REVIEW

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Time to re-think prevention of stillbirths in South Africa?

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THE BURDEN OF STILLBIRTHS

Stillbirths reflect care during the third trimester and the intrapartum period.[1] Stillbirths are virtually invisible to the public and most healthcare professionals. As such they are neglected to the great detriment of the families concerned.[2] However, stillbirths remain high, 2.0 million stillbirths occurred worldwide.[2] Ninety-eight percent occur in low and middle-income countries (LMIC).[2] South Africa (SA) is classified as an upper middle-income country, with respect to the stillbirth rate we perform very poorly, ranking 50th of 54 countries and 6th of 7 in Africa[2] compared to similarly classified countries.[2] SA has about 20 000 stillbirths per year and more than twice as many stillbirths as neonatal deaths for babies over one kilogram.[3]

Contrary to perceived wisdom SA has far more antenatal stillbirths compared to intrapartum stillbirths (66% macerated versus, alive on admission 10% and dead-on admission 22% (unknown 2%).[3] Stillbirths classified as unexplained are 46% more common than intrapartum and neonatal deaths due to intrapartum asphyxia and birth trauma combined.[4] The most common causes of antenatal stillbirths are unexplained stillbirths, hypertensive disorders of pregnancy (HDP) and abruptio placentae.[5] Prevention of stillbirths thus needs to focus on antenatal prevention targeting these issues.

Preventing the deaths due to HDP has been relatively straight forward. Local and global data showed an increased risk in perinatal mortality associated with reduced focused antenatal contact model.[5,6] The new antenatal policy of Basic Antenatal Care Plus (BANC Plus) increased contacts and its implementation has led to an increased detection of HDP and subsequent reduction in stillbirths due to HDP.[1,7,8]

The major issue is tackling the issue of unexplained stillbirths. The majority (53.9-59.8%) of stillbirths in SA are classified as unexplained.[3,5,9] Most occur in women regarded as having low-risk pregnancies and undiagnosed small for gestational age (SGA) babies is common in this group.[10] Mahdi et al.[11] demonstrated placental insufficiency and infection are major causes of stillbirths in SA. Placental insufficiency leads to fetal growth restriction (FGR) and SGA babies are often growth restricted thus FGR might be a major cause of the unexplained stillbirths.

Currently, there are no effective clinical tools that detect FGR. 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.[12] Fetal movement counting has also been found to be ineffective.[13] 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.[14] As many as three quarters of babies with FGR are not recognised as such before delivery.[15] In a low-risk pregnancy with a lower threshold of suspicion the detection rate is even lower, at approximately 15%.[16]

The WHO recommendations suggest that all pregnant women should receive an imaging ultrasound to determine or confirm the gestational age.[17] It was hoped that routine imaging ultrasound would be an effective method in helping to detect FGR. 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.[18]

Umbilical artery Doppler as an intervention

Doppler ultrasound of the umbilical artery measures the fetal blood flow through the placenta. Poor fetal blood flow through the placenta leads to ineffective transfer of nutrients and oxygen and correlates well with placental function. It is a measure of placental insufficiency and thus correlates well with FGR.[19] 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.[19] Continuous wave Doppler ultrasound sends a continuous stream of sound waves and reflects any movement through which the sound passes. The umbilical cord is surrounded by amniotic fluid so this creates a sound wave through which the classic signature of the umbilical artery (pulsatile) and umbilical vein (not pulsatile and flowing in the opposite direction) can be observed. This means no imaging ultrasound is necessary to identify the vessel which makes the device considerably less expensive than imaging ultrasound. Pulsed wave Doppler ultrasound is somewhat different in that pulses of waves are sent and by using a range gate and imaging ultrasound different vessels can be identified and studied. This however, makes for a considerably more complex and expensive machine. The umbilical artery Doppler resistance index (peak systolic-end diastolic/peak systolic) decreases with increasing gestational age as the resistance in the tertiary arterioles of the placenta open.[19] Placental insufficiency usually results in a decrease in placental blood flow due to obliteration of the tertiary arterioles and is reflected as a fall in the end diastolic flow and thus a rise in resistance index (RI).[19] This rise in RI is associated with FGR and once absent end diastolic flow (AEDF) (RI=1; end diastolic flow=0) or reversed end diastolic flow (REDF) is detected there is end stage placental disease and is associated with severe adverse perinatal outcomes.[20] AEDF is associated with FGR, neuro-developmental sequelae, chromosomal, structural anomalies and increased perinatal deaths.[21,22]

