

Early detection of poor fetal prognosis by serial Doppler velocimetry in high-risk pregnancies

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Summary

Fifty-three high-risk pregnancies were followed up serially with Doppler velocimetry of the umbilical artery and uterine vessels from early on to investigate whether abnormalities in Doppler waveforms can predict the outcome of pregnancy accurately before other clinical signs develop. Results of Doppler velocimetry were withheld from the clinicians managing the patients. When the absence of end-diastolic velocities was first detected (in 13 fetuses) (AEDV group) there was no clinical difference between these pregnancies and those in which end-diastolic velocities were present (EDV group). Nine of the 13 fetuses with AEDVs died, compared with 3 of 40 with EDVs ($P < 0,0001$). In deaths associated with AEDVs, the latter were detected a median of 5,5 (range 3 - 11) weeks before death and are present from the first Doppler examination. In the 4 fetuses with AEDVs that survived, the AEDVs were not persistent. The only significant association of Doppler velocimetry of the uterine vessels was with proteinuric hypertension ($P < 0,05$), but the prediction was not strong enough to be of clinical value. Persistent AEDVs of the umbilical artery are an accurate predictor of poor fetal outcome and occur before other clinical signs of impending problems.

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Serious obstetric complications such as pre-eclampsia and intra-uterine growth retardation probably result from poor placentation.¹ Insufficient development of the placental vasculature or fibrosis and destruction of the tertiary villi is characterised by increased resistance in the umbilical artery and hence reduced diastolic flow.² This abnormal blood flow can be detected with Doppler velocimetry. For the first time the clinician has the chance to study the utero- and fetoplacental circulation easily and non-invasively in large numbers of patients. Abnormal umbilical artery flow velocity waveforms (FVWs) have been associated with growth retardation, fetal distress and perinatal death,³ and abnormal uterine vessel FVWs have been associated with growth retardation and proteinuric hypertension.^{4,5} The changes in the FVWs may precede any clinical evidence of problems.³⁻⁵ Consequently, serial Doppler velocimetry, from early in pregnancy, may identify patients at risk of obstetric complications related to abnormal blood flow before any other investigation. If true, this may create a 'therapeutic window' enabling selective intervention in these pregnancies.

A cohort analytic study was performed on women at high risk of obstetric complications to ascertain whether early serial

Doppler velocimetry of the umbilical artery and uterine vessels can predict the outcome of pregnancy accurately and whether these changes occur before other clinical signs.

Methods

Women at high risk of obstetric complications who book at or are referred to Tygerberg Hospital are transferred to a special care antenatal clinic. The most common reasons for transfer are repeated pregnancy losses or previous severe proteinuric hypertension before 34 weeks' gestation. Women transferred to the clinic before 28 weeks were asked to participate in the study. If they agreed, Doppler velocimetry of the umbilical artery and uterine vessels was performed every 4 weeks from 16 to 28 weeks and fortnightly thereafter. If the patient was admitted to hospital, Doppler velocimetry was performed weekly.

The measurements were performed by specially trained medical personnel. Velocity waveforms were obtained with a 4 MHz continuous-wave Doppler ultrasound instrument and analysed with a spectrum analyser (Doptek 9000; Doptek, Chichester, UK). A thump filter of 200 Hz was used throughout. All examinations were performed with the patients tilted slightly on the left side. The umbilical artery was identified by its characteristic appearance. These FVWs were only recorded if the umbilical vein was clearly visible and when the pattern was stable, indicating fetal apnoea and absence of fetal activity. If end-diastolic velocities were found to be absent (AEDV group), multiple areas on the patient's abdomen were examined to confirm that no Doppler shift at end-diastole could be detected in the umbilical artery. If any FVWs with end-diastolic velocities (EDVs) were detected, these were used for analysis. The uterine vessel was also identified using its characteristic FVWs. Where possible, readings on both sides of the uterus were obtained. For each vessel, the resistance index (RI) was calculated from five consecutive waveforms and the mean result determined. An abnormal RI for the umbilical artery was regarded as greater than the 95th centile on curves established for our population.⁶ An abnormal uterine vessel RI was regarded as being greater than 0,58.⁷

The Doppler velocimetry results were withheld from the managing clinicians (R.C.P. and A.B.). The data from every pregnancy were collected after each antenatal visit and the neonatal data were collected while the baby was still in hospital. Each patient was managed according to standard protocols relating to her specific problem. The clinical signs used to determine fetal jeopardy were a decrease in the symphysis-fundus measurement of the uterus, decreased perception of fetal movements, and a deterioration of the mother's clinical condition (for example, a rise in the blood pressure or onset of proteinuria).

