AN ASSESSMENT OF THE ROLE OF DOPPLER ULTRASOUND VELOCITY WAVEFORM ANALYSIS OF THE UMBILICAL ARTERY IN THE DIAGNOSIS OF FETAL DISTRESS IN LABOUR

A dissertation submitted to the Faculty of Medicine of the University of Cape Town in fulfilment of the requirements for the degree of MSc(Med)

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DECLARATION

I, Ian Peter Stuart, hereby declare that this dissertation is my own work and has not been presented for any degree at another university. The work reported is this dissertation was performed in the Department of Obstetrics & Gynaecology, University of Cape Town.

Signed: Signed by candidate

Signature Removed

Date: 28 January 1993

DEDICATION

To my wife, Gill

List of Publications and Verbal Presentations

Publications

Stuart IP, Lindow SW and van der Elst CW (submitted for publication). Fetal acidosis and Doppler velocimetry of the umbilical arteries in labour.

Presentations

Stuart IP, Lindow SW and van der Elst CW. Doppler velocimetry of the umbilical arteries remains constant in fetuses developing acidosis in labour. Department of Obstetrics and Gynaecology, University of Cape Town, Research Day, 22 November 1991.

Stuart IP, Lindow SW and van der Elst CW. Fetal acidosis and Doppler volcimetry of the umbilical arteries in labour. South African Society of Obstetricians and Gynaecologists 26th Biennial Congress 14 - 18 September 1992.

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ABSTRACT

Introduction

An assessment of the role of Doppler ultrasound velocity waveform analysis of the fetal umbilical arteries in the diagnosis of fetal distress in labour is made from a review of the literature and clinical study.

Study objectives

1) To determine the value of screening with Doppler ultrasound in high-risk labours in the prediction of the development of indicators of fetal distress.

2) To determine whether Doppler velocimetry indices of the umbilical arteries change with the development of indicators of fetal distress in labour.

Design

Repeated Doppler velocimetry in selected high risk labours.

Setting

Groote Schuur Hospital, Cape Town, South Africa, a large tertiary referral centre.

Subjects

Thirty six women with singleton pregnancies complicated either by gestational proteinuric hypertension or by intrauterine growth retardation or both with a normal cardiotocographic tracing at the onset of labour.

Main outcome measures

1) Acid-base status of the fetus was assessed after delivery by analysis of umbilical artery blood.

2) Apgar score was recorded at 1 and 5 minutes.

3) Neonates were carefully examined for clinical signs of perinatal hypoxia.

Results

Twenty seven fetuses were followed through labour. No relation was found between umbilical artery Pourcelot ratio (resistance index) on admission in labour and umbilical artery base deficit. Six fetuses were born with an umbilical artery base deficit of more than 10 mmol l^{-1}. Zero change in mean Pourcelot ratio was noted in both normal and acidotic fetuses. None of the acidotic fetuses showed a change in Pourcelot ratio of more than 0.03. The study had an 80% power to detect a change in mean Pourcelot ratio of 0.07 in the normal fetuses and 0.16 in the acidotic fetuses at a 95% confidence level. No relation was found between Pourcelot ratio on admission in labour or change in Pourcelot ratio during labour and Apgar score.

None of the neonates showed clinical signs of perinatal hypoxia.

Conclusions

Doppler velocimetry of the umbilical arteries in labour as measured by the Pourcelot ratio does not contribute to the diagnosis of fetal distress in labour.

Table of Contents

1 Introduction

This dissertation presents an assessment of the role of Doppler ultrasound velocity waveform analysis of the umbilical arteries in the diagnosis of fetal distress in labour. In these introductory pages, an overview of the definition, origin, incidence, diagnosis and fetal responses to fetal distress is given, followed by a review of the current status of Doppler ultrasonography of the umbilical arteries.

1.1 Fetal distress

1.1.1 Definition of fetal distress

Fetal distress is a widely used term but is often poorly or incorrectly defined thus leading to problems with diagnosis, treatment and clinical research. Fetal distress results from acute metabolic disturbance of the fetus which, if untreated, may cause neurological deficit in the neonate (Beard 1970, Parer and Livingstone 1990). The final common pathway of such metabolic disturbance is thought to be hypoxia. Fetal hypoxia may give rise to physical signs in the fetus and neonate such as meconium passage, fetal heart rate abnormality and birth asphyxia (ie failure to establish respiration at birth) which although useful in the diagnosis of fetal distress are not synonymous with the condition.

1.1.2 Incidence of fetal distress

Fetal distress is a rare condition. The Caesarean section rate for fetal distress in the general population is

approximately 1%, see for example Zalar and Quilligan (1979) who report this incidence from an American University Hospital. The incidence of cerebral palsy attributable to fetal distress alone in a cohort of 54 000 children born in 12 American university hospitals between 1959 and 1966 (the American Collaborative Study of Cerebral Palsy) was 0.03% (Nelson and Ellenberg 1986).

1.1.3 Origin of fetal distress

Fetal distress is commonly caused by uteroplacental insufficiency or umbilical cord compression. However, any event causing metabolic disturbance in the fetus may give rise to fetal distress. For example maternal hypoxia, diabetic ketoacidosis, hypotension, toxin ingestion or haemolysis, fetal infection or inborn errors of metabolism may contribute to fetal compromise.

1.1.4 Diagnosis of fetal distress

1.1.4a General principles concerning diagnostic tests

In the clinical evaluation of a diagnostic test, patients who do and who do not have the disease of interest undergo the diagnostic test. This requires an accepted "gold standard" for diagnosis of the disease against which the diagnostic test is evaluated. A definition of normality is also required. The clinical efficiency of the test is expressed in terms of sensitivity, specificity and predictive value.

The sensitivity of a test is the proportion of cases with

the disease who have an abnormal test result. The specificity of a test is the proportion of cases without the disease who have a normal test result.

The positive predictive value of a test is the proportion of cases with an abnormal test result who have the disease. The predictive value of a diagnostic test (unlike the sensitivity and specificity) depends upon the prevalence of the disease to be tested for. Extreme caution should be exercised in the interpretation of figures for the clinical efficiency of a diagnostic test. Even if the test has no relation to the disease of interest, chance association can produce erroneous calculations for sensitivity, specificity and predictive value. The clinical significance of the apparent clinical efficiency of a diagnostic test will become clear from the investigation of its utility. The utility of a test may be defined as its true worth after consideration of the benefits and side effects arising from diagnosis and treatment of the disease, along with the extra risks arising from false-positive and false-negative results. Utility is best assessed from a prospective randomized controlled trial of the test.

These general principles have special importance in consideration of diagnostic tests for fetal distress. A "gold standard" for the diagnosis of fetal distress and "normality" are both hard to define. Fetal distress is a rare condition, and so the clinical efficiency of a diagnostic test for fetal distress may be more easily

studied in a population at high risk for developing fetal distress. Conversely, a seemingly good test in a high-risk population may have very low positive predictive value and utility in an unselected population. To test the utility of a diagnostic test for a rare condition by means of a prospective randomized controlled trial, very large numbers would be required.

1.1.4b Intrapartum diagnosis of fetal distress

i Cardiotocographic monitoring

The cardiotocograph (CTG) is a recording of fetal heart rate and maternal uterine activity against time. This is achieved using either Doppler ultrasound detection of fetal heart movements, or a fetal scalp electrode recording of the fetal electrocardiogram, and either an external or an internal uterine pressure transducer.

Terminology (Gillmer and Beard 1979, Bracero et al. 1986)
An acceleration (or deceleration) of the fetal heart rate is an increase (or decrease) of at least 15 beats per minute in the rate from the baseline, lasting for at least 15 seconds. A tachycardia (or bradycardia) of the fetal heart rate is an increase (or decrease) in rate to above 160 beats per minute (or below 120 beats per minute), lasting for at least 2 minutes. Short-term variability describes excursions of the heart rate by amounts insufficient to be described as accelerations or decelerations.

Decelerations may be classified according to their relationship with uterine activity. If the trough of the deceleration occurs at the peak of the contraction, the deceleration is described as early. If the trough of the deceleration occurs after the peak of the contraction, the deceleration is described as late. If the deceleration and uterine activity are unrelated, the decelerations are described as variable.

Definition of normality (Gillmer and Beard 1979, Bracero et al. 1986)

A normal CTG is one with a rate of between 120 and 160 beats per minute, with a baseline variability of 5 to 15 beats per minute and no decelerations. In the second stage of labour, early decelerations without other abnormality may be classified as normal.

Pathophysiology of fetal heart rate abnormalities

Short-term variability of the fetal heart rate demonstrates the normal functioning of cardiovascular autoregulation. This depends upon a normally functioning nervous system. Loss of short-term variability may imply neurological dysfunction due to metabolic disturbance. Many other factors, however, may affect short-term variability. Nervous function may be affected by drugs (notably opiates, benzodiazepines, anticholinergies and beta-adrenergic agonists), congenital abnormalities of the nervous system or heart, prematurity and congenital heart block. Local anaesthetic agents may directly suppress the

myocardium. Fetal breathing movements will cause variation in venous return to the heart and hence sinus arrythmia. Rate abnormalities may signify metabolic disturbance of the fetus. Tachycardia may, however, commonly arise from maternal or fetal infection. Bradycardia may result from compression of the fetal head.

Decelerations may also signify metabolic disturbance of the fetus. Late decelerations have the strongest association with fetal hypoxia. Early decelerations can arise from head compression, or tightening of the umbilical cord around the neck.

Clinical interpretation of fetal heart rate abnormalities

The CTG may be regarded almost as a screening test for fetal distress. The probability of fetal distress being present will depend not only upon the presence of CTG abnormality, but also the degree and duration and, most importantly, the associated clinical features. Indications for intervention according to fetal heart rate abnormality and duration (in the absence of associated adverse clinical feature) have been proposed by Murphy et al. (1990) and are reproduced with modification in table 1.

It should be noted that even ominous CTG abnormalities in the absence of other adverse clinical features have a relatively low chance of associated fetal acidosis. For example, in the Dublin randomized controlled trial of intrapartum fetal heart rate monitoring (MacDonald et al.

1985), of those fetuses with a bradycardia of less than 100 beats per minute, late decelerations or severe variable decelerations undergoing fetal blood sampling, only 27% were acidotic (Grant, 1985).

Table 1

Indications for intervention according to fetal heart rate abnormality and duration (in the absence of associated adverse clinical features). Modified from Murphy et al. 1990

Fetal heart rate abnormality	Duration (min)
Early deceleration	120
Tachycardia 160 - 180 bpm	120
Tachycardia >180 bpm	60
Bradycardia <100 bpm	20
Variable deceleration >50 bpm, <60 s	120
Variable deceleration <50 bpm, >60 s	40
Late deceleration (lag time >20 s)	40
Reduced baseline variability (<5 bpm)	60
Complicated tachycardia >160 bpm with decelerations and/or reduced baseline variability	40

bpm = beats per minute

Table 2

Clinical efficiency of CTG monitoring for the prediction of severe fetal acidosis at birth (umbilical artery pH <7.085). From Steer et al. 1989

Sensitivity	83%
Specificity	60%
Positive predictive value	7%
Negative predictive value	99%
Incidence of severe acidosis	3.4%

Table 3

Clinical efficiency of CTG monitoring for the prediction of low Apgar score (<7 at 1 minute). From Steer et al. 1989

Sensitivity	51%
Specificity	61%
Positive predictive value	21%
Negative predictive value	86%
Incidence of low 1 minute Apgar score	17%

Table 4

Clinical efficiency of CTG monitoring for the prediction of low Apgar score (<7 at 5 minutes). From Steer et al. 1989

Sensitivity	44%
Specificity	59%
Positive predictive value	2.4%
Negative predictive value	98%
Incidence of low 1 minute Apgar score	2.3%

Clinical efficiency of CTG monitoring in labour

In a prospective study in a London teaching hospital (Steer et al. 1989) the clinical efficiency of an abnormal CTG for the prediction of severe fetal acidosis at birth (umbilical artery pH <7.085) and low Apgar score (<7 at 1 and 5 minutes) was assessed. The results are presented in tables 2 to 4, and demonstrate the very low positive predictive value of intrapartum CTG monitoring for the prediction of adverse fetal outcome.

Utility of CTG monitoring in labour

Controversy exists as to the benefit of CTG monitoring in labour. This is because the monitoring may result in increased operative delivery rates without fetal benefit. For example, in an audit of 1210 consecutive deliveries in an Oxford teaching hospital (Sykes et al. 1983), continuous fetal monitoring was associated with a much higher incidence of operative delivery for fetal distress than was intermittent fetal heart rate auscultation. There was little difference between the two groups in the incidence of severe acidosis at birth (figure 1). It should be noted that the assignment of women to the two groups was not random and that fetal blood sampling was not used frequently in the event of an abnormal CTG.

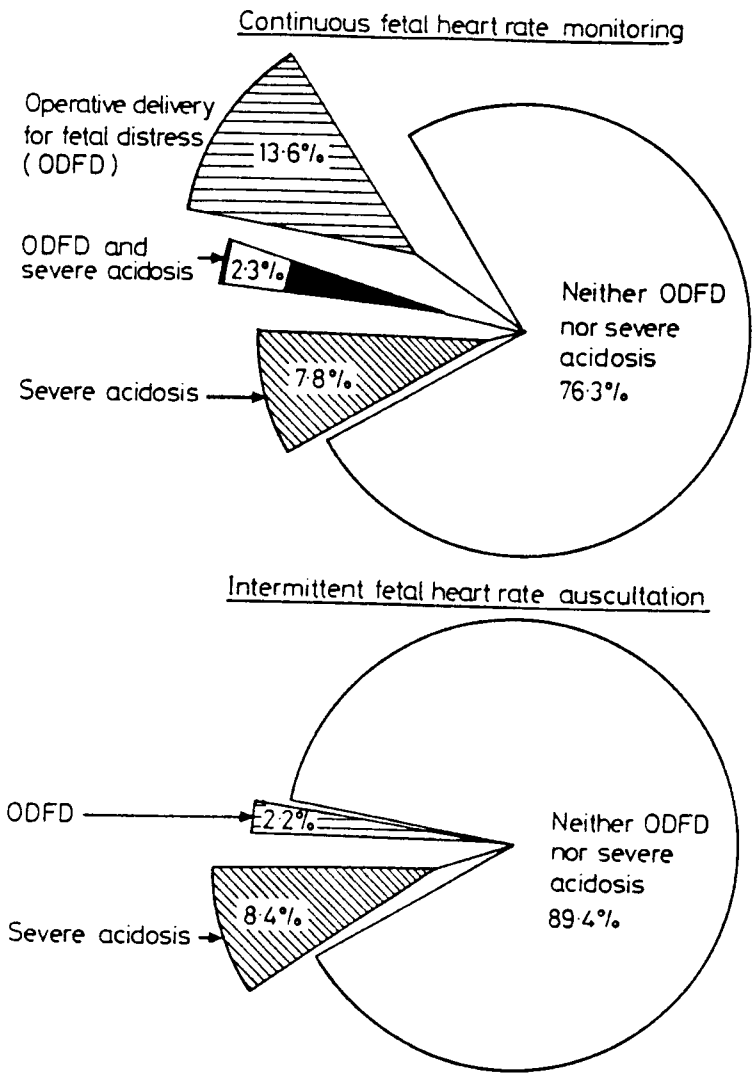


Figure 1

Incidence of operative delivery for fetal distress and severe acidosis in groups followed by continuous fetal heart rate monitoring or intermittent heart rate auscultation. From Sykes et al. 1983, with permission.

None of the randomized trials of electronic intrapartum fetal heart monitoring has shown a reduction in fetal mortality attributable to CTG monitoring (Kelso et al. 1978, Haverkamp et al. 1979, Wood et al. 1981, MacDonald et al. 1985), although prior to the Dublin trial (MacDonald et al. 1985) the numbers of patients in each trial (less than 1000) were insufficient to demonstrate an effect. The Dublin trial involving 12 964 women, however, showed that the babies of women allocated to CTG monitoring had a reduced incidence of neonatal seizures compared with those allocated to intermittent auscultation (relative risk 0.45, 95% confidence intervals (CI) 0.22 to 0.91) with little increase in operative delivery rate (8.2% vs 6.3%, $P < 0.001$). The effect was only demonstrated in labours lasting for more than 5 hours. There was no difference in the incidence of permanent handicap at 1 year of age in this study.

Summary

CTG monitoring has a high negative predictive value but low positive predictive value in the diagnosis of fetal distress in the general population. The CTG may be regarded as a screening test for fetal distress which, if abnormal, demonstrates the need for further fetal evaluation.

ii Fetal blood sampling

Fetal acid-base status can be assessed by obtaining a capillary blood sample from the fetal scalp. By this means, metabolic changes affecting the fetus in labour can

be studied.

Fetal acid-base balance

Under normal conditions, fetal acid-base homeostasis is maintained by the placenta. The fetal umbilical artery transports blood to the placental villi which consist of multiple capillary loops covered by trophoblast. Maternal blood is transported to the intervillous space of the placenta via the spiral arteries. Rapid exchange of gases and metabolites occurs; the fetal blood returns through the umbilical vein, and maternal blood through the uterine veins. In normal labour, feto-maternal differences in base deficit are relatively small, and the fetal base deficit follows the maternal base deficit closely. With the development of fetal distress, fetal acidosis is thought to develop as a result of hypoxia due to impaired uteroplacental exchange or impaired umbilical blood flow. An increase in fetal-maternal base deficit difference develops with decreasing correlation between fetal and maternal levels (Kubli 1968). The acidosis per se, unless very severe, has little effect on the fetus (Bruns et al. 1963), rather it is the underlying hypoxia which adversely affects the fetus.

Clinical interpretation of fetal acid-base status

Sources of error in the determination of fetal acid-base status by scalp blood sampling include:

1) Impaired blood flow through the fetal scalp caused by caput formation in labour

2) Contamination of fetal blood with maternal blood, amniotic fluid or meconium

3) Exposure of fetal blood to air

4) Methodological errors in the determination of acid-base and blood gas levels

5) Maternal origin of the fetal acidosis

There is little information concerning sources of error of fetal blood sampling in the literature. Kubli (1968), studying 31 women in normal labour, has shown a good correlation between acid-base analysis of fetal scalp blood taken within 5 minutes of delivery and umbilical artery blood. The correlation was better for base deficit ($r = 0.90$) than for pH ($r = 0.76$). These results suggest that the flow of blood through the fetal scalp is not impaired enough in labour to alter the pH and base deficit significantly.

Mean changes in maternal arterial pH and base deficit in labour are shown in table 5 (Jacobson and Rooth 1971). The maternal pH is remarkably stable in the first stage of labour. In the second stage of labour the mother may develop a metabolic acidosis due to the voluntary effort of pushing and a respiratory acidosis due to breath-holding with pushing. The stability of maternal pH in the first stage of labour makes it unlikely that infusion

acidosis will be a common cause of apparent fetal acidosis in the first stage of labour. The effect of infusion acidosis on cord blood pH is discussed in section 1.1.4c below.

Table 5

Mean changes in maternal pH and base deficit in labour. From Jacobson and Rooth 1971

Cervical dilatation (cm)	Mean pH	Mean base deficit(mmol l^{-1})
5	7.46	4.1
9	7.47	4.1
fully, with head on perineum	7.38	7.1

Table 6

Clinical efficiency of fetal blood sampling for the prediction of severe fetal acidosis at birth (umbilical artery pH <7.1). From Bowe et al. 1970

Sensitivity	100%
Specificity	64%
Positive predictive value	33%
Negative predictive value	100%
Incidence of severe fetal acidosis	15%

Definition of normality is usually taken from a point two standard deviations below the mean pH in healthy fetuses. Several studies indicate that the critical pH level is 7.20 (reviewed by Beard 1970). Such a definition of normality is problematical. For example, the acceptance of this approach automatically defines 2.5% of healthy fetuses as being diseased because they fall outside of 2 standard deviations.

Clinical efficiency of fetal blood sampling in labour

In a study from a New York University Hospital (Bowe et al. 1970) the clinical efficiency of fetal blood sampling for the prediction of severe acidosis at birth (umbilical artery pH < 7.1) and low Apgar score (<7 at 1 minute) was assessed. The results are presented in tables 6 to 9, with adjustments made for the prevalence of severe acidosis and low Apgar score in order to compare the data with the study of Steer et al. (1989) (tables 2 to 4). The positive predictive value (table 7) for the severe acidosis at birth is surprisingly low. In this study, scalp blood was obtained just before delivery. The low positive preditive value arose because many of the fetuses with a scalp pH of less than 7.20 were born with a cord artery pH of between 7.1 and 7.2. The predictive power of fetal blood sampling for low Apgar score would appear to be greater than that of CTG monitoring.

Table 7

Figures from table 6 adjusted to an incidence of severe fetal acidosis of 3.4% (to allow comparison with table 2)

Sensitivity	100%
Specificity	64%
Positive predictive value	9%
Negative predictive value	100%

Table 8

Clinical efficiency of fetal blood sampling for the prediction of low Apgar score (<7 at 1 minute).

From Bowe et al. 1970

Sensitivity	63%
Specificity	89%
Positive predictive value	70%
Negative predictive value	86%
Incidence of low 1 minute Apgar score	28%

Table 9

Figures from table 8 adjusted to an incidence of low Apgar score of 17% (to allow comparison with table 3)

Sensitivity	63%
Specificity	89%
Positive predictive value	54%
Negative predictive value	92%

Complications of fetal blood sampling

Fetal scalp blood sampling is a relatively safe procedure. The incidence of significant fetal haemorrhage is reported as 0.25% and of scalp abscess 0.25% (Balfour et al. 1970). Factors such as vacuum extraction, fetal coagulation defect and maternal infection may predispose the fetus to these complications.

The increased risk of transmission of the human immunodeficiency virus from an infected mother to the fetus through fetal blood sampling has not been determined.

Utility of fetal blood sampling

No prospective randomized controlled trial has been performed to assess the utility of fetal blood sampling.

Summary

Fetal blood sampling is commonly used in clinical practice to evaluate the acid-base status of a fetus with an abnormal CTG tracing. Whilst regarded by many as the accepted gold standard for the diagnosis of fetal distress, this is not the case. The sensitivity and positive predictive value of fetal blood sampling for low Apgar score are both low. The utility of blood sampling has not been established. In addition fetal blood sampling is an invasive procedure which may be unacceptable to the mother; it occasionally results in fetal complication, and sometimes it is not technically possible. Some obstetric units have abandoned fetal blood

sampling because of the suspected increased risk of intrapartum transmission of human immunodeficiency virus. For these reasons, alternative methods of fetal monitoring require investigation.

iii Current areas of research

The two main fields of research for new intrapartum diagnostic tests for fetal distress are continuous measurement of fetal oxygen saturation using pulse oximetry and the monitoring the fetal electrocardiogram. Further research will be necessary before these tests can be considered for clinical practice.

1.1.4c Postpartum diagnosis of fetal distress

i Apgar score

The Apgar score (Apgar 1953) was introduced as a method for assessing the need for resuscitation of the newborn infant. The scoring system is shown in table 10. Since its introduction, the Apgar score has become used as a predictor of neurological damage due to fetal distress.

The American Collaborative Study of Cerebral Palsy (Nelson and Ellenberg 1981) showed that only 27% of children who developed cerebral palsy had an Apgar score of less than 7 at 5 minutes. However, the proportion of cerebral palsy that can be accounted for by intrapartum asphyxia is low, estimated as being between 3 and 13% by Nelson and Ellenberg (1986) and as 4.9% by Stanley and Watson (1988).

Table 10

The Apgar score

Heart rate/min	None	0
	<100	1
	>100	2
Respiratory effort	None	0
	Weak/irregular	1
	Good	2
Muscle tone/activity	Limp	0
	Some flexion	1
	Active/well flexed	2
Response to stimulation	None	0
	Some response	1
	Vigorous cry	2
Colour	Centrally cyanosed	0
	Peripherally cyanosed	1
	Pink	2
Total		10

A very low (>10 min) late Apgar score identifies infants that one needs to respond to with resuscitation for an extended period and is a good predictor for subsequent death or neurological handicap. Schmidt et al. (1988) have reviewed the available data on this subject and conclude that the risk of death or cerebral palsy is about 75% if the Apgar score is 3 or less at 10 minutes.

ii Cord blood analysis

The correlation of fetal acidosis with low Apgar score is poor. Sykes et al. (1982) showed that only 19% of babies with a 5 minute Apgar score of less than 7 had a severe acidosis (umbilical artery pH less than 7.1 and base deficit greater than 13 mmol l^{-1}) and 17% of babies with a severe acidosis had a 5 minute Apgar score of less than 7.

Low et al. (1985) have studied the relationship between fetal acidosis and newborn encephalopathy in high-risk infants. Only 24% of those born with severe acidosis developed encephalopathy and 22% of those with encephalopathy had been born with severe acidosis.

It has been suggested that infants born with low Apgar score but normal acid-base balance constitute a high risk group for the subsequent development of neurological abnormality (Dennis et al. 1989, Visser and Dijxhoorn 1988). It should be noted that the analysis of samll subgroups in studies should be viewed with caution.

One reason for the poor association of acid-base status at

birth with subsequent neurological deficit may be the confounding factor of infusion acidosis. By the time of delivery, the mother may have developed a significant acidosis. The origin of the fetal acidosis may be determined by measurement of both fetal and maternal acid-base balance as outlined in table 11. Tejani et al. (1977) confirmed that cord compression leads to umbilical artery-vein differences significantly greater than those in controls, mainly due to a decrease in arterial pH. Infusion acidosis is suspected when the difference in umbilical artery and maternal arterial or venous base deficit is small (less than 4 mmol l^{-1}).

Infusion acidosis is, however, thought to be uncommon, reported as accounting for 10% (Beard 1970) to 25% (Bowen et al. (1986) of cases of fetal acidosis.

Table 11

Maternal and umbilical vessel acidaemia according to the origin of the fetal acidosis

Origin	Maternal artery/vein	Umbilical artery	Umbilical vein
Uteroplacental insufficiency	Normal	Acidotic	Acidotic
Cord compression (Small difference between umbilical vein and maternal vessel base deficits)	Normal	Acidotic	Normal
Infusion acidosis (Small difference between base deficits)	Acidotic	Acidotic	Acidotic

iii Hypoxic ischaemic encephalopathy

The infant destined to develop permanent neurological deficit as a result of intrapartum hypoxia usually shows clinical signs of illness in the neonatal period. These include both neurological and systematic signs. Neurological signs include depression of the level of consciousness, tone and reflexes, difficulty with feeding and convulsions. Systemic signs include organ failure of heart, lung, liver and kidney.

Sarnat and Sarnat (1976) have described staging criteria for neonatal encephalopathy following fetal distress. Stage 1 infants recovered without neurological deficit, as did stage 2 infants with signs and electroencephalogram changes lasting 5 or fewer days. Infants with stage 3 disease either died or were left with permanent deficit. Levene et al. (1986) reported that 96% of infants with moderate or severe encephalopathy die or are left with neurological deficit.

iv Summary

Currently available indicators of fetal distress, both intrapartum and in the immediate newborn period, are poor predictors of permanent neurological disability. The best available indicator in the immediate newborn period is a prolonged low Apgar score.

In contrast, neonatal encephalopathy ("hypoxic-ischaemic encephalopathy"), if severe, has an extremely high positive predictive value for subsequent neurological

deficit, and is proposed as the accepted standard for the diagnosis of fetal distress.

1.1.5 Fetal cardiovascular responses to metabolic disturbance

There are numerous causes and forms of metabolic disturbance to which the fetus may be exposed. An important component of fetal distress is impaired tissue respiration which is commonly caused by ischaemia and hypoxia. It has been established in animal models that cardiorespiratory compensatory adjustments may occur in hypoxic fetuses. Hypoxia in the fetal lamb produces increased blood flow to the brain, heart and adrenals, with decreased blood flow to the rest of the body (Cohn et al. 1974, Peeters et al. 1979, Block et al. 1984). Thus the re-distribution of cardiac output (the so-called "diving reflex" or "brain sparing effect") may serve to preserve respiration in vital organs.

