DETERMINANTS OF DOPPLER FLOW VELOCITY WAVEFORMS IN THE UTEROPLACENTAL AND UMBILICAL ARTERIES

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Dedication

This thesis is dedicated to my family

Declaration

I declare that the preparation and writing of this thesis has been carried out by myself.

The research described in this thesis was performed by myself.

Kevin P Hanretty

Table of Contents **Page**

Declaration 3

Tables 8

Figures 9

Aknowledgements 13

Summary 14

Chapter 1 Introduction. 19

1.1 A brief historical perspective. 20

1.2 Physics of Doppler velocimetry in obstetrics. 24

1.3 Safety aspects of Doppler in obstetrics. 28

Chapter 2 The uteroplacental and fetoplacental circulations in clinical practice. 36

Chapter 3 The aims of this thesis. 55

Chapter 4 Methodology of obtaining Doppler waveforms. 57

4.1 Methods used in this thesis. 58

4.2 Indices used to describe flow velocity waveforms. 59

4.3 Discussion. 61

Chapter 5 Cross sectional study of umbilical and uteroplacental flow velocity waveforms in pregnancy induced hypertension (PIH). 79

5.1 Definitions of pregnancy induced hypertension. 80

Chapter 5 (cont'd)

5.2 The clinical problem of pregnancy induced hypertension. 83

5.3 The aetiology and pathogenesis of pregnancy induced hypertension. 84

5.4 Diagnostic methods in pregnancy induced hypertension. 88

5.5 Patients and methods. 92

5.6 Results. 93

5.7 Discussion. 94

Chapter 6 Cross-sectional study of umbilical and uteroplacental flow velocity waveforms in pregnancies in which the fetus is small for dates. 99

6.1 The clinical significance of the small-for-dates fetus. 100

6.2 The aetiology and pathogenesis of intra-uterine growth retardation. 102

6.3 The identification of the small-for-dates fetus. 106

6.4 Methods. 109

6.5 Results. 110

6.6 Discussion. 111

Chapter 7 The effect of percutaneous umbilical blood sampling and intravascular transfusion for rhesus disease on umbilical artery flow velocity waveforms. 124

Chapter 7 (cont'd)

7.1 Blood flow and viscosity. 125

7.2 Doppler and rhesus disease. 128

7.3 Methods and patients. 129

7.4 Results. 130

7.5 Discussion. 131

Chapter 8 Umbilical and uteroplacental artery flow velocity waveforms in pregnancies with high maternal serum alphafetoprotein (AFP) measurements. 138

8.1 The clinical significance of high maternal serum AFP levels. 139

8.2 Methods. 141

8.3 Results. 142

8.4 Discussion. 143

Chapter 9 The use of Doppler velocimetry in developmental pharmacology. 146

Chapter 10 Effect of established therapy with the beta blocker, atenolol, given for pregnancy induced hypertension on umbilical and uteroplacental artery flow velocity waveforms. 154

10.1 Drug therapy of pregnancy induced hypertension. 155

10.2 The pharmacology of atenolol. 162

10.3 Methods. 163

Chapter 10 (cont'd)

10.4 Results. 164

10.5 Discussion. 166

Chapter 11 Effect of acute therapy with a calcium channel blocker, nifedipine, on umbilical and uteroplacental artery flow velocity waveforms in pregnancy induced hypertension. 183

11.1 Introduction. 184

11.2 Clinical pharmacology of nifedipine. 185

11.3 Methods and patients. 187

11.4 Results. 187

11.5 Discussion. 188

Chapter 12 Conclusions. 197

References 202

Tables **Page**

Table 2.1 Uteroplacental and fetoplacental perfusion in intra-uterine growth retardation and pregnancy induced hypertension: a synopsis. 52

Table 4.1 The clinical Features of patients studied. 63

Table 4.2 Correlations between Doppler waveform indices for the uteroplacental and umbilical arteries. 63

Table 5.1 Comparison of results from PIH and control groups. 97

Table 6.1 Outcome data for the small-for-dates and control groups. 118

Table 8.1 Complications occurring in the high AFP and control groups. 145

Table 11.1 Maternal and fetal indices following oral nifedipine. 191

Figures **Page**

Figure 1.1 The relationship between blood velocity and and the change in frequency of a returning signal as a result of the Doppler shift. 34

Figure 1.2 Illustration of the ultrasound equipment used in the study. 35

Figure 2.1 The inter-relations of the maternal and fetoplacental circulations. 53

Figure 2.2 Two waveforms obtained synchronously from uteroplacental vessels flowing in opposite directions. The upper channel shows a vessel of high vascular resistance and the lower channel a vessel of low resistance. 54

Figure 4.1a Normal umbilical artery flow velocity waveform of low resistance. Figure 4.1b High resistance umbilical artery flow velocity waveform. 64

Figure 4.2a Low resistance uteroplacental flow velocity waveform. Figure 4.2b High resistance uteroplacental flow velocity waveform obtained from a patient with pregnancy induced hypertension. 65

Figure 4.3 Scheme representing the method of calculating the pulsatility index, resistance index and systolic/diastolic ratio. 66

Figure 4.4 Relationship between pulsatility index and gestational age in the umbilical artery. 67

Figure 4.5 Relationship between resistance index and gestational age in the umbilical artery. 68

Figure 4.6 Relationship between the systolic/diastolic ratio and gestational age in the umbilical artery. 69

Figure 4.7 Relationship between pulsatility index and gestational age in the uteroplacental arteries. 70

Figure 4.8 Relationship between resistance index and gestational age in the uteroplacental arteries. 71

Figure 4.9 Relationship between the systolic/diastolic ratio and gestational age in the uteroplacental arteries. 72

Figure 4.10 Relationship between the systolic/diastolic ratio and the pulsatility index in the umbilical artery. 73

Figure 4.11 Relationship between resistance index and systolic/diastolic ratio in the umbilical artery. 74

Figure 4.12 Relationship between resistance index and pulsatility index in the umbilical artery. 75

Figure 4.13 Relationship between systolic/diastolic ratio and pulsatility index in the uteroplacental arteries. 76

Figure 4.14 Relationship between resistance index and systolic/diastolic ratio in the uteroplacental arteries. 77

Figure 4.15 Relationship between resistance index and pulsatility index in the uteroplacental arteries. 78

Figure 5.1 Factors influencing uteroplacental perfusion in pregnancy induced hypertension. 98

Figure 6.1 Factors influencing fetal growth and their relationships with uteroplacental and fetoplacental perfusion. 119

Figure 6.2 Umbilical artery resistance index in small-for-dates and appropriately grown fetuses. 120

Figure 6.3 Umbilical artery pulsatility index in small-for-dates and appropriately grown fetuses. 121

Figure 6.4 Uteroplacental artery resistance index in small-for-dates and appropriately grown fetuses. 122

Figure 6.5 Uteroplacental artery pulsatility index in small-for-dates and appropriately grown fetuses. 123

Figure 7.1 Fetal heart rates before and after intravascular transfusion. 134

Figure 7.2 Fetal heart rates before and after fetal blood sampling alone. 135

Figure 7.3 Umbilical artery systolic/diastolic ratios before and after intravascular transfusion. 136

Figure 7.4 Umbilical artery systolic/diastolic ratios before and after fetal blood sampling alone. 137

Figure 10.1 Systolic blood pressure before and after establishment of therapy with atenolol. 169

Figure 10.2 Diastolic blood pressure before and after establishment of therapy with atenolol. 170

Figure 10.3 Umbilical artery pulsatility index before and after establishment of therapy with atenolol. 171

Figure 10.4 Umbilical artery resistance index before and after establishment of therapy with atenolol. 172

Figure 10.5 Fetal heart rate before and after establishment of therapy with atenolol. 173

Figure 10.6 Uteroplacental pulsatility index before and after establishment of therapy with atenolol. 174

Figure 10.7 Uteroplacental resistance index before and after establishment of therapy with atenolol. 175

Figure 10.8 Systolic blood pressure in treated and untreated cases of PIH. 176

Figure 10.9 Diastolic blood pressure in treated and untreated cases of PIH. 177

Figure 10.10 Umbilical artery pulsatility index in treated and untreated cases of PIH. 178

Figure 10.11 Umbilical artery resistance index in treated and untreated cases of PIH. 179

Figure 10.12 Fetal heart rates in treated and untreated cases of PIH. 180

Figure 10.13 Uteroplacental pulsatility index in treated and untreated cases of PIH. 181

Figure 10.14 Uteroplacental resistance index in treated and untreated cases of PIH. 182

Figure 11.1 Blood pressure changes after oral nifedipine. 192

Figure 11.2 Maternal pulse after oral nifedipine. 193

Figure 11.3 Fetal heart rates following oral nifedipine. 194

Figure 11.4 Umbilical artery pulsatility index following oral nifedipine. 195

Figure 11.5 Uteroplacental pulsatility index following oral nifedipine. 196

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DETERMINANTS OF DOPPLER FLOW VELOCITY WAVEFORMS IN THE UTEROPLACENTAL AND UMBILICAL ARTERIES

SUMMARY

Non-invasive assessment of blood flow in the uteroplacental and umbilical arteries using Doppler velocimetry is a promising technique for the identification of fetal compromise and seems likely to be introduced widely into clinical practice. Nevertheless, many problems remain to be resolved regarding the potential use of Doppler in obstetrics. These problems arise in part from a lack of understanding of which indices are most appropriate for describing waveforms and of the factors determining abnormal waveforms.

In a cross sectional study of 356 normal and complicated pregnancies the three most commonly used indices, the pulsatility index, resistance index and systolic/diastolic ratio were found to be highly correlated with each other and could be used interchangeably unless absence of end diastolic velocities was observed. The association between advancing gestational age and umbilical artery waveform indices, showing reduced placental vascular resistance, was confirmed although no such association was seen in uteroplacental patterns.

Placental vascular pathology has been implicated in the production of abnormal uteroplacental and umbilical artery Doppler waveforms. It has been postulated that Doppler studies in mid-trimester might identify pregnancies at risk of later complications. Elevated maternal serum

alphafetoprotein (AFP) in pregnancies with normally formed fetuses is also known to be associated with a high risk of perinatal complications and a placental pathology has recently been suggested as underlying this. To determine if Doppler might identify such a lesion, 40 patients with unexplained elevation of maternal serum AFP underwent Doppler studies in the mid trimester. Although there was a significant difference in the incidence of later complications from a matched group of control patients there was no difference from controls in Doppler indices from the uteroplacental or umbilical circulations. Consequently the hypothesis that Doppler might identify a placental lesion associated with later complications is rejected. Furthermore, despite a 40% incidence of complications in the elevated AFP group the values obtained were within previously published normal ranges for the gestation of study and the findings do not support a role for Doppler in screening in mid trimester for later complications.

Abnormal waveforms have been reported in pregnancies in which the fetus is small-for-dates and in those complicated by hypertension but few controlled studies have been performed to determine the role played by these conditions in producing changes in waveform indices.

A controlled study was performed to determine if uteroplacental and umbilical artery waveforms are altered in pregnancies in which the fetus is small-for-dates. Waveforms were obtained in 32 such pregnancies. No difference in uteroplacental waveform indices was identified. In contrast, the indices from the umbilical artery were significantly

higher, though not necessarily abnormal, compared with matched controls. These data suggest that haemodynamic changes occur in such fetuses even when, as determined by Doppler, uteroplacental perfusion is maintained.

It is known that in some small-for-dates fetuses blood viscosity is increased. From Pouseille's equation it is known that blood flow is dependent on blood viscosity and the need for intra-uterine intravascular transfusion in some cases of rhesus disease provided the opportunity to determine if an increase in blood viscosity following transfusion is associated with an increase in Doppler indices of resistance. Twenty women underwent a total of 35 percutaneous umbilical blood sampling procedures and on 22 occasions intra-vascular transfusion was indicated from the results obtained. The systolic/diastolic ratio was measured immediately before and 1 hour after sampling or, if performed, transfusion. A reduction in the systolic/diastolic ratio was seen whether transfusion was performed or not indicating that a reduction in resistance to blood flow occurred. This surprising finding suggests that umbilical cord puncture itself may result in the release of vasodilator substances and this must be investigated in further studies.

To determine if pregnancy induced hypertension (PIH) and absolute levels of blood pressure influenced waveforms, a group of 48 untreated carefully defined patients were compared with an individually matched control group. In the hypertensive patients the Doppler indices of vascular resistance in the uteroplacental vessels were significantly

higher than controls. In contrast, the results from the umbilical artery analysis showed increased resistance, reflected in higher values for waveform indices, only when significant proteinuria was present. There was no relationship in either circulation between absolute levels of blood pressure and waveform indices.

Since Doppler is likely to be employed to assess fetal well being in hypertensive pregnancies knowledge of the effects of antihypertensive agents on Doppler waveform indices is important for interpretation of any changes seen. Furthermore, Doppler methods provide the first repeatable non-invasive method of assessing the effects of vasoactive drugs on uteroplacental and fetoplacental perfusion.

To determine if beta blockade with atenolol given for PIH influenced waveforms, ten patients were studied immediately before treatment and after treatment was established for 6 or 7 days. Doppler indices in both uteroplacental and umbilical arteries were unaltered from pre-treatment values and were not different from a matched group of untreated cases.

To determine if acute reductions in blood pressure, as occasionally required in severe PIH, influenced waveforms, a group of 9 women with severe PIH were studied following the oral administration of nifedipine, a calcium channel blocker. Despite significant and rapid reductions in blood pressure, no effect was seen on Doppler waveforms in either of the circulations studied.

These data suggest that these antihypertensive agents do not influence Doppler waveforms and that uteroplacental and

fetoplacental perfusion is unaltered following treatment.

In conclusion, uteroplacental waveforms are altered in pregnancies complicated by PIH but not in those in which the fetus is small-for-dates. Therapy for PIH appeared not to influence uteroplacental waveforms. The association between elevated AFP levels and later adverse perinatal outcome was confirmed but not associated with alterations in uteroplacental waveforms.

Umbilical artery waveforms were altered in proteinuric PIH and in pregnancies in which the fetus is small-for-dates suggesting that a redistribution of cardiac output occurs.

Treatment with atenolol or nifedipine did not influence waveforms. Similarly, elevated maternal AFP levels were not associated with changes in umbilical waveform indices.

Surprisingly, an increase in haematocrit occuring after intravascular fetal transfusion was associated with a reduction in waveform indices. This probably results from the production or release of local vasoactive agents following percutaneous umbilical blood sampling.

Finally, the determinants of Doppler waveforms in uteroplacental and umbilical vessels have been studied in a controlled fashion and this information should place the clinical application of the technique on a firmer foundation.

Chapter 1 Introduction

1.1 A brief historical perspective.

1.2 Physics of Doppler velocimetry in obstetrics.

1.3 Safety aspects of Doppler in obstetrics.

Chapter 1

Introduction

Chapter 1.1 A brief historical perspective.

The observation that the perceived frequency of a wave source moving towards an observer depended on the velocity of the source was first predicted on theoretical grounds in 1843 by Christian Johan Doppler (1803-1857), Professor of Experimental Physics at the Imperial University in Vienna. Doppler's theory was postulated to explain the changes in wavelength of light from double stars and experimental proof for the effect which now carries his name was obtained by Buys Ballot. This enterprising Dutchman used the newly completed Amsterdam to Utrecht railway line to demonstrate that the pitch of a horn played by a traveller on a moving railway carriage was perceived by a stationary observer to increase as the train approached.

The change in pitch became greater as the angle between the railway track and the observer's line of sight of the train became more acute. The use of horn players may have been a factor in determining the publication of this observation in a journal of musical appreciation (Buys-Ballot 1845).

Shortly after this the development of ultrasound began with the discovery by the Nobel laureate, PJ Curie, of the piezo-electric properties of certain materials. These materials resonate when subjected to a voltage and Curie's pupil Langevin, used this property of certain ceramics to produce ultrasound which had its first practical application

in the detection of submarines during the First World War. The Austrian brothers Dussik first used ultrasound to aid diagnosis when they attempted to visualise intracranial structures using a transmission technique (Dussik 1942) but their work was interrupted by the Second World War and was, in any case, flawed by a number of technical and methodological problems. However, the rapid advances made in the first world war were repeated in the second war as a result of renewed military interest. Both ASDIC (anti-submarine detection) and RADAR (Radio Detection and Range) advanced rapidly and much of the equipment and principles developed at this time became available for peace time use. On the completion of hostilities, Wild and Reid using ex-US navy equipment were the first to obtain 2 dimensional ultrasound images although Howry and co-workers, using the disused gun turret of an air force bomber, were the first to obtain images of diagnostic value (Hill 1973).

The possibility of combining the Doppler effect with ultrasound to identify moving structures was being investigated by Satomura (1957) who recorded heart action with a continuous wave system. Advances in technology over the next four years made Doppler analysis of backscattered ultrasound for velocimetry possible. In the meantime, the application of ultrasound to obstetrics was being established by Ian Donald and his colleagues in Glasgow who produced the first contact B mode scanner. Synchronously Callagan, Rowland & Goldman (1964) and Johnson et al (1965) were working in the US to develop the ultrasonic flow meter to detect fetal heart action.

Johnson's group even identified different flow patterns from a variety of fetal and maternal vessels which they could not at that time visualise. Bishop (1966) was the first to suggest, however, that Doppler ultrasound could be used to study fetal and maternal vasculature in continuing pregnancies.

Before these developments study of the cardiovascular physiology of the human fetus had been limited by its relative inaccessibility and indeed it was only in 1822 that the first recorded mention was made by the Breton physician, Baron Jacques Alexandre Le Jumeau de Kergaradec, of the auscultation of the human heart in utero as a method of assessing fetal well being. Auscultation of the fetal heart may have been accomplished earlier (Pinkerton 1969) but it was with 'prophetic foresight' that Kergaradec, quoted by Pinkerton (1976), asked "from the variations that have arisen in the ...beats of the fetal heart will it not be possible to judge the state of health or disease of the fetus?"

It was exactly the issue of variations of the fetal heart rate that was addressed by Hon (1960) who, using scalp electrodes to measure the fetal electrocardiograph, identified changes in the fetal heart rate during labour which were associated with fetal hypoxia. Abnormal fetal heart rate reactivity may now be determined using developments of the Doppler apparatus described by Johnson and Callagan and fetal cardiotocography is currently the mainstay of antepartum assessment.

Nevertheless knowledge of heart rate patterns alone

provides only a relatively crude assessment of fetal cardiovascular physiology. More sophisticated evaluation required invasive measurements on fetuses undergoing termination of pregnancy by hysterotomy. Most of this work, done by Assali, Rauramo & Peltonen (1960) produced reliable and reproducible results but the required techniques were obviously not applicable to the study of ongoing pregnancies.

Almost twenty years later, FitzGerald and Drumm (1977) in Dublin, and McCallum et al (1978) in the United States, developed a Doppler system to obtain flow velocity waveforms from the fetal circulation. The former group, who studied patterns from the umbilical artery from 12 weeks to term suggested that this new technique of Doppler velocimetry may be of value in evaluating conditions like pre-eclampsia and intra-uterine growth retardation (IUGR). Since the first reports were made there has been an expansion in the use of Doppler velocimetry of the fetal vasculature and an associated improvement in technology which has permitted the study of the fetal aorta and cerebral vasculature as well as the fetoplacental circulation.

Early attempts to study the uteroplacental circulation were also hampered by the invasive nature of the radio-isotopic studies required to obtain blood flow values based on clearance rates from the chorio-decidual and myometrial components of this circulation. The first application of Doppler velocimetry to the study of the maternal supply to the fetus was made by Campbell et al in 1983 and a number of groups have used Doppler to study

pregnancies complicated by hypertension and IUGR.

Nevertheless, while there is much enthusiasm for this new technique both the role of Doppler in obstetrics and the underlying physiology and pathophysiology remain incompletely understood. The general aim of the studies presented in this thesis is to identify some of the determinants of Doppler flow velocity waveforms in the uteroplacental and fetoplacental circulations in order to place the clinical application of this promising technique on a sound scientific base.

Chapter 1.2 Physics of Doppler ultrasound in obstetrics.

The use of measurement of Doppler shift frequency in the evalutaion of blood flow relies on the reflection of a transmitted ultrasound beam back from the moving column of blood in the vessel being studied, to the receiver, both transmitter and receiver being housed in the same transducer.

More specifically, the Doppler principle states that the difference between transmitted and received frequencies is inversely related to c, the velocity of sound in the insonated tissue (in human tissues 1540m/s), and directly related to the transmitted frequency, the velocity of the reflecting blood cells, and to the cosine of the angle subtended by the ultrasound beam and the propagating velocity of the blood vessel being studied (Figure 1.1).

The Doppler shift frequency obtained using modern equipment represents the processed signal from the vessel

under study. Different shift frequencies will be received by the transducer which represent different velocities of blood cells within the vessel, since blood velocity will not be uniform accross the vessel. The technique of Fast Fourier Transform (FFT) allows amplitude of the different shift frequencies to be measured. The amplitude of any given frequency shift is proportional to the number of reflectors, ie. blood cells, travelling at that velocity. This is usually represented on a grey scale or colour image with greater amplitude being represented by darker shades. This method of analysis permits easier vessel identification. FFT is now available on all modern Doppler equipment (Burns 1987) of which there are 2 types, pulsed and continuous wave.

a) Pulsed Doppler

All pulsed Doppler apparatus consists of a conventional imaging transducer and screen and a Doppler system. The transmitting and receiving functions are performed by the same transducer. An interrupted, or pulsed, beam of ultrasound is generated and echoes constantly received from varying depths which correspond to the time delay between signal production and the echo being received. This time delay can be used to produce the so-called "gating" mechanism whereby vessels at a predetermined depth can be studied by only analysing signals returning after a certain time delay and consequently from a known depth. Signals returning after the selected time delay represent changes in vessels deeper than the one being studied and these frequency shifts are also excluded in order to produce a

discreet signal from the desired vessel. Signals received early, before the "gate" is opened, are also rejected. As can be seen from equation 1 (Figure 1.1) since c is treated as a constant, the blood velocity can be calculated if the angle of the ultrasound beam is known.

The angle is calculated on the conventional ultrasound image screen of these machines using adjustable calipers. The change in frequency may be plotted instantaneously against time to provide a flow velocity waveform. Volume blood flow can however be calculated with the information available from the system since measurement of the vessel diameter and of the angle of insonation is possible. In practice, calculation of the volume of blood flow in a given vessel per unit time, although achieved by a number of workers who have derived values for blood flow in the fetal aorta (Eik Nes, Bruback & Ulsten 1980), is subject to large errors. Thus. although there is a high correlation between ultrasound methods and electromagnetic methods (Eik Nes, Marsal & Kristofferson 1984; Gill 1985) it is now recognised that the cumulative errors of measurement of the angle of insonation and vessel diameter, including the change in diameter over the cardiac cycle, results in cumulative errors of 30%, and consequently qualitative methods are felt to provide more clinically reliable data. This is the case even when pulsed systems are available. Furthermore, as the two most frequently investigated circulations, the fetoplacental or umbilical artery, and the uteroplacental vessels follow tortuous paths the measurement of insonation angle in these vessels is not currently possible.

b) Continuous wave Doppler

Continuous wave Doppler systems are cheaper, more portable and easier to use than pulsed systems. The transmitted signal is emitted and received continuously by two separate transducers. It is not possible therefore to determine if the echo being received is from a superficial or deep vessel and although conventional imaging systems can be coupled to continuous wave systems the errors of insonation angle are subject to even greater error than pulsed methods.

Nevertheless the portability and ease of use of continuous wave systems makes their use attractive and all the studies described here were performed using such a system.

A number of workers have compared Doppler indices obtained using continuous wave systems with pulsed Doppler; Van Vugt et al (1988) studied umbilical artery waveforms in 14 uncomplicated pregnancies between 28 and 40 weeks gestation and found no significant difference between the methods. Brar et al (1988a) reported on 200 patients with high risk pregnancies and found a correlation coefficient of 0.98 for the same indices of umbilical artery waveforms measured using continuous wave and pulsed systems. Mehalek et al (1988), in a smaller study of 85 patients, measured both umbilical and uterine artery waveforms and found a correlation of 0.93 for the umbilical artery when the measurements were made by the same observer. The correlation for the uterine artery was 0.57 which was also highly significant, and the conclusion reached was that pulsed

Doppler systems are not routinely necessary for the identification and measurement of umbilical and uterine artery waveforms.

