
The effect of introducing Basic Antenatal Care Plus and Umbiflow on antenatal care and perinatal mortality

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The effect of introducing Basic Antenatal Care Plus and Umbiflow on antenatal care and perinatal mortality.

PhD Obstetrics and Gynaecology

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Declaration

I, TMAG Hlongwane, hereby declare that the dissertation I submit to the University of Pretoria for my PhD in Obstetrics and Gynaecology is my own work and has not been submitted to any other faculty or university.

SIGNATURE:  Dr TMAG Hlongwane

DATE: 25-01-2022

Dedication

This thesis is dedicated to all women who allowed us to share in their pregnancy journey, without whom this work would not have been possible, and to the many silent women who have experienced the tragic loss of a stillbirth.

Finally, to my parents, extended family and my mentors Prof RC Pattinson and Dr Spencer Nkosi who have encouraged my dreams and taught me valuable lessons on my journey to being a clinician scientist.

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Ethical Approval

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 22 May 2002 and Expires 20 Oct 2016.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 22/04/2017.



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Faculty of Health Sciences Research Ethics Committee

27/11/2014

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New Application**

Ethics Reference No.: 473/2014

Title: Can continuous wave Doppler ultrasound (Umbilflow) be used to screen an unselected pregnant population in a low and middle income(LMIC) setting to detect fetuses at risk of stillbirth

Dear Dr Bongani Nkosi

The **New Application** as supported by documents specified in your cover letter for your research received on the 30/10/2014, was approved by the Faculty of Health Sciences Research Ethics Committee on the 26/11/2014.

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We wish you the best with your research.

Yours sincerely

*** Kindly collect your original signed approval certificate from our offices, Faculty of Health Sciences, Research Ethics Committee, H W Snyman South Building, Room 2.33 / 2.34.*

Dr R Sommers; MBChB; MMed (Int); MPharMed.

Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

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15/11/2018

**Approval Certificate
Amendment**

(to be read in conjunction with the main approval certificate)

Ethics Reference No.: 473/2014

Title: Can continuous wave Doppler ultrasound (Umbiflow) be used to screen an unselected pregnant population in a low and middle income (LMIC) setting to detect fetuses at risk of stillbirth

Dear Bongani Nkosi

The **Amendment** as described in your documents specified in your cover letter dated 24/05/2017 received on 24/05/2017 was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 31/05/2017.

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We wish you the best with your research.

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18 March 2022

Approval Certificate Amendment

Dear Dr TMAG Hlongwane,

Ethics Reference No.: 473/2014 – Line 1

Title: The effect of introducing Basic Antenatal care Plus and Umbilical flow on antenatal care and perinatal mortality.

The **Amendment** as supported by documents received between 2022-02-09 and 2022-03-16 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on 2022-03-16 as resolved by its quorate meeting.

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We wish you the best with your research.

Yours sincerely

On behalf of the FHS REC, Dr R Sommers

MBChB, MMed (Int), MPharmMed, PhD

Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

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Fakhefakhe Gaeandibodwatsokappa
Lefapha la Lisense lea Naphela

Summary

Objective: Stillbirths are a global challenge, especially in South Africa where we rank 50th of 54 upper middle income-countries in the world and 6th of 7 in Africa. The majority of antenatal stillbirths are categorised as unexplained or secondary to hypertensive disorders of pregnancy (HDP). Strategies to detect HDP are simple, namely measuring the blood pressure, but if not performed at the right time hypertension might not be detected and a stillbirth may result. Unexplained stillbirths are thought to be due to unrecognised placental insufficiency. No effective strategies to detect placental insufficiency are available in low- and middle-income countries. The objective of this thesis is to test strategies which if implemented would reduce these two major categories of stillbirth. The first strategy was to test whether increased antenatal contacts in the third trimester improved detection of HDP. The second strategy was to use an innovative approach viz. continuous wave Doppler ultrasound of the umbilical artery (CWDU-UmA) at a primary care level to detect placental insufficiency. (CWMU-UmA assesses the fetal blood flow to the placenta, and this has been shown to correlate very closely with placental function).

Method: There were two major studies, the first examined the effect of implementing the new World Health Organisation (WHO) recommendations which among other things entailed increasing the antenatal contacts in the third trimester. These recommendations were integrated into the national basic antenatal care (BANC) guideline and called BANC Plus. An observational study was performed in four sites throughout South Africa over 15 months. The impact of the implementation had on contacts, measuring the blood pressure and identifying HDP was assessed. The second major study was a cohort analytic study involving nine catchment areas across South Africa. CWDU-UmA was implemented at primary healthcare clinics in these catchment areas and the incidence of abnormal placental blood flow and the effect of detecting this on stillbirths in women classified as having low-risk pregnancies was assessed. The lessons learnt from implementing CWDU-UmA in the various sites were explored.

Results: Introduction of the BANC Plus guideline in the study sites significantly increased the antenatal contacts from an average of 4.7 to 5.9 over one year and women with HDP were identified significantly more frequently (12.0% to 19.5%). Screening with CWDU-UmA was

performed using the Umbiflow™ device. Screening the low-risk pregnant populations demonstrated a high incidence of abnormal placental blood flow (13.0%) and absent end-diastolic flow (1.2%). The CWDU-UmA information together with an active standard management protocol demonstrated a significant reduction in the stillbirth rate (10.1/1000 vs 17.8/1000, RR 0.57, 95% CI 0.29–0.85) with no increase in the neonatal death rate.

Conclusion: The implementation of BANC Plus resulted in an increase in antenatal contacts and detection of HDP. The high prevalence of absent end-diastolic flow and the step-change reduction in stillbirths found in the second study warrants screening of low-risk pregnant women in South Africa. Integrating CWDU-UmA into BANC Plus at the 30 week visit is feasible and should result in a significant reduction in stillbirths.

Keywords: Antenatal care, Hypertensive disorders of pregnancy, Doppler ultrasound, Stillbirths, Fetal growth restriction, Absent end-diastolic flow

List of abbreviations

AEDF – Absent end diastolic flow

ANC – Antenatal care

APH – Antepartum haemorrhage

BANC – Basic antenatal care

BANC Plus – Basic antenatal care Plus

CHC – Community Health Centre

CSIR – Council for Scientific and Industrial Research

DCST – District Clinical Specialist Team

FGR – Fetal growth restriction

GA – Gestational age

HIV – Human immunodeficiency virus

HDP – Hypertensive disorders of pregnancy

LBW – Low birthweight

LMIC – Low- and middle-income country

MOU – Midwife run Obstetrics Unit

PMNR – Perinatal mortality rate

PIIP – Perinatal Problem Identification Program

RI – Resistance index

REDF – Reverse end diastolic flow

SA – South Africa

SAMRC – South African Medical Research Council

SB – Stillbirth rate

SBR – Stillbirth rate

SGA – Small for gestational age

WHO – World Health organisation

Introduction to the study

Preface to the study

Summary of motivation for this thesis

In South Africa (SA), between 2015-2017 there were nearly three stillbirths for every neonatal death.¹ The most common categories were unexplained stillbirth, hypertensive disorders in pregnancy (HDP) and antepartum haemorrhage (APH).¹

HDP should be simple to detect and stillbirths mostly preventable as detection is by taking the blood pressure. All clinics have blood pressure measurement devices and the blood pressure should be taken at every antenatal visit. However, detection of HDP is dependent on taking the blood pressure at the right time. Physiologically the blood pressure normally drops during the second trimester and pre-eclampsia mainly is detected in the third trimester.² The national antenatal care guideline (called Basic Antenatal Care - BANC) introduced in as a national guideline in 2008³ and in place in 2017 followed the focused antenatal care recommendations of the World Health Organisation (WHO) stated that only two contacts were required in the third trimester, at 32 weeks' and 38 weeks' gestation.⁴ Concern about this guideline has been expressed lately and a recent systematic review of focused antenatal care with reduced contacts found that the perinatal mortality increased by on average 15%.⁵ The WHO revised its antenatal care guidelines in 2016⁶ and these amongst other recommendations suggested that there be five antenatal visits in the third trimester; at 30, 34, 36, 38 and 40 weeks' gestation with referral for induction of labour if delivery had not occurred by 41 weeks' gestation.⁶

SA was one of the first countries to adopt the new WHO recommendations and BANC was adapted to include the new recommendations including the increased number of antenatal contacts. This new national guideline was called BANC Plus.⁷

It was hypothesised that the increased contacts in BANC Plus would increase detection of HDP and thereby decrease the stillbirth rate due to HDP. This first aspect of this hypothesis was tested in this thesis under section 1.

The largest category of perinatal deaths in SA were unexplained intrauterine death - which mostly presents as macerated stillbirths.^{1,8} It is estimated that one in four of the perinatal deaths were recorded as unexplained stillbirths, and more than a quarter were small for gestational age

(SGA) (SGA defined as a birth weight less than the 10th centile for gestational age).⁸ SGA is used as a surrogate to diagnose fetal growth restriction (FGR), but many more fetuses are growth restricted but are born above the 10th centile.^{1,8,9} FGR is defined as a fetus that does not reach his/her full genetic growth potential.¹⁰ Placental insufficiency is the main cause of FGR but this is often not recognised.^{10,11,12} Studies have shown that SGA babies are at an increased risk of stillbirth compared to non-SGA babies at all gestations, and the risk of stillbirth for SGA babies increases with increasing gestation.¹¹⁻¹⁴ These fetuses are often not detected by imaging ultrasound.¹¹⁻¹³

Interest in the use of Doppler ultrasound in pregnancy started in the 1980's when the technology using continuous wave Doppler ultrasound (CWDU) was developed to identify flow in different directions.¹⁵ Continuous wave Doppler is an effective and inexpensive tool; it allows the classic signature of umbilical artery and vein to be identified without the use of imaging ultrasound. As the technology advanced continuous wave Doppler was replaced by pulsed wave Doppler that came with commercial ultrasound machine. This enabled different vessels to be identified and selected.¹⁵ However, with this advancement, what was affordable, simple and non-invasive became very expensive and technical¹² and CWDU fell into disuse in obstetrics.¹⁵⁻¹⁷

CWDU can detect the velocity of blood flow within the umbilical cord of a fetus, and this has been shown to be an accurate measure of placental function.¹⁵⁻¹⁸ (As placental function decreases the resistance of blood flow into it by the umbilical artery increases. The velocity of the blood flow measured by using Doppler waveform thus decreases, and from this an assessment is made on the ability of the placenta to supply sufficient oxygen and nutrition to the growing fetus).^{17,18} This information is then used to identify the fetus at risk and when identified a full investigation of the fetus is required.¹⁸ Where placental insufficiency is confirmed a specific plan for further management is required to prevent fetal complications.¹⁷ Imaging ultrasound requires specialist skill, or highly trained staff and requires multiple biometry measures. It has been widely used in resource efficient areas, but its use alone does not reduce mortality, and it does not improve survival of the fetus.^{8,17,19} A Cochrane review examined the use of Doppler ultrasound in high-risk pregnant populations and the use of Doppler ultrasound was found to be effective and it reduced perinatal mortality by 38%.¹⁷ Another Cochrane review examined the use of Doppler ultrasound in low-risk or unselected populations of pregnant women²⁰ and concluded that there

was insufficient evidence on whether the use of routine umbilical artery Doppler ultrasound in low-risk or unselected pregnant populations benefits either the mother or baby.²⁰ They also recommended that further studies are needed to establish whether this intervention could potentially prevent perinatal deaths. The WHO guideline group agreed that the value of single Doppler ultrasound assessment of the fetal blood vessels during the third trimester needs more rigorous evaluation, particularly in low- and middle-income countries (LMICs).⁶ An important research gap was identified and they recommended future trials should be designed to address the value of screening pregnancies with Doppler ultrasound with respect to changes in perinatal outcomes, and should focus on preventing deaths.⁶

Section 2 of this thesis investigates the impact of the integration and implementation of CWDU of the umbilical artery (CWDU-UmA) screening with BANC Plus in a low-risk pregnant population in South Africa. CWDU-UmA screening was performed with an UmbiflowTM device. This device was developed by the South African Medical Research Council (SAMRC) and the Council for Scientific and Industrial Research (CSIR). The thesis also documents the implementations challenges and lessons from the field. It is hypothesised that many stillbirths are due to undetected placental insufficiency which leads to FGR. BANC Plus together with UmbiflowTM screening should help determine if FGR is a major cause of perinatal deaths, and whether screening a pregnant population with Doppler ultrasound in South Africa is worthwhile.

Aims and Objectives

The overall aim was to assess the impact of introducing BANC Plus and UmbiflowTM screening at the primary healthcare level. In doing this the detection of HDP and incidence of abnormal placental blood flow and end stage placental disease as determined by absent end-diastolic flow (AEDF) in the umbilical artery will be determined. It will further assess the feasibility of introducing UmbiflowTM screening in a low-risk pregnant population, its effect on the referral hospitals and impact on stillbirths in the South Africa.

Hypothesis

Null hypothesis: The introduction of BANC Plus and UmbiflowTM will not reduce stillbirths due

to HDP and other antenatal causes.

Alternative hypothesis: The introduction of BANC Plus and Umbiflow™ will reduce stillbirths due to HDP and other antenatal causes.

Objectives

Section 1

1. To assess the effect of introducing BANC Plus on detection of HDP at primary healthcare clinics
2. (Its impact on antenatal stillbirths and perinatal deaths due to HDP – completed independently of this thesis).

Section 2

3. To determine the incidence of abnormal Doppler velocimetries in a low-risk population between 28-34 week's gestation in South Africa.
4. To assess the impact of introducing BANC Plus and Umbiflow™ on stillbirths.
5. To determine the resources required to implement Umbiflow™ screening at scale.

Section 1 and 2: The thesis is structured as follows:

Section 1

Chapter 1: BANC Plus: Implementing antenatal care recommendations, South Africa

Section 2

Chapter 2: Antenatal detection and prevention of stillbirths and fetal growth restriction in low- and middle-income countries: a gap in current knowledge

Chapter 3: The prevalence of abnormal Doppler ultrasound of the umbilical artery in low-risk pregnant population in South Africa

Chapter 4: The use of continuous wave Doppler ultrasound of the umbilical artery to prevent unexplained stillbirths in a low-risk population in South Africa

Chapter 5: The outcome of absent end diastolic flow in fetuses of clinically healthy pregnant women in South Africa.

Chapter 6: Implementation experiences of Umbiflow™ screening across nine sites in South Africa

General methods

Section 1. A descriptive study was conducted in four sites. Study ethical approval was obtained from the University of Pretoria's faculty of Health Sciences (473/2014 approved 01 June 2017).

Section 2. A multicentre, multi-province cohort of women classified as having low-risk pregnancies was collected in South Africa. Study ethical approval was obtained from the University of Pretoria's faculty of Health Sciences (473/2014 approved 01 June 2017). 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.

Detailed study methods are described per study in each of the chapters in the thesis.

References:

1. National Perinatal Morbidity and Mortality Committee (NaPeMMCo). Perinatal Problem Identification Program (PIIP) 2015–2017. South African National Department of Health, 2018.
2. Moodley J, Soma-Pillay P, Buchmann E, Pattinson R. Hypertensive disorders in pregnancy: 2019 National guideline. *S Afr Med J* 2019; 109(9):12723.
3. National Department of Health. Guideline for maternity care in South Africa. A manual for clinics, community health centres and district hospitals. Fourth edition, 2016, South Africa.
4. Vogel JP, Habib NA, Souza JP, Gülmezoglu AM, Dowswell T, Carroli G, et al. Antenatal care packages with reduced visits and perinatal mortality: a secondary analysis of the WHO Antenatal Care Trial. *Reprod Health* 2013; 10 (1): 19. <https://doi.org/10.1186/1742-4755-10-19> PMID:23577700 (accessed Oct 10, 2021)
5. Dowswell T, Carroli G, Duley L, Gates S, Gülmezoglu A, Khan-Neelofur D, Piaggio G. Alternative versus standard packages of antenatal care for low-risk pregnancy. *Cochrane Database of Syst Rev* 2015, Issue 7. Art. No.: CD000934. <https://doi:10.1002/14651858.CD000934.pub3>.
6. World Health Organisation. WHO recommendations on antenatal care for a positive pregnancy experience. World Health Organization. Geneva 2016. <https://apps.who.int/iris/bitstream/10665/250796/1/9789241549912-eng.pdf> (accessed Oct 10, 2021).
7. Hofmeyr GJ, Mentrop L. Time for ‘basic antenatal care plus’ in South Africa? *S Afr Med J* 2015; 105(11): 902–3. <https://doi.org/10.7196/SAMJ.2015.v105i11.10186> PMID:26632313. (accessed Oct 10, 2020)
8. Allanson ER, Muller M, Pattinson RC. Causes of perinatal mortality and associated maternal complications in a South African province: challenges in predicting poor outcomes. *BMC Pregnancy and Childbirth* 2015; 15: 37. <https://doi.org/10.1186/s12884-015-0472-9> (accessed Oct 10, 2021).
9. 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.

- Maternal Health Neonatol Perinatol 2016; 2: 11. <https://doi.org/10.1186/s40748-016-0039-4> (accessed Oct 10, 2021).
10. Malhotra A, Allison BJ, Castillo-Melendez M, Jenkin G, Polglase GR, Miller SL. Neonatal Morbidities of Fetal Growth Restriction: Pathophysiology and Impact. *Front Endocrinol* 2019; 10: 55. <https://doi.org/10.3389/fendo.2019.00055> (accessed July 10, 2021).
 11. Katz J, Lee AC, Kozuki N, Lawn JE, 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: 417–425. [https://doi.org/10.1016/S0140-6736\(13\)60993-9](https://doi.org/10.1016/S0140-6736(13)60993-9) (accessed Oct 10, 2021).
 12. Gardosi J, Mul T, Mongelli M, Fagan D. Analysis of birth weight and gestational age in antepartum stillbirths. *Br J Obstet Gynaecol* 1998; 105: 524–530. <https://doi.org/10.1111/j.1471-0528.198tb10153.x>. (accessed Oct 10, 2021).
 13. Hirst JE, Villar J, Victora CG, Papageorghiou AT, Finkton D, Barros FC, et al. The antepartum stillbirth syndrome: risk factors and pregnancy conditions identified from the INTERGROWTH-21st Project. *BJOG* 2018; 125: 1145–1153. <https://doi.org/10.1111/1471-0528.14463> (accessed April 24, 2021).
 14. Malhotra A, Allison BJ, Castillo-Melendez M, Jenkin G, Polglase GR, Miller SL. Neonatal Morbidities of Fetal Growth Restriction: Pathophysiology and Impact. *Front Endocrinol* 2019; 10: 55. <https://doi.org/10.3389/fendo.2019.00055> (accessed July 10, 2021).
 15. Pattinson RC, Theron GB, Thompson ML, Lai Tung M. Doppler ultrasonography of the fetoplacental circulation- normal reference values. *S Afr Med J* 1989; 76: 623–625.
 16. 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: 233–239. <https://doi.org/10.1080/14767050601134926> (accessed Oct 10, 2021).
 17. Alfievic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev* 2017; 6: CD007529. <https://doi.org/10.1002/14651858.CD007529.pub3> (Accessed July 24, 2021).

18. Pattinson RC, Theron GB, Thompson ML, Lai Tung M. Doppler ultrasonography of the fetoplacental circulation- normal reference values. *S Afr Med J* 1989; 76: 623–625.
19. Goldenberg RL, Nathan RO, Swanson D, et al. Routine antenatal ultrasound in low- and middle-income countries: First look- a cluster randomised trial. *BJOG* 2018; 125: 1591–1599. <https://doi.org/10.1111/1471-0528.15287> (accessed Oct 10, 2021).
20. Alfievic Z, Stampalija T, Medley N. Doppler ultrasound of fetal blood vessels in normal pregnancies. *Cochrane Database Syst Rev* 2015; 4: CD001450.

Chapter 1

Implementing new WHO antenatal care recommendations, South Africa.

1.1 Introduction to Chapter 1

Antenatal care is an essential health care service, it offers opportunity and entry to other important health care services. The importance of antenatal care has been clearly established, it offers unique preventative health care and interventions.

Antenatal care was introduced as a quality improvement strategy, to reduce maternal and perinatal mortalities and improve general maternal health. However, routine antenatal care was initially introduced into practice with little scientific evaluation for its effectiveness in reducing maternal and neonatal morbidity and mortality. Its value was questioned in the 1990s and early 2000s with much debate in the Lancet, and multiple commentaries; on the “Rationalisation of antenatal care”.¹

This ultimately led to a global multicentre randomised trial run by the World Health Organization (WHO) which introduced a new model of antenatal care with fewer antenatal contacts down to four routine contacts from the standard twelve visits.² In this trial they stated that the provision of routine antenatal care by the new reduced contact model did not affect maternal and perinatal outcomes, there was no increase in mortality with the reduced contacts. This reduced contact model was adopted in South Africa, and was included in the national guidelines in 2008, called Basic Antenatal Care (BANC). However, concern that the reduced contacts were associated with an increased perinatal mortality rate developed over time. Global and local data showed that the new model with the reduced contacts was associated with an increase in perinatal mortality.^{3,4}

An audit done in South African on the timing and causes of stillbirths showed that hypertensive disorders of pregnancy (HDP) and unexplained stillbirths were the most common causes of adverse perinatal outcomes and the third trimester was identified as the crucial time, with a

peak in stillbirths between 32 and 38 weeks.³ The two peaks of stillbirths (32 and 38 weeks' gestation) correlate with the antenatal contacts using the reduced contact BANC model where women were seen at 32 and 38 weeks. The interpretation of this was that we were diagnosing stillbirths at these times as the women were attending clinics then; **we were not preventing stillbirths, just diagnosing them.** This together with the other global data that the reduced contact could increase the perinatal mortality was the motivation for the increased contacts and other changes for antenatal care. Since then, the WHO has updated and released new antenatal care recommendations for a positive pregnancy experience, with a minimum of eight antenatal contacts and other quality improvement interventions that are evidence based.⁵

As part of efforts to improve maternal and perinatal health, the South African National Department of Health has adopted its antenatal care package to align with the World Health Organization guidelines on routine antenatal care for pregnant women and adolescent girls- “WHO recommendations for a positive pregnancy experience”. This is termed Basic antenatal care Plus (BANC Plus); it was developed and implemented at scale from the 1st of April 2017. It is hypothesized that following the introduction of BANC Plus the number of antenatal contacts and the proportion of women detected with antenatal hypertensive disorders of pregnancy will increase and that over time the stillbirth rate would decline. We monitored and evaluated BANC Plus implementation in South Africa, and supported four diverse circumscribed catchment areas encompassing urban, peri-urban and rural areas. This with the hope to identify the women at risk earlier and to intervene where there are problems so as to potentially avert adverse perinatal outcomes.

The next chapter documents the implementation process, findings and lessons learnt from the South African adoption of the WHO guidelines. I attended stakeholder engagement meetings in January 2017, prior to the implementation. The stakeholder meeting included representatives from all the nine provinces and detailed the motivation for BANC Plus implementation, training needs, training package, proposed training teams and training dates. After the initial provincial training sessions, I supported the nine study sites with BANC Plus training and materials, and documented the number of antenatal contacts in four purposively selected study sites. I extracted data retrospectively from 50 consecutive maternity case records of women

who delivered in four geographically different study sites (total of 1000 women) over a time period. This chapter details the process and findings.

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<https://dx.doi.org/10.2471/BLT.20.278945>

1.2 References

1. Hall MH. Rationalisation of antenatal care. Lancet 2001; 357 (9268):1546.
[https://doi:10.1016/S0140-6736\(00\)04777-2](https://doi:10.1016/S0140-6736(00)04777-2) (accessed Oct 10, 2021).
2. Carroli G, Villar J, Piaggio G, et al. WHO systematic review of randomised controlled trials of routine antenatal care. Lancet. 2001; 357 (9268):1565–1570.
[https://doi:10.1016/S0140-6736\(00\)04723-1](https://doi:10.1016/S0140-6736(00)04723-1) (accessed Oct 10, 2021).
3. Dowswell T, Carroli G, Duley L, Gates S, Gülmezoglu A, Khan-Neelofur D, Piaggio G. Alternative versus standard packages of antenatal care for low-risk pregnancy. Cochrane Database of Syst Rev 2015, Issue 7. Art. No.: CD000934. <https://doi:10.1002/14651858.CD000934.pub3> (accessed Oct 10, 2021).
4. 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. Maternal Health Neonatol Perinatol 2016; 2: 11. <https://doi.org/10.1186/s40748-016-0039-4> (accessed Oct 10, 2021).
5. World Health Organisation. WHO recommendations on antenatal care for a positive pregnancy experience. World Health Organization. Geneva 2016.
<https://apps.who.int/iris/bitstream/10665/250796/1/9789241549912-eng.pdf> (accessed Oct 10, 2021).

Implementing antenatal care recommendations, South Africa

1.3 Abstract

Despite progress in reduction in maternal deaths in South Africa, deaths due to complications of hypertension in pregnancy remain high at 26 deaths per 100 000 live births in 2016. The South African health ministry modified its existing four-visit antenatal care model to align with the WHO 2016 recommendations for the number and content of antenatal care contacts. Implementation of the eight-contact antenatal care recommendations began in April 2017, after adaptation to the national context and nationwide trainings. In this article, we describe the stages of implementation and the monitoring of key indicators. We share lessons, particularly from the important early stages of nationwide scale-up and an analysis of the early results. We analysed samples of maternity case records in four catchment areas in the first year of the updated care model. The mean number of antenatal care contacts among five monthly samples of 200 women increased steadily from 4.76 (standard deviation, SD: 2.0) in March 2017 to 5.90 (SD: 2.3) in February 2018. The proportion of women with hypertension detected who received appropriate action (provision of medical treatment or referral) also increased from 83.3% (20/24) to 100.0% (35/35) over the same period. South Africa's experiences with implementation of the updated antenatal care package shows that commitment from all stakeholders is essential for success. Training and readiness are key to identifying and managing women with complications and developing an efficient antenatal care system accessible to all women.

1.4 Introduction

South Africa is a middle-income country with a population of more than 59 million.¹ In 2017, Sub-Saharan Africa had the highest estimated maternal mortality ratio worldwide at 542 deaths per 100 000 live births and stillbirths at 28.7 per 1000 total births.² While progress has been made in sub-Saharan Africa, the sustainable development goals and the United Nations' global strategy for women's, children's and adolescent's health (2016–2030) seek to improve on gains and aim to reduce the global maternal mortality ratio to 70 deaths per 100 000 live births.^{3,4} Access to quality antenatal care is crucial to achieve these goals and improve the lives of both mothers and babies.^{5,6} Antenatal care is also a key component of the continuum of care for women, babies and their families. While most women in low- and middle-income countries attend at least one antenatal care visit, the content and quality of these contacts are not standardized.⁷ Therefore, improving antenatal care services and to update indicators that track antenatal care performance is needed.

Evidence of a higher risk of perinatal death associated with four or fewer antenatal care visits prompted the WHO to develop a new guideline.⁸ In November 2016, WHO released its comprehensive *Recommendations on antenatal care for a positive pregnancy experience*,⁹ prioritizing person-centred care and well-being as well as prevention of mortality and morbidity.¹⁰ Following these recommendations, in April 2017 the South African health ministry modified its existing four-visit basic antenatal care model to align with the new WHO recommendations including the number of contacts, content of each contact (such as respectful care and clinical enquiry for intimate partner violence) and the basic skills needed for antenatal care.

The nationwide scale-up of South Africa's updated package of care, called Basic Antenatal Care Plus, aimed to improve the quality of antenatal care through the provision of evidence-based interventions across a minimum of eight antenatal care contacts, with an increased number of contacts during the third trimester. The package aims to improve pregnancy care, outcomes and women's experiences, yielding an improvement in screening and detection of pregnancy-related complications and, ultimately, to improve antenatal care quality.¹¹ In this

paper we document the adaptation and implementation of the WHO 2016 antenatal care recommendations in South Africa and share some lessons learnt, particularly in the crucial early stages of nationwide scale-up.

1.5 Local setting

There are 52 districts in South Africa, with a majority having more than 500 000 inhabitants.¹ Since 2008 South Africa has been implementing a basic antenatal care model to achieve four goal-orientated visits. An audit of the timing and causes of all stillbirths in three of South Africa's provinces (Limpopo, Mpumalanga and Western Cape) from 2013 to 2015 showed that hypertensive disorders of pregnancy and unexplained stillbirths were the most common adverse outcomes.¹² The third trimester was identified as a crucial time, with a peak in stillbirths between 32 and 38 weeks. While the majority (75.5%) of pregnant women in South Africa attended four antenatal care visits in 2016,¹³ due to the extended period in the schedule between 32 and 38 weeks, stillbirths were diagnosed but not being prevented. Additionally, although maternal deaths due to non-pregnancy-related infections fell by 47% (from 59 deaths per 100 000 live births in 2011 to 31 deaths per 100 000 in 2016), deaths due to complications of hypertension in pregnancy remained high (14% increase from 23 deaths per 100 000 live births to 26 deaths per 100 000 during the same period).¹⁴ Increased antenatal care contacts in the third trimester may help to identify and prevent hypertension-related complications.^{12,15}

1.6 Public health approach

The updated antenatal care recommendations were adapted and implemented into clinical practice following a systematic approach along four steps: (i) developing the guidelines, related protocols and training materials; (ii) preparing the necessary resources and training; (iii) implementing the updated care package across the country; and (iv) monitoring and evaluation.

1.6.1 Developing guidelines and training

Two ministerial committees – the South African National Committee for the Confidential Enquiries into Maternal Deaths and the National Perinatal Morbidity and Mortality Committee – and a health ministry task team reviewed the WHO 2016 antenatal care recommendations. The committees also reviewed local data which demonstrated the association between the number of antenatal care visits (fewer than eight contacts) and increased maternal and perinatal mortality and morbidity. The task team presented a report detailing the implications and findings to the ministerial teams. Following discussions, the South African Medical Research Council Maternal and Infant Health Strategies Unit and major stakeholders (subject matter experts, academics, and professional bodies) updated the basic antenatal care guidelines and prepared a training package for staff.

The training package included: guidance for heads of departments and facility managers on organizing antenatal care, a guide for training facilitators, a guide for trainers, health-care facility manager's and referral hospital notes, checklists, a task book, an antenatal care handbook, protocol guides, and standards of operation for all health-care professionals offering antenatal care to facilitate the incorporation of the changes. For example, the checklists and related documents detailed the recommended content for each antenatal care contact with a pregnant woman, including the rationale behind the interventions and actions. The package contained guidance on how to identify, triage, investigate, manage and arrange follow-up and referral of all pregnant women. Government ministerial committees and the medical research council's maternal and infant health care strategies unit played an integral role in adapting the 2016 WHO recommendations to the South African clinical context. It was important to ensure that all the steps for implementing change were taken based on the theory of change used by the research council for their maternal and infant programmes.¹⁶

The updated model of antenatal care was presented at a meeting of the South African health ministry (National Health Council) in November 2016 and accepted by the ministry, who then instructed the members of the executive council to implement the updated recommendations beginning 1 April 2017.

1.6.2 Mobilizing resources and training

The health ministry commissioned the medical research council's maternal and infant health care strategic unit to prepare the implementation package and to facilitate workshops to ensure every health-care worker providing antenatal care was familiar with the updated package of care. The implementing stakeholders (medical research council, health ministry, ministerial committees and heads of provincial and district departments) facilitated stakeholders' meetings, compiled the relevant training materials, conducted the training-of-trainers for district clinical specialist teams, and trained health-care providers. The initial training was held in all provinces (usually in a centralized location) and consisted of training-of-trainers for a range of stakeholders including managers, administrators and health-care workers from different levels. The role of the district clinical specialist teams was to ensure quality in clinical services; to provide clinical mentorship, monitoring and evaluation; and to support the health system and district-level organizational activities and clinical training. These teams therefore played a central role in connecting all facilities within the districts. The district teams used different methods depending on the unique circumstances of their catchment area. Training activities included: learning the new antenatal care contact schedule; using checklists, protocol books and standard operational manager's booklets; and ensuring referral to the appropriate level of care for women with complicated conditions. Overall, there were six key stakeholder discussions and eight provincial training-of-trainers workshops where 334 provincial and district teams were trained.

The implementation of the updated care package was supported via additional resources (handbooks, checklists), training by specialized trainers and the district clinical specialist teams, and planned supervision visits from the district clinical specialist teams and the maternal child women health coordinators. The training packages were distributed through the provincial and district maternal, newborn and child health offices and to all Essential Steps in Managing Obstetrics Emergencies (ESMOE) trainers. ESMOE is a focused training programme to support and build the capacity and confidence of health-care workers to enable them to work effectively and efficiently to deliver emergency obstetric care to reduce maternal and neonatal

mortality in South Africa.^{17,18} Trainers, provincial teams, district clinical specialist teams, managers and health-care providers supported the roll-out of training across the country. Health-care providers were given a one-day training on the updated care package at a central location or at health facilities.

Staff in primary health-care clinics, community health centres and hospitals continued to provide the services required for the new model of antenatal care. Managers planned with their teams for changes in how to triage and to ensure that pregnant women received the appropriate care as described in the updated recommendations.

1.7 Guideline implementation

1.7.1 Dissemination and implementation

The health ministry was responsible for disseminating information on the updated antenatal care package to over 3000 public health-care facilities throughout South Africa. Plans for initial and continued scale-up aimed to facilitate and guide implementation across the country. The stakeholders engaged in this implementation process and their roles are summarized in Table 1. The government also disseminated information on the benefits of the new model of care to the public through educational leaflets, national radio stations and other media platforms. Examples of innovative dissemination include MomConnect, an initiative to support maternal health using cell phone-based technologies integrated into maternal and child health services;¹⁹ and Phila, an online government platform to provide health information and encourage healthy living.²⁰ Messages on these platforms, and others, focused on the increase from four to eight antenatal care contacts, on the benefits of the eight-contact care model and its related schedule, and on general antenatal care tips.

1.7.2 Supporting sustainability

Adoption of the updated recommendations into clinical practice was enhanced through the managers and district teams working together. District clinical specialist teams have continued to support and mentor facilities in their districts. Trainers have continued training, with one-day

refresher sessions conducted within their facilities. Facility managers follow standards of operations and ensure that there is continuous learning and reinforcement of the principles of the care model. This process was enhanced by incorporating an antenatal care training module into the three-day ESMOE training. Every district has individuals trained in the Essential Steps method. Health-care facilities across the country have trained individuals in Essential Steps and receive continuous professional development points for every module of the programme that they perform during the year.

Effective communication was essential for implementation and sustainability. Managers at all levels of care and individual health-care providers and emergency personnel were informed of the new guidelines through provincial and district teams including district clinical specialists, maternal child and women's health coordinators, and staff from academia and professional bodies. Health-care managers shared the information with their clinical and support staff. Provincial and district reporting lines ensured continuous communication and feedback of information from the health-care providers and managers at the various levels of care. Additionally, continuous trainings and refresher sessions for health-care providers to reinforce the guidelines allowed for real-time monitoring of progress in implementation and for provincial and district teams to proactively address logistical challenges.

1.8 Monitoring and evaluation

1.8.1 Before implementation

Before implementation of the updated care package, two-day focus groups were held with key stakeholders in districts around the country in January and March 2017 to discuss the implementation (Box 1). Important challenges identified included: increased workload due to the increased antenatal care contacts and the possible increase in referrals of women with high-risk pregnancies; lack of availability of transport to clinics for women with high-risk pregnancies; and possible shortage of hospital beds for admitting referrals.

1.8.2 Table 1. Stakeholders' roles and tasks in the implementation of the World Health Organization's 2016 antenatal care recommendations, South Africa

Role or task	Stakeholder				
	National Committee for Confidential Enquiry into Maternal Deaths and National Perinatal Morbidity and Mortality Committee	Health ministry	South African Medical Research Council, maternal and infant strategic unit	District clinical specialist teams, maternal child women's health coordinators and heads of departments ^a	Emergency medical services
Role	Address high maternal mortality ratio by improving recording and analysis of maternal deaths	Approve and lead implementation process of Basic Antenatal Care Plus programme	Coordinate implementation of new guideline; Facilitate and organize stakeholders and districts	Provide clinical mentorship and guidance to health facilities to improve their ability to provide effective maternal, neonatal and child health services	Provide emergency transport services for all patients

Task

Audit reviews and compile Saving Mothers, Saving Babies report; Report findings to health ministry	Make decisions regarding new guideline and their implementation; Appoint stakeholders to implement updated guidelines; Approve new guidelines, protocols and permission for trainings	Outline WHO's 2016 recommendations on antenatal care for a positive pregnancy experience; Update existing national maternal health guideline; Update existing antenatal care to Basic Antenatal Care Plus programme to align with WHO's 2016 antenatal care recommendations; Coordinate teams: stakeholders and districts; Facilitate training-of-trainers workshops for provincial teams to implement Basic Antenatal Care Plus	Be trained and knowledgeable about the new guidelines; Conduct trainings across districts and facilities; Monitor implementation process at district level	Provide inter-facility transfers for mothers and babies; Provide home-to-health facility transport for mothers and babies
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^a Including obstetrics and gynaecology and nursing departments.

Multidisciplinary implementation teams in the focus groups identified four approaches to manage the likely increased load of high-risk pregnancies. First, an advanced antenatal care practitioner (advanced midwife or doctor) would be trained to see the referrals at primary health-care clinics once a week. These practitioners would decide whether to manage the women at the clinic or refer her to the next level of care, such as a hospital. The practitioners would also have a direct contact to the hospital and specialists. Support would be done on a rotational basis allowing one professional nurse or doctor with specific training to service several clinics. The second approach was to train the doctors of the primary care clinics to see referrals. The doctor would decide whether to manage the woman at the clinic or refer her to the hospital or specialist. The maternal and infant health care strategies unit developed a training course for this purpose. A third approach was outreach visits by doctors from the hospital maternity unit to see women at the primary care clinic, mostly at midwife obstetric care units. A fourth approach was outreach by district clinical specialist teams to see women at the primary care clinics. Advanced midwives or family physicians from the district clinical specialist teams were suitable for this role.

Solutions for women who could not provide their own transport included planned patient transport run by the emergency medical units or use of maternity waiting homes for some women with high-risk pregnancies.

Data collected showed that between 1 February 2017 and 1 April 2017, 524 health-care personnel from 46 districts had been trained on the updated care package before implementation at scale was initiated.

1.8.3 During implementation

Facility or district clinical specialists led audits of case records using a monitoring and evaluation system based on audit tools and a patient checklist. The aim was to ensure that guideline actions were being implemented as intended and that potential problem areas were being identified and adequately documented.