1.1.5a Umbilical blood flow

There is no evidence to demonstrate autoregulation of the umbilical placental circulation. Increase in aortic pressure produces a linear increase in umbilical blood flow in the fetal lamb (Berman et al. 1976). Hypoxia in the fetal lamb causes an increase in aortic blood pressure and a fall in pulse rate (Cohn et al. 1974). Several studies have shown that umbilical blood flow in the fetal lamb is unaltered by hypoxia (Cohn et al. 1974, Peeters et al. 1979, Block et al. 1984). It is possible that the umbilical flow remains constant because the rise in blood pressure is balanced by the fall in heart rate.

1.2 Doppler ultrasound

Until recently, our knowledge about feto-placental blood flow had mainly been derived from invasive animal experiments. The advent of Doppler ultrasonography as a simple, non-invasive procedure applicable to the study of feto-placental blood flow in the human fetus is therefore a major advance in obstetrics and perinatal medicine.

1.2.1 Physics of Doppler ultrasound

If a waveform is reflected from a moving structure, the returning waveform will have undergone a frequency shift. This is the Doppler effect. The shift in frequency is given by the formula:

$$\text{Doppler shift} = \frac{2\ Fv\ \cos\ \Theta}{c}$$

where F is the transmitted frequency

v is the velocity of the moving target

Θ is the angle between the direction of movement of the waveform and the target

c is the velocity of the waveform

Doppler-shifted signals from diagnostic ultrasound frequencies of 2-10 MHz are within the audible range. These signals can be converted to a visual display by spectrum analysis, using the Fourier transform, producing a display called the Doppler flow velocity waveform.

1.2.2 Doppler ultrasound equipment

1.2.2a Continuous-wave Doppler ultrasound equipment

These devices emit ultrasound continuously and reflected Doppler signals are obtained from all moving structures in the line of the ultrasound beam. This makes continuous-wave machines unsuited to studying the fetal or uteroplacental circulation, but adequate for studying the umbilical circulation. The umbilical vessels are recognized by their characteristic waveform, with a saw-tooth artery pattern and constant umbilical flow in the opposite direction (figure 2). A clear umbilical signal is usually obtainable using continuous wave equipment because the umbilical cord is well separated from other vessels by the amniotic fluid. Continuous wave Doppler equipment is usually conveniently small and portable.

1.2.2b Pulsed Doppler ultrasound equipment

By controlling the time from emitting to detecting the reflected Doppler signal, the depth from which the signal arises can be precisely determined. The combination of pulsed Doppler and real-time ultrasound is called a duplex system and allows for identification and recording from individual blood vessels. Compared with continuous-wave equipment however, pulsed Doppler equipment is expensive and cumbersome.

1.2.2c Colour flow equipment

This equipment superimposes real time ultrasound images with blood flow information coded in colour. This allows for more easy identification of vessels and calculations of blood flow, but the equipment is extremely expensive.

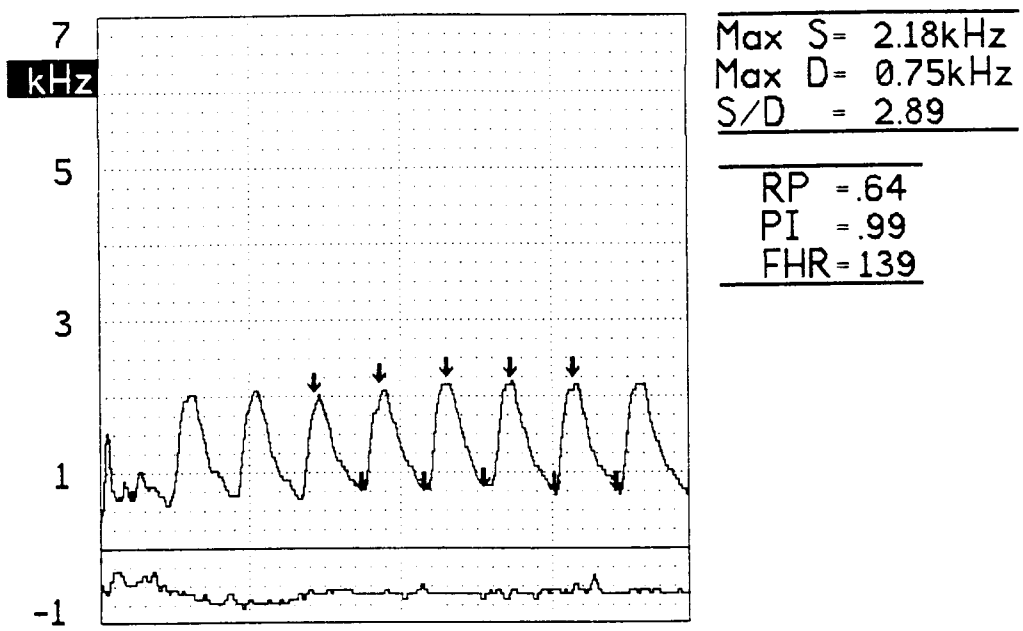


Figure 2

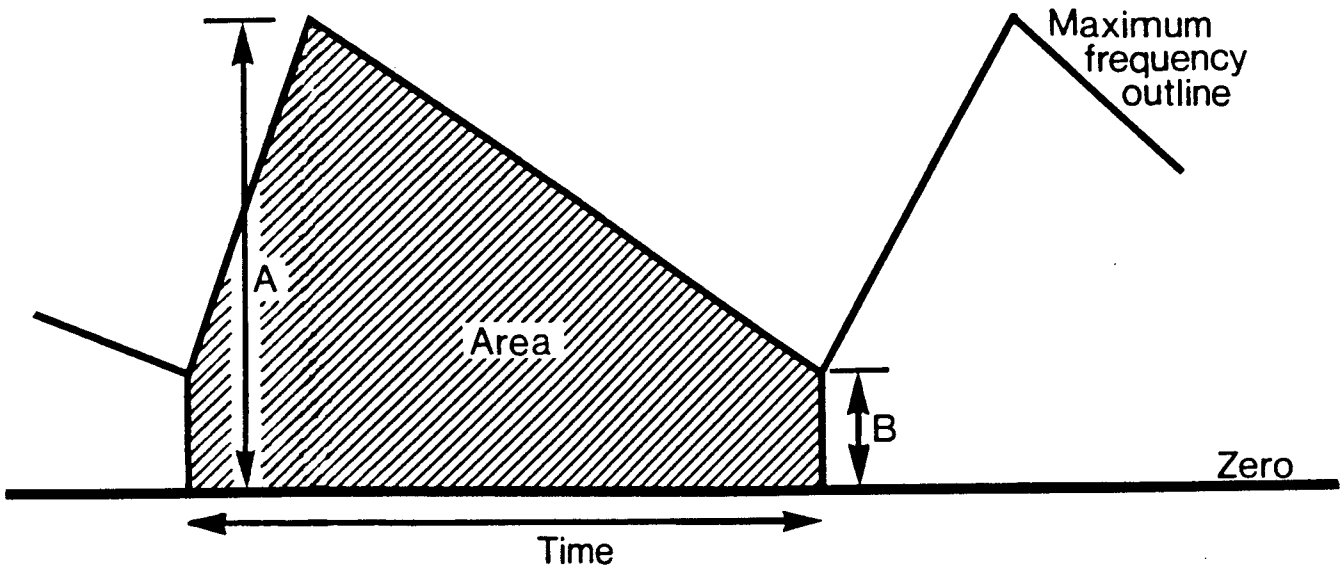
An example of an umbilical artery flow velocity waveform recorded by the Sonicaid Vasoflo -3c machine

1.2.3 Doppler analysis of blood flow

The calculation of absolute blood flow in a vessel is problematical. It requires knowledge of the cross-sectional area of the vessel (which changes with the cardiac cycle) and the angle of insonation of the ultrasound signal with the vessel. Assumptions have to be made about the flow velocity profile of the blood across the cross-sectional area of the vessel, and about the density of the tissue through which the ultrasound passes to reach the vessel. Duplex pulsed Doppler equipment is required and even then significant errors in the calculation of blood flow may arise.

Fortunately, the maximum frequency outline of the flow velocity waveform provides a reproducible qualitative analysis of blood flow within the vessel.

The indices commonly used to characterize the maximum frequency outline are described in figure 3. These indices are independent of the intensity of the Doppler signal and the angle of insonation of the ultrasound wave with the vessel, allowing for comparison between indices measured at different times and in different individuals.



$\frac{A}{B}$ = systolic/diastolic ratio (Stuart et al. 1980)

$\frac{A-B}{B}$ = Pourcelot ratio (also known as the resistance index) (Pourcelot 1974)

$\frac{A-B}{mean}$ = Pulsatility index (Gosling and King 1975)

where A = peak systolic shift
B = end diastolic shift
mean = area/time

Figure 3

The commonly used indices to characterize the maximum frequency outline of the Doppler flow velocity waveform

1.2.4 Sources of error and variation with continuous wave Doppler ultrasonography of the umbilical arteries

a Detection of wrong vessel

The umbilical arteries may be recognized by the distinctive waveform (see section 1.2.2a). It is however possible that the wrong vessel may be visualized, giving totally erroneous results!

b Disparity between umbilical arteries

The two umbilical arteries normally have identical waveforms and a continuous wave machine will record from either or both vessels at any given time with no resulting change in Doppler velocimetry indices. Occasionally a marked difference in the flow velocity waveforms of the two umbilical arteries exists (Trudinger and Cook 1988). This is usually the result of placental infarction. Marked variation in the Doppler flow velocity waveform will result as the proportional contribution from each vessel varies.

c Noise

Background noise, particularly from other vessels, will contribute to the flow velocity waveform.

d Filter

A major component of background noise originates from the pulsating vessel wall. The Doppler frequencies originating from the vessel wall are low in frequency but high in intensity. To remove these frequencies, a high-pass filter is used, usually a 100 Hz filter. This filter may also remove low frequency Doppler frequencies arising from the blood flow, and may thus give rise to errors particularly in circumstances of reduced end-diastolic flow.

e Angle of insonation with vessel

Although Doppler velocimetry indices are generally independent of the angle of insonation with the blood vessel, very acute angles can result in the generation of mainly low frequencies which may also be removed by the high-pass filter.

f Site of vessel sampling

Umbilical artery flow velocity waveforms vary along the length of the umbilical cord (Skoll et al. 1992). The Doppler indices tend to be higher at the abdominal end of the umbilical arteries but this difference disappears towards the end of pregnancy. Skoll et al. reported a difference in Pourcelot ratio measured at the abdominal and placental ends of the umbilical arteries at 36

weeks gestation of 0.05, but this difference was not statistically significant. However, in fetuses with severe intrauterine growth retardation they noted a difference of 0.33 (S.D. 0.20, n = 28, $P < 0.05$).

The position of recording cannot be determined using continuous wave equipment. In obtaining a clear signal from the umbilical arteries, it is likely that one has sampled from a site distant from either end of the cord.

g Fetal breathing

Fetal breathing will cause cardiac output to vary with the respiratory cycle. This can easily be observed on the visual display of the maximum frequency outline, and recordings should be made during a period of absent fetal breathing. Fetal breathing movements are uncommon in labour (Boylan et al. 1985).

h Spectrum analysis

Spectrum analysis in Doppler ultrasonography is achieved by computer implementation of the fast Fourier transform. Fourier analysis will achieve a good approximation but not an exact description of the Doppler-shifted signals, limited by the number of calculations possible with real-time analysis.

i Calculation of Doppler indices

Errors in estimating the flow velocity waveform dimensions will give rise to errors in the calculation of the Doppler indices. Thompson et al. (1988a) have shown, by consideration of theoretical waveform shapes, that small errors in the estimation of A and B (figure 3) lead to larger errors in the calculations of the indices. The error so arising increases with increasing value of systolic/diastolic ratio, and increases with decreasing value of Pourcelot ratio and pulsatility index.

j Number of waveforms sampled

An increase in the number of waveforms sampled for the calculation of mean Doppler indices will improve the confidence intervals for the estimate of the indices.

k Heart rate

Heart rate may affect the Doppler flow velocity waveform (see section 1.2.7). To minimize this effect, observations should be made in the absence of fetal heart rate abnormality (see section 1.1.4bi). Correction for fetal heart rate may be necessary.

1 Range of normality

Normality is usually defined as having a Doppler velocimetry index within two standard deviations of the mean of a normal population. The population mean is dependent upon gestation, and errors in the estimate of gestation may place an individual erroneously within or outside of the normal range. The range of normality may differ slightly for different populations.

1.2.5 Safety of ultrasound

Diagnostic ultrasound is widely used in obstetrics and generally held to be harmless (Meire 1987). Almost all human studies have demonstrated no adverse effect of insonation of the fetus (reviewed by Ziskin and Petitti, 1988). Few studies of the effects of Doppler ultrasound on the human fetus have been published, and the only positive finding has been increased fetal activity (David et al. 1975).

There is a lack of consensus on what constitutes a safe level of Doppler ultrasound. The American Institute of Ultrasound in Medicine advise a limit of 100 $mWcm^{-2}$ (Wells 1987).

Nevertheless, the exposure of patients to ultrasound should be limited to the duration and intensity appropriate for the clinical objective.

1.2.6 Doppler ultrasound of the umbilical arteries in normal pregnancy

In normal pregnancy the umbilical artery flow velocity waveform is characterized by high end-diastolic velocity. Reference ranges for normal pregnancy have been published by many groups - for example, in Cape Town (Pattinson et al. 1989), in London (Pearce et al. 1988) and in Sydney (Thompson et al. 1988b). Only minor differences exist between the reference ranges for different centres. A decrease in all the indices is seen with advancing gestation. Reproducibility can be very good. Pearce (1987), using duplex pulsed Doppler, reported intra-observer coefficient of variation to be 3.3% and inter-observer coefficient of variation to be 7.5% for the Pourcelot ratio.

1.2.7 Doppler ultrasound of the umbilical arteries in normal labour

Studies of normal labour have shown that umbilical artery velocity waveform is not significantly affected by uterine activity, rupture of membranes, oxytocin infusion and progress in labour (Stuart et al. 1981, Fairlie et al. 1989). Change in fetal heart rate (Mires et al. 1987, Fairlie et al. 1988, Mansouri et al. 1989) and spontaneous acceleration of the fetal heart rate (Morrow et al. 1989) may affect umbilical artery flow velocity waveforms to a small extent. However, within the normal range of fetal

heart rate, the variation in Doppler indices attributable to fetal heart rate is small compared with the confidence intervals for the estimates of the Doppler indices. All the above results confirm that Doppler measurements can provide reliable, reproducible accurate results not significantly distorted by normal labour-related effects.

1.2.8 Doppler ultrasound of the umbilical arteries in abnormal pregnancy

In pregnancy complicated by fetal compromise the umbilical artery flow velocity waveform commonly has low or absent end-diastolic velocity. This loss of end-diastolic velocity is thought to represent increased placental resistance (Erskine and Ritchie 1985b): this is discussed further in section 1.2.10.

a Doppler ultrasound of the umbilical arteries and intrauterine growth retardation

The association between intrauterine growth retardation and reduced or absent end-diastolic velocity in the umbilical arteries has been reported by various authors, including Fleischer et al. (1985) and Erskine and Ritchie (1985b). Although umbilical artery velocimetry indices are commonly abnormal in growth retarded fetuses, Doppler ultrasound has proved disappointing as a screening test for fetal growth retardation (Beattie and Dornan 1989). This is perhaps not surprising, since the initial reports were from a highly selected group of compromised fetuses.

It is interesting to note that ultrasound screening for intrauterine growth retardation against which Doppler ultrasound might be compared is also without proven utility (Neilson et al. 1984).

Doppler ultrasound of the umbilical arteries appears to be useful in the prediction of morbidity in the growth retarded fetus. Burke et al. (1990) have suggested that intrauterine growth retardation with normal umbilical artery Doppler flow velocity waveform is a relatively benign condition. Comparing 55 pregnancies with abnormal Doppler velocimetry (systolic/diastolic ratio greater than 2 standard deviations above the mean) with 124 pregnancies with normal flow, the relative risk of adverse outcome (and 95% confidence intervals) was:

Perinatal death	3.4	(1.0 to 11.5)
Preterm delivery	12.2	(5.2 to 28.4)
Caesarean section for fetal distress	7.2	(2.2 to 23.8)

1.2.8b <u>Doppler ultrasound of the umbilical arteries and hypertensive pregnancy</u>

Hypertension in pregnancy is a heterogeneous group of disorders. Hypertensive women tend to have an increased incidence of reduced or absent end-diastolic Doppler frequencies compared with the general population. Ducey et al. (1987) showed that, in hypertensive women, abnormal Doppler indices are more common in women with gestational proteinuric hypertension than in women with either

gestational hypertension or chronic hypertension (Davey and MacGillivray 1987 classification). This may reflect the typical placental vascular lesions of pre-eclampsia (a common cause of gestational proteinuric hypertension), with retention of small high resistance maternal arterioles (Dixon and Robertson 1958) leading to ischaemia of the intervillous space and possibly spasm or occlusion of the fetal tertiary stem villi. However, Cameron et al. (1988), in a study of women with pre-eclampsia, showed that 70% had normal umbilical artery indices with no clear correlation between the Doppler indices and the level of hypertension. The relation of placental vascular resistance to umbilical artery Doppler indices is discussed in section 1.2.10. Several of the randomized controlled trials of the utility of Doppler ultrasound discussed in section ciii below include a proportion of hypertensive patients.

1.2.8c Clinical studies of umbilical artery Doppler ultrasound in the assessment of fetal health

i Correlation of umbilical artery flow velocity waveform with antenatal fetal hypoxia and acidosis

Nicolaides et al. (1988), in a study of healthy pregnant women referred for investigation of fetal growth retardation, performed cordocentesis in 59 fetuses with absent end-diastolic umbilical artery flow. Twelve percent of the fetuses had normal oxygen tensions and pH,

42% were hypoxic, 8% were acidotic, and 37% were hypoxic and acidotic.

Tyrrell et al. (1989) studied the relationship between pre-operative umbilical artery Doppler velocimetry and umbilical vein pO_2 and pH in 112 women undergoing elective Caesarean section. The clinical efficiency of absent diastolic flow in the prediction of fetal hypoxia and acidosis is given in table 12. Their findings of a high sensitivity and positive predictive value of absent end-diastolic flow for fetal acidosis were not confirmed by Vintzileos et al. (1991) (table 13).

Table 12

The clinical efficiency of absent end-diastolic flow on Doppler velocimetry of the umbilical arteries in the prediction of fetal hypoxia and acidosis. From Tyrrell et al. 1989

	Hypoxia	Acidosis
Sensitivity	78%	90%
Specificity	98%	92%
Positive predictive value	88%	53%
Negative predictive value	98%	99%
Incidence	16%	9%
17 of 116 fetuses had absent end-diastolic flow		

Table 13

The clinical efficiency of absent end-diastolic flow on Doppler velocimetry of the umbilical arteries in the prediction of fetal acidosis. From Vintzileos et al. 1991

Sensitivity	11%
Specificity	89%
Positive predictive value	14%
Negative predictive value	85%
Incidence of acidosis	15%
7 of 62 fetuses had absent end-diastolic flow	

Ferrazzi et al. (1988) found a linear relationship between pulsatility index and base deficit in 14 high-risk patients undergoing Caesarean section. Although the relationship was statistically significant, the result was clinically unimportant with an increase in base deficit of only 1.5 mmol l^{-1} over the range of pulsitility index studied. Arduini et al. (1989), in a study of 50 women undergoing elective Caesarean section, were unable to find a relationship between umbilical artery Doppler velocimetry and umbilical cord acid-base analysis.

ii Comparison of umbilical artery Doppler indices with antenatal cardiotocography

Trudinger et al. (1986) compared antenatal CTG monitoring with umbilical artery Doppler ultrasound in the prediction of either low birthweight or a low 5 minute Apgar score in high risk obstetric patients. They concluded that Doppler ultrasound was more sensitive than CTG monitoring, with similar predictive values. It should be noted, however, that CTG monitoring is not an accepted diagnostic test for low birthweight. In the prediction of low Apgar score alone, CTG monitoring had a much higher sensitivity (70% vs 40%) and positive predictive value (21% vs 8%).

Subsequent studies have given conflicting results. Farmakides et al. (1988) suggested that an abnormal umbilical artery Doppler waveform predicted the development of an abnormal CTG. Pattinson et al. (1991)

suggested that Doppler ultrasound of the umbilical artery could replace the CTG as the initial investigation in at-risk fetuses, since the negative predictive value of Doppler ultrasound for an abnormal CTG was 99.8% in their study. However, in the randomized study of Hofmeyr et al. (1991), comparing antenatal assessment by CTG monitoring with umbilical artery Doppler velocimetry, no significant difference in perinatal outcome was detected between the two groups, except that emergency as opposed to elective Caesarean section was less frequent in the Doppler group (14% vs 20%).

Similarly, in the randomized study of Almström et al. (1992) comparing antenatal assessment of growth retarded fetuses with either CTG monitoring or umbilical artery Doppler velocimetry, emergency Caesarean section for fetal distress was less common in the Doppler group (5.1% vs 14.2%). The overall Caesarean section rate and neonatal outcome were similar in the two groups.

Comparisons of Doppler ultrasound with antenatal CTG monitoring are likely to be difficult to interpret because the utility of antenatal CTG monitoring is uncertain (Kidd et al. 1985).

iii Randomized controlled trials of antenatal surveillance using umbilical artery Doppler ultrasound

Trudinger et al. (1987a), in a study of antenatal in-patients, showed that knowledge of umbilical artery Doppler indices reduced the incidence of emergency Caesarean section from 23% to 13%; they could identify no difference in fetal or neonatal outcome.

Tyrrell et al. (1990), in a study of women at high risk of intrauterine growth retardation comparing routine or highly selected use of Doppler ultrasound and biophysical scoring (Manning et al. 1981), showed that routine surveillance reduced the incidence of low 5 minute Apgar score (Odds ratio 0.24, 95% CI 0.06 to 0.86) and serious neonatal morbidity (Odds ratio 0.12, 95% CI 0.02 to 0.98). Data concerning obstetric intervention were missing from 15% of patients in this study.

Newnham et al. (1991) assessed the effect of Doppler studies of umbilical and uteroplacental circulation in women referred to a tertiary centre for ultrasound diagnosis. No significant effect upon obstetric management or neonatal outcome was identified. The studies of Hofmeyr et al. (1991) and Almström et al. (1992), showing a decrease in emergency as opposed to elective Caesarean section in the Doppler group, have been discussed above, confirming the findings of Trudinger et al. (1987a).

Davies et al. (1992) studied the effect of routine Doppler ultrasound examinations of the umbilical and uterine arteries in pregnancy. They could not demonstrate any improvement in neonatal outcome by routine Doppler ultrasound screening of a general obstetric population.

In summary, a knowledge of umbilical artery Doppler indices in high risk patients may help to identify fetuses with insufficient reserve to withstand labour, and so reduce the incidence of emergency Caesarean section in labour and neonatal morbidity. These conclusions cannot be applied to the general population.

1.2.9 Doppler ultrasound of the umbilical arteries in abnormal labour

1.2.9a Pre-labour assessment

The study of Burke et al. (1990) and the randomized trials of Trudinger et al. (1987a), Tyrrell et al. (1990), Hofmeyr et al. (1991) and Almström et al. (1992) discussed above suggest that umbilical artery Doppler velocimetry is useful in determining which fetuses from a high risk population will be able to withstand the stress of labour.

Puzey and Lindow (1992) studied the value of umbilical artery Doppler analysis for the prediction of fetal acidosis in fetuses with CTG abnormalities in labour. A

negative correlation between the umbilical artery pulsatility index and the umbilical vein pH was found. However, many of the fetuses in their study appeared to be compromised before the onset of labour. Of the 10 fetuses with an abnormal pulsalitity index, 7 were delivered by Caesarean section for fetal distress early in labour. Exclusion of these patients abolished the supposed relationship between the umbilical vein pH and the pulsatility index. Details of the mode of delivery of the 32 fetuses with a normal pulsatility index were not given. In the same study, 21 fetuses had proceeded in labour sufficiently to allow for a fetal blood sample to be taken with the development of CTG abnormality. These subjects showed no correlation between scalp pH measurements and pulsatility index. Puzey and Lindow have provided further evidence for the use of Doppler velocimetry to indicate which fetuses are able to withstand labour.

1.2.9b Screening in labour

Several groups have studied the value of a single umbilical artery Doppler velocimetry measurement in labour for the prediction of adverse fetal outcome.

Feinkind et al. (1989) studied 273 unselected women in active labour. They found a negative correlation between the umbilical artery systolic/diastolic ratio and the 5 minute Apgar score. From the data presented it is not possible to assess whether this relationship is the

result of events occurring before or during labour. No correlation was found between the systolic/diastolic ratio and umbilical artery pH in the total sample, although these data were collected from only 135 patients. Analysis of subgroups showed that, in 16 fetuses with a systolic/diastolic ratio of 3 or more, negative and positive relationships existed between systolic/diastolic ratio and umbilical artery pH ($r = -0.74$, $P < 0.05$) and base deficit ($r = 0.86$, $P < 0.003$). It should be noted that analysis of subgroups may lead to erroneous conclusions (see, for example, Lee et al. 1980).

Sarno et al. (1989), studying 109 unselected women in the latent phase of labour, could find no relation between systolic/diastolic ratio and low Apgar score; however, the numbers in their study were small with only 8 subjects with an abnormal systolic/diastolic ratio.

Malcus et al. (1991) studied 575 women, including 198 high risk patients. Doppler examinations were made on admission in labour. The pulsatility index was abnormal in 88 fetuses. Umbilical artery pH was measured at birth in 371 cases. No relation was found between the pulsatility index and the umbilical artery pH or Apgar score.

The study of Puzey and Lindow (1992), discussed above, shows no relation between umbilical artery pulsatility

index and umbilical vein pH.

Howarth et al. (1992), in a study of 100 low risk labouring women, could find no relation between the umbilical artery Pourcelot ratio and intrapartum fetal compromise. However, their numbers were small, with 12 having an abnormal Pourcelot ratio, 6 having a 5 minute Apgar score less than 7, and 1 developing signs of hypoxic ischaemic encephalpathy.

1.2.9c Evaluation of an abnormal cardiotocographic tracing in labour

Brar et al. (1989) performed Doppler velocimetry in 50 patients with persistent late decelerations. They reported a significantly increased incidence of small for gestational age infants (75% vs 7.7%), meconium staining of the amniotic fluid (92% vs 15.4%), Caesarean section 67% vs 7.7%) and an Apgar score less than 7 at 5 minutes 42% vs 7.7% in 24 infants with systolic/diastolic ratios more than 2 standard deviations above the mean compared with 26 infants with systolic/diastolic ratios within 2 standard deviations of the mean. It is not clear from the data presented how many women were in labour.

Ogunyemi et al. (1992) performed Doppler velocimetry in 102 patients with cardiotocographic tracing abnormalities in labour. Twenty patients had abnormal systolic/diastolic ratios and 90% of these had at least

one indicator of adverse perinatal outcome compared with 15.8% of those with normal systolic/diastolic ratios. Like Puzey and Lindow (1992), Ogunyemi et al. concluded that umbilical artery Doppler velocimetry may be useful as an adjunct in the assessment of intrapartum CTG abnormalities suggestive of fetal distress. Both studies are probably referring to pre-labour fetal compromise. For example, in the study of Ogunyemi et al., the mean birthweight in those patients with normal systolic/diastolic ratios was 3351 g compared with 2775 g in those patients with abnormal systolic/diastolic ratios.

1.2.9d Summary

The available published studies to date indicate that Doppler velocimetry of the umbilical arteries may contribute to the pre-labour assessment of the high-risk pregnancy in deciding the mode of delivery. A role for Doppler ultrasound in labour in the assessment of the fetus has not been established.

1.2.10 Pathological correlations of reduced umbilical artery end-diastolic Doppler frequencies

1.2.10a Doppler indices, blood flow and impedance to flow

Impedance is the total effective resistance to flow arising from distal resistance and reactance of the vessel wall. Physical and animal models have proved useful in achieving an understanding of a relationship of Doppler

indices to flow and impedance.