The indices used to describe these waveforms will be detailed in chapter 4.

Chapter 1.3

The safety of Doppler ultrasound in obstetrics.

The well recognised adverse effects of ionizing radiation on the fetus (Brent 1983) have led to considerable interest in the possible adverse sequelae which might be induced by exposure in utero to diagnostic ultrasound. It is impossible to prove definitively that ultrasound is safe (Meire 1987) but the proliferating use of diagnostic ultrasound, and Doppler in particular, highlight the need to identify any adverse biological effects which may be associated with their use.

One of the problems in determining biological effects of ultrasound is the lack of standardisation of the power output of ultrasound machines and the best indices to use in determining this.

Indices of Doppler power output.

The commonly used indices of power output relate to pulsed diagnostic ultrasound and describe sound intensity at the peak of a pulse of ultrasound (temporal peak, TP) or averaged over the time from pulse emission until the begining of the next pulse (temporal average, TA). The units used are those for power ie. Watts or Milliwatts per square

centimetre surface area. Since the average pulse of ultrasound lasts one microsecond and the intervening period until the next pulse is, on average, one millisecond the actual exposure time is small compared to scanning time. Continuous wave Doppler apparatus has a higher power output since sound is being constantly produced.

Power output across the ultrasound beam is not uniform and indices which account for this may also be used to describe power output; spatial average (SA) is the average of the intensity across the beam and spatial peak (SP) describes the point of maximum intensity. With continuous wave systems power output may be described therefore in terms of spatial peak temporal average (SPTA) or spatial average temporal average (SATA). Continuous wave apparatus in common usage has a SATA intensity of between 10 and 400 mW/square centimetre.

The importance of Doppler transducer characterisation has recently been discussed (Boote & Zagzebeski 1988) and was highlighted by Long et al (1987) who demonstrated that as many as 20% of continuous wave Doppler transducers were unsuitable for clinical use.

Possible Adverse Effects

Chromosomal Effects

The possible adverse effects of ultrasound, and in particular that produced by obstetric diagnsotic ultrasound, were first highlighted by a report by MacIntosh and Davey (1970) who reported an increase in chromosomal aberrations in cultures of human white blood cells. They compared a number of chromosomal abnormalities, including chromatid

breaks and achromatic lesions, in cultures exposed to ultrasound with a control group of cultures. The authors pointed out that the data from their experimental model should not necessarily be extrapolated to conclude that these abnormalities would occur in clinical practice. Nevertheless their preliminary communication provoked considerable interest. A large number of workers repeated these studies and have been unable to reproduce the results obtained by MacIntosh and Davey. Eventually the experiment was repeated by the principal author and the original results were not confirmed (MacIntosh, Brown & Coakley 1975).

More subtle forms of chromosomal damage which might be associated with diagnostic ultrasound were then investigated, particularly sister chromatid exchanges. Initial reports of such responses following ultrasound (Liebeskind, Bases & Mendez 1979) have not been confirmed in further studies (Ciaravino et al 1985) In any case, the dangers of extrapolating any of the in vitro results to the clinical situation are considerable (Barnett & Kossoff. 1984).

Studies of the effects of ultrasound in the human in vivo have been limited; Bause, Niebyl & Sanders (1983) investigated maternal erythrocyte fragility following Doppler ultrasound monitoring in labour and observed no change although the analysis of the data was limited by the use of inappropriate control cases.

Physical Effects

Although the evidence for adverse cellular effects in

vivo is not convincing the recognised associations of tissue heating and cavitation following ultrasound exposure are well documented (Campbell et al 1984). In vivo data are very scanty and the only investigation of heating effects within the uterus following diagnostic ultrasound exposure was reported by Soothill et al (1987) who inserted thermocouples into the pregnant uterus prior to termination of pregnancy. No change in the fetal or amniotic fluid temperature was observed following ultrasound. These workers also evaluated the effect of Doppler ultrasound in these patients and found no effect. The specific effects of Doppler equipment have not been fully investigated and knowledge of the particular effects of the increasing use of obstetric Doppler must be obtained as a matter of some urgency (Preston 1988).

Effects on fetal growth and wellbeing

The effects of diagnostic ultrasound on fetal growth have been investigated and the relationships described between ultrasound exposure and fetal growth retardation appear to relate to shared common risk factors that is, ultrasound examinations will be more commonly requested in cases of clinically small fetuses (Moore, Diamond & Cavalieri 1988).

More subtle effects of Doppler have also been investigated; behavioural effects on the fetus have been investigated since the observation that Doppler insonation increased fetal movement (David, Weaver & Pearson 1975). In a well controlled study Doppler was shown not to have any such effect (Murrills et al 1983).

Delayed effects on childhood development

The problems associated with evaluating fetal growth and its relationship to ultrasound exposure also apply to later potential effects. Neurodevelopmental delay may be a feature of the hostile intra-uterine environment which prompted an ultrasound examination. Adequate case control studies have generally been lacking. Stark et al (1984) did however perform such a study and detected no difference in a number of outcomes between ultrasound exposed cases and controls. These workers looked in detail at adverse physical, neurological and developmental effects. Among the variables examined were cognitive function, behavioural scores, dyslexia and hearing acuity. This extensive study had the benefit of twelve year follow up. The more widespread use of ultrasound since the first exposure of the index cases means that such a controlled study is no longer possible. Consequently the negative findings are very reassuring.

Ultrasound and oncogenesis

Two large simultaneously published studies (Kinnier-Wilson & Waterhouse 1984; Cartwright et al 1984) demonstrated no difference in childhood cancers and leukaemias between a total of over 2000 cases and 2800 controls.

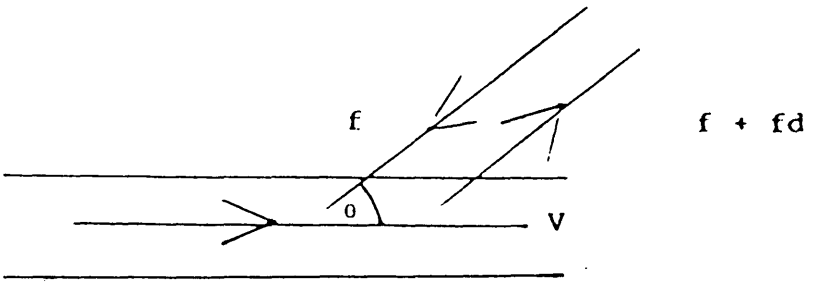
Although the evidence to date suggests that obstetric ultrasound, including Doppler, is without risk to mother or fetus the same opinion was held of X rays in pregnancy (Oakley 1986; Mole 1986) and ideally controlled trials are still required although these seem unlikely to be performed because of the already widespread use of ultrasound during

pregnancy.

In the meantime, it seems prudent to use equipment which provides reliable data with the lowest possible power output.

All the studies described in this thesis were performed with a Doptek 4MHz continuous wave Doppler system with on-line spectral analysis. This system was coupled to a conventional dynamic imaging ultrasound with 3.5MHz curvilinear transducer. This system has a SATA intensity of 42.4mW/cm^2 and SPTA of 81.6 mW/cm^2 at a depth of 14mm from the transducer.

The specific apparatus is illustrated (Figure 1.2).



$$fd = \frac{2.f.\cos\theta}{c}$$

hence,

$$v = \frac{fd.c}{2.f.\cos\theta}$$

Where f is the transmitted frequency and fd the Doppler shift frequency. Theta is the angle subtended by the ultrasound beam and the direction of blood flow.
V, the velocity of blood, can be calculated when these are known, since c, the velocity of ultrasound in human tissue is considered as a constant.

Figure 1.1 The relationship between blood velocity and the change in frequency of a returning signal as a result of the Doppler shift.

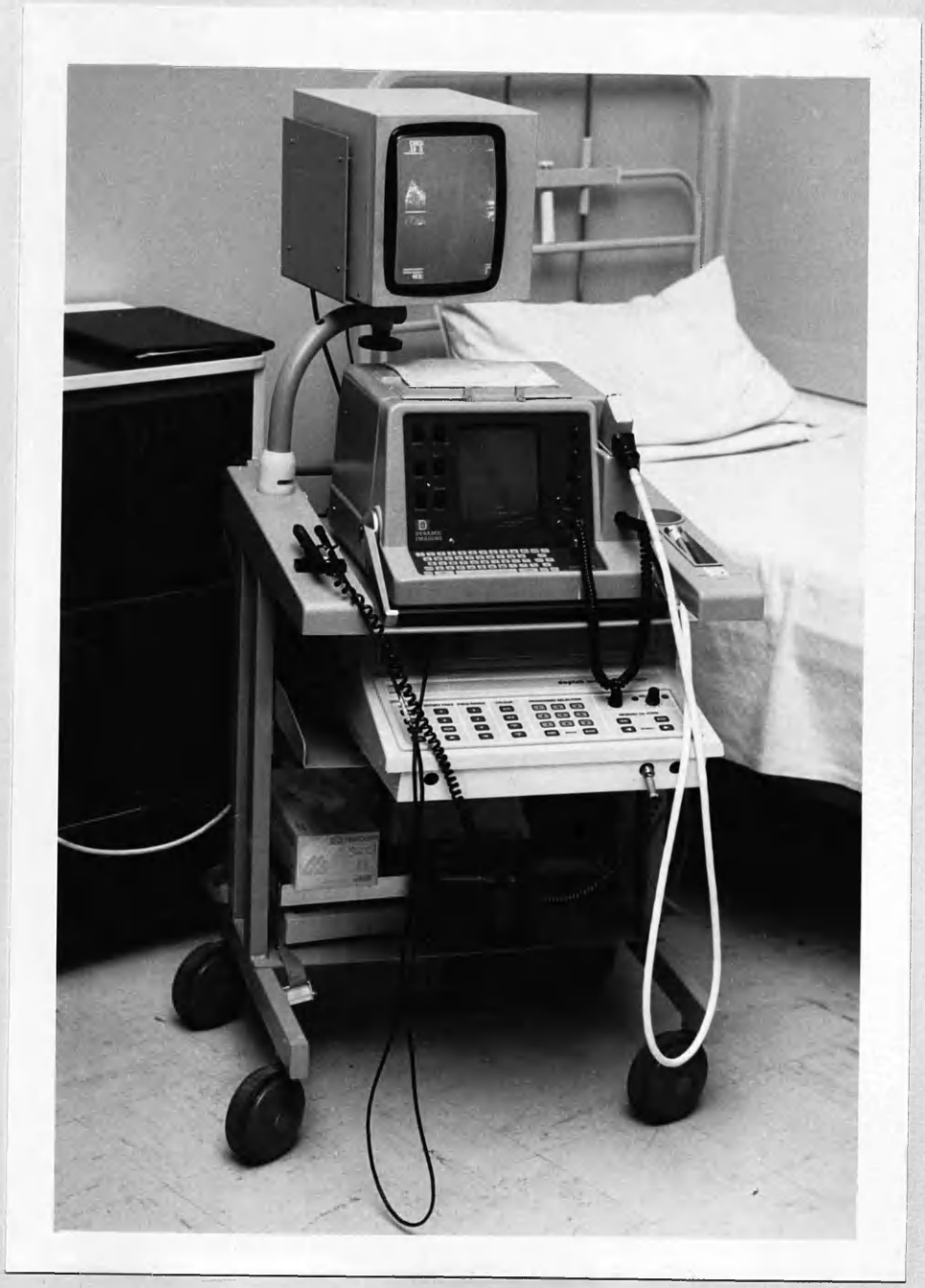


Figure 1.2 Illustration of the ultrasound equipment used in the study. A conventional Dynamic Imaging (Livingstone, Lothian) "Concept" real time ultrasound scanner is coupled to a Doptek continuous wave Doppler apparatus (Doptek Ltd, Chichester) with instantaneous Fast Fourier Transformation.

Chapter 2 The uteroplacental and fetoplacental circulations in clinical practice.

Chapter 2

The uteroplacental and fetoplacental circulations in clinical practice.

The placenta provides respiratory, nutritional and excretory functions for the fetus and is anatomically defined by the eighth week of pregnancy. By term it is a substantial structure weighing, on average, 600g, or just over a fifth of the fetal weight. The development of the placental circulation is complex, the mesoderm of the primary villi giving rise to the ultimate placental vasculature which is appropriately rich and interconnected. The primitive fetoplacental circulation is formed about half way through the second post-conceptional week and the fetal heart circulates fetal blood from about the fourth week after conception (Moore 1982). Placentation invokes a series of processes at the implantation site which have important implications for the maternal supply to the developing pregnancy. Invasion of the decidua by the syncitiotrophoblast is an early event which ensures a secure nutrient supply for the developing blastocyst (Pijnenborg et al 1983). This process continues until, early in the second trimester, cytotrophoblast invades the maternal spiral arteries. This invasion proceeds until about 24-26 weeks by which time the normally tortuous and narrow resistance vessels have lost their muscularis layer. This results in the formation of flask-shaped low resistance vessels which provide a rich and unimpeded maternal blood supply to the bed of the growing placenta (Brosens, Robertson & Dixon

1972; Moll, Kunzel & Harberger 1975; Sheppard and Bonnar 1981).

Even though fetal condition is absolutely dependent upon the integrity of both the uteroplacental and fetoplacental circulations, knowledge about their function and control remains limited. The interaction of these physically separate but contiguous circulations is undoubtedly complex (Figure 2.1) and there is increasing evidence that changes in one circulation may modulate changes in the other. Certainly, the fetoplacental circulation should not be regarded as passive. The placental circulation will respond to a number of vasoactive substances such as 5 hydroxytryptamine and angiotensin 11. and vessel tone appears to be controlled by a number of systems at least one of which is cyclo-oxygenase dependent. In addition angiotensin 11 and atrial natriuretic peptide have been located in, and appear to be active in, the placental vessel walls (McQueen et al In Press). The role of paracrine systems remains unclear but endothelial derived relaxing factor has been isolated from cord endothelium and an effector machanism has been shown to be present. The role of these systems in maintaining placental vessel tone remains speculative but it is conceivable that they regulate shunting of fetal blood within the placenta to optimise gas and nutrient transfer. Some evidence that events on the maternal side may influence the fètoplacental unit come from experiments using microsphere embolisation of the uterine circulation in sheep. The fetal response to the resultant diminished maternal blood supply is a parallel reduction in

umbilical blood flow (Clapp et al 1981).

This chapter discusses some of the methodology for studying uteroplacental and fetoplacental blood flow and some of the determinants which have been identified in improving understanding of the vascular physiology and pathology of placentation.

Methods of assessing uteroplacental blood flow.

Although pathological disturbances in uterine blood flow have been implicated in some pregnancies complicated by essential hypertension, pregnancy induced hypertension (PIH) and intra-uterine growth retardation (IUGR), no direct data exist because of the difficulties in measurement. However, a number of strategies have been developed over the years including clearance rates of endocrine and radioisotope markers and, more recently, Doppler ultrasound velocimetry.

The findings of Browne and Vealle (1953), which were later confirmed by Dixon, Browne & Davey (1963), did suggest that there was a reduction in uteroplacental perfusion in some complicated pregnancies. The methods used measured the rate at which radioisotopes disappeared from the choriodecidual space, this change correlating with the extent of perfusion. The use of radioisotopic methods of assessing placental perfusion in humans is no longer acceptable not only because of concerns about radioactivity but also because technical problems tended to make results uninterpretable. For example it has been shown in monkeys that the blood supply from the spiral arteries is patchy rather than uniform which might invalidate some of the

radioisotope data. However, recently, Nylund et al (1983), using more sophisticated methods, have demonstrated the feasibility of studying normal and complicated pregnancies using very low radiation dosages although because of the nature of these investigations their methods have not found widespread acceptance.

Direct measurement of uterine blood flow has been performed using electromagnetic flow meters and has provided physiologically interesting data. However, the studies were performed on pregnancies being terminated by hysterotomy (Assali, Rauramo & Peltonen 1960) and could not be used for routine investigation. Another invasive method, not yet applied to the pregnant uterus, is the use of thermistor techniques (Randall et al 1988) but the possible role for such an approach remains unclear.

Doppler methods to study the uterine circulation were introduced by Campbell et al (1983). Conceptually Doppler only provides an indirect measure of flow but it has been considered useful in assessing the uteroplacental circulation because of the relationship between vascular resistance and Doppler indices. Although this relationship in the uterine circulation has recently been questioned (Clewell et al 1988) Doppler methods do provide a qualitative technique for describing flow velocity waveforms which has been widely used to investigate uteroplacental perfusion.

Numerous studies have shown the uteroplacental circulation to be characterised by low resistance patterns in normal pregnancy and high resistance patterns have been

described in some complicated pregnancies. However, because of the non-uniform perfusion of the uteroplacental bed the value of the Doppler technique in this circulation remain to be established (Redman 1989a). Recent evidence suggests that the uteroplacental circulation and the haemodynamics within it are more complex than originally thought (Bewley, Campbell & Cooper 1989).

The use of colour flow mapping may be helpful since uteroplacental vessels can be more clearly identified although this currently expensive method has still to be adequately evaluated.

Methods of assessing the fetoplacental circulation.

The fetoplacental circulation is established early in gestation and, like the uteroplacental circulation, is characterised by low vascular resistance.

Invasive methods of measuring fetal blood flow using electromagnetic flow meters are of interest and Assali, Rauramo & Peltonen (1960), demonstrated a flow rate of 110mls/min in the umbilical artery in fetuses being terminated by hysterotomy which is about 50% of the total cardiac output and highlights the dynamic nature of this circulation. Clearly these methods are not appropriate for the study of continuing pregnancies and FitzGerald and Drumm (1977) and McCallum et al (1978), the pioneers of Doppler velocimetry in obstetrics, suggested that Doppler would contribute to the understanding of complications such as PIH and IUGR. Doppler methods permit non-invasive assessment of the fetoplacental circulation but, as with the

uteroplacental circulation, only qualitative measurements can be made.

Pregnancy complications and the measurement of uteroplacental and fetoplacental blood flow.

Assessment of uteroplacental and umbilical artery blood flow may provide important information concerning both the physiology and pathology of these circulations and the availability of non-invasive techniques such as Doppler are potentially of enormous value. The possible role of Doppler lies both in the evaluation of placental circulation as a screening tool and in the direct determination of the fetal condition in defined disease states. In addition these methods may provide an insight into the effects of maternal (and fetal) therapy.

Uteroplacental blood flow in hypertensive pregnancies.

Brosens, Robertson & Dixon (1972) indicated that in pregnancies complicated by hypertension the physiological invasion of spiral arteries was incomplete. This led to a failure to convert the maternal vasculature to a low resistance system with the implication that blood flow is thereby reduced and inadequate to sustain a pregnancy (Gerretsen, Huisjes & Elema 1981).

The concept of placental ischaemia as a factor in the pathogenesis of pre-eclampsia had previously led Browne and Vealle (1953) to investigate the maternal blood flow using Na24 clearance rates. While the definitions that they used would not be acceptable today, these workers showed that

perfusion was reduced in some hypertensive pregnancies. They later confirmed their findings using larger numbers (Dixon, Browne & Davey 1963) and also observed that the changes in blood flow were related to the degree of hypertension, being most marked when proteinuria was superimposed on hypertension. Using a different isotope, Xe 133, Kaar et al (1980) confirmed that a reduction in intervillous blood flow occurred in pre-eclampsia, although there was a wide variation both in normal and complicated pregnancies.

Further support for reduced flow in PIH comes from the clearance rates of C19 steroids which have been shown to correlate with uterine blood flow (Edman et al 1981; Senner et al 1985). Gant et al (1971) showed a reduced metabolic clearance of dehydro-isoandrosterone sulphate in pregnancies complicated by pre-eclampsia and also demonstrated that this reduction preceeded clinically detectable disease.

The possibility of identifying changes in perfusion in advance of clinical signs prompted Doppler studies of the maternal arcuate arteries as a screening test for high risk pregnancy. In a study of 126 consecutive women attending their antenatal clinic at 16 to 18 weeks gestation Campbell et al (1986) showed a higher incidence of IUGR and PIH in women with abnormal, compared with normal, uteroplacental Doppler waveforms. The very high incidence of abnormal waveforms demonstrated in this series and in a later study reported by Steel, Pearce & Chamberlain (1988) may be spurious and suggests that the normal ranges obtained initially were possibly inappropriate for the general

population to which they were applied. Other workers, who have shown differences in uterine artery waveforms from either side of the uterus, have suggested that this may represent abnormal placentation which might be associated with hypertension (Schulman et al 1987; Kofinas et al 1988), although the basis for this hypothesis is unclear. However, Pearce (1987) has reported an association between the resistance index in the uteroplacental vessels and depth of invasion of trophoblast into the spiral arteries. Unfortunately most studies of Doppler uteroplacental waveforms in hypertensive pregnancies have studied mixed populations of patients receiving varieties of antihypertensive agents which themselves have unknown effects on Doppler indices.

In a recent study of untreated cases of PIH the pulsatility index was no different from matched controls (Hanretty, Whittle & Rubin 1988a). Although the method of obtaining the waveforms has been criticised (Pearce & McParland 1988) it was apparent that markedly different waveforms may be obtained from uteroplacental vessels, a finding which probably relates to the focal nature of the placental pathology in PIH. Figure 2.2 shows two such waveforms, one highly abnormal and the other normal, obtained synchronously in opposite channels from the uteroplacental vessels. These waveforms, which were unequivocally uteroplacental in origin were obtained from a patient with severe PIH. However, uniformly abnormal uteroplacental waveforms may be significant and this was observed in one of two pregnancies leading to perinatally

related deaths in the series suggesting therefore that the vascular pathology was widespread and severe.

Doppler colour flow mapping of the uterine vasculature may provide useful information but is still to be fully evaluated. The clear identification of vessels and direction of flow afforded by this method is, however, promising.

In general therefore, it does appear that, in hypertensive pregnancy, maternal perfusion of the placenta is reduced as demonstrated by a number of different techniques. Doppler waveforms appear to be abnormal in some hypertensive pregnancies and may help to distinguish cases of essential hypertension from those with severe PIH, but the value of the technique both as a screening test and in the assessment of the clinically affected pregnancy is as yet unproven and there seem to be major methodological problems which may limit the application of this technology (Redman 1989a).

Fetoplacental blood flow in hypertensive pregnancies.

Almost all of the data concerning fetoplacental blood flow has been obtained from studies using Doppler velocimetry. However, a recent in vitro study has investigated umbilical flow to the placenta in a series of 10 pregnancies complicated by PIH (Abitbol et al 1987). Although only pregnancies at around term were included, suggesting that the disease was relatively mild, these workers showed reduced umbilical blood flow compared with uncomplicated pregnancies. Placental angiography was performed and showed "functional" normality in 79% of

cotyledons from the control placentas compared with 51% in the study group. This highly significant difference also highlighted the focal nature of the pathology on the fetal side of the placenta.

Extensive in-vivo studies have been performed using Doppler to obtain flow velocity waveforms in PIH. A number of groups have shown high resistance patterns and reduced diastolic flow velocities in some cases but the definitions used and the inclusion criteria for study have not always been consistent.

Ducey et al (1987) classified the types of hypertension complicating pregnancy as chronic, PIH and pre-eclampsia and showed abnormal waveforms more commonly associated with the last diagnosis. Cameron et al (1988) in a prospective study of well defined cases of pre-eclampsia have shown normal Doppler indices in 70% of cases with no clear correlation between Doppler indices and the absolute level of hypertension. Nevertheless, clinical outcome appeared to correlate with the waveform as, in cases with an abnormal pattern, growth retardation, fetal distress and admission to the neonatal intensive care unit were commoner.

The mechanism whereby these abnormal waveforms occur is uncertain although it presumably relates to increased downstream impedance within the placental vascular tree. This may be the result of obliteration of tertiary stem villus arterioles (Giles et al 1985; McCowan, Mullen & Ritchie 1987; Bracero et al 1989) but whether this is the end result of prolonged vasoconstriction or intravascular coagulation is not clear. Other factors such as increased

blood viscosity may be also be important in pathogenesis.

Nevertheless, repeated embolisation of the fetoplacental circulation of the sheep fetus has been shown to produce Doppler waveforms similar to those seen in severely compromised hypertensive human pregnancies (Trudinger et al 1987a). The production of these waveforms was not associated with fetal compromise as evidenced by retarded growth in Trudinger's study so it is possible that Doppler methods tell us more about the health of the placenta rather than about fetal wellbeing directly.

