RESEARCH ARTICLE

Intrauterine deaths in high-risk pregnancies with normal and borderline umbilical artery Doppler flow velocity waveforms

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Objective. To investigate the use of a personal computer (PC)-based, continuous-wave Doppler device by a trained midwife at the fetal evaluation clinic at a tertiary hospital to assess flow velocity waveforms (FVWs) of the umbilical artery flow in referred women.

Methods. Pregnant women referred for suspected poor fetal growth were evaluated from June 2002 through December 2004. The Umbiflow device (still prototype, developed by CSIR/MRC/Stellenbosch University), consisting of a Pentium 3 PC with an ultrasound transducer plugged into the USB port, was used to analyse the FVW of the umbilical artery. Pregnancies in which the resistance index (RI) was <75th percentile (<P75) were not further evaluated for fetal well-being unless the clinical condition of the mother had changed. Pregnancies with an RI >P75 were followed up according to a specific protocol. Primary endpoints were intrauterine death and intrauterine growth restriction.

Results. Doppler FVWs were assessed in 955 pregnancies. The RI was <P75 in 529 participants (55.4%), between the P75 and P95 percentile in 350 (36.6%) and >P95 in 53 (5.5%). In 23 cases (2.4%) end-diastolic flow was absent or reversed (AREDF). Intrauterine death within 1 week of the test occurred in 1, 4, 0 and 2 women respectively in these four groups, and 16.7%, 34.5%, 54.9% and 65.5% respectively gave birth to infants that were small for gestational age.

Conclusions. Intrauterine death, within 1 week of the test, was extremely rare when the RI was <P75 (0.2%). Relatively more deaths within a week of the Doppler examination occurred in the P75 - P95 group. This group should be regarded as being at high risk and needs careful antenatal surveillance.

Placental insufficiency may precede the birth of a small-for-gestational-age (SGA) infant. In addition, it is associated with an increased risk of intrauterine death, intrapartum fetal distress and neonatal morbidity and mortality.[1-4] Doppler ultrasound assessment of the flow velocity waveforms (FVWs) in the umbilical artery of the fetus with poor growth has been shown to improve perinatal outcome.[5,6] Thornton and Lilford[7] believe that absent or reversed end-diastolic flow (AREDF) velocity is of particular importance as these fetuses are 80 times more likely to die than fetuses where end-diastolic flow velocity is present. Two additional meta-analyses[8,9] confirmed the value of FVWs of the umbilical artery in high-risk pregnancies in identifying the fetus at risk. In addition, in a meta-analysis of 12 randomised control trials, Alfirevic and Neilson[6] demonstrated that the use of FWVs reduced the odds of perinatal death by 38%.

Although it has been shown that the use of Doppler FVW assessment improves perinatal outcome, it is still uncertain how many intrauterine deaths, particularly those due to placental insufficiency, may occur in pregnancies where the FVWs have been regarded as normal, and what the causes of these deaths may be. It should be remembered that abnormal FVWs are not always an indication for immediate delivery as this decision would also depend on other important findings such as the clinical condition of the mother, gestational age and fetal condition. In this regard, monitoring of the fetal heart rate pattern provides valuable information on when to deliver.

Patients and methods

The study was done at the Fetal Evaluation Clinic (FEC) at Tygerberg Hospital (TBH), a tertiary referral hospital in the Western Cape where exclusion of placental insufficiency in cases of poor fetal growth on the symphysis pubis fundus (SF) growth chart and maternal hypertension

are the most common indications for referral. At the FEC, FVWs of the umbilical artery are assessed by an experienced midwife (AMT) with a continuous-wave Doppler device (Umbiflow; still prototype, developed by CSIR/MRC/Stellenbosch University), which consists of a standard personal computer with the ultrasound probe plugged into the USB port. The software has been designed to analyse FVWs, expressing the result as the resistance index (RI). A comparative study at our unit has shown that the accuracy of the Umbiflow compares favourably with that of a well-known commercial continuous wave Doppler machine.[10] Poor SF growth was defined as a measurement below the 10th percentile for gestational age according to the percentile chart for the local population.[11] The nomogram of TBH was used to categorise the RI into four different zones.[12] Further management of the referred pregnant women depended on the RI (Table I).[13]

Table I. Management according to resistance index (RI)

RI management	
<P75	No further tests unless new clinical indication
P75 - 95	Repeat after 2 weeks
	No CTG
	No ultrasound
>P95	Weekly Doppler
	Weekly CTG
AREDF	Admit to hospital
	Daily CTG
	Ultrasound
	Individualise management

<P75 = less than 75th percentile for gestational age; P75 - 95 = between 75th and 95th percentile; >P95 = above 95th percentile; CTG = cardiotocography; AREDF = absent or reversed end-diastolic flow.