Erskine and Ritchie (1985a) created a model consisting of a phantom blood vessel immersed in a water bath with citrated blood pumped through the system in a pulsatile manner. True mean blood velocity was found to be related to the average maximum Doppler shifted frequency in a linear manner.

Thompson and Stevens (1989) devised an electric circuit model of the branching patterns of the umbilical-placental circulation, with each vessel having resistance and capacitance. This model shows that the pulsatility index of the Doppler waveform depends both upon the pulsatility of the input pressure waveform and on the ratio of the resistance of the placental vascular bed to the resistance of the umbilical artery.

Trudinger et al. (1987b) performed embolization of the fetal lamb umbilical-cotyledon circulation. This procedure increased the resistance of the peripheral vascular bed, decreased umbilical flow and increased the umbilical Doppler systolic/diastolic ratio. Reduction of the uterine vascular bed by pre-pregnancy carunculectomy in the ewe results in fetal growth retardation but with normal umbilical artery Doppler indices (Giles et al. 1989). These animal models suggest that umbilical artery Doppler indices in the fetal lamb reflect the size of the

vascular bed and its resistance in the fetal umbilical-placental circulation.

1.2.10b Histological correlates of reduced end-diastolic frequencies

Giles et al. (1985) have shown that patients with a systolic/diastolic ratio greater than 3 standard deviations above the mean had significantly fewer small arteries in the tertiary stem villi than did controls. They postulate that antenatal studies of umbilical artery flow velocity waveforms identify patients with a specific neurovascular lesion in the placenta characterized by obliteration of small muscular arteries in the tertiary stem villi. These findings have been confirmed by McCowan et al. (1987).

1.2.11 Doppler ultrasound and fetal cardiovascular responses to metabolic disturbance

The cardiovascular responses occurring in animal models in response to acute hypoxia have been described in section 1.1.5, showing that in these models umbilical blood flow is unchanged by acute hypoxia. Using Doppler ultrasound to calculate blood velocity, Bilardo et al. (1990) have shown that, in the growth-retarded human fetus, an increase in blood velocity in the common carotid artery relative to the descending thoracic aorta is associated with (presumably chronic) hypoxic acidosis.

The shape of the umbilical artery flow velocity waveform is influenced by many haemodynamic factors, including impedance to flow and the pulsatility of the input pressure waveform. Even if umbilical artery blood flow remains constant with acute metabolic disturbance in the fetus, cardiovascular responses in the fetus might be reflected by a change in the umbilical artery Doppler waveform.

Morrow et al. (1990) have shown that in fetal sheep umbilical blood flow and the Doppler systolic/diastolic ratio remain constant during progressive hypoxic acidosis to a pH of 6.95!

Doppler velocimetry during development of acute fetal acidosis in the human fetus has not been studied.

1.2.12 Current areas of research into Doppler ultrasound and fetal distress

The current status of our knowledge concerning the use of Doppler ultrasound for screening in labour and evaluation of an abnormal CTG in labour is outlined in section 1.2.9.

An exciting development in the field of Doppler ultrasound and diagnosis of fetal compromise has been the work of Vine et al. (in press). They note that in the normal fetus the ductus venosus is hard to visualize ultrasonographically. They postulate that the ductus

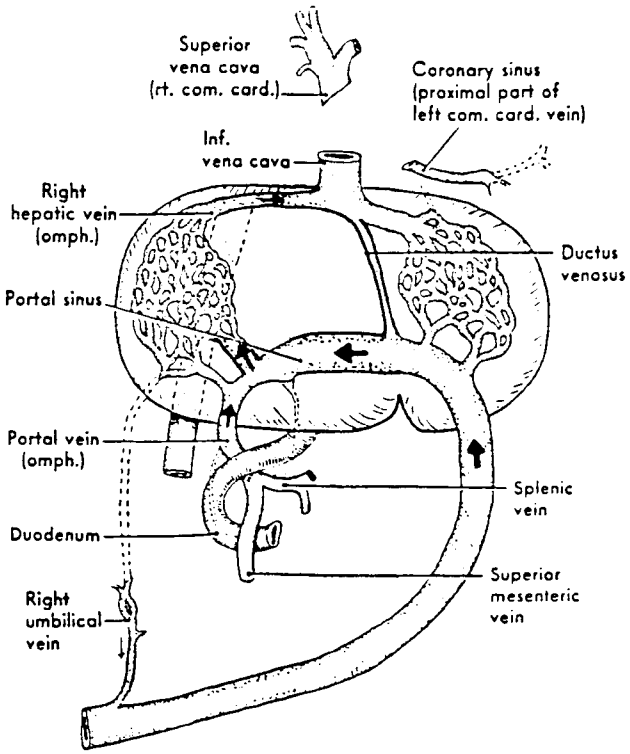
venosus may dilate in response to fetal hypoxia and this might reverse the flow of blood in the portal sinus (figure 4). In their study of 245 normal subjects, the portal sinus could not be visualized in 9 fetuses, the flow was from left to right in 232 and from right to left in 4. Three of the fetuses died in the study group - 1 from the group with left to right flow (this fetus had a congenital cardiac anomoly) and 2 out of the 4 with flow from right to left.

One of these died from hypoxia, and the other from multiple congenital anomolies. The other 2 fetuses in the right to left flow group were healthy but had an anomolous development of the right umbilical vein.

The findings of Vine et al. correlate with the demonstration by Peltonen and Hirvonen (1965) and Reuss and Rudolph (1980) that the fetal lamb ductus venosus dilates with hypoxia.

Localization of the portal sinus requires duplex pulsed Doppler equipment. Another consequence of dilation of the ductus venosus in response to hypoxia might be that the impulse of closure of the mitral valve might become apparent in the umbilical vein flow velocity waveform, and this could be detected with continuous wave equipment.

A.



B.

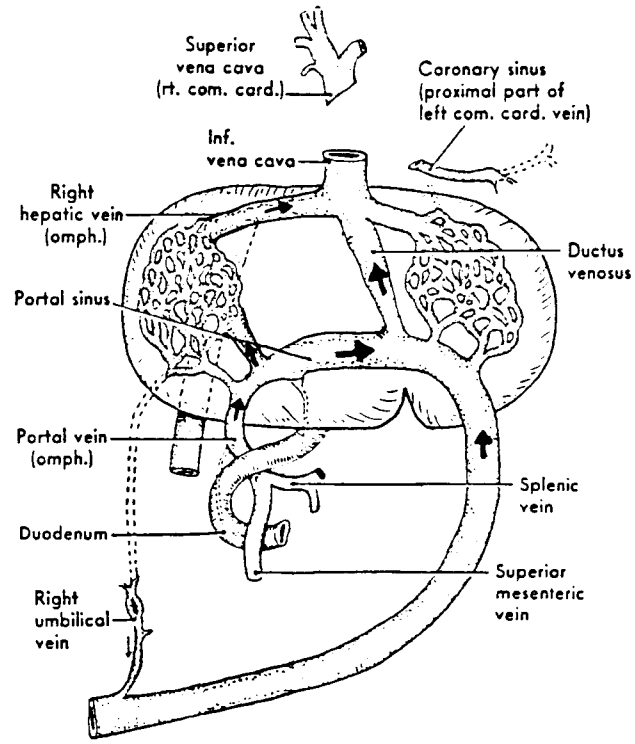


Figure 4

The fetal venous circulation

A. The circulation in health with constriction of the ductus venosus

B. The response to hypoxia with dilatation of the ductus venous and reversal of direction of blood flow in the portal sinus.

1.3 Summary

Currently available indicators of intrapartum fetal distress are poor predictors of permanent neurological disability. Alternative methods of fetal monitoring in labour require assessment. Doppler velocimetry of the umbilical arteries has not previously been studied in the human fetus developing fetal distress in labour. The haemodynamic changes in the fetus occurring with the development of fetal distress may be reflected by changes in the umbilical artery Doppler velocimetry indices, and this possibility provided the motivation for the clinical study presented in this dissertation.

2 Aim of the study

The aim of the study was to assess the role of Doppler ultrasound velocity waveform analysis of the fetal umbilical arteries in the diagnosis of fetal distress in labour. Consideration of the available literature reviewed in section 1 led to the formulation of two hypotheses to be tested.

2.1 Predictive testing

Fetal distress is thought commonly to arise through utero-placental insufficiency (section 1.1.3). Umbilical artery flow velocity waveform indices are commonly increased in pregnancy complicated by fetal compromise through utero-placental insufficiency (section 1.2.8). This has led previous groups to study in low risk populations the value of a single umbilical artery Doppler velocimetry measurement in labour for the prediction of adverse fetal outcome (section 1.2.9b). The first aim in this study was to assess the value of umbilical artery Doppler velocimetry, in a high risk labouring population, in the prediction of fetal distress as measured by umbilical artery acid-base parameters, Apgar score and neonatal clinical assessment.

2.1.1 Hypothesis One

Abnormal umbilical artery flow velocity waveform indices are predictive for the development of fetal distress in labour.

2.1.2 Null Hypothesis One

There is no difference in fetal outcome as measured by indicators of fetal distress between patients with normal and abnormal umbilical artery flow velocity wave forms.

2.2 Diagnostic testing

Animal models have shown that acute hypoxia induces cardiovascular responses in the fetus resulting in redistribution of the blood flow in favour of the vital organs (section 1.1.5). Similar responses in the human fetus might be associated with changes in one or more of the factors that determine the umbilical artery flow velocity waveform (sections 1.2.10 and 1.2.11). The second aim in the study was to see whether the Doppler velocimetry indices change with the development of indicators of fetal distress.

2.2.1 Hypothesis Two

Umbilical artery flow velocity waveform indices change with the development of fetal distress in labour.

2.2.2 Null Hypothesis Two

There is no difference in the change of mean flow velocity waveform indices between fetuses who develop indicators of fetal distress in labour and those who do not.

3 Subjects and methods

3.1 Ethics Committee approval

The study was approved by the Ethics and Research Committee of the Faculty of Medicine of the University of Cape Town (see appendix 1).

3.2 Subjects

3.2.1 Population

The study was performed in the Maternity Centre of Groote Schuur Hospital which forms part of the Peninsula Maternal and Neonatal Service (PMNS) (van Coeverden de Groot and Howland 1990). The PMNS delivers some 30 000 women per annum, constituting approximately 80% of the deliveries in the region, the remaining 20% being delivered in the Private Sector.

3.2.2 Sample

A sample of women at high risk for the development of fetal distress in labour was selected. Such a sample was chosen to facilitate the study of the clinical efficiency of Doppler ultrasound in the prediction and diagnosis of fetal distress (see section 1.1.4a). Subjects were selected with either gestational proteinuric hypertension (Davey and MacGillivray 1987) or intrauterine growth retardation (ultrasound estimate of abdominal circumference below the 5 percentile for our range) or

both, with a normal cardiotocographic tracing at the onset of labour. Placental insufficiency is often associated with these two conditions, with the resultant high risk for the development of fetal distress.

3.2.3 Exclusions

Patients at less than 34 completed weeks gestation were excluded because of the technical difficulty of recording umbilical artery Doppler flow velocity waveform with continuous wave equipment in small babies. The patient's responsible clinician had to be planning a vaginal delivery at the time of recruitment to the study.

Patients were excluded if the pregnancy was complicated by fetal abnormality, diabetes mellitus, multiple pregnancy, breech presentation, or acute fetal distress due to cord prolapse or placental abruption.

3.2.4 Controls

The Maternity Centre at Groote Schuur Hospital serves as the tertiary referral centre for the PMNS. Women at low risk for pregnancy complications are delivered in the Midwife Obstetric Units (van Coeverden de Groot and Howland 1990). Controls should consist of normal women, defined for the purposes of this study as being women without previous medical disease, with a normal past obstetric history (notably no second or third trimester fetal loss, no history of recurrent (ie 3 or more) first

trimester miscarriages, no small for dates babies, no hypertension or diabetes; a previous Caesarean section per se did not exclude a woman as being considered normal), no antenatal problems in the current pregnancy (notably no hypertension, antepartum haemorrhage, diabetes, nor intrauterine growth retardation) presenting at term in spontaneous labour with a single fetus presenting by the vertex.

3.2.4a Doppler velocimetry

Doppler velocimetry was performed as described in section 3.3.1a. The portability of the continuous wave Doppler machine allowed for control subjects to be sought outside the Maternity Centre at Groote Schuur. Normal women, as defined above, were studied at three Midwife Obstetric Units (St Monica's Hospital, Retreat and Hanover Park), two Maternity Hospitals (Peninsula Maternity Hospital and Somerset Hospital) and Groote Schuur Hospital. Gestation was calculated by reference to the last menstrual period, using Naegele's rule.

An abnormal Doppler velocimetry index was defined as an index greater than the 95th percentile for the gestation.

3.2.4b Umbilical cord blood acid-base balance

Machines for blood acid-base analysis are not portable and so a meaningful reference range from normal women could not be obtained. Reference was made to published

reference ranges for normal women (table 14). Sykes et al. (1982) reported a reference range for a total teaching hospital population. D'Souza et al. (1983) reported from a teaching hospital population but excluded those delivered by Caesarean section. Miller et al. (1990) reported a reference range for term, healthy newborns, excluding babies born with Apgar scores of less than 7, and those with evidence of neonatal neurological compromise. The reference range of Miller et al. would therefore seem to be the most appropriate for use in this study as a control reference range. They reported 5th percentile boundaries of a pH of 7.12 and a base deficit of 10.1 mmol l^{-1}.

Table 14

Reference ranges for umbilical arterial pH and base deficit in normal women

Author	Number studied	pH		Base deficit (mmol l^{-1})	
		mean	S.D.	Mean	S.D.
Sykes et al. (1982)	1039	7.20	0.08	8.33	3.97
D'Souza et al. (1983	453	7.27	0.08	3.76	4.16
Miller et al. (1990)	147	7.27	0.06	3.3	2.8

S.D. = standard deviation

3.3 Methods

3.3.1 Techniques

3.3.1a Umbilical artery Doppler flow velocity waveform

The machine used was a Sonicaid Vasoflo-3c continuous wave machine with a 4MHz low power probe and 100 Hz filter. The maximum acoustic intensity of the probe is 78 $mWcm^{-2}$. The machine was loaned by ART Medical, Cape Town.

Measurements were taken after ensuring adequate maternal hydration (using intravenous fluid if necessary) and exclusion of maternal hypotension, with the patient in the left lateral position. Measurements were made in between contractions in the absence of fetal heart rate abnormality (section 1.1.4b).

The likely location of the umbilical cord was found by palpating the fetal back, and the probe was placed on the opposite side of the uterus, midway between the fetal anterior shoulder and feet, directed towards the fetus. The umbilical vessels were recognized by the characteristic saw-tooth pattern of the umbilical artery and continuous venous flow in the opposite direction (figure 2). As clear and intense a signal as possible was obtained. Readings were taken in the absence of fetal breathing movements ie. with a constant maximum frequency outline of the flow velocity waveform.

The machine provided a print-out of the flow velocity waveform and analysis (figure 2). Doppler indices were calculated by the machine from 5 waveforms. Where possible, readings were repeated to allow for calculation of methodological error. All measurements were taken by the author.

3.3.1b Cardiotocography

Continuous cardiotocography tracings were obtained in labour from each subject by means of available machines (usually a Hewlett Packard 8040A machine) using either external or fetal scalp electrode monitoring of the fetal heart. This is standard obstetric practice for fetuses at high risk of developing fetal distress in labour.

3.3.1c Fetal blood sampling

This was performed by the clinicians responsible for the patient, as he or she thought indicated. The membranes if intact were ruptured and swept aside. A vaginal speculum was used to visualize the fetal head, blood and liquor cleaned away, the scalp was anaesthetized using ethyl chloride, and an incision was made in the scalp. The droplet of blood so formed was collected in a glass capillary tube, and transferred to a heparinized tube before analysis using an Instrument Laboratory 1306 pH/Blood Gas analyser.

3.3.1d Cord blood analysis

At delivery a length of umbilical cord was clamped at either end and clamped again in the middle. Both arterial and venous cord pH and base deficit were measured immediately after birth from one half of the cord, along with maternal artery blood if available. The measurements were then repeated using the other half of the cord. The cord was kept at room temperature in between measurements. The timing of measurements in relation to delivery time was recorded. The above-mentioned pH/blood gas analyser was used.

3.3.1e Apgar score

This was recorded by the attending midwife or paediatrician.

3.3.1f Birthweight

This was also recorded by the attending midwife or paediatrician. Reference ranges are available for the PMNS (Woods 1984).

3.3.1g Gestation

A clinical estimate of gestational age was made in each newborn infant, according to the method of Dubowitz et al. (1970). All assessments were made by the same investigator, Dr C.W. van der Elst.

3.3.1h Neurological assessment of the newborn infant

Each baby was carefully examined for clinical signs of perinatal hypoxia (Sarnat and Sarnat 1976). All measurements were made by the same investigator, Dr C.W. van der Elst. A sample record sheet is shown in appendix 2.

3.3.2 Procedure

Subjects were counselled regarding the purpose of the study and the procedure to be undertaken. Verbal consent was obtained. Doppler velocimetry indices were obtained at the onset of labour and again shortly before delivery. In addition, if the attending clinician performed a fetal blood sample, the Doppler velocimetry indices were measured prior to the procedure. The attending clinician, midwife and patient were not informed of the result of the Doppler analysis. The performance of the Doppler velocimetry was not allowed to interfere with the clinical management of the patient. For example, if the attending clinician felt that immediate delivery was indicated, this was not delayed in order to obtain Doppler velocimetry indices. After delivery, acid-base status of the fetus and, if available, of the mother were assessed by analysis of cord and maternal arterial blood. The Apgar score, gestational age and neurological status of the newborn were recorded as described in section 3.2.1. A sample record sheet is shown in appendix 2.

A record of any patients refusing to enter the study, or failure to obtain Doppler velocimetry indices or cord blood for analysis was kept.

3.3.3 Statistical methods

Departure from normality for the distributions of the Doppler velocimetry indices was tested using the normal plot, Pearson's moment test, the Shapiro-Wilk test and the Chi-squared test. Confidence intervals and power calculations in the subsequent analysis were made on the assumption that samples and sample differences were normally distributed. For these calculations the normal distribution was replaced by the t distribution. Pearson's correlation coefficient, and for non-parametric analysis, Spearman's rank correlation coefficient, the Mann-Whitney U test and Fisher's exact test were used.

A discussion of statistical principles and methods used in this dissertation is given in appendix 3.

4. Estimate of numbers required for the study

4.1 Predictive testing

Null Hypothesis One is stated in section 2.1. A difference in means of umbilical artery base deficit between subjects with normal and abnormal Doppler velocimetry indices of 4 mmol l^{-1} or more might be regarded as clinically useful. This represents a difference of about 1 standard deviation or more in the distribution of the umbilical artery base deficit (Sykes et al. 1982, D'Souza et al. 1983, Miller et al 1990). It is assumed that in the selected population of the study about 25% of subjects will have abnormal umbilical artery Doppler flow velocity waveforms.

For an 80% power to disprove the null hypothesis at a 95% confidence level for a difference of 1 standard deviation or more, the number of subjects required (n) is given approximately by:

$$1 - P(x) = 0.80$$

$$P(x) = 0.20$$

$$x = -0.8416$$

$$-0.8416 = 1.96 - \frac{\sigma}{\sqrt{\frac{4\sigma^2}{n-1} + \frac{4\sigma^2}{3(n-1)}}}$$

$$\underline{n = 43}$$

4.2 Diagnostic testing

The distribution of change in Doppler velocimetry indices in labour is not known, and so the number of subjects required to disprove the null hypothesis cannot be estimated.

5. Results

A summary of the study data is given in appendix 4.

5.1 Numbers

5.1.1 Controls

Twenty-two normal women were studied in labour to obtain reference ranges for Doppler velocimetry indices (see table 15).

Table 15

Doppler velocimetry indices obtained from 22 normal labouring women

	Mean	S.D.
Pourcelot ratio	0.566	0.066
Pulsatility index	0.863	0.155
Systolic/diastolic ratio	2.425	0.383

5.1.2 Subjects

Thirty-six patients were approached between 16/05/91 and 27/07/91 with regard to recruitment to the study. The investigator was not aware of any other patients during this period eligable for recruitment. All patients accepted and satisfactory Doppler velocimetry measurements

were obtained from all subjects early in labour. Nine patients delivered without repeat Doppler velocimetry and cord blood analysis. The reasons for this were not being called to the delivery (8 patients) and being unable to obtain repeat Doppler velocimetry measurements (1 patient).

5.2 Timing of Doppler velocimetry

The median duration of labour following the initial Doppler velocimetry was 390 minutes (range 132 to 1080 minutes). The median time from repeat Doppler velocimetry to delivery was 30 minutes (range 5 to 180 minutes)