We documented the numbers of antenatal care contacts and the detection and management of hypertension in samples of women over the first year (March 2017 to February 2018; Box 2). We extracted data retrospectively from 50 consecutive patient charts of women who gave

birth in four geographically diverse catchments areas in five selected months (200 women in each phase, a total of 1000 women). Most of the women were between 24 and 26 years old. These results show an increase in total antenatal care contacts and hypertension detection. The mean total number of antenatal care contacts increased from 4.76 (standard deviation, SD: 2.0) in March 2017 to 5.9 (SD: 2.3) in February 2018 (Table 2). Almost all the women in each sample phase had their blood pressure measured at every contact, while detection of hypertension showed an overall increasing trend over time. The proportion of women with hypertension detected who received appropriate action (provision of medical treatment or referral) increased from 83.3% (20/24) in March 2017 to 100.0% (35/35) in February 2018.

1.8.4 Box 1. Identifying challenges to implementation of the World Health Organization's 2016 antenatal care recommendations in South Africa

Before implementation of the updated antenatal care package, two-day workshops on antenatal care and emergency medical services were held in January to March 2017. During the workshops the maternal and infant strategies health care unit of the South African Medical Research Council facilitated a series of focus groups in six of the nine provinces (Mpumalanga, North West, Gauteng, Eastern Cape, Free State and Northern Cape) which comprise 31 of the 52 districts in the country. A total of 22 focus groups were held with 329 participants. Participants included all cadres from the health department, provincial, districts and facility representatives within the maternal and child health programme and emergency medical unit. The focus groups described the maternal, stillbirth and neonatal mortality for the province, district and facilities. This presentation was followed by discussions of antenatal care cases and led to brainstorming of innovative solutions to overcome implementation issues.

1.8.5 Box 2. Monitoring initial implementation of the World Health Organization's 2016 antenatal care recommendations in South Africa

We documented the numbers of antenatal care contacts and success in detection and management of hypertension over the first year after implementation of the updated antenatal care package.

We included four geographically diverse catchment areas based on the following criteria: more than 2500 deliveries per annum and in accordance antenatal care attendance; established referral routes; and familiarity with the perinatal problem identification programme. The areas encompassed urban, semi-urban and rural areas to represent the

different landscapes across South Africa: Ekurhuleni (two clinics and one hospital) in Gauteng province; Mafikeng (two clinics and one hospital) in North West province; Thohoyandou (one health centre and one hospital) in Limpopo province; and Upington (four clinics and one hospital) in Northern Cape province. The audited catchment areas across four districts represented 5.9 million inhabitants in those districts.

We extracted data retrospectively from 50 consecutive patient charts of women who gave birth in March, July, September, November 2017 and February 2018 in the four areas (a total of 1000 women). We recorded the total number of antenatal care contacts in each month of data collection and calculated the mean (and standard deviation) number of contacts per woman. We calculated the proportion of women having their blood pressure measured at each contact, the proportion with hypertension detected and the proportion of women receiving appropriate action when elevated blood pressure was identified. Ethical approval for data collection was obtained from the ethics committee of the University of Pretoria (approval no. REC 473/2014).

1.9 Evaluating health outcomes

The effect of the updated package of care on maternal and perinatal outcomes nationally has not yet been rigorously evaluated. However, the observed trends in maternal and perinatal mortality since implementation of the package are encouraging. Evidence from 2019 demonstrates that South Africa has been able to reduce its maternal mortality for the first time in over a decade (from 189 deaths per 100 000 live births to 99 deaths per 100 000 live births), with a reduction in almost all underlying causes of maternal mortality.²¹

In South Africa, where hypertensive disorders of pregnancy are the most common direct cause of maternal mortality and account for 14.8% of all maternal deaths, efforts to manage hypertensive disorders of pregnancy are important for detecting potentially preventable maternal deaths.²² Maternal deaths in health facilities due to hypertensive disorders of pregnancy were 23, 20 and 19 per 100 000 live births in 2017, 2018 and 2019, respectively, compared with an overall institutional maternal mortality ratio of 126, 118 and 99 per 100 000 live births, respectively.²¹ A trend of decreasing perinatal mortality has been shown in Mpumalanga district.²³ Furthermore, data from 2017 identified major health-system factors associated with poor care of women with hypertensive disorders of pregnancy, which the updated care package aims to alleviate.^{24,25} Health-system problems identified included a lack

of proper assessment and making a diagnosis at the primary level of care. Moreover, not adhering to standard protocols was the most significant problem at regional, tertiary and national central hospitals.²⁴

1.9.1 Table 2. Monitoring initial implementation of the World Health Organization's 2016 antenatal care recommendations in selected sites, South Africa, March 2017 to February 2018

Month and year	Total no. of women sampled	Mean (SD) no. of antenatal care contacts per woman	No. (%) of women		
			Having blood pressure measured at each contact	With hypertension detected	Receiving appropriate action when elevated blood pressure identified ^a
March 2017	200	4.76 (2.0)	185 (92.5)	24 (12.0)	20 (83.3)
July 2017	200	4.87 (2.2)	185 (92.5)	27 (13.5)	24 (88.9)
September 2017	200	5.46 (2.2)	197 (98.5)	23 (11.5)	21 (91.3)
November 2017	200	5.36 (2.4)	190 (95.0)	39 (19.5)	36 (92.3)
February 2018	200	5.90 (2.3)	198 (98.0)	35 (17.5)	35 (100.0)

SD: standard deviation.

^a The denominator is the number of women who had hypertension detected.

Note: Implementation of the updated antenatal care package began in 1 April 2017. We analysed 50 consecutive antenatal care contacts in four areas in each month, a total 1000 women (Box 2).

1.10 Lessons learnt and challenges

Our experience in South Africa shows that with commitment and allocation of resources, evidence-based recommendations can be implemented at scale. For implementation and adaptation, it was important that the health ministry led in committing to change and improving outcomes for pregnant women and their children. This commitment was necessary as districts relied on the ministry's approved guidelines in their facilities. Following the ministry's lead, other relevant stakeholders in all provincial departments, academic faculties, professional bodies and health-care provider forums were engaged to drive the changes and to commit to supporting all the steps of pre-implementation, implementation and monitoring and evaluation.

1.10.1 Box 3. Summary of main lessons learnt

- Commitment from all stakeholders and main decision-makers is necessary for successful implementation of the new antenatal care package at scale.
- Preparation and training are key to identifying women with high-risk pregnancies and referral to the appropriate services.
- Monitoring and long-term evaluation of scale up should be planned before implementation of the updated package of care.
- Health system changes must be planned and anticipated before implementation, which should enable access to the appropriate next level of expertise.

Implementation of the eight-contact antenatal care model posed new challenges and lessons to the South African health system, which other countries can learn from (Box 3). While antenatal care contacts are generally increasing, these gains are uneven. In our analysis, 23 (2.3%) of the sample of 1000 women across our four areas of study had zero contacts before birth since implementation of the updated care package. We also noted regional differences between the catchment areas (urban, semi-urban and rural communities). Factors such as population size, health-seeking behaviour, resources and staff capacity may exacerbate heterogeneity in implementation.²⁶ Thus, implementation and scale-up plans must respond to the unique circumstances and challenges that each district may face across the continuum of the health system. An unintended consequence of the new care model could be an initial decrease in quality of care, as more antenatal care contacts could mean less time per woman. The workload at both primary health-care clinics and referral hospitals has increased during this period. To offset this, the maternal, child and women's health co-ordinator, district clinical specialist teams and training-of-trainers staff visited primary health-care clinics, health centres and hospitals to support and train health-care providers as part of the implementation. Some facilities employed a booking system for routine antenatal care.

Involving different stakeholders allowed for consideration of the diverse circumstances across the country and for brainstorming unique solutions tailored to the challenges, for example the development of new strategies to manage the increased patient workload due to better identification of hypertensive disorders of pregnancy. The National Executive Council has since further investigated the management of hypertensive disorders of pregnancy in South Africa and developed new guidelines. The Council has also supported the concept of

next-level expertise – an innovative approach that promotes having some medium-high expert services at the primary health-care level to increase accessibility to higher-level care for all women. The extensive engagement, planning and training for implementation was continually repeated and based on lessons learnt through the country's scale-up of the Essential Steps in Managing Obstetrics Emergencies programme.

Important next steps include impact analyses on maternal and perinatal outcomes; understanding implementation strategies to improve access to services and cost to the health system; and documenting the perspectives of health-care providers and women on the timing, number, content and quality of antenatal care contacts in the context of implementation. In conclusion, these early results show a promising increase in total antenatal care contacts and hypertension detection. However, implementation of the eight-contact antenatal care model poses new challenges to the health-care systems that require prior planning, active monitoring and proactive management. As countries update their antenatal care policies in line with the 2016 WHO antenatal care guideline, our experience and learning from South Africa can help to inform implementation in other countries and the development of an antenatal care monitoring framework.^{27–29}

1.11 References

1. Mid-year population estimates 2020, P0302 [internet]. Pretoria: Department of Statistics South Africa; 2020. Available from: <https://www.statssa.gov.za> (cited 2020 Nov 20).
2. Trends in maternal mortality: 2000 to 2017: estimates by WHO, UNICEF, UNFPA. Geneva: World Bank Group and the United Nations Population Division; 2019. Available from: <https://apps.who.int/iris/handle/10665/327596> (cited 2019 Aug 1).
3. Sustainable development goals [internet]. New York: United Nations; 2015. Available from: <https://sustainabledevelopment.un.org/?menu=1300> (cited 2016 Jun 8).
4. The Global Strategy for Women's, Children's and Adolescents' Health. New York: United Nations; 2015. pp. 2016–30.
5. Koblinsky M, Moyer CA, Calvert C, Campbell J, Campbell OMR, Feigl AB, et al. Quality maternity care for every woman, everywhere: a call to action. *Lancet* 2016; 388(10057): 2307–20. [https://doi.org/10.1016/S0140-6736\(16\)31333-2](https://doi.org/10.1016/S0140-6736(16)31333-2)
6. Kuhnt J, Vollmer S. Antenatal care services and its implications for vital and health outcomes of children: evidence from 193 surveys in 69 low-income and middle-income countries. *BMJ Open* 2017; 7(11): e017122. <https://doi.org/10.1136/bmjopen-2017-017122> PMID:29146636
7. Benova L, Tunçalp Ö, Moran AC, Campbell OMR. Not just a number: examining coverage and content of antenatal care in low-income and middle-income countries. *BMJ Glob Health* 2018; 3(2): e000779. <https://doi.org/10.1136/bmjgh-2018-000779> PMID:29662698
8. Vogel JP, Habib NA, Souza JP, Gülmezoglu AM, Dowswell T, Carroli G, et al. Antenatal care packages with reduced visits and perinatal mortality: a secondary analysis of the WHO Antenatal Care Trial. *Reprod Health* 2013; 10(1): 19. <https://doi.org/10.1186/1742-4755-10-19> PMID:23577700
9. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016. Available from: <https://apps.who.int/iris/bitstream/10665/250796/1/9789241549912-eng.pdf?ua=1> (cited 2020 Dec 8).
10. Tunçalp Ö, Pena-Rosas JP, Lawrie T, Bucagu M, Oladapo OT, Portela A, et al. WHO recommendations on antenatal care for a positive pregnancy experience – going

- beyond survival. BJOG 2017; 124(6): 860–2. <https://doi.org/10.1111/1471-0528.14599> PMID:28190290
11. Hofmeyr GJ, Mentrop L. Time for ‘basic antenatal care plus’ in South Africa? S Afr Med J 2015; 105(11): 902–3. <https://doi.org/10.7196/SAMJ.2015.v105i11.10186> PMID:26632313
 12. 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> PMID:27795833
 13. Health service coverage data by country. Geneva: World Health Organization; 2017. Available from: <https://apps.who.int/gho/data/node.main.REPWOMEN39?lang=en> (cited 2018 Dec 20).
 14. Saving Mothers 2014–2016: seventh triennial report on confidential enquiries into maternal deaths in South Africa: short report. Pretoria: National Committee for the Confidential Enquiries into Maternal Deaths; 2018. Available from: https://www.westerncape.gov.za/assets/departments/health/saving_mothers_2014-16_-_short_report.pdf (cited 2018 Jul 10).
 15. Lavin T, Pattinson RC. Does antenatal care timing influence stillbirth risk in the third trimester? A secondary analysis of perinatal death audit data in South Africa. BJOG 2018; 125(2): 140–7. <https://doi.org/10.1111/1471-0528.14645> PMID:28317228
 16. Belizan JM, Bergh AM, Cilliers C, Pattinson RC, Voce A, Synergy Group. Stages of change: a qualitative study on the implementation of a perinatal audit in South Africa. BMC Health Serv Res 2011; 11: 243. <https://doi.org/10.1186/1472-6963-11-243>
 17. Pattinson RC, Makin JD, Pillay Y, Van den Broek N, Moodley J. Basic and comprehensive emergency obstetric and neonatal care in 12 South African health districts. S Afr Med J 2015; 105(4): 256–60. <https://doi.org/10.7196/SAMJ.9181>
 18. Bergh A-M, Allanson E, Pattinson RC. What is needed for taking emergency obstetric and neonatal programmes to scale? Best Pract Res Clin Obstet Gynaecol 2015; 29(8): 1017–27.
 19. Barron P, Peter J, LeFevre AE, Sebidi J, Bekker M, Allen R, et al. Mobile health messaging service and helpdesk for South African mothers (MomConnect): history, successes and challenges. BMJ Glob Health 2018; 3 Suppl 2: e000559. <https://doi.org/10.1136/bmjgh-2017-000559> PMID:29713503

20. Mother and child, women's health: early booking, adherence to antenatal care [internet]. Pretoria: Department of Health of the Republic of South Africa; Available from: http://phila.org.za/mother_child_womens_health/ (cited 2018 Jul 10).
21. Saving Mothers 2019: annual report on confidential enquiries into maternal deaths in South Africa. Pretoria: South African National Department of Health; 2019.
22. Moodley J, Soma-Pillay P, Buchmann E, Pattinson RC. Hypertensive disorders in pregnancy: 2019 national guideline. *S Afr Med J* 2019; 109(9) Suppl 1: 12723.
23. Lavin T, Pattinson RC, Kelty E, Pillay Y, Preen DB. The impact of implementing the 2016 WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience on perinatal deaths: an interrupted time-series analysis in Mpumalanga province, South Africa. *BMJ Glob Health* 2020; 5(12): e002965.
<https://doi.org/10.1136/bmjgh-2020-002965>
24. The 2017 annual Saving Mothers report. Pretoria: South African National Department of Health; 2017. Available from: <https://www.westerncape.gov.za/general-publication/saving-mothers-2017-annual-report> (cited 2020 Nov 8)
25. Pattinson RC, Hlongwane TMAG, Vannevel V. Challenges to improve antenatal and intrapartum care in South Africa. *S Afr Med J* 2019;109 11b: 15–9.
<https://doi.org/10.7196/SAMJ.2019.v109i11b.14248> PMID:32252862
26. Okedo-Alex IN, Akamike IC, Ezeanosike OB, Uneke CJ. Determinants of antenatal care utilisation in sub-Saharan Africa: a systematic review. *BMJ Open* 2019; 9(10): e031890. <https://doi.org/10.1136/bmjopen-2019-031890>
27. Lattof SR, Moran AC, Kidula N, Moller AB, Jayathilaka CA, Diaz T, et al. Implementation of the new WHO antenatal care model for a positive pregnancy experience: a monitoring framework. *BMJ Glob Health* 2020; 5(6): c002605.
28. Lattof SR, Tunçalp Ö, Moran AC, Bucagu M, Chou D, Diaz T, et al. Developing measures for WHO recommendations on antenatal care for a positive pregnancy experience: a conceptual framework and scoping review. *BMJ Open* 2019; 9(4): e024130.
29. Barreix M, Lawrie TA, Kidula N, Tall F, Bucagu M, Chahar R, et al. Development of the WHO antenatal care recommendations adaptation Toolkit: a standardised approach for countries. *BMC. Health Res Policy Syst* 2020; 18(1): 70.
<https://doi.org/10.1186/s12961-020-00554-4> PMID:32564777

Section 1 objective and hypothesis

Since countrywide scale-up of the 2016 WHO recommendations for a positive pregnancy experience, there has been a sustained increase in the number of antenatal contacts and a reduction in stillbirths and perinatal deaths due to hypertensive disorders of pregnancy (HDP) as hypothesised. This was demonstrated in a follow-up study on the introduction of BANC Plus in Mpumalanga.¹ The implementation of BANC Plus may be an effective health system strategy to reduce stillbirths due to HDP in South Africa.^{1,2}

References:

1. Lavin T, Pattinson RC, Kelty E, Pillay Y, Preen DB. The impact of implementing the 2016 WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience on perinatal deaths: an interrupted time-series analysis in Mpumalanga province, South Africa. *BMJ Glob Health* 2020; 5 (12): e002965.
<https://doi.org/10.1136/bmjgh-2020-002965>
2. Hlongwane TMAG, Bozkurt B, Barreix MC, Pattinson R, Gülmezoglu M, Vannevel V, Tunçalp Ö. Implementing antenatal care recommendations, South Africa. *Bulletin of the World Health Organization* 2021, 99 (3); 220–227.
<https://dx.doi.org/10.2471/BLT.20.278945>

Chapter 2

Antenatal detection and prevention of stillbirths and fetal growth restriction in low- and middle-income countries: a gap in current knowledge

2.1 Introduction to Chapter 2

This chapter aims to describe the need to improve the quality of antenatal care and demonstrate that contrary to common belief, improving the quality of antenatal care is not enough; new techniques need to be introduced into antenatal care to identify the high-risk fetus in the low-risk mother.

2.2 Introduction

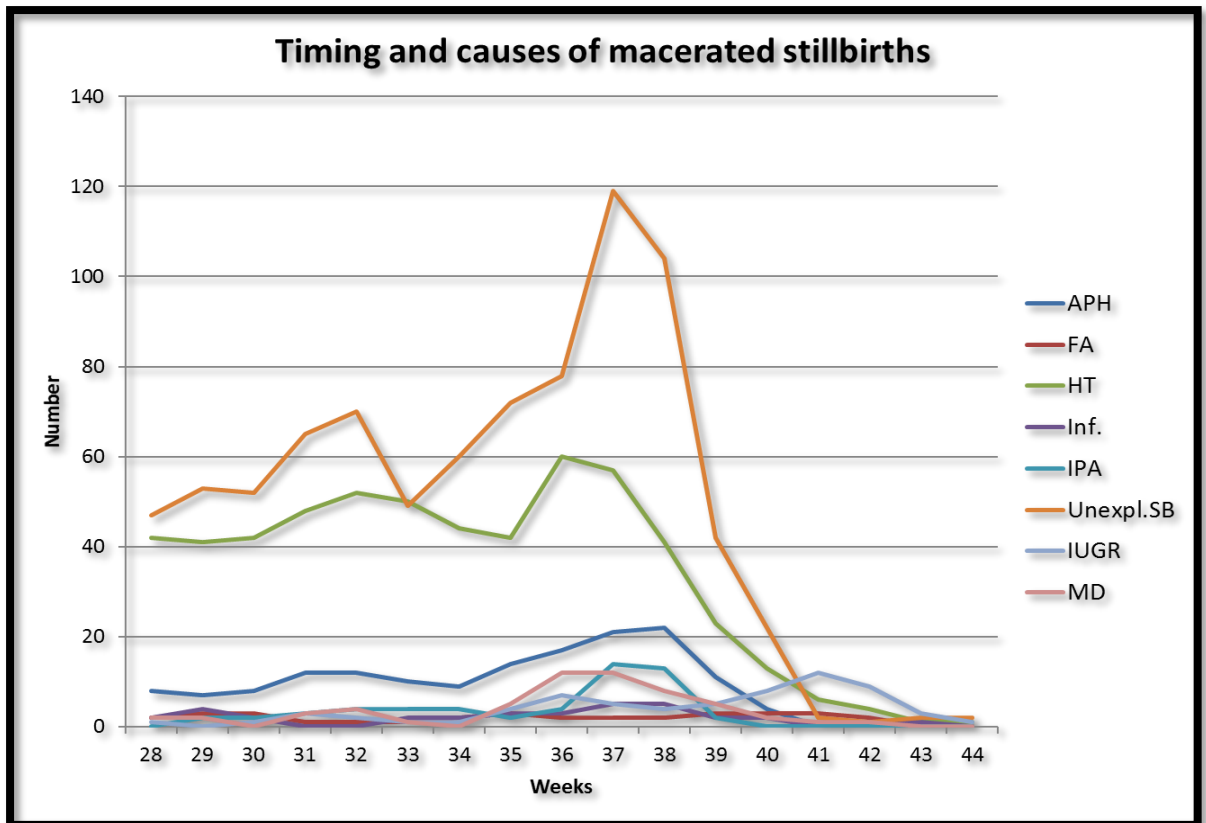
Stillbirths are a neglected tragedy as so eloquently described by UNICEF's report.¹ Stillbirths reflect care during the third trimester and the intrapartum period.² Stillbirths remain high, 2.0 million stillbirths occurred worldwide.¹ The majority occur in low- and middle income countries (LMIC).^{1,3} To put this into a global perspective, two-thirds of stillbirths occur in Southeast Asia, Africa and Latin America.^{1,2} Notably 55% of stillbirths occur in rural families from these areas, in women who were apparently clinically healthy and expecting healthy babies.^{1,3} In South Africa there are approximately 20000 stillbirths per year.⁴ South Africa is classified as an upper middle-income countries ranks 50th of 54 of these countries.¹ Regarding Africa, South Africa ranks 6th of 7 upper middle-income countries with regard to the stillbirth rate.¹ The majority (53.9-59.8%) of stillbirths in South Africa are classified as unexplained.⁴⁻⁶

It is assumed that by improving the quality of maternal and infant health that maternal and infant mortality will decrease.⁷ Research has shown that four out of ten maternal deaths are preventable if women are given proper care.^{2,7} In many cases improving the quality of care results in a reduction in mortality especially intrapartum, however, this is not universally true.^{2,7-10} There are knowledge gaps, particularly in detecting high-risk fetuses in healthy women.⁸ These fetuses are not being identified as the effective methods to detect these fetuses have not been discovered or are not available.⁸⁻¹⁰ The deaths of these fetuses are mostly classified as unexplained.^{5,11} These knowledge gaps for identifying high-risk fetuses in a healthy women is particularly true for LMICs.¹² Fetal growth restriction is thought to be a

common cause of antenatal stillbirths^{11,12}, but methods for effectively screening and diagnosing fetal growth restriction are not readily available in LMICs.^{13,14}

Antenatal care is a unique preventive health intervention offered routinely to pregnant women.⁷ The care is aimed at detecting problems already present and those that can develop during the antenatal period that affect the pregnant woman and or her unborn child.^{2,7} The overall objectives of antenatal care include health education, dietary supplementation, and to improve pregnancy outcomes for mother and child by early detection and prevention of complications.⁷ The consistency in identifying women's health problems and assessing the health risk of a patient is important in antenatal care. Women regarded as having a low-risk pregnancy, but having an unidentified high-risk fetus are particularly vulnerable to this lack of consistency. Antenatal care is frequently delivered by a diverse population of care providers, and this promotes challenges in identification, recognition and reporting of problems, especially where clinical methods are relied upon to detect abnormalities (i.e. symphysis fundal measurement). Further, there is a need to methodically identify and stratify patients in need of specialized care as many interventions for specific risks are dependent on timely identification and intervention. However, if specific problems are not identified, these will not be addressed and a stillbirth may result. For example, a fetus that has unidentified growth restriction is five times more likely to die than a fetus identified as having fetal growth restriction.¹¹ For these reasons antenatal care can fail the healthy pregnant woman.

Local and global data showed an increased risk in perinatal mortality associated with reduced focused antenatal contact model.^{5,15} A Cochrane review published in 2015 for low- and middle-income countries, the perinatal mortality rate was significantly higher in the reduced contact group, and there was no difference between models with eight visits when compared to 11-15 contacts.¹⁵ An audit done in Mpumalanga province in South Africa on the timing and causes of stillbirths (figure 1) identified hypertensive disorders of pregnancy (HDP) and unexplained stillbirths as the most common causes of adverse perinatal outcomes and the third trimester was identified as the crucial time, with a peak in stillbirths between 32 and 37 weeks.⁵ These periods were the times when women presented for their routine antenatal contacts, (not the time of the complication leading to a stillbirth); we were diagnosing stillbirths, not preventing them. These findings were part of the compelling evidence that supported the review of antenatal program.



2.2.1 Figure 1: Timing and causes of stillbirths. Antepartum haemorrhage (APH), Fetal abnormality (FA), Hypertensive disorders in pregnancy (HT), Infections (Inf), Intrapartum asphyxia (IPA), Unexplained stillbirth (Unexpl SB), Intrauterine fetal growth restriction (IUGR), Medical disorders (MD).

2.3 Discussion

There is a growing global commitment to reducing the unacceptably high maternal and perinatal mortality rate in developing countries.^{7,16,17} In November 2016, the World Health Organization (WHO) released its recommendations on routine antenatal care (ANC) for a positive pregnancy experience.⁷ The recommendations are intended to “respond to the complex nature of issues surrounding antenatal practice, organisation and delivery of ANC within the health systems, and to prioritise person-centred care, well-being and the prevention of death and morbidity”.⁷ WHO envisions that ‘every pregnant woman and newborn infant receives good quality care throughout pregnancy, childbirth and the postnatal period’, where quality refers to provision and experience of care from a health systems perspective, enabling a positive pregnancy experience. The recommendations include a minimum of eight contacts in the course of the pregnancy, since recent empirical evidence has shown that eight contacts suffice for uncomplicated pregnancies, and may assist to identify previously missed

complications that resulted in adverse outcomes in the low-risk pregnant women.^{7,17,18} The recommendations also recognise there are gaps in our knowledge and thus include research areas and priorities.

SA has a high burden of maternal, perinatal and child mortality.⁴ Three South African reports, namely the Saving Mothers from the National Committee on Confidential Enquiries into Maternal Deaths (NCCEMD), Saving Babies from National perinatal mortality and morbidity committee (NaPeMMCo) and Perinatal Problem Identification Programme (PPIP) and Saving Children from Child Problem Identification Programme (Child PIP) all offer a review of the healthcare provided to the mothers, babies and children in South Africa.^{4,19} The committees emphasized that in any given year a significant proportion of maternal death, stillbirths, neonatal death and children who die before their fifth birthday experience a poor quality of care.⁴ The reports made recommendations to strengthen the quality of care provided to mothers, babies and children at the time when they need it the most.^{4,19} Provision of quality antenatal care is listed amongst these recommendations.^{4,19}

The South African National Department of Health included maternal and perinatal health care amongst its priorities in healthcare service provision and the recommendations specifically included improving antenatal care as one of the key points because of the local surveys indicating the shortcomings in the performance of antenatal care.³ The Basic Antenatal Care (BANC) programme has been the official antenatal care guideline since 2007.²⁰ Following the recognition of the failings of antenatal care in South Africa and in line with the WHO recommendations, the BANC program was updated.³ The new package is termed BANC Plus. The previous WHO four-contact focused antenatal care model is no longer recommended, and the antenatal contacts were increased to eight.⁷ At scale implementation of the new BANC Plus programme started in April 2017.³ BANC Plus aims to re-enforce all the principles of antenatal care and improve the quality of antenatal care, pregnancy outcomes and the pregnancy experience and yield an improvement in screening and detection of complications.^{3,7}

Unfortunately, routine clinical methods to detect poor fetal growth (palpation or symphysis fundal height) are ineffective and have not shown effect on the rate of stillbirths or perinatal mortality.^{21,22} Routine screening using symphysis-fundal height assessment has substantial inter-observer variation, and serial symphysis-fundal height needs to be performed by the same provider to demonstrate an effect.²¹ This is not an option in most of the antenatal clinics in

South Africa. Detection of the fetuses that are at risk of growth restriction thus remains a challenge due to the subjectivity of the current available antenatal fetal growth monitoring tools particularly in LMIC.²³

The WHO recommendations also suggested that all pregnant women should receive an imaging ultrasound scan to determine/confirm the gestational age.⁷ It was hoped that routine imaging ultrasound would be an effective method in helping detect fetal growth restriction. However, 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.²⁴ Further, routine fetal movement counting has also been shown to be ineffective and cannot be used as a method to detect fetuses at risk.²² The WHO recommendations do not offer a solution to identifying the growth restricted fetus, but recognise this and recommend research into this area.

Imaging ultrasound measures size and is regarded as the gold standard of detecting small for gestational age babies (SGA) as it can assess the fetal biometry.²³ Detecting small babies is important. Approximately 25 % of children born in LMICs are SGA, these SGA newborns are at increased risk of mortality and neonatal morbidity.^{9,12} These fetuses are at an eight fold higher risk of stillbirth, neonatal death, perinatal morbidity and non-communicable disease.^{9,12,13} The only effective treatment of small fetuses at risk of stillbirth is delivery at the appropriate time.¹⁰ Getting the timing wrong, due to delay in identification and treatment or misdiagnosis can lead to lifelong consequences for both mother and child and or even a catastrophic event such as an unwarranted preterm birth or stillbirth.^{9,12,13,25} Detecting SGA fetuses is not sufficient as it does not detect a significant proportion of fetuses with growth restriction.

Fetal growth restriction (FGR) is defined as failure of a fetus to reach his/her full genetic growth potential.²⁵ In most cases FGR is caused by placental insufficiency; however growth failure is often not detected antenatally in routine clinical practice.^{10,23,25} As many as three quarters of babies with FGR are not recognised as such before delivery.^{9,10,23} In a low-risk pregnancy with a lower threshold of suspicion the detection rate is even lower, at approximately 15%.^{9,10,23f}

The purpose of identifying SGA and FGR, would be to recognise those most at risk of poor outcomes.^{9,10} A SGA baby is usually defined as a baby whose birthweight is less than the 10th centile for its gestational age.¹² Thus using this definition, 10% of normal babies will thus classify as SGA. This definition does not satisfy the requirement of a truly growth-restricted

fetus, as for instance a fetus genetically destined to have a birthweight on the 75th centile but who is born on the 25th centile is not reaching his/her growth potential, and does not fulfil the criteria of being SGA. This growth restricted fetus is at much greater risk of adverse outcomes than a fetus destined to be on the 8th centile and who is born on the 8th centile, who is SGA, but not growth-restricted. Alternatively delivering this small baby on the 8th centile might result in delivering a normal but small preterm infant, causing an iatrogenic problem. A once-off imaging ultrasound to determine size might lead to incorrect diagnoses. Imaging ultrasound uses centile charts to detect poor fetal growth and requires repeated measurements to detect a fall-off in growth.²³ This requirement results in increasing the complexity and cost of any imaging system making it less desirable as a screening test. Thus, despite the use of imaging ultrasound, the task of accurately identifying fetuses at risk of stillbirth from placental diseases continues to elude us.^{10,23}

Doppler ultrasound of the umbilical artery measures the blood flow through the placenta and is a good measure of placental function, and thereby detects placental insufficiency and FGR.²⁶ The umbilical Doppler RI decreases with increasing gestational age.^{8,26} Doppler ultrasound technique uses Doppler principles, where high frequency sound waves bounce off circulating red blood cells and the reflection of the sound wave is measured as a shift in frequency. The direction of the blood flow and velocity is calculated.²⁶ Placental insufficiency usually results in a decrease in placental blood flow and is thus detected by a rise in RI (abnormal RI).²⁶ This rise in RI is associated with adverse outcomes; once absent end diastolic flow (AEDF) or reversed end diastolic flow (REDF) is detected it is associated with adverse perinatal outcomes.^{10,26} AEDF is associated with FGR, neuro-developmental sequelae, chromosomal, structural anomalies and increased perinatal deaths.^{25,27}

Furthermore, umbilical artery Doppler ultrasound has been well studied in high-risk pregnancies, and has demonstrated a significant reduction in perinatal mortality (38%).²⁸ Most studies assessing the clinical significance of the AEDF and REDF on the umbilical artery have been performed in high-risk populations and there is insufficient evidence for use of routine umbilical artery Doppler ultrasound in low-risk women.^{28,29} The advantage of Doppler ultrasound of the umbilical artery is that it is a test of function rather than of size, and is able to detect poor placental function irrespective of the fetal growth centile with a single reading.¹⁰ This gives screening with Doppler ultrasound a big advantage over screening by measuring size, which would require serial measurements to determine the

growth pattern, which is much more expensive and difficult for a health system to manage.^{10,23} Thus a Delphi consensus³³ on defining FGR includes Doppler abnormalities in their definition.³⁰ Furthermore, the dropping of centiles (even though not below 10th centile) is also included in their definition as contributory parameters in diagnosing FGR, supporting the definition of a fetus not reaching its genetic growth potential.

A low-cost continuous wave Doppler device (Umbiflow™) has been developed by the Council for Scientific and Industrial Research (CSIR) in SA.^{31,32} Umbiflow™ is a mobile-connected Doppler device that uses a continuous-wave waveform to detect blood flow within the fetal umbilical cord. 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.³¹ Umbiflow™ measures the resistance index (RI) in the umbilical cord and plots it against the estimated gestational age to identify the fetus at risk for FGR. An integrated 3G card facilitates a mobile internet connection and the automatic upload of Doppler results to a central server for remote expert support and electronic health record management.^{31,32} 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”.^{31,32} A critical advantage of the device is that it facilitates task-sharing of Doppler ultrasound screening to non-specialists and has the potential to substantially increase coverage to women receiving care in peripheral and rural health facilities.³² A study demonstrated that the Umbiflow™ can be operated by nurses and midwives at the primary healthcare centres.³¹⁻³³ The device has a short learning curve and thus empowering primary healthcare givers and non-specialist providers.^{32,33} The use of Umbiflow™ has been shown to prevent unnecessary referrals to secondary level of care without increasing morbidity, and has the potential to identify pregnant women at risk of poor perinatal outcome.³²

A cohort among a low-risk pregnant population in Pretoria, Mamelodi showed that the prevalence of abnormal RI as detected by Umbiflow™ was ten-fold higher than in the high-income countries - they found the prevalence of abnormal RI to be 11.7%, and 1.5% of this low-risk population had AEDF.³³ When women identified with abnormal RI using Umbiflow™ were managed using a standardized protocol at the next level of care, the overall perinatal mortality rate was significantly lower in the Umbiflow™ group compared to the control group, this was most significant in the macerated stillbirth group (4.3/1000 births vs 11.2/1000 births, RR 0.40, 95% CI 0.23-0.68). The perinatal mortality risk reduction was 42% among women who had Umbiflow™ assessment (11.4/1000 births vs 21.3/1000 births, RR 0.58, 95% CI 0.42-

0.081).³³

The finding of AEDF is of importance as these fetuses are eight fold more likely to die than fetuses where end diastolic flow velocity was present.^{10,23,27} The Umbiflow™ device would be an ideal screening tool if found to be effective. This has prompted the current studies to explore the prevalence of abnormal Doppler RI in low-risk populations in South Africa and the effect of its introduction in combination with BANC Plus. Research into Umbiflow™ Doppler waveforms use in low-risk population may be a viable strategy to increase the detection of the fetus at risk of stillbirth.³³

2.4 Conclusion

There is a need to develop appropriate screening tools that go beyond subjective measures for monitoring during antenatal period so that facilities can consistently monitor and assess progress towards improved antenatal care, and prevention of morbidity and stillbirths. The findings will inform the provincial work and progress in antenatal care, and may inform a comprehensive antenatal care model. The quality of healthcare that a pregnant woman receives during antenatal care has an impact on the health of the woman and an impact on the outcome of pregnancy. Effective antenatal care in SA can make a major contribution to improving pregnant women's health and saving some lives, and significantly improve the health and survival of unborn babies.

2.5 References

1. A Neglected Tragedy: The global burden of stillbirths. Report of the UN Inter-agency Group for Child Mortality Estimation, United Nations Inter-agency Group for Child Mortality Estimation (UN IGME) United Nations children's Fund. New York, 2020
2. Hofmeyr GJ, Mentrop L. Time for 'basic antenatal care plus' in South Africa?. *S Afr Med J* 2015; 105(11): 902–903.
3. de Bernis L, Kinney MV, Stones W, et al. Stillbirths: ending preventable deaths by 2030. *Lancet* 2016; 387(10019): 703–716. [https://doi:10.1016/S0140-6736\(15\)00954-X](https://doi:10.1016/S0140-6736(15)00954-X) (accessed June 01, 2021).
4. National Perinatal Morbidity and Mortality Committee (NaPeMMCo). Perinatal Problem Identification Program (PPIP) 2015–2017. South African National Department of Health, 2018.
5. 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. *Maternal Health Neonatol Perinatol* 2016; 2: 11. <https://doi.org/10.1186/s40748-016-0039-4> (accessed June 01, 2021).
6. Stats SA (Statistics South Africa). Perinatal deaths in South Africa, 2014. Statistical release 2016. Pretoria: South Africa. <https://statssa.gov.za>
7. World Health Organisation. WHO recommendations on antenatal care for a positive pregnancy experience. World Health Organization. Geneva 2016. <https://apps.who.int/iris/bitstream/10665/250796/1/9789241549912-eng.pdf> (accessed June 01, 2021).
8. Odendaal HT, Theron AM, Carstens MH, de Jager M, Grovè, D. Intrauterine deaths in high-risk pregnancies with normal and borderline umbilical artery Doppler flow velocity waveforms. *SAJOG* 2008; 14: 33–37.
9. Gardosi J, Mul T, Mongelli M, Fagan D. Analysis of birth weight and gestational age in antepartum stillbirths. *Br J Obstet Gynaecol* 1998; 105: 524–530. <https://doi.org/10.1111/j.1471-0528.198tb10153.x> (accessed June 01, 2021).
10. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. *Fetal Diagn Ther* 2014; 36: 86–98. <https://doi:10.1159/000357592> (accessed July 24, 2021).
11. Hirst JE, Villar J, Victora CG, Papageorgiou AT, Finkton D, Barros FC, et al. The antepartum stillbirth syndrome: risk factors and pregnancy conditions identified from

- the INTERGROWTH-21st Project. *BJOG* 2018; 125: 1145–1153.
<https://doi.org/10.1111/1471-0528.14463> (accessed April 24, 2021).
12. Katz J, Lee AC, Kozuki N, Lawn JE, Cousens S, Blencowe H, 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: 417–425.
[https://doi.org/10.1016/S0140-6736\(13\)60993-9](https://doi.org/10.1016/S0140-6736(13)60993-9) (accessed April 24, 2021).
 13. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: Population based study. *BMJ* 2013; 346: f108.
<https://doi.org/10.1136/bmj.f108> (accessed Oct 10, 2021).
 14. Gardosi J, Mul T, Mongelli M, Fagan D. Analysis of birth weight and gestational age in antepartum stillbirths. *Br J Obstet Gynaecol* 1998; 105: 524–530.
<https://doi.org/10.1111/j.1471-0528.198tb10153.x>. (accessed Oct 10, 2020).
 15. Dowswell T, Carroli G, Duley L, Gates S, Gülmezoglu A, Khan-Neelofur D, Piaggio G. Alternative versus standard packages of antenatal care for low-risk pregnancy. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No.: CD000934. <https://doi.org/10.1002/14651858.CD000934.pub3> (accessed June 01, 2021).
 16. Every Woman, Every Child (2015) The Global Strategy for Women’s, Children’s and Adolescents’ Health (2016 – 2030). Survive, Thrive, Transform. Every Woman, Every Child. New York: EWEC.
 17. Koblinsky M, Moyer CA, Calvert C, Campbell J, Campbell OMR, Feigl AB, et al. Quality maternity care for every woman, everywhere: a call to action. *The Lancet* 2016; 388 (10057): 2307-20.
 18. Lavin T, Pattinson RC. Does antenatal care timing influence stillbirth risk in the third trimester? A secondary analysis of perinatal death audit data in South Africa. *BJOG* 2018; 125: 140–7.
 19. National Committee for the Confidential Enquiries into Maternal Deaths. Saving Mothers 2014-2016: Seventh triennial report on confidential enquiries into maternal deaths in South Africa: Short report. Health Department - Republic of South Africa, 2018.
 20. National Department of Health. Guidelines for Maternity care in South Africa: A manual for clinics, community health centres and district hospitals. 2016; 4. South Africa. <https://www.idealhealthfacility.org.za/App/Document/Download/42> (accessed June 01, 2021).

