

Uterine artery Doppler in the investigation of pregnancies with raised maternal serum alpha-fetoprotein

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Summary. Uterine artery flow velocity waveforms (FVW) were obtained prospectively by continuous wave Doppler at 18–22 weeks gestation from 98 women with an unexplained elevation in maternal serum alpha-fetoprotein (MSAFP). A notch in either the left or right uterine artery FVW was present in 18 pregnancies of which seven resulted in perinatal death and six in the birth of very immature and/or severely growth retarded babies. Conversely, in 66 of 80 pregnancies the absence of a notch was associated with the livebirth of an infant beyond 32 weeks gestation, with a birthweight above the 5th centile. It is suggested that the presence of a notch in the uterine artery FVW is a good predictor of poor perinatal outcome.

Measurement of maternal serum alpha-fetoprotein (MSAFP) is an established screening method for neural-tube defects (NTD) (UK Collaborative Study 1977). More recent emphasis on low MSAFP has resulted in its use for the prediction of trisomy 21 (Schoenfeld *et al.* 1987). A third possible use for MSAFP has arisen from reports that high levels in the absence of fetal malformations, incorrect dating, and multiple pregnancies are associated with an increased risk of perinatal death, preterm delivery and intra-uterine growth retardation (IUGR). The reported perinatal mortality is 3.5–16.7%, while the rate for low birthweight (<10th centile) is as high as 33.3% and that for preterm (<37 weeks)

delivery as high as 26% (Table 1) (Hamilton *et al.* 1985; Gordon *et al.* 1978; Wald *et al.* 1977; Leggc *et al.* 1985; Mwambingu 1985).

Perinatal death, IUGR, and immaturity have also been associated with abnormal Doppler uterine artery flow velocity waveforms (FVW) (Campbell *et al.* 1983, 1986; Fleischer *et al.* 1986). In this study we investigated both the uterine artery resistance index (RI) and the presence or absence of an early diastolic notch on the uterine artery FVW for their ability to predict poor perinatal outcome in pregnancies with an unexplained elevation of MSAFP.

Patients and methods

Uterine artery FVW were obtained prospectively by continuous-wave Doppler at 18–22 weeks gestation from 98 women with elevated MSAFP levels and in whom detailed ultrasound scans had shown singleton fetuses with no malformations. All the women were referred from other hospitals for ultrasound examination because the 16-week MSAFP level, as determined by their reference ranges, was >2.5

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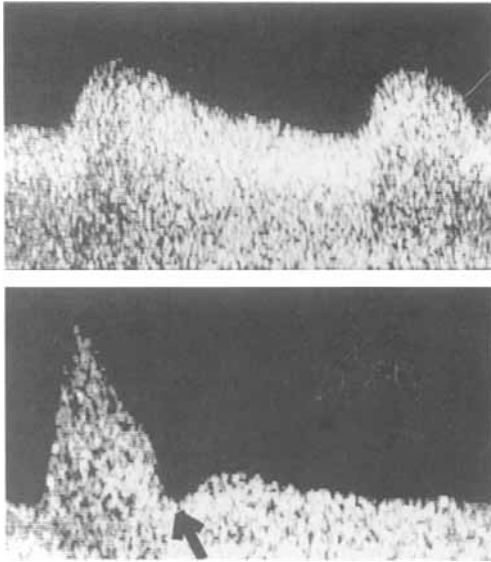


Fig. 1. Flow velocity waveform of the uterine artery from a normal pregnancy (top) and one with unexplained elevation of maternal serum alpha-fetoprotein (bottom); in the latter there is a notch in early diastole (arrow).

multiples of the median (MoM). The exact level of MSAFP and the extent of further local pre-selection of the women could not be defined. Gestational age was determined from the menstrual data and confirmed by ultrasound measurements at the referring hospitals.

In our unit the maternal height and weight were measured and an ultrasound examination was performed for exclusion of fetal malformations, assessment of amniotic fluid volume, and fetal biometry. Oligohydramnios was diagnosed when the largest measurable vertical pool of fluid was ≤ 2 cm.