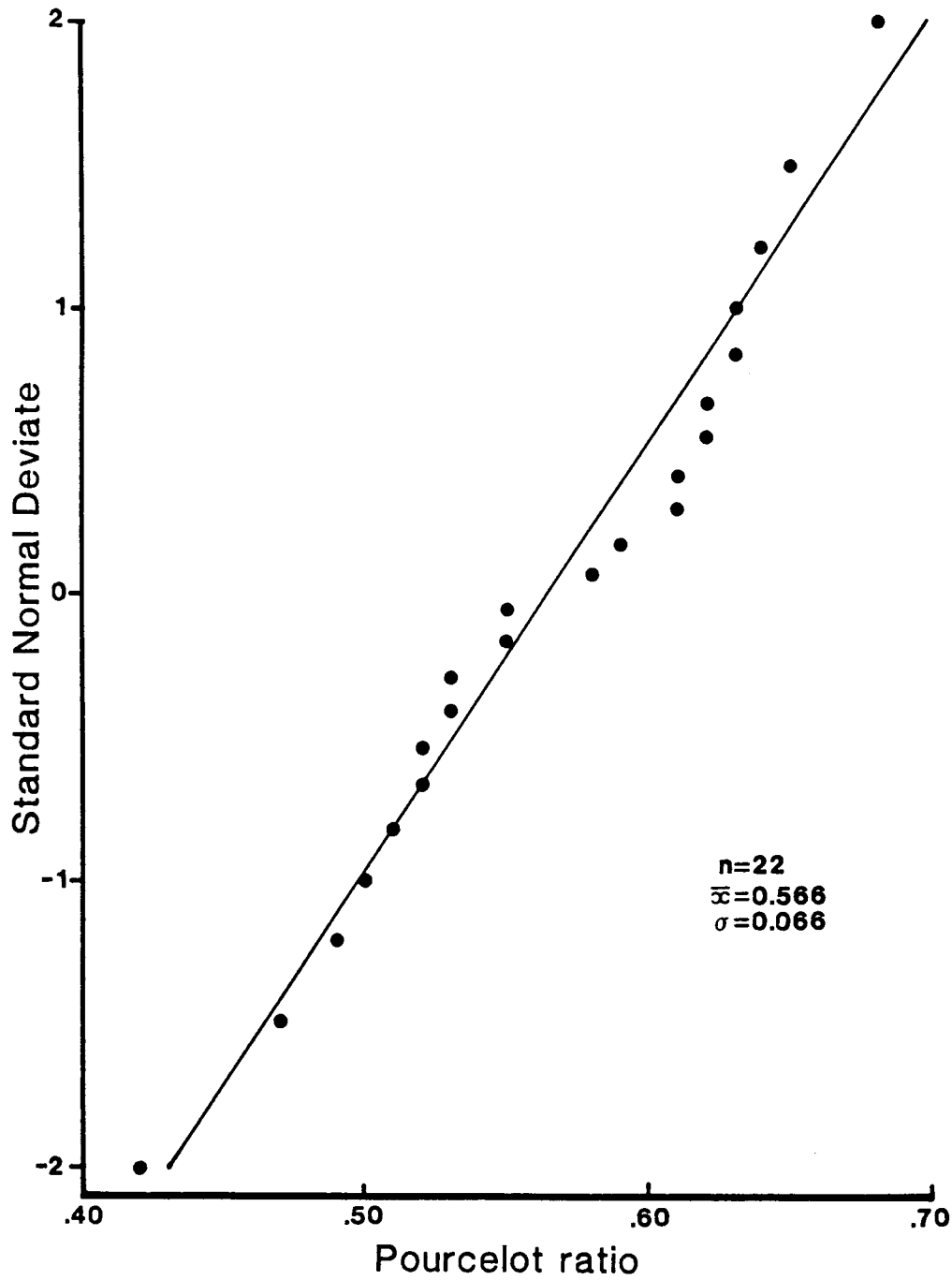


Figure 5

Normal plot of umbilical artery Pourcelot ratio of normal subjects in labour

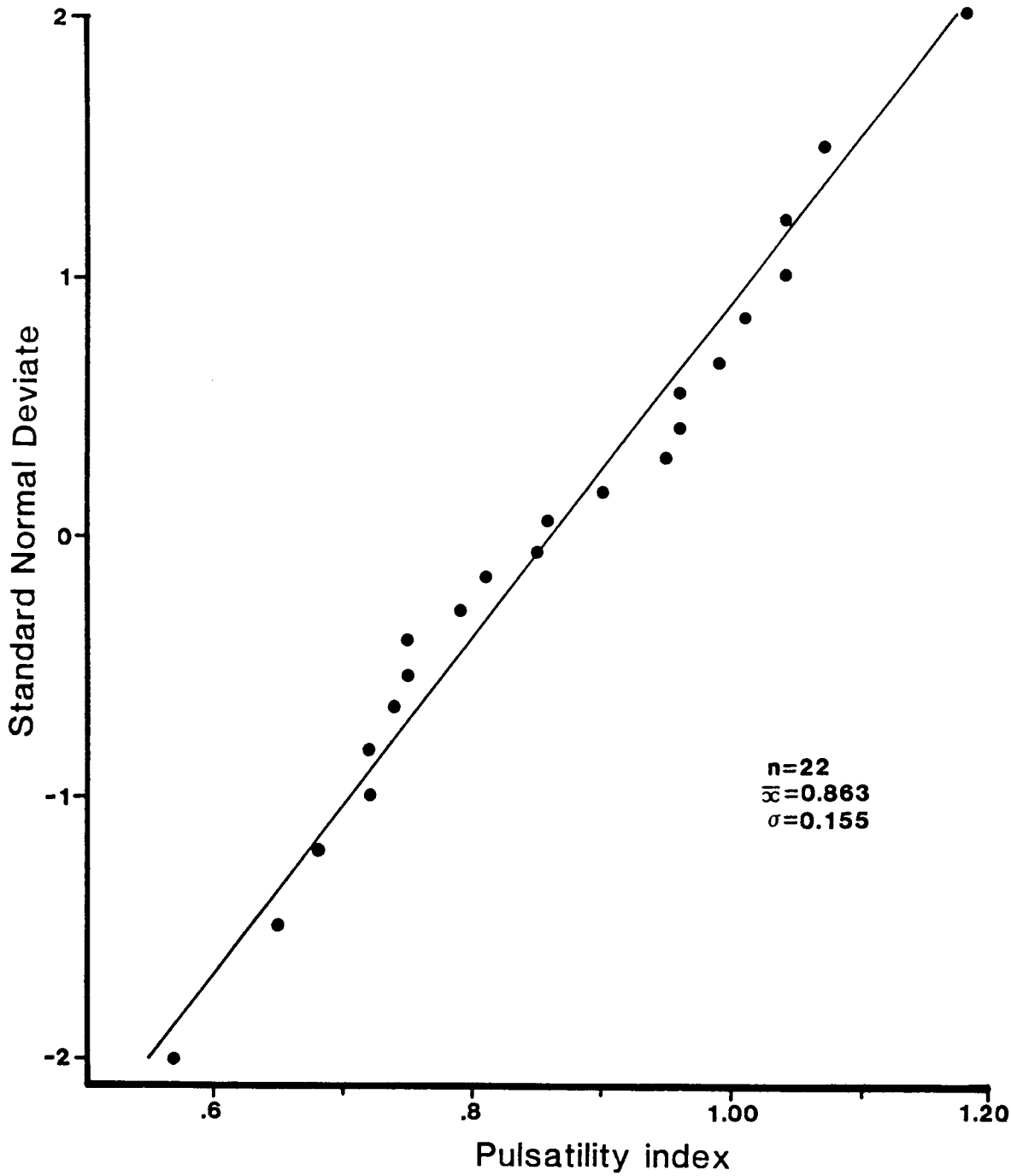


Figure 6

Normal plot of umbilical artery Pulsatility index of normal subjects in labour

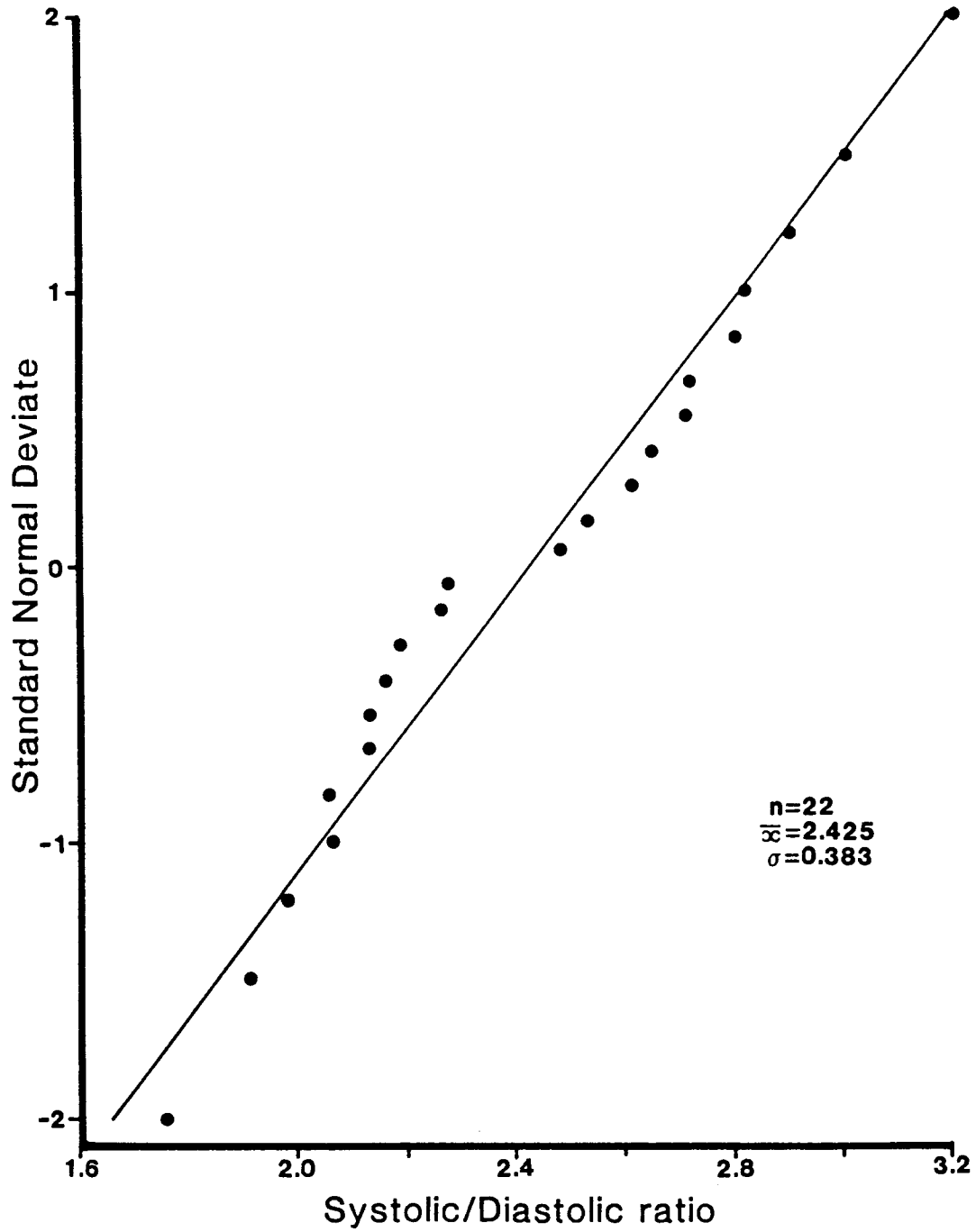


Figure 7

Normal plot of umbilical artery systolic/diastolic ratio of normal subjects in labour

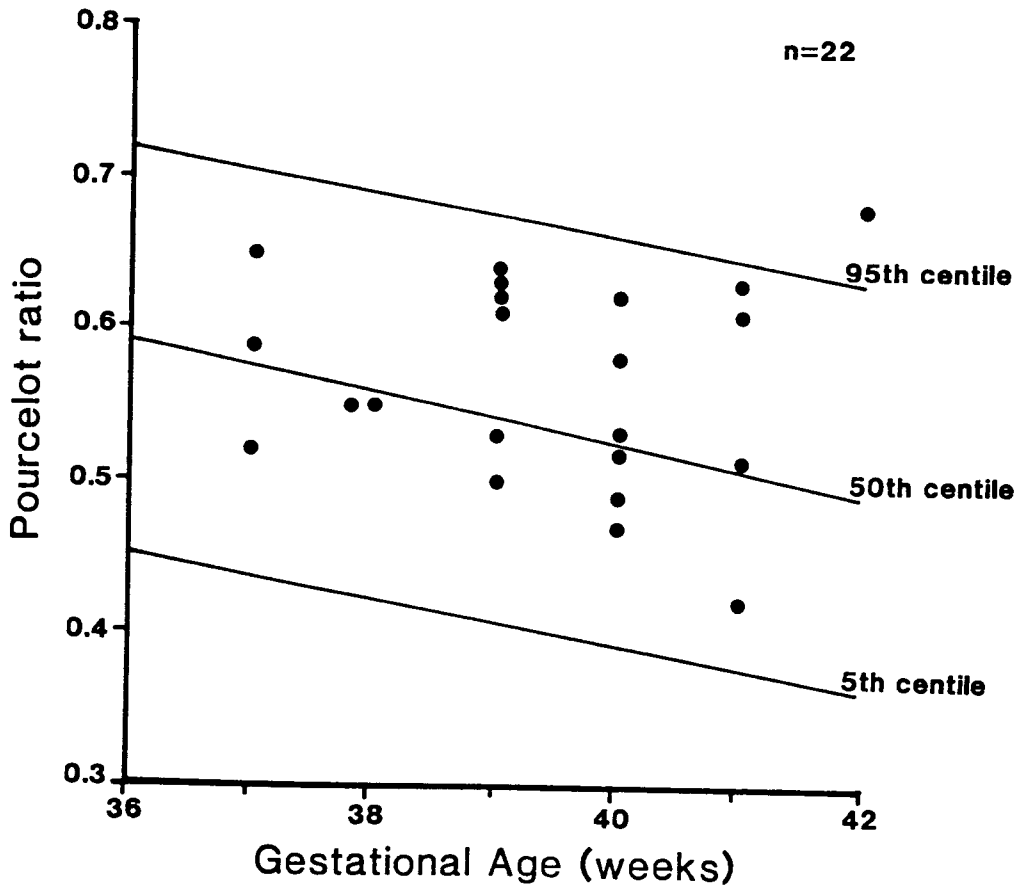


Figure 8

Plot of umbilical artery Pourcelot ratio of normal subjects in labour with reference to published normal values from Cape Town (Pattinson et al. 1989)

5.3 Tests for the normal distribution

5.3.1 Doppler flow velocity waveform indices

5.3.1a Controls

Normal plots suggested that the Pourcelot ratio, pulsatility index and systolic/diastolic ratio were all normally distributed (figures 5 to 7). Proof of normality at a 95% confidence level could not be obtained by formal numerical testing (Shapiro-Wilk W test, W = 0.965 (Pourcelot ratio), 0.976 (pulsatility index) and 0.963 (systolic/diastolic ratio), with $0.1 < P < 0.5$ for each). Means and standard deviations for the three indices are given in table 15.

The distribution of the Pourcelot ratio at successive gestations closely followed the reference range for Cape Town published by Pattinson et al. (1989), shown in figure 8.

The reference range of Pattinson et al. was therefore used in the subsequent analysis, with an abnormal Pourcelot ratio being defined as one greater than the 95th percentile for the gestation.

5.3.1b Study sample

Normal plots showed that the Pourcelot ratio, pulsatility index and systolic/diastolic ratio were all positively

skewed from normal (figures 9 to 11). The degree of skewness was least for the Pourcelot ratio ($\sqrt{b_1}$ = 1.42, P < 0.002; D'Agnostino and Tietjen 1973), greater for the pulsatility index ($\sqrt{b_1}$ = 2.33, P < 0.002) and not calculable for the systolic/diastolic ratio. The Shapiro-Wilk W test conclusively showed non-normality for the Doppler indices of the complete study sample (for the Pourcelot ratio, W= 0.908, P < 0.01 at lower tail).

Further assessment of normality was made using the Chi-Squared test, after the exclusion of subjects with a velocimetry index more than two standard deviations above the mean of the control sample (table 15). Contingency tables with an expected number of 3 in each compartment were used. This provided good evidence of normality for the distribution of the Pourcelot ratio (χ^2 = 2 with 7 degrees of freedom, P > 0.95) while the distributions of the pulsatility index and the systolic/diastolic ratio were demonstrated not to be normal (for the pulsatility index, χ^2 = 14.33 with 5 degrees of freedom, P < 0.025; for the systolic/diastolic ratio, χ^2 = 10.33; with 4 degrees of freedom, P < 0.05). For this reason, the Pourcelot ratio alone was used in the subsequent analysis.

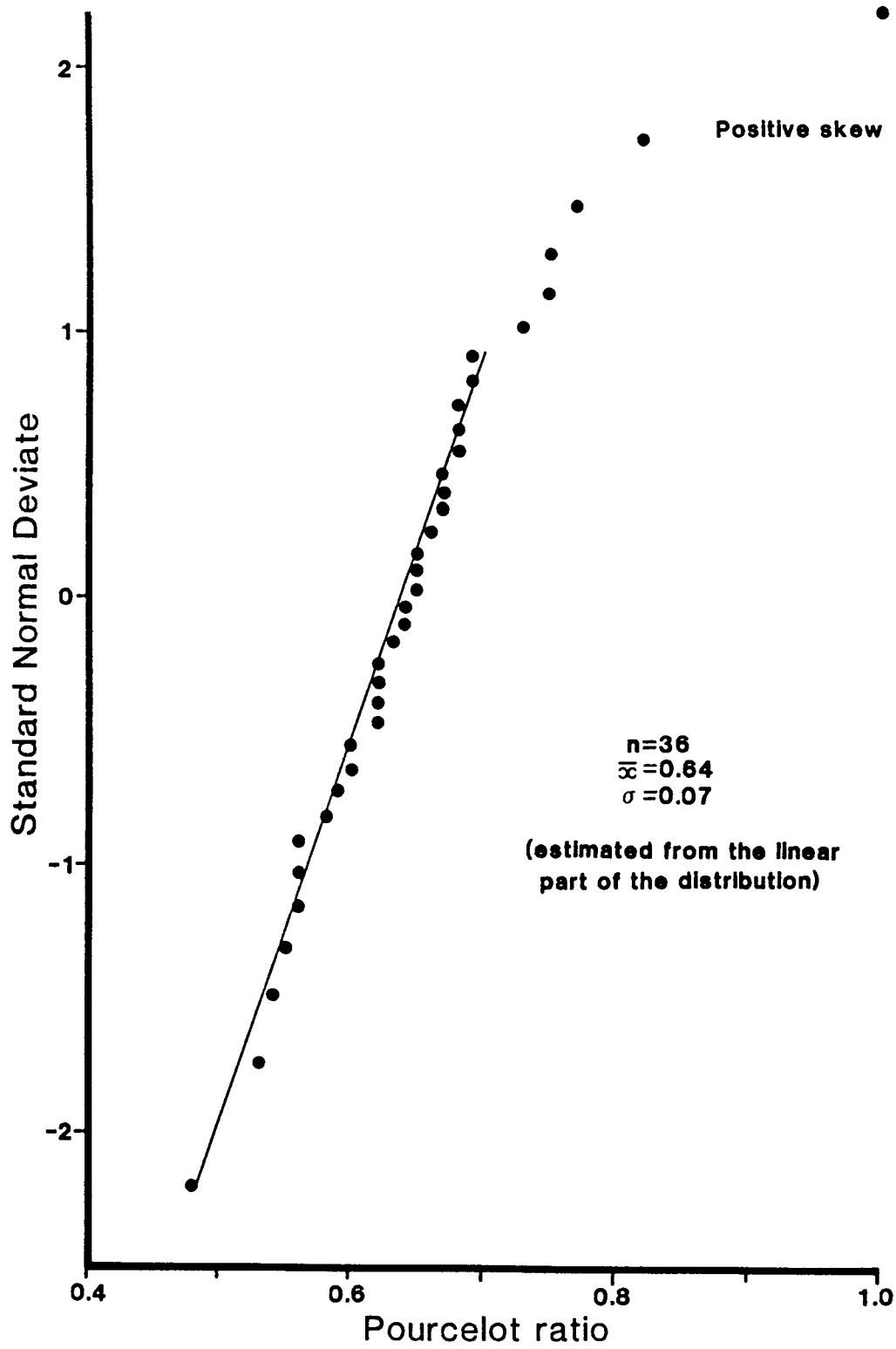


Figure 9

Normal plot of umbilical artery Pourcelot ratio from the study sample on admission in labour

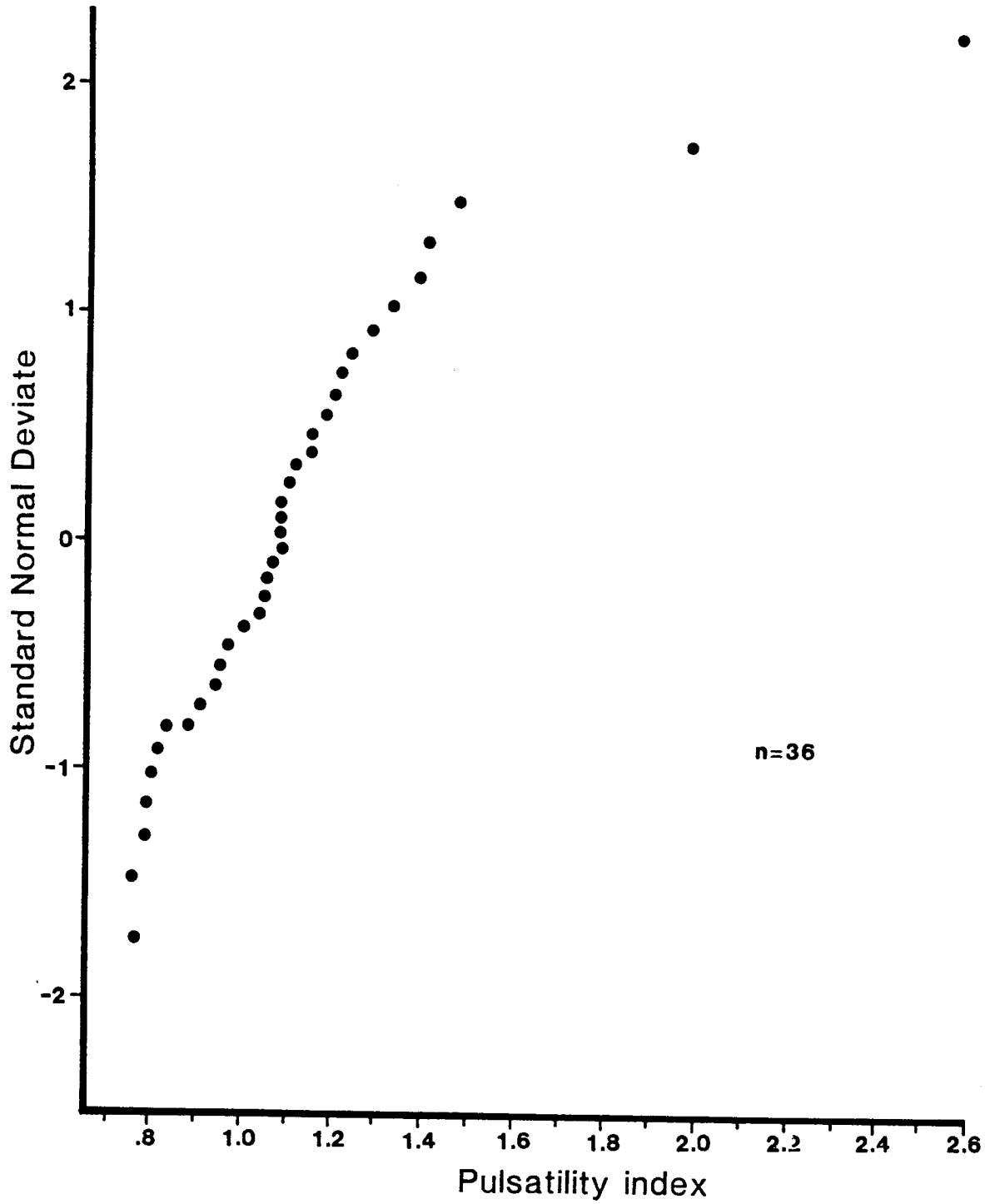


Figure 10

Normal plot of umbilical artery pulsatility index from the study sample on admission in labour

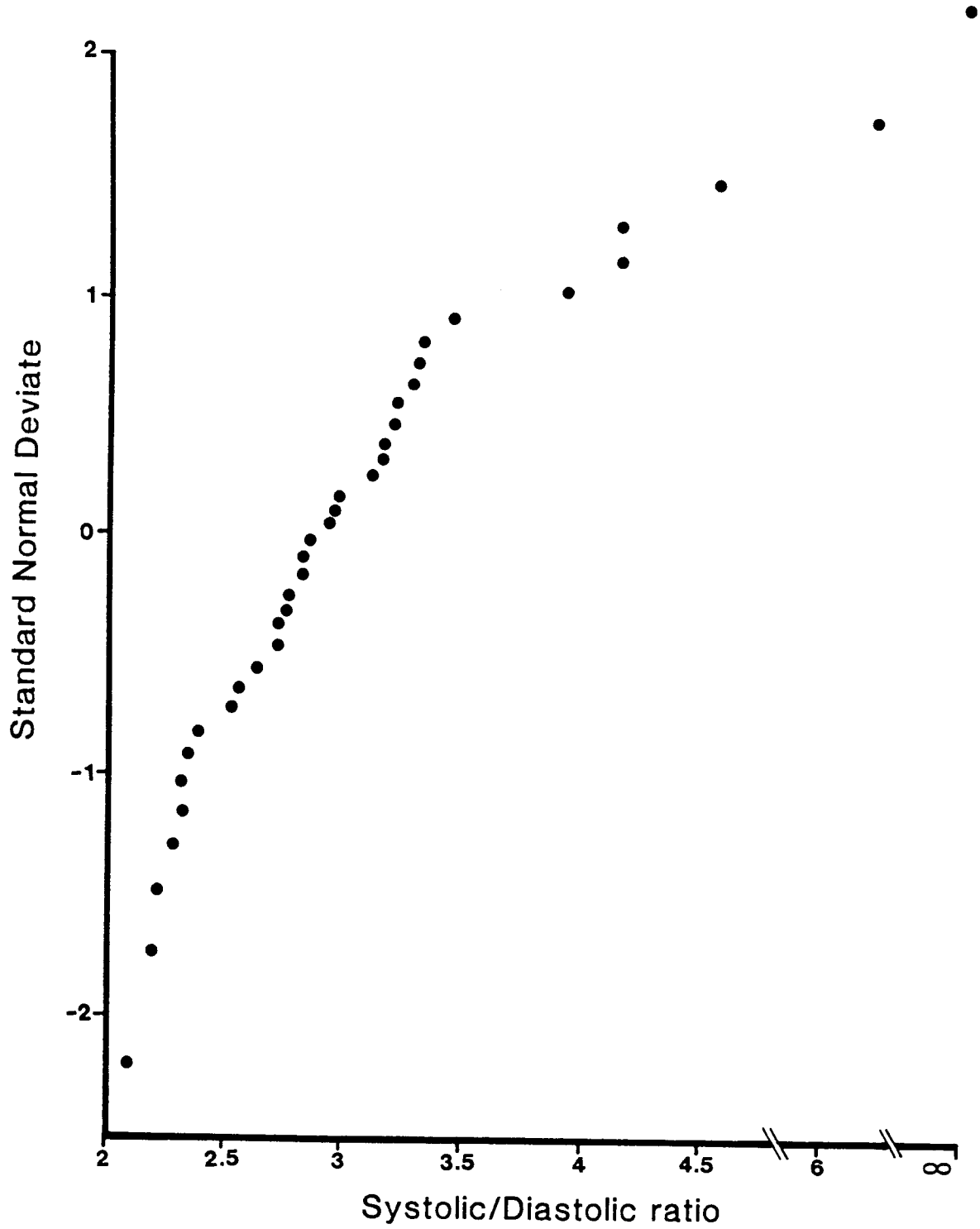


Figure 11

Normal plot of umbilical artery systolic/diastolic ratio from the study sample on admission in labour

5.3.2 Umbilical artery pH and base deficit

A normal plot of umbilical artery pH demonstrated marked departure from normality in the tails of the distribution, with a positive skew at low pH's and negative skew at high pH's (figure 12). Distributions of derivatives of umbilical artery pH were not studied. Formal testing using the Shapiro-Wilk W test confirmed that the distribution of pH was not normal ($W = 0.493$, $P < 0.01$, lower tail). Inspection of the central portion of the normal plot suggested normality within one standard deviation of the mean. The mean pH was 7.20 with standard deviation 0.08, derived by inspection of the normal plot.

A normal plot suggested that the distribution of the umbilical artery base deficit in the study sample was normally distributed (figure 13). Proof of normality could not be confirmed by formal numerical testing (Shapiro-Wilk W test, $W=0.9624$, $0.1 < P < 0.5$, lower tail) nor by the chi-squared test. The mean base deficit was 8 mmol l^{-1} with a standard deviation of 3.5 mmol l^{-1}, derived from the normal plot.

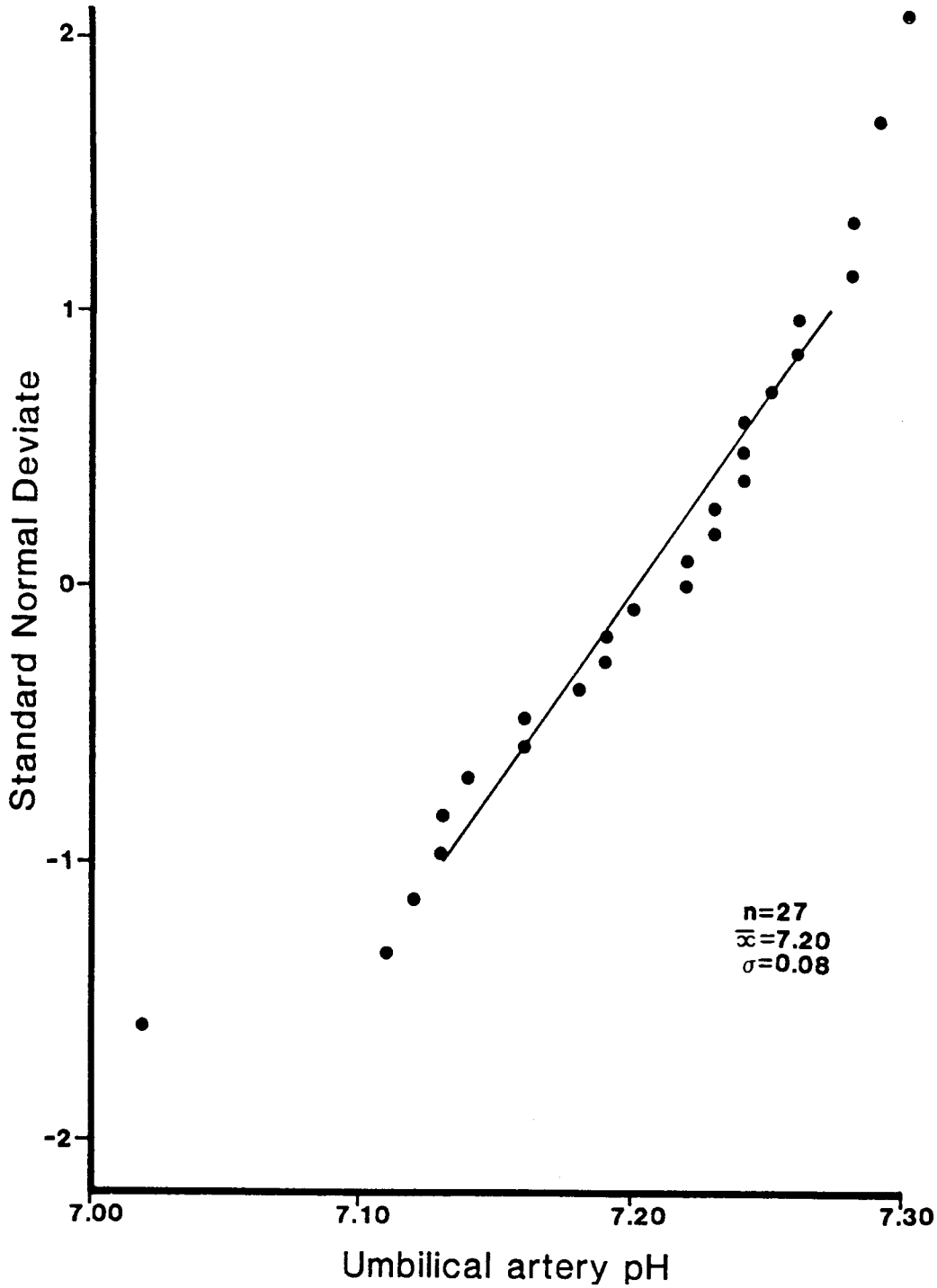


Figure 12

Normal plot of umbilical artery pH in study sample

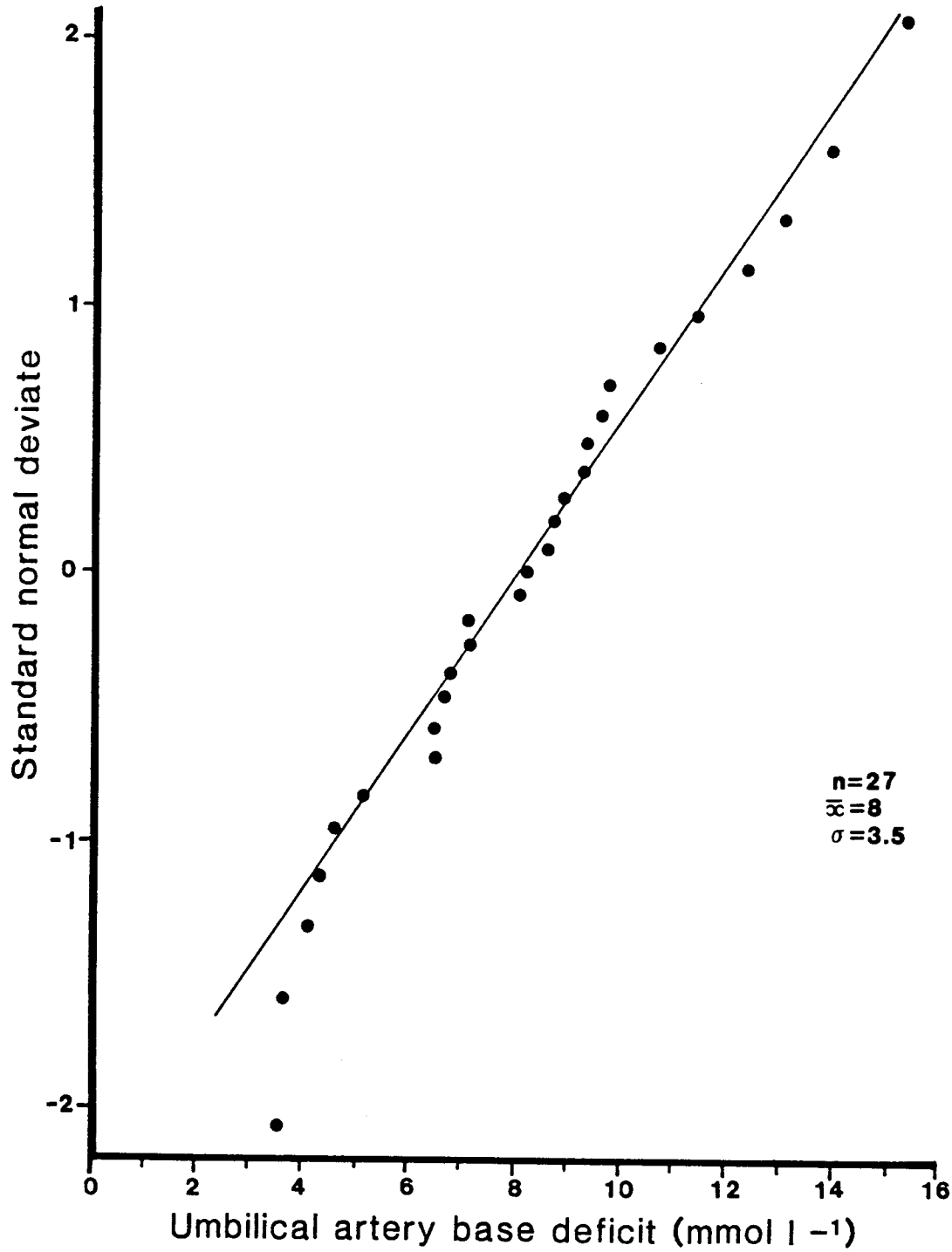


Figure 13

Normal plot of umbilical artery base deficit in study sample

Insufficient cord artery blood from some subjects resulted in only 12 paired measurements of umbilical artery pH and base deficit. The t distribution was used for analysis (appendix 3 section 5).