21. Robert Peter J, Ho JJ, Valliapan J, Sivasangari S, Symphysis fundal height (SFH) measurement in pregnancy for detecting fetal growth. Cochrane database Sys Rev 2015; 9: CD008136.
22. Norman JE, Heazell AEP, Rodriguez A, et al. Awareness of fetal movements and care package to reduce fetal mortality (AFFIRM): a stepped wedge, cluster-randomised trial. Lancet 2018; 392: 1629–1638. [https://doi.org/10.1016/S0140-6736\(18\)31543-5](https://doi.org/10.1016/S0140-6736(18)31543-5) (accessed Oct 10, 2021).
23. Francesc F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal care surveillance, diagnosed and management. Am J Obstet Gynecol 2011; 204: 288–299. <https://doi.org/10.1016/j.ajog.2010.08.055> (accessed Oct 10, 2021).
24. Goldenberg RL, Nathan RO, Swanson D, et al. Routine antenatal ultrasound in low- and middle-income countries: First look- a cluster randomised trial. BJOG 2018; 125: 1591–1599. <https://doi.org/10.1111/1471-0528.15287> (accessed Oct 10, 2021).
25. Malhotra A, Allison BJ, Castillo-Melendez M, Jenkin G, Polglase GR, Miller SL. Neonatal Morbidities of Fetal Growth Restriction: Pathophysiology and Impact. Front Endocrinol 2019; 10: 55. <https://doi.org/10.3389/fendo.2019.00055> (accessed July 10, 2021)
26. Pattinson RC, Theron GB, Thompson ML, Lai Tung M. Doppler ultrasonography of the fetoplacental circulation-normal reference values. S Afr Med J 1989; 76: 623–625.
27. Karsdorp VH, van Vugt JM, van Geijn HP, Kostense PJ, Arduini D, Montenegro N, Todros T. Clinical significance of absent or reversed end diastolic velocity waveforms in umbilical artery. Lancet 1994; 344: 1664–1668. [https://doi.org/10.1016/s0140-6736\(94\)90457-x](https://doi.org/10.1016/s0140-6736(94)90457-x) (accessed July 24, 2021).
28. Alfievic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev 2017; 6: CD007529. <https://doi.org/10.1002/14651858.CD007529.pub4>. (accessed July 24, 2021).
29. Alfievic Z, Stampalija T, Medley N. Doppler ultrasound of fetal blood vessels in normal pregnancies. Cochrane Database Syst Rev 2015; 4: CD001450.
30. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol 2016; 48(3): 333–339. <https://doi.org/10.1002/uog.15884> (accessed June 01, 2021).
31. Theron GB, Theron AM, Odendaal HJ, Bunn AE. Comparison between a newly developed PC-based Doppler umbilical artery waveform analyser and a commercial unit. S Afr Med J 2005; 95: 62–64.

32. Mufenda J, Gebhardt S, van Rooyen R, Theron G. Introducing a mobile connected umbilical Doppler device (Umbiflow) into a primary care maternity setting: Does this reduce unnecessary referrals to a specialised care? Results of a pilot study in Kraaifontein, South Africa. *Plos One* 2015; 10: e0142743.
<https://doi.org/10.1371/journal.pone.0142743> (accessed Oct 10, 2021).
33. Nkosi S, Makin J, Hlongwane T, Pattinson RC. 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: 347–352.
<https://doi:10.7196/SAMJ.2019.v109i5.13611> (accessed June 01, 2021).

Chapter 3

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

3.1 Introduction to Chapter 3

South Africa was one of the first countries to scale up the new World Health Organisation's (WHO) antenatal recommendations. This is a great step in the pursuit of activities to improve the quality and outcomes in maternal and neonatal health care. The implementation of the new BANC Plus guideline has taken effect as evidenced by the previous chapter; overall women visiting the clinic more often, the blood pressure taken at most antenatal clinic visits, an increasing number of women with hypertensive disorders of pregnancy detected and an increasing number of women with HDP having the appropriate action taken. The observed trends in maternal and perinatal mortality since implementation of the package are encouraging.¹

This will help improve the quality of care for our women and improve outcomes in pregnancy and help inform national and global indicators for antenatal care. However, the burden of stillbirths remained high.^{2,3}

In South Africa there are almost three stillbirths for every neonatal death.⁴ A high proportion of the antenatal stillbirths are classified as unexplained intrauterine deaths, and the mothers were thought to be clinically healthy and expected a good pregnancy outcome.^{5,6}

The use of fetal umbilical artery Doppler has been well documented since the late 1980s. Doppler ultrasound can be used to detect blood flow within the umbilical cord vessels as a measure of placental function, thereby detecting the fetus at risk of placental insufficiency and fetal growth restriction (FGR). Doppler ultrasound of the umbilical artery has been shown to reduce the perinatal mortality rate by 38% when used in managing high-risk pregnancies.⁷ However, some systematic reviews and a Cochrane review on the use of Doppler ultrasound in low-risk women concluded that there was insufficient evidence on whether the use of routine umbilical artery Doppler ultrasound in low-risk populations was beneficial.⁸ These recommendations were based on low-risk and unselected populations from

high income countries, with low stillbirth numbers and there is insufficient data from low- and middle-income countries (LMICs) and further research is required. The WHO antenatal care recommendations for a positive pregnancy experience noted that the value of a single Doppler ultrasound should be investigated in the third trimester, particularly in low- and middle-income countries (LMICs) where stillbirth numbers are high and imaging ultrasound is not routinely unavailable.⁹

A study done in Mamelodi, a township in the east of Pretoria looked at screening and use of umbilical artery Doppler in a low-risk pregnant population. This study showed a prevalence of abnormal resistance index (RI) of 11.7% and absent end diastolic flow (AEDF) was found in 1.5% of the screened low-risk population.¹⁰ Use of umbilical artery RI, with a standard management protocol, in this low-risk population demonstrated a significant reduction in perinatal mortality. The prevalence of AEDF in this low-risk population was ten times higher than reported in literature. This was an unexpected finding.

There is limited evidence on the use of umbilical artery RI in low-risk women and prevalence of abnormal RIs in low-risk women particularly in LMICs where the burden of stillbirth high. Identifying low-risk women with an abnormal RI may identify the fetus at risk. Screening low-risk women and determining the prevalence of AEDF and abnormal RIs as defined by standard curves used in South Africa, will possibly allow for suitable interventions to prevent stillbirths.

The standard RI curves used in South Africa, and imbedded in the Umbiflow™ apparatus, were developed in the 1980s in a tertiary hospital using women with high-risk pregnancies.¹¹ Subsequently, the cut-off values were refined for a secondary level hospital using perinatal mortality as the end point.¹² This gave an RI above the 75th percentile as indicating a fetus at risk. An abnormal RI was thus classified for this study as being above the 75th percentile for the standard curves.

This chapter was conducted to determine the prevalence of AEDF and abnormal RIs in low-risk pregnant populations across South Africa, and see if the initial findings are reproducible. This article has been published- Hlongwane T, Cronje T, Nkosi S, Pattinson RC. The prevalence of abnormal Doppler's of the umbilical artery in a low-risk pregnant population in South Africa. *EClinicalMedicine* 2021; 34: 100792. <https://doi:10.1016/j.eclinm.2021.100792>

3.2 References:

1. Lavin T, Pattinson RC, Kelty E, Pillay Y, Preen D. The impact of implementing the 2016 WHO Recommendations on Antenatal Care for a Positive Pregnancy experience on perinatal deaths: an interrupted time-series analysis in Mpumalanga province, South Africa. Impact of the implementation of WHO 2016 antenatal care positive pregnancy guidelines on perinatal deaths in a South African province. *BMJ Global Health* 2020; 5: e002965. <https://dx.doi.org/10.1136/bmjgh-2020-002965> (accessed April 24, 2021).
2. World Health Organisation. WHO recommendations on antenatal care for a positive pregnancy experience. World Health Organization. Geneva 2016. <https://apps.who.int/iris/bitstream/10665/250796/1/9789241549912-eng.pdf> (accessed April 24, 2021).
3. Hlongwane TM, Bozkurt B, Barreix MC, Pattinson R, Gülmezoglu M, Vannevel V, Tunçalp Ö. Implementing antenatal care recommendations, South Africa. *Bull World Health Organ* 2021; 99: 220–227. <https://doi:10.2471/BLT.20.278945> (accessed April 24, 2021).
4. National Perinatal Morbidity and Mortality Committee (NaPeMMCo). Perinatal Problem Identification Program (PPIP) 2015–2017. South African National Department of Health, 2018.
5. Allanson ER, Muller M, Pattinson RC. Causes of perinatal mortality and associated maternal complications in a South African province: challenges in predicting poor outcomes. *BMC Pregnancy and Childbirth* 2015; 15: 37. <https://doi.org/10.1186/s12884-015-0472-9> (accessed April 24, 2020).
6. 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. *Maternal Health Neonatol Perinatol* 2016; 2: 11. <https://doi.org/10.1186/s40748-016-0039-4> (accessed April 24, 2020).
7. Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev* 2017; 6: CD007529. <https://doi:10.1002/14651858.CD007529.pub3> (accessed April 24, 2021).
8. Alfirevic Z, Stampalija T, Medley N. Doppler ultrasound of fetal blood vessels in normal pregnancies. *Cochrane Database Syst Rev* 2015; 4: CD001450.

9. World Health Organisation. WHO recommendations on antenatal care for a positive pregnancy experience. World Health Organization. Geneva 2016.
<https://apps.who.int/iris/bitstream/10665/250796/1/9789241549912-eng.pdf> (accessed Oct 10, 2020).
10. Nkosi S, Makin J, Hlongwane T, Pattinson RC. 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: 347–352.
<https://doi.org/10.7196/SAMJ.2019.v109i5.13611> (accessed April 24, 2021).
11. Pattinson RC, Theron GB, Thompson ML, Lai Tung M. Doppler ultrasonography of the fetoplacental circulation- normal reference values. *S Afr Med J* 1989; 76: 623–625.
12. 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: 233–239. <https://doi.org/10.1080/14767050601134926> (accessed April 24, 2021).

The prevalence of abnormal Dopplers of the umbilical artery in a low-risk pregnant population in South Africa.

3.3 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%) of 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.

3.4 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 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

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's 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 SA. This study was undertaken to ascertain if the findings of Nkosi et al.²¹ could be repeated in other areas in SA and to establish the true prevalence of abnormal RIs and AEDF.

3.5 Research in context

3.5.1 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- and middle-income countries and further research is required.

3.5.2 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.

3.5.3 Implications of all available evidence: implications for practice, policy and future research

There is limited evidence on umbilical artery Doppler use in low-risk women and prevalence of abnormal Doppler resistance indices in low- 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- and middle-income countries.

3.6 Methods

3.6.1 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 recruitment¹², 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, or

previous pregnancy significant pregnancy losses.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 1000g or more. Facilities had access to emergency medical services for ease of patient transportation when necessary and were familiar with the Perinatal Problem Identification Program¹³ (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.

3.6.2 Ethics

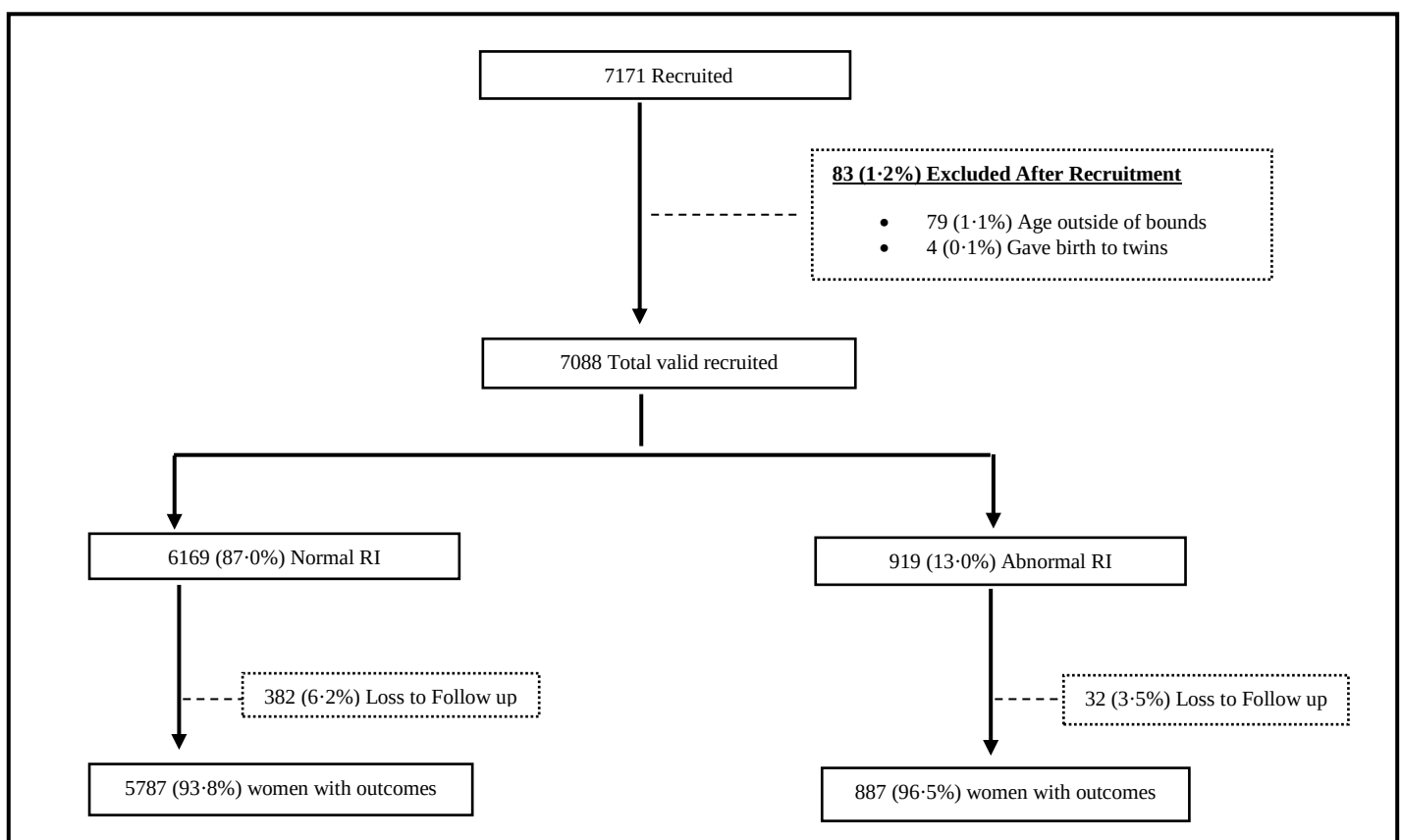
Ethics approval was obtained from the University of Pretoria faculty of Health Sciences (473/2014), and the study was registered with the South African National Research database. Written, informed consent was obtained from all women prior to conducting the UmbiflowTM screening.

3.6.3 Study participants

A sub-set of women classified as having low-risk pregnancies, between 28 to 34 weeks gestations or a symphysis fundal height of more than 26cm if gestational age was unknown were recruited by health care workers for an UmbiflowTM 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 care²³ 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. Figure 1 illustrates the flow diagram of women recruited in the study.



Flow diagram of participants screened with Umbiflow. RI=Resistance index

3.6.3.1 Figure 1: Flow diagram of participants in the Umbiflow study

3.6.4 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 South Africa (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 and RI, which was plotted on a graphic representation using the 75th centile as a cut off.^{26,27} Screened women with a RI finding 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 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 every two weeks 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

3.6.5 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 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.

3.6.6. 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 2500g), neonatal admission to neonatal unit post-delivery, mode of delivery, and stillbirths (defined as an infant with no signs of life at 1 minute and 5 minute [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/>.

3.6.7 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.

3.7 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.

3.7.1 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.*

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.

3.7.2 Table 2: Demographic and outcome information on the Umbiflow™ population

Demographic information on the Umbiflow screened population				
Indicator	Normal RI	Abnormal RI	Total	p-value
	(N= 6169, 87.0) n (%)	(N= 919, 13.0%) n (%)	(N=7088) n (%)	
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	Abnormal RI	Total	p-value
	(N= 5787) n (%)	(N= 887) n (%)	(N= 6674) n (%)	
Birth Weight in grams (g)				
Categories at Delivery				
1000g- 1499g	11 (0.2%)	21 (2.4%)	32 (0.5%)	<0.0001
1500g - 1999g	83 (1.4%)	42 (4.8%)	125 (1.9%)	
2000g -2499g	472 (8.2%)	118 (13.4%)	590 (8.9%)	
>2500g	5189 (90.2%)	701 (79.5%)	5890 (88.7%)	
missing	32 (0.6%)	5 (0.6%)	37 (0.6%)	
LBW <2500g	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	Abnormal RI	Total	

	(N= 5787)	(N= 887)	(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.

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 positive women (29.9% vs 33.2%, p 0.048). The abnormal RI group had more low birth weight newborns (9.8% vs 20.5%, p <0.0001), SGA babies (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).

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 1150g, and demised in the neonatal unit due to complications of prematurity. Two were admitted with severe preeclampsia and developed fetal distress and delivered a 1390g infant and 1600g respectively, the 1390g infant demised in NICU on day eight of life and the 1660g infant demised on day five of life. The other two abnormal RI group neonatal deaths, delivered and both mothers and babies 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.

3.7.3 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

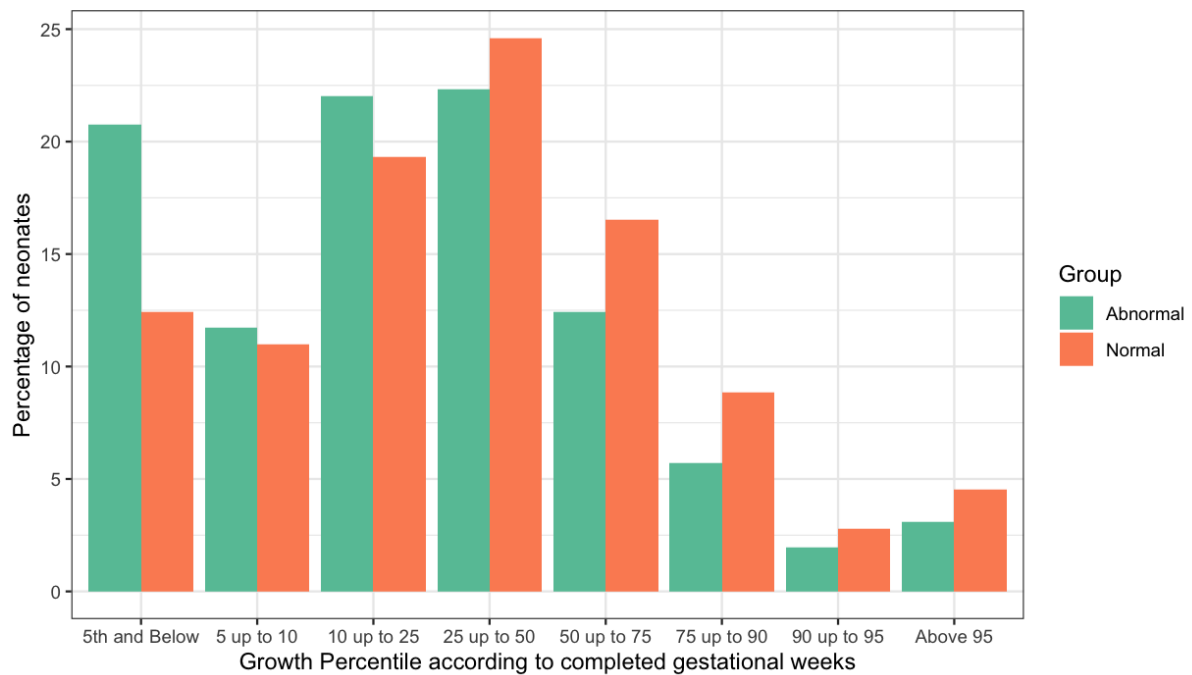
RI= resistance index

3.7.4 Table 4: Primary causes of neonatal mortality 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	3	3

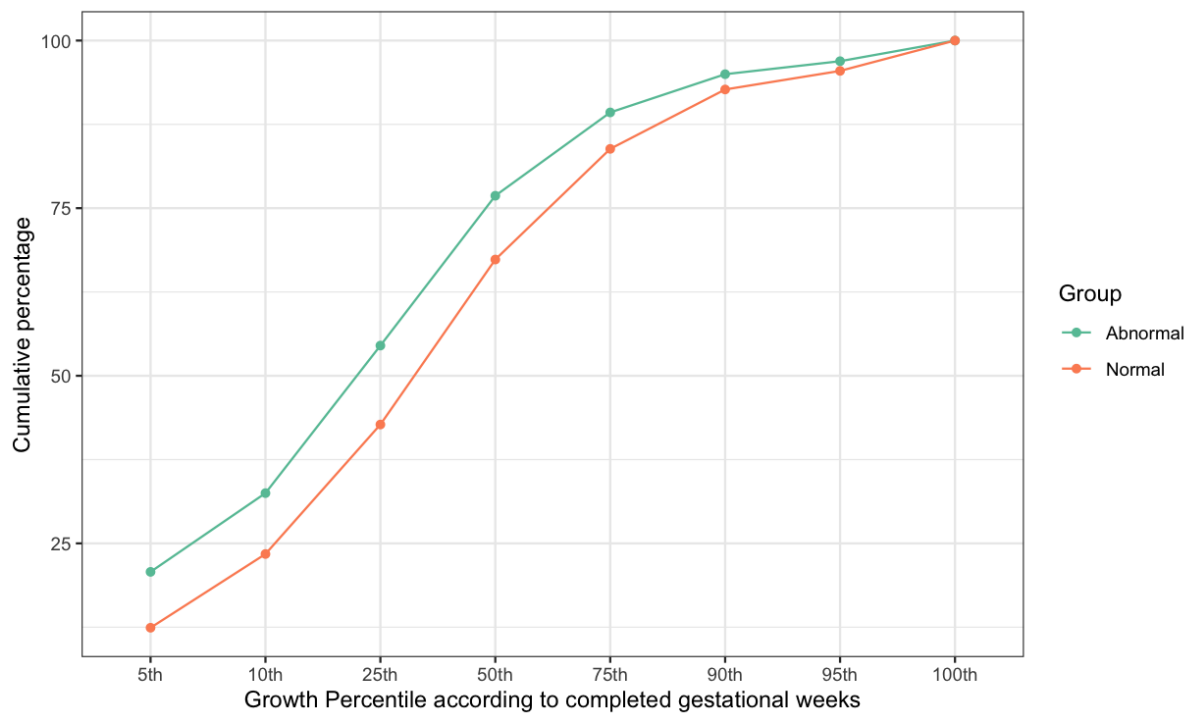
RI= resistance index

Figures 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

3.7.5 Figure 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 (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 $p = 0.0304$.

3.7.6 Figure 3. Cumulative growth patterns in normal and abnormal RI groups.

3.8 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 UmbiflowTM 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 UmbiflowTM screening were initially considered as having low-risk pregnancies, and had uncomplicated pregnancies according to SA guidelines (based on the World health Organizations recommendations¹²) 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 birthweight 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 UmbiflowTM 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 (Figures 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. UmbiflowTM 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. The use of umbilical artery Doppler RI correlates better with customised growth curves detection of growth restriction than standard SGA charts.^{7–9} The other approach includes the use of customised growth charts or neonatal compositions such as muscle or fat.^{8,9,28} 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}

UmbiflowTM 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 UmbiflowTM 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- 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 settings where 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 RIs in this low-risk antenatal population was higher than reported in high income countries.^{19–21} The prevalence of AEDF in this low risk population is comparable to another SA study, and about 10 times higher than that previously recorded in high income countries making it worthwhile to screen a pregnant population in SA. Screening with UmbiflowTM is effective in detecting FGR and SGA babies 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. The high incidence of AEDF warrants screening of low-risk pregnant women in SA. Screening a low-risk pregnant population using continuous wave Doppler ultrasound may reduce the prevalence of unexplained stillbirths in SA.

3.9 References

1. Lavin T, Pattinson RC. Does antenatal care timing influence stillbirth risk in the third trimester? A secondary analysis of perinatal death audit data in South Africa. *BJOG* 2018; 125: 140–147.
2. 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.
3. Lawn JE, Blencowe H, Waisava R, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet* 2016; 387: 587–603.
[https://dx.doi.org/10.1016/S0140-6736\(15\)00837-5](https://dx.doi.org/10.1016/S0140-6736(15)00837-5) (accessed Oct 10, 2020).
4. Robert Peter J, Ho JJ, Valliapan J, Sivasangari S, Symphysis fundal height (SFH) measurement in pregnancy for detecting fetal growth. *Cochrane database Sys Rev* 2015; 9: CD008136.
5. Goldenberg RL, Nathan RO, Swanson D, et al. Routine antenatal ultrasound in low- and middle-income countries: First look- a cluster randomised trial. *BJOG* 2018; 125: 1591–1599. <https://doi.org/10.1111/1471-0528.15287> (accessed Oct 10, 2020).
6. Norman JE, Heazell AEP, Rodriguez A, et al. Awareness of fetal movements and care package to reduce fetal mortality (AFFIRM): a stepped wedge, cluster-randomised trial. *Lancet* 2018; 392: 1629–1638. [https://doi.org/10.1016/S0140-6736\(18\)31543-5](https://doi.org/10.1016/S0140-6736(18)31543-5) (accessed Oct 10, 2020).
7. 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: 233–239. <https://doi.org/10.1080/14767050601134926> (accessed Oct 10, 2020).
8. Francesc F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal care surveillance, diagnosed and management. *Am J Obstet Gynecol* 2011; 204: 288–299. <https://doi.org/10.1016/j.ajog.2010.08.055> (accessed Oct 10, 2020).
9. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: Population based study. *BMJ* 2013; 346: f108.
<https://doi.org/10.1136/bmj.f108> (accessed Oct 10, 2020).
10. Alfievic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev* 2017; 6: CD007529.

11. Alfirevic Z, Stampalija T, Medley N. Doppler ultrasound of fetal blood vessels in normal pregnancies. *Cochrane Database Syst Rev* 2015; 4: CD001450.
12. World Health Organisation. WHO recommendations on antenatal care for a positive pregnancy experience. World Health Organization. Geneva 2016.
<https://apps.who.int/iris/bitstream/10665/250796/1/9789241549912-eng.pdf> (accessed Oct 10, 2020).
13. National Perinatal Morbidity and Mortality Committee (NaPeMMCo). Perinatal Problem Identification Program (PPIP) 2015–2017. South African National Department of Health, 2018.
14. 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. *Maternal Health Neonatol Perinatol* 2016; 2: 11.
<https://doi.org/10.1186/s40748-016-0039-4> (accessed Oct 10, 2020).
15. Lavin T, Pattinson RC, Kelty E, Pillay Y, Preen DB. The impact of the implementing the 2016 WHO recommendations on antenatal care for a positive pregnancy experience on perinatal deaths: an interrupted time series analysis in Mpumalanga province, South Africa. *BMJ Glob Health* 2020; 5: e002965.
<https://doi.org/10.1136/bmjgh-2020-002965> (accessed Dec 10, 2020).
16. Gardosi J, Mul T, Mongelli M, Fagan D. Analysis of birth weight and gestational age in antepartum stillbirths. *Br J Obstet Gynaecol* 1998; 105: 524–530.
<https://doi.org/10.1111/j.1471-0528.198tb10153.x>. (accessed Oct 10, 2020).
17. Allanson ER, Muller M, Pattinson RC. Causes of perinatal mortality and associated maternal complications in a South African province: challenges in predicting poor outcomes. *BMC Pregnancy and Childbirth* 2015; 15: 37.
<https://doi.org/10.1186/s12884-015-0472-9> (accessed Oct 10, 2020).
18. Katz J, Lee AC, Kozuki N, Lawn JE, 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: 417–425. [https://doi.org/10.1016/S0140-6736\(13\)60993-9](https://doi.org/10.1016/S0140-6736(13)60993-9) (accessed Oct 10, 2020).
19. Goffinet F, Paris J, Heim N, Nisand I, Breart G. Predictive value of Doppler umbilical artery velocimetry in low risk population with normal fetal biometry. A prospective study of 2016 women. *Eur J Obstet Gynecol Reprod Biol* 1997; 71: 11–19.
[https://doi.org/10.1016/s0301-2115\(96\)02606-1](https://doi.org/10.1016/s0301-2115(96)02606-1) (accessed Oct 10, 2020).

20. Doppler French Study Group. A randomised controlled trial of Doppler ultrasound velocimetry of the umbilical artery in low risk pregnancies. *Br J Obstet Gynaecol* 1997; 104: 419–424. <https://doi.org/10.1111/j.1471-0528.1997.tb11492.x> (accessed Oct 10, 2020).
21. Nkosi S, Makin J, Hlongwane T, Pattinson RC. 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: 347–352. <https://doi.org/10.7196/SAMJ.2019.v109i5.13611> (accessed Oct 10, 2020).
22. Hlongwane TMAG, Bozkurt B, Barreix MC, Pattinson RC, et al. Implementing antenatal care recommendations, South Africa. Accepted for publication in *Bulletin WHO* 2020.
23. Benova L, Tuncalp Ö, Moran AC, Campbell OMR. Not just a number: examining coverage and content of antenatal care in low-income and middle-income countries. *BMJ Glob Health* 2018; 3: e000779. <https://doi.org/10.1136/bmigh-2018-000779> (accessed Oct 10, 2020).
24. Theron GB, Theron AM, Odendaal HJ, Bunn AE. Comparison between a newly developed PC-based Doppler umbilical artery waveform analyser and a commercial unit. *S Afr Med J* 2005; 95:62–64.
25. Mufenda J, Gebhardt S, van Rooyen R, Theron G. Introducing a mobile connected umbilical Doppler device (Umbiflow) into a primary care maternity setting: Does this reduce unnecessary referrals to a specialised care? Results of a pilot study in Kraaifontein, South Africa. *Plos One* 2015; 10: e0142743. <https://doi.org/10.1371/journal.pone.0142743> (accessed Oct 10, 2020).
26. Pattinson RC, Theron GB, Thompson ML, Lai Tung M. Doppler ultrasonography of the fetoplacental circulation- normal reference values. *S Afr Med J* 1989; 76: 623–625.
27. Torvid Kiserud, Alexandra Benachi, Kurt Hecher, Rogelio González Perez, José Carvalho, Gilda Piaggio, Lawrence D Platt. The World Health Organization fetal growth charts: concept, findings, interpretation, and application. *Am J Obstet Gynecol* 2018; 218: 619–629. <https://doi.org/10.1016/j.ajog.2017.12.010> (accessed Oct 10, 2020).
28. Alberry M, Soothill P. Management of fetal growth restriction. *Arch Dis Child Fetal Neonatal Ed* 2007; 92: 62–67. <https://doi.org/10.1136/adc.2005.082297> (accessed Oct 10, 2020).

29. Salafia CM, Minior VK, Pezzullo JC, Popek EJ, Rosenkrantz TS, Vintzileos AM. Intrauterine growth restriction in infants of less than thirty-two weeks' gestation: Associated placental pathologic features. *Am J Obstet Gynecol* 1995; 173: 1049–1057.
30. Dlamini P. Nehawu vows to continue fight in North West. Timeslive. 2018; published online May 16. <https://www.timeslive.co.za/news/south-africa/2018-05-16-nehawu-vows-to-continue-fight-in-north-west/>. (accessed Feb 4, 2020)

Chapter 4

Preventing antenatal stillbirths: An innovative approach for primary healthcare

4.1 Introduction to Chapter 4

The prevalence of AEDF in this low-risk South African pregnant population was higher than previously reported in high-income countries.¹ The prevalence is comparable to the previous Mamelodi study and is about ten times higher than that previously recorded.² Umbilical artery Doppler screening further demonstrated a significantly higher small for gestational age (SGA) neonates, and growth differences across all growth centiles in the population with abnormal resistance indices (as defined by standard curves). Doppler ultrasound has the advantage over conventional ultrasound in that it detects placental insufficiency irrespective of the fetal size, as demonstrated in this low-risk population.

Abnormal Resistance Indices (RI) and absent end diastolic flow (AEDF) is associated with adverse perinatal outcomes, including stillbirths. Stillbirths remain a global public health concern with approximately 2.0 million stillbirths occurring annually. It is estimated that a significant proportion of these stillbirths are due to fetal growth restriction (FGR). Local South African data suggests that the largest category of perinatal deaths are ‘unexplained stillbirths’.³ It is hypothesised that many of these deaths are due to undetected placental insufficiency.

Placental insufficiency is the leading cause of fetal growth restriction (FGR). FGR and small for gestational age (SGA) babies represent a significant proportion of stillbirths in low-income and high-income countries (LMICs).^{4,5} FGR describes a pathological inhibition of fetal growth that prevents the fetus from reaching its genetic growth potential.⁶ These infants are at an increased risk of adverse perinatal outcomes and so get a poor start in life.^{6,7} In South Africa the majority of antenatal stillbirths (72.6%) are low birthweight (LBW), of all LBW stillbirths 46% were unexplained.⁸ The previous chapter demonstrated that screening a low-risk population can identify SGA babies (32.1% vs 23.1%, $p < 0.0001$) and women with an abnormal RI had more growth restricted babies across all growth centiles. Other studies have demonstrated that there is an excess of SGA babies in the unexplained stillbirth group.⁴⁻

⁹ FGR is a risk factor for perinatal morbidity and mortality, and can increase the risk of stillbirth by up to 8-fold.^{6,7} Despite the high prevalence of FGR, it is often not detected during the antenatal period. Lack of detection increases the risk of adverse fetal complications, making the recognition and appropriate and timely management of FGR critical to preventing adverse perinatal outcomes.^{7,10}

As part of an effort to improve perinatal outcomes, we explored the impact of using the umbilical artery RI information together with a standard management protocol on pregnancy outcomes in the same cohort which was used to determine the prevalence of abnormal Resistance Indices.

The next chapter compares the outcome between the UmbiflowTM screened group and the UmbiflowTM not screened group attending the same antenatal clinics. The article has been submitted and is under review- Hlongwane T, Cronje T, Nkosi B, Pattinson RC. Preventing antenatal stillbirths: An innovative approach for primary healthcare.

4.2 References:

1. Hlongwane T, Cronje T, Nkosi B, Pattinson RC. The prevalence of abnormal Doppler's of the umbilical artery in a low-risk pregnant population in South Africa. *EClinicalMedicine* 2021; 34: 100792. <https://doi.org/10.1016/j.eclinm.2021.100792> (accessed July 24, 2021).
2. Nkosi S, Makin J, Hlongwane T, Pattinson RC. 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: 347–352. <https://doi.org/10.7196/SAMJ.2019.v109i5.13611> (accessed July 24, 2021).
3. 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. *Maternal Health Neonatol Perinatol* 2016; 2: 11. <https://doi.org/10.1186/s40748-016-0039-4> (accessed July 24, 2021).
4. 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.
5. Katz J, Lee AC, Kozuki N, Lawn JE, 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: 417–425. [https://doi.org/10.1016/S0140-6736\(13\)60993-9](https://doi.org/10.1016/S0140-6736(13)60993-9)
6. Malhotra A, Allison BJ, Castillo-Melendez M, Jenkin G, Polglase GR, Miller SL. Neonatal Morbidities of Fetal Growth Restriction: Pathophysiology and Impact. *Front Endocrinol* 2019; 10: 55. <https://doi.org/10.3389/fendo.2019.00055>
7. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. *Fetal Diagn Ther* 2014; 36: 86–98. <https://doi.org/10.1159/000357592> (accessed July 24, 2021).
8. National Perinatal Morbidity and Mortality Committee (NaPeMMCo). Perinatal Problem Identification Program (PPIP) 2015–2017. South African National Department of Health, 2018.
9. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: Population based study. *BMJ* 2013; 346: f108.
10. Francesc F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal care surveillance, diagnosed and management. *Am J Obstet Gynecol* 2011; 204: 288–299. <https://doi.org/10.1016/j.ajog.2010.08.055> (accessed July 24, 2021).

Preventing antenatal stillbirths: An innovative approach for primary healthcare

4.3 Abstract

Background: Stillbirths are a neglected tragedy. In South Africa, approximately 16000 stillbirths occur per year. Most are classified as unexplained intrauterine deaths and occur in district hospitals. Many of these deaths maybe due to undetected fetal growth restriction (FGR). Current primary care screening methods for FGR are ineffective. Continuous wave Doppler ultrasound of the umbilical artery (CWDU-UmA) is a simple method of assessing placental function. Screening with it may detect these growth restricted fetuses allowing for appropriate management.

Method: A cohort study was conducted in nine sites around South Africa. Pregnant women attending primary healthcare clinics around 30 week's gestation, were screened using CWDU-UmA on specific days of the week. Women not screened at those antenatal clinics served as control group 1. Control group 2 consisted of the sub-set of control group 1 with women detected with antenatal complications at any time excluded from analysis. Women with fetuses identified with an abnormal CWDU-UmA test were referred and managed according to a standard protocol. A comparison between the study and control groups was performed.

Results: The study group consisted of 6536 pregnancies and there were 66 stillbirths (stillbirth rate– SBR 10.1/1000 births). In control group 1 there were 193 stillbirths in 10832 women (SBR 17.8/1000 births) and in control group 2, 152 stillbirths in 9811 women (SBR 15.5/1000 births) [Risk Ratio 0.57, 95% Confidence Intervals 0.29–0.85 and 0.65, 0.36–0.94 respectively].

Conclusion: Screening a low-risk pregnant population as described was associated with a step-change reduction in stillbirths.