With the woman in the semi-recumbent position, the uterine artery FVW was recorded by an experienced operator using continuous-wave Doppler (Doptek Ltd, Chichester, UK). Characteristic FVW were recorded from both the right and left uterine arteries by directing the transducer along the lateral wall of the uterus at a level 2–3 cm below the anterior superior iliac spine. The presence or absence of a notch was noted (Fig. 1), and the RI (peak systolic frequency – end diastolic frequency/peak systolic frequency) was calculated and the highest value recorded.

Of the 98 women scanned at 18–22 weeks, 53 had further Doppler studies at 24–26 weeks ges-

tation. These women were unselected as they were not informed of the Doppler findings and returned only if it was convenient. Likewise, the results of the Doppler studies were not given to the managing obstetricians. The gestational age at delivery, infant survival, birthweight and gender were obtained from the referring hospitals and were used, together with maternal height, weight, and parity data, to calculate the birthweight centile (Altman & Coles 1980).

Additionally, 85 pregnant women were recruited from the King's College Hospital antenatal clinic to form a reference range for uterine artery RI values at 18–22 weeks gestation. In each woman both uterine arteries were examined and the highest RI was used for further analysis. Inclusion criteria were a normal MSAFP level and an ultrasound scan showing a normal singleton pregnancy. Of these 85 pregnancies, 79 ended in normal term deliveries and from this group a normal reference range (mean and 95% CI) was generated.

In the normal pregnancies, regression analysis was used to describe the association between uterine artery RI and gestation. In the pregnancies with raised MSAFP, data were analysed using contingency tables, and the predictive ability of the uterine artery notch to detect any of the complications was calculated in terms of the sensitivity, specificity, and predictive values of a positive and negative test. Fisher's exact test was used to estimate the significance of any association between poor outcome and the presence of a uterine artery notch for the 98 women examined at 18–22 weeks gestation and for the subgroup of 53 women who were studied again at 24–26 weeks gestation.

Results

Normal pregnancies

In the 79 normal pregnancies with term deliveries of appropriate-for-gestational-age infants, the uterine artery RI decreased significantly with gestation ($n = 79$, $r = -0.226$, $P < 0.05$, constant = 1.105, slope = -0.024 , residual SD = 0.114), in five of the records (6%) notches were noted in the FVW.

Pregnancies with raised MSAFP

Of the 98 pregnancies examined at 18–22 weeks gestation, 14 (14%) resulted in perinatal death, while of the remaining 84 livebirths, 21 (25%)

Table 1. Reported experience of association between unexplained MSAFP elevation and perinatal complications

Author (year)	<i>n</i>	Entry criteria†	MSAFP level	Low birthweight* (%)	Preterm birth** (%)	PNM (%)
Gordon <i>et al.</i> (1978)	80	U	>95th	6.3	7.5	3.8
Hamilton <i>et al.</i> (1985)	86	U	>2.5 MoM	20.9	20.9	3.5
Hamilton <i>et al.</i> (1985)	100	U	Repeat normal >2.5 MoM ×2	25.0	26.0	8.0
Wald <i>et al.</i> (1977)	94	U	>3.0 MoM	22.0	24.0	4.3
Legge <i>et al.</i> (1985)	30	U	>2.0 MoM	33.3	26.7	16.7
Mwambingu (1985)	31	U	>2.5 MoM or >97th×2	25.8	32.2	9.7
Mwambingu (1985)	98	U	>2.5 MoM or >97th×1	8.2	11.2	1.0
Present study	98	R	>2.5 MoM	20.2	25.0	14.3

MSAFP, Maternal serum alpha-fetoprotein.

PNM, Perinatal mortality.

*Defined as <10th centile birthweight or ≤ 2.5 kg in the study by Wald *et al.* (1977).

**Defined as gestational age at delivery <37 weeks or <36 weeks in the study by Gordon *et al.* (1978).

†U, Unselected; R, referred.

were born at ≤ 37 weeks gestation and 17 (20%) were ≤ 10 th centile in birthweight. These results are compared with previous studies in Table 1.

The RI values were >97.5th centile of our reference range in only 3 of the 27 (11%) pregnancies with poor perinatal outcome (perinatal death or livebirth ≤ 32 weeks or birthweight ≤ 5 th centile).