The null hypothesis that the change in mean pH was zero was tested, giving t = 0.839 with 11 degrees of freedom, 0.5 > P > 0.1. The mean change in arterial pH was + 0.0017 (95% CI -0.0027 to +0.0060). The potential size of the change in pH, given by the 95% confidence intervals, was considered too small to be clinically important.

The null hypothesis that the change in base deficit was zero was tested, giving t = 1.875 with 11 degrees of freedom, 0.1 > P > 0.05 (i.e. the null hypothesis was disproved at a 90% but not a 95% confidence level). The mean change in base deficit was + 0.45 (95% CI - 0.08 to +0.98). The potential size of the change in base deficit, while not of any clinical importance for the testing of an individual, might be significant in terms of a study relying upon distribution cut-off points.

5.4 Verification of methodology

5.4.1 Confidence intervals for measurement of Pourcelot ratio

Paired observations were used to calculate 95% confidence intervals for the estimate of the Pourcelot ratio (appendix 4 section 4). These were found to be x - 0.08

to x + 0.12 before delivery (n = 24) where x was the measured Pourcelot ratio. The corresponding coefficients of variation were 4.7% and 6.5%.

5.4.2 Change in Pourcelot ratio with fetal heart rate

Paired observations (n = 104) were used to assess the effect of change in fetal heart rate on the Pourcelot ratio. No effect was demonstrated (95% CI - 0.0015 to +0.0015 per beat per minute).

5.4.3 Change in pH and base deficit in cord blood in relation to time from delivery to measurement

The umbilical artery pH and base deficit was measured immediately after delivery. The median time from delivery to measurement of the cord blood pH was 4 minutes, with a range of 4 to 7 minutes. Measurements were repeated 9 minutes later, allowing for other measurements (umbilical venous and maternal blood if available) in between. The cord was kept at room temperature until final analysis of the blood. The purpose of this temporal analysis was to give some indication of what change in pH and base excess might occur between delivery and initial measurement, and the effect of delayed measurement in any individual.

5.4.4 Confidence intervals for pH and base deficit estimates

The repeated measurements described in section 5.4.3 were used to calculate 95% confidence intervals for the measurement of umbilical artery pH and base deficit.

Adjustment was not made for the small potential changes in pH and base deficit. 95% confidence intervals were found to the (pH -0.035) to (pH +0.035) for the measurement of pH and (base deficit -2.05) to (base deficit +2.15) mmol l^{-1} for the measurement of base deficit. Corresponding coefficients of variation were 0.16% and 17.9%.

5.5 Characteristics of subjects followed and not followed through labour

Of the 36 patients recruited to the study, 9 delivered without repeat Doppler ultrasound and umbilical artery pH measurements. Characteristics of these 9 subjects were studied and were compared with the remaining 27 subjects (see table 16) to assess whether the loss of the 9 from the subsequent analysis might bias the results.

5.5.1 Doppler flow velocity waveform

The Pourcelot ratios at the onset of labour in the 9 subjects not followed through labour (median 0.67) tended to exceed those of the 27 followed through labour (median 0.63) (Mann-Whitney U test, U = 58, P = 0.01). One of the 9 subjects had absent end-diastolic flow compared with none of the 27.

5.5.2 Mode of delivery

Using Fisher's exact test, no difference in mode of delivery was noted between the subjects followed and not followed through labour.

5.5.3 Apgar score

Using the Mann-Whitney U test, no difference in 1 and 5 minute Apgar scores was noted between the subjects followed and not followed through labour.

5.5.4 Birthweight

Again, using the Mann-Whitney U test, no difference in birthweight was noted between subjects followed and not followed through labour.

Table 16

Characteristics of subjects followed and not followed through labour

Characteristic	Subjects followed through labour	Subjects not followed through labour
Number	27	9
Pourcelot Ratio at onset of labour*		
Median	0.63	0.67
Range	0.48 to 0.77	0.62 to 1.00
Intrapartum diagnosis of fetal Distress+	8/27 = 30%	4/9 = 44%
Mode Of Delivery		
Spontaneous Vaginal Delivery +	18/27 = 67%	4/9 = 44%
Instrumental Delivery +	0 = 0	1/9 = 11%
Caesarean Section +	9/27 = 33%	4/9 = 44%
Umbilical Artery pH		
Median	7.22	
Range	7.00 to 7.30	
Umbilical Artey Base Deficit (mmol l^{-1})		
Median	8.2	
Range	3.6 to 15.3	
Apgar Score at 1 Minute ǂ		
Median	9	9
Range	2 to 10	6 to 9
<7	6/27 = 22%	2/9 = 22%
Apgar Score at 5 Minutes ǂ		
Median	10	9
Range	6 to 10	9 to 10
<7	1/27 = 4%	0/9 = 0%
Birthweight (g) ǂ		
Median	2590	1750
Range	1410 to 4100	1450 to 3300

* P = 0.01 (Mann-whitney U Test)
\+ Not Significant (Fisher's Exact Test)
ǂ Not Significant (Mann-whitney U Test)

5.6 Incidence of indicators of fetal distress

5.6.1 Fetal acidosis

Six fetuses were born acidotic (table 17). Each had developed cardiotocographic tracing abnormalities prior to delivery (appendix 5). Infant number 57 (table 17) was the only acidotic fetus to have had an additional fetal blood sample taken before the immediate delivery period. This was taken 10 hours prior to delivery and showed a pH of 7.31 and base deficit of 3.5 mmol l^{-1}.

Characteristics of subjects giving birth to normal and acidotic fetuses are given in table 18. Fetuses delivered by Caesarean section were significantly more acidotic than those delivering normally (mean pH 7.12 vs 7.23 P = 0.0005, Mann-Whitney U test; mean base deficit 10.4 mmol l^{-1} vs 7.2 mmol l^{-1} P = 0.0047, Mann-Whitney U test). In 8 of the 9 delivered by Caesarean section, an intrapartum diagnosis of fetal distress had been made, compared with none of the 18 delivering normally.

5.6.2 Apgar score

Six of the 27 fetuses followed through labour and 8 of the total sample had an Apgar score of less than 7 at 1 minute. One of the 27 fetuses followed through labour had an Apgar score of less than 7 at 5 minutes.

5.6.3 Neonatal Encephalopathy

None of the fetuses in the total sample of 36 developed clinical signs of perinatal hypoxia in the neonatal period.

Table 17

Details of the six acidotic fetuses

Infant No.	Complication	Pourcelot ratio		Mode of delivery	Umbilical artery pH	base deficit mmol 1^{-1}	Weight g	Gestation (weeks)
		Early labour	Pre-delivery					
2	GPH	.48	.46	CS	7.00	15.3	4100	42
3	IUGR	.68	.70	SVD	7.16	11.4	2450*	42
17	IUGR	.62	.59	SVD	7.19	13.9	2590*	40
35	GPH	.63	.62	CS	7.11	12.3	2000*	39
37	GPH	.62	.64	CS	7.02	13.0	2500*	40
57	GPH	.60	.61	CS	7.16	10.7	2700	41

Abbreviations : GPH = gestational proteinuric hypertension, IUGR = intrauterine growth retardation, CS = Caesarean section, SVD = spontaneous vaginal delivery.

Gestation was assessed clinically in the newborn infant (Dubowitz et al. 1970)

* : Weight below 10^{th} percentile for sex and gestation (Woods 1984)

Table 18

Characteristics of subjects giving birth to normal and acidotic fetuses

Characteristic	**Subjects giving birth to normal fetuses (umbilical artery base deficit < 10 mmol l^{-1})**	**Subjects giving birth to acidotic fetuses (umbilical artery base deficit > 10 mmol l^{-1})**
Number	21	6
Mean Pourcelot ratio at onset of labour NS	0.632	0.605
Mean change in Pourcelot ratio in labour NS	0.000	-0.003
Intrapartum diagnosis of fetal distress *	4	4
Mode of delivery +		
Spontaneous vaginal delivery	16	2
Caesarean section	5	4
Apgar score at 1 minute ++		
Median	9	8
Range	2 - 10	5 - 9
<7	5	1
Apgar score at 5 minutes ++		
Median	10	10
Range	6 - 10	9 - 10
<7	1	0
Birthweight (g) ++		
Median	2600	2545
Range	1410 - 3100	2000 - 4100
Gestation ++		
Median	40	40.5
Range	34 - 42	39 - 42

\+ Not sigificant (Fisher's exact test)
++ Not significant (Mann-Whitney U test)
* P = 0.044 (Fisher's exact test)
NS Not significant (t distribution)

5.7 Clinical efficiency of Doppler velocimetry in the prediction of indicators of fetal distress

Eight of the 27 subjects followed through labour and 5 of the 9 subjects not followed had a Pourcelot ratio above the 95th percentile (Pattinson et al. 1989). One of those not followed had absent end-diastolic flow.

5.7.1 Prediction of fetal acidosis

The relationship of the Pourcelot ratio on admission in labour to the cord artery base deficit is shown in figure 14. The correlation coefficient was -0.23 which is compatible with the null hypothesis that r = 0 (appendix 4 section 7).

The clinical efficiency of an abnormal umbilical Pourcelot ratio for the prediciton of fetal acidosis is shown in table 19. Clearly, in the absence of a demonstrable relationship between the Pourcelot ratio and cord artery base deficit, the figures for the clinical efficiency quoted in table 19 are meaningless.

Null Hypothesis One (section 2.1) was tested by comparing the means of the umbilical artery base deficits of subjects with normal and abnormal Pourcelot ratios at the onset of labour. The t-distribution was used, assuming that the two groups had uniform variance. The test statistic was calculated to be 1.29 with 25 degrees of freedom ($P > 0.1$) which is compatible with Null Hypothesis

One, i.e. Null Hypothesis One was not disproved.

In fact, the group of subjects with a normal Pourcelot ratio at the onset of labour had a greater umbilical artery base deficit at birth than the groups with an abnormal Pourcelot ratio (difference 1.68 mmol l^{-1}, 95% CI -1.00 to 4.37 mmol l^{-1}).

Table 19

Clinical efficiency of Pourcelot ratio on admission in labour for the prediction of fetal acidosis (umbilical artery base deficit > 10 mmol l^{-1})

Sensitivity	17%
Specificity	67%
Positive predictive value	13%
Negative predictive value	74%
Incidence of fetal acidosis	22%

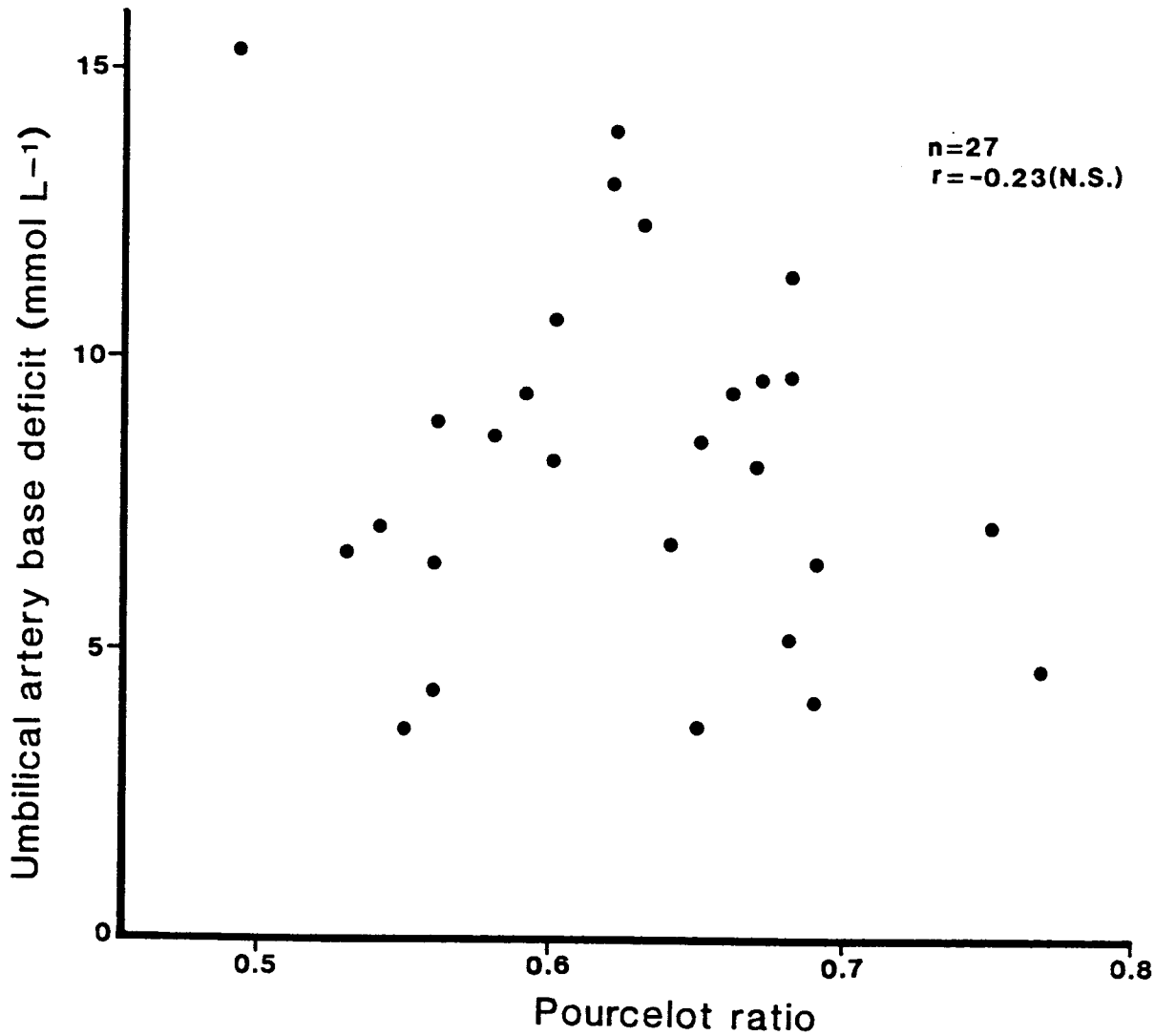


Figure 14

The relationship of the Pourcelot ratio on admission in labour the cord artery base deficit

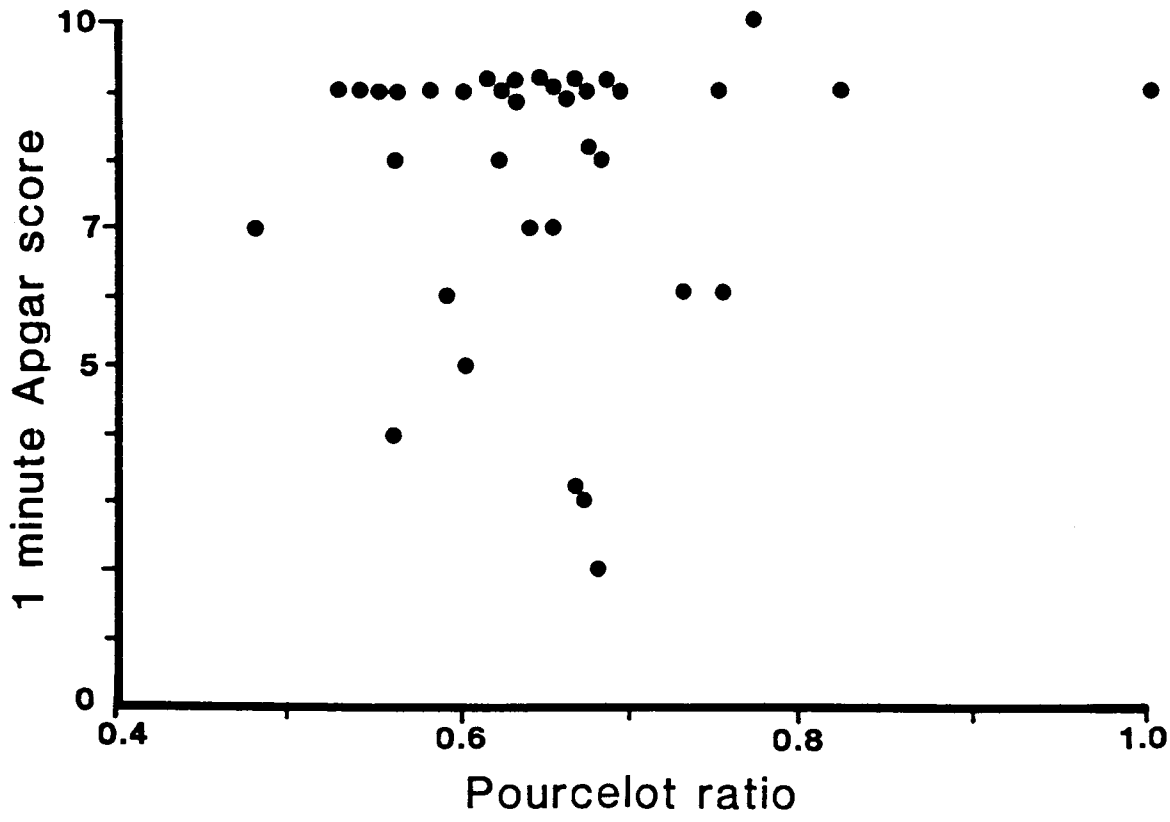


Figure 15

The relationship of the Pourcelot ratio on admission in labour and 1 minute Apgar score

n = 36 P = 0.04 (NS)

5.7.2 Prediction of low Apgar score

The relationship of the Pourcelot ratio on admission in labour to the 1 minute Apgar score at birth is shown in figure 15. Spearman's rank correlation coefficient ρ was 0.04, which is compatible with the null hypothesis that P = 0 (appendix 4 section 8.2).

The clinical efficiency of an abnormal umbilical artery Pourcelot ratio for the prediction of a low 1 minute Apgar score is shown in table 20. Again, in the absence of a demonstrable relationship between the Pourcelot ratio and the Apgar score, the figures for the clinical efficiency quoted in table 20 are meaningless, and can be assumed to have arisen by chance.

Table 20

Clinical efficiency of Pourcelot ratio on admission in labour for the prediction of an Apgar score at 1 minute of less than 7

Sensitivity	50%
Specificity	68%
Positive predictive value	31%
Negative predictive value	83%
Incidence of Apgar score less than 7 at 1 minute	22%

5.8 Evaluation of an abnormal cardiotocographic tracing

Of the 27 subjects followed through labour, 15 developed an abnormal CTG tracing (section 1.1.4b). The mean cord artey base deficit in those subjects with an abnormal CTG was 9.6 mmol l^{-1} compared with 6.6 mmol l^{-1} for those with a normal CTG throughout labour ($P < 0.05$ using the t-distribution to test the null hypothesis that no difference exists, assuming a uniform standard deviation of 3.5 mmol l^{-1}, 95% confidence intervals for the difference 0.3 to 5.9 mmol l^{-1}).

Of the 15 subjects with an abnormal CTG tracing, no difference in mean umbilical artery base deficit was noted in 4 subjects with an abnormal Pourcelot ratio (9.3 mmol l^{-1}) compared with the 11 with a normal Pourcelot ratio (9.8 mmol l^{-1}). An abnormal Pourcelot ratio was defined as being above the 95th percentile for gestation.

5.9 Change in Pourcelot ratio in relation to indicators of fetal distress

5.9.1 Fetal acidosis and change in Pourcelot ratio

No change in the Pourcelot ratio was identified during labour in both normal and acidotic fetuses (figure 16), with zero change in the mean Pourcelot ratio for both groups. No relationship was found between the change in Pourcelot ratio and umbilical artery base deficit (figure 17). None of the acidotic fetuses showed a change in

Pourcelot ratio of more than 0.03 (figure 18).

Null Hypothesis Two (section 2.2) was tested by comparing the means for the change in Pourcelot ratio in subjects with normal and abnormal umbilical artery base deficits. The t-distribution was used as before. The test statistic was calculated to be 0.13 with 25 degrees of freedom ($P > 0.1$) i.e. Null Hypothesis Two was not disproven. 95% confidence intervals for the difference in mean change in Pourcelot ratio between normal and acidotic fetuses were -0.06 to 0.06.

The study had an 80% power to demonstrate a change in mean Pourcelot ratio of 0.07 in the normal fetuses, 0.16 in the acidotic fetuses, and 0.06 in the total sample at a 95% confidence level.

Correction for fetal heart rate within the confidence intervals stated in section 5.4.2 had no effect on these results.

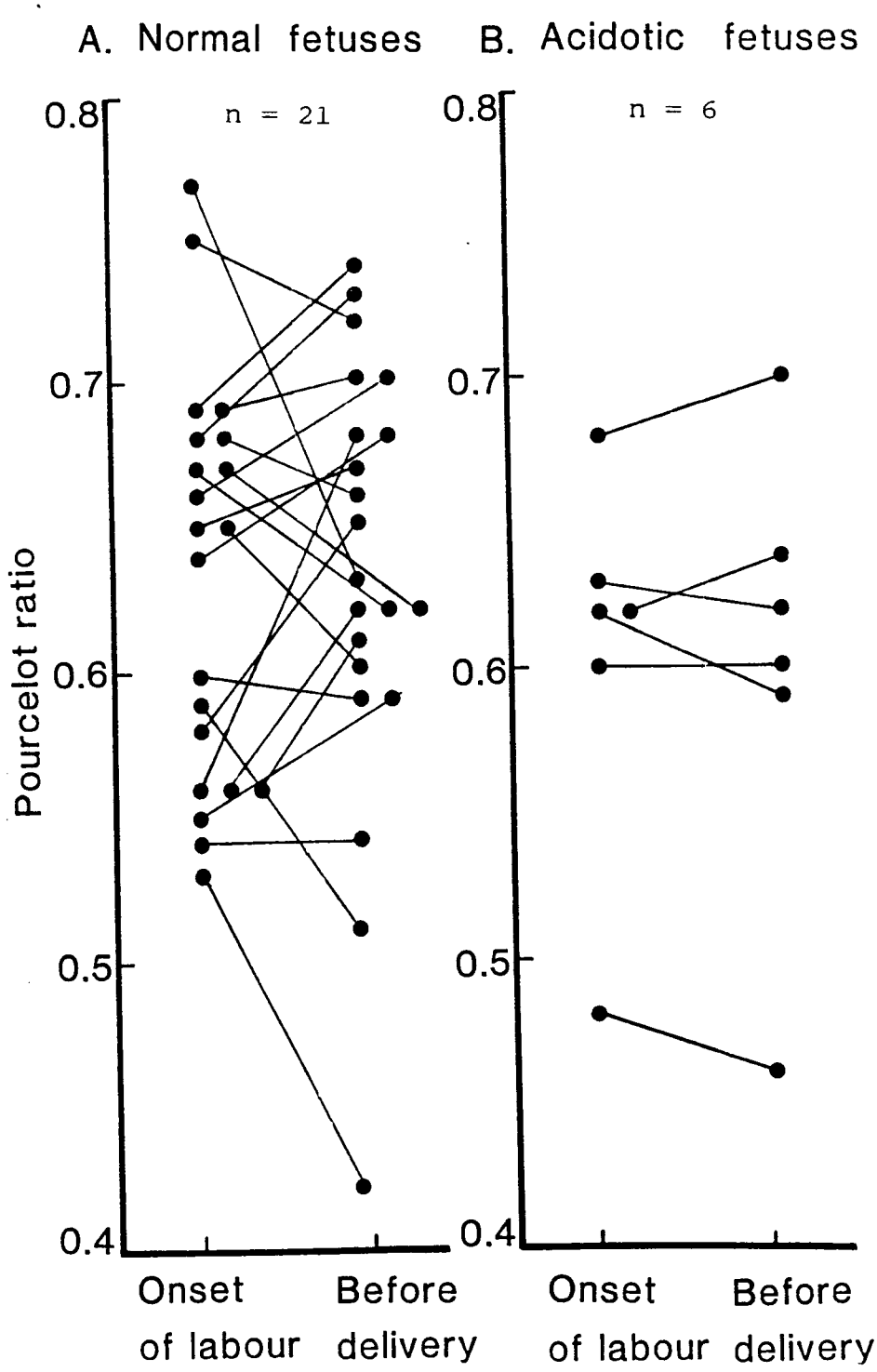


Figure 16

Change in umbilical artery Pourcelot ratio during labour in 27 fetuses classified as either normal or acidotic at birth.