4.4 Introduction

Stillbirths are mostly hidden. Few clinicians except the midwife and doctor directly involved see the stillbirth, and the woman mostly does not discuss the event with others outside of the immediate family. It leads to great anguish.^{1,2}

Stillbirths are a global public health challenge and the majority occur in low- and middle-income countries (LMICs).^{1,2} Approximately 2.0 million stillbirths occur worldwide each year.² Approximately 55% of stillbirths occur in sub-Saharan Africa.^{2,3} South Africa (SA) is classified as an upper middle-income country and is ranked 50th of 54 similar countries, and within Africa, SA is ranked 6th of the 7 upper middle-income countries.²

District hospitals and community health centres reported 2.5 stillbirths for every neonatal death and 43% of the approximately 16000 stillbirths per year (1000g or more) in South Africa.⁴ The most common category of perinatal deaths is unexplained stillbirth accounting for approximately a quarter of perinatal deaths (30% in district hospitals and community health centres) and for 36% of stillbirths (52% of these stillbirths were in the District hospitals and community health centres).³⁻⁵ The majority of the mothers and fetuses were regarded as healthy at the time of the fetal demise and had not been referred for more specialised care.²⁻⁵ Fetal growth restriction (FGR) is a major factor associated with stillbirth.⁵⁻⁹

Small for gestational age (SGA) fetuses (defined as babies born <10th centile for gestational age and used as a surrogate of FGR) not detected during the antepartum period had a 4-fold increased risk of adverse fetal complications compared to SGA fetuses detected before delivery.⁶⁻¹¹ FGR increases the risk of adverse outcomes by 8-fold, and is associated with perinatal morbidity and mortality, and adulthood diseases.^{9,12,13} Three-quarters of growth-restricted infants are not recognised before delivery⁶⁻¹³ and in low-risk pregnancies with lower threshold of suspicion, the detection rate is even lower (15–20%).³⁻¹³

The tools required to detect FGR in LMICs and especially at the primary level of care, where most women with low-risk pregnancies attend, are extremely poor, potentially explaining the high unexplained stillbirth rate. Palpation and symphysis-fundal height measurement are commonly used in LMICs to detect FGR, despite the limited evidence to support this as an effective method to detect growth restriction and show improved maternal or neonatal outcomes.¹⁴ Symphysis-fundus measurements have a poor ability to detect growth restricted babies and routine fetal movements counting has also been shown to be ineffective.^{14,15} Routine

imaging ultrasound¹⁶ in LMICs surprisingly was also shown to have no effect on perinatal or maternal death or on antenatal attendance.^{14–16}

Better detection of FGR is desperately needed in South Africa and other LMICs, especially at the primary level of care. Doppler ultrasound of the umbilical artery measures the arterial blood velocity.¹⁷ Reduced blood flow, due to increased resistance downstream in the placenta, correlates very well with placental insufficiency, which is one of the major causes of FGR.^{17,18} This reduced blood flow is detected by the Doppler ultrasound and measured as the resistance index (RI): the higher the RI, the more compromised the blood flow.^{17–19} When the placenta is damaged to the extent that no blood flow can be detected during diastole of the fetal heart, the placenta is close to failure and the fetus is at high risk of intra-uterine demise. This phenomenon is called absent end-diastolic flow (AEDF).^{18,19} Four of five fetuses with AEDF at or beyond 28 weeks' gestation, in mothers who declined treatment, had stillbirths.²⁰ Acting on the result of the Doppler ultrasound of the umbilical artery has been shown to reduce perinatal deaths by more than a third in high-risk pregnancies.²¹ Another Cochrane systematic review found there was not sufficient evidence to support its use in low-risk pregnancies.²² However, this recommendation was based only on study populations from high-income countries. Screening for AEDF, or a clearly defined abnormally high RI, could potentially reduce stillbirths if the prevalence of AEDF and abnormal RI was high enough in a pregnant population to warrant screening. These circumstances might be found in LMICs.

The UmbiflowTM device is a low-cost mobile CWDU device developed by the Council for Scientific and Industrial Research (CSIR) and SAMRC in South Africa.²³ It measures the Resistance Index (RI) in the umbilical artery and plots it against the estimated gestational age to identify the fetus at risk for FGR.^{23,24} The accuracy of UmbiflowTM in measuring the RI in the fetal umbilical artery has been proven to be comparable to the commercial standard unit “gold standard”.²⁴ The device has significant advantages in that it can be performed by low level workers, requires only a week of training, the data is recorded on the device which allows for quality control at a later date, it can run on battery power, is portable and is at least ten times less expensive than imaging ultrasound.^{24,25} These factors make it a good choice for a screening tool, if it is effective in detecting FGR. An initial study using UmbiflowTM performed in Mamelodi township found use of UmbiflowTM reduced the stillbirth rate in women classified as having low risk pregnancies by 43%.²⁵

Building on from this initial study, we investigated whether screening a low-risk pregnant population using Umbiflow™ in primary healthcare clinics throughout SA, together with a standard referral protocol for fetuses with abnormal RI, results in a reduction in the stillbirth rate.

4.5 Methods

4.5.1 Study design

A cohort of low-risk pregnant women attending primary healthcare antenatal care eligible for screening using the Umbiflow™ device were screened. The population of low-risk women, were defined as women attending non-specialist antenatal care clinics, who have been classified as “low-risk” at the time of recruitment and screening according to local clinical guidelines as defined by the South African basic antenatal care plus guideline based on the WHO guideline.^{26,27}

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

4.5.2 Study participants

Women from a specific geographic area, attending the primary healthcare clinic were considered for screening. The inclusion criteria were all women with a singleton pregnancy, aged at or more than 18 years and classified as low-risk between 28 weeks and 34 weeks gestation, (if the gestational age (GA) was unknown, a symphysis-fundal height of 26cm or above was used) who gave written consent. Women were screened with Umbiflow™ on specific days of the week and those not attending the clinics on those days served as the control group. A comparison between those who were screened using Umbiflow™ (study group) and those not screened (control group) was performed. Control group 1 represents all women 18 years or more, who attended the antenatal clinics, had a singleton pregnancy and delivered a neonate of 1000g or more from the clinic who did not get Umbiflow™ screening; control group 2 represents the same population, but excludes those who subsequently developed antenatal complications (hypertensive disorders of pregnancy, prolonged rupture of membranes, diabetes mellitus, antepartum haemorrhage and sepsis). This was to ensure the screened population was a low-risk population as possible.

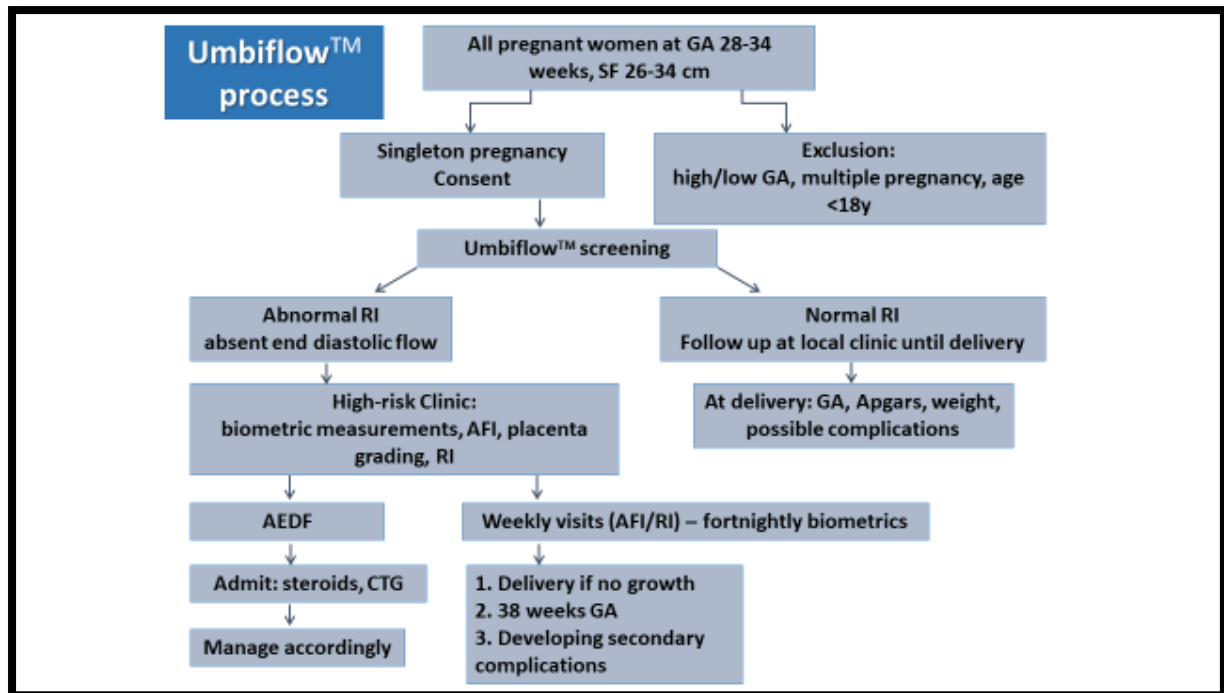
4.5.3 Study setting

The study sites included nine catchment areas linked to regional or tertiary hospitals. This included rural, peri-urban and urban sites across eight provinces in SA. The sites had a healthcare worker screening eligible women on specific days of the week, and there was an established communication and referral route to refer women with abnormal RI.²⁸

4.5.4 Measurement

The UmbiflowTM screening was classified as either normal RI or abnormal RI depending on the Doppler value in relation to GA and RI. This is automatically plotted on a graphic representation using the 75th centile as a cut off.^{19,28} Screened women with RI findings below the 75th centile for their GA were considered as having a normal RI result, and continued their routine antenatal care at their local primary healthcare clinics. The Mamelodi study found that approximately 10% of a low-risk population was identified with abnormal RI by using the 75th percentile cut-off.²⁵ Those with RI findings above the 75th centile for their GA were considered to have abnormal RI and were referred to a high-risk clinic at their local referral hospitals for further review and management.²⁸

Women with abnormal RIs were followed-up weekly or fortnightly at the high-risk clinic and received a Doppler ultrasound at each visit and a fetal growth scan every two weeks. All were managed according to standard protocol.²⁸ Figure 1 illustrates the management protocol for women with an abnormal RI UmbiflowTM result. The stillbirths in the UmbiflowTM screened population (study group) was compared with control groups 1 and 2.



SF= symphysis fundal height, AFI=amniotic fluid index, RI= resistance index, AEDF=absent end diastolic flow, CTG= cardiotograph

4.5.5 Figure 1: Flow diagram of study participant management

4.5.6 Data collection

Data collection of the screened women and delivery outcomes started in September 2017 and stopped in February 2020 allowing time for the pregnant women to deliver. The Umbiflow™ screening outcome was recorded. Maternal clinical information was collected at the time of enrolment in the study. This is described in detail elsewhere.²⁸ The outcome of all women Umbiflow™ screened (study group) or not screened (control groups) was recorded. Outcome data was obtained from the electronic birth register at the various delivery sites. SGA was defined as a birth weight for gestational age <10th centile according to the WHO fetal growth chart.²⁹

4.5.7 Statistical analysis

The maternal demographics are reported as frequencies, mean and standard deviations. Categorical characteristics were investigated using chi square tests to express differences between the screened and not screened 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 centiles, and corrected for GA at delivery and neonatal sex.²⁹ All tests were performed at a 5% level of significance. The relative risk was calculated using the incidence proportions of total stillbirth rate and perinatal mortality rate between the screened and not screened groups. All statistical analyses were done with R Core Team (2020) <https://www.R-project.org/>.

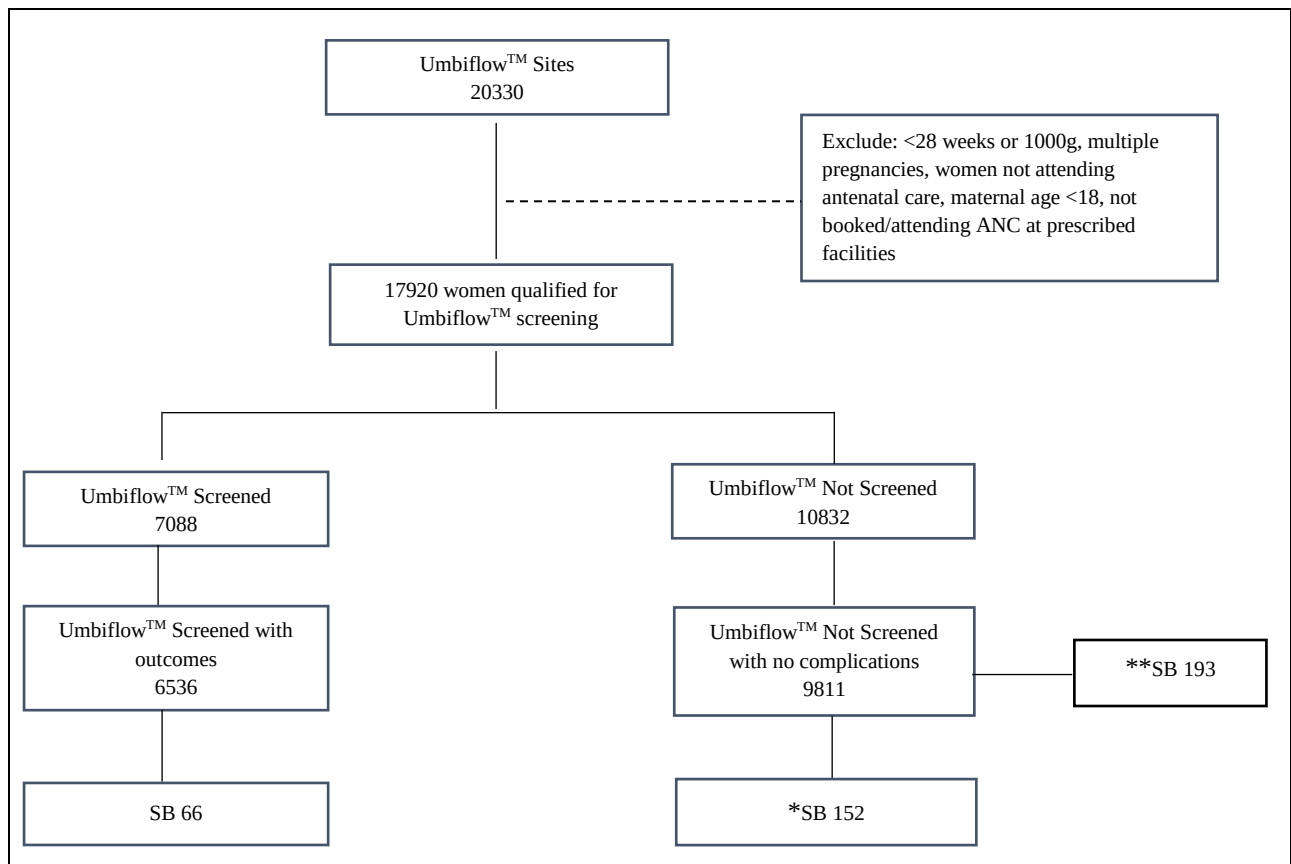
4.5.8 Ethical considerations

Ethics approval was obtained from the University of Pretoria's 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 individual participants involved in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

4.6 Results

During the study period, there were 20330 women who attended antenatal care at the designated primary healthcare clinics and delivered at the clinic or hospital. After excluding women below the age of 18 years, deliveries below 28 weeks gestation or who gave birth to newborns weighing less than 1000g if GA was unknown, women with no maternal and neonatal outcome and multiple pregnancies, 17368 pregnancies were analysed.

The study group consisted of 7088 women who had Umbiflow™ screening, 6536 (92.2%) women had pregnancy outcomes and were analysed. Control group 1 had 10832 women, and control group 2 had 9811 women. Figure 2 gives a breakdown of the women included in the study.



ANC=antenatal care, SB=stillbirth, MSB=macerated stillbirth, FSB= fresh stillbirth, AEDF=absent end diastolic flow, *=control group 1 SB, **= control group 2 SB

4.6.1 Figure 2: Flow chart of women included in the study

The incidence of abnormal RI in the screened group was 13.0%, and 1.2% of the screened population had absent end diastolic flow (AEDF).²⁸ Details are documented elsewhere.²⁸ (<https://doi.org/10.1016/j.eclinm.2021.100792>)

Table 1 gives a comparison between the study group and the two control groups. There was no difference in the age of study group and control groups and in the HIV status; however, the study group had significantly more nulliparous women. The control groups had more low birthweight babies than the study group, but the study group had more SGA babies and more admissions to neonatal nursey. There was no difference in the mode of delivery between study group and control group 1 (caesarean section: 29.5% vs 28.5%, p 0.155), but there were more caesarean section deliveries in the study group than control group 2 (29.5% vs 26.4%, p

0.0001).

4.6.2 Table 1: Comparison of the Umbiflow™ screened group and control group 1 and 2

Demographic information on the Umbiflow screened population					
Indicator	Total Screened	Not Screened (Control 1)	Screened vs Control 1	Not Screened (Control 2)	Screened vs Control 2
			p-value	No ANC Complications	p-value
	(N=6536) n (%)	(N=10832) n (%)		(N=9811) n (%)	
Age					
18-19	465 (7.1%)	785 (7.2%)	0.3421	690 (7.0%)	0.2770
20-34	4993 (76.4%)	8351 (77.1%)		7592 (77.4%)	
35+	1078 (16.5%)	1696 (15.7%)		1529 (15.6%)	
Parity					
0 to 0	2179 (33.3%)	2886 (26.6%)	<0.0001*	2537 (25.9%)	<0.0001*
1 to 4	4288 (65.6%)	7762 (71.7%)		7108 (72.4%)	
5+	69 (1.1%)	184 (1.7%)		166 (1.7%)	
HIV					
positive	2002 (30.6%)	3305 (30.5%)	0.8825	2973 (30.3%)	0.6682
negative	4534 (69.4%)	7527 (69.5%)		6838 (69.7%)	
Outcomes information of the Umbiflow screened population					
Indicator	Total Screened	Not screened (Control 1)	Screened vs Control 1	Not screened (Control 2)	Screened vs Control 2
	(N= 6536) n (%)	(N= 10832) n (%)	p-value	(N=9811) n (%)	p-value
Birthweight (g) Categories at Delivery					
1000g- 1499g	31 (0.5%)	235 (2.2%)	<0.0001*	174 (1.8%)	<0.0001*
1500g - 1999g	124 (1.9%)	357 (3.3%)		276 (2.8%)	
2000g -2499g	575 (8.8%)	854 (7.9%)		752 (7.7%)	
>2500g	5806 (88.8%)	9386 (86.7%)		8609 (87.7%)	
Mean birth weight (SD)	3074 (517)	3050 (552)		3059 (536)	
Mean GA at birth (SD)	39 weeks (1.8)	38 weeks (2.3)		38 weeks (2.2)	
LBW <2500	730 (11.2%)	1446 (13.3%)	<0.0001*	1202 (12.3%)	0.0379*
SGA** (10th centile)	1580 (24.2%)	2235 (20.6%)	<0.0001*	2002 (20.4%)	<0.0001*
Admission Nursery	420 (6.4%)	363 (3.4%)	<0.0001*	226 (2.3%)	<0.0001*

Delivery Mode					
Caesarean Section	1930 (29.5%)	3088 (28.5%)	0.1555	2591 (26.4%)	<0.0001*
Vaginal Delivery	4606 (70.5%)	7744 (71.5%)		7220 (73.6%)	
Impact on the Umbiflow screened population					
Indicator	Total Screened	Not Screened Control 1		Not Screened Control 2	
	(N= 6536) n (/1000)	(N=10832) n (/1000)		(N=9811) n (/1000)	
Impact			RR (95% CI)		RR (95% CI)
Number (SBR/1000)	66 (10.1)	193 (17.8)	0.57 (0.29–0.85)	152 (15.5)	0.65 (0.36–0.94)

Data are n/N (%), HIV= human immunodeficiency virus, g=grams, GA= gestational age, LBW= low birthweight, CS= caesarean section, NVD= normal vaginal delivery, RR= Risk ratio, CI= confidence interval, SB= stillbirth, SBR= Stillbirth rate. **SGA determined using the WHO growth charts

There were 66 stillbirths in the screened group (53 normal RI, 13 abnormal RI) and 193 in the control group 1 and 152 in control group 2. The stillbirth rate was significantly lower in the Umbiflow™ screened study group compared with both control groups (study group vs control 1: 10.1/1000 births vs 17.8/1000 births, RR 0.57, 95% CI 0.29–0.85), (study group vs control 2: 10.1/1000 vs 15.5/1000, RR 0.65, 95% CI 0.36–0.94).

Table 2 describes all the primary causes of stillbirths in the study group. There were nine neonatal deaths in the screened group (neonatal death rate 1.4/1000 live births); two were due to intrauterine growth restriction, two due to congenital abnormalities (cardiac, and multiple abnormalities), and two due to hypertensive disorders in pregnancy and one due to intrapartum asphyxia. In a further two cases no obstetric cause could be identified. (One neonate died at home thought to be due to aspiration following breast feeding and the other died unexpectedly in the postnatal ward, and was classified as sudden infant death syndrome).

4.6.3 Table 2: Primary causes of stillbirths and neonatal deaths for the study group

Primary causes of Stillbirths in the screened group	Umbiflow screened SB (N= 66)
Proteinuric hypertension	3
Eclampsia	0
Unexplained intrauterine death - macerated	30
Unexplained intrauterine death - fresh	3
Abruptio placentae	1
Labour related intrapartum asphyxia	16
Cord around the neck	1
Meconium aspiration	1
Cord prolapse	1
Traumatic breech delivery	1
Amniotic fluid infection	1
Fetal chromosomal abnormality	1
Abnormality of multiple systems	3
Idiopathic intrauterine growth restriction	3
Postmaturity	1
Primary causes of Neonatal deaths in screened group	Screened NND (N= 9)
Proteinuric hypertension	2
Labour related intrapartum asphyxia	1
Abnormality of multiple systems	1
Cardiovascular system abnormality	1
Idiopathic intrauterine growth restriction	2
No obstetric cause / not applicable / Unknown	2

N=number of cases, SB=stillbirth, NND=neonatal death

Unfortunately, we have been unable to reliably trace all the neonatal outcomes of the women that attended the same primary healthcare clinics as the study group. Our electronic birth register records all stillbirths, but does not record all the neonatal deaths. The Perinatal Problem Identification Programme records all the neonatal deaths for the maternity units, but is not granular enough to identify the clinics that the women attended. The overall neonatal deaths for the nine catchment areas was 658 neonates from 69301 live births for women 18 years or older, who attended antenatal care, had a singleton pregnancy and delivered an alive baby of 1000g or more (excluding the neonates of the study group). It gives a neonatal death rate of 9.5/1000 live births. The major neonatal causes were intrapartum asphyxia 29.9%,

spontaneous preterm labour 29.3%, fetal anomalies 10.5%, HDP 10.3%, antepartum haemorrhage 4.9% and infections 3.8%.

4.7 Discussion

Screening a low-risk pregnant population with CWDU-UmA (Umbiflow™) at primary care clinics and referral of fetuses with abnormal RIs to the next level of care, resulted in a significant (43%) reduction in the stillbirth rate (RR 0.57, 95% CI 0.29–0.85); even with the unscreened population who developed antenatal complications excluded there was a significant (35%) reduction in the stillbirth rate (control group 2, RR 0.65, 95% CI 0.36–0.94). There was no increase in the neonatal deaths that was discernible. This reduction in the stillbirth rate was achieved with only a slight increase in resources, namely increased use of neonatal nursery (6.4% vs 3.4% vs 2.3, p 0.0001) and increased caesarean section rate (29.5% vs 28.5%, p 0.155 in control group 1, and 29.5% vs 26.4%, p 0.0001 in control group 2). This finding is similar to the Mamelodi study which showed a reduction in stillbirths, an increase in preterm deliveries without increasing neonatal mortality.²⁵

The incidence of AEDF at 1.2% in the low-risk pregnant population and setting the abnormal RI at approximately 10% of the population meant for every 100 women screened, 10 women were referred and of these 10 women, one fetus had end-stage placental disease. This incidence warrants screening at a primary care level given that the natural history of AEDF is a stillbirth.²⁰

The largest category of stillbirths delivering at district hospitals and community health centres is unexplained stillbirth, and majority of the mothers are clinically healthy, but the majority of these stillbirth had undetected FGR or were SGA.^{3–7,8–13} It is well documented that growth failure is associated with adverse perinatal outcomes and disease later in adulthood.^{6–11} Antenatal care of apparently healthy women occurs mainly at primary healthcare clinics and to reduce the antenatal stillbirth rate the clinicians at the primary healthcare clinics need to identify the high-risk fetus (mostly growth restricted) in the healthy woman. Current methods of detecting FGR are ineffective.^{14–16} We now know CWDU-UmA is a feasible tool to detect FGR and its use in screening at primary healthcare clinics is associated with a step-change reduction in stillbirths, thus potentially solving this problem.

There was no difference in the age or HIV status between the study group and control groups, but the screened group had more primigravid women. Primigravid women are more likely to

attend antenatal care more frequently³⁰ as such they were more likely to have been there on the days of the UmbiflowTM screening. However, there were more low birthweight (LBW) babies in the control groups (13.3% and 12.3% vs 11.2% in the study group) but the study group had more SGA babies (24.2% versus 20.6% and 20.2%). This imbalance between the study group and control groups might have been avoided if a randomised trial had been conducted.

Other limitations of this study include that UmbiflowTM screening was only performed in women 18 years or more, and women were screened on specific days of the week; those not attending on those days did not get an UmbiflowTM screening. We chose not to randomise women so a larger sample of women could be recruited in a shorter period of time for budgetary reasons. There was some loss to follow-up but unknown outcomes were only 7.8%, this is particularly good for low- and middle-income setting where women are considerably mobile. Another limitation of the study has been the inability to trace the neonatal outcomes of all the women that attended the same clinics as the screened study group. We did not have a pregnancy neonatal follow-up system that was granular enough to record neonatal deaths at clinic level and the contact details in the birth register were insufficient to trace all the neonates from the specific clinics. However, the neonatal outcomes of all the neonates whose mothers were screened was available, as we had detailed contact details of the women. This data indicates that there was not a shift to an increased neonatal death rate in the screened group, despite significantly reducing the stillbirths.

A strength of the study is in having two control groups; control group 2 excluded women who developed antenatal complications. We did not remove women from the study group that developed complications, and if anything, they were a slightly higher-risk group than control group 2. This demonstrated that the screened population compared with a low-risk population as possible with similar conditions still had a 35% (RR 0.65, 95% CI 0.36–0.94) reduction in stillbirths. This reinforces the value of screening the umbilical artery for an abnormal RI in low-risk populations. Another strength of the study was the use of nine different geographical sites and the large number involved.

Thirty of the 66 stillbirths in the study group were still unexplained. Only one screening test was performed at around the 30 week visit. It is possible that a subsequent screening at a later time (e.g. 36 weeks) in those women whose fetuses had a normal RI might detect more

fetuses at risk. Further research is needed to answer this question. Alternatively, these fetuses might have died due to undiagnosed congenital infection as described by Madhi et al.³¹

This study demonstrates that screening for FGR using Umbiflow™ was feasible at primary healthcare clinics and highly effective in preventing stillbirths. As mentioned previously, this screening system is ideal for a primary healthcare setting. It is recommended that CWDU-UmA should be used to screen pregnant populations for abnormal RIs of the umbilical arteries. Research should concentrate on the timing of screening and methods to implement the CWDU-UmA screening in primary healthcare clinics in districts throughout SA. Special attention should be paid to the resources that would be required at the referral hospital, namely increased maternity and neonatal high care and intensive care resources.

4.8 Conclusion

CWDU-UmA offers the solution to providing a simple and accurate method of detecting FGR in pregnant women and preventing stillbirths. The high prevalence of AEDF found in South Africa warrants population screening.

4.9 References

1. Kiguli J, Munabi IG, Ssegujja E, et al. Stillbirths in sub-Saharan Africa: unspoken grief. *Lancet* 2016; 387(10018): e16-e18.
2. 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.
3. 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. *Maternal Health Neonatol Perinatol* 2016; 2: 11. <https://doi.org/10.1186/s40748-016-0039-4> (accessed Oct 10, 2021).
4. National Perinatal Morbidity and Mortality Committee (NaPeMMCo). Perinatal Problem Identification Program (PPIP) 2015–2017. South African National Department of Health, 2018.
5. Allanson ER, Muller M, Pattinson RC. Causes of perinatal mortality and associated maternal complications in a South African province: challenges in predicting poor outcomes. *BMC Pregnancy and Childbirth* 2015; 15: 37. <https://doi.org/10.1186/s12884-015-0472-9> (accessed Oct 10, 2021).
6. Katz J, Lee AC, Kozuki N, Lawn JE, 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: 417–425. [https://doi.org/10.1016/S0140-6736\(13\)60993-9](https://doi.org/10.1016/S0140-6736(13)60993-9) (accessed Oct 10, 2021).
7. Gardosi J, Mul T, Mongelli M, Fagan D. Analysis of birth weight and gestational age in antepartum stillbirths. *Br J Obstet Gynaecol* 1998; 105: 524–530. <https://doi.org/10.1111/j.1471-0528.198tb10153.x>. (accessed Oct 10, 2021).
8. Alberry M, Soothill P. Management of fetal growth restriction. *Arch Dis Child Fetal Neonatal Ed* 2007;92:62–67. <https://doi.org/10.1136/adc.2005.082297> (accessed Oct 10, 2021).
9. Malhotra A, Allison BJ, Castillo-Melendez M, Jenkin G, Polglase GR, Miller SL. Neonatal Morbidities of Fetal Growth Restriction: Pathophysiology and Impact. *Front Endocrinol* 2019; 10: 55. <https://doi.org/10.3389/fendo.2019.00055> (accessed July 10, 2021).

10. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: Population based study. *BMJ* 2013; 346: f108. <https://doi.org/10.1136/bmj.f108> (accessed Oct 10, 2021).
11. Francesc F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal care surveillance, diagnosed and management. *Am J Obstet Gynecol* 2011; 204: 288–299. <https://doi.org/10.1016/j.ajog.2010.08.055> (accessed Oct 10, 2021).
12. Hirst JE, Villar J, Victora CG, Papageorghiou AT, Finkton D, Barros FC, et al. The antepartum stillbirth syndrome: risk factors and pregnancy conditions identified from the INTERGROWTH-21st Project. *BJOG* 2018; 125: 1145–1153. <https://doi.org/10.1111/1471-0528.14463> (accessed Oct 10, 2021).
13. Lawn JE, Blencowe H, Waisava R, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet* 2016; 387: 587–603. [https://dx.doi.org/10.1016/S0140-6736\(15\)00837-5](https://dx.doi.org/10.1016/S0140-6736(15)00837-5) (accessed Oct 10, 2021).
14. Robert Peter J, Ho JJ, Valliapan J, Sivasangari S, Symphysis fundal height (SFH) measurement in pregnancy for detecting fetal growth. *Cochrane database Sys Rev* 2015; 9: CD008136.
15. Norman JE, Heazell AEP, Rodriguez A, et al. Awareness of fetal movements and care package to reduce fetal mortality (AFFIRM): a stepped wedge, cluster-randomised trial. *Lancet* 2018; 392: 1629–1638. [https://doi.org/10.1016/S0140-6736\(18\)31543-5](https://doi.org/10.1016/S0140-6736(18)31543-5) (accessed Oct 10, 2021).
16. Goldenberg RL, Nathan RO, Swanson D, et al. Routine antenatal ultrasound in low- and middle-income countries: First look- a cluster randomised trial. *BJOG* 2018; 125: 1591–1599. <https://doi.org/10.1111/1471-0528.15287> (accessed Oct 10, 2021).
17. 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: 233–239. <https://doi.org/10.1080/14767050601134926> (accessed Oct 10, 2021).
18. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. *Fetal Diagn Ther* 2014; 36: 86–98. <https://doi.org/10.1159/000357592> (accessed Oct 10, 2021).
19. Pattinson RC, Theron GB, Thompson ML, Lai Tung M. Doppler ultrasonography of the fetoplacental circulation- normal reference values. *S Afr Med J* 1989; 76: 623–625.

20. Hlongwane TMAG, Botha T, Nkosi BSS, Pattinson RC. The outcome of absent end diastolic flow in fetuses of clinical healthy pregnant woman in South Africa (under review).
21. Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev* 2017; 6: CD007529. <https://doi:10.1002/14651858.CD007529.pub3>. (accessed Oct 10, 2021).
22. Alfirevic Z, Stampalija T, Medley N. Doppler ultrasound of fetal blood vessels in normal pregnancies. *Cochrane Database Syst Rev* 2015; 4: CD001450.
23. Mufenda J, Gebhardt S, van Rooyen R, Theron G. Introducing a mobile connected umbilical Doppler device (Umbiflow) into a primary care maternity setting: Does this reduce unnecessary referrals to a specialised care? Results of a pilot study in Kraaifontein, South Africa. *Plos One* 2015; 10: e0142743. <https://doi.org/10.1371/journal.pone.0142743> (accessed Oct 10, 2021).
24. Theron GB, Theron AM, Odendaal HJ, Bunn AE. Comparison between a newly developed PC-based Doppler umbilical artery waveform analyser and a commercial unit. *S Afr Med J* 2005; 95:62–64.
25. Nkosi S, Makin J, Hlongwane T, Pattinson RC. 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: 347–352. <https://doi.org/10.7196/SAMJ.2019.v109i5.13611> (accessed Oct 10, 2021).
26. World Health Organisation. WHO recommendations on antenatal care for a positive pregnancy experience. World Health Organization. Geneva 2016. <https://apps.who.int/iris/bitstream/10665/250796/1/9789241549912-eng.pdf> (accessed Oct 10, 2021).
27. Hlongwane TM, Bozkurt B, Barreix MC, Pattinson R, Gülmezoglu M, Vannevel V, Tunçalp Ö. Implementing antenatal care recommendations, South Africa. *Bull World Health Organ* 2021; 99: 220–227. <https://doi:10.2471/BLT.20.278945> (accessed Oct 10, 2021).
28. Hlongwane T, Cronje T, Nkosi B, Pattinson RC. The prevalence of abnormal Doppler's of the umbilical artery in a low-risk pregnant population in South Africa. *EClinicalMedicine* 2021; 34: 100792. <https://doi:10.1016/j.eclinm.2021.100792> (accessed Oct 10, 2021).
29. Torvid Kiserud, Alexandra Benachi, Kurt Hecher, Rogelio González Perez, José Carvalho, Gilda Piaggio, Lawrence D Platt. The World Health Organization fetal

- growth charts: concept, findings, interpretation, and application. *Am J Obstet Gynecol* 2018; 218: 619–629. [https://doi.org/ 10.1016/j.ajog.2017.12.010](https://doi.org/10.1016/j.ajog.2017.12.010) (accessed Oct 10, 2021).
30. Benova L, Tuncalp Ö, Moran AC, Campbell OMR. Not just a number: examining coverage and content of antenatal care in low-income and middle-income countries. *BMJ Glob Health* 2018; 3: e000779. <https://doi.org/10.1136/bmigh-2018-000779> (accessed Oct 10, 2021).
31. Madhi SA, Briner C, Maswime S, Mose S, Mlandu P, Chawana R, Wadula J, Adam Y, Izu A, Cutland CL. Causes of stillbirths among women from South Africa: a prospective, observational study. *Lancet Glob Health* 2019; 7: e503–12.

Chapter 5

The outcome of absent end diastolic flow in fetuses of clinically healthy pregnant women in South Africa

5.1 Introduction to Chapter 5

Umbilical artery Doppler screening in a low-risk population in South Africa has demonstrated a significant impact on the stillbirth rate. The stillbirth rate was significantly reduced in the screened population (10.1/1000 births), compared to a stillbirth rate of 17.8/1000 births in control group of pregnant women not screened with Umbiflow™, attending the same antenatal clinics (RR 0.57, 95% CI 0.29–0.85). When pregnant women who developed antenatal complications in the control were removed, there was still a significant reduction in the stillbirth rate in the screened population 10.1/1000 vs 15.5/1000, RR 0.65, 95% CI 0.36–0.94. Umbiflow™ screening was able to identify the high-risk fetus at risk of stillbirth in the third trimester in a low-risk healthy mother.

In this Umbiflow™ screened low-risk population approximately one in ten women screened had an abnormal umbilical artery resistance index (RI) and one in ten of those had absent end diastolic flow (AEDF). The RI is a measure of placental function, it normally should decrease with increasing gestation. The higher it is, the more adverse neonatal and maternal effects. The rise in gestational age leads to a decline of fetoplacental blood flow resistance which ensures a positive flow in the end-diastolic flow velocity. A rising impedance in the fetoplacental bed results in an increase in the end-diastolic velocity which results in AEDF and eventually reversed end diastolic flow (REDF) and is associated with a worsening prognosis. AEDF represents end stage placental disease, and is associated with fetal growth restriction, neuro-developmental sequelae, chromosomal and structural anomalies and if untreated results in perinatal deaths.^{1,2}

The prevalence of abnormal RI and AEDF in a high-risk population varies from 2.1% to 56%.³⁻⁵ Most studies assessing the clinical implications of abnormal RI and AEDF on the umbilical artery have been performed in high-risk populations.⁶ In contrast to the high-risk population, there is insufficient data on abnormal RI and AEDF in low-risk women and previously available evidence suggests that the prevalence of abnormal RI and AEDF are rare (0.05–2.1%) in low-risk or unselected pregnancies.^{7,8} The cut-off value for an abnormal RI will vary depending on the sensitivity, specificity and positive predictive value chosen for the

cut-off value. However, there is no debate about the presence of AEDF and that it is abnormal in the third trimester.

The next chapter details the characteristics and outcome of AEDF fetuses in clinically healthy low-risk pregnant women in South Africa. The implications and natural history of AEDF are discussed in the next chapter. This chapter (Hlongwane T, Cronje T, Nkosi B, Pattinson RC. The outcome of absent end diastolic flow in fetuses of clinically healthy pregnant women in South Africa) has been submitted to the South African Journal of Obstetrics and Gynaecology, a peer review journal.

