n/N (%). Testing to see if differences exist between normal and abnormal points.
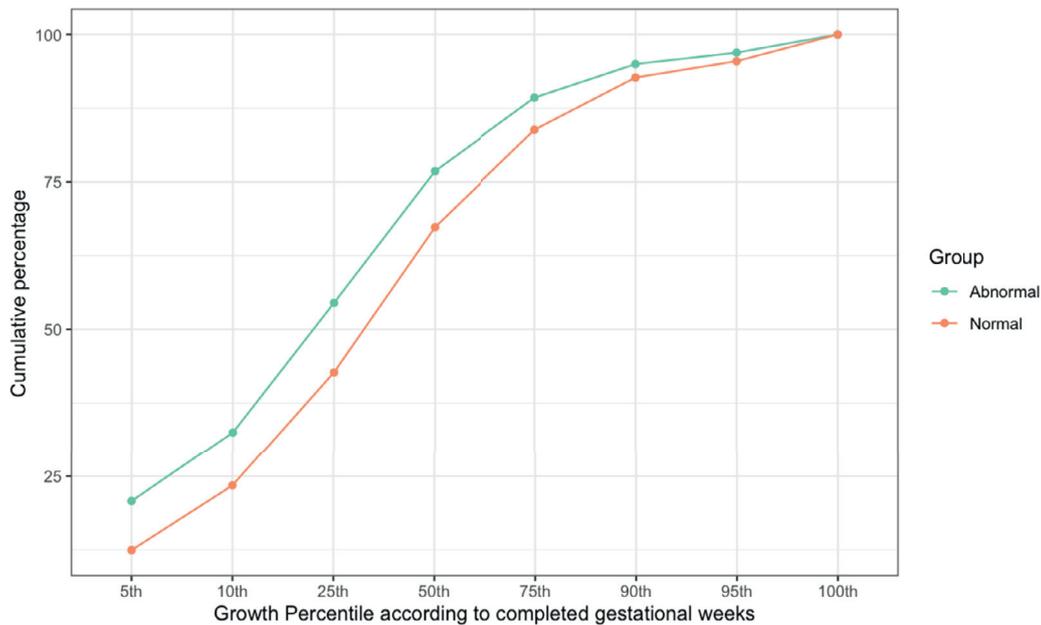
Data are n/N (%), Testing to see if differences exist between normal and abnormal points (Testing if abnormal is higher than normal) p-value. 5th and below 5th percentile p<0·0001, 5th to 10th percentile p<0·0001, 10th to 25th percentile p<0·0001, 25th up to 50th percentile p<0·0001, 50th to 75th percentile p<0·0001, 75th to 90th percentile p 0·0082, 90th to 95th percentile p 0·0304.

Fig. 3. Cumulative growth patterns in normal and abnormal RI groups.
Data are n/N (%), Testing to see if differences exist between normal and abnormal points (Testing if abnormal is higher than normal) p-value. 5th and below 5th percentile p<0·0001, 5th to 10th percentile p<0·0001, 10th to 25th percentile p<0·0001, 25th up to 50th percentile p<0·0001, 50th to 75th percentile p<0·0001, 75th to 90th percentile p 0·0082, 90th to 95th percentile p 0·0304.

4. Discussion

This descriptive study was multi-centred and included nine sites across SA; encompassing urban, peri-urban and rural sites across the SA landscape. This design was used to minimise selection and report bias and allowed determination of the prevalence of the outcomes in different settings across SA. The performance of Umbiflow™ screening between 28 and 34 weeks' gestation in a low-risk pregnant population identified high RIs in 13·0% (CI 7·7−17·2%) of screened women. AEDF was found in 1·2% (CI 0·89−1·61%) of the screened women. This is comparable to a study done in a low-risk pregnant population in Mamelodi which found the prevalence of AEDF of 1·5%, and a raised RI of 11·7% in the screened population [21]. These findings are higher than what is recorded in older studies done in low-risk or unselected pregnant population, mostly done in high income countries [19,20].

Literature reports that majority of stillbirths occur in mothers who are considered low-risk or clinically healthy [1,2]. In South Africa majority of the macerated stillbirths are unexplained and a number of these are low birth weight or small for their gestational age [1,14].

Women who were identified as having abnormal RI based on their Umbiflow™ screening were initially considered as having low-risk pregnancies, and had uncomplicated pregnancies according to SA guidelines (based on the World health Organizations recommendations [12]) prior to their screening. They were thus not expected to have any maternal or fetal problems; but 87 women had AEDF, and seven of these fetuses had adverse outcomes. Three declined admission and treatment and subsequently delivered macerated stillbirths. Active follow-up and management of women identified with abnormal (high) RIs might have improved the perinatal outcomes, as literature shows that high RI's and AEDF is associated with adverse outcomes [7,9]. In this group those who declined treatment, or missed their follow-up appointments had adverse outcomes. The abnormal RI group had a significantly higher number of low birth weights, SGA and neonatal admissions, and more perinatal deaths. There was a higher macerated stillbirth rate within the abnormal RI group, particularly within the AEDF group who declined admission, follow-up or treatment. This is a similar finding in other studies looking at high Doppler velocimetry's and its association with placental insufficiency and FGR [21,28,29].