Umbilical artery Doppler ultrasound has been well studied

in high-risk pregnancies and its use has demonstrated a significant reduction in perinatal mortality.[23] 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 populations.[24] 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.[14] The Delphi consensus on defining FGR includes Doppler abnormalities in their definition.[25]

A low-cost continuous wave Doppler device (Umbiflow™) has been developed by the Council for Scientific and Industrial Research (CSIR) and South African Medical Research Council (SAMRC) in SA.[26,27] Umbiflow™ is a mobile-connected Doppler device that uses a continuous-waveform to detect blood flow within the fetal umbilical cord. It consists of a handheld Doppler probe (transducer) with a universal serial bus (USB) cable that connects to any windows-based notebook on which the necessary Umbiflow™ software is installed.[26] Umbiflow™ measures the RI in the umbilical cord and plots it against the estimated gestational age to identify the fetus at risk for FGR. It also has the option of an integrated 3G card to facilitate a mobile internet connection and the automatic upload of Doppler results to a central server for remote expert support and electronic health record management.[26,27] 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".[26,27,28] 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.[27] Studies have demonstrated that the Umbiflow™ can be operated by nurses and midwives at the primary healthcare centres.[26,27,28] The device has a short learning curve empowering primary healthcare givers and non-specialist providers.[27,28] 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.[27]

Continuous wave Doppler outcomes

Three population-based studies using Umbiflow™ have recently been performed in SA.[28,29,30] All three studies screened women classified as having low-risk pregnancies between 28-34 weeks' gestation and found similar prevalence's of abnormal RI and AEDF of approximately 10% and 1% respectively in SA. Importantly, the prevalence of AEDF is about ten times that reported in other countries, especially the high-income countries.

The Hlongwane et al.[29], study explored fetuses that had AEDF and compared women with fetuses with AEDF to women attending the same clinics who had normal RIs. The AEDF group had a mean birthweight of 2106 grams (±656.4) and 3099.[6] grams (±500.9) in the normal RI group. The AEDF group had significantly more low birthweight babies (71.8%), more SGA neonates (64.4%) and more preterm deliveries (mean GA at delivery 35.6 weeks [SD 3.1]). Of the neonates with AEDF, 38.6% required admission to the neonatal unit. Baseline characteristics for these women are presented in supplementary Table 1 and 2.

The perinatal mortality rate was 91.9/1000 births compared to 9.9/1000 births in the normal RI group. One of the AEDF stillborn neonate had congenital abnormalities of the cardiopulmonary system. Important to note, all these women with AEDF at the time of screening were attending primary healthcare clinics and thought to be healthy, thus the test was detecting a high-risk fetus in a low-risk mother.

Unfortunately, in both the Nkosi et al.[28], and Hlongwane et al.[29] studies some women, whose fetuses had AEDF, declined further management. In the case of Hlongwane et al., 4 of the 5 women declining treatment delivered macerated stillbirths (see supplementary table 2) and in Nkosi et al., 3 of 4 women declining treatment had macerated stillbirths. The natural history of AEDF in the third trimester appears to be a stillbirth. Importantly, there was no increase in the neonatal deaths in both studies, so preventing stillbirths did not transfer potential stillbirths to neonatal deaths. If the women who declined treatment and the fetus with the congenital abnormality are removed from the outcomes of the AEDF group, the perinatal mortality is 35.7/1000 births. This is far lower than the perinatal mortality described in the literature of around 500/1000 births.[31]