Uteroplacental blood flow in IUGR.

The study by Kaar et al (1980), already mentioned, also included a group of babies whose birth weights were less than the 10th centile for gestational age and showed a reduction in perfusion in these cases. More recently, Nylund et al (1983) in a study of small-for-gestational-age babies and matched controls used intravenous Indium 113 and demonstrated reduced scintillation counts over the placental site. A uterine blood flow index was derived and in the small-for-gestational age fetuses was less than half that of the values obtained from controls. This difference remained significant when a group of pre-eclamptics, in whom reduced flow might be attributable to a recognised pathology, were removed from the series. Six of thirty cases were complicated by fetal abnormality and although there was no difference in blood flow index between the normally formed and abnormal fetuses, it remains unclear what proportion of otherwise unexplained IUGR is associated with reduced

uterine blood flow.

Although Doppler waveform indices in the uteroplacental circulation also appear to be abnormal in some cases of IUGR (Trudinger et al 1985a; McCowan et al 1988) the results are variable and the methodological criticisms mentioned in relation to hypertension make the observations of dubious significance in clinical practice. However, it would not be surprising if widespread pathology in the spiral arteries was associated with severe IUGR and waveform abnormalities.

Fetoplacental circulation in IUGR.

Re-distribution of blood flow within the fetal circulation is a likely feature of "placental insufficiency" which may result in growth retardation. Whether increased vascular resistance in the placenta is a cause or consequence of this redistribution is not clear but, as in some cases of hypertension, abnormal Doppler waveforms have been described from the umbilical arteries of growth retarded fetuses. Erskine and Ritchie (1985) demonstrated abnormal waveforms in a small series of severely growth retarded fetuses and considerable interest was aroused in the potential use of Doppler to identify these high risk cases. Furthermore, from their work, it seemed that Doppler might identify cases of genuine growth retardation with fetal compromise rather than fetuses which although small-for-dates show normal growth velocity and are well.

One problem in the evaluation of Doppler velocimetry in the identification of the small-for-dates fetus is the appropriateness of the end-point. Thus many studies are

faulted by the use of birthweight charts not derived from the population under study. Not surprisingly the data from Doppler studies are conflicting: in 168 high risk cases Berkowitz et al (1988a) demonstrated a sensitivity of 45% when using umbilical artery Doppler to identify fetuses weighing less than the tenth centile at birth. Mulders et al (1987) in a smaller series obtained a corresponding figure of 53%. In contrast, Gaziano et al (1988) showed abnormal waveforms in 79% of such cases. It is possible that Doppler may be more useful in identifying the fetus which has failed to reach its growth potential but which is not necessarily small-for-dates and preliminary data from an on-going study of umbilical artery Doppler in an unselected population tends to confirm this (Hanretty et al 1989). This will be further discussed in chapter 6.

However, most studies strongly suggest that umbilical flow abnormalities detected by Doppler in the already small-for-dates fetus may identify those at increased risk for perinatal morbidity and mortality (Reuwer et al 1987, Berkowitz et al 1988b).

Doppler assessment of umbilical artery blood flow and the identification of fetal wellbeing in high risk pregnancy.

Doppler study of the umbilical circulation may play some role in monitoring the identified high risk pregnancy, not only in the familiar problems of hypertension and IUGR but also in less common conditions such as rhesus disease (Rightmire et al 1986), lupus inhibitor (Trudinger et al 1988) and diabetes (Bracero et al 1986) and the

categorisation of pregnancies complicated by severe oligohydramnios and fetal abnormality may be aided by Doppler evaluation of the umbilical artery (Hsieh et al 1988).

There is a need for a method which identifies all pregnancies at risk in early pregnancy and initially Doppler of the umbilical artery appeared promising although many of the previously reported studies are difficult to interpret because end-points used to define fetal compromise tend to be ill defined and to vary between studies. In spite of reservations about the use of Doppler it does seem that, in general, normal results are associated with a normal perinatal outcome. The situation is less clear when velocimetry indicates reduced, absent or reversed diastolic flow. Some reports suggest that such findings imply imminent fetal demise indicating the need for immediate delivery (Woo, Liang & Lo 1987). Others, whilst agreeing that such abnormal patterns do indeed signify fetal compromise, suggest that they indicate a need for intensive supervision, using established monitoring techniques, rather than urgent intervention and have shown that the interval between the finding of abnormal waveforms and the necessity for delivery can vary from hours to weeks (Rochelson et al 1987).

The use of Doppler to evaluate high risk pregnancy has been studied in a randomised controlled trial by Trudinger et al (1987b). Three hundred pregnancies were studied but the only difference in outcome parameters between the group of patients for whom the result was available to clinicians and the control group related to a reduction in the numbers

of caesarean sections performed during labour in the former. The conclusion was that decision making had been improved by knowledge of the Doppler results leading to a better selection of patients suitable for labour. However, this is not supported by the simultaneous observation of no difference in rates of induction of labour or elective caesarean section between groups.

It is likely that either larger studies with similar inclusion criteria or studies of strictly defined higher risk pregnancies would be required to have sufficient power to demonstrate a difference in fetal and neonatal outcome attributable to the availability of Doppler results.

While such studies are essential, and the results eagerly awaited, an improved understanding of the determinants of Doppler waveforms both in the uteroplacental and fetoplacental circulations is required in order to more accurately identify specific clinical problems in which the technique may be of value. The currently available data on uteroplacental and fetoplacental blood flow in IUGR and PIH are summarised in Table 2.1. Much remains to be done in investigating the possible role of Doppler in these conditions. Chapters 5 and 6 describe controlled studies to determine the effect of these conditions on Doppler waveforms.

Table 2.1
Uteroplacental and fetoplacental perfusion in IUGR and PIH: a synopsis.

	Uteroplacental	Fetoplacental
PIH		
In Vitro	Not Known	41% reduction in umbilical blood flow.
Steroid clearance	Reduced metabolic clearance rates representing reduced perfusion precede clinical disease.	Not Known
Radioisotopes	Reduced blood flow of up to 60% demonstrated. No clear evidence that antihypertensives change perfusion.	Not Known
Doppler:screening	Similar incidence of PIH in those with normal and abnormal uteroplacental waveforms when screened at 24 weeks.	Not Known
Doppler:diagnosis	Waveforms representing high resistance to flow seen in some cases but methodological problems significant.	Abnormal umbilical artery Doppler waveforms appear to be a feature of fetal compromise rather than diagnostic of PIH.
IUGR		
Radioisotopes	Uterine blood flow index 44% of normal in cases of IUGR.	Not Known
Doppler:screening	Fourfold increase in small-for-dates cases with abnormal waveform compared with normals at 24 weeks.	Sensitivity of 45% in detecting Small-for-dates fetuses but within this group Doppler does identify some cases at increased risk of morbidity and neonatal mortality

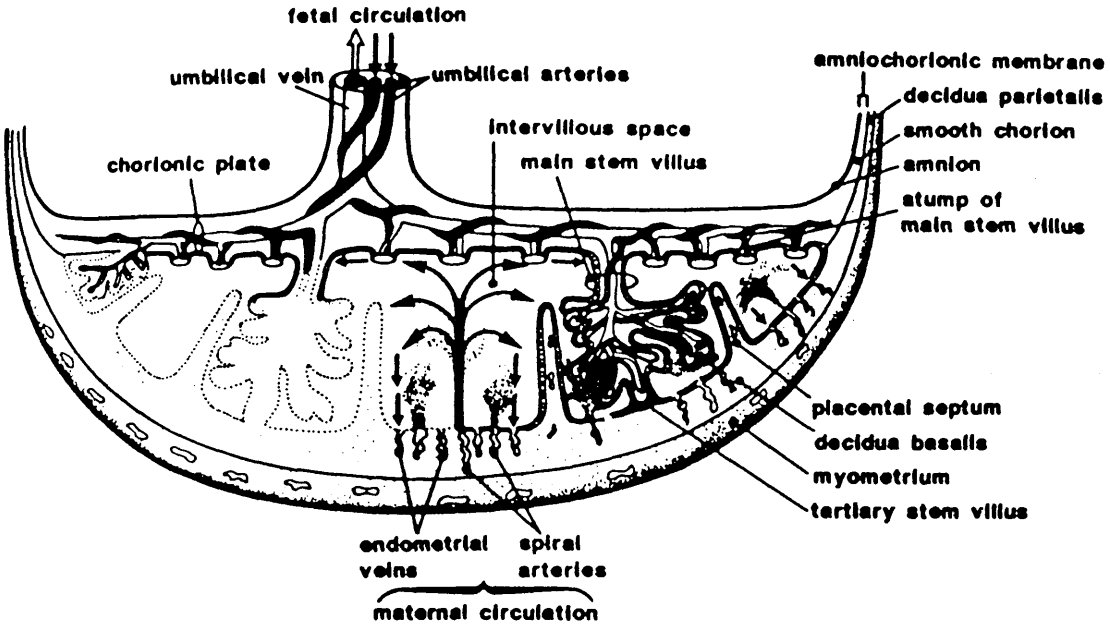


Figure 2.1 The inter-relations of the maternal and fetoplacental circulations.

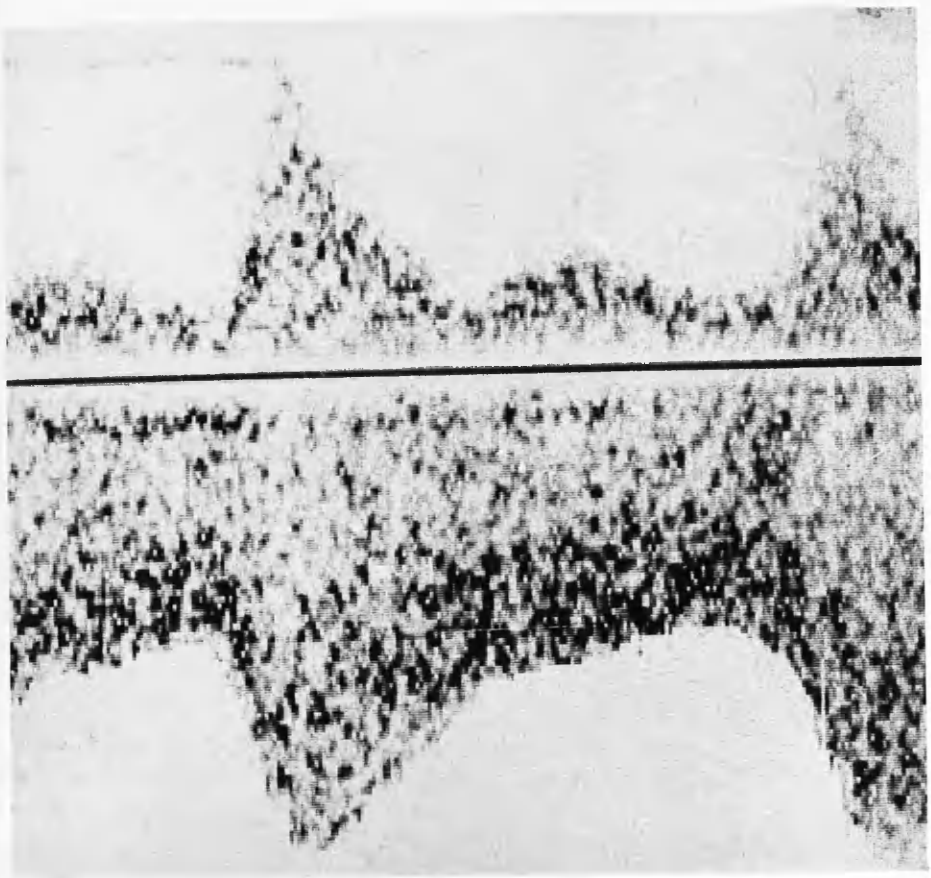


Figure 2.2 Two waveforms obtained synchronously from uteroplacental vessels flowing in opposite directions. The upper channel shows a vessel of high vascular resistance and the lower channel a vessel of low resistance.

Chapter 3 The aims of this thesis.

Chapter 3

The aims of this thesis

The aims of this thesis are to determine the relationships between common clinical problems and uteroplacental and umbilical artery Doppler waveforms and identify, if possible, the determinants of abnormal waveforms in these conditions.

Questions addressed in this thesis.

What are the relationships of the different Doppler indices used to describe flow velocity waveforms in obstetric practice? (Chapter 4)

Are uteroplacental and umbilical artery flow velocity waveforms altered in pregnancy induced hypertension and is this influenced by the degree of hypertension? (Chapter 5)

Are uteroplacental and umbilical artery flow velocity waveforms altered in those pregnancies in which the fetus is small-for-dates? (Chapter 6)

Does a change in fetal blood viscosity occuring after intravascular transfusion for rhesus disease influence flow velocity waveforms? (Chapter 7)

Is elevation of maternal serum alphafetoprotein associated with a placental lesion which is detectable using Doppler methods? (Chapter 8)

Does antihypertensive therapy alter uteroplacental or umbilical artery flow velocity waveforms? (Chapters 10 and 11)

Chapter 4 Methodology of obtaining Doppler waveforms.

4.1 Methods used in this thesis.

4.2 Indices used to describe flow velocity waveforms.

4.3 Discussion.

Chapter 4

Methodology of obtaining Doppler waveforms.

Chapter 4.1 Methods used in the present studies.

All studies described in this thesis were performed after informed verbal consent was obtained from the patient. Patients were studied in the semi-recumbent position and blood pressure was measured frequently using an automatic sphygmomanometer (Bard Sentron) to exclude supine hypotension.

The Doppler studies were preceded by conventional visualisation of the fetus and the umbilical cord identified. Doppler waveforms were identified from the umbilical artery and when five waveforms of adequate quality were visualised on screen synchronously with the umbilical venous signal the waveforms were frozen on the screen and the systolic, diastolic and mean frequency were obtained for each of 5 waveforms. The use of this number of cardiac cycles has previously been shown to produce a high level of reproducibility (Hastie et al 1988). Figures 4.1a and 4.1b show representative umbilical artery waveforms. Fetal heart rate was also recorded.

The maternal signals were obtained by a process of pattern recognition and the waveforms selected were those of greatest clarity which represented vessels of low resistance. Figures 4.2a and 4.2b show representative uteroplacental waveforms. Since a continuous wave system was used, and it is not possible to determine the specific vessel being insonated, the lowest resistance vessels were

taken for analysis since high resistance signals could be obtained from the iliac and epigastric arteries. This approach has been questioned (Campbell, Vyas & Bewley 1988; Fairlie et al 1988; Pearce & McParland 1988) but remains in use (Chambers et al 1989) and, given the constraints of the continuous wave system, is internally consistent. This will be discussed in detail later.

Results of Doppler examinations were not made available to clinicians and management was not influenced by the performance of the Doppler examinations.

Chapter 4.2 Indices used to describe flow velocity waveforms.

Three indices are commonly used to describe Doppler flow velocity waveforms qualitatively. These are the systolic/diastolic, alternatively referred to as the A/B ratio, the resistance index (RI) and the pulsatility index (PI). These indices are illustrated in Figure 4.3. Only one large published study has reported on the relationship between all these indices (Thompson, Trudinger & Cook 1988). In this study of 65 patients studied on a total of 133 occasions in the last trimester a high correlation was shown between all three indices.

Unfortunately, as this study included multiple measurements from the same patients, the values obtained were not independent of each other thus invalidating the correlation coefficients and regression equations obtained.

This point was made by Pearce et al (1988) who reported reference ranges of all three indices for uteroplacental and

umbilical arteries but did not obtain correlations between them.

Table 4.1 shows the clinical features of 356 patients who had a total of 690 Doppler examinations. The result of the last examination was used to determine the relationship between the systolic/diastolic ratio (SDR) and pulsatility index for both uteroplacental and umbilical arteries.

The reduction in all indices of vascular resistance in the umbilical artery with advancing gestation is now well recognised and reflects a relative increase in the cross sectional area of the developing placental vasculature. This effect was seen in this series and the effect of gestation for all patients is shown on pulsatility index, resistance index and systolic/diastolic ratio in figures 4.4-4.6. The correlations for PI, RI and systolic/diastolic ratio with gestational age were -0.49, -0.67 and -0.47 respectively. These were highly significant in all cases ($p<0.0001$). The coefficients of determination were 24% 44.5% and 22% respectively.

Figures 4.7-4.9 show the same indices for the uteroplacental circulation plotted against gestational age and in this series no relationship between any of the indices and gestational age was seen.

Table 4.2 shows the correlation between PI, RI and systolic/diastolic ratio in each circulation. Figures 4.10-4.15 illustrate the relationships between the indices. The lack of a linear relationship explains the coefficients being less than 1.

Chapter 4.3 Discussion.

The method used to obtain umbilical artery waveforms described earlier is standard and widely accepted. More contentious is that which has been used to obtain uteroplacental patterns. Differences in the uteroplacental waveforms have been related to placental site (Chambers et al 1988) and the vascular resistance appears to lessen the more proximal to the placenta that measurements are made. Thus the use of the lowest resistance waveform improves the likelihood of signals being obtained from the subplacental vessels as has been advocated by some workers (Trudinger, Giles & Cook 1985b; Chambers et al 1989). These issues have recently been reviewed by Bewley, Campbell & Cooper (1989) and it is now realised that the uteroplacental circulation is more complex and difficult to characterise than previously thought. Consequently a consistent approach, such as described here, is required in order to identify the determinants of uteroplacental waveforms using continuous wave ultrasound.

There is no general agreement about which index best describes qualitatively the Doppler waveforms obtained from the uteroplacental and umbilical arteries. Thompson, Trudinger & Cook have shown high correlations in both normal (1986) and complicated (1988) pregnancies and concluded that no index was preferable to the others. Like Thompson's group the highest linear correlation obtained in in the umbilical artery in this series was for RI with PI. This suggests that although the calculation of PI theoretically provides more information about the whole waveform, rather than just

maximum and minimum Doppler shift frequencies, the additional information has a value.

Thompson and her colleagues point out that this relationship may not be the same for other vessels, and in this series a better correlation was found in the uteroplacental vessels for the systolic/diastolic ratio and PI. This reflects the more linear relationship between these indices in this circulation.

In this thesis all three indices have been used; in chapters 4 and 5 the results from measurement of RI and PI have been given. In chapters 7 and 10 the systolic/diastolic ratio has been used since, because there were changes in fetal heart rate in the studies presented there, corrections for this counfounding variable were required and could more readily be made. In chapter 9 the number of cases with absent end diastolic flow velocities necessitated the use of the pulsatility index only.

Statistical methods used in the Thesis.

Data are presented as means with standard deviations shown in parentheses unless specifically stated.

Comparisons between groups have been made with paired t tests or two sample t tests where data are normally distributed, and the Mann Whitney U test or Wilcoxon test used if this is not the case. Other statistical methods used are described in the relevant text.

Table 4.1 The clinical features of patients studied.

Suspected Intra-Uterine Growth Retardation	36
Pregnancy Induced Hypertension	112
Normal	179
Maternal Diabetes	2
Systemic Lupus Erythematosus	2
Trisomy 21	1
Trisomy 18	1
Chronic Renal Failure	1
Essential Hypertension	22
	356

Table 4.2 Correlations between Doppler waveform indices for uteroplacental and umbilical arteries.

Uteroplacental Arteries

	RI	SDR
PI	0.90	0.98
RI	----	0.86

Umbilical Artery

	RI	SDR
PI	0.87	0.61
RI	----	0.72

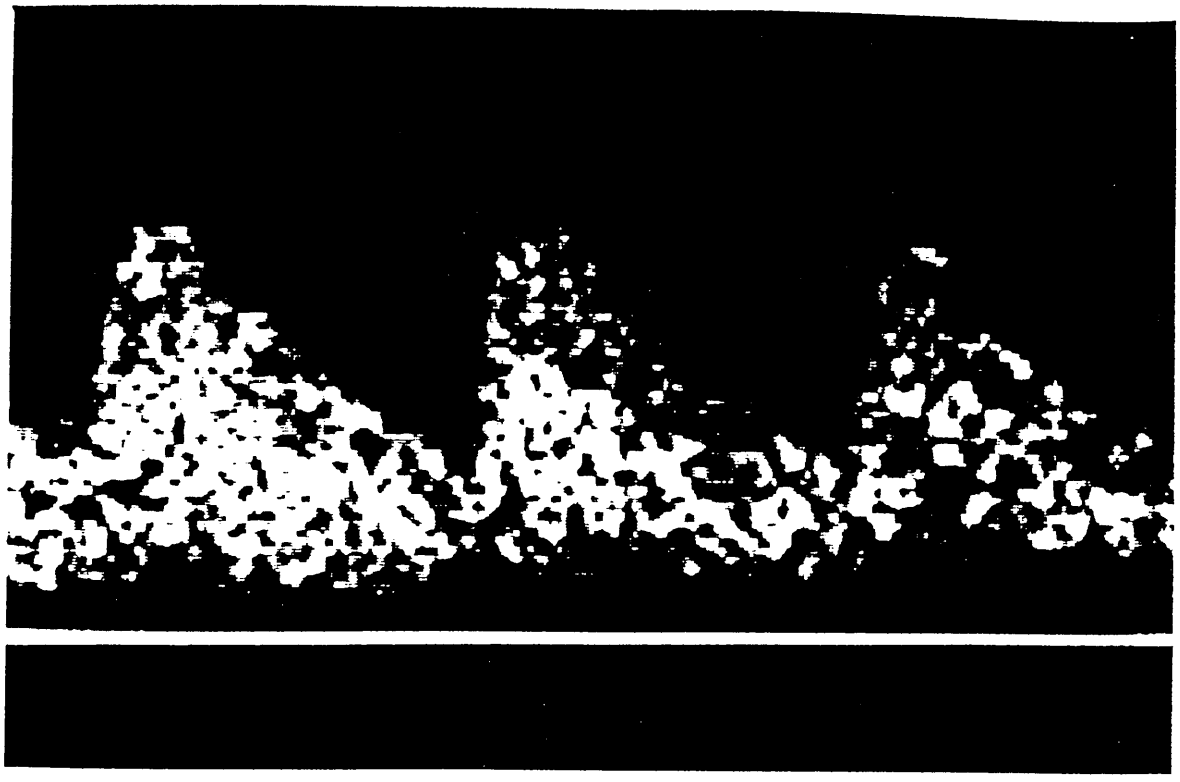


Figure 4.1a Normal umbilical artery flow velocity waveform of low resistance.

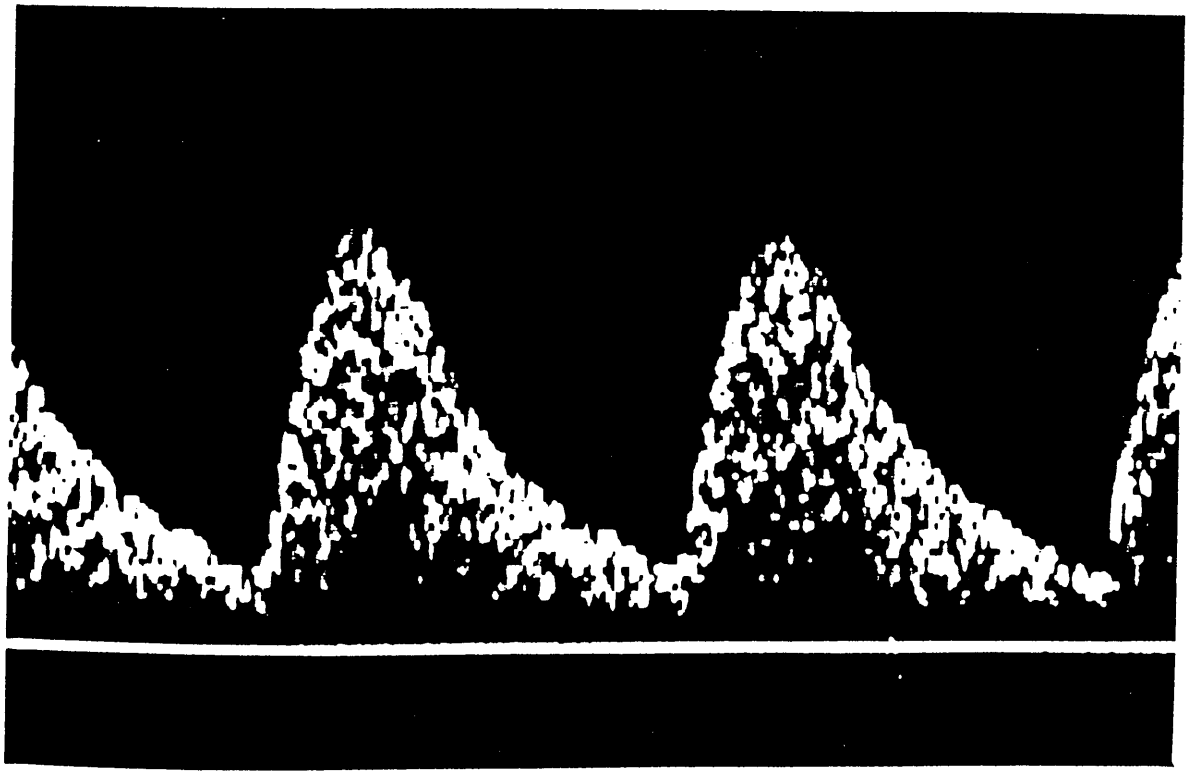


Figure 4.1b High resistance umbilical artery flow velocity waveform.