5.2 References:

1. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. *Fetal Diagn Ther* 2014; 36: 86–98. <https://doi:10.1159/000357592> (accessed July 24, 2021).
2. Malhotra A, Allison BJ, Castillo-Melendez M, Jenkin G, Polglase GR, Miller SL. Neonatal Morbidities of Fetal Growth Restriction: Pathophysiology and Impact. *Front Endocrinol* 2019; 10: 55. <https://doi:10.3389/fendo.2019.00055> (accessed July 10, 2021).
3. Alfievic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev* 2017; 6: CD007529. <https://doi:10.1002/14651858.CD007529.pub3>. (Accessed July 24, 2021)
4. Maulik D, Figueroa R. Absent end-diastolic velocity in the umbilical artery and its clinical significance. In: *Doppler ultrasound in obstetrics and gynaecology*. Berlin: Springer; 2005. p. 362–373. https://doi.org/10.1007/3-540-28903-8_25 (accessed June 01, 2021).
5. Beattie RB, Dornan JC. Antenatal screening for intrauterine growth retardation with umbilical artery Doppler ultrasonography. *BMJ* 1989; 298: 631–635. <https://doi:10.1136/bmj.298.6674.631> (accessed April 24, 2021).
6. Alfievic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev* 2017; 6: CD007529. <https://doi:10.1002/14651858.CD007529.pub3>. (accessed July 24, 2021).
7. Alfievic Z, Stampalija T, Medley N. Doppler ultrasound of fetal blood vessels in normal pregnancies. *Cochrane Database Syst Rev* 2015; 4: CD001450.
8. Vogel JP, Vannevel V, Robbers G, Gwako G, Lavin T, Adanikin A, Hlongwane T, Pattinson RC, Qureshi ZP, Oladapo OT. Prevalence of abnormal umbilical arterial flow on Doppler ultrasound in low-risk and unselected pregnant women: a systematic review. *Reprod Health* 2021; 18: 38. <https://doi:10.1186/s12978-021-01088-w> (accessed April 24, 2021).

The outcome of absent end diastolic flow in fetuses of clinically healthy pregnant women in South Africa

5.3 Abstract

Background: The use of umbilical fetal blood flow using Doppler waveform may be a useful tool to identify placental insufficiency and the fetus at risk of stillbirth due to fetal growth restriction (FGR). Absent end-diastolic flow (AEDF) is recognised as end-stage placental disease and known to have a high perinatal mortality.

Objective: This study was performed to describe the prevalence and outcome of low-risk pregnant women found to have fetuses with AEDF.

Methods: Low-risk pregnant women were screened using a continuous wave Doppler ultrasound device (Umbiflow™) across nine sites in South Africa. Women were screened between 28 and 34 weeks' gestation. Women with fetuses with an abnormal resistance index according to the standard curves used were referred to a high-risk clinic and were managed according to a standard protocol. The outcomes of all screened women were recorded.

Results: Umbiflow™ screening was performed in 7088 women; AEDF was found in 87 (1.2%) of fetuses. Of the 87 women, 21 (24.1%) developed hypertensive disorders in pregnancy, 23 (26.4%) were HIV reactive on antiretroviral therapy, 61 (71.8%) newborns were low birth weight and 56 (64.4%) newborns were small for gestational age (SGA). The perinatal mortality was 91.9/1000 births. Five women declined treatment, and 4 had stillbirths.

Conclusion: If not managed, AEDF leads to stillbirths. Intervention did not transfer the potential stillbirths to neonatal deaths. This plus the prevalence of AEDF warrants screening in South Africa.

5.4 Introduction

The assessment of fetal blood flow using the analysis of umbilical Doppler flow velocity waveform is one of the innovative methods of fetal surveillance.¹ It is a good tool to identify fetuses at risk of dying due to severe fetal growth restriction²⁻⁴ and been shown to reduce perinatal mortality by 38% in high risk pregnancies.²

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.^{1,3} Doppler ultrasound of the umbilical artery on the other hand detects 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) – defined as failure to reach genetic growth potential.²⁻⁴ A rising impedance in the fetoplacental bed results in decline in the end-diastolic velocity which results in absent end diastolic flow (AEDF) and eventually reversed end diastolic flow (REDF) and is associated with a worsening prognosis in high-risk pregnancies.¹⁻⁵ AEDF is associated with FGR, neuro-developmental sequelae, chromosomal, structural anomalies and increased perinatal deaths.¹⁻⁵ The perinatal mortality of AEDF is often reported as more than 50%, and there is concern that identifying the fetus with AEDF will result in increased neonatal mortality and morbidity due to the interventions. All of these studies have been reported in high-risk pregnancies. Very few studies have described AEDF detected in women classified as having low-risk pregnancies.²

Placental insufficiency usually results in a decrease in placental blood flow and is detected by a rise in Doppler indices.^{1,3,4} Despite the use of conventional ultrasound, the task of accurately identifying fetuses at risk of stillbirth from placental diseases continues to elude us.^{3,4} Doppler ultrasound can detect placental insufficiency with a single reading compared with the serial measurements required for imaging ultrasound.³

In South Africa (SA), the largest category of perinatal deaths is unexplained intrauterine death.^{6,7} One in four of the perinatal deaths were recorded as unexplained stillbirths.⁶⁻⁹ The majority of these mothers were recorded as clinically healthy women and the highest prevalence of stillbirth was between 34 and 38 weeks' gestation.^{6,7} It is hypothesised that many of these deaths are due to undetected growth restriction.^{6,7}

This descriptive study examines the characteristics and outcomes of fetuses with AEDF detected during umbilical Doppler screening of low-risk pregnant women between 28 and 34

weeks gestation. This should help determine if FGR is a major cause of perinatal deaths, the effect on neonatal mortality and whether screening a pregnant population with Doppler ultrasound in South Africa is worthwhile.

5.5 Methods

5.5.1 Study design

This descriptive study explored the prevalence of AEDF of the umbilical artery in a low-risk pregnant population. Low-risk pregnant women, aged at or above 18 years at a gestational age (GA) between 28 and 34 weeks' qualified to be screened. Low-risk was defined as pregnant woman attending non-specialist primary healthcare clinics; this classification was based on local SA clinical guideline and antenatal care policy guided the World Health organization (WHO) antenatal care recommendations for a positive pregnancy experience.^{10,11}

5.5.2 Study participants

Women qualifying were recruited at the primary healthcare clinics for a continuous wave Doppler ultrasound screening examination using the UmbiflowTM device. The exclusion criteria included women with multiple pregnancies, women with a gestational age below 28 weeks or a symphysis fundal height below 26 cm, or aged below 18 years. UmbiflowTM screening was done between 28 and 34 weeks' gestation, at this gestation most fetuses would have weighed more than 1000 grams (g) at the time of recruitment into the study and if clinical intervention was required, there was a reasonable chance of survival of the fetus.

5.5.3 Study setting

The recruitment sites were primary healthcare clinics in catchment areas of nine hospitals across South Africa. The study sites were purposively selected, and had a study healthcare worker screening eligible women on specific days of the week.¹² Each site had an established referral route, with an established mode of communication with the referral hospitals. Women with abnormal resistance indices (abnormal RI) screening were referred for further clinical evaluation and management by a hospital team at the appropriate referral hospital. The receiving hospital had a maternal and neonatal care unit, clinicians, access to theatre and blood products and the capacity to care for neonates of 1000g or more. All the study sites used the

Perinatal Problem Identification Program¹³ (PPIP) data system that tracks maternal and perinatal mortality in SA.

5.5.4 Measurements

UmbiflowTM device was used to screen umbilical artery for abnormal RI.^{9,12,14} The UmbiflowTM screening was classified as either normal or abnormal RI depending on the RI value in relation to GA. This was plotted on a graphic representation using the 75th percentile as a cut off.¹⁵ Women with RI findings below the 75th percentile for their gestational age were considered as normal RI, and continued their routine antenatal care at their local primary healthcare clinics. Those with RI findings above the 75th percentile for gestational age were considered as high (abnormal RI) and were referred to a high-risk clinic at their local hospitals for detailed clinical evaluation and management. The 75th percentile was used as a cut-off as Nkosi et al.⁹ has shown previously that it detected approximately 10% of fetuses at risk of FGR in a low-risk pregnant population.

At the high-risk clinic a detailed ultrasound examination and pulsed wave Doppler were performed and the women were managed according to a standard protocol.¹² AEDF was defined where no end diastolic flow was visible during a pulsed wave examination, and chosen as it is accepted as a reproducible and clearly represents abnormality.^{1,3,4} The AEDF group was compared with a group of pregnancies where the RI was regarded as normal with respect to standard curves used in South Africa.^{12,15} Women with AEDF at the high-risk contact were offered admission, corticosteroids (unless gestational age was more than 34 weeks) and the fetus was monitored using a cardiotocograph. If the maternal condition or fetal condition deteriorated or the women reached 34 weeks' gestation with AEDF delivery was recommended. The prevalence of abnormal Doppler and the outcome of the population screened has been described in detail elsewhere.¹²

5.5.5 Data collection

The screened women's information including sociodemographic, lifestyle and behavioural factors, medical and obstetric history were obtained at the time of recruitment through an interview and medical record review. The screening result of the UmbiflowTM was printed for assessment of quality of the umbilical artery Doppler waveform. The UmbiflowTM screening

findings were documented. The details of all the women delivering at the primary healthcare clinics and the referral hospitals were recorded in the birth registers.

5.5.6 Statistical analysis

Analysis of the prevalence of AEDF 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 and birth weight.

Variables reported in this manuscript include maternal age in years, parity, gravidity, HIV status, hypertensive disorders in pregnancy (HDP), birth weight in grams (g), low birthweight (defined by birthweight below 2500g), neonatal admission to neonatal unit post-delivery, mode of delivery, and stillbirths (defined as an infant with no signs of life at 1 minute and 5 minute of life [APGAR of zero]) and neonatal deaths (defined as death of neonate in the first 28 days of life). The WHO growth charts were used to diagnose SGA fetuses.¹⁶ Categorical characteristics were investigated using chi square tests to express differences between the screened and not screened groups and the two-proportion z tests for cases where only certain categories were compared. Continuous variables were evaluated using the Shapiro Wilk test of normality and were compared using the independent t-test or the Mann Whitney U test. All tests were performed at a 5% level of significance. The relative risk was calculated using the incidence proportions of total stillbirth rate, and the overall perinatal mortality rate. All statistical analyses were done with R Core Team (2020) <https://www.R-project.org/>.

5.5.7 Ethics

Ethical approval was obtained from the University of Pretoria's faculty of Health Sciences (473/2014). 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.

5.6 Results

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. Overall, 7088 pregnant women classified as having low-risk pregnancies

were screened with Umbiflow™, 919 had an abnormal RI greater than the 75th centile and were referred to the high-risk clinic. At the high-risk clinic 87 had or subsequently developed AEDF. Outcomes were available for 6674 (94.2%) women screened. Of the 6169 normal RI group, 5787 (94.8%) had delivery outcomes. The prevalence of AEDF in the abnormal RI group was 9.5% and 1.2% of the whole population screened. Table 1 outlines the demographics and outcomes of the AEDF group and the normal RI group.

5.6.1 Maternal characteristics

The mean age of women with AEDF was 29.8 years (SD 6.2), compared to a mean of 27.7 years (SD 6.6) in the normal RI group, with median parity of 1 (IQR 0–2, and gravidity of 2 (IQR 1–3) in both groups. Twenty one (24.1%) of the AEDF group had HDP during follow-up, and 212 (3.4%) in the normal RI group. Gestational age at delivery of those with AEDF and developed HDP and those with AEDF without HDP did not differ- 35 weeks. There were 23 (26.4%) women who were HIV reactive in the AEDF group, 1842/6169 (29.9%) women in the normal RI group and all were on antiretroviral treatment. Thirty six (41.9%) women delivered vaginally (4 having had stillbirths after declining further treatment). The caesarean delivery (CD) rate was 58.1%. The indications for CD were six (12.0%) for AEDF, 39 (78.0%) had AEDF and fetal distress, and five (10.0%) previous CD. AEDF was detected at the first abnormal RI antenatal contact in 48 (55.2%) of the women, and 39 (44.8%) developed AEDF at subsequent follow up contacts. Twenty four (27.6%) fetuses of the 87 fetuses with AEDF had positive end diastolic flow transiently return following the administration of corticosteroids. Antenatal follow up continued as per the abnormal RI group.

5.6.2 Table 1: Demographic and outcome of the Umbiflow™ population with AEDF and Normal RI

Indicator	AEDF (87) (N= %)	Normal RI (6169) (N= %)	p value
Age			
18-19	5 (5.7)	446 (7.2)	0.1668
20-34	62 (71.3)	4751 (77.1)	
35+	20 (23.0)	964 (15.6)	
unknown	0 (0.0)	8 (0.1)	
mean Age (SD)	29.8 (6.2)	27.7 (6.6)	0.0017*
Parity			
0 to 0	30 (34.5)	2097 (34.0)	0.0751
1 to 4	54 (62.1)	4004 (65.0)	
5+	3 (3.4)	61 (1.0)	
unknown	0 (0.0)	7 (0.1)	
Median Parity (IQR)	1 (0 - 2)	1 (0 - 2)	0.9412
Gravidity			
1	26 (29.9)	1921 (31.2)	0.7650
2 to 4	55 (63.2)	3921 (63.6)	
5+	6 (6.9)	319 (5.2)	
unknown	0 (0.0)	8 (0.1)	
Median Gravidity (IQR)	2 (1 - 3)	2 (1 - 3)	0.2721
HIV			
pos	23 (26.4)	1842 (29.9)	0.5634
neg	64 (73.6)	4324 (70.1)	
missing	0 (0.0)	3 (0.05)	
HDP			
HDP	21 (24.1)	212 (3.4)	<0.0001*
Outcomes	AEDF (87) (N= %)	Normal RI (5787) (N= %)	
GA @ Delivery			
28-33	19 (22.1)	91 (1.6)	<0.0001*
34-37	37 (43.0)	1005 (17.5)	
38+	30 (34.9)	4647 (80.9)	
unknown	1 (1.1)	44 (0.8)	
Mean GA @Del	35.6 (3.1)	38.6 (1.8)	<0.0001*
Weight @Delivery			
1.0g-1.49g	14 (16.5)	11 (0.2)	<0.0001*
1.5g-1.99g	23 (27.1)	83 (1.4)	
2.0g-2.49g	24 (28.2)	472 (8.2)	
>2.5g	24 (28.2)	5189 (90.2)	

missing mean weight	2 (2.3) 2106.8 (±656.4)	32 (0.6) 3099.6 (±500.9)	<0.0001*
LBW			
<2500	61 (71.8)	566 (9.8)	<0.0001*
SGA**	56 (64.4)	1335 (23.1)	<0.0001*
Admission Nursery	32 (38.6)	350 (6.5)	<0.0001*
Congenital abnormalities	1 (1.1)	10 (0.2)	0.3997
Delivery Mode			
CS	50 (58.1)	1603 (28.2)	<0.0001*
NVD	36 (41.9)	4086 (71.8)	
unknown	1 (1.2)	98 (1.7)	
Impact			
Total SB (/1000)	7 (80.4)	54 (9.3)	
MSB	5 (57.5)	34 (5.9)	
FSB	2 (23.0)	20 (3.5)	
NND	1 (11.5)	3 (0.5)	
PNMR (/1000)	8 (91.9)	57 (9.9)	

Data are n/N (%), LBW= low birthweight, HDP=hypertensive disorders in pregnancy, GA= gestational age, HIV= human immunodeficiency virus, pos= positive, neg= negative, LBW=low birth weight, SGA= small for gestational age, NVD= normal vaginal delivery, CS= caesarean section, 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

5.6.3 Perinatal outcome

Five women identified with AEDF declined hospital treatment, and all their pregnancy outcomes were subsequently traced. Four had macerated stillbirths as demonstrated on Table 2. One woman was lost to follow-up, but the fetus survived. The other 3 stillbirths; one developed fetal distress, and at emergency caesarean section a fresh stillborn was delivered, one had no fetal heart activity at admission and was induced. One had fetal congenital abnormalities involving the cardiopulmonary system. There was one neonatal death. The mother was admitted and received steroids, subsequently developed fetal distress and delivered at 31 weeks. The neonate weighed 1150g, and demised in the neonatal unit due to complications of prematurity.

5.6.4 Table 2: Perinatal mortality in the AEDF group

GA at Delivery	Birth weight (g)	Delivery Mode	Perinatal outcome	Indication
30	970	NVD	MSB	Defaulted, No heart activity at admission
36	1750	NVD	MSB	Defaulted, Declined intervention
36	1900	NVD	MSB	Defaulted follow up, declined intervention
31	1600	NVD	MSB	Declined intervention
36	1800	NVD	MSB	Congenital abnormalities- cardiopulmonary
31	1286	NVD	FSB	Admitted, No heart activity in ward
32	1300	C/S	FSB	Developed fetal distress
31	1150	C/S	NND	Developed fetal distress, prematurity

GA= Gestational age, SB= stillbirth, HDP= hypertensive disorders of pregnancy, MSB= macerated stillbirth, FSB= fresh stillbirth, NND= neonatal death.

5.6.5 Newborn characteristics

The mean gestational age at delivery was 35.6 weeks (SD 3.1) in the AEDF group compared to a mean of 38.6 weeks in the normal RI group. The mean birthweight was 2106.8g (± 656.4) in the AEDF group and 3099.6g (± 500.9) in the normal RI group. Neonates with AEDF, 61 (71.8%) had low birthweight, and 56 (64.4%) were small for gestational age (SGA). Of the AEDF group, thirty two (38.6%) neonates were admitted to the neonatal high care unit, compared with 350 (6.5%) of the normal RI neonates. The perinatal mortality rate was 91.9/1000 births in the AEDF group compared with 9.9/1000 births in the normal RI group. One of the AEDF neonates was found to have congenital abnormalities of the cardiopulmonary system, ten of the normal RI neonates had congenital abnormalities; these include two involving the neurological system, one involving multiple systems, one suspected trisomy 18, two with clubbed foot, one with polydactyly, one cleft palate and two other congenital abnormalities not defined.

5.7 Discussion

The prevalence of AEDF in the low-risk population screened was 1.2%, which is much higher than previously recorded in other studies using Doppler to screen women with low-risk pregnancies in other countries.^{2,17} The prevalence of HDP was significantly higher (24.1% vs 3.4%) than those women with normal RIs. Four of the five women whose fetuses had AEDF declined treatment had stillbirths. The perinatal mortality in the AEDF group was 91.9/1000 births considerably higher than those with normal RIs.

There was one neonatal death in the AEDF group, demonstrating the intervention did not transfer potential stillbirths into neonatal deaths. As expected there was a significant difference in the use of neonatal services in the AEDF group (38.6% vs 6.5 % $p < 0.0001$), this will put a burden on neonatal services. Neonatal services need to be prioritised if such an intervention is to be used at scale. Furthermore, almost half of the fetuses that developed AEDF did so on follow-up for an abnormal RI. Active follow-up and management of women identified is essential.^{1-4,9}

This descriptive study is different from most described in the literature as the women were clinically healthy and regarded as having low-risk pregnancies. Identifying the high-risk fetus in the low-risk mother is an under researched area and this study contributes in this area.

The lower prevalence of HIV infection (26.4%) in the AEDF groups compared to the normal RI group (29.9%) was unanticipated. It was expected that there would be an increase in AEDF because of the effect of HIV on small vessels and thrombosis.¹⁸ This needs to be explored further. Placental histology might have helped understand the pathology better, but unfortunately was not performed.

The incidence of finding AEDF in a high-risk population varies from 2.1% to 56 %.² In contrast to the high-risk population, the prevalence of abnormal Doppler and AEDF in low-risk populations has been reported to be between 0.1% and 0.29%.^{2,17,19} This study confirms the high prevalence of AEDF found in South Africa by Nkosi et al.⁹ and Vannevel et al.¹⁹ The reason for this is unclear. AEDF is normally associated with HDP 40–70% typically described^{2,5}, and HDP was found in 24.1% of women with fetuses with AEDF in this study. One can speculate if AEDF in this study is just the end of the pre-eclampsia spectrum or a new condition.

The perinatal mortality rate for AEDF is reported around 500/1000¹⁻³ and that high RI's and AEDF is associated with adverse outcomes.²⁻⁵ Maulik et al.²⁰ reviewed 1126 cases of AEDV and REDF and reported 193 stillbirths, 312 neonatal deaths (170/1000 stillbirths, 280/1000 in neonatal mortality rate and with the overall 450/1000 in perinatal mortality rates). This mortality rate was considerably higher than that recorded in this study of 91.9/1000 births although their data was from a mixed population, and these findings were found despite intervention. Only starting screening in the third trimester may be a reason for this. This starting point was chosen in this study in view of the neonatal resources available in the catchment areas used and is likely to apply to most LMICs.

The natural history of AEDF is hard to determine now because of interventions, but early studies suggested AEDF would lead to stillbirth.^{2-4,20} Beatie and Dornan²¹ reported three cases of abnormal Doppler that led to unexplained stillbirths in their cohort analytic study where the results were not revealed to the clinicians described. Nkosi et al,⁹ also described perinatal deaths in three of the four fetuses with AEDF in women declining medical management. This is similar to the four stillbirths in five women whose fetuses had AEDF who declined treatment in this study. It appears that most fetuses with AEDF and left unattended will result in stillbirths. AEDF in the umbilical artery was previously considered as a permanent structural change, however in this series end-diastolic flow returned in 24 (27.6%) of the 87 cases with AEDF. This has been reported before and although there was positive end diastolic flow, the fetuses were still at risk of SGA.²²

Literature reports that majority of stillbirths occur in mothers who are considered low-risk or clinically healthy.^{7,23} 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.^{6,7} Hirst et al.²⁴ describes a five-fold increase in stillbirths where fetal growth restriction is not detected. The AEDF group in this study had a significantly higher number of low birth weights, SGA and neonatal admissions, and more stillbirths.

Assuming, conservatively, that half of the one million births in South Africa per year are apparently low-risk pregnancies and 1% have undetected AEDF and, conservatively, half of these fetuses die then 2 500 stillbirths per year $[(500\,000 \times 0.01) \times 0.5]$ could be ascribed to AEDF. Unexplained stillbirths account for approximately 25% of the 20 000 stillbirths per year in SA, (approximately 5000 stillbirths)^{6,7,13} so approximately 50% of the unexplained stillbirths could be due to undetected AEDF. Abnormal RIs is associated with placental insufficiency and fetal growth restriction so undetected fetal growth restriction is probably a major cause of stillbirth.^{1-5,20} Given the very high SGA rate in LMICs (Katz et al.²⁵) the finding in this study might be important in other LMICs.²⁵

5.8 Conclusion

This descriptive study helps explain some of the unexplained stillbirths that are so common in apparently healthy pregnant women in South Africa. AEDF was about ten times higher than that previously recorded in high-income countries making it worthwhile to screen a pregnant population in SA to prevent stillbirths. Doppler ultrasound was effective in detecting SGA

babies and may be a more effective method of detecting fetal growth restriction than imaging ultrasound. This will need to be researched further. Understanding why the prevalence of AEDF was so much higher in the South African population also requires further research. These findings suggest that screening a low-risk pregnant population from 28 weeks gestation with UmbiflowTM is potentially a viable way to reduce the large burden of unexplained stillbirths in South Africa, without increasing neonatal deaths.

5.9 References

1. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. *Fetal Diagn Ther* 2014; 36: 86–98. <https://doi: 10.1159/000357592> (accessed Dec 10, 2021).
2. AlfIREVIC Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev* 2017; 6: CD007529. <https://doi: 10.1002/14651858.CD007529.pub4>. (accessed Dec 10, 2021).
3. Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. *Am J Obstet Gynecol* 2011; 204: 288–300. <https://doi: 10.1016/j.ajog.2010.08.055>. (accessed Dec 10, 2021).
4. Karsdorp VH, van Vugt JM, van Geijn HP, Kostense PJ, Arduini D, Montenegro N, Todros T. Clinical significance of absent or reversed end diastolic velocity waveforms in umbilical artery. *Lancet* 1994; 344: 1664–1668. [https://doi:10.1016/s0140-6736\(94\)90457-x](https://doi:10.1016/s0140-6736(94)90457-x) (accessed Dec 10, 2021).
5. Odendaal HT, Theron AM, Carstens MH, de Jager M, Grovè, D. Intrauterine deaths in high-risk pregnancies with normal and borderline umbilical artery Doppler flow velocity waveforms. *SAJOG* 2008; 14: 33–37.
6. Allanson ER, Muller M, Pattinson RC. Causes of perinatal mortality and associated maternal complications in a South African province: challenges in predicting poor outcomes. *BMC Pregnancy and Childbirth* 2015; 15: 37. <https://doi.org/10.1186/s12884-015-0472-9> (accessed Dec 10, 2021).
7. 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. *Maternal Health Neonatol Perinatol* 2016; 2: 11. <https://doi.org/10.1186/s40748-016-0039-4> (accessed Dec 10, 2021).
8. Gardosi J, Mul T, Mongelli M, Fagan D. Analysis of birth weight and gestational age in antepartum stillbirths. *Br J Obstet Gynaecol* 1998; 105: 524–530. <https://doi.org/10.1111/j.1471-0528.198tb10153.x>. (accessed Dec 10, 2021).
9. Nkosi S, Makin J, Hlongwane T, Pattinson RC. 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: 347–352.
<https://doi:10.7196/SAMJ.2019.v109i5.13611> (accessed Dec 10, 2021).
10. Hlongwane TM, Bozkurt B, Barreix MC, Pattinson R, Gülmezoglu M, Vannevel V, Tunçalp Ö. Implementing antenatal care recommendations, South Africa. *Bull World Health Organ* 2021; 99: 220–227. <https://doi:10.2471/BLT.20.278945> (accessed Dec 10, 2021).
 11. World Health Organisation. WHO recommendations on antenatal care for a positive pregnancy experience. World Health Organization. Geneva 2016.
<https://apps.who.int/iris/bitstream/10665/250796/1/9789241549912-eng.pdf> (accessed Dec 10, 2021).
 12. Hlongwane T, Cronje T, Nkosi B, Pattinson RC. The prevalence of abnormal Doppler's of the umbilical artery in a low-risk pregnant population in South Africa. *EClinicalMedicine* 2021; 34: 100792. <https://doi:10.1016/j.eclinm.2021.100792> (accessed Dec 10, 2021).
 13. National Perinatal Morbidity and Mortality Committee (NaPeMMCo). Perinatal Problem Identification Program (PPIP) 2015–2017. South African National Department of Health, 2018.
 14. Mufenda J, Gebhardt S, van Rooyen R, Theron G. 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: e0142743.
<https://doi:10.1371/journal.pone.0142743> (accessed Dec 10, 2021).
 15. Pattinson RC, Theron GB, Thompson ML, Lai Tung M. Doppler ultrasonography of the fetoplacental circulation-normal reference values. *S Afr Med J* 1989; 76: 623–625.
 16. Kiserud T, Benachi A, Hecher K, Perez RG, Carvalho J, Piaggio G, Platt LD. The World Health Organization fetal growth charts: concept, findings, interpretation, and application. *Am J Obstet Gynecol* 2018; 218: S619–S629.
<https://doi:10.1016/j.ajog.2017.12.010> (accessed Dec 10, 2021).
 17. Vogel JP, Vannevel V, Robbers G, Gwako G, Lavin T, Adanikin A, Hlongwane T, Pattinson RC, Qureshi ZP, Oladapo OT. Prevalence of abnormal umbilical arterial flow on Doppler ultrasound in low-risk and unselected pregnant women: a systematic review. *Reprod Health* 2021; 18: 38. <https://doi:10.1186/s12978-021-01088-w> (accessed Dec 10, 2021).

18. López M, Palacio M, Goncé A, Hernández S, Barranco FJ, García L, et al. Risk of intrauterine growth restriction among HIV-infected pregnant women: a cohort study. *Eur J Clin Microbiol Infect Dis* 2015; 34: 223–30. <https://doi.org/10.1007/s10096-014-2224-6> (accessed Dec 10, 2021).
19. Vannevel V, Voge JP, Pattinson R, Adanu R, Charantimath U, Goudar S, et al. Prevalence of abnormal Doppler in low-risk pregnant women: a multi-country cohort study. RCOG World Conference, 9–12 June 2021, London. Abstract 1428.
20. Maulik D, Figueroa R. Absent end-diastolic velocity in the umbilical artery and its clinical significance. In: *Doppler ultrasound in obstetrics and gynaecology*. Berlin: Springer; 2005. p. 362–373. https://doi.org/10.1007/3-540-28903-8_25 (accessed Dec 10, 2021).
21. Beattie RB, Dornan JC. Antenatal screening for intrauterine growth retardation with umbilical artery Doppler ultrasonography. *BMJ* 1989; 298: 631–635. <https://doi.org/10.1136/bmj.298.6674.631> (accessed Dec 10, 2021).
22. Thuring A, Malcus P, Maršál K. Effect of maternal betamethasone on fetal and uteroplacental blood flow velocity waveforms. *Ultrasound Obstet Gynecol* 2011; 37: 668–672. <https://doi.org/10.1002/uog.8879> (accessed Dec 10, 2021).
23. A Neglected Tragedy: The global burden of stillbirths. Report of the UN Inter-agency Group for Child Mortality Estimation, United Nations Inter-agency Group for Child Mortality Estimation (UN IGME) United Nations children’s Fund. New York, 2020.
24. Hirst JE, Villar J, Victora CG, Papageorgiou AT, Finkton D, Barros FC, et al. The antepartum stillbirth syndrome: risk factors and pregnancy conditions identified from the INTERGROWTH-21st Project. *BJOG* 2018; 125: 1145–1153. <https://doi.org/10.1111/1471-0528.14463> (accessed Dec 10, 2021).
25. Katz J, Lee AC, Kozuki N, Lawn JE, Cousens S, Blencowe H, 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: 417–425. [https://doi.org/10.1016/S0140-6736\(13\)60993-9](https://doi.org/10.1016/S0140-6736(13)60993-9) (accessed Dec 10, 2021).

Chapter 6

Implementation experiences of Umbiflow™ screening across nine sites in South Africa

6.1 Introduction to chapter 6

We implemented Umbiflow™ screening in nine catchment areas across eight provinces in South Africa. Implementing change can be difficult, particularly in areas with set ideals as there may be crucial health system needs and unique circumstances to be carefully considered.

The introduction of Umbiflow™ screening across different catchment areas allows for a learning experience with different challenges and enablers. This offered a learning experience to implementation practice in the introduction of a new health screening device. There are some prerequisites to implementing and adopting any new guideline in clinical practice, we learnt from the stages of change and adopted some steps in our review of the implementation experience.¹

I developed the study protocols, study tools, training material and visited all the provinces and engaged all stakeholders. This included stakeholder communication, catchment area review, study team development and composition. I further trained the study teams- study nurses on the use of the Umbiflow™ device (theoretical and practical sessions) and data clerks on the use of data and the electronic birth register, and use of study tools. I supported the study sites with the Umbiflow™ clinic set up, screening, recruitment, participant flow and decision making, and high-risk clinic setup. This also included site visits, monitoring and evaluation, weekly follow-up with the study nurses and data clerks, and field notes were collected during this time. Detailed involvement will be described in this chapter.

This chapter documents the adaptation and implementation of Umbiflow™ screening and shares critical lessons, particularly in the development and training on the use of Umbiflow™. Implementation of Umbiflow™ required support and adoption of the introduction by all stakeholders and acceptance of the need to screen women at primary healthcare clinics. This required training, rearrangement of patient flow, continuous communication between the different levels of care, functional referral systems and

functional maternal and neonatal services. The characteristics, strengths and weakness of the nine sites will be discussed.

6.2 References

1. Belizán M, Bergh AM, Cilliers C, Pattinson RC, Voce A, for the Synergy Group. Stages of change: A qualitative study on the implementation of a perinatal audit programme in South Africa. BMC Health Serv Res 2011; 11: 243. <https://doi.org/10.1186/1472-6963-11-243> (accessed Oct 18, 2021).

Implementation experiences of Umbiflow™ screening across nine sites in South Africa

6.3 Introduction

In November 2016, the World Health Organization (WHO) released its recommendations on routine antenatal care (ANC) for a positive pregnancy experience.¹ The guidance is intended to respond to the complex nature of the issues surrounding antenatal care practice, organisation and delivery of ANC within the health system in order to prioritise person-centred care, client well-being and the prevention of death and morbidity. The WHO envisions that ‘every pregnant woman and newborn infant receives good quality care throughout pregnancy, childbirth and the postnatal period’, where quality refers to provision and experience of care from a health systems perspective, enabling a positive pregnancy experience.¹ 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 to identify placental insufficiency needed more rigorous evaluation, particularly in low- and middle-income country (LMIC) settings.^{1,2} The recommendation that future trials should be designed to address modest changes in perinatal outcomes and should focus on potentially preventable deaths, opened a window for research in this field in South Africa.

South Africa has three audit programmes monitoring maternal, perinatal and child deaths in South Africa, respectively: the Maternal Morbidity and Mortality Audit System (MaMMAS); the Perinatal Problem Identification Programme (PPIP); and the Child Problem Identification Programme (Child PIP). The reports derived from these programmes - *Saving Mothers, Saving Babies* and *Saving Children* – all offer a review of the healthcare provided to the mothers, babies and children in South Africa and set recommendations based on the local findings.³⁻⁵ These findings also highlight avoidable causes of deaths and make recommendations to strengthen the quality of care provided to mothers, babies and children at the time when they need it the most.³⁻⁵ Following the recommendations in these reports to alleviate the high burden of preventable maternal and perinatal deaths, the South African National Department of Health (NDOH) instructed the adoption of Basic Antenatal Care Plus (BANC Plus) in all health facilities offering antenatal care.⁶ BANC Plus is an adaptation of the WHO antenatal care recommendations.⁶

In South Africa, the majority of stillbirths are categorized as unexplained, while others are caused by hypertensive disorders of pregnancy and abruptio placenta.^{7,8} Studies have shown that there is a peak in stillbirths between 32-38 weeks’ gestation. The peak is more evident in small for gestational age (SGA) newborns where most of the mothers are said to be clinically

healthy and stillbirth is categorized as unexplained. There are approximately three stillbirths for every neonatal death, and the majority of stillbirths occur antenatally.^{3,7,8}

Early antenatal detection of the fetus at risk of stillbirth or SGA in low-risk pregnant women remains a challenge, as these fetuses are not detected by conventional imaging ultrasound.⁹ Most stillbirths occur in the late preterm or term period, where survival of live born infants in well-resourced units is feasible. Reducing the number of unexplained intrauterine deaths remains an important challenge in resource-limited settings because of the subjectivity of the current available antenatal fetal growth monitoring tools.^{9,10} Access to quality ANC is a crucial component to improved maternal and neonatal outcomes and improved quality of life for both mothers and babies.^{1,11} The nationwide scale-up of BANC Plus aimed to improve the quality of ANC through the provision of evidence-based interventions. One intervention is having a minimum of eight antenatal contacts, with more contacts concentrated in the third trimester. Another potential intervention is the improved screening for placental insufficiency by means of the Umbiflow™ device described in other chapters. Both interventions seek to improve pregnancy care and outcomes. An improvement in the screening and detection of fetuses at risk of stillbirth might ultimately improve antenatal care quality and reduce perinatal mortality (as seen in the previous chapters).

This chapter documents the adaptation and implementation of Umbiflow™ screening across nine sites in eight provinces in South Africa and shares critical lessons, particularly with regard to healthcare provider training on the use of Umbiflow™ and the preparation and rollout of the screening. Implementation of Umbiflow™ requires agreement by the health management team, clinicians, the screening clinics and hospitals receiving the referrals, and not least the pregnant women themselves. All these aspects – as well as the characteristics and daily challenges – will be described for the nine study sites that implemented Umbiflow™ screening. Each study site comprised recruiting clinics and a referral hospital.

6.4 Framework for implementation

The introduction and implementation of Umbiflow™ screening were informed by existing theories of change used in other implementation projects of the SAMRC Research Unit for Maternal and Infant Health Care Strategies (SAMRC Unit). The implementation framework has a number of points of departure or prerequisites for adapting and implementing an intervention or guideline.¹² This is complemented by the use of a stages-of-change model for

planning implementation and tracking progress^{13,14} and a decision-making model that highlights the interfaces where these decisions take place as part of planning and implementation.¹⁵

6.4.1 Points of departure

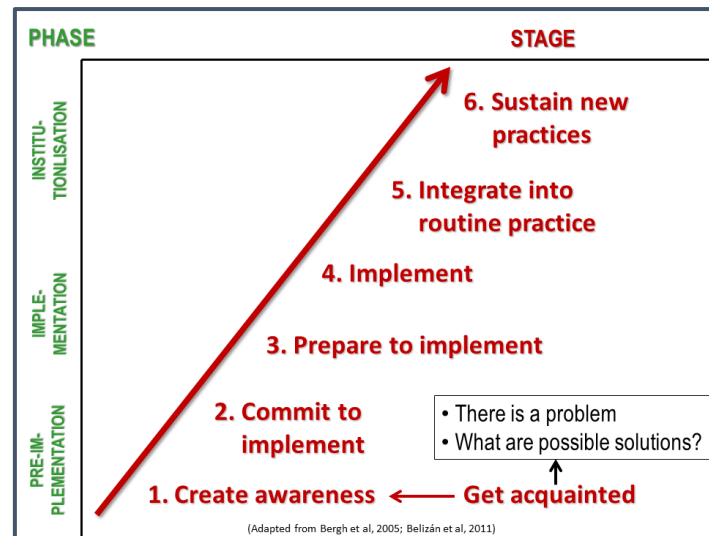
There are three conditions for being able to adapt and implement any new guideline in clinical practice:

- a. Know what to do, (i.e. have clear guidelines on tasks to be performed);
- b. Have the means to do it (i.e. have resources to perform the tasks); and
- c. Do it (i.e. perform the task/activity).

Cross-cutting to these three prerequisites are the conditions of effective communication at all levels and monitoring and evaluation to ensure that the tasks are performed. For the implementation and adaptation to be efficient, decision-making and communication are essential.

6.4.2 Stages of change

A stages-of-change model provides guidance on the steps to follow in the implementation of a new healthcare intervention (Figure 1). There are three phases, each with two stages: pre-implementation (create awareness and commit to implement), implementation (prepare to implement and implement) and institutionalisation (integrate into routine practice and sustain practice).¹³ In our study, we concentrated on the first four stages included in the pre-implementation and implementation phases. The implementation of Umbiflow™ screening was triggered by the challenge of finding solutions for decreasing the number of unexplained stillbirths in the maternal population. One of the potential solutions was the introduction of screening low-risk pregnant women for placental insufficiency by means of continuous-wave Doppler ultrasound using the Umbiflow™ device. Table 1 gives a short summary of how some of the more important implementation issues were addressed within this framework.



6.4.2.1 Figure 1. The stages-of-change model¹³

6.4.3 Making decisions

When implementing change two main factors remain crucial, namely a decision-making process that we adhere and uphold and act on, and a communication process that is frequent and allows for decision making, feedback from sites and feedback to make new decisions and communicate them across the sites. Figure 2 illustrates the interfaces that must be targeted to ensure that all role players know what needs to be done and have the resources to do it.¹⁵ The red numbers in the diagram indicate the position of different decisions that have to be made. Because Umbiflow™ was a pilot study, not all the interfaces were equally involved in the implementation process. For the implementation and scale-up of BANC Plus, which is the system in which the implementation of Umbiflow™ screening is embedded, these decision points had to be covered. Once Umbiflow™ becomes part of routine ANC, substantive decisions will be needed at all interfaces. These will link up with Stages 5 and 6 of the stages-of-change model. Table 2 describes the interfaces as well as the types of decisions to be made once there is a national policy decision to make Umbiflow™ screening part of routine antenatal care.