Hypertensive conditions were defined according to Davey and MacGillivray.⁸ Light-for-gestation babies were defined as weighing less than the 3rd centile for gestational age using the growth curves of Yudkin *et al.*⁹ All patients had an ultrasound examination to confirm dates and exclude congenital abnormalities between 16 and 20 weeks' gestation. Where there was a discrepancy of more than 2 weeks between the ultrasound estimation of gestation and gestation according to the last nor-

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mal menstrual period, the former was used. The ultrasound scan was only repeated if indicated by decreased symphysis-fundus growth.

The data were analysed using the χ^2 -test (with Yates's correction), or Fisher's exact test where the numbers were small, to compare proportions, and Student's *t*-test for normally distributed continuous variables. A value of $P < 0,05$ was regarded as significant. To estimate the value of Doppler velocimetry of the umbilical artery and uterine vessels as screening tests the sensitivity, specificity and positive predictive value with an overall assessment of the test expressed by means of the kappa index¹⁰ were calculated. Kappa combines the predictive power of the test with the prevalence of the disease in the study population. Kappa values below 0,4 represent results that are no better than chance alone, values of 0,40 - 0,75 a test moderately better than chance, and values more than 0,75 an excellent screening test.

The study was approved by the Tygerberg Hospital Ethics Committee.

Results

From July 1987 to August 1989, serial Doppler velocimetry was performed on 50 women in 53 pregnancies. In all, these women had had 157 pregnancies and only 30 of their babies had survived.

When AEDVs were first detected, there was no clinical difference between these pregnancies and those in which EDVs were present (Table I). All patients had a normal ultrasound scan between 16 and 20 weeks and the amniotic fluid was regarded as normal.

TABLE I. PREVIOUS OBSTETRIC HISTORY AND CLINICAL CONDITION IN THE AEDV AND EDV GROUPS AT FIRST DOPPLER VELOCIMETRY

| | AEDV (N = 13) | EDV (N = 40) |
|--|------------------|-----------------|
| Previous obstetric history | | |
| Severe proteinuric hypertension < 34 weeks | 5 (38%) | 14 (35%) |
| Recurrent mid-trimester abortions | 4 (31%) | 11 (28%) |
| Two previous abruptio placentae | — | 6 |
| Severe IUGR | 2 | 3 |
| Other | 2* | 5† |
| Age (yrs) (mean ± SD) | 28,5 ± 4,7 | 28,9 ± 5,5 |
| Parity | 1 (0 - 2) | 1 (0 - 4) |
| Gravidity | 3 (0 - 5) | 3 (0 - 8) |
| Gestational age, first Doppler study (wks) | 20 (15 - 26) | 22 (14 - 26) |
| Hypertensive | 7 (54%) | 18 (45%) |
| Antihypertensive therapy | 4 (31%) | 8 (20%) |
| Proteinuria | 3 | 1 |

*Primary renal disease (1 patient), severe early hypertension (blood pressure persistently > 160/110 mmHg in the first trimester) (1).

† Systemic lupus erythematosus (2 patients), chronic active hepatitis (1), early severe hypertension (1), primary renal disease (1).

IUGR = intra-uterine growth retardation.

4 - 223). The baby in the AEDV group whose death was due to proteinuric hypertension was born to a woman with chronic hypertension and neurofibromatosis, who suddenly developed severe proteinuric hypertension at 26 weeks' gestation and required delivery for maternal reasons. The initial Doppler velocimetry had been normal, but just before termination of the pregnancy AEDVs were detected. In the 8 cases in which death was associated with severe intra-uterine growth retardation, AEDVs were detected at the first Doppler examination at a median gestation of 20 weeks (range 19 - 25 weeks) and persisted in all. In these cases death occurred at a median gestation of 27,5 weeks (range 26 - 29 weeks), a median of 5,5 weeks (range 3 - 11 weeks) from first detection. Six babies died *in utero* and 2 neonatally; the latter were delivered for fetal distress at 29 weeks' gestation, and weighed 498 g and 705 g. Both died within 48 hours owing to complications of ventilation. Four babies in the AEDV group survived; in these cases the AEDVs had not been persistent. In 2 they were detected at the first examination (at 16 and 24 weeks respectively), but subsequently the resistance indexes were always normal and the infants were pre-emptively delivered at 35 and 37 weeks respectively. In the 3rd case AEDVs were detected initially but the waveforms became normal (at 26 weeks' gestation) at the same time as the mother developed gestational diabetes. The abnormality reappeared when she developed superimposed pre-eclampsia at 29 weeks' gestation. Delivery was performed for fetal distress at 31 weeks. In the remaining case AEDVs were detected at the first examination at 20 weeks but waveforms were normal on subsequent examinations until the mother developed superimposed severe pre-eclampsia at 29 weeks, when the abnormality reappeared and delivery was performed for fetal distress at 30 weeks.