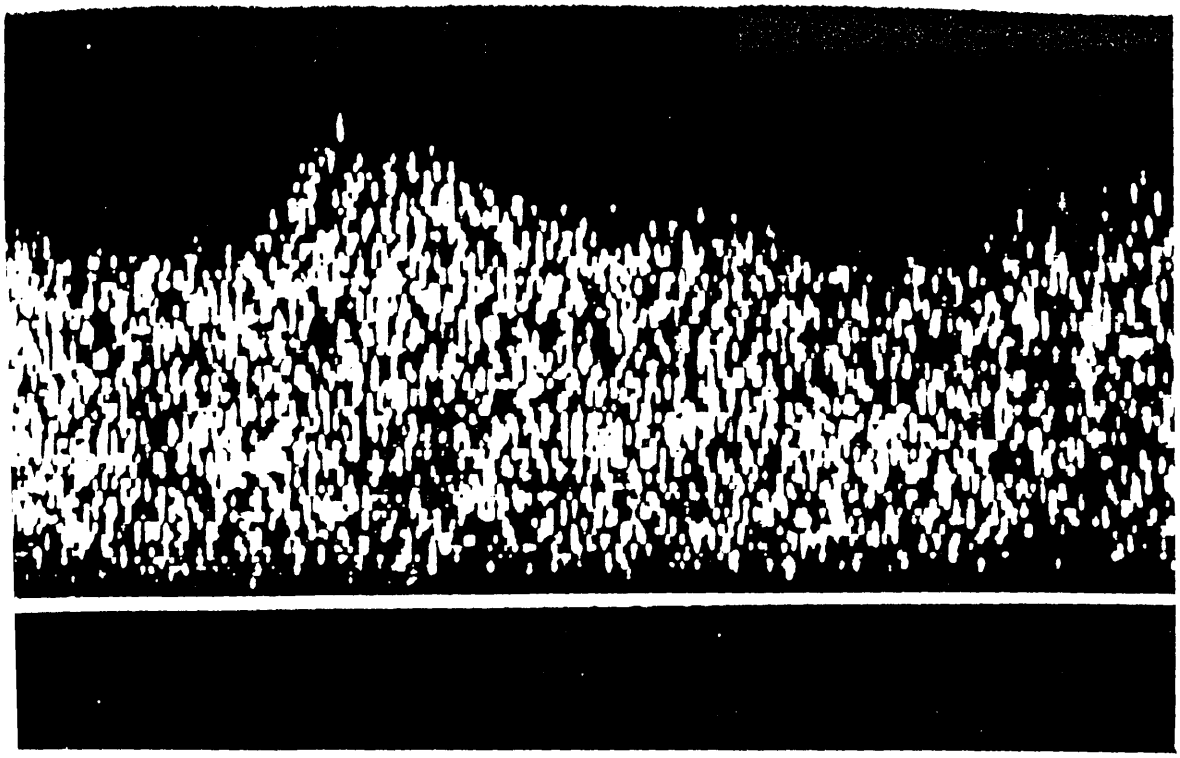


Figure 4.2a Low resistance uteroplacental flow velocity waveform.

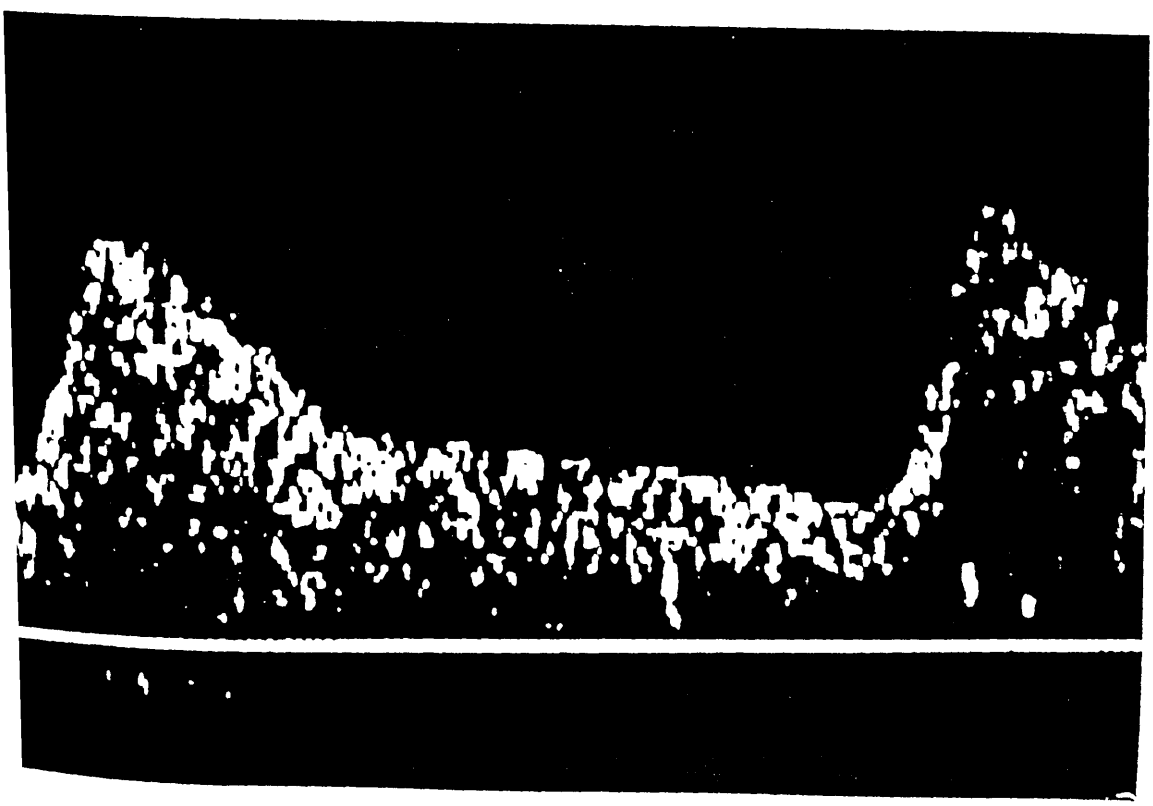
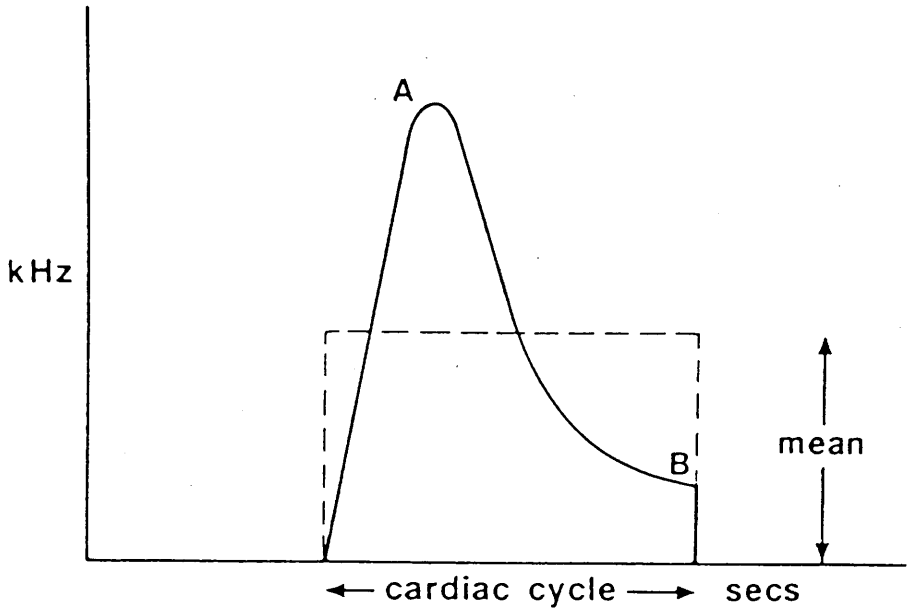


Figure 4.2b High resistance uteroplacental flow velocity waveform from a patient with pregnancy induced hypertension.



$$PI = \frac{A-B}{mean} \qquad RI = \frac{A-B}{A} \qquad SDR = \frac{A}{B}$$

Figure 4.3 Scheme representing the method of calculating the pulsatility index (PI), resistance index (RI) and systolic/diastolic ratio (SDR) .

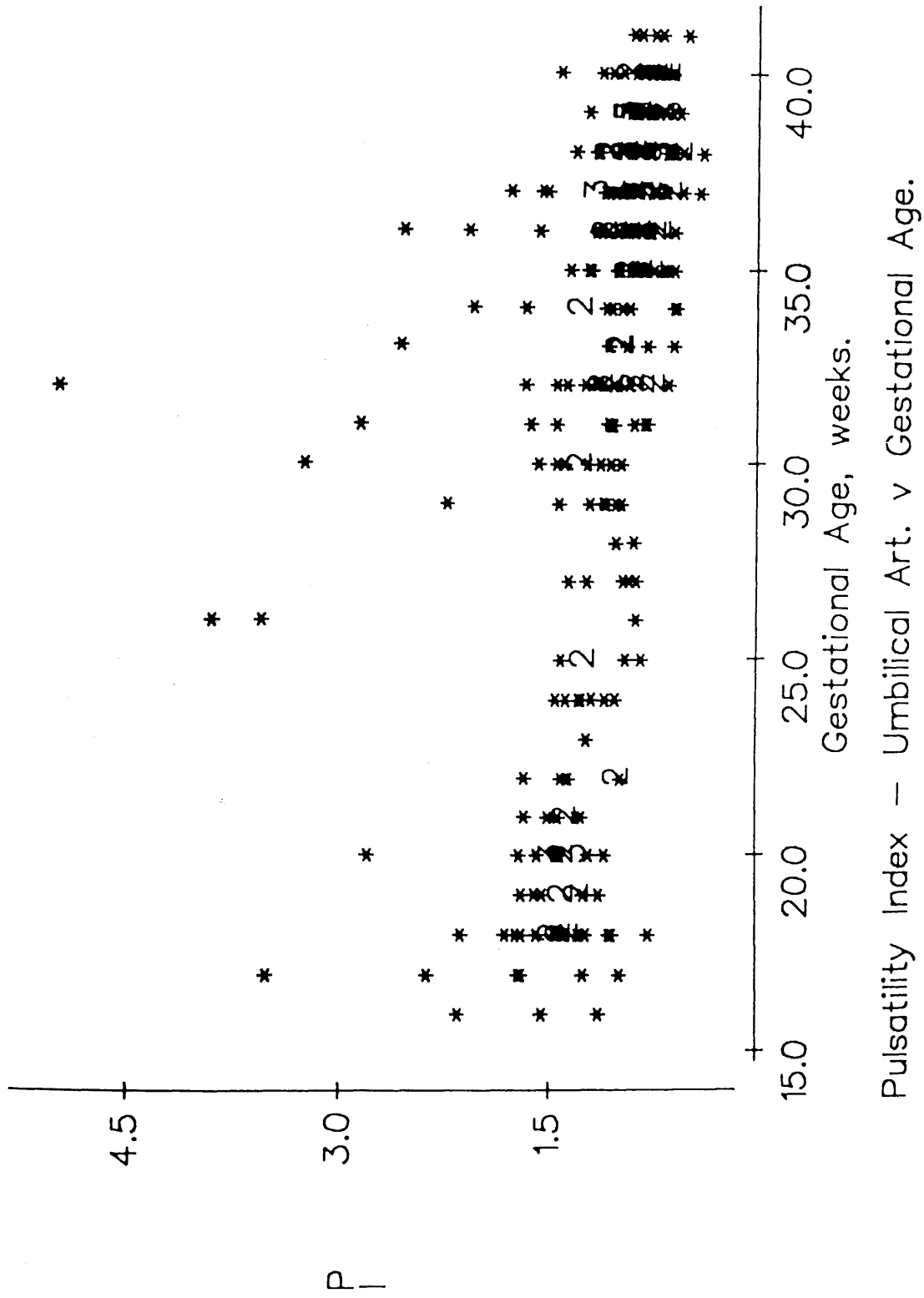


Figure 4.4 Relationship between pulsatility index and gestational age in the umbilical artery.
Where two or more results have the same co-ordinates these are shown numerically. More than ten data points having the same value are represented by a large cross.

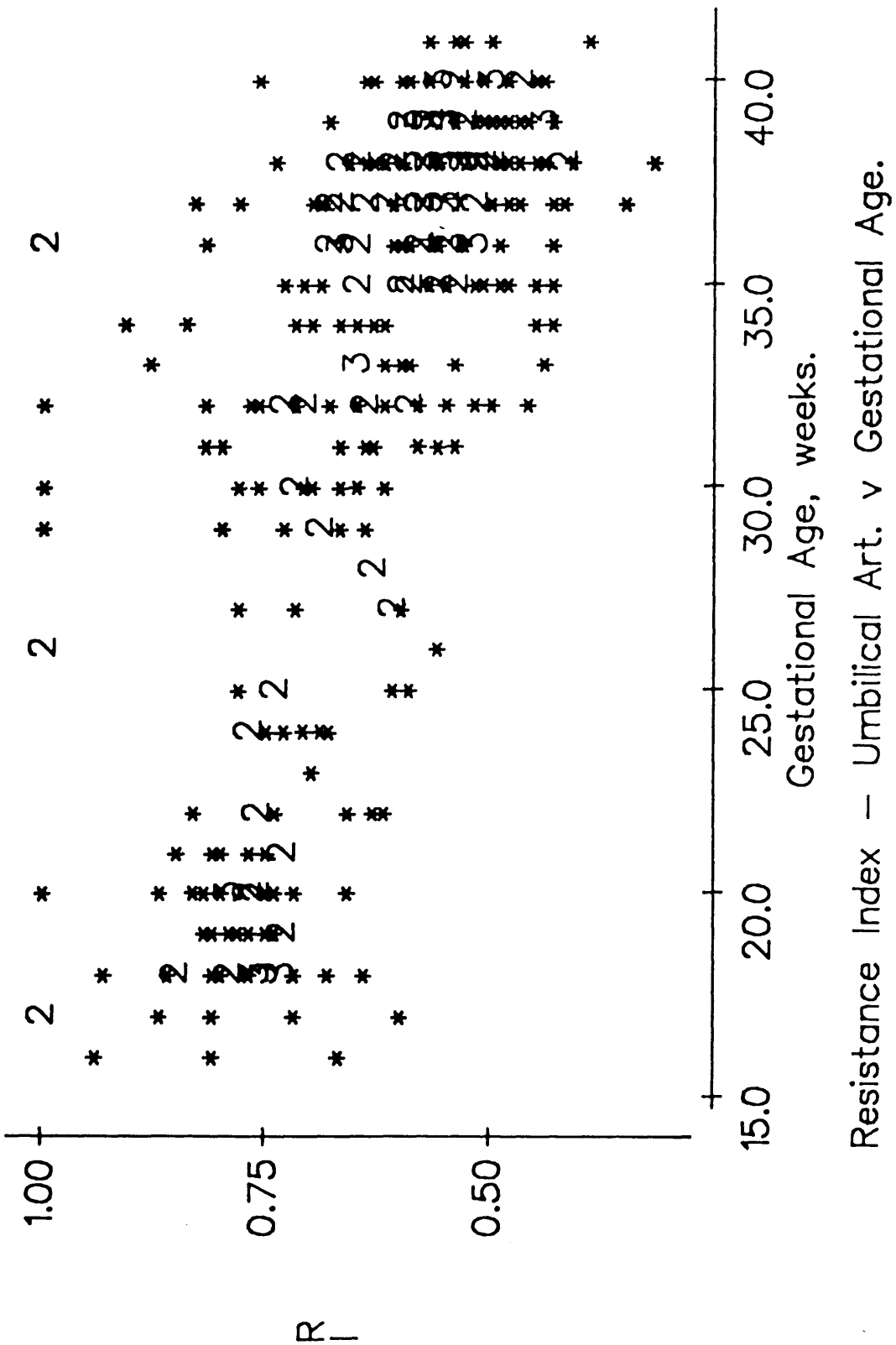


Figure 4.5 Relationship between resistance index and gestational age in the umbilical artery.

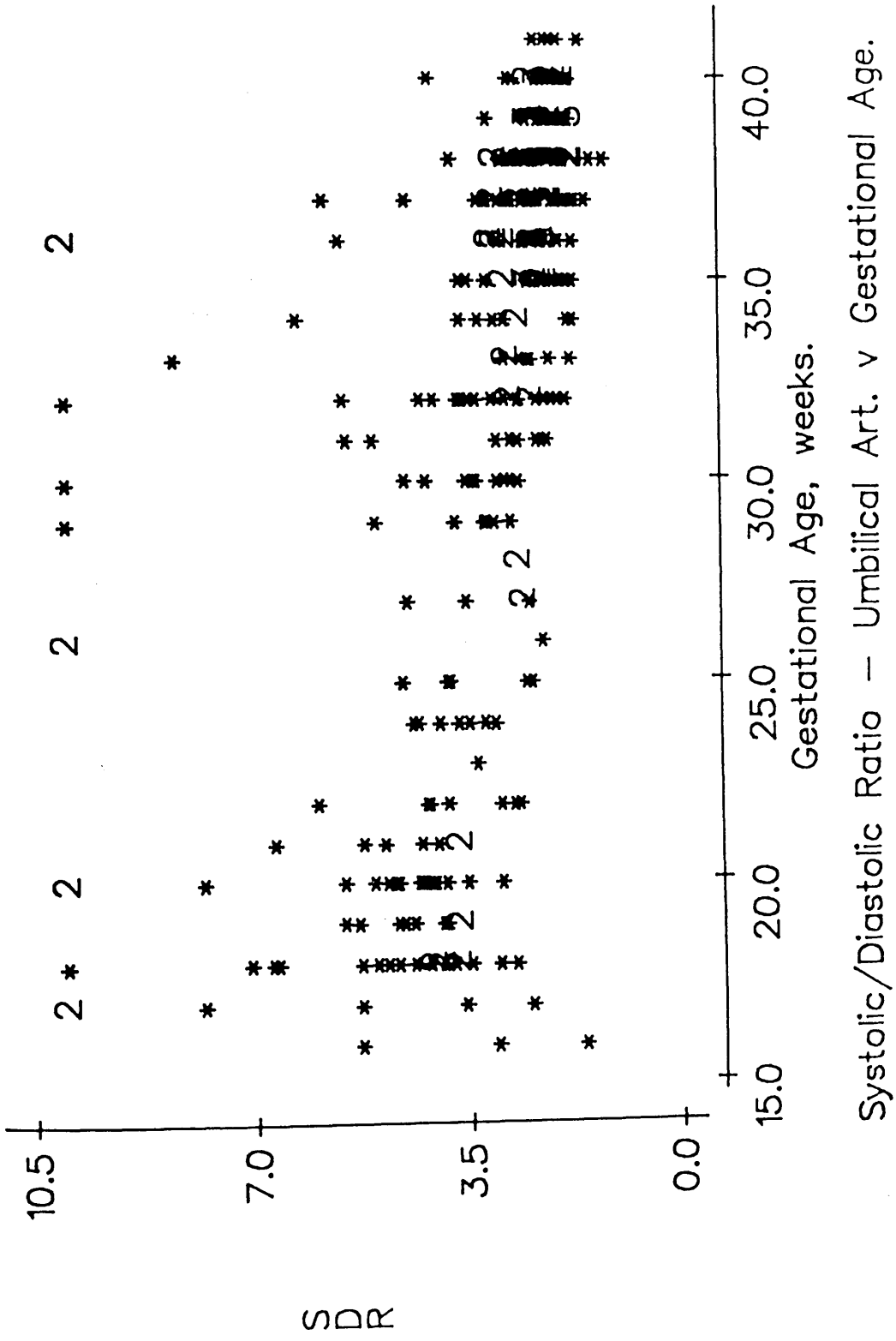


Figure 4.6 Relationship between the systolic/diastolic ratio and gestational age in the umbilical artery.

(In order to represent cases with absent end-diastolic velocities graphically, these have been given an arbitrary systolic/diastolic ratio value of 10.0)

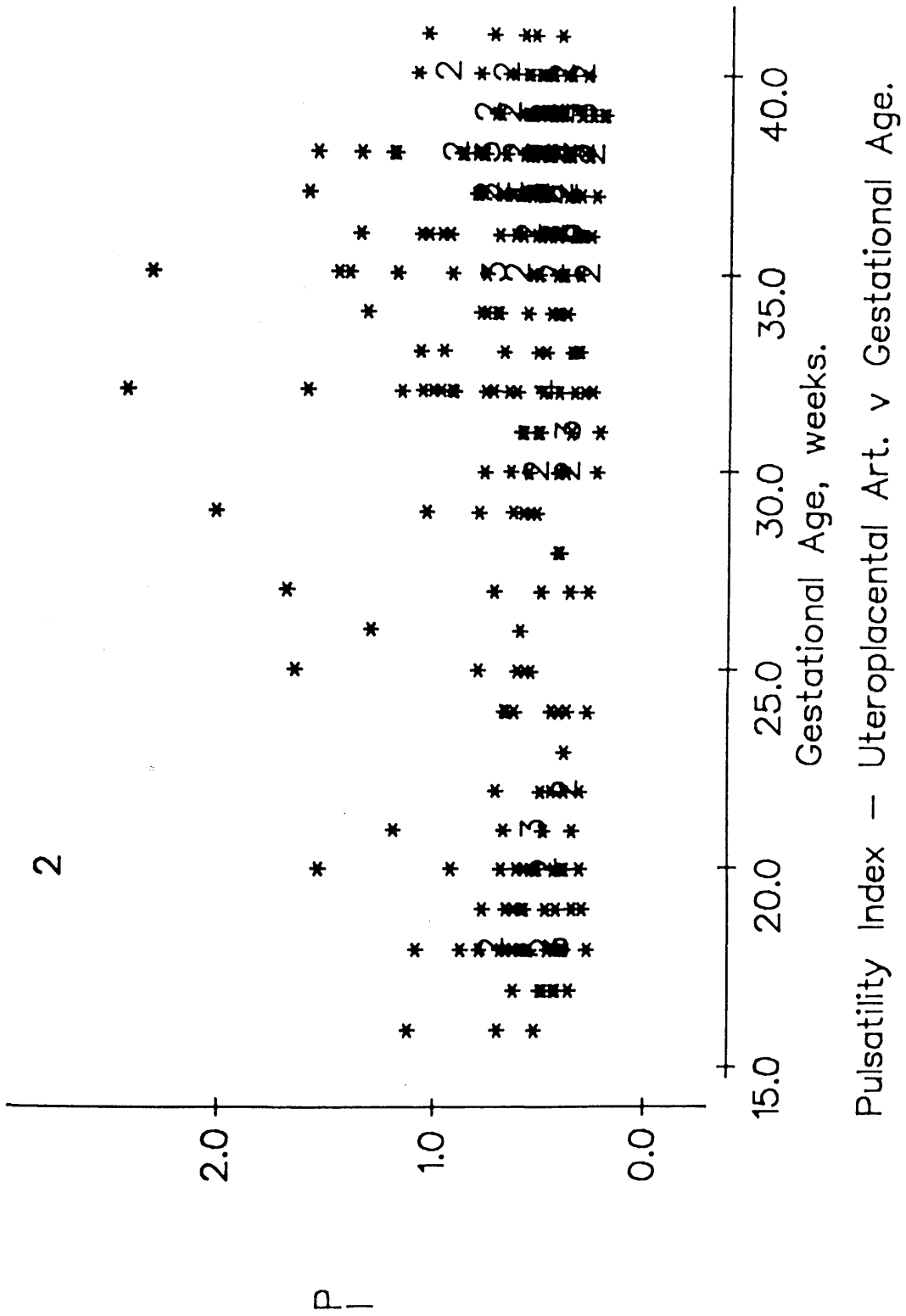


Figure 4.7 Relationship between pulsatility index and gestational age in the uteroplacental arteries.