6.4.3.1 Figure 2. Interfaces to be addressed¹⁵

6.4.3.2 Table 1. Stages of change and fulfilling the prerequisites for implementation

Stages	Prerequisites	Cross-cutting conditions	Actions/Tasks
1 Create awareness	a. Know what is the problem (unexplained stillbirths) b. Know what to do (= introduce Umbiflow™ screening)	COMMUNICATION DECISION MAKING (Figure 2) MONITORING & EVALUATION	• Advocacy for fundraising • Stakeholder engagement • Health messages developed for constant and consistent messages to stakeholders
2 Commit to implement	a. Higher-level stakeholder engagement and commitment (possible solution to the problem accepted) b. Commit resources for implementation		• Permissions from relevant authorities obtained • Directives for implementation of Umbiflow™ screening issued • Funding secured
3 Prepare to implement	a. Identify study site(s) b. Obtain site buy-in (ownership) c. Develop study protocol d. Do baseline assessment e. Site orientation and set-up f. Allocate resources		• Study protocol and tools developed and submitted for ethics approval • Study sites identified – inclusion criteria: - PPIP data available - Maternity birth register - High-risk antenatal clinic • Study discussed with key stakeholders • Site implementation team nominated • Referral and transfer system assessed • Resources allocated: - Essential equipment procured - Study staff employed - Training package prepared • High-risk and PHC clinics prepared

Stages	Prerequisites	Cross-cutting conditions	Actions/Tasks
4 Implement	a. Do the task (implementing Umbiflow™ screening) b. Solve implementation problems		• Designated healthcare workers trained • Umbiflow™ screening according to the study protocol: - Eligible women screened - Referral as per protocol - Communication according to protocol • Regular site visits for supervision and support • Screening team implements knowledge and skills and uses resources and protocol to provide - care to patient within protocol and local ANC guideline - adequate information to enable discussion with and appropriate decision-making by the patient and healthcare provider
5 Integrate into routine practice	• Findings from Umbiflow™ and their implications conveyed to stakeholders • Stakeholders decide on policy and scaling up • Umbiflow™ screening and referral rolled out to all ANC clinics in a particular district or province as part of routine ANC – processes of the first four stages repeated for each province, district and facility (procurement and allocation of essential resources, staff training, strengthening referral pathways) • Lessons learned from Umbiflow™ to inform the management of each ANC clinic with a permanent Umbiflow™ screening service		
6 Sustain practice	• Once Umbiflow™ screening has been rolled out to all antenatal clinics, screening has to be sustained and the referral pathways have to continue being functional • Regular monitoring of the continued implementation of Umbiflow™ screening and the impact on stillbirths • Continue to provide knowledge, skills and support for Umbiflow™ screening to healthcare workers, especially novices		

ANC: antenatal care; PHC: primary health care; PPIP: Perinatal Problem Identification Programme

6.4.3.3 Table 2. Decision interfaces in the implementation of Umbiflow™ screening

Interface	Decisions relative to implementation and scale-up of Umbiflow™ screening
1. Policy makers ↓ National head of health ↓ Provincial heads of health	• Decide to scale-up Umbiflow™ screening (Make a policy) • Convey this policy
2. National head of health and healthcare managers [MCWH] ↓ Provincial heads of health ↓ Provincial healthcare managers ↓ District healthcare managers	• Convey Umbiflow™ screening policy • Decide and/or convey strategy and communication of Umbiflow™ messages for healthcare providers and healthcare users (pregnant women)
3. Provincial and district healthcare managers ↓ Health promotion managers ↓ Community	• Develop appropriate health messages for pregnant women and their families • Provide constant and consistent messages
4. Provincial and district healthcare managers ↓ Community	• Enable Umbiflow™ screening policy to be implemented at all ANC clinics • Ensure community access to healthcare (e.g. ANC for pregnant women)
5. Provincial and district heads of health ↓ Sub-district and facility healthcare managers	• Convey Umbiflow™ screening policy • Decide on the allocation of resources necessary to implement Umbiflow™ screening
6. District/Sub-district and facility healthcare managers ↓ Healthcare providers	• Convey Umbiflow™ screening policy • Provide essential resources (including staff and screening equipment) • Provide knowledge and skills necessary to implement Umbiflow™ screening to healthcare providers
7. Healthcare providers ↓ Healthcare users	• Provider implements knowledge and skills and uses resources (e.g. Umbiflow™ device and screening protocol) to provide care to the patient and make the correct referral to a next level of care when needed • Adequate information to enable discussion with and appropriate decision-making by the patient and family

To make appropriate screening, diagnosis and treatment decisions a team of clinicians in the field needs to be available and accessible to enable decision-making. Decision-making relates to who to screen, who to refer, where and when to refer, and how to manage referred patients

(e.g. when to do biometry, when to admit, when to offer corticosteroids for fetal lung maturity, and when to deliver).

6.4.4 Effective communication

There are two types of communication that need sufficient attention in the rollout of a new intervention. The first type spans across Stages 1 to 4 of the change (implementation) process, whereas the second type is more limited to Stage 4:

1. Stages 1-4: Communication of decisions made at various levels of the health system concerning the *implementation of Umbiflow™ screening* – from national to facility level and beyond.

It is essential that the study team and managers at all levels of care and individual healthcare providers and emergency personnel know what is expected of them. This includes study teams, managers at provincial departments, districts and all healthcare facilities with antenatal, labour and postnatal care services.

2. Stage 4: Communication across levels of care (inter- and intra-facility) regarding decisions for *referral and treatment of individual women* identified as high risk or with an abnormal resistance index (RI) through Umbiflow™ screening.

Effective communication to facilitate screening, referrals and collaboration between the primary healthcare (PHC) facilities and the referral hospitals is crucial. Communication between the women and the healthcare providers is an essential component to screening and follow-up, particularly in women identified with abnormal RIs. The referral hospitals and clinics for booking women for follow-up assessments enable improved care and follow-up.

The roles, tasks and actions required of the managers at the various levels of care, the chief executive officers (CEOs) and managers of healthcare facilities are illustrated in Table 2. There must also be continuous communication and feedback of information between study teams, healthcare providers and managers at the various levels of care.

At health-facility level, managers have a crucial communication role. They need to be well informed about roles, tasks and actions and should work out how to perform the tasks with the team under them. Managers also need to ensure that clinicians and support staff (doctors, midwives and nurses, emergency medical services personnel, and clerks) are informed and

know what to do when a woman with placental insufficiency is referred. In this regard, the community and pregnant women should also receive appropriate information on their wellbeing and the actions to be taken. In the Umbiflow™ study the managers and their clinical teams worked through the Umbiflow™ study protocol in order to understand the reason for referral, the management protocol and what was required.

6.4.5 Monitoring and evaluation

Monitoring and evaluation, together with communication between the different levels of care, aids decision-making and feedback to and from the screening sites to accurately communicate progress, challenges and new decisions. In the Umbiflow™ study, a monitoring and evaluation system was developed to track screening at each study site and to evaluate the implementation of the screening. The checklist tracked information on participants' demographics, eligibility for screening and the Umbiflow™ screening results, referral and management plan. Through the use of an eligibility screening form, eligible patients were easily identified and those not eligible were advised accordingly. Those with early gestational age (GA) were counselled and offered screening when they reached an eligible GA. The facility-led entry of data (study files and pregnancy outcomes) helped detail the actions performed, referrals and new problem areas were identified and possible solutions were sought.

6.5 Key features of the implementation process

Implementation of Umbiflow™ screening across the nine study sites was done in a step-wedge fashion to allow for stakeholder discussions and study site planning and training. This was to ensure adequate training and monitoring per study site and allowed for adjustment to local circumstances. BANC Plus training and support was also offered and this implementation and support are documented elsewhere.⁶

6.5.1 Creating awareness

The Umbiflow™ device was developed by the South African Medical Research Council (SAMRC) and the Council for Scientific and Industrial Research (CSIR) and was first tested in the Western Cape Province in 2005.^{16,17} This was followed by the Khulelwe Umbiflow™ screening study in Mamelodi, Pretoria, which found a higher than expected prevalence of

abnormal Doppler findings in a low-risk population.¹⁸ Referring pregnant women with an abnormal Doppler from an ANC clinic to a high-risk clinic at the regional hospital resulted in a significant reduction in antenatal stillbirths. This was the motivation for the Umbiflow™ study across SA.

6.5.1.1 Stakeholder engagement at national and provincial level

The positive findings from the Mamelodi study were documented and motivated us to advocate for further exploration of the prevalence of abnormal Dopplers across South Africa. The findings were shared with representatives from the NDOH, provincial governments, district management teams and other relevant stakeholders. We engaged them on the burden of stillbirth at specific sites and urged them to explore a possible feasible solution by replicating and building on the Mamelodi study.

6.5.1.2 Advocacy for fundraising

The findings were also shared with the SAMRC and the CSIR. These agencies were interested to continue supporting the further testing and rollout of the Umbiflow™ device. The University of Pretoria's SAMRC Unit submitted a funding application for testing the device and screening processes in nine sites in eight provinces.

6.5.2 Committing to implementation

The SAMRC, CSIR and the SAMRC Unit, in collaboration with province and district representatives, engaged on the use of Umbiflow™. We had support from the NDOH through the maternal, neonatal and child health programme managers, who sent out communication to each province detailing Umbiflow™ and the promising results from the initial study. Each province responded to the call to collaborate in different ways. Seven study sites had commitment and engagement from the province and the district, the district clinical specialist team (DCST) and the hospital and clinic managements. Two sites had commitment and engagement from the district, hospital and clinic managements. These stakeholders committed to implementation and conveyed the study process to their different bodies, organisational structures and facilities to enable screening and referral at the identified facilities. Engagement of all the stakeholders was varied and was guided by provincial requirements and response

from the provincial teams (provincial ethics committees, clinic management, hospital management, hospital research committees, and departmental responsiveness). It was easier to communicate with study sites regarding local requirements where there was provincial buy-in. Eagerness to commit to implementation was guided by local maternal and neonatal indicators.

6.5.2.1 Continued stakeholder engagement and commitment

Through a process of continued engagement with stakeholders such as provincial and district representatives, facility managers, hospital CEOs, heads of department and healthcare providers it was possible to get the necessary buy-in for implementing Umbiflow™ screening. This included updating the stakeholders on the implementation progress and screening progress throughout the study time.

6.5.2.2 Securing funding and resources

The funding application of the University of Pretoria's SAMRC Unit was successful and a contract was signed with the SAMRC and CSIR. In addition to funding study staff and other expenses related to the research, these agencies provided the computers, thermal printers and other equipment. The CSIR was responsible for Umbiflow™ probe and software development, maintenance and technical support.

6.5.3 Preparing for implementation

The preparation for implementation was guided by reviewing available literature and reflecting on lessons from the Mamelodi study. We engaged stakeholders to identify nine study sites. The research team responsible for the execution and oversight of the research project was finalised and study staff were recruited for each site. The necessary resources to implement Umbiflow™ screening were procured. Each site had extensive engagement and site visits to assess the feasibility, staffing, flow plan and space, and how Umbiflow™ would fit in the patient flow through the health system. The referral routes were reviewed and each site was oriented in the Umbiflow™ equipment and screening process.

6.5.3.1 Development of the study protocol and tools

We conducted literature searches and reviews to support the rationale for the study. Developing the study protocols and study tools was critical to the fidelity of implementation and uniform training. They give the guidelines on how to identify, triage, screen, treat, manage, and arrange follow-up and referral of all screened pregnant women. Our protocol detailed the patient pathway by starting with the identification of the population eligible for Umbiflow™ screening, the screening itself, and the referral and follow-up processes.

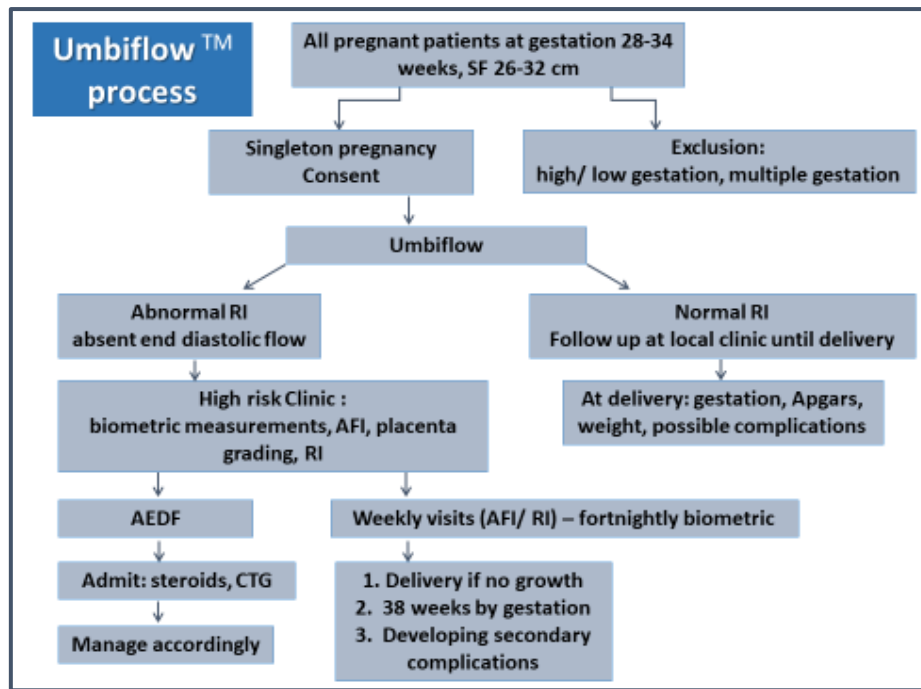
The protocol was accompanied by a number of study tools. These included the forms and questionnaires covering eligibility, contact, demographics, patient history and lifestyle, Umbiflow™ examination findings, and the delivery forms. For women with abnormal RIs a referral form and a follow-up form were created to document the high-risk clinic contacts. Figure 3 illustrates the flow of participants as documented in the study protocol. The tools are contained in Appendix 1 to Appendix 10 of the thesis.

The study protocol was submitted as an amendment of the original Mamelodi study (473/2014) to the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria. Approval was granted on the 1 July 2017. Each study site's research ethics committee also granted permission for the study and the study was registered with the South African National Research database.

6.5.3.2 Selection of study sites

To implement the study protocol, we identified nine study sites across South Africa. The study sites included nine catchment areas of referral hospitals in eight provinces; these included urban, peri-urban and rural catchment areas. Five hospitals were regional hospitals and four were provincial tertiary hospitals. Each study site consisted of recruiting clinics and a referral hospital. Each of the selected study sites had to fulfil the following criteria:

- Sufficient throughput of pregnant women as evidenced by the number of deliveries in the catchment area and a high burden of perinatal mortality.
- Baseline data of the scope of problems in perinatal and maternal morbidity and mortality.



RI = resistance index; SF = symphysis fundal height; AFI = amniotic fluid index; AEDF = absent end diastolic flow; CTG = cardiotocograph

6.5.3.3 Figure 3. Flow diagram of participants in the Umbiflow™ study protocol

- A birth register to record pregnancy outcomes.
- PHC clinics offering antenatal care with healthcare professionals, a healthcare professional trained in the use of Umbiflow™ and nursing and medical professionals with sufficient knowledge and experience of obstetrics and neonatal care.
- Antenatal clinics should have a working environment with a clinic floor plan making it feasible for conducting Umbiflow™ examinations.
- The referral hospital should be able to take special care of small newborns of 1000 grams or above, with facilities to perform caesarean sections and with a blood bank and laboratory.
- An established system of referral to the next level of care for women identified as high risk or having an abnormal RI.
- A next level of care with medical professionals with sufficient obstetrics and neonatal care knowledge and providers competent in using pulsed-wave Doppler ultrasound and familiar with antenatal care for high-risk women.
- Familiarity with collecting data and using the maternity birth register and PPIP.

Primary healthcare facilities in the catchment areas of the referral hospitals were assessed for feasibility to screen based on the following criteria: infrastructure; established referral routes; effective communication; number of pregnant women seen on a daily basis; delivery statistics; familiarity with PPIP; and available transport to connect the different facilities.

Each study site covered the catchment area of a referral hospital and included two or more implementation sites or facilities: at least one PHC clinic (recruitment site where Umbiflow™ screening took place) and a referral hospital with a high-risk clinic for evaluation and management of women identified with abnormal Dopplers. Each study site had unique characteristics and different numbers of clinics based on their location, population size and referral patterns. The final selection of referral hospitals and antenatal clinics is listed in Table 3 below. Study sites are named after the names of the referral hospitals. Tables 7 and 8 at the end of the chapter describe the characteristics of the clinics and hospitals included in the study in more detail.

6.5.3.4 Table 3. Umbiflow™ clinics and hospitals

Provincial study site	Hospital	Clinics and distance from hospital (km)	Data capturing
Gauteng	Pholosong (Tsakane, Brakpan)	Nokuthela Ngwenya MOU (11 km) Pholosong Hospital (0 km)	Nokuthela Ngwenya MOU Pholosong Hospital KwaThema Clinic
Northern Cape	Dr Harry Surtie (Upington)	Progress Clinic (1.9 km) Sara Strauss Clinic (3.2 km) Louisvale Clinic (5.7 km)	Dr Harry Surtie Hospital
North West	Mafikeng Provincial (Mahikeng)	Montshiwa Stadt Clinic (5.1 km) Monsthoa Town Clinic (7.5km)	Mafikeng Provincial Hospital Montshiwa Stadt Clinic Monsthoa Town Clinic
Limpopo	Tshilidzini (Thohoyandou)	Thohoyandou CHC (8.9 km)	Tshilidzini Hospital Thohoyandou CHC
Free State	Bongani (Welkom)	Welkom Clinic (7.6 km) Khotsong Clinic (5.9 km)	Bongani Hospital Virginia Hospital Thusanong Hospital
North West	Klerksdorp (Klerksdorp)	Jouberton Clinic (9.8 km) Empilisweni Clinic (7.1 km) Town Clinic (1.6 km)	Klerksdorp Hospital Jouberton Clinic

Provincial study site	Hospital	Clinics and distance from hospital (km)	Data capturing
KwaZulu-Natal	General Justice Gizenga Mpanza (KwaDukuza, Stanger)	Sundumbili CHC (41 km) Kwadukuza Clinic (6.1 km)	General Justice Gizenga Mpanza Hospital Sundumbili CHC
Mpumalanga	Themba (Kabokweni)	Phola Clinic (35 km) Buga Clinic (6.1 km)	Themba Hospital Phola Clinic Bhuga Clinic
Eastern Cape	Dora Nginza (Gqeberha)	Kwazakhele Clinic (12 km) Motherwell CHC (4.7 km)	Dora Nginza Hospital Kwazakhele Clinic Motherwell CHC

CHC = community health centre; MOU = midwife-run obstetric unit

6.5.3.5 Constituting implementation teams

We engaged all the relevant stakeholders at each study site, including, district and sub-district managers, DCSTs, managers of facilities with ANC services, and hospital CEOs, clinical managers and departmental heads to facilitate incorporation of the local study team in the patient pathway. Stakeholder engagement in each catchment area facilitated the implementation process and the fluidity of recruitment, training needs and support. Table 9 at the end of the chapter gives an overview of the nature of the stakeholder engagement in each of the study sites with regard to support received from district management, the DCST, clinic and hospital management and the obstetrics and paediatrics departments.

Each study site had a research team at the referral hospital consisting of an obstetrician and or medical officer in obstetrics, a neonatologist or paediatrician, a study nurse and a data clerk. Each team was orientated onsite by a researcher based at the SAMRC Unit. The team was supported by other clinicians working in maternal and neonatal care. As an additional study nurse was recruited for each study site, no intensive training on the use of the Umbiflow™ device was needed for the implementation team (at PHC or hospital level). There were no other requirements or demands made on a study-site research team.

6.5.3.6 Procuring and checking essential equipment

The implementation of the study protocol is dependent on the resources that are provided. The healthcare providers in PHC clinics, community healthcare centres and hospitals continued to provide the services required.

Each study site received a set of the essential equipment to enable continuous screening every day or on alternate days when the study team was available, namely a Microsoft computer and two Umbiflow™ probes, a thermal printer, and sonar gel. The equipment was kept by the study nurse who moved the items to whichever clinic was scheduled for screening on a particular day. Each referral hospital had commercial ultrasound equipment with pulsed-wave Doppler function, a theatre(s), a blood bank, a laboratory unit, and a neonatal unit. There was no other added equipment needs.

6.5.3.7 Preparing the training package

The Umbiflow™ training package built on the Mamelodi study's training and included theoretical and practical sessions. There were presentations on Doppler use, BANC Plus, symphysis fundal height measurement, fetal growth restriction and referral systems between facilities. With regard to the use of Doppler, the content included how it worked, what it told us, how to interpret the findings, the benefits or harms of Doppler ultrasound and what we were hoping to achieve with screening a low-risk population. The practical sessions included a discussion on Umbiflow™ software and device components, which allowed for familiarisation with the device and troubleshooting for software-related matters. There were also sessions on patient engagement and real-time patient sessions, which allowed for real-time learning and peer involvement. The training participants (study nurses) were able to visit Umbiflow™ screening facilities, learn from their peers in real time and observe the facility set-up, the patient follow-up and the use of the study tools.

6.5.2.8 Employing study staff (nurse and data clerk per site)

For each study site, a local study nurse and data clerk were employed. The study nurse was responsible for the day-to-day screening and referral of women. Her roles included engaging the patients and informing them about the study, obtaining informed consent, screening eligible women, sharing the results with the women and referring them according to the study protocol. This also included accompanying the patients to the referral hospital for ease of communication and high-risk clinic follow-up. This helped with the completion of study tools and tracing patients who did not arrive or defaulted on follow-up. Table 4 gives a summary of the qualifications of the study nurses.

The data clerks were responsible for data entry and capturing the birth outcomes on the electronic birth register.

6.5.3.9 Table 4. Characteristics of the qualifications of the study nurses

Nurses	Number	Sites
Midwifery, Ophthalmology	1	Mafikeng
Midwifery, Psychiatry	1	Pholosong
Midwifery, Tuberculosis	1	Klerksdorp
Advanced midwifery	6	Dr Harry-Surtie, General Justice Gizenga Mpanza, Tshilidzini, Dora Nginza, Themba, Bongani

6.5.3.10 Scale-up of BANC Plus in preparation of Umbiflow™ screening

Because the ultimate aim would be to integrate Umbiflow™ screening into routine ANC, the piloting of the screening in the nine sites was done in conjunction with the introduction of BANC Plus in the months prior to implementation of Umbiflow™. Country-wide scale-up started on 1 April 2017. Upon the launch, every district in every province had representatives who had been trained as trainers. They included DCST members, area managers and clinical managers. This training has been described in detail elsewhere (see Chapter 2).⁶

We offered continuous support and training related to BANC Plus, with all the training lectures, checklists, handbooks and protocol books, to the nine sites involved in the Umbiflow™ study. Four of the circumscribed catchment areas included in the study were purposively selected for further BANC Plus review: one urban area: Pholosong Hospital; two peri-urban areas: Mafikeng and Dr Harry Surtie Hospitals; and one rural area: Tshilidzini Hospital.

6.6 Implementing Umbiflow™ screening

6.6.1 Umbiflow™ training for designated healthcare workers (study nurses and data clerks)

Umbiflow™ screening was implemented in a step-wise fashion, one study site at a time, to allow sufficient time for teams to engage with the equipment and familiarize themselves with the study process. Figure 4 gives an overview of the activities of the research team and the local study teams over the period of three years. Detailed timelines for each of the study sites

are contained in Figure 5 at the end of the chapter. Each site had a week of Umbiflow™ training followed by a weeklong visit to an ongoing recruiting site where participants were involved with recruitment and Umbiflow™ screening. The first four site teams were trained at the Mamelodi study site (Stanza Bopape Clinic and the high-risk clinic at Mamelodi Hospital), whereas the next five site teams had their practical training at the first Umbiflow™ study site (Pholosong Hospital and Nokuthula Ngwenya MOU).

6.6.2 Umbiflow™ screening according to the study protocol

Screening for placental insufficiency by means of a single continuous-wave Doppler examination with the Umbiflow™ device was made possible by the study nurses, data clerks, DCSTs, managers and provincial teams. Umbiflow™ has a digital interface with a visual Umbiflow™ screen. This displays patient information and the Doppler waveform and has a settings button that allows for the set-up of the interface and sound. This allows for set-up of Doppler waveform and sound preferences of the classic Doppler waveform and sound representation. Each patient's unique waveform was recorded in real time and saved on the laptop, and a printout was made available for the study file. The recorded Doppler waveforms are interpreted as low risk, medium risk and high risk. Umbiflow™ software interprets Doppler values using standardised indices charts as per local and international standards.¹⁹

Activity \ Year: Month:	2017												2018												2019													
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12		
Site engagement																																						
Baseline assessment																																						
Site feasibility																																						
Umbiflow™ training																																						
EBR training																																						
BANC Plus																																						
Umbiflow screening																																						
Data collection																																						
Site visits and follow-up																																						

EBR: electronic birth register; BANC: basic antenatal care

6.6.3 Figure 4. Overview of activities of the research team and the local study teams across the nine sites

In all nine study sites it was necessary to plan triage and screening of eligible women and aligning pregnant women as described in the study protocol, to incorporate and sustain the screening in routine practice during the study period and to ensure that all women received the appropriate care.

Low-risk women presenting for antenatal care at the PHC clinics between 28 and 34 weeks' gestation were eligible for Umbiflow[™] screening and were screened by the onsite study nurse on four days of the week or on alternate days of the week. Women with a normal resistance index (RI) continued their antenatal care at the local clinic. Women with an elevated RI (i.e. abnormal RI included medium-risk and high-risk Doppler waveform) were referred to the high-risk clinic at the referral hospital.

Each data clerk recorded all the births at community health centres (CHCs), midwife-run obstetric units (MOUs) and hospitals in the catchment area of their study site. This allowed us to track all deliveries in the catchment areas on the electronic birth register. The clerks also supported the study nurses with the documentation of the Umbiflow[™] examinations and updating the study checklists.

The referral process for a woman with an abnormal RI required good communication between the study nurse and the referral hospital's high-risk team. The study nurse made appointments for all women with an abnormal RI for further clinical evaluation by the hospital team and accompanied them to their appointment. One day of the week was reserved for high-risk assessment at the hospital. The high-risk investigations included a pulsed-wave imaging Doppler ultrasound review, fetal biometry and placental assessment. Further management was guided by the findings. Follow-up was biweekly or weekly at the appropriate level of care, based on the clinical assessment and was supported by the study nurse. The high-risk clinic followed a standard management protocol and delivery was recommended if the pregnancy reached 38 weeks or earlier if there was no fetal growth, absent end diastolic flow or if there were other complications.

If a woman failed to attend the referral high-risk clinic, the study nurse attempted to contact her or her next of kin by telephone, using the contact information provided at recruitment. This was to ascertain the reasons for her inability to attend and to arrange another contact appointment for her. If women had been contacted on two occasions at different times of the day without any response she was considered lost to follow-up. High-risk clinic attendance was

fair, with a loss to follow-up of 0% to 31% of women with an abnormal RI.²⁰ Table 5 gives an overview of the number of women who attended the high-risk clinic.

6.6.4 Table 5. Number of women with abnormal RI who attended high-risk clinic referral

Site	Recruited (N=7088) n	Normal RI (N= 6169) n (%)	Abnormal RI (N= 919) n (%)	AEDF (N= 87) n (%)	Abnormal RI attended HR clinic (N=730) n (%)
Pholosong	1111	883 (79.5%)	228 (20.5%)	10 (0.90%)	157 (69.0%)
Dr Harry Surtie	509	467 (91.7%)	42 (8.3%)	6 (1.18%)	32 (72.2%)
Mafikeng	476	449 (94.3%)	27 (5.7%)	4 (0.84%)	22 (81.5%)
Tshilidzini	673	616 (91.5%)	57 (8.5%)	7 (1.04%)	52 (91.2%)
Bongani	629	520 (82.7%)	109 (17.3%)	9 (1.43%)	98 (89.9%)
General Justice Gizenga Mpanza	1097	972 (88.6%)	125 (11.4%)	10 (0.91%)	125 (100%)
Klerksdorp	982	919 (93.6%)	63 (6.4%)	14 (1.43%)	47 (74.6%)
Themba	749	582 (77.7%)	167 (22.3%)	18 (2.40%)	107 (64.1%)
Dora Nginza	862	761 (88.3%)	101 (11.7%)	9 (1.04%)	90 (89.1%)
Mean		87.5%	12.5%	1.24%	730 (79.4%)
(95% CI)		(83.8; 92.3)	(7.7; 17.2)	(0.87; 1.61)	

RI= resistance index; AEDF= absent end diastolic flow; HR= high-risk

The follow-up of women with abnormal RIs was challenged by referral system issues such as transport and social responsibilities. Financial cost of reaching the hospital was a major factor influencing attendance of the high-risk clinic. In rural areas with large distances between the PHC clinics and the hospital women found it difficult to meet the additional out-of-pocket expenses required to attend at the referral hospital. All the Umbiflow™ study sites experienced better follow-up rates from nearby clinics. Five clinics were in a radius of <5 km from the hospital and 10 were 5-10 km away. The remaining four clinics were 11, 12, 35 and 41 km from the hospital, respectively. The 100% follow-up rate achieved at General Justice Gizenga Mpanza was due to the patient transport made available from the remote Sundumbili CHC to the hospital. Regular outreach from Dora Nginza Hospital's obstetric unit to PHC clinics

assisted in women's acceptance of the importance to follow-up at the high-risk clinic. It served as a motivating factor as women were familiar with the doctors at the hospital. At the other two study sites with a follow-up rate of more than 89% (Tshilidzini and Bongani) it was observed that the study nurses had a very good rapport with the patients. The four study sites with the highest high-risk follow-up rate had employed an advanced midwife as the study nurse.

6.6.5 Regular supervision and support

The central research team monitored the implementation of the Umbiflow™ screening on a continuous basis. Continuous communication facilitated tasks, actions, and decision-making during the training and implementation period. This allowed for adjustment when challenges such as service provision protests, referral pathways gaps and follow-ups needed attention. We conducted short weekly discussions (15-30 minutes depending on matters arising at the study sites) with each of the study nurses through telephone and team viewer with a view to: get an update on site data, recruitment and referrals; review and decide on changes in the process; and facilitate support needs. All technical aspects pertaining to the Umbiflow™ probes were addressed with the technical team through the CSIR. This included the initial troubleshooting for all study sites related to the digital Umbiflow™ interface, namely testing software settings and adjusting the probe sound. At some study sites the study nurse and data clerk were able to remotely solve most of the technical issues. Two sites had issues with the probe and received a new one in the course of the study. Discussions around stationary and equipment needs were conducted with all sites (printing paper, printer cable, study booklets, referral forms, delivery forms). Sites also reported on recruitment challenges such as identifying sufficient numbers of eligible women on specific days of the week and the disruption of recruitment and screening and the safety of patients and staff during national service provision protests. Two sites also reported challenges with follow-up at the high-risk clinic due to unavailability of the head of department; however, the reviews at these clinics could continue with the available medical officers. One site also had to deal with the logistics of the relocation of a clinic site due to renovations.

In addition to this continuous communication and virtual support for all the study sites, the researcher also conducted site visits, once in the first quarter of implementation and thereafter six-monthly. During the first site visit, we reviewed the study progress, recruitment, probe use, screening process and progress, and the screening results and addressed any new challenges.

The referral and follow-up of women identified with abnormal RIs were assessed and we also reviewed the management protocol at the high-risk clinics and outcomes, if available at the time of the visit.

At all study sites time was spent on reviewing the Doppler waveforms and attending to waveform capturing, management plans and further troubleshooting. The review of the study files included checking the correct completion of all files, the details on the high-risk clinic forms, the tracing of women lost to follow-up and the data entry of delivery outcomes. Progress with the implementation of the electronic birth register was also reviewed. Completed study files were collected to be collated at the SAMRC Unit for data to be captured on RedCap software. The same recruitment challenges mentioned during remote support also featured during the onsite visits, namely finding women eligible for Umbiflow™ screening and the effects of the national protests on recruitment and follow-up. At some study sites it was possible for the study nurse to move to another recruitment clinic if there were no or few eligible women available on a particular day. Support was also provided to the high-risk clinic teams and at three sites the new specialists received further orientation in the Umbiflow™ study and requirements for high-risk follow-up.

6.7 Implementation at the individual sites

The study started with training and recruitment in August 2017 in a stepwise fashion to allow for appropriate support and quality assessment across the different study sites (see Figure 4). The order of site implementation was purposive, according to site readiness and stakeholder responsiveness. Site implementation started with stakeholder engagements and site visits.

Table 6 at the end of the chapter gives a more detailed overview of the implementation at each of the individual study sites. Implementation was facilitated by stakeholder engagement and continuous communication and support. Seven of the nine sites had DCST involvement and good provincial and district involvement, which facilitated communication, facility discussions and acceptance of the new innovation.

Post Umbiflow™ training, each team went back to their sites with an initiation plan that addressed recruitment days at ANC clinics and follow-up days at the referral hospital's high-risk clinic. This also included site plans for where to recruit and where the study team would be stationed within the recruitment facilities. All study sites recruited on multiple days of the week and had one day of high-risk clinic at the referral hospital. Eight sites alternated between

different clinics on different days of the week. Six study sites recruited participants in two clinics and two study sites in three clinics on different days of the week; one study site had only one clinic and recruited four days of the week (Tables 3 and 6). Alternating between different recruitment sites affected recruitment numbers, as some clinics were busier on certain days of the week and we could not achieve 100% recruitment at all the sites. Some PHC clinics had their contacts for first pregnancy bookings on certain days of the week and Umbiflow™ screening on those days did not recruit a lot of women if they had booked early. Some late bookers may also have been missed. In clinics where Umbiflow™ screening was not integrated into the antenatal contact, some women may not have been offered the screening or may not have been willing to wait for Umbiflow™ screening consultation. One of the challenges for women was waiting times – waiting for their antenatal contact and then waiting for the screening. This needs to be considered in future implementation work.

Study sites considered their local circumstances for determining the day of the week for running the high-risk clinic. Wednesday was the most popular day, with only one site using a Friday. One study site started out on a Monday but also moved to a Wednesday during implementation.

All clinics at the nine sites had morning antenatal talks with all the pregnant women who attended the clinic for that day, followed by one-on-one discussions with the women to check for eligibility for recruitment and screening. The in-house nursing staff then referred eligible women to the study team. All the clinics in two study sites were able to integrate Umbiflow™ screening into the routine antenatal care consultation, where a woman was assessed and had her Umbiflow™ screening during the same consultation. Three study sites had the Umbiflow™ examination in the same room but with a different provider. The remaining four study sites had the Umbiflow™ examinations after the antenatal consultation in a different room.

The integrated clinics reported that waiting times were unaffected and that there had been a better patient flow, as the whole pregnancy was reviewed by the study nurse at the Umbiflow™ screening point. This arrangement was well received by facility staff, as the engagement between the study and facility teams encouraged mutual support with patient care.

The majority of clinics and hospitals were near to each other, which facilitated patient follow-up and meant decreased patient costs for follow-up. Larger distances between some PHC clinics and the hospital might have impeded patient follow-up, especially if public transport was scarce and no routine patient transport was available. One study site with a remote

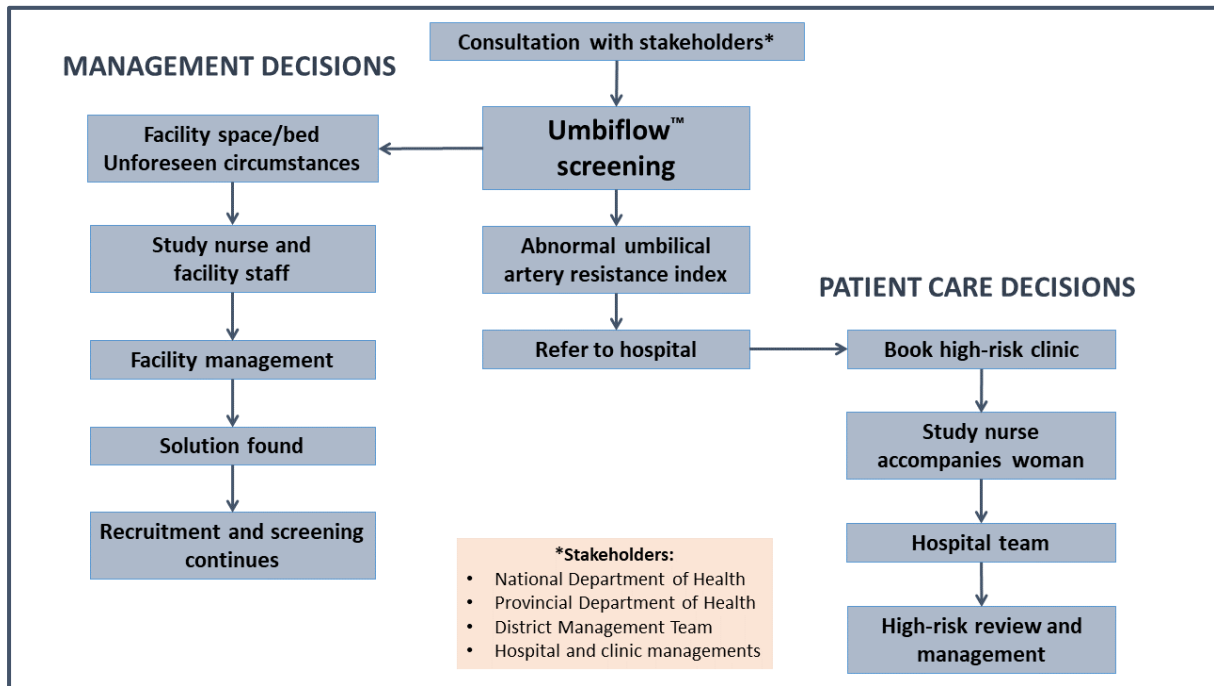
recruitment facility, a CHC with maternity services, had onsite patient transport that assisted with referral to the hospital and high-risk clinic attendance. This study site also had an onsite sonographer at the hospital who did sonars for their high-risk women. This was helpful to the site team, as their high-risk women all had sonars done by the sonographer, followed by a consultation with the specialists. It is therefore important to consider all the patient and facility factors before implementation to allow for swift patient care.

In addition to the service provision protests already mentioned, there were other unforeseen circumstances encountered in some of the sites. Firstly, there were delays that influenced the commencement of Umbiflow™ screening. The delays included approval from one provincial research committee and the setting up of the screening space in two clinics. Secondly, some key team members relocated during the course of the study. One was the case of a new study nurse that has already been mentioned. There was also a change in the head of department or the specialist in charge of the high-risk clinic at three sites.