Two studies have looked at the impact of screening women classified as having low-risk pregnancies in SA, where screening in total just under 10 000 women has been performed.[28,32] A standard protocol was followed for all women whose fetuses demonstrated an abnormal RI. The protocol is described in detail elsewhere[28, 32] but includes referral to a high-risk clinic, full fetal assessment using imaging ultrasound, and admission, fetal monitoring, and corticosteroids where necessary. In both studies there was a significant reduction in stillbirths when comparing the screened group to women from the same area, same primary healthcare clinics and more than 28 weeks' pregnant who did not have the Umbiflow™ screening. (Hlongwane et al. found a SBR 10.1/1000 births in the screened population and 17.8/1000 births in the unscreened group[32] (RR 0.57, 95% CI 0.29–0.85), and in Nkosi et al.,28 the perinatal mortality rate in the Umbiflow™ screened group was 11.4/1000 births and in the unscreened group was 21.3/1000 births (RR 0.58, 95% CI 0.42 - 0.81). It appears that screening with Umbiflow™ and adhering to the standard protocol of further management is associated with a step change reduction in stillbirths.

AEDF is an indication of end stage placental disease associated with placental insufficiency and severe FGR so undetected FGR is probably a major cause of stillbirth in SA. Given the poor performance of SA with respect to its stillbirth rate compared to other similar countries, and the demonstrated inability to detect FGR antenatally with current methods, screening with Umbiflow™ might be of value if it is associated with a reduction in stillbirths.

The final question is whether screening with Umbiflow™ is scalable to primary healthcare clinics. A costing analysis was performed by Rossouw et al.,[33] who found that compared to estimates of cost and impact of scaling up interventions to save lives of mothers and children in SA[34], the Umbiflow™ is more cost-effective than scaling up clean-birth practices, immediate assessment and stimulation during childbirth, breastfeeding promotion, appropriate complementary feeding, the hygienic disposal of children's stools, the DPT, Pneumococcal, Rotavirus or Measles vaccines, therapeutic feeding (for severe wasting), and antiretroviral treatment.

However, the Umbiflow™ is less cost-effective than scaling up labour and delivery management, neonatal resuscitation, antenatal corticosteroids for preterm labour, antibiotics for preterm rupture of membranes, handwashing with soap, the Hib vaccines, Kangaroo mother care, oral rehydration solution, oral antibiotics, case management of pneumonia in children and PMTCT.[33,34] It has been shown that non-specialist healthcare workers can effectively perform the screening test, that training takes about one week, the results of the test are immediate and the management depending on the result very clear cut, the test takes about 10 minutes and is painless. Furthermore, the results are auditable and quality control is simple as there is a record of each test, so the quality of the waveforms used can be easily assessed. The device can be battery powered and is estimated as ten times less expensive than a portable imaging ultrasound. Studies are underway at present to identify the barriers to full scale-up in a district in SA.

CONCLUSION

In re-thinking our approach to preventing antenatal stillbirths we need to appreciate that the main problem lies antenatally not intrapartum. FGR is a major cause of antenatal stillbirth; we do not have the means currently to detect FGR accurately at primary healthcare clinics; and undetected FGR leads to stillbirths. The seriousness of our failure to detect FGR is illustrated by Hirst et al., who showed that a fetus that has unidentified growth restriction is five times more likely to die than a fetus identified as having FGR.35 Studies in SA have demonstrated that the prevalence of abnormal RI and AEDF is high enough to warrant screening; we can identify the fetus at risk of stillbirth; and with this knowledge act to prevent the stillbirth without increasing neonatal deaths. Perhaps, we should be implementing screening with continuous wave Doppler ultrasound of the umbilical artery at all primary healthcare clinics performing antenatal care to prevent unexplained stillbirths in SA, and that it is cost effective to do so. We owe it to our mothers to enhance a positive pregnancy experience and a positive pregnancy outcome.

Table 1: Demographic and outcome of the UmbiflowTM 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	2 (2.3)	32 (0.6)	
mean weight	2106.8 (±656.4)	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*

Table 2: Perinatal mortality in the AEDF group

GA at Delivery	Birth weight (g)	Delivery Mode	Perinatal outcome	Perinatal outcome
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.

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