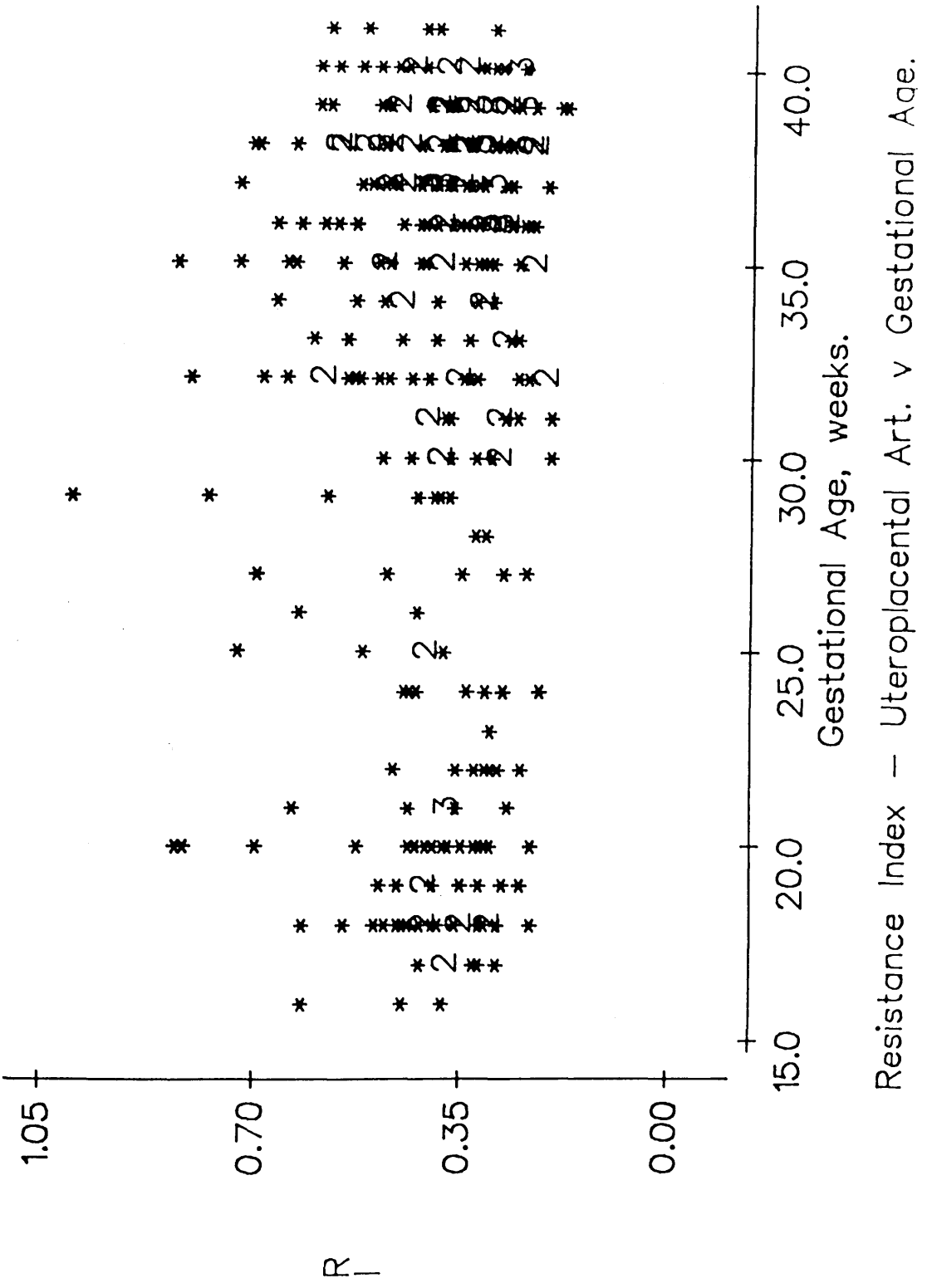


Figure 4.8 Relationship between resistance index and gestational age in the uteroplacental arteries.

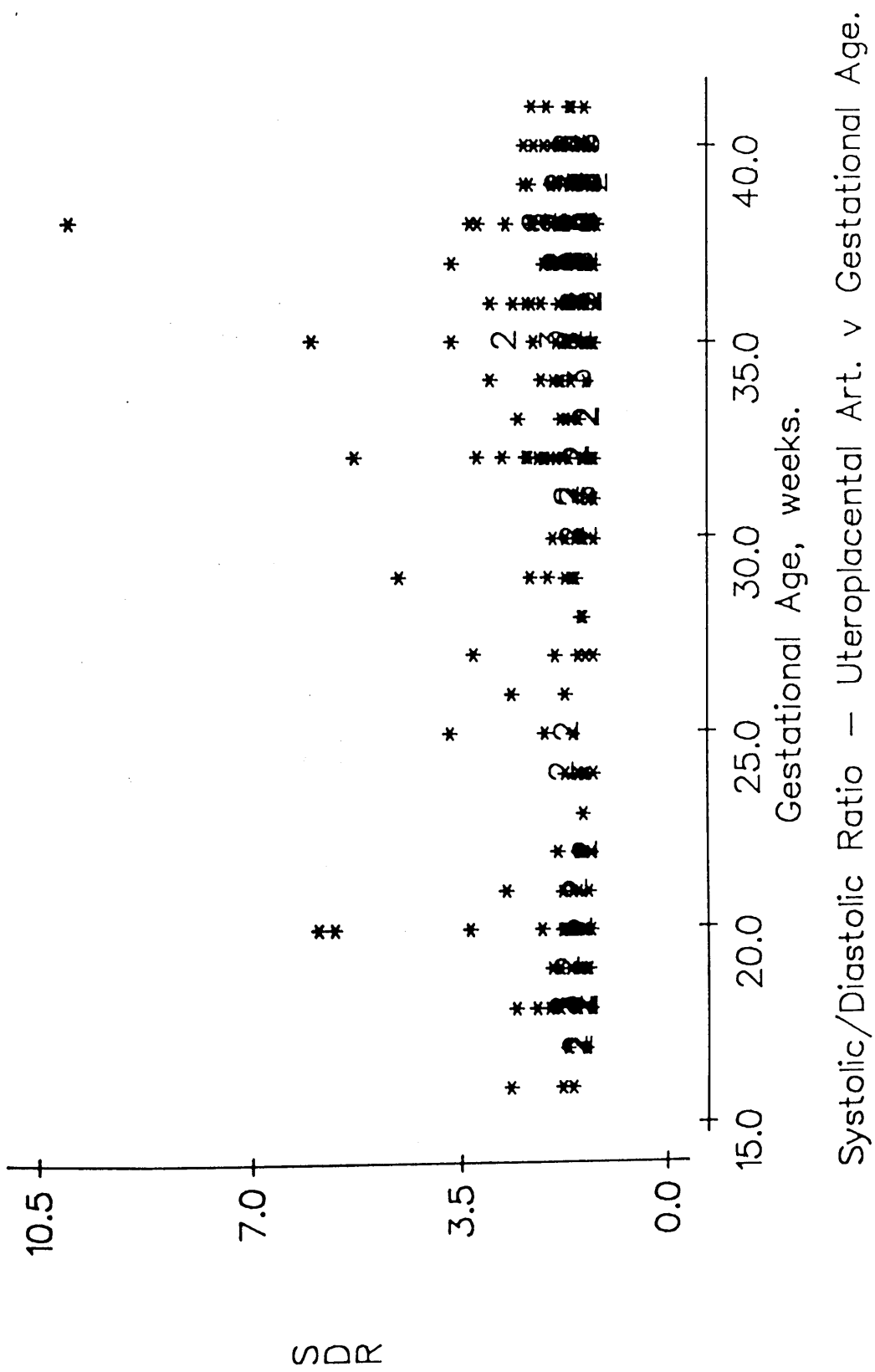


Figure 4.9 Relationship between the systolic/diastolic ratio and gestational age in the uteroplacental arteries.

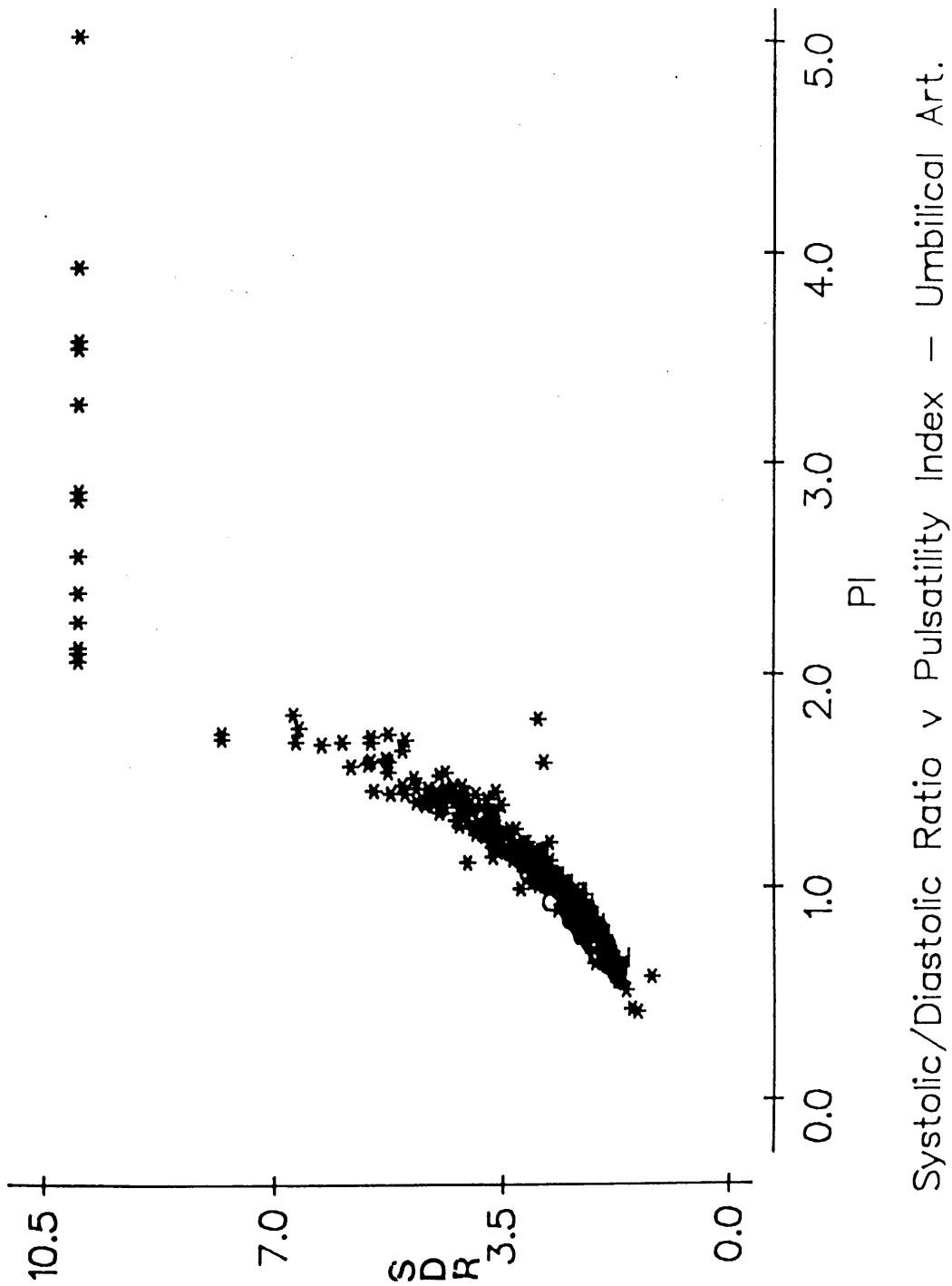


Figure 4.10 Relationship between the systolic/diastolic ratio and the pulsatility index in the umbilical artery.

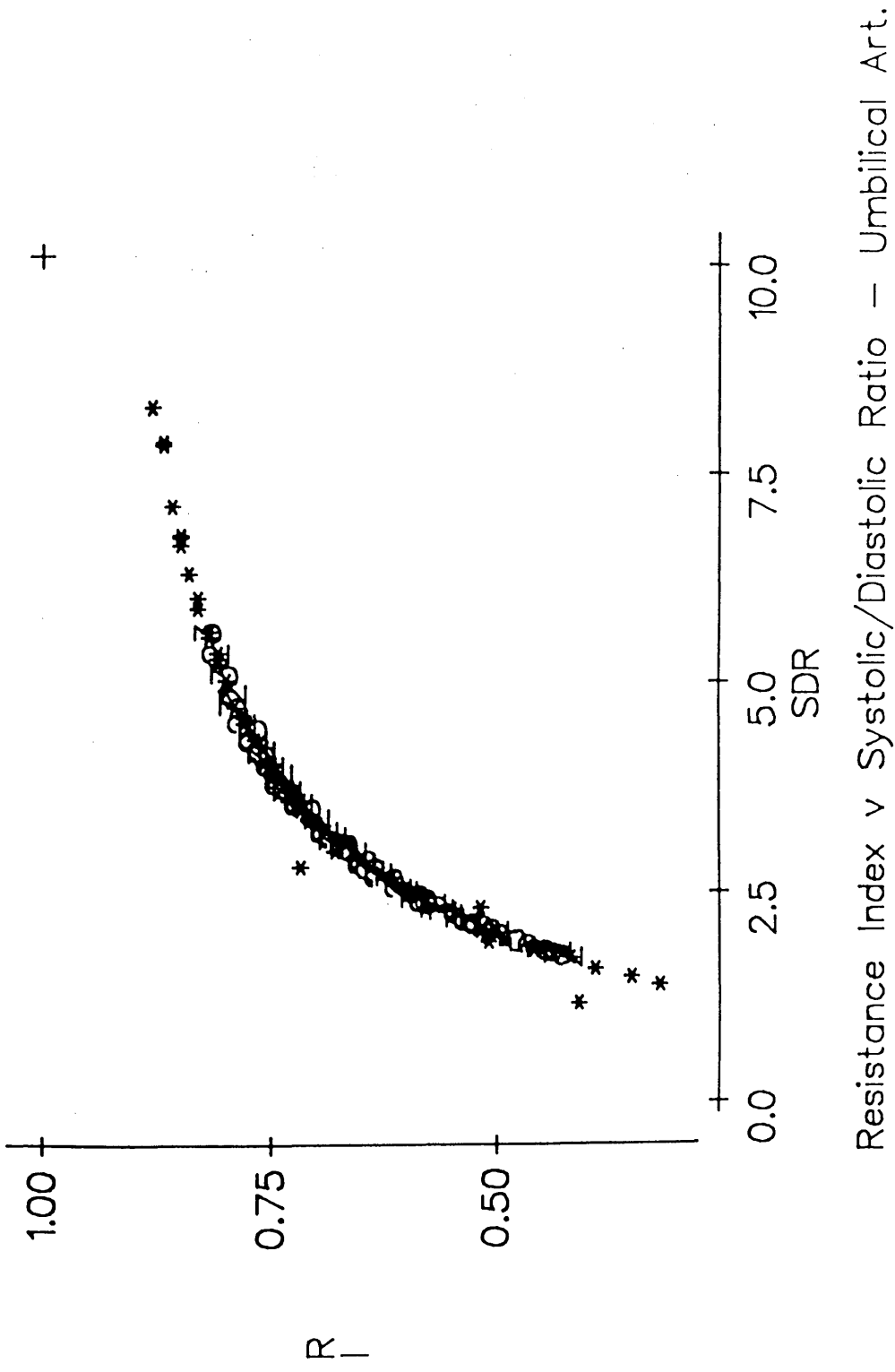


Figure 4.11 Relationship between resistance index and systolic/diastolic ratio in the umbilical artery.

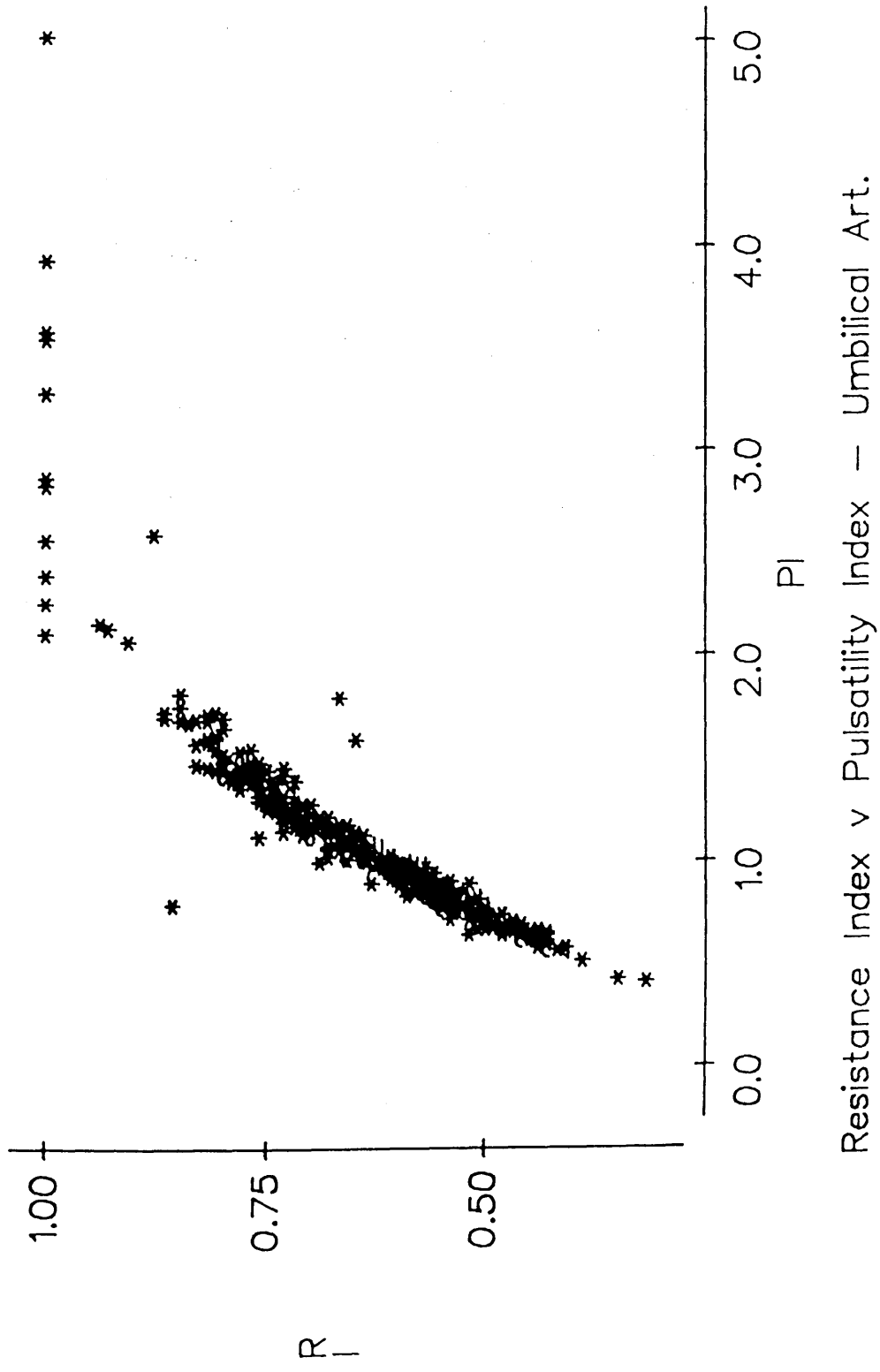


Figure 4.12 Relationship between resistance index and pulsatility index in the umbilical artery.

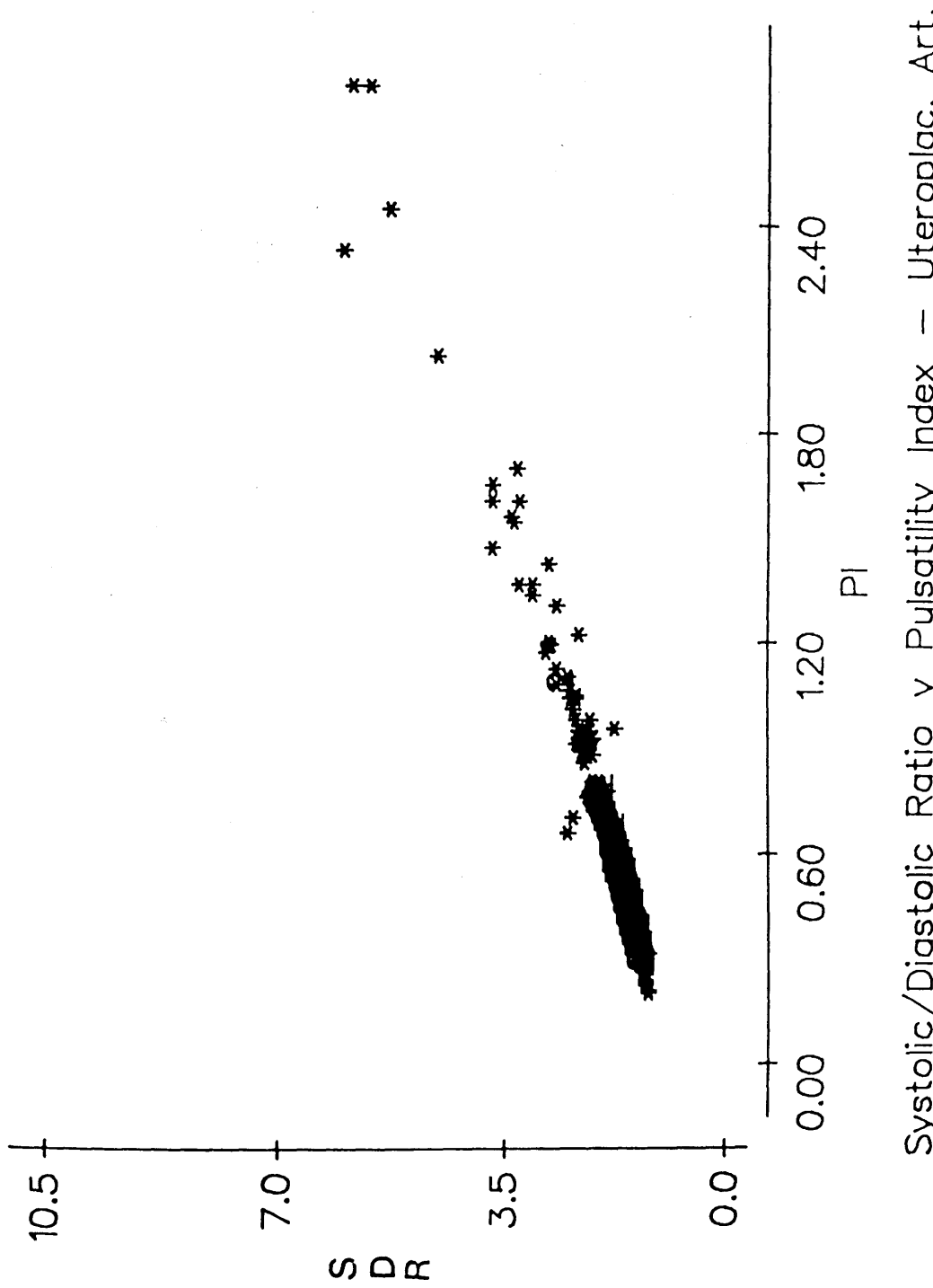


Figure 4.13 Relationship between systolic/diastolic ratio and pulsatility index in the uteroplacental arteries.