Absent end-diastolic flow as the only abnormal finding was only accepted as an indication for delivery after 34 weeks' gestation. Reversed flow as the sole indication for delivery was only applied to viable fetuses, usually beyond 28 weeks' gestation and when the reversed flow was noted at successive examinations. In all the other cases, the non-stress test, ultrasound findings and clinical condition of the mother were considered in the decision about when to deliver. For this study, the medical records of 955 consecutive pregnant women who had delivered between 13 November 2002 and 5 January 2004 were assessed to determine the perinatal outcome. Detailed information was collected on intrauterine deaths at 28 weeks or more by reviewing the antenatal and hospital records of the mother. Gestational ages were preferably determined by an early ultrasound scan, but when this information was not available, the date of the last menstrual period was used or, when this was also unknown, the best clinical judgement. Growth curves of TBH were used for the diagnosis of SGA newborns.[14] Pregnant women were categorised into four different groups according to the RI: group 1 – RI <75th percentile (<P75), group 2 – P75 - P95, group 3 – >P95, and group 4 – AREDF. At the end of the study, the list of intrauterine deaths and abnormal FVWs was compared with the records of the Department of Anatomical Pathology to determine in how many cases an autopsy or histological examination of the placenta had been done.

For statistical analysis the Statistical Package for Social Science (SPSS) version 12 was used. The number and percentage of qualitative variables and the mean and standard deviation (SD) of quantitative data were calculated. Comparisons between the mean values of quantitative variables were calculated using Student's *t*-test, while the chi-square test was used for qualitative data. A 95% confidence interval (CI) was calculated where applicable. All tests of significance used were at the 5% level of significance.

As this was a retrospective study addressing a well-accepted investigation, no informed consent could be obtained. To maintain strict confidentiality, participants are not identified in the results of the analysis and the database is kept secured by two people only.

Results

There were 955 women in the study. Their ages ranged from 13 to 46 years with a mean of 29 years (Table II). Data on 930 newborns were available for analysis. Information for 25 (2.6%) newborns was lost as mothers had moved out of the catchment area or delivered at other hospitals. Birth weights ranged from 496 g to 4 880 g with a mean of 2 668 g. Gestational age at delivery ranged from 25 to 46 weeks. There were 509 deliveries in group 1, 346 in group 2, 53 in group 3 and 22 in group 4 Intrauterine death, between the test and delivery, occurred in 1.96%, 1.73%, 1.89% and 18.18% of the four groups, respectively. These differences were significant when groups 1 and 2 were compared with group 4 (Table III). There were 14 late abortions or terminations of pregnancy, which are included in the number of deliveries (Table III). Mean birth weight and gestational age at delivery also differed significantly between the four groups (Table IV).

There were 21 intrauterine deaths at a gestational age of 28 weeks or more (Table V). These occurred from 1 to 67 days after the last Doppler examination (the fetus that died after 67 days had severe congenital abnormalities – no intervention was recommended, and delivery was at 38 weeks). In 1 of these cases the RI was >P95, in 6 between P75 and P95, and in 10 <P75; there were 4 cases of AREDF. In the <P75 group the cause of death was unknown in 3 cases, maternal diabetes in 3, severe congenital abnormalities in 1, abruptio placentae in 1, and growth restriction and syphilis/growth restriction in 1 each. In the P75 - P95 group, 2 of the deaths were due to abruptio placentae, 2 to unknown causes and 1 each to growth restriction and preterm prelabour rupture of membranes (PPROM). The 1 death in which the RI was above P95 was probably due to growth restriction. In the AREDF group the most likely cause of death was severe placental insufficiency, in 2 cases due to severe pre-eclampsia.