In 38 pregnancies serial Doppler velocimetry of the umbilical artery consistently demonstrated EDVs. Only 1 of these babies died, owing to complications of probable Hirschsprung's disease at 38 days. The remaining 2 mothers only had one Doppler examination each, because they aborted owing to cervical incompetence before follow-up examinations could be performed. They presented in advanced labour, at 20 and 26 weeks' gestation respectively, after complaining of minimal lower abdominal pain and delivered live fetuses shortly thereafter; the infants did not survive.

The value of Doppler velocimetry of the umbilical artery in predicting poor pregnancy outcome was as follows: sensitivity 75%, specificity 90%, positive predictive value 69%, and kappa index 0,63. If pregnancy wastage and fetal distress are combined the sensitivity was 69%, specificity 95%, positive predictive value 85% and kappa index 0,67.

Nine of the 13 babies in the AEDV group weighed less than the 3rd centile, but this applied to only 3 of 39 in the EDV group ($P < 0,0001$; odds ratio 39; 95% confidence limits 5 - 372) (the baby with EDVs who aborted at 20 weeks' gestation was not included in this analysis).

There was no significant association between Doppler velocimetry of the uterine vessels and pregnancy loss, pregnancy-induced hypertension, and light-for-gestational-age babies. However, there was a significant association with proteinuric hypertension, with 6 of the 7 patients who developed proteinuric hypertension having an abnormal result; however, 14 women who did not develop proteinuric hypertension also had an abnormal result ($P = 0,014$). In this population the sensitivity was 86%, the specificity 67%, the positive predictive value 30% and the kappa index 0,29.

Discussion

In this very-high-risk population, persistent AEDVs of the umbilical artery were the earliest sign of fetal compromise

The pregnancy losses are shown in Table II. There was a significant association between AEDV of the umbilical artery and pregnancy loss; 9 of the 13 fetuses in the AEDV group died, compared with 3 of 40 in those in which EDVs were present ($P < 0,0001$, odds ratio 28, 95% confidence limits

TABLE II. PREGNANCY LOSSES

| Gestational age (wks) | Birth weight (g) | Doppler velocimetry | Centile | Primary cause of death |
|-----------------------|------------------|---------------------|---------|--------------------------|
| 25 | 440 | AEDV | < 3 | Severe IUGR |
| 26 | 400 | AEDV | < 3 | Severe IUGR |
| 27 | 300 | AEDV | < 3 | Severe IUGR |
| 28 | 480 | AEDV | < 3 | Severe IUGR |
| 28 | 470 | AEDV | < 3 | Severe IUGR |
| 29 | 705 | AEDV | < 3 | Severe IUGR |
| 29 | 498 | AEDV | < 3 | Severe IUGR |
| 29 | 300 | AEDV | < 3 | Severe IUGR |
| 26 | 700 | AEDV | < 50 | Proteinuric hypertension |
| 20 | 300 | EDV | < 50 | Incompetent cervix |
| 26 | 880 | EDV | < 50 | Incompetent cervix |
| 33 | 1 485 | EDV | < 10 | Hirschsprung's disease |

IUGR = intra-uterine growth retardation.

and were a very good predictor of poor fetal outcome. This finding is supported by numerous authors.¹¹⁻¹³ Babies with persistent AEDVs born at less than 30 weeks have a particularly poor outcome, as illustrated by this study and others.^{12,13} Mires *et al.*¹⁴ have hypothesised that when AEDVs are detected it may be too late to improve the prognosis by aggressive intervention, because asphyxia has already occurred. In our study this was probably the case in 8 pregnancies, since the AEDVs were persistent and were detected on entry to the study. However, in some situations the pattern can revert to normal, as found in this study and in others,^{15,16} suggesting that permanent damage has not taken place in all placentas and manipulation of the blood flow might help some fetuses. Perhaps low-dose aspirin¹⁷ or allenestronyl¹⁸ may be of use. The observation that umbilical artery Doppler velocimetry changes before other clinical signs appear therefore creates a 'therapeutic window' that may be of clinical use.

The fetuses in the study with persistent EDVs had good outcomes. This has also been observed in babies who are light for gestational age.¹⁹ The exceptions in our study were the cases of cervical incompetence and Hirschsprung's disease. Blood flow abnormalities are not associated with these conditions, and Doppler velocimetry would obviously not be able to predict these problems. A fetus with EDVs of the umbilical artery has a good prognosis, and the mother can therefore be reassured that the outcome of pregnancy is likely to be favourable. It may also encourage the clinician to regard the fetus as normal and discourage unnecessary intervention.