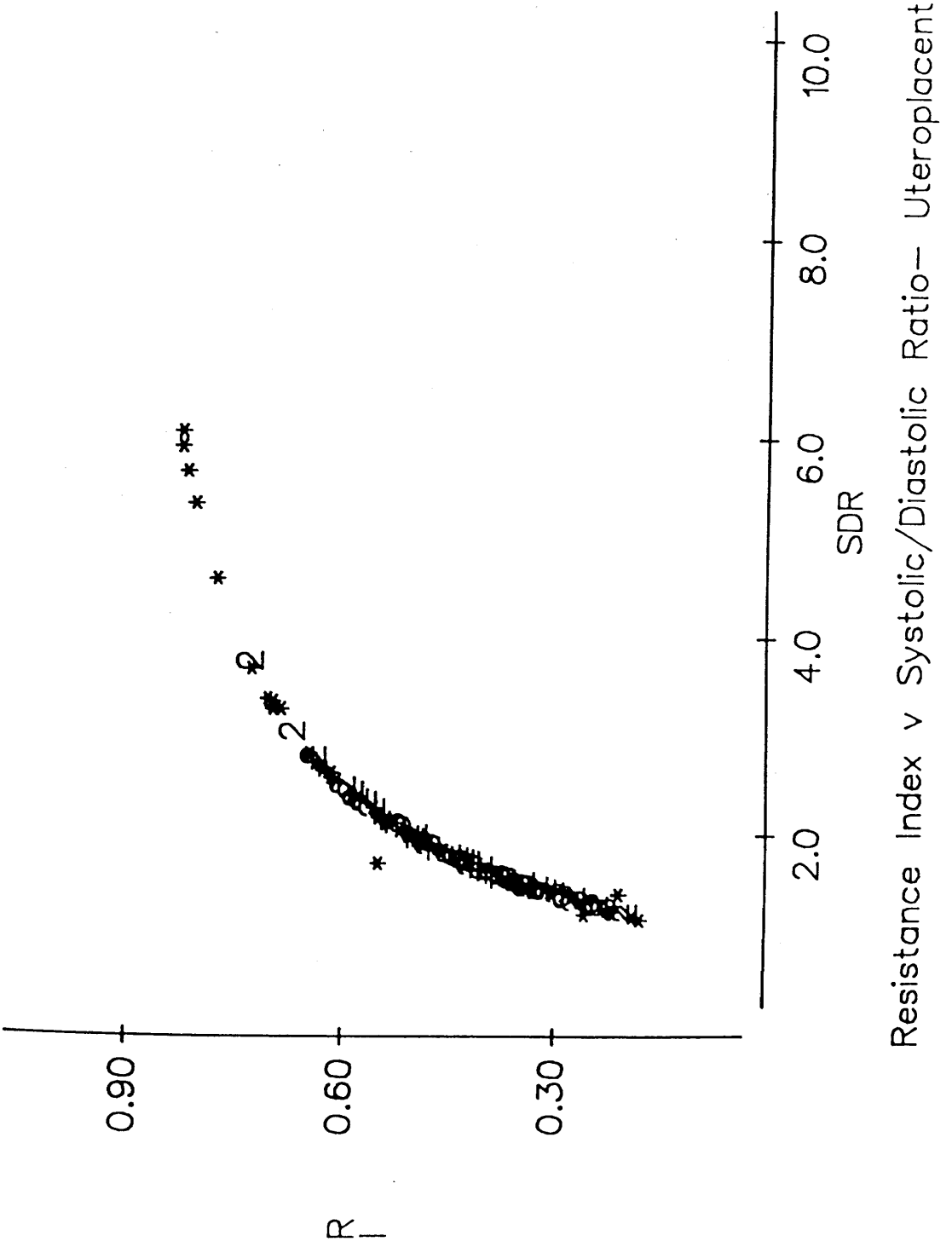


Figure 4.14 Relationship between resistance index and systolic/diastolic ratio in the uteroplacental arteries.

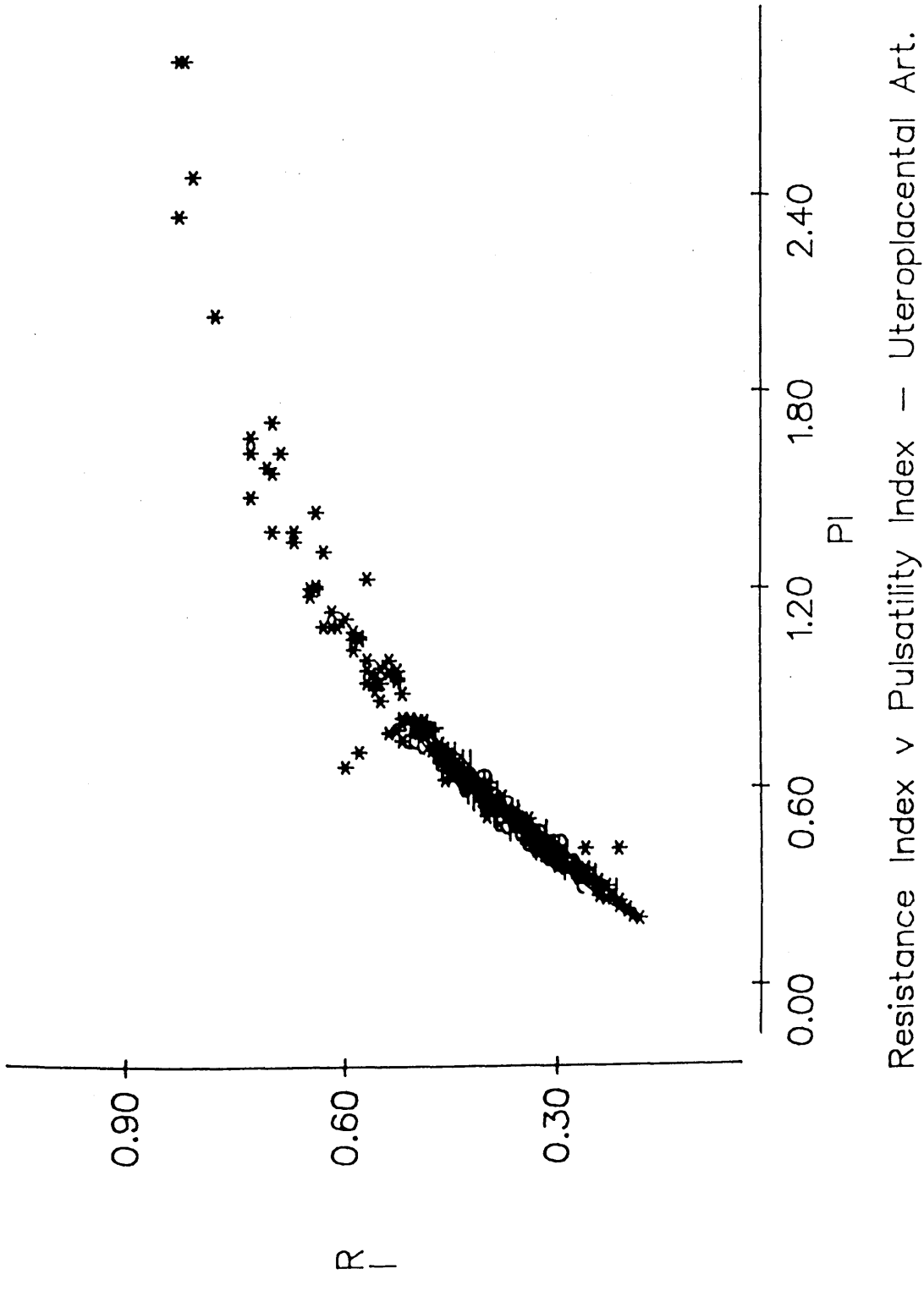


Figure 4.15 Relationship between resistance index and pulsatility index in the uteroplacental arteries.

Chapter 5 Cross sectional study of umbilical and uteroplacental flow velocity waveforms in pregnancy induced hypertension (PIH).

5.1 Definitions of pregnancy induced hypertension.

5.2 The clinical problem of pregnancy induced hypertension.

5.3 The aetiology and pathogenesis of pregnancy induced hypertension.

5.4 Diagnostic methods in pregnancy induced hypertension.

5.5 Patients and methods.

5.6 Results.

5.7 Discussion.

Chapter 5

Cross sectional study of umbilical and uteroplacental flow velocity waveforms in pregnancy induced hypertension (PIH)

Chapter 5.1 Definitions of PIH.

The association between high blood pressure and the eclamptic process was recognised and reported in the English language over one hundred years ago in Edinburgh by Ballantyne (1885).

The Edinburgh pioneer of antenatal care reported on three cases of what were then thought to represent Bright's disease and described "sphygmographic traces of high tension." It was however eighteen years later that two residents in Johns Hopkins hospital suggested that sphygmomanometry might predict eclampsia (Seligman 1987).

Unfortunately this recognition of the importance of hypertension has tended to obscure the appreciation of the condition as not primarily one of high blood pressure (Redman 1989b). Furthermore the emphasis placed on levels of hypertension has led to confusion about the level of blood pressure which is clinically relevant. Problems associated with the actual measurement of blood pressure are also significant and both of these problems have recently been reviewed as they apply to non-pregnant subjects (Kaplan 1987). Kaplan highlighted the existence of "White-Coat Hypertension," that is hypertension induced by its measurement by a physician! The rapid settling of initially high blood pressure in pregnant women admitted to hospital is probably a reflection of this phenomenon rather than a

genuine disorder.

Even in patients with sustained high levels of blood pressure there is still debate about whether the fourth or fifth Korotkoff sound should be used to record diastolic values. This is of importance in comparing different studies both of epidemiology and of treatment.

On average, diastolic blood pressure is 5 to 10 mmHg greater using the fourth sound than when using the point at which complete cessation occurs (Seligman 1987). Consequently in studies of PIH the diagnostic criteria and the measurement technique used must be clearly defined.

The commonly used definitions of PIH have been those devised for use in epidemiological studies (Redman 1989b) and generally comprise three features: hypertension, proteinuria and oedema. In British practice the level of hypertension which has been considered abnormal is 140/90mmHg or greater (Nelson 1955) occuring in the second half of pregnancy, This arbitrary value has the merit of being widely used. Gallery et al (1979) have suggested that levels greater than 85mmHg diastolic are pathological but, in any case, absolute levels may not be informative about the prognosis of the disease; an increase in levels of blood pressure may be more helpful in predicting disease progression and some workers have advocated definitions based on increases in blood pressure over non-pregnant or first trimester levels. Nevertheless, increasing fetal and neonatal mortality and maternal morbidity are associated with the greater degrees of hypertension (Friedman and Neff 1977).

The classification and definition of the hypertensive disorders in pregnancy have recently been reviewed and suggestions made for reclassification (Davey & MacGillivray 1988; Redman and Jefferies 1988). Davey and MacGillivray have suggested that hypertension should be defined as a diastolic blood pressure recording of 90mmHg or greater, as suggested by Nelson (1955), and that this approach has the advantage of simplicity, convenience and is justifiable since this level corresponds to two standard deviations above the mean in the third trimester. Furthermore this level represents the point of inflexion of the curve relating perinatal mortality to diastolic blood pressure. Redman and Jefferies (1988) suggested that this approach biased diagnosis of PIH towards the inclusion of women with chronic hypertension. Basing their conclusions on a database of over 16000 singleton pregnancies they suggested that an increase in blood pressure was a more important diagnostic criterion. They suggested that PIH should be diagnosed in women who have an initial diastolic pressure of less than 90mmHg before 20 weeks gestation, a maximum subsequent diastolic blood pressure of 90mmHg or more and an increase of 25mmHg or more. These workers emphasised the importance of the diastolic increment. The American definition (Hughes 1972) also includes an increment though this is less than suggested by Redman and Jefferies (15mmHg).

Although the limitations of all these arbitrary diagnostic criteria must be recognised, the absence of a universally accepted marker for PIH means that blood pressure measurements remain the basis upon which the

diagnosis of this multi system disease is based.

All patients in the study to be described met the following criteria:-

Blood pressure of less than 140/90mmHg before or during the first trimester of pregnancy.

Maximum subsequent blood pressure of 140/90mmHg or greater.

Increase of 15mmHg in diastolic blood pressure or 30mmHg in systolic blood pressure over first trimester or non-pregnant levels.

Chapter 5.2 The clinical problem of PIH.

The effort which has gone into the classification and definition of PIH emphasises the magnitude of the clinical problem associated with this condition.

Maternal mortality from PIH, whilst decreasing, remains significant. As a proportion of maternal deaths in England and Wales , hypertensive diseases of pregnancy increased from 12.5% in the triennium 1970-1972 to 18.1% for 1982-1984, the period for which the most recent data are available (Department of Health 1989).

The psychological and physical morbidity associated with elective premature delivery in the maternal or fetal interest because of hypertension can never be calculated. Nor have the costs of hospitalisation been evaluated but must be significant since the condition affects approximately 5 to 7 percent of pregnancies.

As regards fetal and neonatal morbidity, pregnancy hypertension is the leading definable cause of premature delivery, and it has been suggested that the rate of

associated neurodevelopmental defects may be as high as 25% (Friedman and Neff 1977).

PIH is associated with twice the number of perinatal deaths which are due to placental abruption and the perinatal mortality is four times greater than for congenital abnormality and five times that of cord prolapse (Friedman and Neff 1977; MacGillivray 1983). Although enormous effort has been directed at reducing the toll of PIH it is unlikely that major improvements will continue to be made in the management of this difficult condition until more is known about its aetiology and pathogenesis.

Chapter 5.3 The aetiology and pathogenesis of PIH.

The aetiology of PIH remains enigmatic. The multi-system nature of the disorder means that as investigators find disordered physiology in many different systems confusion arises between what is an aetiological factor and what is an effect. The following is a brief outline of some of the major factors which have been implicated.

Genetic Factors.

The abnormalities which develop in PIH often precede pre-clinical disease and the extensive work by Chesley and co-workers over many years pointed to the condition being "highly heritable" and demonstrated a single gene pattern of inheritance (Chesley & Cooper 1986). Different rates of gene prevalence might also explain the wide geographic variation in the incidence of the condition (Golding et al 1988).

A subsequent report from Chesley's group (Cooper et al 1988) suggested that the fetal genotype might also

contribute to the maternal susceptibility to the condition.

Immunological Factors.

The immunology of the trophoblast has been extensively investigated and whilst the trophoblast has only low grade antigenicity (Petrucco 1981) overloading of the maternal immune response with fetal antigenic stimuli may play a role in pre-eclampsia. Antigenic overloading has been implicated in the higher incidence of PIH in multiple pregnancy and hydatidiform mole and may explain the association between fetomaternal bleeding and the later development of hypertension in pregnancy (Jones, McNay & Walker 1969).

Paradoxically there seems to be a closer match between women with PIH and their partners for HLA antigens and a hypo-responsiveness in mixed lymphocyte cultures against paternal antigens. (Jenkins et al 1978). In vitro fertilisation studies seem likely to help determine the contribution of the maternal/paternal antibody-antigen interactions occuring in PIH (Serhal & Craft 1989).

Renin Angiotensin System.

It has long been recognised that women at increased risk of PIH have increased responsiveness to infused angiotensin compared to controls (Talledo, Rhodes & Livingstone 1966) and angiotensin 11 may play an important role in controlling maternal vascular responsiveness in the condition (Broughton-Pipkin 1988). Angiotensin 11 may cause separation of endothelial cells and the renin-angiotensin system may be involved as a mediator between genetic-immunological factors and the vascular damage associated with PIH.

Prostaglandins.

Other locally acting hormones have been implicated in this vascular damage and it seems clear that prostacyclin/thromboxane interactions are important (Ylikorkala & Makila 1985). These have recently been reviewed by Friedman (1988) who found a reduction in prostacyclin levels in all fifteen studies of hypertensive pregnancies in which diagnostic criteria were given. All four studies which reported a prostacyclin/thromboxane ratio showed a reduction in severe PIH. Manipulation of the arachidonic acid pathway producing these compounds using aspirin may reduce the incidence of PIH (Beaufils et al 1985) but whilst the data from studies of aspirin thus far suggest a causative role for prostacyclin deficiency (Wallenburg et al 1986) this requires further evaluation.

Haematological Indices.

Abnormal prostacyclin responses may be responsible for the neutrophil and platelet activation seen in PIH (Greer et al 1989) and the histological abnormalities of the placental bed described in PIH may be explained in part by the subclinical disseminated intravascular coagulation seen in conjunction with the thrombocytopenia of the disease.

Uteroplacental Vascular Pathology.

The state of intravascular coagulation has been implicated in the reduction in uteroplacental perfusion seen in PIH but, as discussed in chapter 2, in some pregnancies complicated by PIH the normal physiological invasion of the maternal spiral arteries does not occur (Gerretson, Huisjes & Elema 1981; Khong, Pearce & Robertson 1986) and this

finding accounts for the reduced perfusion in some growth retarded pregnancies in the absence of hypertension. In addition to absent "physiological change," atherosis of the spiral arteries has also been described in association with hypertension. This may also occur in IUGR without hypertension although this is a contentious issue. In some hypertensive pregnancies atherosis with inadequate physiological change may be found without any apparent effect of birthweight (Frusca et al 1989). The effect of atherosis and inadequate physiological change in reducing perfusion in such pregnancies is now well established but the association between an inadequate blood supply and the aetiology of the condition, although intensively investigated, remains unclear.

Beker compared uterine artery diameters in primigravid and multigravid cows using intravascular barium (1929) and found reduced size in the former group. Since PIH is usually a disease of primigravidas he concluded that maternal hypertension developing during pregnancy was a response developed in order to maintain uterine blood flow and showed similar findings in human hysterectomy specimens. His findings prompted Beker to suggest that the use of the term "toxaemia of pregnancy" should be discouraged since all of the findings could be explained in terms of a response to reduced uterine perfusion and proposed the use of the word hypertonia (Beker 1948).

It was observations such as these which led to a number of studies which aimed to reduce uterine perfusion by clamping large maternal vessels, the inferior part of the

aorta or the uterine arteries themselves, to induce hypertension in the pregnant animal. These studies have been reviewed by Cavanagh et al (1974) who developed their own primate model in which uterine arteries were identified in the non-pregnant baboon and clips applied to prevent enlargement during pregnancy (Cavanagh et al 1977). This procedure produced hypertension and renal changes typical of PIH. It is arguable if this model truly represents the type of "uterine ischaemia" occuring in complicated human pregnancy (Greiss 1977). Nevertheless, it is clear that such a process plays a major role in the pathology of PIH.

A scheme representing ways in which different factors involved in the aetiology of PIH may interact to alter uteroplacental perfusion is presented in Figure 5.1.

Since Doppler velocimetry indirectly measures perfusion its use has been proposed to aid the early diagnosis and investigation of PIH. Before discussing the effect of hypertension on Doppler indices it is relevant to briefly review some of the techniques which have already been suggested for this purpose.

Chapter 5.4 Diagnostic methods in PIH.

More than 100 different techniques have been described for the early diagnosis of PIH (Sibai 1988). These can be categorised as tests which measure blood pressure in response to a specific stimulus or biochemical or haematological tests on maternal blood.

Tests measuring blood pressure responses.

One of the diagnostic dilemmas present in some cases of PIH is that of distinguishing it from underlying or pre-existing hypertension. It was with the aim of differentiating these conditions that Chesley and Valenti (1958) investigated a battery of tests described previously by others as being helpful. These included the blood pressure response to cold (the cold pressor test), the intravenous administration of tetramethylammonium chloride and the response to intravenous vasopressin. Only the last measure appeared to discriminate patients with PIH from those with chronic hypertension.

None of these tests was however sufficiently specific for clinical use. In contrast Gant et al (1974) found that 93% of normotensive primigravidae who would subsequently develop PIH demonstrated an increase of 20mmHg in diastolic blood pressure when turned from the lateral recumbent to supine position. Support has been given to this work by Karbhari, Harrigan & LaMagra (1977) and Phelan (1977) among others but not by others (Kassar, Aldridge & Quirk 1980) and despite the encouraging results of Gant and colleagues studies with false positive rates between 6 and ninety percent and false negative rates between 4 and thirty percent have been described (Redman 1982).

The blood pressure response to infused angiotensin 11 has a more sound physiological basis as a diagnostic test and 50% of women destined to develop PIH have a hypertensive response to infusion. Nevertheless the invasive nature of this investigation is too great for routine clinical use.

None of the tests thus far described are appropriate for use as effective techniques for the routine early detection of PIH.

Tests on maternal blood.

In 1918 Slemons and Bogert reported their findings of a study to determine the "placental interchange" of uric acid. They found elevated levels in cases of syphilis and pyelitis but most noticably in PIH. The biochemistry of uric acid in normal pregnancy has since been extensively investigated (Dunlop and Davison 1977; Lind, Godfrey & Otum 1984) but despite considerable interest it was not until 1956 that Lancet and Fisher suggested that uric acid determinations could be relied upon in diagnosing PIH. Kuhlback and Widholm (1964) suggested that elevated levels of urate were prognostically important for fetal outcome. A trend towards increasing levels may also be important (Connon and Wadsworth 1968) but Redman et al (1977) reported that single levels over 0.35 uM/l were associated with higher perinatal mortality rates. Although the mechanism underlying the elevated levels of uric acid remains unresolved (Fadel, Northrop & Misenhimer 1975) the measurement of urate is now a central component of the diagnosis and monitoring of PIH.

An important observation made by McFadyen et al (1986) was of an association between plasma urate and vascular adaptation in the placental bed. These workers studied placental bed biopsies in 34 women for whom uric acid levels were available within 72 hours before delivery. The urate levels were significantly higher in those women with atherosis or inadequate physiological change in the spiral

arteries. All but one of the 19 hypertensive patients in the series had urate value of greater than 300 uM/l. The only hypertensive patient with a normal urate level was also the only patient in that group who did not have atherosis, inadequate physiological change, or both in the spiral arteries.

Haematological indices.

Redman used the association between hyperuricaemia and PIH to identify women with early onset disease and observed a reduction in platelet count resulting from activation of the coagulation system (Redman, Bonnar & Beilin 1978). Since then regular measurement of platelet count has also become standard practice in monitoring pre-eclamptic patients although individual measurements are not of diagnostic value because of the large variation in platelet count in normal pregnancy.

Other diagnostic methods.

The possible role of uteroplacental and umbilical artery Doppler in the diagnosis and management of PIH has been discussed briefly in chapter 2 but one application of the Doppler technique which may be of value in the early diagnosis of PIH is the study of flow velocity waveforms in the maternal renal artery. Tyrrell, Bates & Lilford (1987) have reported one patient in whom the renal artery resistance index was elevated before the development of abnormal uteroplacental and umbilical artery waveforms. They suggested that this was an effect of the condition on renal perfusion rather than evidence of primary renal disease. Further investigation is required to confirm the value of

this promising approach.

The value of Doppler velocimetry of the uteroplacental and umbilical arteries in the management of PIH remains to be determined in sufficiently powerful controlled trials, but before these can be designed it is important to determine if PIH does influence flow velocity waveforms and if the finding of abnormal patterns is related to the degree of hypertension. The remainder of this chapter describes a study addressing this issue.

Chapter 5.5 Patients and methods.

Patients who met the criteria for the diagnosis of PIH defined in chapter 5.1 were invited to undergo Doppler examination. No patient was receiving antihypertensive therapy at the time of study.

Since blood pressure was regularly monitored before and during Doppler study a number of patients who failed to meet the strict blood pressure criteria were excluded at this stage.

Furthermore because of the limitations of inclusion criteria based on blood pressure measurement, data were only analysed for the 44 patients with elevated serum uric acid values measured within 72 hours before Doppler studies. A level of 350 uM/l or greater was considered as indicating hyperuricaemia. This criterion has the value of identifying patients in whom the disease process is likely to be associated with failure of physiological change or atherosis in the maternal spiral arteries (McFadyen et al 1986). Patients with proteinuria detected on ward testing had this

confirmed by quantitative analysis on 24 hour urine specimens. Greater than 500mg was considered significant.

Each patient was matched to within 2 years for maternal age and to within 10 days for gestational age with a control. The controls were normal volunteers who had no complications during pregnancy and who delivered appropriately grown fetuses with Apgar scores of greater than 6 at one and five minutes at term. Data which were normally distributed were compared using a two sample t test and those from non-parametric data were compared using a Mann Whitney test.

Chapter 5.6 Results.

Table 5.1 summarises the results obtained from hypertensive and control cases. For ease of presentation data are presented as means and standard deviations even when non-parametric analyses have been used.