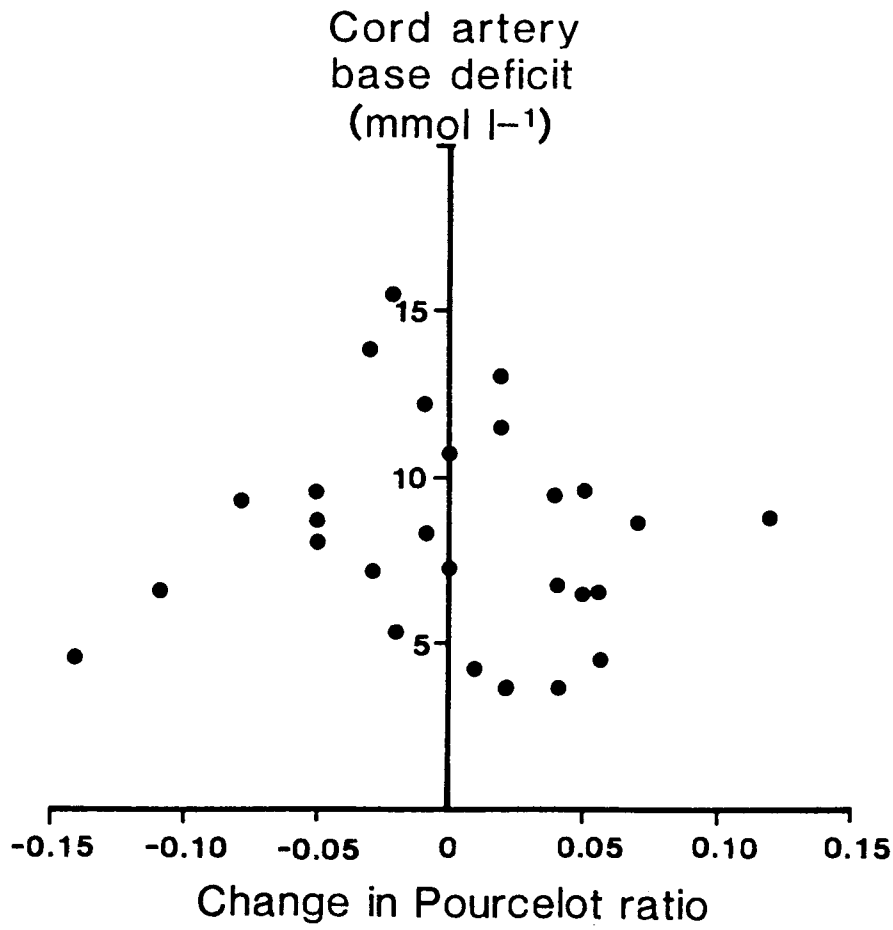


Figure 17

Relationship of change in Pourcelot ratio in labour with cord artery base deficit.

r = 0.03 (NS)

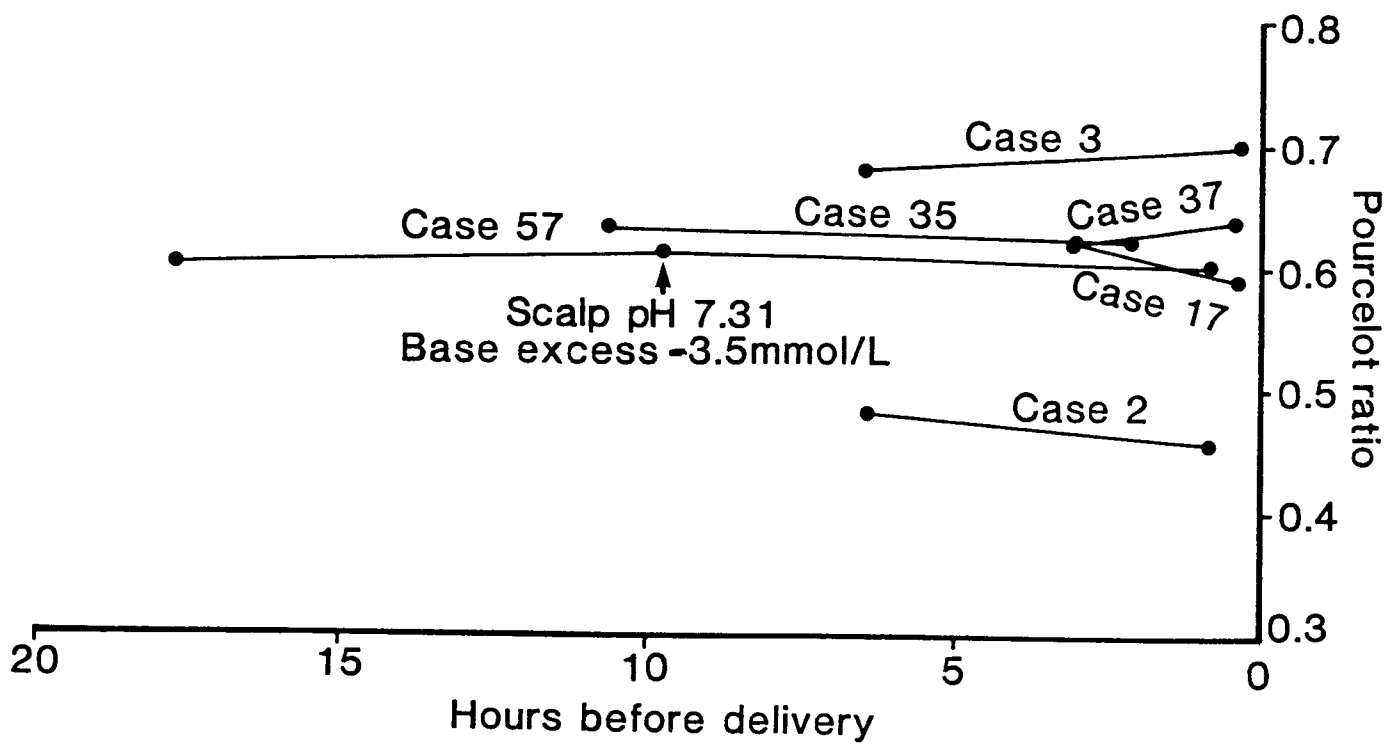


Figure 18

Relationship of Pourcelot ratio with time in fetuses developing acidosis in labour

5.9.2 Apgar score and change in Pourcelot ratio

No relationship was found between the 1 minute Apgar score and change in the Pourcelot ratio (figure 19): Spearman's rank correlation coefficient was calculated to be 0.30 (N.S.).

5.10 Correlation between Apgar score and umbilical artery base deficit

Although a poor relationship was found between 1 minute Apgar score and umbilical artery base deficit, no babies were born with a low Apgar score but normal base deficit (figure 20). Spearman's rank correlation coefficient was calculated to be 0.19 (N.S.).

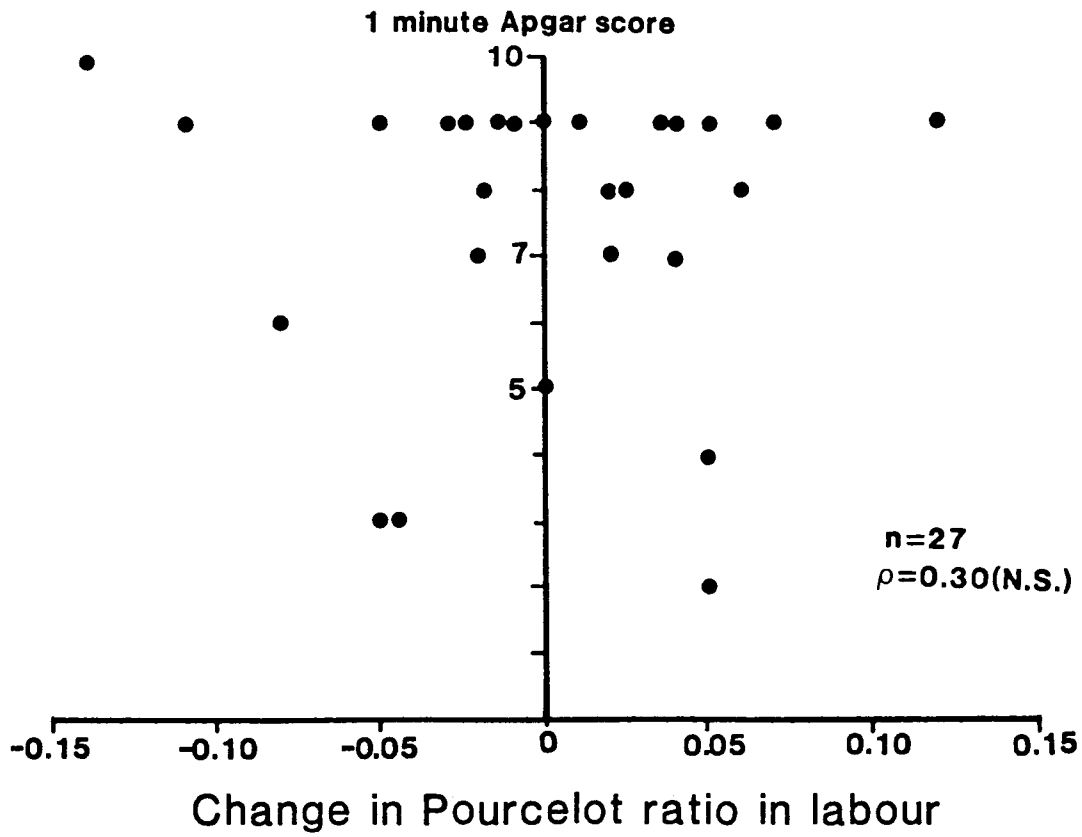


Figure 19

Relationship of 1 minute Apgar score to change in Pourcelot ratio in labour

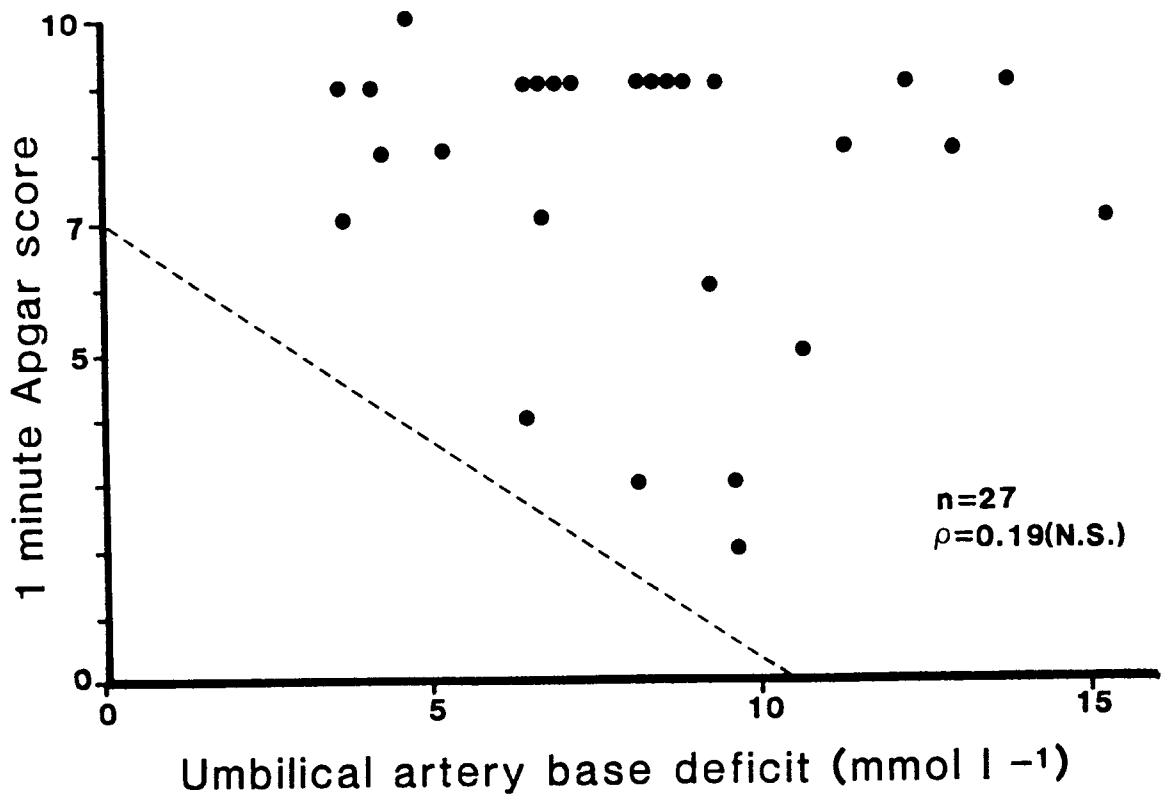


Figure 20

Relationship of 1 minute Apgar score to umbilical artery base deficit. No babies were born with low Apgar and low base deficit (indicated by dashed line)

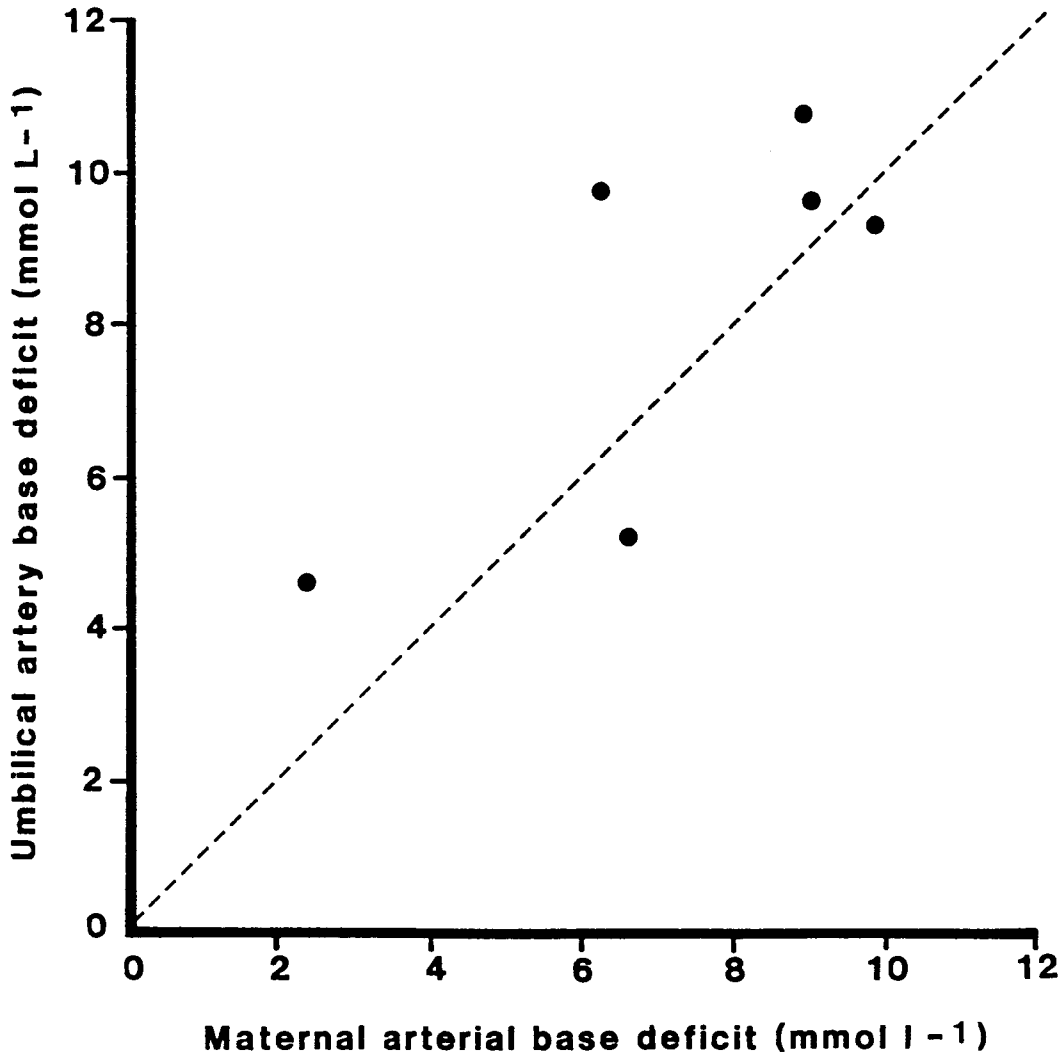


Figure 21

Relationship of maternal and fetal acid base status in 6 subjects undergoing Caesarean section

5.11 Fetal-maternal acid-base difference

Maternal artery pH and base deficit were not routinely measured in this study. In six of the subjects undergoing Caesarean section under general anaesthetic, maternal arterial blood was analysed; the results are presented in table 21 and figure 21. In these 6 subjects, the cord artery base deficit follows the maternal artery base deficit

Table 21

Relationship between maternal arterial pH and base deficit and cord artery pH and base deficit

Patient	Maternal artery		Cord artery	
	pH	Base deficit (mmol l^{-1})	pH	Base deficit (mmol l^{-1})
6	7.28	9.0	7.12	9.6
7	7.45	2.4	7.19	4.6
11	7.32	9.8	7.18	9.3
15	7.31	6.6	7.23	5.2
18	7.34	6.2	7.13	9.7
57	7.28	8.9	7.16	10.7

5.12 Umbilical vein flow velocity waveform and the cardiac impulse

None of the flow velocity waveforms recorded in the study contained a cardiac impression upon the umbilical artery flow velocity waveform.

5.13 **Summary of results**

No relation was found between the Pourcelot ratio at the onset of labour and the subsequent development of fetal acidosis (figure 14). The data were compatible with Null Hypothesis One. The Pourcelot ratios of the subjects not followed through labour with resultant loss of cord blood analysis were significantly greater than those followed through labour, which may have given rise to bias in the testing of Null Hypothesis One.

No relation was found between the Pourcelot ratio at the onset of labour and Apgar score at 1 minute (figure 15), this is also compatible with Null Hypothesis One.

No change in Pourcelot ratio was identified during labour in both normal and acidotic fetuses (figure 16) with zero change in mean Pourcelot ratio for both groups. The data were compatible with Null Hypothesis Two.

No relation was found between the change in Pourcelot ratio in labour and 1 minute Apgar score (figure 19). This is also compatible with Null Hypothesis Two.

Despite an incidence of fetal acidosis of 22% and a 1 minute Apgar score of less than 7 of 22%, none of the newborn infants developed clinical signs of perinatal hypoxia.

6 Discussion

6.1 Methodology

6.1.1 Tests for the normal distribution (section 5.3)

Proof of normality of a sample from a population using formal numerical testing usually requires a large sample (i.e. 100 or more subjects). It is therefore not surprising that proof of normality for the distribution of umbilical artery Pourcelot ratio and umbilical artery base deficit could not be obtained in this study, even though normality was suggested by normal plots. While the chi-square test provided good evidence for normality for the Pourcelot ratio, this should not be regarded as proof of normality (with a P value approaching 1, one should conclude only that there is no evidence to reject the null hypothesis of normality).

Thompson et al. (1988a) found similar results in a study of the distribution of commonly used umbilical artery Doppler ultrasound waveform indices. The systolic/diastolic ratio was not normally distributed, while the Pourcelot ratio distribution was consistent with normality, with a borderline result for the pulsatility index.

Studies of the distribution of umbilical artery pH (D'Souza et al. 1983, Miller et al. 1990) and base deficit (Miller et al. 1990) in normal populations have shown each to be skewed from normal, with an excess of acidotic

neonates.

6.1.2 Confidence intervals for the measurement of Pourcelot ratio (section 5.4.1)

It is not surprising that the confidence intervals widened from the onset of labour to just before delivery, considering the difficulty of obtaining a measurement from a subject in the second stage of labour. Surprisingly, confidence intervals for the measurement of Doppler indices are not generally quoted in the literature, though some authors do quote the coefficient of variation. The limitation of the coefficient of variation is discussed in appendix 4 section 4.

The coefficient of variation for the intra-observer error of the measurement of umbilical artery Pourcelot ratio compares well with the previously published figures of Pearce (1987). Using duplex pulsed Doppler ultrasound in antenatal patients he reported an intra-observer coefficient of variation of 3.3%. This compares with the figure of 4.7% and 6.5% in this study using continuous wave equipment in labouring women at the onset of labour and shortly before delivery respectively.

6.1.3 Change in Pourcelot ratio with fetal heart rate (sections 1.2.4 and 5.4.2)

Several authors stress the need to adjust umbilical artery Doppler velocimetry indices to a standard fetal heart rate. This is largely on the basis of the work of Mires et al. (1987) who stated that, in the normal range of

fetal heart rate in labour, for an increase in fetal heart rate of 1 beat per minute, the pulsatility index decreases by 0.0027. This was obtained from a sample of 60 labouring women. They also reported 8 observations from a single antenatal patient, showing that an increase in fetal heart rate of 1 beat per minute was associated with a decrease in the pulsatility index of 0.0031.

In drawing conclusions from their study, it should be noted that in different patients independent variables may affect both fetal heart rate and Doppler indices. Therefore, it may not be valid to study the effect of fetal heart rate on Doppler indices by studying such differences between patients. Of course conclusions should not be drawn from their study of 8 observations in one patient. Moreover, the confidence intervals for the estimate of the coefficient of the fetal heart rate in the linear relation between fetal heart rate and pulsatility index ("the gradient of the graph") were not given, and could well include zero. Thus it may be unnecessary for any adjustment of the Doppler indices with varying fetal heart rates. Since adjustment for fetal heart rate is generally accepted in the literature, the effect of change in fetal heart rate within individuals in the study sample was assessed. Although no effect was detected, the data were subsequently analysed after adjustment to a standard fetal heart rate of 140 beats per minute at the extremes of the confidence intervals for the effect (-0.0015 to 0.0015 per beat per minute for the Pourcelot ratio). This had no effect on any of the subsequent results and

conclusions. This is probably because, in any given patient, any correction for fetal heart rate will be small compared with the intra-observer error of the Doppler index.

6.1.4 Change in pH and base deficit with time (section 5.4.3)

This possible effect has been little reported in the literature. Tyrell et al. (1989) reported no significant change in pH from 1 to 5 minutes after delivery, but unspecified differences in pH measured at 1 and 10 minutes. Steer et al. (1989) showed that measured pH fell by 0.037 per hour, a much larger effect per minute than that observed in this study over a 9 minute period shortly after delivery. Bartlett et al. (1992) reported less variable results from venous than from arterial blood. This is probably related to the "considerable difficulty" they experienced in obtaining repeated arterial samples from the cord. Such difficulty was not experienced in this study.

The confidence intervals for the estimate of pH and base deficit (section 5.4.4) were large compared with the possible effect of a short delay in analysing the cord blood.

6.1.5 Effect of operative delivery on fetal acid-base balance (section 5.11)

Nine of the 27 subjects followed through labour in this study were delivered by Caesarean section (table 16). It is possible that the administration of a general or

regional anaesthetic to the mother may have affected the fetal acid-base balance. Rorke et al. (1968) found no relation between maternal inspired pO_2 and umbilical artery pH and base deficit in patients delivered by Caesarean section under general anaesthetic. This was despite an increase in pCO_2 in both mother and fetus with increased maternal inspired pO_2.

Khoury et al. (1991) studied 18 women undergoing elective Caesarean section under epidural anaesthesia, comparing umbilical vein acid-base analysis obtained by cordocentesis prior to induction of epidural anaesthesia with umbilical venous blood obtained at Caesarean section. Despite the absence of fetal heart rate abnormality and maternal hypotension in all patients from the time of cordocentesis to delivery, significant differences in pH (7.36 vs 7.31, $P < 0.0001$) and base deficit (0.79 vs 2.36 mmol l^{-1}, $P < 0.0003$) were found.

In this study, an intrapartum diagnosis of fetal distress had been made in 8 of the 9 subjects delivered by Caesarean section (the other being a failed induction) and in none of the 18 subjects delivering normally. It is therefore not surprising that the fetuses delivered by Caesarean section tended to be born more acidotic than those born normally (section 5.6.1). However, an effect of anaesthesia upon the acid-base balance cannot be ruled out.

6.1.6 Infusion acidosis

The umbilical artery pH at birth will be affected not only by hypoxic acidosis of the fetus but also by maternal metabolic acidosis and respiratory acidosis or alkalosis. Primary consideration of the fetal umbilical artery base deficit rather than pH should remove the influence of maternal respiration on the fetal acid-base balance.

Maternal arterial blood gas analysis was not performed as a routine in this study because of the discomfort this would have given the mother with no clinical benefit. However, in 6 of the subjects undergoing Caesarean section under general anaesthetic, maternal arterial blood was analysed (table 21). In these 6 subjects, the cord artery base deficit followed the maternal artery base deficit (figure 20), suggesting that infusion acidosis may be common. Unfortunately, only one of the 6 acidotic fetuses in the study had maternal arterial blood available for comparison.

It would have been useful to have measured the maternal venous acid-base balance in all subjects since arterial and venous pH and base deficit are similar in pregnancy. Although less painful than an arterial puncture, this still would have given the mother discomfort at the time of delivery with no clinical benefit.

The origin of the fetal acidosis may not be of clinical importance to this study. It is common clinical practice to measure fetal acid-base balance without simultaneous

measurement of maternal acid-base balance, and the clinician will simply be concerned with the relationship of Doppler velocimetry indices to fetal acidosis in labour.

6.1.7 Success in obtaining umbilical artery Doppler waveform recordings

Doppler velocimetry signals were successfully recorded in 97% of subjects. This was undoubtedly aided by only recruiting women who were 34 or more weeks pregnant. This success rate compares favourably with reported success rates in studies of the use of umbilical artery Doppler ultrasound as a screening test (96%, Pattinson et al. 1991; 74%, Hofmeyr et al. 1991).

6.2 Sources of bias

6.2.1 Recruitment

All eligible patients during the study period were approached regarding recruitment to the trial and none refused. It is unlikely that bias existed in patient recruitment to the trial.

6.2.2 Subjects not followed through labour

Those subjects not followed through labour tended to have higher Pourcelot ratios than those followed through labour (section 5.5.1). Although no difference was noted between those two groups in terms of mode of delivery, Apgar score or birthweight, such patient drop-out might seriously bias the results obtained from only those subjects followed

through labour. Such bias is likely to be greater in the testing of Hypothesis One (section 5.7.1) than Hypothesis Two (section 5.9.1), because in the testing of Hypothesis Two, every subject with serial Doppler velocimetry recordings had successful cord artery pH and base deficit measurements.

6.3 The study of high-risk patients

This study was performed in fetuses who were at high risk of developing fetal distress in labour with the purpose of evaluating Doppler velocimetry as a useful test of fetal well-being in labour. The clinical efficiency of a diagnostic test for fetal distress may be more easily studied in a sample at high risk for developing fetal distress (section 1.1.4a).

If this study had shown a clinically useful change in umbilical artery Pourcelot ratio to occur with the development of fetal acidosis, such a change could not be assumed to occur in normal low-risk patients. A second, much larger study of low-risk patients would have been required subsequently. In the absence of a change in umbilical artery Pourcelot ratio with the development of acidosis in high-risk patients, it is very unlikely that a change would have occured in low-risk patients.

6.4 Development of acute acidosis

It is speculated that the 6 fetuses born acidotic may have developed acute acidosis while in labour. One of the 6 had a normal scalp capillary blood pH measured 10 hours

before delivery, and this was the only acidotic fetus to have had a fetal blood sample taken before the immediate delivery period. Each had a normal cardiotocographic tracing at the onset of labour, becoming abnormal by the time of delivery (see appendix 5). Steer et al. (1989) have shown that a normal cardiotocographic tracing in labour has a 99% negative predictive value for severe fetal acidosis in the general population (section 1.1.4bi). None had absent diastolic frequencies on Doppler velocimetry and only one had a Pourcelot ratio above the 95th percentile at the beginning of labour. In the study of Tyrrell et al. (1989), the demonstration of forward end-diastolic flow on Doppler velocimetry of the umbilical arteries had a negative predictive value for fetal acidosis in a mixed high risk and low risk population of 99% (section 1.2.8ci).

In view of the predictive values of both the normal CTG and Doppler velocimetry of the umbilical arteries for fetal acidosis it is highly improbable that any of these fetuses were acidotic at the onset of labour but that all developed acute acidosis in labour.

A more rigorous approach to document the development of acute acidosis in labour would have been to perform fetal blood sampling on all the fetuses as soon as practical in the labour. This would have been hard to justify clinically or ethically.

6.5 Predictive testing in labour - Hypothesis One

The studies of Feinkind et al. (1989), Sarno et al. (1989), Malcus et al. (1991) and Howarth et al. (1992) have been discussed in section 1.2.9. These studies did not show screening with Doppler velocimetry in labour to be of benefit in the prediction of fetal distress. This is the first study in a high risk population to show no benefit in screening with Doppler ultrasound in labour for the prediction of fetal distress.

The work of Burke et al. (1990), Trudinger et al. (1987a), Tyrrell et al. (1990), Hofmeyr et al. (1991) Almström et al. (1992) and Puzey and Lindow (1992), discussed in sections 1.2.8 and 1.2.9, suggest that Doppler velocimetry may be of use in the pre-labour assessment of high risk pregnancies. This correlation of outcome and Doppler velocimetry in the steady state of the pre-labour situation may give an indication that the fetus is not acidotic and can therefore begin the stress of labour.

The results presented do not allow comment on this particular aspect due to the number of cases not followed throughout labour.

6.6 Fetal distress and change in Doppler indices - Hypothesis Two

This study shows that serial umbilical artery Doppler velocimetry, as measured by the Pourcelot ratio, is not useful in detecting acute fetal acidosis in labour. The extremes of likely difference in change in mean Pourcelot

ratio between the normal and acidotic fetuses are -0.06 to 0.06 indicated by 95% confidence intervals (section 5.9.1). These are clinically unimportant given the wide 95% confidence intervals for the measurement of Pourcelot ratio (section 5.4.1).