6.8 Lessons from integration and sustainable practice

Lessons learnt from the Umbiflow™ implementation will be valuable in future implementation studies and scaling up Umbiflow™ screening. This section provides a flow diagram of the decisions taken in the course of the study and a list of lessons learned for consideration in future implementation and scale-up activities.

Three types of decisions were fundamental to the execution of the Umbiflow™ study”. Firstly, stakeholders from national to facility level had to decide if and where the study would take place and which facilities would be included. During the study there were management decisions and patient care decisions. Management decisions pertained to the selection of facilities and the set-up in each clinic, as well as to unforeseen circumstances such as low recruitment numbers at some clinics and the management of the study during the national service provision protests. Decisions on the patient care side pertained to the identification of women with an abnormal RI who were then referred to the high-risk clinic at the hospital. Figure 5 gives a graphic depiction of the flow of decisions during the study. Figure 3 has a more detailed flow diagram of the movement of patients with normal and abnormal RIs.



6.8.1 Figure 5. Graphic depiction of the flow of decisions during the course of the Umbiflow™ study

Below is a list of important findings from the implementation of Umbiflow™ screening at the study sites and some of the implications for future implementation and scale-up.

1. Stakeholder involvement and continuous communication was crucial, especially in the early stages of implementation:
 - Assisted with acceptance and better integration.
 - Encouraged and strengthened facility engagements and communication between management and facility staff.
2. Recruiting and screening at PHC clinic level:
 - Empowered the clinic healthcare providers.
 - Enhanced their responsiveness to monitoring fetal growth and assessing for placental insufficiency.
 - Led to heightened awareness of the importance of recognising the pregnancy at risk.
3. Integrating Umbiflow™ screening into routine work required training and acceptance from the staff. If Umbiflow™ screening is scaled up elsewhere in future:
 - Considerations should be made for staffing, resources and arrangement of staff duties to help integrate screening into routine work.

- Daily screening would be needed to ensure the coverage of all pregnant women.
 - Availability of pulsed-wave ultrasound at PHC clinics would allow outreach doctors to evaluate placental function at the clinic.
4. Training and learning when Umbiflow™ screening is introduced:
- There was a fast learning curve, with nursing teams able to use the probe after a short period of training.
 - Onsite training allowed for better learning.
 - Peer learning was encouraged at the recruitment clinics through observation of the study nurses, learning from them and feeling reassured that other staff too would be able to use the Umbiflow™ device.
5. Communication:
- Continuous communication with the study team allowed for timeous solutions and planning of next steps, if necessary.
 - Use of team viewer allowed for real-time access to study data and information and allowed troubleshooting issues to be solved timeously.
 - Good rapport between a study nurse and patients may have contributed to better follow-up rates at some of the high-risk clinics.
6. Site support visits allowed for continuous stakeholder engagement:
- Useful to the study team as data collection, data entry, recruiting and screening challenges could be addressed and solutions could be sought timeously.
 - Study team reassured that they were conducting the study as planned.
7. Referral after introducing Umbiflow™ screening:
- Facilitated improvement of the referral pathways and communication between the different levels of care.
 - Available patient transport facilitated women's attendance of the high-risk antenatal clinic.
 - An open communication pathway, a functional referral system and transport would in future assist screening and the further management of women identified with abnormal RIs.
 - Outreach needs and possibilities to be considered in future – if the hospital has staff to visit the clinics and if the clinic are able to book women to be seen by the outreach doctors.
 - Continuum of care could be enhanced in urban areas with mobile populations by ensuring that women who move from one area to another or who request to be

referred to a different hospital receive a detailed referral letter that includes the Doppler findings to enable the next health team to manage these women appropriately

8. The referral hospitals accepted patients with surprising ease. This may perhaps not be as big a factor as thought previously.
 - Four hospitals saw women with abnormal RIs during the usual high-risk antenatal clinic, four had dedicated abnormal RI clinics and one hospital started with a dedicated clinic but later changed to the usual high-risk clinic model.
 - With the further rollout of Umbiflow™ screening, each referral hospital must establish a high-risk antenatal clinic for women with abnormal RIs, or re-organise ANC to incorporate women identified with abnormal RI in the current high-risk clinics at the hospital.
 - Neonatal services were not overrun and none of the neonatal teams reported new challenges related to admissions of Umbiflow™-screened neonates.
 - However, neonatal services will need to be prioritised as more LBW and FGR babies may be delivered. For such a screening system to function and be impactful an established referral route with functional maternal and neonatal services is crucial.
9. The Umbiflow™ equipment set was moved from clinic to clinic on a daily basis. It was able to withstand a lot of handling and proved to be low on maintenance:
 - Only two high-volume sites required replacement of the probe cord. This demonstrated how robust and durable the probes were. The new upgraded probes are cordless and allow for even better mobility and accessibility.
 - The small thermal printers did not need any ink and did not require frequent paper changes.

6.9 Factors still needing exploration

6.9.1 Acceptance of Umbiflow™ screening

What remains to determine is the acceptability of integrating Umbiflow™ screening in routine antenatal care services **without additional staff and resources**. This can be investigated with consideration to the Umbiflow™ user perspective on time, ease of device use and waiting times. The field notes of study teams and catchment area healthcare providers reported that the referral hospitals saw the importance of screening. However, in one study site, maternity ward staff

mentioned that they noticed that the majority of patients identified with abnormal RIs were more likely to develop fetal distress and intrapartum care complications. Maternity staff at five study sites mentioned that when they consulted with an Umbiflow™-screened woman, they were more alert as they had noticed more antenatal and intrapartum care needs in the screened women.

Field notes made at the time of implementation show that PHC clinic staff were excited to see Umbiflow™ in practice. The clinic staff asked the study team to demonstrate how the device worked and were keen to learn. In almost all the study sites, the PHC staff referred women they were concerned about to the Umbiflow™ study nurses for assessment and a clinical opinion. They also asked the study nurses about complicated patients needing a referral and for help in reaching the referral hospital if they were struggling to make contact. This facilitated the necessary referrals and improved communication between the clinics and the hospitals' high-risk antenatal clinics. Once recruitment was completed, the clinic staff at six of the study sites requested the Umbiflow™ device to remain at their facilities for continuation of screening for placental insufficiency. However, further engagement with stakeholders on the continued effects of screening and future integration of Umbiflow™ is first needed in order to develop a holistic plan on the way forward.

6.9.2 Flexibility in implementation

The unique circumstances in each study site needed to be constantly evaluated. This allowed for time to address challenges and find feasible solutions. Three sites were affected by provincial and national service provision protests and during those times recruitment was halted or alternative arrangements were considered for screening and follow-up, for example continued screening in areas where there was no protest, continuing the high-risk clinic if the hospital was accessible, and telephonically checking up on women if their follow-up date was affected by the protests to make alternative arrangements for follow-up. Changes in patient flow within the health system may affect implementation and this needs to be considered and solutions sought to assist with implementation progress. Two study sites adopted a different model with integration in the antenatal contact. This allowed for better patient flow, less waiting time, less consultation time and improved staff morale and interaction with the study team. In future, different contextually responsive 'models' of Umbiflow™ implementation should be explored to enable a smooth transition to routine practice (see section 7).

6.9.3 Integration of Umbiflow™ screening into routine antenatal care services

At the end of the Umbiflow™ study, the district management teams in KwaZulu-Natal, Mpumalanga, Gauteng and the Free State requested Umbiflow™ screening to be introduced in other PHC clinics in their catchment areas. Colleagues from other districts also requested to be part of the study or to be considered in future for Umbiflow™ work.

Umbiflow™ only completed the first four stages of the stages-of-change model illustrated in Table 1 above. For scaling up, Umbiflow™ screening needs to be integrated into routine antenatal care services (Stage 5). Firstly, stakeholders (policy makers and implementers) have to consider existing results from Umbiflow™ and other studies and decide on policy and scale-up. Then Umbiflow™ screening and referral would be rolled out to all antenatal clinics in a particular district or province as routine. The processes of the first four stages of change are repeated for each province, district and facility and would include procurement and allocation of essential resources, staff training and strengthening referral pathways.

Attending to the health system requirements needed to sustain and integrate screening and management of women identified with abnormal RIs is essential for successful implementation. The catchment areas need maternity and neonatal services adequate to manage high-risk pregnancies and small neonates. This includes maternal and neonatal services such as specialists or dedicated medical officers and paediatricians, a laboratory, a theatre(s), blood services and functioning referral pathways. Of particular importance is the initial training of antenatal nurses and doctors who would be responsible for conducting the Umbiflow™ screening. In Umbiflow™, the study nurses were an additional human resource who conducted the examinations and helped share the daily clinical patient load. With any further rollout the screening should be done by the nurses and doctors who are in the system already.

6.9.4 Towards sustainable Umbiflow™ screening in the health system

Once Umbiflow™ screening has been rolled out to all antenatal clinics in a particular administrative area, screening has to be sustained and the referral pathways have to continue being functional (see Table 1, Stage 6). Umbiflow™ equipment should become part of essential equipment lists. This would only be possible if there is regular monitoring of the continued implementation of Umbiflow™ screening and the impact on stillbirths. Knowledge, skills and

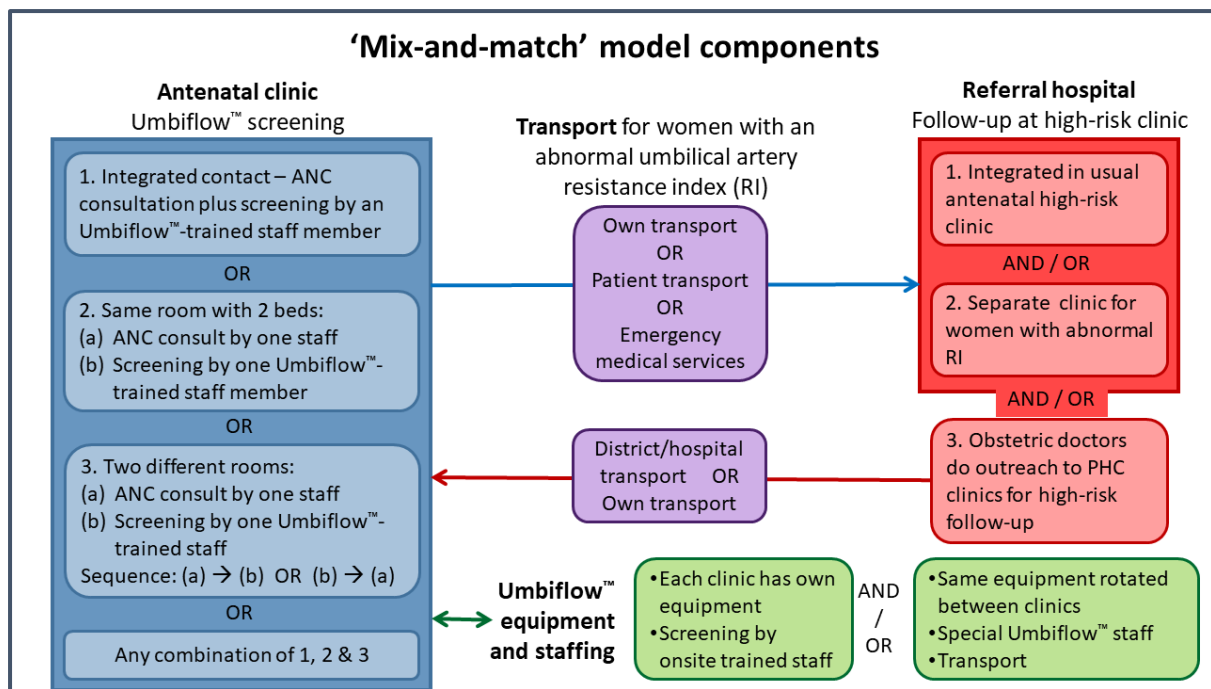
support for Umbiflow™ screening should be continued to be provided to healthcare professionals, especially novices.

6.10 Models for implementing and scaling up Umbiflow™ screening across antenatal care services

For implementing and scaling up Umbiflow™ across antenatal care services in an administrative or geographic area, policy makers and implementers need to make a number of decisions on which model for the implementation of Umbiflow™ screening would be the most appropriate for their context. A flexible model of implementation should be considered based on the unique circumstances of each catchment area, taking into consideration the screening, referral and transport availability in the area. Figure 6 presents the various implementation components that emanated from the Umbiflow™ study. There are four components to consider:

1. The way Umbiflow™ screening will be done during the antenatal contact at each individual clinic earmarked for Umbiflow™ services (blue)
2. The way in which the follow-up of women with abnormal RIs will be accommodated in a high-risk clinic at the referral hospital (red)
3. Transport arrangements to facilitate access for women with abnormal RIs high-risk antenatal care and treatment at the referral hospital (purple)
4. How the Umbiflow™ equipment will be distributed and managed between clinics and implications for staffing requirements (green)

At the antenatal clinic, the clinic set-up may determine the patient flow (blue blocks in Figure 6). The ideal would be to have one point of contact for the ANC consultation and the Umbiflow™ screening by the same staff member trained in the application of Umbiflow™. It would be preferable to have at least two staff members trained in Umbiflow™ to cover for leave and vacations of one of the two. Other options are having the consultations and the screening in the same room, but done by different staff members or having the two activities in two different rooms. In high-volume clinics with only one Umbiflow™-trained person, one of the last two options may have to be considered.



6.10.1 Figure 6. Components for building implementation models for Umbiflow™ screening

Another choice to make pertains to the Umbiflow™ equipment and staffing for screening (green blocks in Figure 6). The ideal would be for each clinic to have its own equipment and have staff trained in Umbiflow™ screening. Where that is not possible, mobile devices with specially trained nurses who rotate between clinics could be considered. A potential advantage of having onsite screening equipment is higher coverage of women being screened and implicitly better attendance of the high-risk clinic, but this requires training of large numbers of staff to have a nursing team at each clinic that can screen women daily. The benefit of a model with mobile equipment and rotation between clinics may allow for wider access and less expense on procuring equipment, but would require additional staff and transport for the travelling between clinics.

Part of the implementation model is to consider what would be the most efficient referral and follow-up systems (red blocks in Figure 6). Screened women with an abnormal RI need to be referred to the appropriate next level of care, which may be a regional, provincial tertiary or central hospital. At the referral hospital these women could be seen during the usual high-risk antenatal care clinic, which would mean that existing work- and patient flows could be maintained. The second option would be a separate clinic with its own timeslot at the hospital, which may be a practical or acceptable option for hospitals with large volumes of patients in

the usual high-risk antenatal clinic. A third option would be for doctors at the hospital's obstetric unit to follow up high-risk women near to their homes through their outreach activities to PHC facilities. Although this may allow for close to 100% follow-up of women and less cost to the patient, this may not be possible in the case of clinics with low antenatal bookings.

Accessibility to high-risk antenatal follow-up is key for women with an abnormal RI. Transport to and from clinics to the referral hospital is a crucial factor that affects follow-up (purple blocks in Figure 6). In the Umbiflow™ sites, women stated transport costs as a reason for not being able to attend hospital follow-up. Therefore, transport options should be worked out to ensure that no woman is left behind in getting the necessary high-risk antenatal care. Feasible solutions such as patient transport, involving emergency medical services, and outreach services mentioned above should be considered to alleviate the financial burden on women.

6.11 Conclusion

This study across South Africa shows that, with commitment and resources at scale, implementation efforts can be conducted. Implementation of the BANC Plus programme demonstrated that an increase in antenatal contacts improved the detection of antenatal hypertensive disorders in pregnancy. The implementation of Umbiflow™ screening demonstrated that different clinical professionals can learn how to operate the Umbiflow™ device with ease. Integration into antenatal care can be achieved with commitment and consideration to BANC Plus.

Umbiflow™ screening has demonstrated a significant impact on reducing stillbirths, which will be beneficial for patient experience of care and for maternal and neonatal outcomes and will empower healthcare providers. For sufficient integration and scaling up, resources and maternal and neonatal facilities should receive prioritised consideration for better care and better outcomes. This includes acceptance of the necessity for healthcare providers to screen women at the PHC clinics, willingness to release healthcare providers for training, and a reorganisation of patient flow. These actions may require additional resources. Furthermore, there needs to be agreement on the referral process and acceptance by the receiving hospital of the extra load on both maternity and neonatal services. This might require a shift in resources, e.g. creating new referral clinics and extra beds in the neonatal service.

Implementation of Umbiflow™ screening across nine sites in South Africa was aided by stakeholder engagement and continuous support. Findings and lessons from this Umbiflow™

implementation can contribute to future Umbiflow™ scale-up innovations and help inform decisions on improving antenatal care and pregnancy outcomes in South Africa and other similar low and middle-income countries.

6.12 References

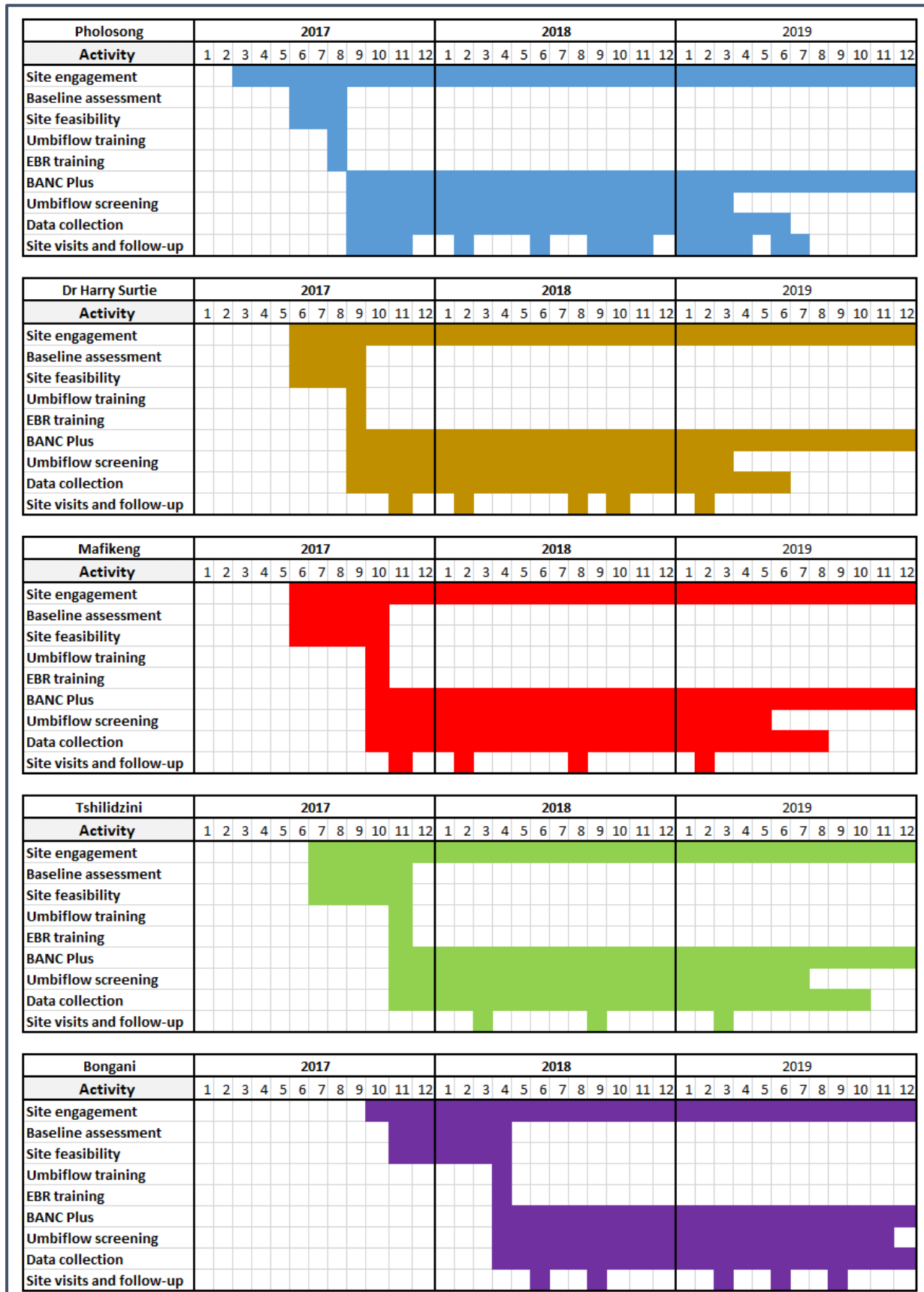
1. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016.
<https://apps.who.int/iris/bitstream/10665/250796/1/9789241549912-eng.pdf> (accessed Oct 10, 2021).
2. Pattinson RC, Hlongwane TMAG, Vannevel V. Challenges to improve antenatal and intrapartum care in South Africa. *S Afr Med J*. 2019; 109 (11b): 15-19.
<https://doi.org/10.7196/SAMJ.2019.v109i11b.14248> (accessed Oct 10, 2021).
3. National Perinatal Morbidity and Mortality Committee (NaPeMMCo). Perinatal Problem Identification Programme (PIIP) 2015–2017. South African National Department of Health; 2018.
4. National Perinatal Morbidity and Mortality Committee (NaPeMMCo). Saving Babies 2014-2016: triennial report on perinatal mortality in South Africa. South African National Department of Health; 2017.
https://www.westerncape.gov.za/assets/departments/health/napemmco_triennial_report_2014-2016_saving_babies.pdf (accessed Oct 10, 2021).
5. The Child Healthcare Problem Identification Programme (ChildPIP).
<https://www.up.ac.za/centre-for-maternal-fetal-newborn-and-child-healthcare/article/2857152/the-child-healthcare-problem-identification-programme> (accessed Oct 10, 2021).
6. Hlongwane TM, Bozkurt B, Barreix MC, Pattinson R, Gülmezoglu M, Vannevel V, Tunçalp Ö. Implementing antenatal care recommendations, South Africa. *Bull World Health Organ* 2021; 99: 220–227. <https://doi.org/10.2471/BLT.20.278945> (accessed Oct 10, 2021).
7. Moodley J, Soma-Pillay P, Buchmann E, Pattinson RC. Hypertensive diseases in pregnancy: 2019 National guideline. *S Afr Med J* 2019; 109 (3 Suppl 1): S3-S16.
<https://doi.org/10.7196/SAMJ.2019.v109i3.14104> (accessed Oct 18, 2021).
8. 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. *Maternal Health Neonatol Perinatol* 2016; 2: 11. <https://doi.org/10.1186/s40748-016-0039-4> (accessed Oct 18, 2021).

9. Francesc F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal care surveillance, diagnosed and management. *Am J Obstet Gynecol* 2011; 204: 288–299. <https://doi.org/10.1016/j.ajog.2010.08.055> (accessed Oct 18, 2021).
10. Katz J, Lee AC, Kozuki N, Lawn JE, Cousens S, Blencowe H, 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: 417–425. [https://doi.org/10.1016/S0140-6736\(13\)60993-9](https://doi.org/10.1016/S0140-6736(13)60993-9) (accessed Oct 18, 2021).
11. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). A neglected tragedy: The global burden of stillbirths. New York: United Nations Children’s Fund; 2020. <https://www.unicef.org/media/84851/file/UN-IGME-the-global-burden-of-stillbirths-2020.pdf> (accessed Oct 18, 2021).
12. SAMRC/UP Maternal and Infant Health Care Strategies Unit. South African Framework and Guidelines for Maternal and Neonatal Care during a Crisis – COVID-19 response (Version 3.5), 16 February 2021. <https://www.samrc.ac.za/sites/default/files/attachments/2021-02-24/COVID-19%20response%20MNH%20FRAMEWORK%20-%20V3.5%20%20%28updated%2016%20Feb%202021%29.pdf> (accessed August 27, 2021).
13. Belizán M, Bergh AM, Cilliers C, Pattinson RC, Voce A, for the Synergy Group. Stages of change: A qualitative study on the implementation of a perinatal audit programme in South Africa. *BMC Health Serv Res* 2011; 11: 243. <https://doi.org/10.1186/1472-6963-11-243> (accessed Oct 18, 2021).
14. Bergh AM, Allanson E, Pattinson RC. What is needed for taking emergency obstetric and neonatal programmes to scale? *Best Pract Res Clin Obstet Gynaecol* 2015; 29 (8): 1017-1027. <https://doi.org/10.1016/j.bpobgyn.2015.03.015> (accessed Oct 18, 2021).
15. Pattinson R, Kerber K, Waiswa P, Day LT, Mussell F, Asiruddin SK, Blencowe H, Lawn JE. Perinatal mortality audit: counting, accountability, and overcoming challenges in scaling up in low- and middle-income countries. *Int J Gynaecol Obstet* 2009; 107 (Suppl 1): S113-121, S121-122. <https://doi.org/10.1016/j.ijgo.2009.07.011> (accessed Oct 18, 2021).
16. Mufenda J, Gebhardt S, van Rooyen R, Theron G. 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: e0142743. <https://doi:10.1371/journal.pone.0142743> (accessed Oct 18, 2021).
17. PATH, SAMRC, CSIR. South Africa's low-cost Doppler ultrasound is reducing stillbirths and improving primary health care services. Daily Maverick. 27 Oct 2020. <https://www.dailymaverick.co.za/article/2020-10-27-south-africas-low-cost-doppler-ultrasound-is-reducing-stillbirths-and-improving-primary-health-care-services/> (accessed Oct 18, 2021).
18. Nkosi S, Makin J, Hlongwane T, Pattinson RC. 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: 347–352. <https://doi:10.7196/SAMJ.2019.v109i5.13611> (accessed June 01, 2021).
19. Pattinson RC, Theron GB, Thompson ML, Lai Tung M. Doppler ultrasonography of the fetoplacental circulation-normal reference values. S Afr Med J 1989; 76: 623–625. <https://www.ajol.info/index.php/samj/article/view/159981/149550> (accessed Oct 18, 2021).
20. Hlongwane T, Cronje T, Nkosi B, Pattinson RC. The prevalence of abnormal Doppler's of the umbilical artery in a low-risk pregnant population in South Africa. EClinicalMedicine 2021; 34: 100792. <https://doi:10.1016/j.eclinm.2021.100792> (accessed Oct 18, 2021).

6.13 Chapter 6 Appendices

6.13.1 Figure 7. Timelines of Umbiflow™ implementation at the individual study sites



General Justice	2017												2018												2019												
Activity	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	
Site engagement																																					
Baseline assessment																																					
Site feasibility																																					
Umbiflow training																																					
EBR training																																					
BANC Plus																																					
Umbiflow screening																																					
Data collection																																					
Site visits and follow-up																																					

Klerksdorp	2017												2018												2019												
Activity	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	
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Umbiflow screening																																					
Data collection																																					
Site visits and follow-up																																					

6.12.2 Table 6. Overview of implementation at individual study sites

Characteristics and processes	Site-specific description
Site 1: Pholosong (Brakpan)	
Stakeholder engagement:	Meeting with Hospital CEO, Head of Department (HOD) and management Meeting with clinics and clinicians Meeting with combined management, including DCST and district representatives on BANC Plus and Umbiflow™
Setting up the facilities:	Pholosong Hospital also runs an ANC clinic for low-risk women based on geographic boundaries and was included as a recruitment site Nokuthela Ngwenya MOU was included based on referral patterns and PPIP data reports Space identified at both recruitment sites
Composition of onsite study team:	Study nurse, data clerk, hospital doctors Hospital team: head of department (HOD) and sonographer
Training of study nurse and data clerk:	Training in Pretoria (10 days) Practical at Mamelodi study site (site in previous study) Electronic birth register data entry
Clinic arrangements for Umbiflow™ screening:	Nokuthela: separate consultation room dedicated for Umbiflow™ screening Pholosong: small space created to labour ward for Umbiflow™ screening and for high-risk patient follow-up (room with bed and table for screening and sonar for the women with abnormal RIs)
Recruitment schedule:	Tuesday to Friday: Nokuthela Ngwenya MOU Monday: Pholosong Hospital low-risk ANC clinic
High-risk clinic:	Initially Mondays, run by HOD and sonographer Changed to Wednesday to coincide with support at usual high risk-clinic (SAMRC Unit research staff visits on Wednesday)
Issues raised during virtual support:	Digital Umbiflow™ interface: - Testing software settings - Adjusting the probe sound Stationary and equipment needs (printing paper, printer cable, study booklets, referral forms, delivery forms)
Issues raised during onsite visits:	Recruitment challenges (number of eligible women on specific days of the week; national protests making facilities inaccessible due to safety reasons for staff and patients) Review of the study files (check that all forms are filled in correctly, high-risk clinic forms are detailed and delivery outcomes are followed up) Progress with implementation of electronic birth register Most raised issue: Waveform capturing (checking the Doppler waveforms and management plans)
Unforeseen circumstances and other observations:	Delays in setting up the site and procuring equipment, resulting in a recruitment delay of 3 weeks Sonographer involvement on high-risk clinic days Provincial, district and DCST not involved in team work

Characteristics and processes	Site-specific description
Site 2: Dr Harry Surtie (Upington)	
Stakeholder engagement:	Site discussions with Province, District, hospital management, clinics, DCST, clinicians Meeting with hospital CEO, HOD and management Meeting with clinics and clinicians discussing BANC Plus and Umbiflow™ Meeting with combined management, including DCST and district representatives for BANC Plus and Umbiflow™
Setting up the facilities:	Based on the PPIP data findings and unique circumstances of this area, 3 ANC clinics were identified for screening on different days of the week Small town and all patients deliver at the hospital irrespective of their risk category At each clinic a dedicated Umbiflow™ consultation room where Umbiflow™ screening and the antenatal consultation done together by Umbiflow™ nurse
Composition of onsite study team:	Study nurse, data clerk, hospital doctors Hospital team: HOD and two medical officers
Training of study nurse and data clerk:	Training in Pretoria (10 days) Practical at Mamelodi study site Electronic birth registers data entry
Clinic arrangements for Umbiflow™ screening:	Screening and recruiting integrated into ANC contact/consultation A consultation allocated to the study nurse Umbiflow™ screening and antenatal consultation done by the study nurse at all three clinics
Recruitment schedule:	Monday: Progress Clinic Tuesday and Friday: Sara Strauss Clinic Thursday: Louisvale Clinic
High-risk clinic:	Wednesday, run by HOD and 2 medical officers
Issues raised during virtual support:	Digital Umbiflow™ interface (testing software settings and adjusting the probe sound) – study nurse and data clerk able to remotely solve most of the technical issues Stationary and equipment needs (printing paper, printer cable, study booklets, referral forms, and delivery forms) Abnormal RI women and follow-up challenges (HOD on extended leave for 6 months, medical officers continued running the high-risk clinic) How to address change in clinic location due to ongoing renovations. New clinic venue was a community hall with partitions for ANC consultations
Issues raised during onsite visits:	Flexibility to visit more than one clinic when the numbers are low at one clinic. Louisvale clinic further from hospital on opposite side of town and more peri-urban and rural than the other 2 clinics Recruitment challenges on certain days of the week. If no eligible women, the study nurse was able to go to another clinic (this was promoted by good communication between study nurse and the clinic staff) Study files review of data entry, tracing women lost to follow up. Progress with implementation of electronic birth register Waveform capturing and saving the Umbiflow™ tracing

Characteristics and processes	Site-specific description
Unforeseen circumstances and other observations:	Progress Clinic had renovation mid-year and the clinic was relocated to local community hall – study team able to move with clinic and continue recruiting DCST actively involved, encouraged the study team and helped with BANC Plus support
Site 3: Mafikeng Provincial (Mafikeng)	
Stakeholder engagement:	Site discussions with Province, District, hospital management, clinics, DCST, clinicians District team meeting to discuss Umbiflow™ and suitable clinics for this initiative Clinic visits with District management for site view and introductions at clinics Meeting with hospital CEO, HOD and management – invited to hospital CEO office for discussion and approvals Meeting with clinics and clinicians discussing BANC Plus and Umbiflow™
Setting up the facilities:	Montshiwa Stadt Clinic has an ANC clinic container with one room and 2 beds Monsthoa Town Clinic has space available – dedicated Umbiflow™ room
Composition of onsite study team:	Study nurse, data clerk, hospital doctors Hospital team: one specialist and one medical officer
Training of study nurse and data clerk:	Training in Pretoria (10 days) Practical at Mamelodi study site Electronic birth register data entry
Clinic arrangements for Umbiflow™ screening:	Montshiwa Stadt Clinic: ANC in clinic container – consultation room with 2 beds partitioned for privacy – women have ANC consult, and if illegible, are offered Umbiflow™ screening on other side of room Monsthoa Town Clinic had space available, with a consultation room dedicated for Umbiflow™ screening on specific days of the week
Recruitment schedule:	Monday and Tuesday: Montshiwa Stadt Clinic Thursday and Friday: Monsthoa Town Clinic
High-risk clinic:	Wednesday, run by specialist and medical officer
Issues raised during virtual support:	Service provision protest disrupting recruiting and screening Digital Umbiflow™ interface (testing software settings and adjusting the probe sound) – study nurse and data clerk able to remotely solve most of the technical issues Stationary and equipment needs (printing paper, printer cable, study booklets, referral forms, and delivery forms)
Issues raised during onsite visits:	Clinic issues related to access during protest times No clinic and hospital access during protest times. Hospital was more accessible, and high-risk clinics continued, but local PHC clinics were closed due to safety issues. Study files (review; and equipment and stationary audits). Delivery of equipment and stationary as per the study needs. Progress with implementation of electronic birth register Waveform capturing (checking the Doppler waveforms and management plans)

Characteristics and processes	Site-specific description
Unforeseen circumstances and other observations:	Study team adjustments when the initial high-risk clinic specialist relocated to a different hospital – joined by new specialist – support visit for new team member to actively take over the role in the high-risk clinic Province severely affected by service provision for over 3 months protests with no safe access to health care facilities – no recruitment during protest months
Site 4: Tshilidzini hospital (Vembe, Thohoyandou)	
Stakeholder engagement:	Site discussions with Province, District, hospital management, clinics, DCST, HOD, clinicians District team meeting to discuss Umbiflow™ and suitable clinics for this initiative Clinic visits with District management for site view and introductions at the clinics Meeting with hospital CEO, HOD and management Meeting with clinics and clinicians discussing BANC Plus and Umbiflow™ District formally involved in recruiting and appointing study team members (study nurse and data clerk) – district advertisement, district shortlisting and interview for both individuals
Setting up the facilities:	Only one recruitment site – one CHC Thohoyandou CHC has a data clerk room available Umbiflow™ recruiting and screening in same room as ANC consultation Clinic consultation has a large room with two beds, one for the ANC consultation and another for Umbiflow™ screening – partition available for privacy
Composition of onsite study team:	Study nurse, data clerk, hospital doctors Hospital team: one specialist and one medical officer
Training of study nurse and data clerk:	Training in Pretoria (10 days) Practical at Mamelodi study site Electronic birth register data entry
Clinic arrangements for Umbiflow™ screening:	Umbiflow™ recruiting and screening in the same room Clinic consultation has a large room with two beds, one for the ANC consultation and another for Umbiflow™ screening – partition for privacy
Recruitment schedule:	Monday, Tuesday, Thursday and Friday: Thohoyandou CHC Study nurse worked with clinic staff in same room – clinic staff did ANC consultation and study nurse did Umbiflow™ screening in a partitioned section of the room
High-risk clinic:	Wednesday, run by the medical officer Umbiflow™ high-risk clinic integrated into main hospital high-risk clinic – same day and setting
Issues raised during virtual support:	Digital Umbiflow™ interface: - Testing software settings - Adjusting the probe sound Stationary and equipment needs (printing paper, printer cable, study booklets, referral forms, and delivery forms)
Issues raised during onsite visits:	Recruitment challenges during the national protests Study files data entry and Doppler waveform review Progress with implementation of electronic birth register

Characteristics and processes	Site-specific description
	Waveform capturing (reviewing the Doppler waveforms and management plans) Delivery of equipment and study files
Other observations and unforeseen circumstances:	Obstetric specialist relocated to the private sector
Site 5: Bongani (Welkom)	
Stakeholder engagement:	Site discussions with Province, District, hospital management, clinics, DCST, HOD, clinicians. District team meeting to discuss Umbiflow™ and suitable clinics for this initiative Clinic visits with District management for site view and introductions at the clinics Meeting with hospital CEO, HOD and management Meeting with clinics and clinicians discussing BANC Plus and Umbiflow™ Meeting with clinicians and HOD – discussions on Umbiflow™ and BANC Plus DCST and Hospital management actively involved in study team recruitment
Setting up the facilities:	Three clinics reviewed for possible inclusion – two included based on feasibility and clinic space Clinics had a dedicated Umbiflow™ consultation room with ANC consultation in separate room
Composition of onsite study team:	Study nurse, data clerk, hospital doctors Hospital team: HOD and medical officers
Training of study nurse and data clerk:	Training in Pretoria (10 days) Practical at Pholosong study site Electronic birth register data entry
Recruitment schedule:	Monday and Tuesday: Welkom Clinic Wednesday and Thursday: Khotsong Clinic
High-risk clinic:	Wednesday, a dedicated abnormal RI clinic Run by HOD and medical officers
Clinic arrangements for Umbiflow™ screening	Dedicated Umbiflow™ consultation room at both clinics Study nurse and facility staff worked together and when clinic was short staffed study nurse did Umbiflow™ and ANC consultation at the same setting
Issues raised during virtual support:	Digital Umbiflow™ interface: - Testing software settings - Adjusting the probe sound Stationary and equipment needs (printing paper, printer cable, study booklets, referral forms, and delivery forms) Recruiting numbers and referral pattern Challenges with high-risk clinic if HOD not available for clinic – medical officers available to review patients – study support of HOD
Issues raised during onsite visits:	Recruitment challenges during the national protests Study files data entry and Doppler waveform review

Characteristics and processes	Site-specific description
	Progress with implementation of electronic birth register, three hospitals for delivery outcomes Waveform capturing and review waveforms Delivery of equipment and study files High-risk clinic support Collecting completed study files for collation
Other observations and unforeseen circumstances:	Change of HOD during recruiting time – new head joined study team Change in high-risk clinic team, with new HOD and staff rotations Thabong Clinic reviewed, but not included as a recruitment site due to space and patient flow issues Three delivery sites included for the implementation of the electronic birth register (Virginia, Thusanong and Bongani Hospitals)
Site 6: Klerksdorp (Klerksdorp)	
Stakeholder engagement:	Site discussions with Province, District, hospital management, clinics, DCST, Head of Department, clinicians District team meeting to discuss Umbiflow™ and suitable clinics for this initiative Clinic visits with District management for site view and introductions at the clinics Meeting with hospital CEO, Head of Department, and management Meeting with clinics and clinicians discussing BANC Plus and Umbiflow™ Meeting with clinicians and HOD, discussions on Umbiflow™ and BANC Plus Hospital safety group discussion DCST actively involved with identifying feasible study nurse and data clerk to join the team
Setting up the facilities:	Jouberton clinic: one room – two bed – partition for privacy Empilisweni clinic: dedicated Umbiflow™ room
Composition of onsite study team:	Study nurse, data clerk, hospital doctors Hospital team: HOD, specialist and medical officers
Training of study nurse and data clerk:	Training in Pretoria (10 days) Practical at Pholosong study site Electronic birth register data entry
Clinic arrangements for Umbiflow™ screening:	Jouberton clinic: large room with ANC consultation with two beds, one for ANC consultation and another for Umbiflow™ screening – partition for privacy – after ANC consultation, women offered Umbiflow™ screening Empilisweni clinic: dedicated Umbiflow™ room on specific days of the week
Recruitment schedule:	Monday and Thursday: Jouberton Clinic Wednesday and Friday: Empilisweni/Town Clinic
High-risk clinic:	Wednesday's run by the specialist and medical officers Abnormal RI clinic incorporated in hospital's main high-risk clinic
Issues raised during virtual support:	Digital Umbiflow™ interface: - Testing software settings - Adjusting the probe sound Stationary and equipment needs (printing paper, printer cable, study booklets, referral forms, and delivery forms)