At the 18–22 week scan, oligohydramnios was noted in seven pregnancies and in five of these the fetal head and abdominal circumferences were <2.5th centile of our reference ranges. All seven pregnancies resulted in perinatal deaths. An additional three women with normal amniotic fluid volumes had fetal head and abdominal circumferences <2.5th centile; however, these pregnancies were redated and all had normal outcomes. Doppler studies demonstrated a notch in the FVW from either the left or right uterine artery in 18 pregnancies of which seven resulted in intrauterine or neonatal death; three of these were associated with oligohydramnios. Therefore, the presence of a uterine artery FVW notch or oligohydramnios correctly predicted 11 of the 14 (79%) perinatal deaths.

In 11 of the 18 pregnancies with a FVW notch the pregnancies resulted in livebirths (Table 2);

however, six of these infants were very preterm (<32 weeks) and/or growth retarded (<5th centile birthweight). Thus, of the 18 pregnancies with a uterine artery notch, 13 (72%) were associated with perinatal complications. Conversely, 66 of the 80 pregnancies with absent notches resulted in livebirths, at >32 weeks gestation with birthweights >5th centile (negative predictive value 82.5%; Table 2).

The relation between the presence of a uterine artery notch and perinatal outcome for the 53 patients assessed again at 24–26 weeks is shown in Table 2. None of the pregnancies with a normal uterine artery FVW at 18–22 weeks went on to develop an abnormal waveform. Of the 18 pregnancies with a notch at 18–22 weeks, 10 were studied a second time and two of them had a normal uterine artery FVW and a normal perinatal outcome. Of the eight pregnancies with a notch on repeat examination, three resulted in perinatal deaths and four resulted in growth retarded (<5 centile birthweight) and/or very preterm (<32 weeks) livebirths. Thus, Doppler assessment at 24–26 weeks gestation improved both the predictive values of a uterine artery FVW notch. The presence of a notch correctly predicted perinatal complications in 7 of 8

Table 2. Perinatal outcome in women with a raised maternal serum AFP who were examined for the presence of a notch on the uterine artery flow velocity waveform (FVW)

FVW	Perinatal outcome*			P**	Sensitivity (%)	Specificity (%)	Predictive value (%)	
	Complications	Normal	Total				Positive	Negative
At 18–22 weeks								
Notch present	13	5	18					
Notch absent	14	66	80					
Total	27	71	98	<0.001	48	93	72	82.5
At 24–26 weeks								
Notch present	7	1	8					
Notch absent	7	38	45					
Total	14	39	53	NS	50	93	87.5	84

*Complicated perinatal outcome includes all perinatal deaths and livebirths ≤ 32 weeks gestation and/or ≤ 5 th centile birthweight. Normal outcome is defined as livebirth > 32 weeks gestation and birthweight > 5 th centile.

**Fisher's exact test.

pregnancies (87.5%), while the absence of a notch was associated with good perinatal outcome in 38 of 45 pregnancies (84%; Table 2).

Discussion

In singleton pregnancies an elevated MSAFP in the absence of fetal malformations is associated with an increased occurrence of perinatal mortality, severe IUGR and preterm delivery. Furthermore, the combination of elevated MSAFP, oligohydramnios and abnormal uterine artery Doppler findings selects a subgroup of pregnancies associated with a very poor perinatal outcome.

The data of this study suggest that the presence of a notch in the FVW from the uterine artery is a better predictor of poor perinatal outcome than the RI. Furthermore, although a notch was present in some normal pregnancies at 18–22 weeks gestation, in those patients with a raised MSAFP this characteristic of the FVW, even at this early gestation, will effectively select a subset of patients prone to perinatal mortality, severe IUGR and preterm delivery (< 32 weeks). Repeating the Doppler studies at 24–26 weeks gestation improved both the predictive values as well as defining a 'high-risk' group at a gestation when further clinical investigations or management may be affected. In some pregnancies with a normal outcome, the abnormality in the uterine artery FVW at 18–22 weeks disappears by 24–26 weeks presumably because of delayed but normal trophoblastic invasion and placental maturation.

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