The number of acidotic fetuses in this study was small, which is reflected in the power calculations of section 5.9.1. The study had an 80% power to demonstrate a change in mean Pourcelot ratio of 0.16 in the acidotic fetuses at a 95% confidence level. To improve the power of the study to give an 80% power to detect a change in mean Pourcelot ratio of 0.05 in the acidotic fetuses at 95% confidence level, the sample number would have to be increased from 27 to 161, assuming a similar incidence of fetal acidosis. Alternatively, the study as it stands has an 8% power to demonstrate a change in mean Pourcelot ratio of 0.05 in the acidotic fetuses at a 95% confidence level.

This is the first study to report serial Doppler velocimetry in labour in fetuses developing acute acidosis. It is also the first study to report power calculations for detection of change in mean Doppler indices in labour. With an 80% power to demonstrate a change in Pourcelot ratio of 0.06 in the total sample at a 95% confidence level, it can be stated that the Pourcelot ratio remains constant within clinically useful limits with progress in labour.

If, indeed, there is no change in the Pourcelot ratio in

labour, the measurement of an apparent change in Pourcelot ratio will, in fact, arise from errors in measurement. Therefore, the standard errors for the measurement of Pourcelot ratio and for the change in Pourcelot ratio should be related:- the standard error for the measurement of Pourcelot ratio should be $\sqrt{2}$ times larger than the standard error for the measurement of the change in Pourcelot ratio.

The standard error of the change in Pourcelot ratio in this study (section 5.9) was 0.029, compared with standard errors for the measurement of Pourcelot ratio at the onset of labour of 0.029 and 0.040 before delivery (section 5.4.1), giving a combined standard error at 0.035. Since $0.035 \div \sqrt{2} = 0.025$, this implies that the observed change in Pourcelot ratio in labour in an individual can be virtually completely explained by errors in measurement of Pourcelot ratio alone.

The results of this study suggest that in the human fetus, as in the sheep fetus (section 1.1.5 and 1.2.11), umbilical artery blood flow is maintained during acute acidosis. It should be noted that none of the newborn infants in the study showed clinical signs of perinatal hypoxia.

It is interesting to speculate why acute fetal acidosis is not associated with changing umbilical artery Doppler velocimetry indices, whereas pregnancies complicated by chronic fetal compromise are commonly associated with low

or absent end-diastolic frequencies in the umbilical artery flow velocity waveform.

Chronic fetal compromise is commonly associated with increased placental vascular resistance (section 1.2.10) and re-distribution of fetal blood flow (section 1.1.5). Loss of end diastolic frequencies in the umbilical artery Doppler waveform could arise from either the increased placental resistance or the re-distribution of fetal blood flow. Indeed, the electrical model of the umbilical-placental circulation devised by Thompson and Stevens (1989) shows that the pulsatility index of the Doppler waveform depends both upon the pulsatility of the input pressure waveform and on the resistance of the placental vascular bed.

Experimental models have shown an increase in placental resistance to affect umbilical blood flow. Embolization of the sheep uterine circulation produces a decrease in the progressive increase in umbilical blood flow normally seen with continuing pregnancy (Clapp et al. 1980). Embolization of the umbilical circulation in the sheep produces a decrease in umbilical artery blood flow and increase in umbilical artery Doppler systolic/diastolic ratio (Trudinger et al. 1987b). It should be noted however that embolization of the uteroplacental circulation will not only increase utero-placental resistance, but also induce hypoxia in the fetus and resultant re-distribution of fetal blood flow. Fetal hypoxia was demonstrated in both the studies of Clapp et

al. (1980) and Trudinger et al. (1987b). Such fetal responses could also contribute to any umbilical artery blood flow and Doppler indices.

Anatomical studies have shown patients with reduced umbilical artery end-diastolic velocities to have abnormalities in placental tertiary stem villi (Giles et al. 1985). Again however, the placental abnormalities may be associated with fetal hypoxia and re-distribution of fetal blood flow contributing to the change in umbilical artery Doppler indices.

The re-distribution of blood flow with chronic hypoxia in the human fetus has been well documented using Doppler ultrasound. Soothill et al. (1986) showed a correlation between umbilical vein oxygen partial pressure and mean blood velocity in the fetal aorta. Wladimirof et al. (1986) showed small-for-dates fetuses to have increased vascular impedence in the aorta and decreased impedence in the internal carotid compared with controls. Bilardo et al. (1990) showed that, in the growth retarded fetus, an increase in blood velocity in the common carotid artery relative to the descending thoracic aorta is associated with hypoxia and acidosis.

The finding in this study that umbilical artery Doppler velocimetry indices remain constant with the development of acute acidosis is in keeping with the blood flow studies of Cohn et al. (1974) and Peeters et al. (1979) and the Doppler study of Morrow et al. (1990) in fetal

sheep. Given that profound circulatory changes were occuring in the current study, it is surprising that no effect upon Doppler velocimetry indices was detectable. It may be that the placental resistance is a much more important determinant of umbilical blood flow than the input pressure waveform and it may be assumed that placental resistance remains constant during labour, apart from transient effects from uterine contractions.

The alternative explanation that no redistribution of fetal blood flow occured in this study with the development of acute acidosis would also account for the constant umbilical artery Doppler indices. This explanation would appear from previous discussions to be unlikely.

If Doppler ultrasound were to prove useful in the diagnosis of fetal distress in labour, study of the fetal cerebral vessels, aorta or ductus venosus may be necessary. This would require duplex Doppler equipment and special expertise which would prevent such a diagnostic procedure from being generally applicable. Furthermore, redistribution of fetal blood flow may occur in both normal and distressed fetuses. Yagel et al. (1992) showed a decrease in fetal middle cerebral artery Doppler velocimetry indices in normal labour compared with non-labouring controls. Such changes have yet to be demonstrated as being greater in distressed fetuses in labour.

6.7 Departure from initial protocol

The initial research proposal submitted to the Higher Degrees Committee of the University of Cape Town was largely adhered to. Normal subjects were studied in labour (section 3.1.4) but, because of the lack of normal subjects at Groote Schuur Hospital, a study of serial Doppler velocimetry in normal subjects was not possible. It had originally been intended to analyse data obtained from subjects with gestational proteinuric hypertension and intrauterine growth retardation separately. In the initial analysis, no differences could be detected between these two groups and, since the total number of subjects in the study was small, the two groups were combined for the final analysis. The clinical study was terminated at the end of the loan-period of the continuous wave Doppler machine, preventing any increase in numbers.

7 Conclusions

A study of the available literature suggests that Doppler velocimetry of the umbilical arteries may contribute to the pre-labour assessment of high-risk pregnancies, particularly in deciding the mode of delivery. However, studies of screening low-risk patients in labour using Doppler velocimetry of the umbilical arteries have not shown a relation between Doppler indices and adverse fetal outcome.

This study has shown no relation between the Pourcelot ratio obtained from Doppler velocimetry of the umbilical arteries in high-risk patients in labour and adverse fetal outcome. The study also showed that serial umbilical artery Doppler velocimetry as measured by the Pourcelot ratio is not useful in detecting acute fetal acidosis in labour. The Pourcelot ratio remained constant in labour within clinically useful limits in both normal and acidotic fetuses.

Further interpretation of the results should be guarded because of the small number of subjects in this study. Although the Pourcelot ratio remained constant in labour within clinically useful limits, the power of the study was not sufficient to detect smaller changes.

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Appendix 1

Ethics and Research Committee approval

UNIVERSITY OF CAPE TOWN

Faculty of Medicine

Observatory, 7925
Tel: (021) 47-1250
Fax No: (021) 47-8955

ERC PROTOCOL NO: 063/91

17 June 1991

Dr I Stuart
Dept. of Obstetrics and Gynaecology
MEDICAL SCHOOL

Dear Dr Stuart

AN ASSESSMENT OF THE ROLE OF DOPPLER ULTRA SOUND VELOCITY WAVE FORM ANALYSIS OF THE UMBILICAL ARTERY IN THE DIAGNOSIS OF FETAL DISTRESS IN LABOUR.
- PROTOCOL NO: 063/91

Thank you for the protocol of your proposed study dated 14th of May 1991.

I have the pleasure in informing you that there have been no objections on ethical grounds and it is therefore in order to proceed. For your information the following comment was made by a reviewer:

> "I believe that a group of `normal´ patients should be included. Problems which may arise will be finding sufficient numbers of patients in groups B and D."

Please note, however, that formal approval can only be granted after the next meeting of the Ethics and Research Committee.

Yours sincerely

Signed by candidate

Signature Removed

PROFESSOR JP deV VAN NIEKERK
CHAIRMAN : ETHICS & RESEARCH COMMITTEE

Appendix 2

Sample of data record sheets used in the study

1

PROJECT NO.

NAME

HOSPITAL NO.

PARITY

MATERNAL WEIGHT (kg)

HEIGHT (cm)

RACE 1 WHITE

2 COLOURED

3 BLACK

GESTATIONAL AGE ESTIMATE (weeks)

ANTENATAL COMPLICATIONS 1 GPH

2 IUGR

3 GPH & IUGR

4 NEITHER

5 OTHER

NOTE OTHER ANTENATAL COMPLICATIONS .....

.....

.....

ADMISSION DOPPLER IN LABOUR/AT INDUCTION

NOTE TIME ..... (= 00.00 Hrs)

MATERNAL BLOOD PRESSURE SYSTOLIC

DIASTOLIC

PULSE

MEAN RP

MEAN PI

FETAL HEART RATE

DOPPLER AT TIME OF SCALP PH (' 'SCALP PH)

HOURS AFTER ADMISSION DOPPLER (Hrs Mins)

MATERNAL BLOOD PRESSURE SYSTOLIC

DIASTOLIC

PULSE

MEAN RP

MEAN PI

FETAL HEART RATE

MEAN pH

MEAN BASE EXCESS

MATERNAL pH

MATERNAL BASE EXCESS

MATERNAL pCO2

MATERNAL p02

REASON FOR SCALP pH (CTG grade)

1 = 1

2 = 2

3A = 3

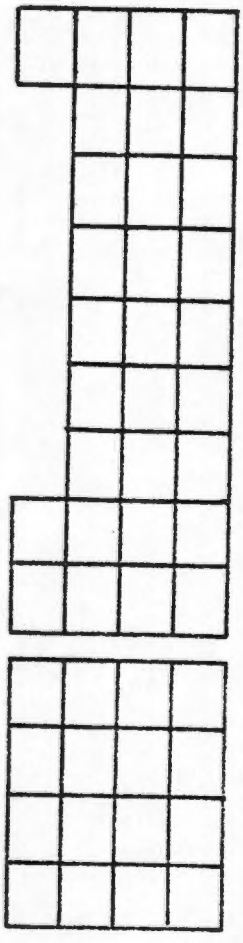
3B = 4

4A = 5

4B = 6

5 = 7

VARIABLE = 8



PRE-DELIVERY DOPPLER

HOURS AFTER ADMISSION DOPPLER (Hrs Mins) ☐☐☐☐

MATERNAL BLOOD PRESSURE SYSTOLIC ☐☐☐

DIASTOLIC ☐☐☐

PULSE ☐☐☐

MEAN RP ☐☐☐

MEAN PI ☐☐☐

FETAL HEART RATE ☐☐☐

EPIDURAL ANAESTHESIA 1 Yes

2 No ☐

OPIATE ANAESTHESIA 1 Yes

2 No ☐

DELIVERY

TIME AFTER ADMISSION (Hrs Mins) ☐☐☐☐

MODE OF DELIVERY 1 SVO
2 FORCEPS
3 VENTOUSE
4 CS ☐

BABY HOSPITAL NO. ☐☐☐☐☐☐☐☐

APGAR 1 Min

5 Min ☐

MECONIUM 1 Yes

2 No ☐

TIME TO SPONTANEOUS RESPIRATION (Min) ☐☐

WEIGHT (g) ☐☐☐☐

GESTATION (Dubowitz) ☐☐

HEAD CIRCUMFERENCE (cm) ☐☐

CORD VEIN pH

BE

pCO2

CORD ARTERY pH

BE

pCO2

MATERNAL ARTERIAL pH

BE

pCO2

pO2

SIGNS OF HIE 1 Yes

2 No

DURATION OF HIE (Days)

WORST HIE SCORE

WORST SARNAT GRADE

HAEMATURIA 1 Yes

2 No

DURATION (Days)

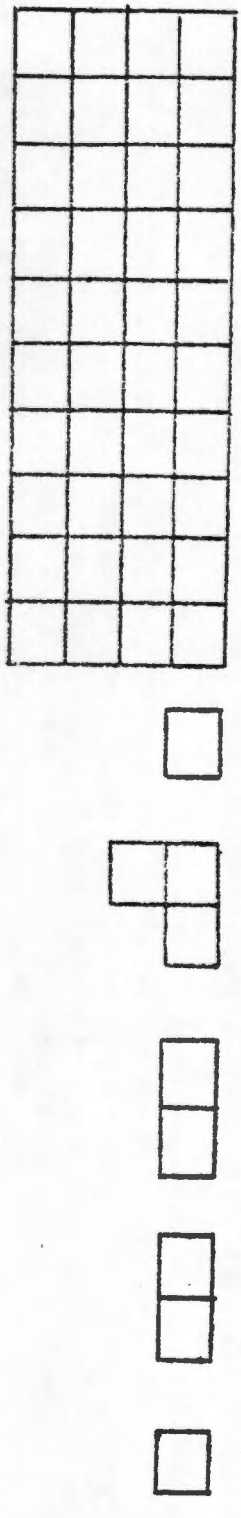
PROTEINURIA 1 Yes

2 No

DURATION (Days)

OTHER ADVERSE OUTCOME 1 Yes

2 No



DETAILS .....

.....

ANY OTHER COMMENTS .....

.....

DOPPLER TRIAL Cont.

BABY Study No.....

Name: .....

Folder No.....

Nursery.....

DOB.....

Time .....

Clinical Data

Birth Weight .....g

Gestational age .....w

Head Circum .....cm

Apgar 1 min .....5min.....Later.....

Cord Artery pH
pCO_2
BE/BD

Cord Vein pH
PCO_2
BE/BD

Mec Stain Liquor yes.....
No .....

Urine Haematuria Yes ..... Duration.....
No .....

Protein yes..... Duration .....
no .....

Signs of HIE YES..... Please attach form
No.....

Details .....
.....
.....

Other adverse outcome .....

.....

GRADING OF HIE

NAME .....
Folder NO. Baby.....
Mother.....

ADDRESS .....
.....
Phone .....

SIGN	SCORE 0	1	2	DAY 1	2	3	4	5	6	7	8	9	10
TONE	norm	hyper	flaccid										
LOC	norm	hyper-alert, stare	lethargic, unconsc										
FITS	none	infreq. <3/day	frequent >3+-/day										
POSTURE	norm	fist, cycle, mild flex	strong flex decere-brate										
MORO	norm	partial, weak	absent										
GRASP	norm	poor	absent										
SUCK	norm	poor	absent +-bites										
RESPIR	norm	brief apnoea	needs IPPV										
FONT	norm	full, not tense	tense										
TOTAL score/day:													

DURATION OF HIE < 3 days ☐ <8 days ☐ >7 days ☐ Died? no ☐ yes ☐

Appendix 3

Statistical methods

1 **Significance testing**

In the statistical test of a hypothesis, the hypothesis is negated to obtain a null hypothesis. The probability of obtaining the observed data if the null hypothesis were true is then calculated. This probability is the P value. If P is very small the null hypothesis can be rejected in favour of the research hypothesis. By convention, a P value of less than 0.05 is taken to be significant, and this is the level used in the present study. If P is large one cannot conclude that the null hypothesis is proven, only that there is no evidence to reject the null hypothesis.

2 **Confidence intervals**

The P value is merely used to reject the null hypothesis in favour of the research hypothesis. It gives no indication as to the size or direction of an observed effect or difference. An alternative approach to hypothesis testing is to make an estimate of the size of the observed effect or difference, together with the uncertainty of this estimate, expressed as a confidence interval. Confidence intervals are particularly useful when studying a small sample and also in the interpretation of non-significant results (ie when P is greater than 0.05).

95% confidence intervals are used in this study (ie there is a 95% chance that the true value of an estimate will

lie within the confidence interval).

3 Tests for the normal distribution

In its simplest form the equation of the normal curve, called the standard normal distribution, is:

$$y = \frac{1}{\sqrt{2\pi}} \exp\left(\frac{-x^2}{2}\right)$$

The normal distribution may be regarded as the fundamental probability distribution of statistics. Many of the statistical methods used for the analysis of a parameter from a sample require the parameter to be normally distributed for the analysis to be valid. Many naturally occurring distributions (or derivatives of the measured parameter) are indeed normal, but this cannot be assumed. Having demonstrated that a parameter from a sample is normally distributed, it is a reasonable assumption that sample differences will also be normally distributed.

3.1 Graphical analysis

Graphical analysis is a useful exploratory technique in testing for the normal distribution. It allows for the identification of skewness and the calculation of mean and standard deviation. It is, however, less rigid than numerical analysis which is often essential to avoid invalid conclusions being reached.

The easiest way to assess whether a small sample is normally distributed is to use a normal plot. This is a plot of the cumulative frequency distribution for the

normal distribution:

for n observations

$P(x) = \frac{1}{2}/n,\ 1\frac{1}{2}/n,\ 2\frac{1}{2}/n \ldots\ldots (n-\frac{1}{2})/n$

where x is the standard normal deviate and is obtained from a table of the standard normal distribution.
The data are ordered from lowest to highest and, if normally distributed, the plot of the data against standard normal deviate is a straight line.

3.2 Numerical tests

3.2a Regression techniques such as the Shapiro-Wilk test (1965) are probably the most powerful of numerical tests for the normal distribution. In the Shapiro-Wilk test the W statistic is derived:

$$W = \frac{(\Sigma\ a_i x)^2}{\Sigma\ (x-\bar{x})^2}$$

The W statistic is analogous to the square of the correlation coefficient from a normal plot. Acceptance or rejection of normality is made by referring to the upper and lower tails of the W distribution respectively.

3.2b Pearson's moment test is useful in calculating the degree of skewness or kurtosis from normality:

$$\sqrt{b_1} = m_3/m_2^{3/2}$$

$$b_2 = m_4/m_2^2$$

where $m_k = \Sigma\ (x_i-\bar{x})^k/n$ for $x_1 = 1$ to n

$\sqrt{b_1}$ indicates skewness: 0 = normal;
negative = negative skew
b_2 indicates kurtosis: 3 = normal
<3 = thicker tails
>3 = thinner tails.

Most formal numerical techniques, such as regression techniques and the moment test, require analysis of the complete sample. In cases where the full sample is not available, or outliers have been identified and excluded, these techniques are not valid. In such circumstances, the chi-squared test may be used. Since the chi-squared test is much less powerful than a regression technique, it should not be used in cases where the full sample is available.

3.2c The chi-squared test for the normal distribution is performed by constructing a contingency table with cell boundaries drawn up using the standard normal distribution and mean and standard deviation derived from the normal plot to contain an equal number of expected observations (E) in each cell. These are compared with actual number of observations (O) in each cell. The number of cells (M) is not critical but may be derived from

$$M = 2n^{2/5} \qquad \text{(Mann and Wald, 1942)}$$

to maximize the chance of a significant result. The value of chi-squared is calculated from

$$\chi^2 = \sum_{1}^{M} \frac{(O-E)^2}{E} \qquad \text{with M-3 degrees of freedom}$$

The null hypothesis is that there is no difference in the distribution of observed and expected data (ie that the observed data is Normally distributed) and this is rejected if χ^2 is high (P value is low). A low value of χ^2 (P value is high) provides strong evidence of normality, but as discussed in section 3.1 does not prove the null hypothesis. An extremely low value of χ^2 carries a low probability and may cast doubt upon the experimental validity of the data.

4 Precision of measurement

Precision of measurement may be estimated from paired measurements from members of the sample. The estimate of the error standard deviation (s) is given by:

$$s = \sqrt{\frac{1}{2(n-1)} \Sigma (x_i - y_i)^2} \qquad \text{for } i = 1 \text{ to } n$$

Providing the measurement errors are from a normal distribution (which is a reasonable assumption if the measurements of the sample are normally distributed), 95% confidence intervals for the estimate of the measurements are given by: $1.96 \times \sqrt{(2s^2)}$

For small samples ($n < 100$), the t distribution should be used rather than the normal distribution, in which case confidence intervals are given by $t \times \sqrt{(2s^2)}$ where the value of t is obtained from tables for (n-1) degrees of freedom at the required confidence level (see section 4.5). Reporting confidence intervals is preferable to

quoting the coefficient of variation. This is the error standard deviation divided by the mean measurement expressed as a percentage, and hence varies according to the mean measurement, and paradoxically implies that precision depends upon the absolute value of the measurement (see for example section 5.4.4).

5 **The t distribution**

The t distribution is used to find confidence intervals for parameters estimated from a small sample from a normal distribution. For a sample from a normal distribution, $(x - \mu)/\sqrt{(s^2/n-1)}$ is from a t distribution with (n-1) degrees of freedom, where s is the variance of the sample. Confidence intervals for the population mean μ are given by:

$$x - t\sqrt{s^2/(n-1)} \text{ to } x + t\sqrt{s^2/(n-1)}$$

where t is obtained from tables for the chosen probability value. The t distribution can be used to find confidence intervals for the difference between two independent samples and also for the difference between two measurements of the same sample:

95% confidence intervals for the difference between the means of two independant samples with similar variance are given by:

$$x_1 - x_2 - t\sqrt{\frac{s^2}{n_1-1} + \frac{s^2}{n_2-1}} \text{ to } x_1 - x_2 + t\sqrt{\frac{s^2}{n_1-1} + \frac{s^2}{n_2-1}}$$

To test the null hypothesis that the mean difference between two measurements of the same sample is zero (the paired t test), the test statistic is:

$$\frac{x}{\sqrt{(s^2/(n-1))}}$$

where x is the mean difference.

Although the t test assumes the population to be normally distributed and requires different populations to have the same variance for comparison, the t test is robust in that minor departures from normality and small differences in variance have little effect on the test.

6 **The power of a test**

The power of a test is the probability that the test will demonstrate a significant difference at a given significance level. The power of a test is given by:

$1 - P(x)$

where $x = 1.96 - (\mu_1 - \mu_2)/\sqrt{\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}}$

or $x = t - (\mu_1 - \mu_2)/\sqrt{\frac{s_1^2}{n_1-1} + \frac{s_2^2}{n_2-1}}$ For small samples ($n_1 + n_2 < 100$)

where t has $(n_1 + n_2-2)$ degrees of freedom and P(x) is obtained from the standard normal distribution.

The power of a test can also be used to calculate the sample size required to detect a given difference. In this study a power of 0.8 was considered acceptable.

7 **Correlation**

The correlation coefficient, r, is based on the sum of products about the mean of two variables and indicates how close the relationship is between the two variables. If the relationship is linear, r = 1 (or -1 for a negative correlation), and if there is no correlation, r = 0.

If the pairs of observations are denoted x_i and y_i and there are n pairs

$$r = \frac{\Sigma x_i y_i - \frac{\Sigma x_i \Sigma y_i}{n}}{\sqrt{\left[\Sigma x_i^2 - \frac{(\Sigma x_i)^2}{n} \right] \left[\Sigma y_i^2 - \frac{(\Sigma y_i)^2}{n} \right]}}$$

Confidence intervals for the correlation coefficient are usually very wide, especially with small samples.

Calculation of confidence intervals for r is difficult and sensitive to departures from normality of x and y.

Therefore, interpretation of a correlation coefficient should be exercised with caution. However, the null

hypothesis that r = 0 (or that there is no linear relationship) is easy to test, and the test requires that only one of the two variables be normally distributed. Two sided points for the distribution of r under the null hypothesis are obtained from tables, with the number of degrees of freedom being (n-2).

8 Non-parametric methods

These are tests which make no assumption about the underlying distribution of the data. They tend to be less powerful than parametric tests and should therefore only be used when parametric testing is inappropriate.

8.1 Mann-Whitney U test

This is used to detect differences in two samples. The observations for the two samples are combined and arranged in rank order.

For each member of one sample the number of members from the other sample preceding it are counted and these numbers are added. This sum is denoted U. The value of U for the other sample can be obtained by subtraction:

$$U_2 = (n_1)(n_2) - U_1$$

The smaller U value is used for subsequent analysis. The distribution of U approximates to a normal distribution with mean $\frac{1}{2}n_1n_2$ and standard deviation:

$$\sqrt{\frac{n_1 n_2 (n_1+n_2+1)}{12}}$$

In the Mann-Whitney U test the null hypothesis is that the two samples came from the same population, and the probability that the value of U could have arisen by chance is calculated:

$$z = \frac{U - (n_1)(n_2)/2}{\sqrt{n_1 n_2 (n_1+n_2+1)/12}}$$

and P(z) is obtained from the one-tail section of the standard normal distribution. If P(z) is small, the null hypothesis is disproven. If P(z) is large one cannot conclude, however, that the null hypothesis is proven.

8.2 Spearman's rank correlation coefficient

This is used to test the hypothesis that two variables from a sample are related. The null hypothesis is that the variables are independent. The Spearman test statistic ρ is calculated by denoting the ranks for the two variables, then:

$$\rho = \frac{\Sigma x_r y_r - \frac{(\Sigma x_r)(\Sigma y_r)}{n}}{\sqrt{(\Sigma x_r{}^2 - \frac{(\Sigma x_r)^2}{n})(\Sigma y_r{}^2 - \frac{(\Sigma y_r)^2}{n})}}$$

The probability that ρ could have arisen by chance is

read from tables, using two-sided points for the distribution of ρ . If P is small, the null hypothesis is disproven.

8.3 Fisher's exact test

This is used to detect association in a 2 x 2 contingency table. The probability of observed or more extreme values arising by chance is calculated and if this probability is small, evidence of association is provided.