Characteristics and processes	Site-specific description
	Recruiting numbers and referral pattern, challenges with high-risk clinic when the team changed
Issues raised during onsite visits:	Recruitment challenges during the national protests (North West province most affected) Study files data entry and Doppler waveform review Progress with implementation of electronic birth register, three hospitals for delivery outcomes Waveform capturing and review waveforms Delivery of equipment and study files High-risk clinic support Taking completed study files back for collation
Other observations and unforeseen circumstances:	Empilisweni Clinic recruitment delays due to space and other programmes at the facility – Umbiflow™ screening on days when other programmes were not at the clinic (shared space with these projects) Study nurse relocated – DCST assisted with identifying new study nurse Recruitment paused while waiting for new study nurse to complete her training
Site 7: General Justice Gizenga Mpanza (KwaDukuza, Stanger)	
Stakeholder engagement:	Site discussions with Province, District, hospital management, clinics, DCST, HOD, clinicians Meeting with combined management, including DCST and district representatives for BANC Plus and Umbiflow™ Meeting with HOD and management Meeting with clinics, clinicians and sonographer
Setting up the facilities:	Both clinics had dedicated Umbiflow™ screening room ANC consultation integrated with screening in same setting
Composition of onsite study team:	Study nurse, data clerk, hospital doctors and sonographer Hospital team: HOD, specialist, medical officers and sonographer
Training of study nurse and data clerk:	Training in Pretoria (10 days) Practical at Pholosong study site Electronic birth register data entry
Clinic arrangements for Umbiflow™ screening:	Study nurse reviewed pregnancy – did ANC consultation and Umbiflow™ screening together in both clinics
Recruitment schedule:	Monday and Thursday: Sundumbili CHC Tuesday and Friday: KwaDukuza Clinic
Day for high-risk clinic:	Wednesday, women seen by sonographer and doctors Clinic combined with hospital's regular high-risk clinic
Issues raised during virtual support:	Digital Umbiflow™ interface: - Testing software settings - Adjusting the probe sound Stationary and equipment needs (printing paper, printer cable, study booklets, referral forms, and delivery forms) Recruiting numbers and referral pattern Probe issues that resulted in a need for a new probe delivery
Issues raised during onsite visits:	Study files data entry and Doppler waveform review

Characteristics and processes	Site-specific description
	Progress with implementation of electronic birth register and delivery outcome data entry Waveform capturing and review of waveforms Delivery of equipment and study files High-risk clinic support Taking study files back to SAMRC Unit office for collation
Other observations and unforeseen circumstances:	Sonographer involvement on high-risk clinic days Patient transport available between Sundumbili CHC and the hospital
Site 8: Themba (Kabokweni)	
Stakeholder engagement:	Site discussions with Province, District, hospital management, clinics, DCST, HOD, clinicians District team meeting to discuss Umbiflow™ and suitable clinics for this initiative Clinic visits with District management for site view and introductions at the clinics Meeting with hospital CEO, Head of Department, and management. Meeting with clinics and clinicians discussing BANC Plus and Umbiflow™ DCST lead clinic visits Meeting with clinicians and HOD, discussions on Umbiflow™ and BANC Plus DCST and nursing management team actively involved with identifying study nurse and data clerk to join the team
Setting up the facilities:	Phola and Bhuga had a dedicated Umbiflow™ room
Composition of onsite study team:	Study nurse, data clerk, hospital doctors Hospital team: HOD, specialist and medical officer
Training of study nurse and data clerk:	Training in Pretoria (10 days) Practical at Pholosong study site Electronic birth register data entry
Clinic arrangements for Umbiflow™ screening:	Dedicated Umbiflow™ room at both clinics
Recruitment schedule:	Monday and Wednesday: Phola Clinic Tuesday and Friday: Bhuga Clinic
High-risk clinic:	High-risk clinic at hospital Monday-Friday Friday dedicated for the abnormal RI clinic
Issues raised during virtual support:	Digital Umbiflow™ interface: - Testing software settings - Adjusting the probe sound Stationary and equipment needs (printing paper, printer cable, study booklets, referral forms, and delivery forms) Recruiting numbers and referral pattern
Issues raised during onsite visits:	Study files data entry and Doppler waveform review Progress with implementation of electronic birth register Waveform capturing and review waveforms Delivery of equipment and study files High-risk clinic support

Characteristics and processes	Site-specific description
Other observations and unforeseen circumstances:	Delay in approval from provincial research committee resulting in a recruitment delay of 3 weeks Study team able to recruit at 2 clinics on the same day based on patient numbers Labour ward and ANC clinic team reported more fetal distress in screened HR women
Site 9: Dora Nginza (Gqeberha)	
Stakeholder engagement:	Hospital CEO, HOD, clinics, clinicians Meeting with hospital CEO, HOD and management Meeting with clinics and clinicians discussing BANC Plus and Umbiflow™ Meeting with clinicians and HOD – discussions on Umbiflow™ and BANC Plus HOD actively involved with identifying study nurse and data clerk to join the team
Setting up the facilities:	Both clinics had space available for a dedicated Umbiflow™ room
Composition of onsite study team:	Study nurse, data clerk, hospital doctors Hospital team: HOD, Specialist, registrars
Training of study nurse and data clerk:	Training in Pretoria (10 days) Practical at Pholosong study site Electronic birth register data entry
Clinic arrangements for Umbiflow™ screening:	Both clinics had space and multiple consultation rooms Umbiflow™ had a dedicated consultation room
Recruitment schedule:	Monday and Thursday: Motherwell CHC Tuesday and Friday: Kwazakhele Clinic
Day for high-risk clinic:	Wednesday, run by Head of Department, specialists and registrars Dedicated abnormal RI clinic
Issues raised during virtual support:	Digital Umbiflow™ interface: - Testing software settings - Adjusting the probe sound Stationary and equipment needs (printing paper, printer cable, study booklets, referral forms, and delivery forms) Recruiting numbers, data entry and referral pattern
Issues raised during onsite visits:	Study files data entry and Doppler waveform review Progress with implementation of electronic birth register, and data entry Delivery of equipment and study files Taking complete files back to UPMRC for collation and RedCap entry High-risk clinic support.
Other observations and unforeseen circumstances:	Clinics have specialist visits weekly, this assisted with high-risk clinic booking. Local service-delivery protests in the area Provincial, district and DCST not involved in team work

6.13.3 Table 7. Umbiflow™ recruiting primary healthcare clinic characteristics

Indicator: Clinics	Umbiflow™ implementation sites								
	Pho	Upi	Maf	Tshi	Bong	The	Klerk	Gen	Dor
Healthcare workers									
Staff availability, nursing capacity	yes	yes	yes	yes	yes	yes	yes	yes	yes
Umbi-sister	yes	yes	yes	yes	yes	yes	yes-redone	yes	yes
Data capturer, clerk	yes	yes	yes	yes	yes	yes	yes	yes	yes
Training and skills	yes	yes	yes	yes	yes	yes	yes	yes	yes
Time, availability (duration)	yes	yes	yes	yes	yes	yes	yes	yes	yes
Site facility									
Umbi area	yes	same setting	yes as ANC	yes as ANC	yes	yes	yes as ANC	same setting	yes
Accessibility	yes	yes	yes	yes	yes	yes	yes	yes	yes
Transport available	yes	yes	yes	yes	yes	yes	yes	yes	yes
Distance to hospitals	yes	yes	yes	yes	yes	yes	yes	yes	yes
Distance to other clinics	yes	yes	yes	yes	yes	yes	yes	yes	yes
Equipment (provided)									
Umbiflow™ probe	yes	yes	yes	yes	yes	yes	yes	yes	yes
Laptop	yes	yes	yes	yes	yes	yes	yes	yes	yes
Thermal printer	yes	yes	yes	yes	yes	yes	yes	yes	yes
Referral route									
Referral hospital	yes	yes	yes	yes	yes	yes	yes	yes	yes
Distance, accessibility	near	n&far	near	inter-med	n&far	n&far	near	far	far
Transportation of patients	yes	yes	yes	yes	yes	yes	yes	yes	yes
EMS	yes	yes	yes	yes	yes	yes	yes	yes	yes
Data									
Collection and recording	yes	yes	yes	yes	yes	yes	yes	yes	yes
Reporting and outcomes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Data storage	yes	yes	yes	yes	yes	yes	yes	yes	yes
Audits	yes	yes	yes	yes	yes	yes	yes	yes	yes
PPIP use	yes	yes	yes	yes	yes	yes	yes	yes	yes
Birth register	yes	yes	yes	yes	yes	yes	yes	yes	yes

Indicator: Clinics	Umbiflow™ implementation sites								
	Pho	Upi	Maf	Tshi	Bong	The	Klerk	Gen	Dor
Referral hospitals									
Local transport	yes	yes	yes	yes	yes	yes	yes	yes	Yes
Patient transport by facility	no	no	no	no	no	no	no	yes	No

Pho = Pholosong; Upi = Dr Harry Surtie; Maf = Mafikeng, Tshi = Tshilidzini; Bong = Bongani; The = Themba; Klerk = Klerksdorp; Gen = General Justice Gizenga Mpanza; Dor = Dora Nginza; Umbi = Umbiflow; EMS = emergency medical services; PPIP = Perinatal Problem Identification Programme

6.13.4 Table 8. Umbiflow™ referral hospitals characteristics

	Umbiflow™ implementation sites								
Indicator: Hospitals	Pho	Upi	Maf	Tshi	Bon	Them	Klerk	Gen	Dora
Healthcare workers									
Staff availability, numbers, capacity	yes	yes	yes	yes	yes	yes	yes	yes	yes
Obstetrics doctor	yes	yes	yes	yes	yes	yes	yes	yes	yes
Sonographer team	yes	no	no	no	no	no	no	yes	no
Umbi-sister	yes	yes	yes	yes	yes	yes	yes	yes	yes
Data capturer, clerk	yes	yes	yes	yes	yes	yes	yes	yes	yes
Training and skills	yes	yes	yes	yes	yes	yes	yes	yes	yes
Time, availability	yes	yes	yes	yes	yes	yes	yes	yes	yes
Neonatal facility	yes	yes	yes	yes	yes	yes	yes	yes	yes
Neonatal doctor	yes	yes	yes	yes	yes	yes	yes	yes	yes
Site facility									
Umbi-specific area	yes	yes	yes	yes	yes	yes	yes	yes	yes
Accessibility	yes	yes	yes	yes	yes	yes	yes	yes	yes
Transport	yes	yes	yes	yes	yes	yes	yes	yes	yes
Referral system	yes	yes	yes	yes	yes	yes	yes	yes	yes
Surrounding area, hospital	yes	yes	yes	yes	yes	yes	yes	yes	yes
EMS availability	yes	yes	yes	yes	yes	yes	yes	yes	yes
Level of hospital	R	R	P	R	R	R	T	T	T
Equipment									
Ultrasound with Doppler function	yes	yes	yes	yes	yes	yes	yes	yes	Yes
Umbiflow™	yes	yes	yes	yes	yes	yes	yes	yes	yes
Theatre available	yes	yes	yes	yes	yes	yes	yes	yes	yes
Blood products available	yes	yes	yes	yes	yes	yes	yes	yes	yes
ANC high-risk clinic	yes	yes	yes	yes	yes	yes	yes	yes	yes
Steroids	yes	yes	yes	yes	yes	yes	yes	yes	yes

Indicator: Hospitals	Umbiflow™ implementation sites								
	Pho	Upi	Maf	Tshi	Bon	Them	Klerk	Gen	Dora
Management Protocols									
Protocols and guidelines	yes	yes	yes	yes	yes	yes	yes	yes	yes
Doctors	yes	yes	yes	yes	yes	yes	yes	yes	yes
ESMOE drills	yes	yes	yes	yes	yes	yes	yes	yes	yes
Neonatal unit									
Doctor - staff	yes	yes	yes	yes	yes	yes	yes	yes	yes
NICU	yes	yes	yes	yes	yes	yes	yes	yes	yes
Neonatal observation/nursery	yes	yes	yes	yes	yes	yes	yes	yes	yes
Equipment: care for >1kg neonate	yes	yes	yes	yes	yes	yes	yes	yes	yes
Data									
Collection and recording	yes	yes	yes	yes	yes	yes	yes	yes	yes
Reporting and outcomes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Data collection, storage, filling	yes	yes	yes	yes	yes	yes	yes	yes	yes
Audits	yes	yes	yes	yes	yes	yes	yes	yes	yes
PIIP	yes	yes	yes	yes	yes	yes	yes	yes	yes
Maternity register	yes	yes	yes	yes	yes	yes	yes	yes	yes

Pho = Pholosong; Upi = Dr Harry Surtie; Maf = Mafikeng; Tshi = Tshilidzini; Bong = Bongani; The = Themba; Klerk = Klerksdorp; Gen = General Justice Gizenga Mpanza; Dor = Dora Nginza; Umbi = Umbiflow; EMS = emergency medical services; ANC = antenatal care; ESMOE = Essential Steps in Managing Obstetric Emergencies; NICU = neonatal intensive care unit; PIIP = Perinatal Problem Identification Programme

6.13.5 Table 9. Catchment area stakeholder engagements

Sites	District Mx	DCST Mx	Clinic Mx	Hospital Mx	Obstetrics	Paediatrics
Pholosong	Partial	Partial	Partial	Involved	Involved	Involved
Dr Harry Surtie	Involved	Involved	Involved	Involved	Involved	Involved
Mafikeng	Involved	Involved	Involved	Involved	Involved	Involved
Tshilidzini	Involved	Involved	Involved	Involved	Involved	Involved
Bongani	Involved	Involved	Involved	Involved	Involved	Involved
Klerksdorp	Involved	Involved	Involved	Involved	Involved	Involved
GJGM	Involved	Involved	Involved	Involved	Involved	Involved
Themba	Involved	Involved	Involved	Involved	Involved	Involved
Dora Nginza	Partial	Partial	Involved	Involved	Involved	Involved

Mx = Management; DCST = district clinical specialist team; GJGM = General Justice Gizenga Mpanza

Conclusion and Recommendations

This thesis was developed to test the effect of introducing Basic Antenatal Care Plus and Umbiflow™ on antenatal care and perinatal mortality in South Africa.

The key findings in the discussed chapters are as follows:

Chapter 1: Implementing antenatal care recommendations, South Africa

The basic antenatal care (BANC) guidelines were based on the previous World Health Organization (WHO) guidelines and were adjusted to a new antenatal package (BANC Plus) based on the new WHO Guidelines. The South African National Department of Health accepted the new antenatal care package and it was implemented in April 2017. The new package focuses on specific contacts and the number of contacts are increased to a minimum of eight. We monitored the implementation and supported 4 catchment areas. There was a steady increase in the number of contacts over the one year period. The mean visits being 4.76, 4.87, 5.46, 5.36 and 5.90 for March, July, September, November and February respectively. More women with hypertensive disorders in pregnancy were detected and there was an average of 30% increase in hypertensive disorders in pregnancy detection from the baseline in March 2017 to February 2018. Overall, women were visiting the clinic more often, the blood pressure was taken at most antenatal clinic contacts, an increasing number of women with hypertensive disorders in pregnancy were detected and an increasing number of women with hypertensive disorders in pregnancy detected had the appropriate management action taken. The observed trends in maternal and perinatal mortality since implementation of the package are encouraging, with a trend of decreasing perinatal mortality shown in some districts. Mpumalanga province has demonstrated a significant reduction in stillbirths and perinatal mortality due to HDP when studying trends before and after the introduction of BANC Plus.

This demonstrated that with all stakeholders' commitment, allocation of resources and health system support evidence-based recommendations can be implemented at scale. Furthermore, involving multiple stakeholders allowed for consideration of diverse circumstances across the diverse catchment areas in South Africa. This allowed the different catchment areas to consider the concept of next-level of expertise; an innovative approach that promotes access to expert care to all women though having a medium-to-high-risk expert services at the

primary healthcare level. This will inform global work in antenatal care, and help develop different models of referral and care for women with identified antenatal problems.

Chapter 2: Antenatal detection and prevention of stillbirths and fetal growth restriction in low- and middle-income countries: a gap in current knowledge

Even with antenatal care programs, adverse pregnancy outcomes prevail. Nearly 2.0 million stillbirths occur globally, this remains a global health concern particularly in low- and middle-income countries (LMIC). It is estimated that a proportion (25–50%) of fetal deaths are due to fetal growth restriction (FGR) secondary to placental insufficiency. This represents a significant proportion of stillbirths in LMIC. Continuous wave Doppler ultrasound of the umbilical artery can detect placental insufficiency and is suitable for screening a pregnant population and thus might be a suitable tool to help reduce antenatal stillbirths.

The number of stillbirths in low-risk ‘healthy’ women is high, particularly in LMICs. Determining the prevalence of abnormal Doppler and absent end diastolic flow in South Africa may help identify the low-risk mother carrying a high-risk fetus. Umbilical artery Doppler screening may help reduce the enormous load of unexplained stillbirths and motivate policy makers to integrate other innovative screening programs into routine antenatal care.

Chapter 3: The prevalence of abnormal Doppler’s of the umbilical artery in low-risk pregnant women in South Africa

The prevalence and use of umbilical artery Doppler in women with high-risk pregnancies has been shown to reduce perinatal deaths. However, the use of umbilical artery Doppler in low-risk women needed further evaluation. The prevalence of abnormal resistance indices was found to be 13.0% in low-risk antenatal South African populations, this was higher than reported in high-income countries. The prevalence of absent end diastolic flow (AEDF) was 1.2%, this was comparable to another South African study, and is about ten times higher than that previously recorded in high-income countries. The prevalence of small for gestational age babies in this screened population was significantly higher in the abnormal RI group (23.1% vs 32.1%). This study also demonstrated that Umbiflow™ screening is an effective tool for detecting fetal growth restriction as neonates with an abnormal resistance index had lower birthweights across all growth centiles. The fetuses were smaller at birth, irrespective

of their gestational age at the time of delivery. Use of Umbiflow™ Doppler has the added benefit over conventional imaging ultrasound in that it identifies placental insufficiency irrespective of fetal size. There was a statistical difference in perinatal mortality between the screened population with abnormal resistance indices demonstrating a higher perinatal mortality (21.4/1000 vs 9.8/1000) than those with normal resistance indices. Screening a low risk pregnant population with Umbiflow™ detected the fetus at risk of adverse outcome.

The high prevalence of AEDF (1.2%) in a pregnant population classified as having low-risk pregnancies warrants screening in South Africa.

Chapter 4: Preventing antenatal stillbirths: An innovative approach for primary healthcare

Stillbirths remain a challenge in low- and middle-income countries. The majority are unexplained, and the mothers are clinically healthy women, assumed to be carrying healthy pregnancies. As a follow-on from the prevalence study the mortality was assessed in the cohort and a similar cohort from the same geographical area and attending the same clinics. There were 66 stillbirths in the 6536 number of screened women in the study group with delivery outcomes and 193 stillbirths in the 10832 women attending the same antenatal clinics who did not have an Umbiflow™ Doppler screening (control group 1) and 152 stillbirths in 9811 of the same women with no detected antenatal complications (control group 2). The stillbirth rate was significantly reduced in the screened population (10.1/1000 births), compared to a stillbirth rate of 17.8/1000 (RR 0.57, 95 CI 0.29-0.85) births in control group of pregnant women not screened, attending the same antenatal clinics. When pregnant women who developed antenatal complications in the control were removed, there was still a significant reduction in the stillbirth rate in the screened population 10.1/1000 vs 15.5/1000 (RR 0.65, 95 CI 0.36-0.94). Umbiflow™ screening was associated with a significant reduction in stillbirths (35% – 43%).

This study demonstrates that screening a low-risk pregnant population with umbilical artery Doppler coupled together with a standard management protocol can substantially reduce the prevalence of antenatal stillbirths in the South African setting.

Chapter 5: The outcome of absent end diastolic flow (AEDF) in fetuses of clinical healthy pregnant woman in South Africa

The prevalence and outcome of AEDF in low-risk pregnancies has not been explored particularly in low- and middle-income countries. AEDF is a recognised phenomenon in high-risk pregnancies, and is associated with adverse perinatal outcomes. This study demonstrated that without appropriate intervention and management, AEDF leads to stillbirths (4 of 5 women detected as having fetuses with AEDF and declining treatment had antenatal stillbirths). This study demonstrated a prevalence of 1.2% (87 women) in otherwise previously healthy low-risk women. Of these, 21 (24.1%) developed hypertensive disorders in pregnancy, only 23 (26.4%) were HIV reactive on antiretroviral therapy. The neonates identified from the pregnancies; 61 (71.8%) were low birthweight and 56 (64.4%) were small for gestational age. The perinatal mortality was 91.9/1000 births, this was high mainly due to the 5 women who declined treatment and subsequently had adverse outcomes (4 of them had stillbirths). If the 5 cases are excluded the PNMR is 48.8/1000 births. There was only one neonatal death, this indicates that if the fetus with AEDF is detected and actively managed they do not become neonatal deaths, but survive.

If not detected and appropriately managed, AEDF leads to stillbirths, however appropriate management leads to survival past the neonatal period. The high prevalence of AEDF provides strong evidence that fetal growth restriction is a major cause of stillbirths in South Africa and this further justifies screening in South Africa.

Chapter 6: Implementing Umbiflow across nine sites in South Africa

Implementation of Umbiflow™ screening across nine sites in South Africa was aided by stakeholder engagement and continuous support. This study demonstrated that with commitment from stakeholders and resource allocation at scale implementation efforts can be achieved. The implementation of Umbiflow™ screening demonstrated that different clinical professionals can learn how to operate the Umbiflow™ device with ease, and the learning curve is fast.

A flexible model of implementation should be considered based on the unique circumstances of each catchment area, taking into consideration the antenatal programme, screening feasibility, referral and transport availability in the area. Integration into antenatal care can be achieved with commitment and consideration to health system pathways.

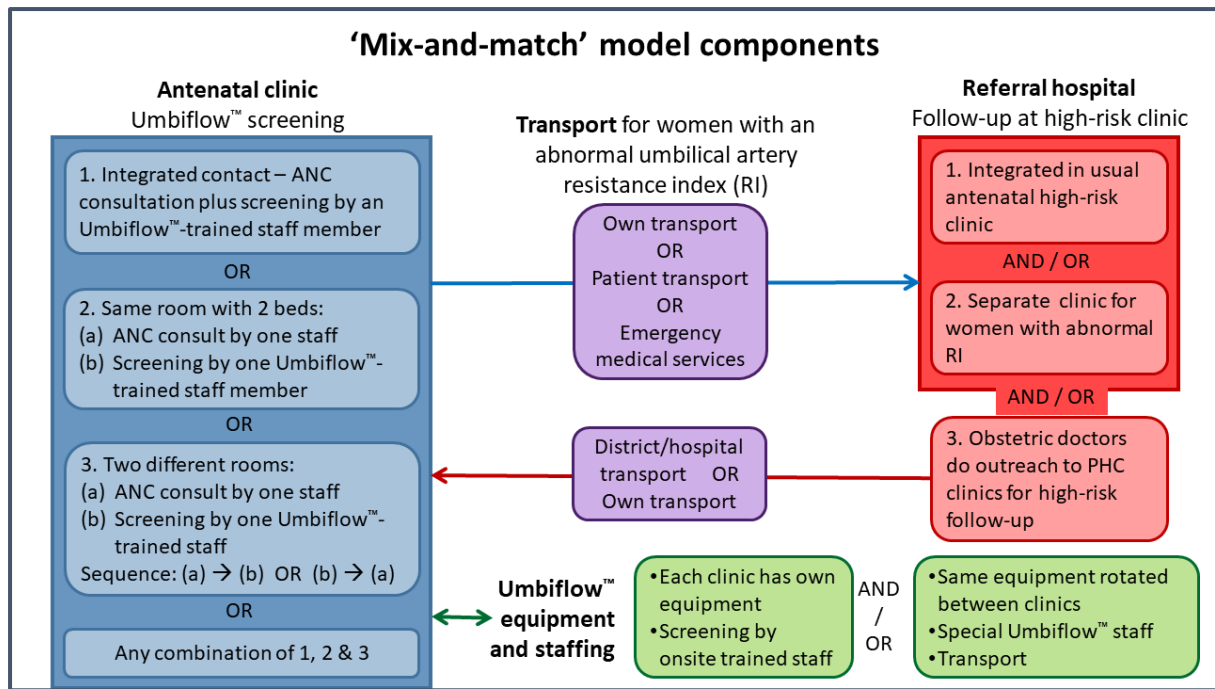


Figure 1. Components for building implementation models for Umbiflow™ screening

Lessons from this Umbiflow™ study can contribute to future Umbiflow™ scale-up innovations and help inform decisions on improving antenatal care and pregnancy outcomes in South Africa and other similar low- and middle-income countries.

Summary:

The finding in this thesis are:

1. Implementation of the new WHO recommendations for antenatal care increase the number of antenatal contacts and the detection of women with hypertensive disorders of pregnancy (and a later study has shown a decrease in stillbirths due to HDP).
2. South Africa has a high prevalence of undetected severe placental disease (AEDF) in women classified as having low-risk pregnancies
3. Action taken once the fetuses were identified resulted in a major reduction in the number of stillbirths.
4. If left unmanaged, women with severe placental disease (AEDF) will mostly have antenatal stillbirths.

5. Screening of pregnant women classified as having low-risk pregnancies, although it increases the burden on the referral hospitals, screening does not result in increased neonatal deaths.
6. Thus, screening of women with low-risk pregnancies with continuous wave Doppler ultrasound (e.g. UmbiflowTM) should be integrated into the BANC Plus package.

Recommendations:

These findings have challenged us to re-imagine antenatal care, where BANC Plus including Umbiflow™ at 28-34 weeks' gestation should be integrated into antenatal care, this will provide a practical solution to improve the antenatal experience of care and pregnancy outcomes by reducing stillbirths until other prevention strategies are available. The Umbiflow™ device is ideally suited for nationwide scale up and recommendations to aid implementation and consideration are as follows:

1. Low-risk pregnant women should be offered placental insufficiency screening using the Umbiflow™ device. The screening can be offered between 28-34 weeks' gestation.
2. Low-risk women identified with abnormal Doppler resistance indices should be referred to the appropriate next level of care for further assessment and clinical management to optimise improve pregnancy outcomes.
3. Catchment areas should establish functional referral pathways, with functional communication between low and high level facilities and emergency medical services.
 - a. Women identified with abnormal Doppler resistance indices to be referred appropriately to hospital for further assessment.
 - b. Open and functional communication should be encouraged between healthcare providers at the different levels of care.
 - c. Available patient transport should be utilised to assist in aiding women to reach the hospital.
4. Create a high-risk clinic at the appropriate referral hospital for women with abnormal resistance indices. This can be considered based on local circumstances and women should be invited to attend regular hospital high-risk antenatal clinic or attend an abnormal Doppler clinic were available.
 - a. Women with abnormal resistance indices should be offered appropriate management based on their clinical findings. This can be achieved by adhering to a standard management protocol, including admission of women with absent end diastolic flow, offering antenatal corticosteroids to women with a gestation below 34 weeks who are at an increased risk of preterm delivery, cardiotocogram for women admitted with abnormal Doppler and fetal growth

and Doppler monitoring and recommending delivery at appropriate time based on the clinical findings.

- b. Women identified with abnormal resistance indices are at an increased risk of fetal growth restriction and extra follow-up and growth monitoring should be done. Umbiflow™ can differentiate between two populations of fetuses, those who are growth restricted and those not growth restricted.
 - c. Encourage women to attend the high-risk clinic follow up and consider transport availability.
 - d. Recognise that untreated absent end diastolic flow potentially leads to mortality, and timely and appropriate intervention may save lives.
 - e. Recognise that fetuses with abnormal resistance indices can develop absent end diastolic flow and need follow-up and appropriate management.
5. Integrate Umbiflow™ into BANC Plus contact. This can be considered as a review contact where the whole pregnancy is reviewed.
6. For implementing and scaling up Umbiflow™ across antenatal care services policy makers and implementers need to make considered decisions on which model for implementation of Umbiflow™ screening would be the most appropriate for their context. A flexible model of implementation should be considered based on the unique circumstances of the catchment area, taking into consideration the screening, referral and transport availability in the area. There are components to consider:
- a. The way Umbiflow™ screening will be done at individual clinics earmarked for Umbiflow™ screening.
 - b. The way in which the follow-up of women with abnormal resistance indices will be accommodated at high-risk clinics at the referral hospitals.
 - c. Transport arrangements to facilitate access for women with abnormal resistance indices to reach the high-risk antenatal care and receive treatment at the referral hospital.
 - d. Consider how the Umbiflow™ equipment will be distributed and managed between clinics.
 - e. Consider Umbiflow™ screening implications for staffing requirements (screen at individual clinics, rotate the equipment, rotate the healthcare professionals screening, screen during antenatal contact, and screen after the antenatal contact).

7. Consideration to resource allocation and improvement of neonatal services and resources. This also involves working together harmoniously between the clinics and hospital obstetrics and neonatal and paediatric department. This also includes stakeholder involvement and management ensuring that appropriate resources are available in neonatal care for improved service provision.
8. Healthcare facilities should continue to implement BANC Plus, and find innovative ways to manage the increased number of contacts and the increased number of women identified with hypertensive disorders in pregnancy. This includes improving access to expert care at primary healthcare levels through creating a next level of expertise. Suggested solutions to create a next level of expertise at primary healthcare level include:
 - a. Training an “advanced antenatal care practitioner” (advanced midwife or doctor) to see the referrals at the primary healthcare clinic once a week. They would decide whether to manage the women further at the clinic or refer to the hospital for antenatal clinic. These practitioners should have direct communication with the hospital and specialists at the hospital.
 - b. Training doctors at the primary healthcare clinics to see the referrals (medium to high-risk women) and decide to manage them at the clinic or to refer to the appropriate hospital.
 - c. Outreach from the hospital obstetrics team by doctors or midwives from the obstetrics department to consult and see women identified with problems at the clinic.
 - d. Outreach from the District Clinical Specialist Teams to see women at the primary healthcare clinics. This can be the advanced midwife or family physician or obstetrician from the district team.
 - e. Telemedicine through a virtual consultation that can be facilitated by the healthcare providers at the clinic and the doctors at the appropriate referral hospital.
9. Antenatal care providers should continue to measure blood pressure at all antenatal contacts, as morbidity and mortality due to hypertensive disorders in pregnancy remains a challenge. Correct diagnosis and appropriate and timely management can decrease adverse events to both mother and neonate.
10. Future research needs to be conducted to determine:

- a. The prevalence of abnormal Doppler low-risk women in other low- and middle-income countries and other countries with high stillbirth rates to ascertain if the reduction in stillbirths can be replicated in other settings. This can be done through a large multicentre randomised trial.
- b. Doppler ultrasound was effective in detecting small for gestational age babies and may be a more effective method of detecting fetal growth restriction than imaging ultrasound, this needs to be researched further to strengthen the narrative.
- c. Analyse the costing of an UmbiflowTM screening implementation programme
- d. Investigate the possible aetiology in the South African context so as to understand why the prevalence of abnormal Doppler and absent end diastolic was so much higher in the South African population.
- e. Investigate the different implementation models to scale up UmbiflowTM screening.
- f. Investigate the different high-risk clinic models improve access for women with abnormal Doppler.
- g. Qualitative research on the view of healthcare providers and women regarding the timing and number of antenatal care contacts.
- h. Qualitative research on the view of healthcare providers and women regarding their user experience with UmbiflowTM screening.
- i. Investigate the health system requirement necessary for successful implementation and whether there are any other effects.

BANC Plus and UmbiflowTM screening has demonstrated a significant impact on identifying the low-risk pregnancy at risk of adverse outcomes. This challenges us to consider a paradigm shift, and move to integrating antenatal care for a comprehensive service that also assesses placental function rather than just measuring fetal size. An integrated and comprehensive antenatal programme will be beneficial for patient experience of care and for maternal and neonatal outcomes and will empower healthcare providers. However, for sufficient BANC Plus with UmbiflowTM integration resources and maternal and neonatal facilities should receive prioritised consideration for improved care and better outcomes.

List of Publications and Addendum

1. Hlongwane TM, Bozkurt B, Barreix MC, Pattinson R, Gülmezoglu M, Vannevel V, Tunçalp Ö. Implementing antenatal care recommendations, South Africa. *Bulletin of the World Health Organization*. 2021; 99(3): 220–227.
<https://doi.org/10.2471/BLT.20.278945> (accessed Oct 10, 2021).
2. Hlongwane TMAG, Cronje T, Nkosi BSS, Pattinson RC. The prevalence of abnormal Doppler's of the umbilical artery in a low-risk pregnant population in South Africa. *EClinicalMedicine*. 2021; 34: 100792.
<https://doi:10.1016/j.eclinm.2021.100792> (accessed Oct 10, 2021)
3. Hlongwane TMAG, Cronje T, Nkosi B, Pattinson RC Preventing antenatal stillbirths: An innovative approach for primary healthcare. Submitted to SAFP
4. Hlongwane TMAG, Cronje T, Nkosi BSS, Pattinson RC. The outcome of absent end diastolic flow in fetuses of clinically healthy pregnant women in South Africa. Submitted to SAJOG
5. Hlongwane TMAG, Bergh AM, Nkosi BSS, Pattinson RC Implementation experiences of UmbiflowTM screening across nine sites in South Africa. For submission

Policy & practice

Implementing antenatal care recommendations, South Africa

Tsakane MAG Hlongwane,^a Burcu Bozkurt,^b Maria C Barreix,^c Robert Pattinson,^a Metin Gülmezoglu,^c Valerie Vannevel^a & Özge Tunçalp^c

Abstract Despite progress in reduction in maternal deaths in South Africa, deaths due to complications of hypertension in pregnancy remain high at 26 deaths per 100 000 live births in 2016. The South African health ministry modified its existing four-visit antenatal care model to align with the World Health Organization's (WHO) 2016 recommendations for the number and content of antenatal care contacts. Implementation of the eight-contact antenatal care recommendations began in April 2017, after adaptation to the national context and nationwide trainings. In this article, we describe the stages of implementation and the monitoring of key indicators. We share lessons, particularly from the important early stages of nationwide scale-up and an analysis of the early results. We analysed samples of maternity case records in four catchment areas in the first year of the updated care model. The mean number of antenatal care contacts among five monthly samples of 200 women increased steadily from 4.76 (standard deviation, SD: 2.0) in March 2017 to 5.90 (SD: 2.3) in February 2018. The proportion of women with hypertension detected who received appropriate action (provision of medical treatment or referral) also increased from 83.3% (20/24) to 100.0% (35/35) over the same period. South Africa's experiences with implementation of the updated antenatal care package shows that commitment from all stakeholders is essential for success. Training and readiness are key to identifying and managing women with complications and developing an efficient antenatal care system accessible to all women.

Abstract in: العربية, 中文, Français, Português and Español at the end of each article.

Introduction

South Africa is a middle-income country with a population of more than 59 million.¹ In 2017, sub-Saharan Africa had the highest estimated maternal mortality ratio worldwide at 542 deaths per 100 000 live births and stillbirths at 28.7 per 1000 total births.² While progress has been made in sub-Saharan Africa, the sustainable development goals and the United Nations' *Global strategy for women's, children's and adolescents' health (2016–2030)* seek to improve on gains and aim to reduce the global maternal mortality ratio to 70 deaths per 100 000 live births.^{3,4} Access to quality antenatal care is crucial to achieve these goals and improve the lives of both mothers and babies.^{5,6} Antenatal care is also a key component of the continuum of care for women, babies and their families. While most women in low- and middle-income countries attend at least one antenatal care visit, the content and quality of these contacts are not standardized.⁷ Therefore, it is necessary to improve antenatal care services and to update indicators that track antenatal care performance.

Evidence of a higher risk of perinatal death associated with four or fewer antenatal care visits prompted the World Health Organization (WHO) to develop a new guideline.⁸ In November 2016, WHO released its comprehensive *Recommendations on antenatal care for a positive pregnancy experience*,⁹ prioritizing person-centred care and well-being as well as prevention of mortality and morbidity.¹⁰ Following these recommendations, in April 2017 the South African health ministry modified its existing four-visit basic antenatal care model to align with the new WHO recommendations including the number of contacts, content of each contact (such as respectful care and clinical enquiry for intimate partner violence) and the basic skills needed for antenatal care.

The nationwide scale-up of South Africa's updated package of care, called Basic Antenatal Care Plus, aimed to improve the quality of antenatal care through the provision of evidence-based interventions across a minimum of eight antenatal care contacts, with an increased number of contacts during the third trimester. The package aims to improve pregnancy care, outcomes and women's experiences, yielding an improvement in screening and detection of pregnancy-related complications and, ultimately, to improve antenatal care quality.¹¹ In this paper we document the adaptation and implementation of the WHO 2016 antenatal care recommendations in South Africa and share some lessons learnt, particularly in the crucial early stages of nationwide scale-up.

Local setting

There are 52 districts in South Africa, with a majority having more than 500 000 inhabitants.¹ Since 2008 South Africa has been implementing a basic antenatal care model to achieve four goal-orientated visits. An audit of the timing and causes of all stillbirths in three of South Africa's provinces (Limpopo, Mpumalanga and Western Cape) from 2013 to 2015 showed that hypertensive disorders of pregnancy and unexplained stillbirths were the most common adverse outcomes.¹² The third trimester was identified as a crucial time, with a peak in stillbirths between 32 and 38 weeks. While the majority (75.5%) of pregnant women in South Africa attended four antenatal care visits in 2016,¹³ due to the extended period in the schedule between 32 and 38 weeks, stillbirths were diagnosed but not being prevented. Additionally, although maternal deaths due to non-pregnancy-related infections fell by 47% (from 59 deaths per 100 000 live births in 2011 to 31 deaths per 100 000 in 2016), deaths due to complications of hyperten-

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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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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 (Umbilflow™) 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: Umbilflow™ 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.

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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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