The mean gestational age at delivery of 36.4 (3.8) weeks in the hypertensive group was significantly less than that of that of the controls which was 39.4 (1.1) weeks ($t=5.0$: $p<0.0001$).

Fourteen of the hypertensive cases were delivered pre-term. Seven babies born in the hypertensive group weighed less than the fifth centile and four died as a result of the effects of prematurity and IUGR.

Uteroplacental waveform indices were significantly higher in the hypertensive group compared with controls.

Although in the hypertensive group overall there was no significant difference in umbilical waveforms from

controls, when the Doppler results from the 22 proteinuric cases were compared with controls the Doppler indices for the umbilical artery were significantly higher ($W=954$, $p<0.04$ for the pulsatility index and $W=921$, $p<0.02$ for the resistance index).

Absent end-diastolic velocities in the umbilical artery were found in five cases, all of which had proteinuria. In four of these cases intra-uterine or neonatal death occurred In the fifth case a growth retarded fetus was delivered which, like the other babies in the study, subsequently did well. There was no consistent relationship between these abnormal umbilical artery patterns and high resistance patterns in the uteroplacental waveforms.

There was no correlation between levels of blood pressure and any Doppler index in either of the circulations studied.

Chapter 5.7 Discussion.

The findings presented here report the first controlled study of the effects of PIH on both uteroplacental and umbilical waveforms measured simultaneously.

Previous studies of the effects of PIH on Doppler uteroplacental waveforms have generally supported the earlier radioisotope studies showing reduced uterine perfusion discussed in chapter 2. The only published controlled study failed however, to demonstrate any difference from controls (Hanretty, Whittle & Rubin 1988a). However, one of the findings in that study was the presence of abnormal waveforms in a pregnancy resulting in

perinatally related death. It was suggested (Campbell, Vyas & Bewley 1988) that, although the vascular pathology of PIH was focal, in severely affected cases it is widespread and therefore might be expected to result in failure to detect waveforms of low vascular resistance. Despite the use of the same inclusion criteria as those in the earlier study of Hanretty, Whittle & Rubin, a higher proportion of cases with early onset disease were recruited by chance and it is possible that in these cases the vascular pathology was more widespread. Additionally the study presented here is larger and in statistical terms more powerful and confirms the findings of earlier uncontrolled studies which had included patients receiving antihypertensive medication with unknown effects on Doppler velocimetry (Campbell et al 1983; Trudinger, Giles & Cook 1985a; Fleischer et al 1986).

Only in the proteinuric cases were the umbilical artery waveforms significantly different from controls and this suggests that the vascular pathology on the fetal side of the circulation results in increased vascular resistance only when the maternal vascular damage is extensive.

There was no correlation between absolute levels of either systolic or diastolic blood pressure and Doppler indices and this confirms this observation in a smaller series of cases of PIH (Hanretty, Whittle & Rubin 1988b).

Whilst these findings confirm the altered haemodynamics in PIH the diagnostic value of Doppler studies remain to be determined since in both umbilical and uteroplacental circulations there is a large normal range with considerable overlap between hypertensive and normal pregnancies.

However, the findings are consistent with those of Cameron et al (1989) who demonstrated that the finding of very abnormal umbilical artery waveforms is associated with a significant fetal morbidity. Such a finding may alter management of a pre-eclamptic patient although controlled studies are required to determine if this results in an improved outcome.

In conclusion, in PIH Doppler uteroplacental waveforms show patterns representing higher vascular resistance compared with controls. When the disease is severe, as defined by the finding of significant proteinuria, umbilical artery flow velocity waveforms are also significantly different from controls reflecting more severe vascular damage in the fetoplacental circulation.

Table 5.1 Comparison of results from PIH and control groups.

	PIH		Controls		Test Statistic	P Value
Maternal age	25.6	(4.9)	26.1	(4.6)	t=0.47	0.64
Gestational age at time of study.	35.5	(3.7)	35.5	(3.7)	W=1985	0.82
SBP	164	(15)	130	(10)	t=12.4	0.0001
DBP	96	(7)	73	(9)	t=14.1	0.0001
Umbilical artery						
PI	1.19	(0.62)	0.91	(0.17)	W=1747	0.08
RI	0.65	(0.16)	0.58	(0.08)	W=1761	0.10
Uteroplacental artery						
PI	0.82	(0.53)	0.58	(0.27)	W=1667	0.02
RI	0.47	(0.16)	0.40	(0.13)	W=1693	0.04

SBP Systolic Blood Pressure

DBP Diastolic Blood Pressure

PI Pulsatility Index

RI Resistance Index

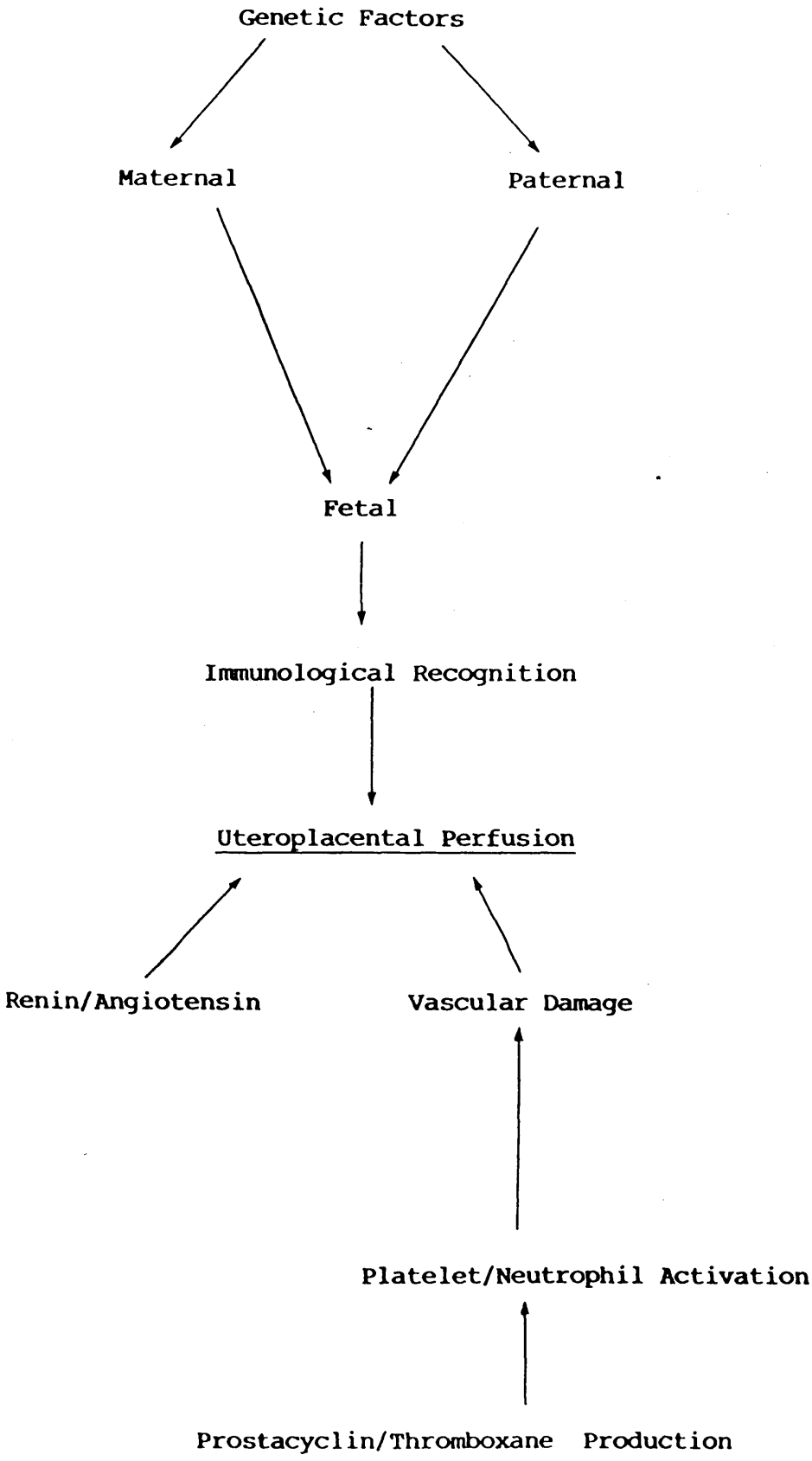


Figure 5.1 Factors influencing uteroplacental perfusion in pregnancy induced hypertension.

Chapter 6 Cross sectional study of umbilical and uteroplacental flow velocity waveforms in pregnancies in which the fetus is small-for-dates.

6.1 The clinical problem of the small-for-dates fetus.

6.2 The aetiology and pathogenesis of intra-uterine growth retardation.

6.3 The identification of the small-for-dates fetus.

6.4 Methods.

6.5 Results.

6.6 Discussion.

Chapter 6

Cross sectional study of umbilical and uteroplacental flow velocity waveforms in pregnancies with small-for-dates fetuses.

Chapter 6.1 The clinical significance of the small-for-dates fetus.

The selection of suitable outcome variables with which to assess investigation and management in obstetrics remains a major problem. The birth of a baby which is small-for-dates has been used for many years although it is unsatisfactory for a number of reasons. The definition of small-for-dates describes the proportion of a population of babies described by a Gaussian curve which lie to the left of a chosen centile; traditionally the tenth centile has been used but many normal babies then meet the criterion for being small-for-dates. The lower centiles, below the fifth and third particularly, are much more likely to include babies from pathological pregnancies (Reuwer et al 1987).

Apart from being constitutionally small, babies may be born small for a number of reasons including intra-uterine infection, structural and chromosomal abnormality, maternal smoking drug abuse and poor diet and placental insufficiency producing IUGR.

Regardless of the cause for being small-for-dates such a fetus is more likely to be compromised in utero and to have greater mortality and morbidity than the appropriately grown fetus. It is difficult to quantify the increased risk for these fetuses because of varying diagnostic criteria used by

different workers and earlier failure to recognise the condition of growth retardation as distinct from prematurity as well as absence of long term follow-up data. Patterson et al (1986), in their study of 44000 patients demonstrated that babies born below the tenth centile after 30 weeks gestation contributed around 30 percent of the cases regarded as having a poor perinatal outcome and this figure varied little over the gestational age range. It is likely that, as well as including abnormal fetuses, this figure represents some morbidity associated with IUGR.

In the perinatal period the small-for-dates fetus suffers an excess of intra-partum hypoxia and the neonate more commonly experiences hypoglycaemia and hypocalcaemia in immediate postnatal life (Chiswick 1985). The longer term outcome is still inadequately evaluated, although it is recognised that neurodevelopmental outcome is poorer in the small-for-date fetus (Taylor & Howie 1989). The more recent literature suggests that the evidence is not by any means unequivocal but there are many problems in the design of these large retrospective studies relating to power calculation and inclusion and exclusion criteria. Nevertheless identification of the compromised small-for-dates fetus before the onset of labour appears to be important since small-for-dates fetuses account for more than half of intrapartum fetal deaths (McIlwaine et al 1979).

This probably relates to the inability of the small-for-dates fetus to sustain adequate acid base balance in labour. Percutaneous umbilical blood sampling, which has

been advocated in the management of the severely growth retarded fetus, both to determine fetal karyotype and acid base balance, confirms that acidosis may precede labour; Pearce and Chamberlain (1987) reported this finding in 8 of 10 cases undergoing sampling and substantiated their results with blood taken from the umbilical vein at delivery.

Chapter 6.2 The aetiology and pathogenesis of IUGR.

The recognition that IUGR may be a diagnosis in some low birth weight babies is a relatively recent event. Many of the large early studies of outcome of low birth weight babies failed to recognise initially the difference between appropriately grown preterm babies and those who were growth retarded, or both. This was in part because of the uncertainty of gestational age.

The step forward in understanding that "intra-uterine malnutrition" could result in the birth of a full term low birth weight baby was critical to the investigation of abnormalities of growth in utero.

Factors determining fetal size, rather than growth, had already begun to be investigated and in the previous decade it had already been shown that the maternal, rather than paternal, genetic contribution was a determinant of birth weight. In a series of cross breeding experiments using horses and ponies Walton & Hammond (1938) had demonstrated the dominant maternal effect on fetal size. They showed that the birth weight of a cross between these animals correlated with the breed of the mother regardless of species.

In the human there are familial trends in birth weight

(Johnstone & Inglis 1974) which support this, the risk of a woman delivering a low birth weight baby being increased 2.4 fold if she herself was of low birth weight. However, the influence of genetic, as opposed to environmental effects, on birthweight has recently been questioned. Carr-Hill et al (1987) showed, from the Aberdeen maternity and neonatal database, that genetic influences and genetic factors play only a small part in determining birth weight.

Genetic abnormalities and certain intra-uterine infections also operate and may retard fetal growth by affecting intrinsic growth control through the genomic defect or by infecting rapidly reproducing cells.

The genetic control of growth is undoubtedly disturbed in some chromosomal defects such as trisomies, sex chromosome abnormalities and mosaics all of which have lower mean birth weights even when corrected for gestational age at delivery. Certain other structural abnormalities anomalies such as renal agenesis and heart disease are also associated with growth retardation.

Viral infections such as rubella and cytomegalovirus appear to exert their growth retarding effect, not by an effect on fetal haemodynamics as seems to be the case in non-infectious abnormality (Hsieh et al 1988), but by a combined action of endothelial damage, cytolysis and localised necrosis.

Abnormal haemodynamics do play a part in some cases of IUGR in multiple pregnancy, where placental vascular anastomoses may produce a twin to twin transfusion syndrome. Even in the absence of this complication between 15 and 20

percent of multiple pregnancies are complicated by poor growth of one or both twins (Houlton, Marivate & Philpott 1981). It has been suggested that, in these cases, the retarded growth is a result of an inadequate uteroplacental unit since, when delivered, these babies post-natal growth matches or exceeds that of appropriately grown singletons.

Adequate substrate is nevertheless required for both placental and fetal growth and there is outstanding evidence for the role of maternal undernutrition in producing poor fetal growth from data aquired as a result of the siege of Leningrad during the Second World War. The prolonged period of near starvation for the population resulted in substantial reductions in birth weight even some time after the seige was lifted, suggesting that nutrition even in the early stages of gestation is important to later growth (Creasy & Resnik 1989).

Environmental Toxins

It is now well recognised that cigarette smoking, alcohol and other drug abuse are associated with fetal growth retardation. The mechanisms whereby these toxins have their effects is unknown but is presumed to be at a cellular level presumably interfering with the complex interactions of fetal growth factors.

Pathology of IUGR

These growth factors are themselves dependent on adequate uterine perfusion and impaired uteroplacental circulation has been implicated in the majority of cases of IUGR.

The pathological correlates of growth retardation appear

to be similar to those of pre-eclampsia. McFadyen, Price & Gierrson (1986) found absence of physiological change and acute atheroma in the maternal spiral arteries also to be a feature of growth retardation in some normotensive cases. The effect of such pathological changes on uteroplacental perfusion has already been discussed in chapter 5. There are, however, difficulties in the interpretation of histological abnormality in IUGR.

More readily understood is the well recognised association between pre-existing vascular disease such as reno-vascular disease, collagen diseases, diabetic vasculopathy and poor fetal growth but reduced perfusion may still be found in the absence of histological abnormality (McFadyen et al 1986) and vasoactive substances such as the eicosanoids may play a role (Friedman 1988) as may changes in blood viscosity. Thorburn et al (1982) demonstrated increased blood viscosity in a group of 16 mothers of small-for-dates fetuses as well as in a group of severely pre-eclamptic pregnancies. Whilst viscosity might therefore have a role in placental insufficiency, Steel et al (1988) showed no association between viscosity at high or low shear rate and uteroplacental resistance index.

Whether a combination of changes in viscosity with ultrastructural changes is responsible for the presumed impaired blood flow to the uteroplacental unit remains to be determined but ideally a method that would detect the fetus at risk of compromise would identify the functional abnormality in the fetoplacental unit, something which Doppler techniques should, on theoretical grounds, achieve

and so, consequently, deserve evaluation.

The inter-relationships between the factors mentioned and the integrity of the fetoplacental and uteroplacental circulations, which might be assessed using Doppler, are shown in Figure 6.1.

Any advantages to the use of Doppler must, however, be compared with currently used techniques.

Chapter 6.3 Identification of the small-for-dates fetus.

The morbidity and mortality associated with the small-for-dates fetus has resulted in the direction of considerable effort towards the early recognition of these cases. It is generally accepted that clinical methods are of limited value in the detection of the small fetus. Clinical estimation of fetal weight by palpation is particularly poor in the small baby (Loeffler 1967) and although additional techniques such as symphysis fundal height measurement were originally found to increase the sensitivity and specificity of the clinical method (Quaranta et al 1981) their performance in clinical practice has been disappointing. In addition, the obstetrician's response to the clinical detection of a fetus thought to be small-for-dates is variable and does not seem to correlate with identified risk factors such as growth retardation in previous pregnancies or subnormal oestriol levels. (Rosenberg, Grant & Hepburn 1982). Consequently a large number of adjunctive methods, usually ultrasound based, have been developed in an attempt to identify this population of fetuses. The early recognition of a pregnancy at risk of being complicated by

fetal growth problems is difficult and will only really become possible with a greater understanding of the aetiology and pathogenesis of the underlying process.

In terms of the currently available diagnostic techniques the clinical identification of intra-uterine growth retardation is disappointing. Hepburn and Rosenberg (1986) found that in clinical practice only 26% of babies born below the tenth centile were identified antenatally and for each of these babies there were two false positive results.

These apparent failures led to adjunctive aids to diagnosis which can be divided into biochemical and biophysical methods.

a) Biochemical

Before the development of widely available portable high resolution ultrasound imagers biochemical evaluation of fetal wellbeing was a mainstay of practice and was commonly used as a screening test for the small-for-dates fetus. Both urinary and maternal serum oestriol measurements were found to be in the low to low-normal range in the small fetus but the discriminative value of measuring this hormone is poor and it has been suggested that measurement of oestriol values is of historical interest only (Creasy and Resnick 1989). Human placental lactogen in maternal serum has been shown to be a more specific marker for the recognition of the small fetus but in general biochemical methods have been superseded by ultrasound (Whittle 1988).

b) Biophysical

Willocks, a pioneer of ultrasound first suggested that it might be used to estimate fetal weight. Campbell & Wilkin (1975) derived a formula relating fetal abdominal circumference to fetal weight and this has become a generally accepted method. Since then a multitude of formulae have been suggested which include measurement of fetal long bones and attempts at indirect measurement of fetal subcutaneous fat using thigh circumference measurement. Unfortunately, in practice the error of the methods is around 10 percent and there is a wide variation in accuracy using any specific technique.

Neilson et al (1984) measured abdominal circumference and crown rump length without deriving a fetal weight and showed that, when applied as a screening test at 34 to 36 weeks gestation, a sensitivity and specificity of greater than 85% could be achieved. Unfortunately, when the technique was applied prospectively in a randomised controlled trial, availability of the result did not influence clinical practice despite the overall accuracy of the method.

The contribution of amniotic fluid volume to the uterine size in intrauterine growth retardation has also been determined by a number of workers but whilst this technique has been extensively investigated it has not been introduced widely into clinical practice. Attempts at measurement of total intra-uterine volume measurement have also been made and seem to have a high sensitivity for detecting the small fetus (Giersson, Patel & Christie 1985) but poor specificity

and has not been widely introduced into clinical practice.

The general dissatisfaction with current methods of pregnancy screening has led to considerable research into new techniques which may have potential use. One of these is Doppler velocimetry and it is interesting that the suggestion that the method may be useful in the identification of the compromised small-for-dates fetus was made initially by FitzGerald and Drumm (1977). Unfortunately, there have, however, been no published studies to determine if Doppler flow velocity waveforms from the uteroplacental and umbilical arteries are significantly different from controls in the small-for-dates fetus. The following section describes such a study.

Chapter 6.4 Methods.

Thirty two patients with singleton fetuses suspected of being small-for-dates were recruited following assessment in the Day Unit of The Queen Mother's Hospital. Gestational age was established from menstrual data and confirmed by ultrasound measurement before 16 weeks gestation in all cases.

All had been identified as clinically small, had fetal abdominal circumference measurements which suggested a fetal weight below the fifth percentile for the local population using birthweight data from a large local study (Forbes and Smalls 1982) and all delivered a baby weighing less than the tenth centile for gestation. Patients with preexisting medical disease or pregnancy induced hypertension were excluded from the study. The uteroplacental and umbilical artery flow velocity waveforms were obtained as previously

described.

A group of 32 women with uncomplicated pregnancies and matched for maternal and gestational age were used as control cases. The hypothesis tested was that increased vascular resistance to flow in both uteroplacental and umbilical circulations of the small-for-dates fetuses would produce significantly different Doppler waveform indices. When patients had a number of measurements made the last one obtained before delivery was used for analysis.

Comparisons between groups were made using Student's t test and the Mann Whitney test for normal and non-normal distributions respectively.

Chapter 6.5 Results.

The results for both SFD and control groups are shown in Table 6.1. For ease of presentation results are expressed as means with standard deviations. Figures 6.2 to 6.5 show graphically the individual data points.

Of the small-for-dates babies 2 weighed between the 5th and 10th centile; of the remainder, 13 (41%) weighed less than the third centile. There was no difference in Doppler uteroplacental waveform indices between the two groups but, in contrast, the umbilical artery resistance index was higher in the small-for-dates cases than controls. Within the small-for-dates group there was no difference in Doppler indices between those above and below the 3rd centile for gestational age.

Using the criterion of a resistance index of greater than 0.67 in the third trimester as being abnormal, as suggested by Schulman et al (1985) only 3 of these babies

had an abnormal pattern.

All of the babies subsequently did well though this size of study would be unlikely to detect a significant difference in neonatal morbidity (Lilford 1989).

Chapter 6.6 Discussion

Abnormal uteroplacental and umbilical haemodynamics may be associated with intra-uterine growth retardation. These haemodynamic changes and their assessment using non-ultrasound technology have been previously been discussed in chapter 2.

Uteroplacental waveforms

Three main groups of workers have investigated the uteroplacental circulation in cases of IUGR: Campbell et al (1983) first introduced the technique for this purpose but the initial studies were performed on a rather disparate group of cases. Pearce (1987) has implied that IUGR occurring before 34 weeks is associated with impaired uterine perfusion and abnormal waveforms but there is little evidence to support this in the literature. Nevertheless, the observation by Pearce (1987) of an association with depth of trophoblast invasion suggests that Doppler might be of value in the identification of cases of IUGR before they are clinically obvious. This issue has been considered in chapter 2 and will be further reviewed in chapter 8.

Trudinger, Giles & Cook reported initially on uteroplacental waveforms in 25 cases associated with the birth of a small-for-dates fetus (1985a). Of the total number of these cases, 15 had abnormal waveforms with

reduced diastolic frequencies, representing high resistance to flow. The aetiology in these cases is not clear from the paper although those cases with severe hypertension were described separately.

It was suggested that cases of IUGR could thereby be subdivided into those primarily of fetal origin and those secondary to poor maternal supply. However, in a larger study (Trudinger, Giles & Cook 1985b) including 53 pregnancies ending in the delivery of small-for-dates fetuses the uterine artery waveform was no more frequently abnormal in the small fetuses than those appropriately grown. The sensitivity calculated from their data (though not shown in the paper) was 34.0% and the specificity was 80.7% for the detection of a small-for-dates fetus using their criterion of an abnormal uteroplacental waveform being above the 95th centile of their normal range for gestational age. When these data are analysed using a chi square test the resulting value, 3.56, shows no significant association between the character of the waveform, normal or abnormal, and being small-for-dates.

McCowan et al (1988) studied Doppler waveforms from the uterine arteries in a series of 12 cases of IUGR. In 9 cases there was underlying maternal hypertension. In the other three cases no cause was found and, in contrast with the pre-eclamptic cases the uterine artery waveforms were normal.

Chambers et al (1989) obtained a sensitivity of 29% in the detection of babies below the 10th centile for gestation, though the aetiology and inclusion criteria were

not stated. Consequently the proportion of cases of IUGR associated with reduced uteroplacental perfusion in the absence of underlying vascular pathology as in pre-eclampsia remains unknown. Radioisotope data from Kaar et al (1980) and from Nylund et al (1983) suggests that uteroplacental perfusion is reduced in IUGR but in the study presented in this chapter the Doppler indices from the uteroplacental vessels were not different between the study and control groups. This is not inconsistent with reduced uterine perfusion but since it is possible that, as in pre-eclampsia, vascular pathology in the placenta is focal, the data obtained from Doppler interrogation of a relatively small part of the uterine vasculature is unlikely to reflect the overall degree of vascular abnormality. However, it must be stated that the cases of IUGR degree described here were not of early onset and all babies subsequently did well. Nevertheless a significant proportion were below the 3rd centile of weight for gestation and significant vascular pathology might be expected in these cases.