FGR and SGA represent a significant proportion of stillbirths in LMICs [8,9,18,29]. They are a common cause of preventable stillbirths. FGR and SGA can be seen as synonymous, and the associations between their smallness and adverse outcomes is blurred. Their aetiology can be partially attributed to common antecedents such as placental insufficiency. This can be adjusted for by the use of customised growth charts, which may improve the link between low birth weight and pathology [8,9,28]. A large proportion of preventable stillbirths have an estimated fetal weight of >10th percentile and this risk steadily rises in small fetuses below a baseline in the 25−75th percentile range of fetal growth [8,9]. Use of Umbiflow™ was able to detect 290 (32·5%) of SGA infants in the abnormal RI group, and more were probably, growth restricted but did not meet the SGA criteria (Figs. 2 and 3). This highlights the problem of the definition of SGA as FGR. We need tools to supplement conventional imaging ultrasound to find the subsets of pregnancies that are vulnerable and at risk of placental dysfunction [8,9,28]. One approach would be to integrate Doppler use even in low-risk pregnancies. Umbiflow™ was able to detect fetuses in pregnancies classified as 'low-risk' as being at risk of FGR, this was demonstrated across all growth percentiles. The fetuses were smaller at birth, irrespective of their gestational age at the time of delivery. Use of Doppler has the added benefit over conventional imaging ultrasound in that it identifies placental insufficiency irrespective of fetal size. Antenatal detection of FGR is an essential component of antenatal care as it can inform the pregnancy that is at increased risk, allowing considerations on the optimal management

and optimal timing for delivery. Literature demonstrates that babies who are not fulfilling their growth potential have a 5- to 10-fold risk of dying in utero, making antenatal detection of FGR crucial [8,9,18,28] Table 4.

Umbiflow™ screening was performed at 28−34 weeks' gestation so as to allow for active management if necessary to aid in survival as the referral facilities were skilled and equipped to look after neonates of gestational age at or above 28 weeks and birth weight around 1000 g. Once an abnormal RI was identified, the woman was referred to a high-risk antenatal clinic, and managed actively according to a standard protocol. Continuous communication and an established referral route are essential if Umbiflow™ Doppler screening to identify fetuses at risk of placental insufficiency is to be conducted at primary health care clinics. Nkosi et al., [21] has shown that the perinatal mortality rate of a group of low-risk women that had an Umbiflow™ examination was significantly lower than the perinatal mortality rate of women also classified as low-risk and from the same clinics but did not have an Umbiflow™ examination.

In this study women with abnormal RI were referred to the next level of care and were more likely to attend more antenatal contacts, and receive more intervention such as caesarean section delivery and their neonates more likely to be admitted after delivery. For Umbiflow™ screening to work local health system circumstances need to be assessed for established referral routes, maternity care services with access to caesarean section and neonatal services. This was feasible in SA's health system and Umbiflow™ Doppler screening was performed in different circumstances (urban, peri-urban and rural areas). In many low-income and middle-income countries antenatal care is provided at primary health care facilities without access to ultrasound and Doppler [23]. The Umbiflow™ device can be safely used by nurses to provide Doppler in settlings were conventional imaging ultrasound is not accessible [21,24,25]. The prevalence of abnormal RI in this South African population is high enough to warrant pregnant population screening to detect abnormal RI and FGR and potentially prevent unexplained stillbirths.

This is the second, but largest study to date, using Umbiflow to detect abnormal Doppler RI waveforms in low-risk pregnant population in SA. Trained health care professionals are able to use the device, and its use is not restricted to specialised professionals [21,24,25]. The continuous wave Doppler is an effective inexpensive tool, that allows the classic waveform signature of umbilical artery and vein to be identified without the use of imaging ultrasound [21,24,25]. It is suitable for screening a pregnant population as low level health care workers can be trained to use it within a short period (7−14 days) and the apparatus is mobile. Thus screening and detecting all pregnancies for fetuses with FGR is possible and where an abnormality is identified and managed according to a standard protocol a significant reduction in stillbirths can be achieved [21].

Limitations of this study included site specific limitations; recruiting on certain days of the week and some sites experienced more disruptions in service provision due to service delivery protests. This affected participant enrolment, as some facilities were not operational during the heavy protest periods (mostly affected Mafikeng, Tshilidzini and Dora Nginza) [30].

Another limitation is that the Doppler RI curves for the SA population were developed in the late 1980s,[26] and since then a lot of changes in the SA population have occurred with HIV and lifestyle factors such as smoking and family dynamics being different [21]. The current curves may need to be updated to reflect the current population. Also, there are no customised ultrasound growth curves for the South African population.

The prevalence of abnormal RI's and AEDF in this low-risk population is high and is comparable to another SA study [21]. This is about 10 times higher than that previously recorded in high income countries making it worthwhile to screen a pregnant population in SA. Screening with Umbiflow™ is effective in detecting FGR and SGA

neonates as a proxy for growth restriction, and the prevalence of abnormality high enough to warrant routine screening. There is a need for an antenatal tool to assess placental function to identify fetuses at risk of dying. Screening a low-risk pregnant population using continuous wave Doppler ultrasound may reduce the prevalence of unexplained stillbirths in SA.

Declaration of Competing Interest

None.

Author contributors

All authors contributed to this article. The study was conceptualised by RP and TH coordinated the writing of the protocol with input from RC and SN. TH conduct the study and supervised all sites, sites training, data collection and interpretation and prepared the manuscript. TC led the statistical analysis. RC, TH, TC and SN reviewed and interpreted the data. TH prepared the manuscript with input from TC, SN, and RC. All authors reviewed and revised the manuscript and approved the manuscript for publication.

Data sharing

The data from this study, which include de-identified participant data that underlie the results reported in this manuscript will be available from the publication date, along with the study protocol. The data will be password protected and made available to researchers. Proposals should be directed to matinfru@up.ac.za, to gain access data requestors will need to sign a data access agreement.

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