Table II. Epidemiological data on 955 pregnant women who had assessment of Doppler flow velocity waveforms of the umbilical artery

	Age	Gravidity	Parity	BMI
Mean	29	2.9	1.5	28.9
SD	6.8	1.6	1.3	7.3
Median	29.2	3	1	27.5
Minimum	14	1	0	16
Maximum	46	11	8	53.6

BMI = body mass index.

Table III. Resistance index (RI) values in 930 deliveries

	Group 1	Group 2	Group 3	Group 4
RI	<75%	75 - 95%	>95%	AREDF
Total	529	350	53	23
Delivered elsewhere	20	4	0	1
Deliveries	509	346	53	22
Abortion/TOP	2	6	2	4
IUD	10 (1.96%)	6 (1.73%)	1 (1.89%)	4 (18.18%)

TOP = termination of pregnancy; IUD = intrauterine death; AREDF = absent/reversed end-diastolic flow.
1 and 2 v. 4: p=0.0000.

Table IV. Mean birth weights and gestational age (GA) at delivery

	Group 1	Group 2	Group 3	Group 4
Mean birth Weight (g)	2 851*	2 572*	2 024*	1 135*
SD	683	736	832	568
Median	2 907	2 635	2 022	1 058
Minimum	725	684	684	496
Maximum	4 566	4 880	3 832	2 840
Mean GA (wks)	37.5*	37.3*	35.4*	31.2*
SD	2.7	3.1	3.7	3.8
Median	38	38	36	30
Minimum	25	28	28	26
Maximum	44	46	42	41
Ultrasound available	499	336	51	160
SGA	83 (16.7%)	116 (34.5%)	28 (54.9%)	10 (65.5%)

1 v. 2: p=0.000.
2 v. 3: p=0.005.
3 v. 4: p=0.592.

*$p \leq 0.001$ between all groups.
SGA = small for gestational age.

Seven intrauterine deaths occurred within 7 days or less of the Doppler examination (Table VI). Only 1 of 10 intrauterine deaths in group 1 (509 deliveries) occurred within 7 days of the Doppler test (0.2%). The cause of death was unknown. The remaining 6 intrauterine deaths within 7 days occurred in groups 2 (4 deaths) and 4 (2 deaths). In group 2, 1 death was due to a complete abruption and 2 deaths were associated with PPROM; the cause of death was unknown in the remaining case. In group 4 the causes of death were severe asphyxia and placental insufficiency. Three of these 7 fetuses had weights below the 10th percentile. No autopsy or histological examination of the placenta was done after any of the stillbirths or in any case of abnormal FVWs.

Discussion

The fact that 55.3% of high-risk mothers (mostly with poor fetal growth according to the SF chart, or hypertension) had normal FVWs of the umbilical artery reflects the unreliability of clinical findings in diagnosing poor placental function. We found AREDF to be associated with a poor outcome, intrauterine death occurring in 18.18% of cases. This association

Table V. Cause of intrauterine deaths at 28 weeks' gestation or later

	<P75	P75 - P95	>P95	AREDF
Resistance index	0	0	0	2
Pre-eclampsia/GR	1	1	1	2
GR	1	0	0	0
Syphilis/GR	3	0	0	0
Diabetes	1	0	0	0
Congenital abnormalities	1	2	0	0
Abruption	0	1	0	0
Infection/PPROM	3	2	0	0
Unknown	10	6	1	4

<P75 = less than 75th percentile for gestational age; P75 - P95 = between 75th and 95th percentile; >P95 = above 95th percentile; GR = growth restriction; PPROM = preterm prelabour rupture of membranes; AREDF = absent/reversed end-diastolic flow.

has been found in previous studies, particularly when the infant was growth restricted,[15-17] and our study also supports the finding at a secondary hospital of a high perinatal mortality rate in cases of AREDF (41.7% in comparison with 13.2% in cases with an RI <P75).[18] In addition, our results confirm a previous observation that abnormal findings on Doppler velocimetry is the best predictor of adverse perinatal outcome.[19] Diabetes could have played a role in 3 intrauterine deaths. All these cases were in group 1, where the RI was <P75. Although none of the Doppler assessments in the IUDs with diabetes was done within 7 days of fetal death, it is important to note that surveillance of diabetic pregnancies by Doppler velocimetry is of little use unless the pregnancy is complicated by fetal growth restriction or hypertension.[20,21]