If the row and column totals are R_1, R_2, C_1, C_2, the probability of observing frequencies O_{11}, O_{12}, O_{22} and O_{21} is:

$$\frac{R_1! \times R_2! \times C_1! \times C_2!}{N! \times O_{11}! \times O_{12}! \times O_{22}! \times O_{21}!}$$

Appendix 4

Summary of study data

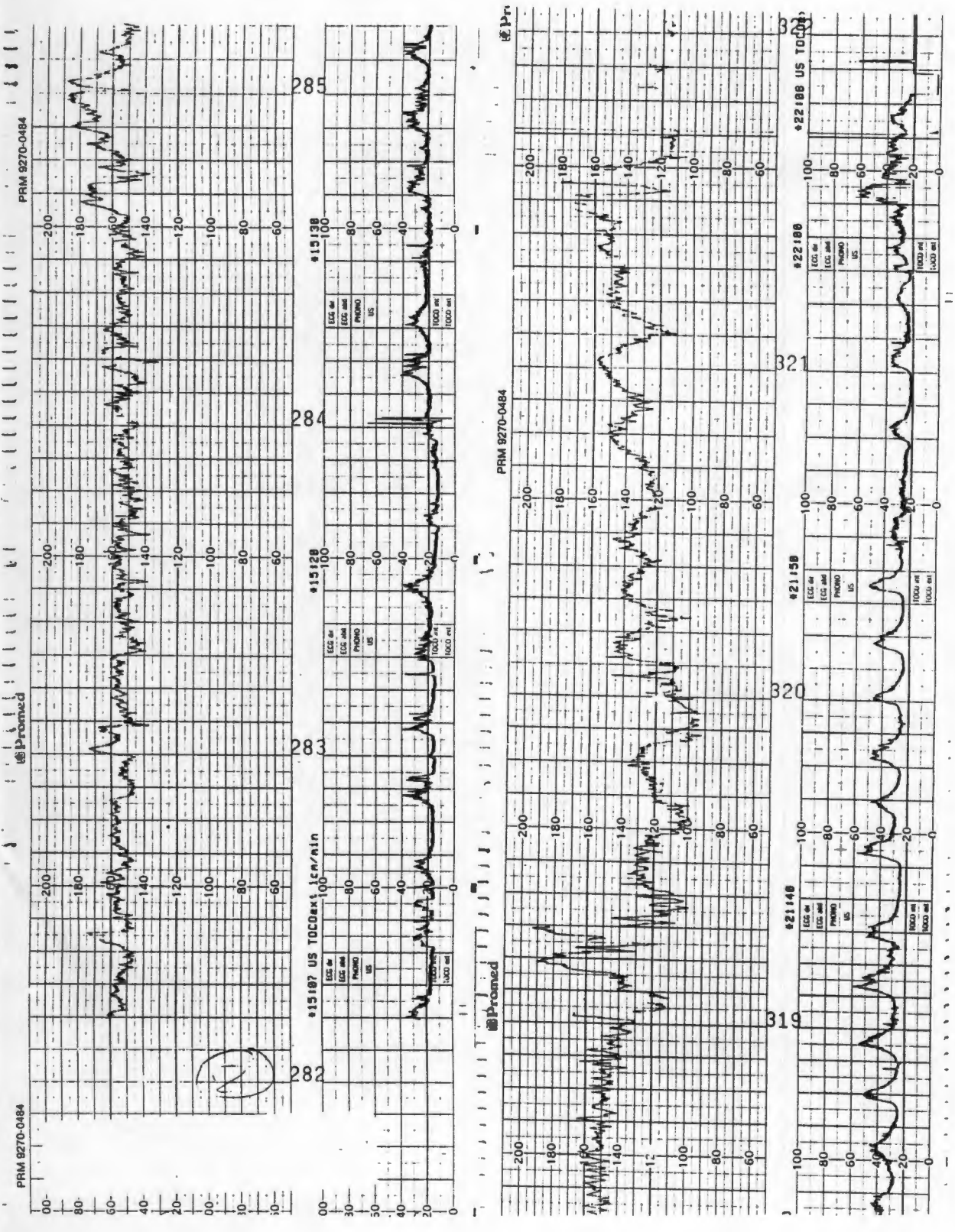
Key		
	Race	2 = Coloured
		3 = Black
	Gestation	weeks
	Complication	1 = Gestational proteinuric hypertension
		2 = Intrauterine growth retardation
	RP	Pourcelot ratio (resistance index)
	PI	Pulsatility index
	FHR	Fetal heart rate
	PH	pH
	BASE	base excess mmol l^{-1}
	PCO2	pCO_2 mmHg
	PO2	pO_2 mmHg

NUMBER	02	03	04	05	06	11	12	13	14	17	18	21	22	23	24	25	26	33	34	35	37	42	47	54	55	57	58
RACE	2	2	2	3	2	2	2	2	2	2	2	3	2	2	2	2	2	2	2	2	3	2	3	2	3	3	2
GESTATION	42	42	40	42	39	42	40	42	34	40	41	35	40	41	40	41	40	38	38	39	40	38	40	39	40	41	37
COMPLICATIONS	1	2	2	1	1	1	1	1	1	2	1	1	2	1	1	2	1	1	1	1	1	1	1	2	1	1	1
MINS BEFORE DEL 1	0390	0391	0346	0447	0184	0536	0500	0340	0307	0100	0200	0131	0298	0220	0175	0415	0195	0630	0320	0639	0104	0512	0373	0720	0707	1070	0447
RP	.48	.60	.55	.69	.67	.59	.56	.67	.73	.62	.60	.63	.56	.56	.69	.60	.53	.63	.56	.63	.62	.66	.58	.77	.60	.69	.64
PI	.69	1.21	.79	1.28	1.00	.96	.77	1.18	1.33	1.06	1.15	1.11	.81	.79	1.24	1.15	.77	1.00	.87	1.00	1.03	1.00	.80	1.38	.91	.95	1.05
FHR	136	142	146	140	130	120	142	127	127	141	127	136	146	146	143	140	146	146	142	121	139	157		146	133	144	132
SCALP 1 MINS BEFORE DEL											0052			0160	0170											0587	
RP											.69			.60	.60											.61	
PI											1.17			.93	1.20											.97	
FHR											142			135	143											136	
PH											7.12			7.30	7.33											7.31	
BASE											-10.10			-03.8	-03.6											-03.3	
SCALP 2 MINS BEFORE DEL														0040	0043												
RP														.65	.70												
PI														1.01	1.36												
FHR														142	138												
PH														7.31	7.33												
BASE														-05.4	-05.7												
MINS BEFORE DEL 2	0050	0016	0030	0047	0071	0054	0030	0039	0031	0020	0023	0022	0018	0005	0045	0010	0009	0040	0100	0124	0019	0072	0019	0013	0022	0050	0018
RP	.46	.70	.59	.70	.62	.55	.54	.62	.72	.59	.73	.67	.62	.61	.74	.66	.62	.60	.60	.62	.64	.70	.63	.63	.59	.60	.60
PI	.62	1.26	.87	1.31	1.02	.73	.77	1.05	1.25	1.02	1.21	1.12	.97	1.05	1.07	1.14	.57	.97	1.10	1.03	1.04	1.25	1.11	1.01	.90	.96	1.22
FHR	150	139	130	133	126	146	162	122	135	151	151	136	142	111	142	124	150	144	130	133	122	160	120	146	146	146	140
CORD VEIN PH	7.03	7.21	7.39	7.20	7.17	7.21	7.34	7.23	7.27	7.33	7.19	7.29	7.36	7.27	7.27	7.33	7.34	7.32			7.10	7.18	7.30		7.26	7.23	7.28
BASE	-10.70	-12.70	-02.70	-04.6	-09.2	-08.9	-04.6	-08.3	-03.6	-02.5	-09.1	-03.3	-02.6	-07	-06.4	-04.9	-03.2	-07.9			-12.00	-09.4	-08.8		-08.4	-06.8	-09.3
PCO2	60.00	33.70	34.10	46.90	50.70	45.40	37.70	44.10	49.30	48.50	47.30	47.20	38.10	40.70	41.90	36.90	39.30	31.70			54.60	48.90	52.30		38.00	48.60	43.50
PO2	21.00	15.00	21.00	25.00	19.00	20.00	42.00	15.00	22.50	50.00	20.00	17.50	27.00	36.00	37.00	25.00	19.00	37.00			13.00	17.00			31.50	23.00	26.00
CORD ARTERY PH	7.00	7.16	7.29	7.26	7.12	7.18	7.23	7.19	7.20	7.19	7.13	7.25	7.26	7.22	7.24	7.26	7.20	7.28	7.24	7.11	7.02	7.13	7.14	7.30	7.22	7.16	7.23
BASE	-15.30	-11.00	-03.6	-04.1	-09.6	-09.2	-07.1	-08.1	-07.1	-13.90	-09.7	-03.7	-04.3	-06.3	-04.3	-05.2	-06.7	-08.6	-08.9	-12.30	-13.00	-09.6	-08.7	-04.6	-08.2	-10.70	-04.8

Appendix 5

CTG tracings from the six acidotic fetuses

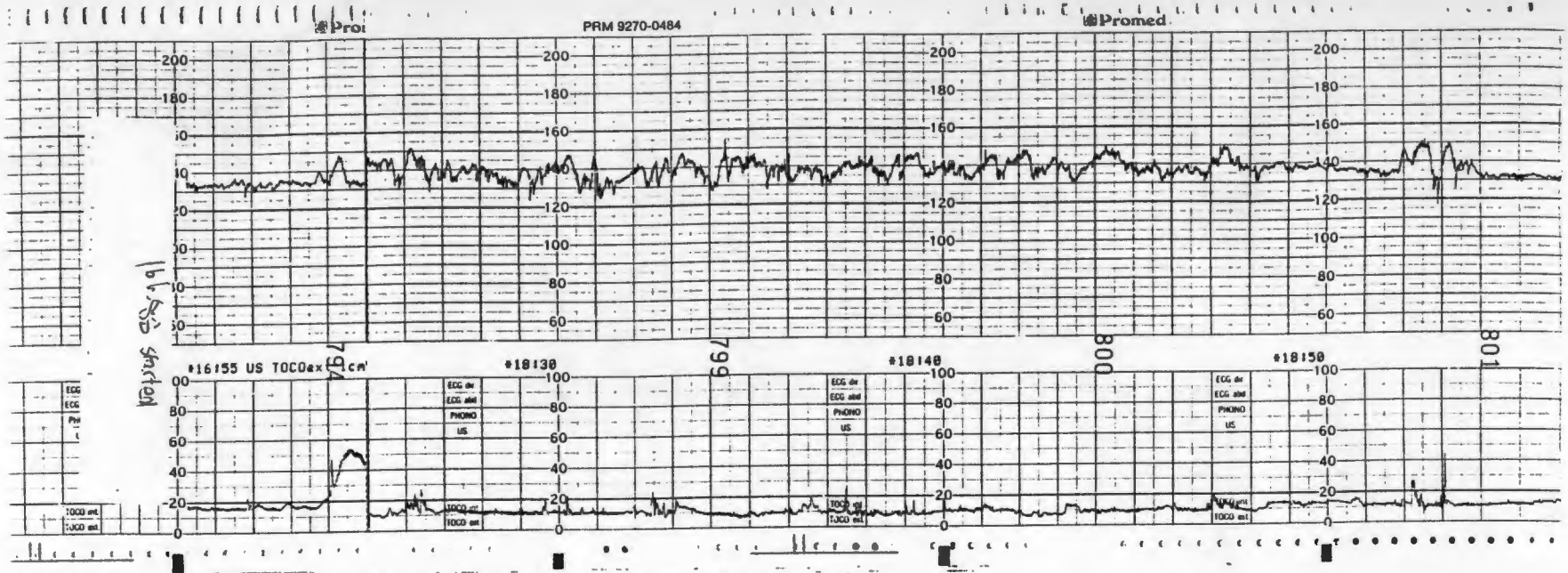
a) early in labour
b) before delivery



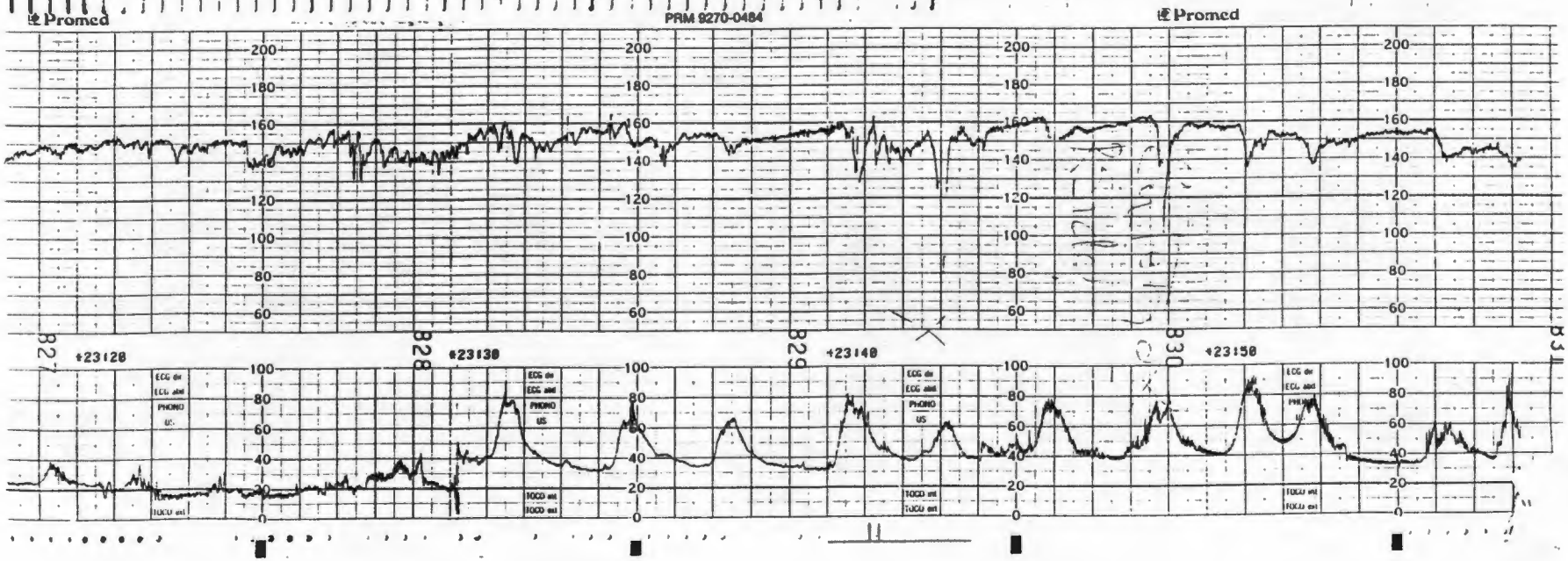
Case 2 a) b)

Case 3

a)


PRM 9270-0484
Promed
#16155 US TOCOax
#18130
#18140
#18150

b)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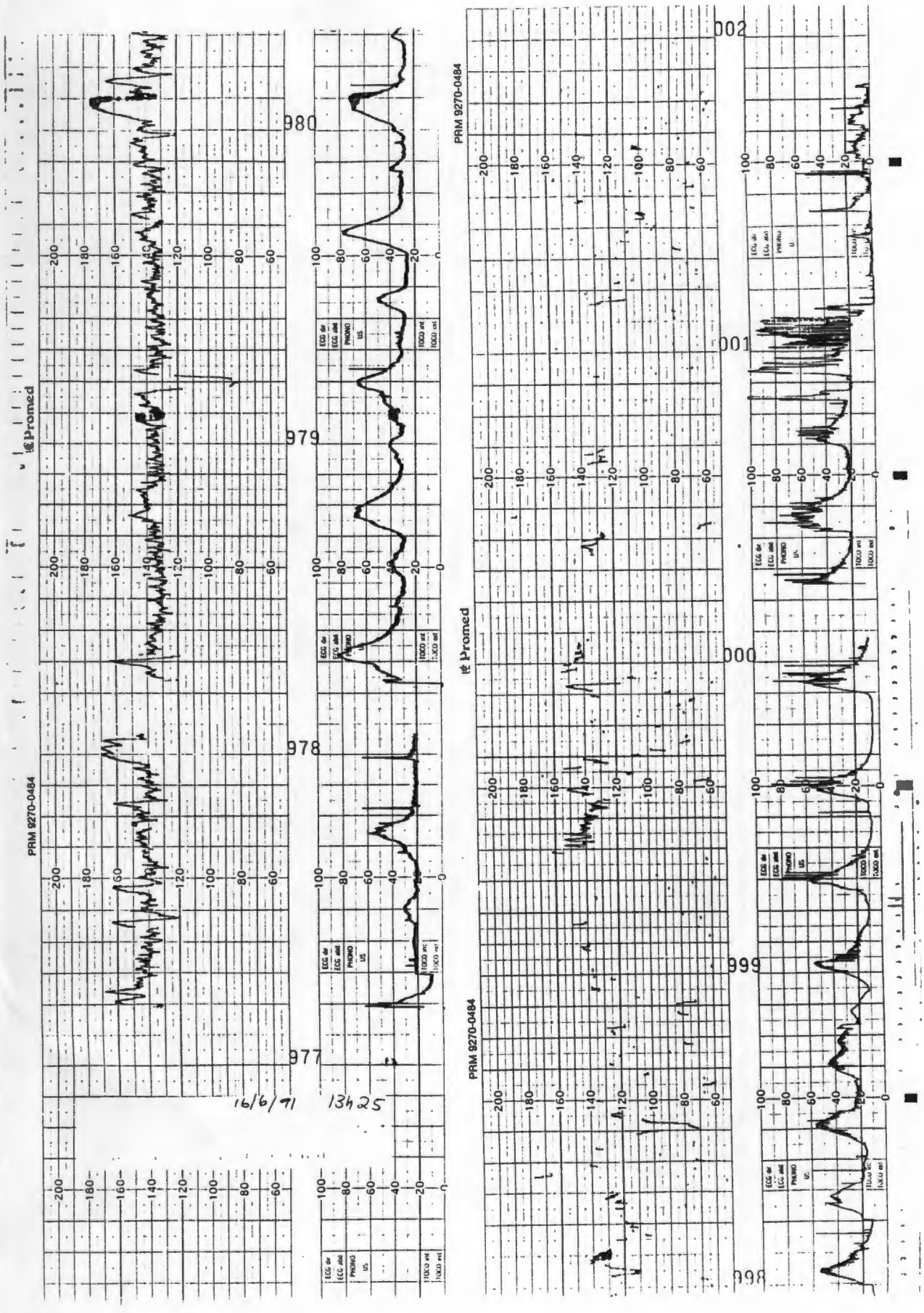
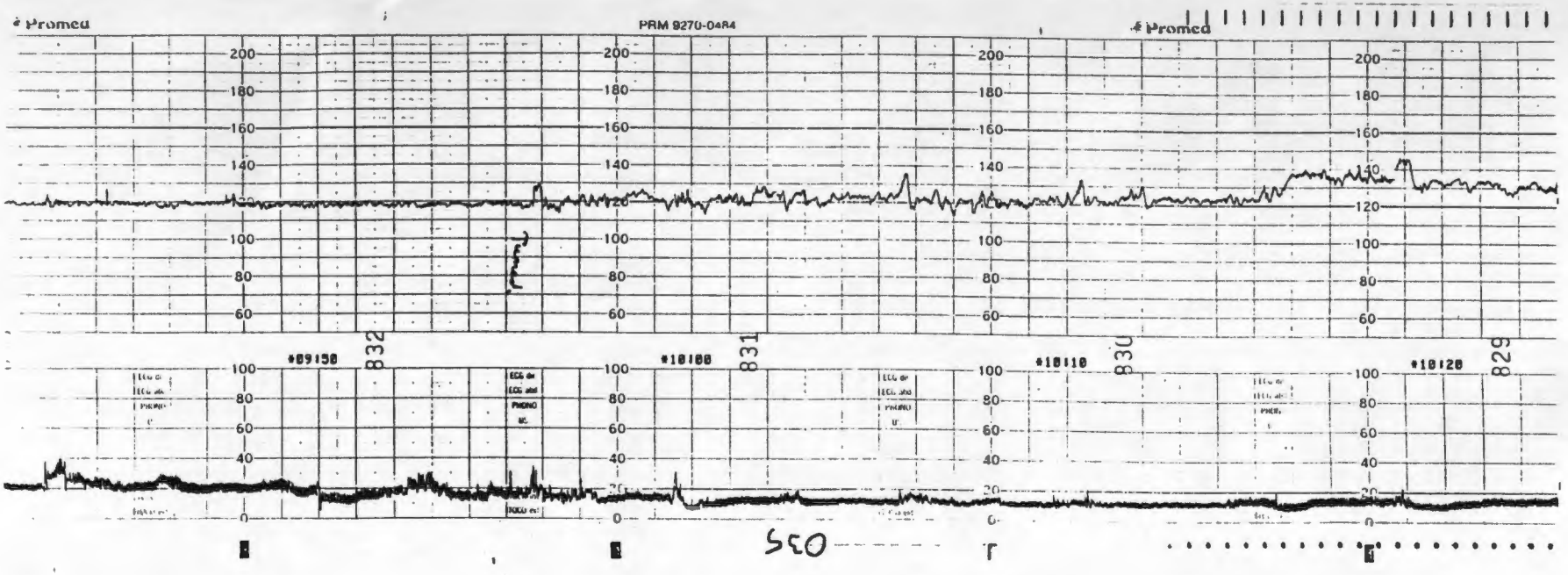
#23120
#23130
#23140
#23150

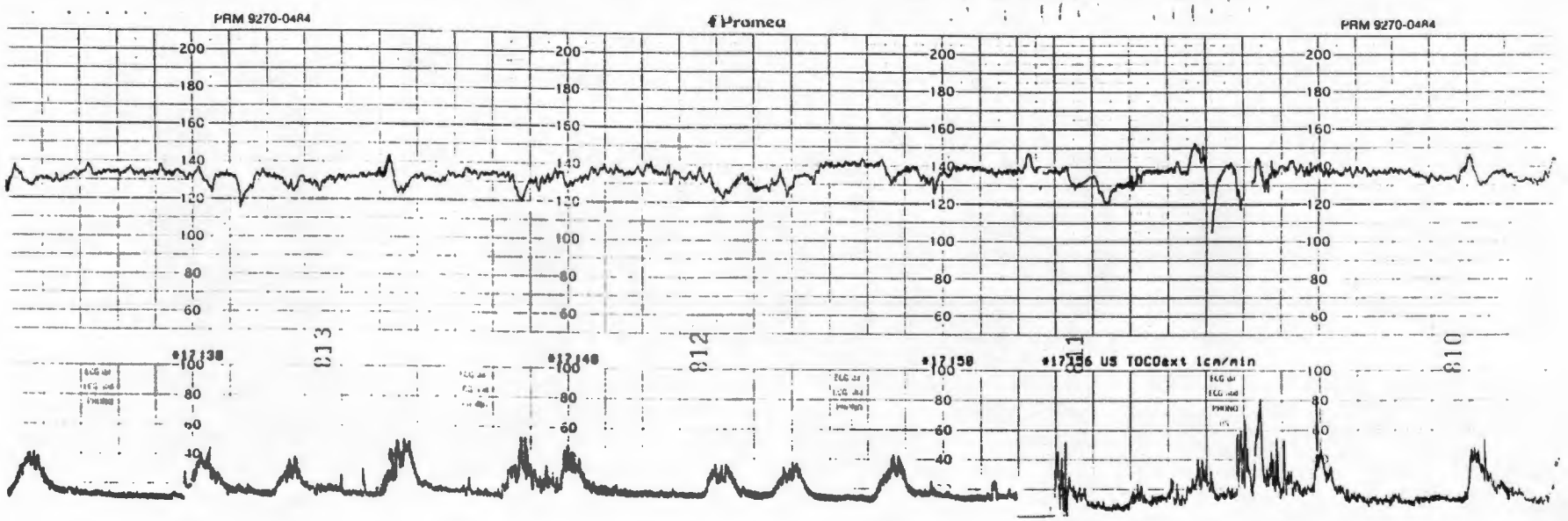

Promed
PRM 9270-0484
980
979
978
977
16/6/91 13:25
002
001
000
999
998

Case 17 a) b)

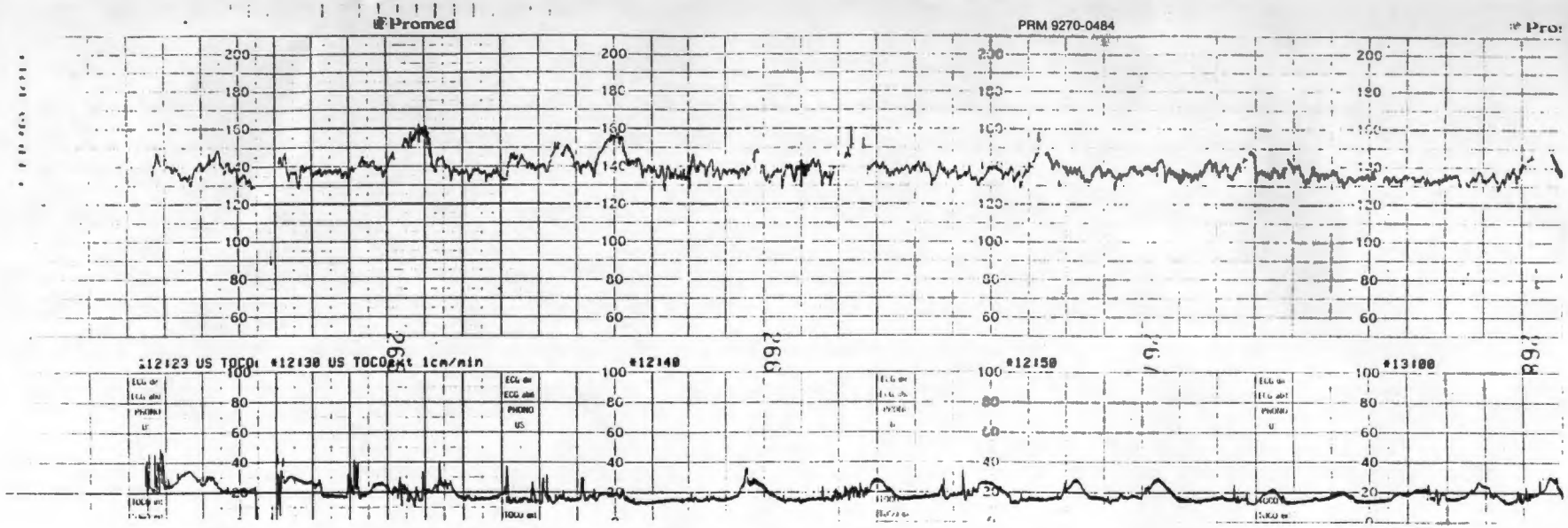
Case 35 a)


Promed
PRM 9270-04R4
Promed
200
180
160
140
120
100
80
60
100
80
60
40
20
0
*09:58
*10:08
*10:18
*10:28
832
831
830
829
035

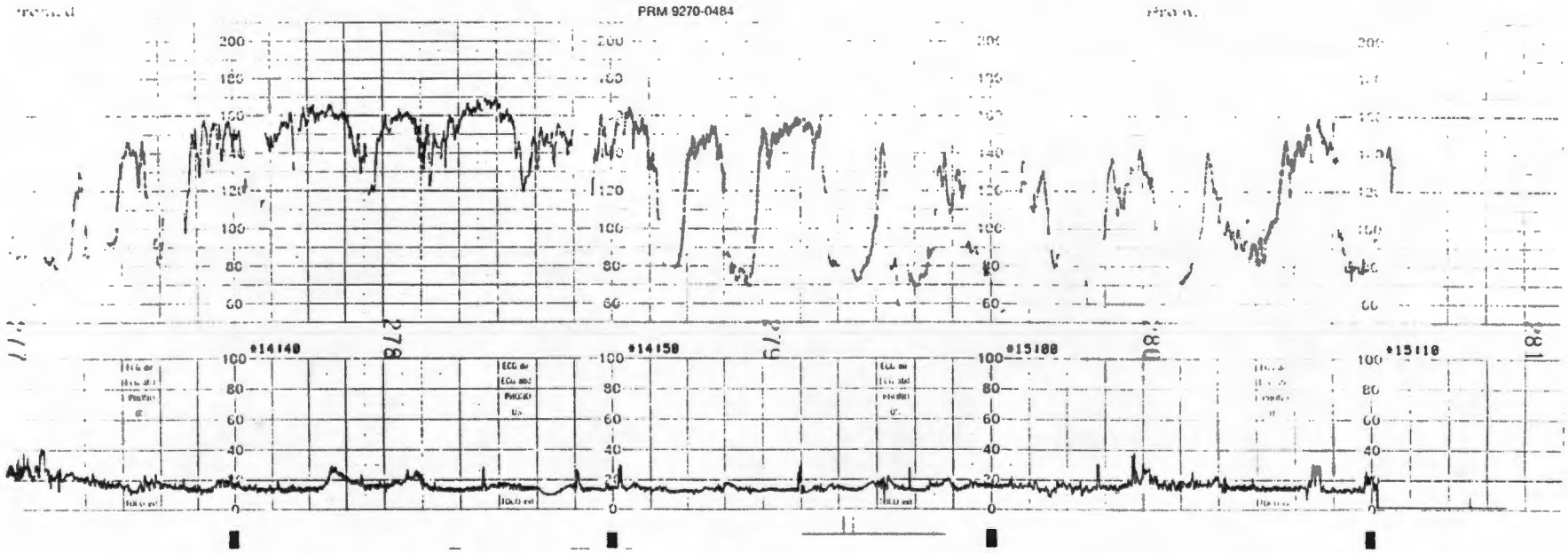
b)


PRM 9270-04R4
Promed
PRM 9270-04R4
200
180
160
140
120
100
80
60
100
80
60
40
*12:38
*12:48
*12:58
*13:08 US TOCOext 1cm/min
813
812
811
810

Case 37 a)


Promed
PRM 9270-0484
212123 US TOCO: #12130 US TOCO set 1cm/min
#12140
#12150
#13100

b)


PRM 9270-0484
#14140
#14150
#15100
#15110

Case 57 a)

b)