Caution must be exercised in extrapolating these findings to the general population. The mothers in our study group were at very high risk, with a high prevalence of pregnancy wastage, light-for-gestational-age babies and proteinuric hypertension. In a general population the prevalence of these conditions would be lower, possibly making the test less useful for screening because the false-positive results might be more numerous. However, this information could form the basis for a study screening a general population with Doppler velocimetry at the time of routine ultrasound to ascertain whether early AEDVs of the umbilical artery are a clinically useful sign.

The association between abnormal findings on Doppler velocimetry of the uterine vessels and proteinuric hypertension has been shown previously,^{4,5} and these workers also found low kappa values. Perhaps the reason for the latter is uncertainty as to which vessel is being examined. Hanretty *et al.*²⁰ have shown that a normal uterine artery has a similar pattern to that of an abnormal arcuate artery. Bewely *et al.*²¹ have demonstrated that the uterine blood flow is complicated and single readings or readings on both sides of the uterus are not

sufficient. Gudmundsson *et al.*²² studied the reproducibility of the FVWs recorded from the umbilical artery and the arcuate arteries on the right and left side of the placenta and found that the umbilical FVWs are reproducible but the arcuate artery FVWs were limited by the wide variation of Doppler signals. For these reasons we do not think that examining the uterine vessels is worth while at this stage.

Although serial Doppler velocimetry of the umbilical artery is promising, further studies, preferably randomised controlled trials, are needed to assess its place in clinical management.

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Hypertension, proteinuria and azotaemia in diabetes

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Summary

The prevalence of hypertension was evaluated in 479 white subjects with diabetes, according to the type of diabetes and the presence of persistent proteinuria as a marker for diabetic nephropathy. Hypertension was uncommon in 178 insulin dependent diabetic subjects without proteinuria (5%) (mean age $25,0 \pm 12,5$ years), but occurred in 23% of 58 patients with proteinuria (mean age $28,9 \pm 14,1$ years) and in 90% with azotaemia ($P < 0,00001$). Among patients with non-insulin-dependent diabetes hypertension was found in 25% of 170 without renal disease (mean age $48,0 \pm 10,3$ years) and in 53% of 53 (mean age $51,4 \pm 13,0$ years) with proteinuria ($P = 0,0002$). We conclude that the prevalence of hypertension among subjects with diabetes depends on the type of diabetes, age, and the presence and severity of diabetic renal involvement.

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Arterial hypertension is frequently associated with diabetes mellitus. While there is some evidence that diabetic microvascular complications are aggravated by hypertension,^{1,2} much if not all of the increased rates of cardiovascular disease and premature mortality seen in populations with both type I and type II diabetes can be attributed to the coexistence of hypertension with the diabetes. The role of other cardiovascular risk factors, such as smoking and hyperlipidaemia, are less clear cut.³⁻⁷ The prevalence of hypertension in diabetic populations has been a matter of controversy for over 70 years, with estimates ranging from 10% to 80%.⁸ The problems in defin-

ing the prevalence of hypertension in diabetes involve the definitions of hypertension and of diabetes (whether type I or type II), the source of the diabetic and control populations and their matching for sex, age, race and degree of obesity,⁹⁻¹¹ and the presence of renal disease. Because of its clinical importance, we have assessed the prevalence of hypertension among 479 patients attending the Diabetes Clinic at Johannesburg Hospital over a 3-month period, with specific reference to the type of diabetes, age, the use of insulin in older patients, and to the presence of renal disease.

Patients and methods

All 479 white patients attending the Adult and Adolescent Diabetes Clinics at the Johannesburg Hospital in the period September - December 1985 were studied. The following data were collected: sex; age; age at diagnosis and type of diabetes; blood pressure; treatment for hypertension; the presence of proteinuria (Albustix positive); and serum creatinine levels. Insulin-dependent diabetes mellitus (IDDM) was defined as diabetes with age of onset less than 35 years and requiring insulin from diagnosis; non-insulin-dependent diabetes mellitus (NIDDM) was defined as diabetes with diagnosis after the age of 35 years, and was further subdivided into those who were treated with diet, with or without oral hypoglycaemic agents, or with diet and insulin. Hypertension was defined as a systolic blood pressure over 140 mmHg and/or diastolic blood pressure over 90 mmHg (Korotkoff V) in subjects aged under 30 years, and a systolic blood pressure over 160 mmHg and/or diastolic blood pressure over 90 mmHg in those older than 30 years, on 3 successive clinic visits, or if the patient was already on antihypertensive treatment. These relatively low levels of blood pressure were used to define hypertension because of the greater impact of a raised blood pressure in diabetic compared with non-diabetic populations.³⁻⁷ A serum creatinine level greater than 120 $\mu\text{mol/l}$ was considered elevated. The prevalence data from a population survey of blood pressure among urban white South Africans¹² was used for comparison.

Data are expressed as mean \pm SD. The χ^2 -test was used in the statistical analyses.

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