Three of the intrauterine deaths were caused by abruptio placentae. One occurred in group 1 and 2 in group 2, 1 of the latter within 7 days of the Doppler test. Although abruptio placentae is associated with growth restriction,[22] a case control study in patients hospitalised for severe pre-eclampsia did not show more abnormal RIs in mothers who developed abruptio placentae.[23]

Two intrauterine deaths were associated with PPROM. As fetal oxygenation may change rapidly in cases of chorioamnionitis, it is unlikely that umbilical artery FVWs in these cases could have given sufficient warning that the fetus was at risk. On the other hand, the combination of ruptured membranes and borderline FVWs may have indicated more frequent fetal assessments, which could have detected fetal risk much earlier.

As Doppler FVWs of the umbilical artery were used as a screening test in referred pregnancies to exclude possible placental insufficiency, no further tests were done when the initial RI was normal unless there was a change in the mother's clinical condition. There were 10 intrauterine deaths in women with a normal RI. No apparent cause could be found in 3 cases. One of these deaths was at 32 weeks, within 7 days of the Doppler examination. The infant weighed 2 088 g, and on clinical examination no obvious cause could be detected. Intrauterine death within a week of a normal Doppler examination is therefore extremely unlikely.

More intrauterine deaths within a week occurred in the borderline group 2 than in any of the other groups. At present the policy is to repeat the Doppler FVW after

Table VI. Intrauterine deaths within 7 days after the Doppler examination

Doppler result	Test-IUD interval (d)	Gestational age (wks)	Birth weight (g)	Weight <10th percentile	Cause
RF	1	33	1 092	Yes	Severe asphyxia
AF	7	29	496	Yes	Placental insufficiency
P75 - P95	5	35	2 184	No	100% abruption
P75 - P95	6	33	1 425	Yes	PPROM, Chr H
P75 - P95	5	39	2 964	No	Unknown
P75 - P95	3	30	1 998	No	PPROM
<P75	7	32	2 088	No	Unknown

IUD = intrauterine death; RF = reversed flow; AF = absent flow; P75 - P95 = between 75th and 95th percentile for gestational age; <P75 = less than 75th percentile; PPROM = preterm prelabour rupture of membranes; Chr H = chronic hypertension.

2 weeks in women with an RI between P75 and P95. Because of the increased risk of intrauterine death in this group, it is advised that the follow-up visit should be within 1 week and that the Doppler examination should be complemented by other tests for fetal wellbeing such as the non-stress test.

It is a defect of the study that no histological examination of the placenta was done in cases where the RI was abnormal and that no autopsy or histological examination of the placenta was requested after stillbirths. Unfortunately this reflects the realities we face in developing countries, especially those with a high HIV prevalence, where other health care matters receive priority. However, it is essential that future studies address this major defect. It is also recommended that future studies be prospective in order to assess the predictive values of abnormal uterine artery FVWs and abnormal biochemistry such as low pregnancy-associated plasmaprotein-A or elevated maternal serum alpha-fetoprotein,[24,25] as the primary aim is to identify specific causes of stillbirths and to learn more about the underlying mechanisms. It could also be regarded as a defect that the underlying causes of the growth restriction in SGA infants are not given. However, the aim of the study was to determine the causes of fetal death.

It is generally accepted that the use of umbilical artery Doppler FVWs improves the management of pregnancies with fetal growth restriction.[26,27] In addition, this investigation has been shown to be superior to non-stress tests in that it is associated with fewer caesarean sections.[28] However, a slight possibility of unexpected fetal death still exists. Some of these deaths were attributed to probable causes, but some causes remained unknown. Many stillbirths from conditions such as abruption, placental insufficiency and pre-eclampsia are related to markers of placental insufficiency in early pregnancy.[29] We are far from knowing the basic mechanisms of poor placental development, and even further from being able to prevent it. In order to reduce perinatal mortality it is therefore essential to screen high-risk pregnancies with Doppler FVWs of the umbilical artery to exclude fetal jeopardy. Patients with borderline placental insufficiency should be carefully managed as they have higher intrauterine death rates than those with normal Doppler FVWs.

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