Umbilical artery waveforms

In this study, in contrast with the uterine circulation, differences in umbilical artery indices were found between groups.

Abnormal umbilical artery flow velocity waveforms were first described in association with intra-uterine growth retardation by Erskine and Ritchie (1985) and since then a number of workers have confirmed this association although this has almost always been observed in cases complicated by pre-eclampsia, essential hypertension, connective tissue

disease, fetal abnormality and multiple gestation.

Abnormal waveforms might logically be expected in cases of IUGR since a number of workers have suggested that a redistribution of blood flow occurs within the fetus and to the placenta (Pearce 1987). Since abnormal umbilical artery waveforms seem to indicate placental disease, it is likely that the redistribution within the fetus is a consequence of a change in fetoplacental perfusion and that this is reflected clinically in the brain sparing effect of assymetrical IUGR (Campbell & Thoms 1977).

However, none of the published studies have examined whether umbilical artery waveforms are abnormal in small-for- dates fetuses in the absence of maternal disease and none have performed controlled comparisons. The interesting finding presented here is that, although 8 cases in the study group had a Resistance Index value of greater than 0.67, corresponding to a systolic diastolic ratio of 3.00, which has been suggested as the upper limit of normality in the third trimester (Schulman 1987), there was a wide range of values for these babies. Since all babies did well it is unlikely that those with abnormal waveforms were more compromised than the others but this cannot be excluded from this study. Reuwer et al (1987) showed that perinatal outcome in the small-for-dates fetus did appear to correlate with Doppler indices rather than birthweight.

The recognition of the "uncompromised" small-for-dates fetus using Doppler seems less promising than had originally been hoped. A number of workers have now shown that Doppler study of the umbilical artery is relatively poor at

detecting small-for-dates fetuses as part of a screening programme, either applied generally to a population (Hanretty et al 1989) or to cases already recognised as at high risk. This is important since a proportion of babies who are apparently well, based on standard criteria, may be at the limit of their reserve and it was such babies that it was hoped Doppler methods would identify early.

Beattie & Dornan (1989) studied 2097 women attending their antenatal clinic at 28, 34 and 38 weeks gestation and correlated outcome with Doppler indices of umbilical flow. The best index for prediction of a baby born below the 5th weight centile for gestation was an abnormal systolic/diastolic ratio and the sensitivity obtained was only 40% with a specificity of 84%. As these authors state "other measures that show poor neonatal nutritional state.... were even less well predicted".

Berkowitz et al (1988a) studied 168 women at high risk of delivering a small-for-dates baby. Forty-two (25%) delivered a baby weighing below the 10th centile and using a systolic/diastolic ratio of 3.0 as the upper limit of normal in the third trimester obtained a sensitivity and specificity of 45% and 89% respectively. This contrasts with the study of Gaziano et al (1988), who comparing Doppler with conventional ultrasound for the identification of babies below the 10th centile, found that 79% of the small-for-dates cases had a ratio of greater than 3.0. Of these pregnancies, 7.8% were multiple and 34% were associated with fetal abnormality.

Dempster et al (1989) measured the systolic/diastolic

ratio in 205 high risk cases and found an abnormal result in only 41% of the babies below the 10th centile for gestation and in a recent report Chambers et al (1989) have shown that, in the detection of the small-for-dates, abdominal circumference measurement is more accurate than either umbilical or uterine Doppler indices. Like Reuwer et al they found that Doppler identified antenatal fetal compromise, defined as an abnormal antepartum cardiotocogram necessitating delivery.

Benson and Doubilet (1988) have reviewed tha published data on all Doppler studies of the identification of IUGR and concluded that no Doppler criteria have yet been established which permit the sensitive identification of the growth retarded fetus. They did point out that the accuracies obtained using uteroplacental and umbilical artery study have been disappointing but data from study of the fetal internal carotid and thoracic aorta are more encouraging since thay may indicate a redistribution of blood flow within the fetus.

The data from the current study would support the hypothesis that there is evidence of increased downstream impedance in the placental vessels as reflected in the statistically significant differences in umbilical artery Doppler indices in the small-for- dates fetus compared with controls. This finding need not necessarily result in abnormal umbilical Doppler indices or indicate fetal compromise. Further work on re-distribution of cardiac output within the fetal circulation is required. Because of the difficulties associated with determining end-points for

study in the small-for-dates fetus, it is suggested that controlled studies such as the one described here, be performed to determine the nature of changes in fetal haemodynamics.

Table 6.1 Outcome data for the small-for-dates and control groups.

	SFD	Controls	Significance
Maternal age	24.7 (5.5)	24.8 (5.7)	NS
Gestation at time of study	36.5 (3.0)	36.8 (2.6)	NS
Gestation at Delivery	38.6 (1.8)	39.2 (1.1)	P=0.11
Birth weight	2.42 (0.39)	3.35 (0.35)	P<0.001
Umbilical artery			
PI	1.04 (0.27)	0.88 (0.16)	P<0.02
RI	0.62 (0.10)	0.56 (0.08)	P<0.02
Uteroplacental Artery			
PI	0.52 (0.16)	0.61 (0.30)	NS
RI	0.38 (0.15)	0.39 (0.13)	NS

SFD Small-for-dates

PI Pulsatility Index

RI Resistance Index

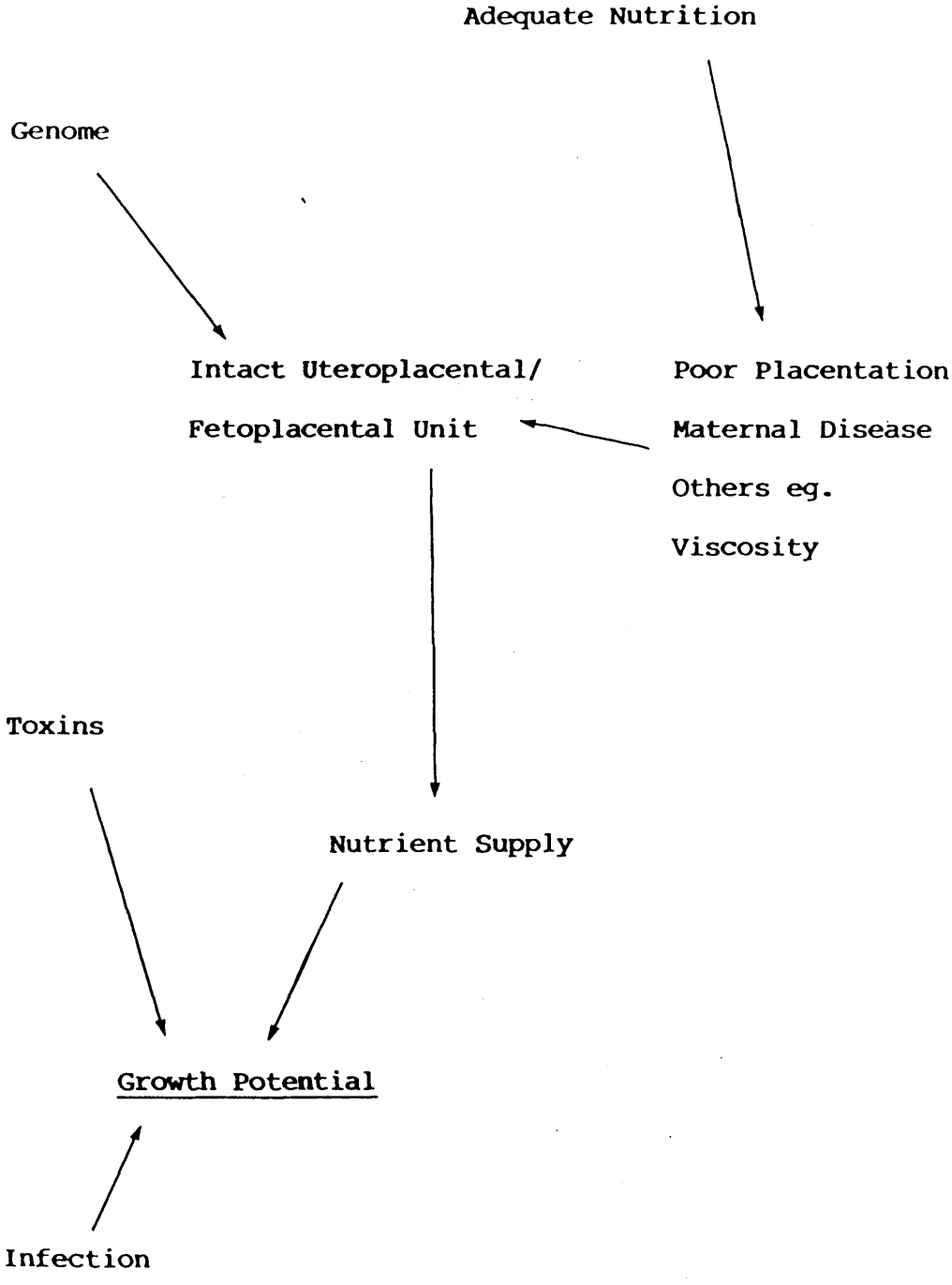


Figure 6.1 Factors influencing fetal growth and their relationships with uteroplacental and fetoplacental perfusion.

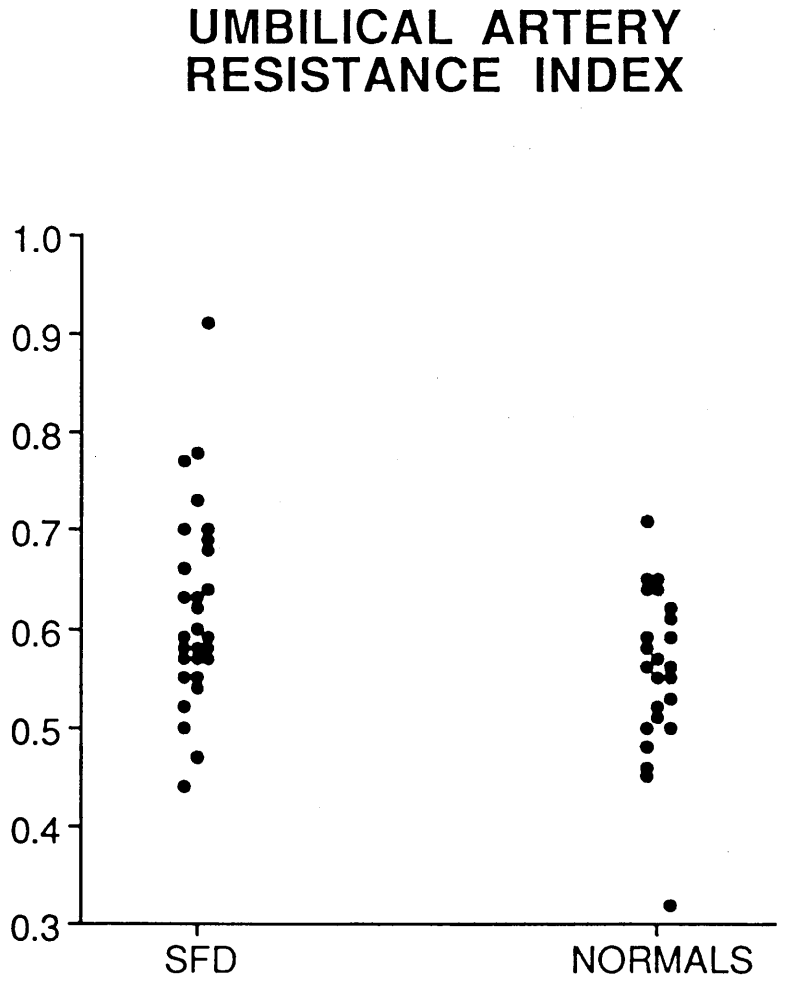


Figure 6.2 Umbilical artery resistance index in small-for-dates (SFD) and appropriately grown fetuses (normals).

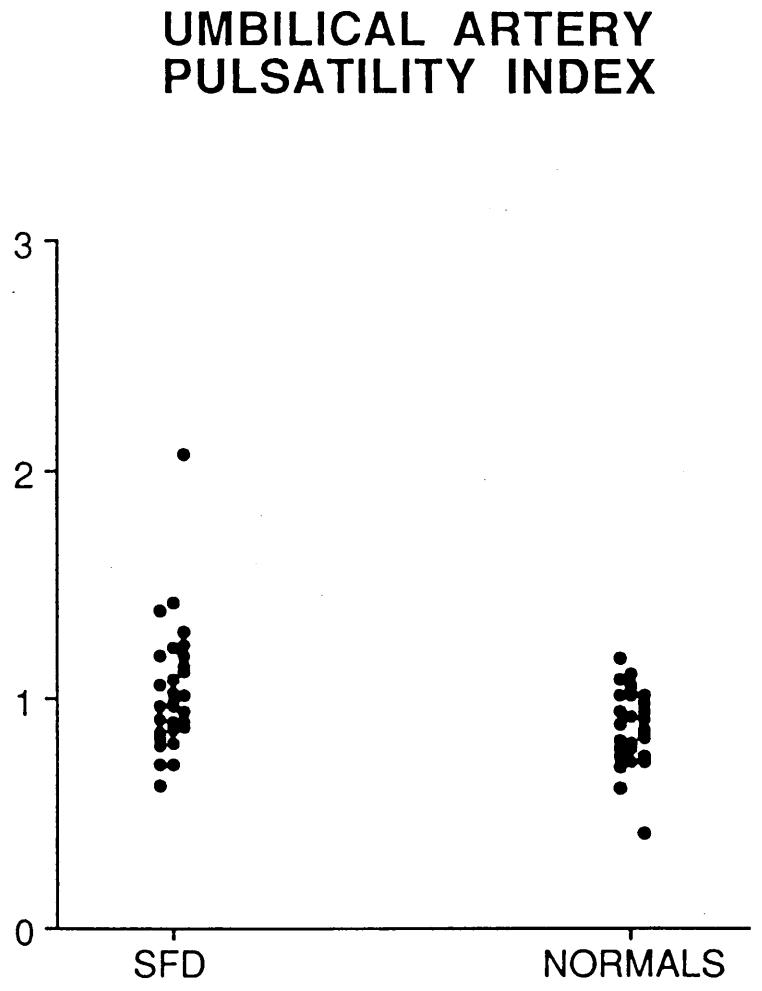


Figure 6.3 Umbilical artery pulsatility index in small-for-dates (SFD) and appropriately grown fetuses (normals).

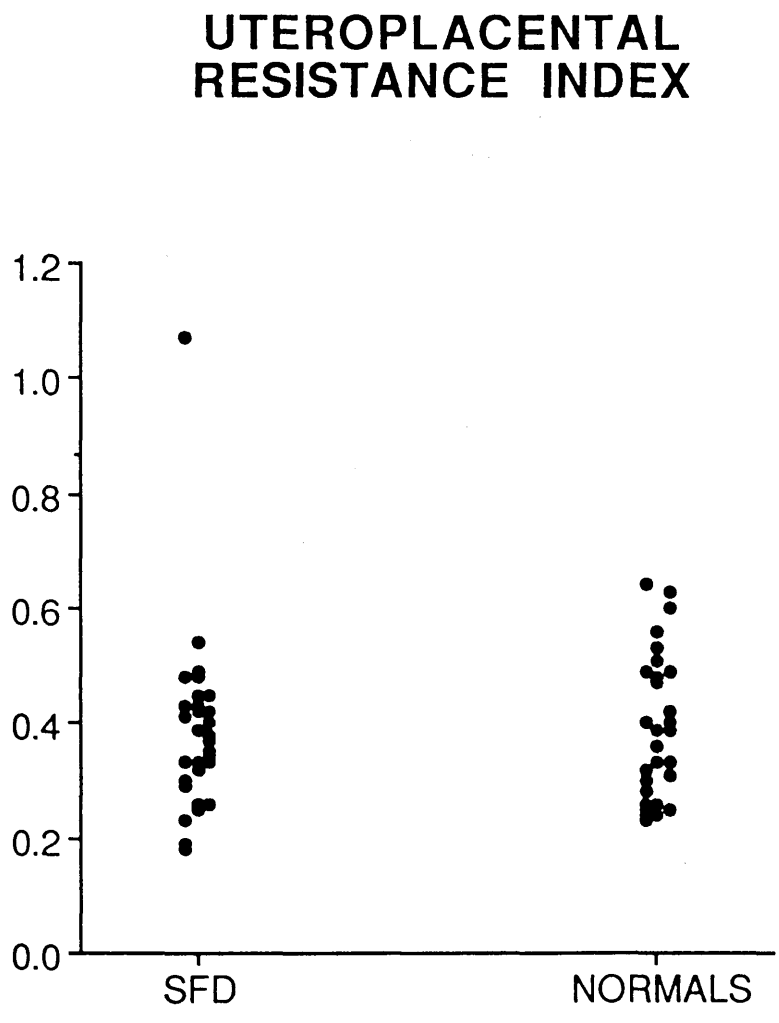


Figure 6.4 Uteroplacental artery resistance index in small-for-dates (SFD) and appropriately grown fetuses (normals).

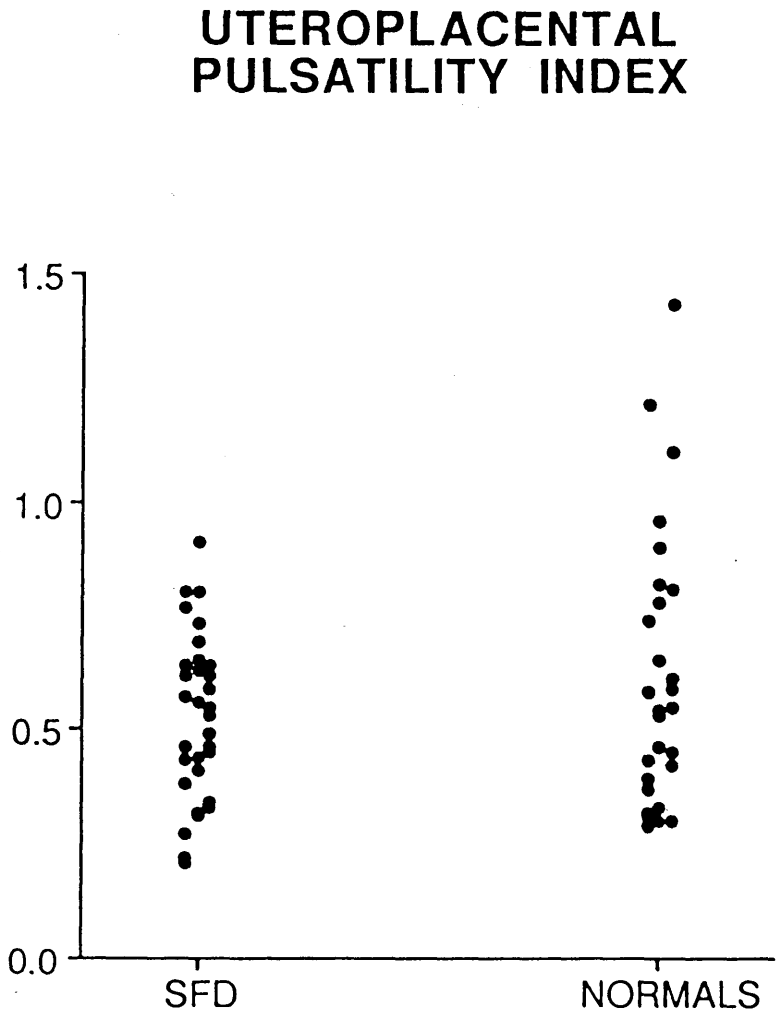


Figure 6.5 Uteroplacental artery pulsatility index in small-for-dates (SFD) and appropriately grown fetuses (normals).

Chapter 7 The effect of percutaneous umbilical blood sampling and intravascular transfusion for rhesus disease on umbilical artery flow velocity waveforms.

7.1 Blood flow and viscosity.

7.2 Doppler and rhesus disease.

7.3 Methods and patients.

7.4 Results.

7.5 Discussion.

Chapter 7

The effect of intravascular transfusion for rhesus disease on umbilical artery Doppler flow velocity waveforms.

Chapter 7.1 Blood flow and viscosity.

Although the mechanisms underlying the changes in Doppler umbilical artery waveforms in some compromised pregnancies are incompletely understood, changes in one important determinant of blood flow, blood viscosity, have been described in association with abnormal waveforms (Giles, Trudinger & Palmer 1986).

The viscosity of a liquid is the intrinsic resistance to flow which is a function of friction between its component particulate and molecular parts (Lowe 1987). From the Hagen-Pouseille equation, flow and viscosity are inversely proportional and, in general this holds for blood flow in vivo although this relationship is only strictly applicable to Newtonian fluids in linear vessels of fixed diameter. Newtonian fluids are those in which shear rate and shear stress are directly proportional. Shear stress is the force applied to a fluid layer which, in linear flow, produces movement of one layer relative to an adjacent layer. Replogle, Meiselman & Merrill (1967) have used the analogy of a deck of playing cards to describe shear stress as the horizontal force required to move a card relative to those below and the shear rate as the distance covered per second by the card relative to its neighbour. Plasma and water, being Newtonian fluids have a shear rate directly proportional to the shear stress thus viscosity remains the

same regardless of shear rate. In Non-Newtonian fluids, such as blood which is particulate, viscosity varies at different shear rates and even within the cardiovascular system shear rates vary such that blood viscosity is usually reported at high and low shear rates.

As well as shear rate, temperature, plasma viscosity, and red cell deformability and aggregation play a role in determining blood viscosity. Haematocrit is also one of the major determinants of viscosity but is independent of these factors. Because of these many elements there are methodological problems associated with measurement of fetal and neonatal whole blood viscosity (Joupilla, Kirkinen & Puukka 1986) but, since a linear increase in haematocrit is associated with a logarithmic increase in viscosity (Lowe 1987) and its measurement is independant of shear rate, the haematocrit can be used as an indirect index of viscosity at all shear rates.

A high haematocrit, such as that seen in neonatal polycythaemia, is associated with hyperviscosity syndrome with reduced blood flow and increased infant mortality (Mentzer 1978). The common associations of neonatal polycythaemia are related to increased erythropoeisis and include placental insufficiency, pre-eclampsia, chromosomal abnormality and chronic maternal lung disease. Foley, Collins & MacDonald (1983) have shown an increased haematocrit in fetuses becoming acidotic in labour, regardless of whether they were growth retarded and suggested that chronic hypoxia was the major aetiological factor in hyperviscosity. They also suggested that

measurement of fetal blood flow might identify fetuses at risk of hypoxia and acidosis.

Tenenbaum et al (1983) addressed the association between blood flow and polycythaemia and hyperviscosity in the sheep fetus. In their study of 8 chronically instrumented fetuses they induced relative polycythaemia by isovolaemic exchange transfusion and recorded a reduction in umbilical blood flow. In the human, Jouppila, Kirkinen & Puukka (1986) measured cord blood haematocrit and high shear rate viscosity in 64 fetuses who had undergone measurement of umbilical venous blood flow by Doppler ultrasound in utero. They found a significant negative correlation between umbilical venous blood flow and whole blood viscosity in babies defined by them as having chronic fetal distress.

This evidence is strongly suggestive of a role for increased blood viscosity in producing abnormal blood flow and Doppler umbilical artery waveforms and Giles, Trudinger & Palmer (1986) found a higher haematocrit in a group of 21 fetuses with abnormal umbilical artery Doppler systolic/diastolic ratios when compared with 33 fetuses in a similar high risk group but with normal waveforms.

Despite this evidence for an association between blood viscosity and fetal blood flow there is very little information about the effect of blood viscosity in isolation in utero on Doppler waveforms in the human.

A suitable model to study the effect of changes in blood viscosity on Doppler waveforms is the anaemic rhesus-affected fetus, undergoing intravascular in-utero transfusion.

Such pregnancies are not complicated by blood hyperviscosity but nevertheless large increases in blood viscosity must ensue from the elevation in haematocrit which results from transfusion. This clinical situation therefore provides an interesting therapeutic experiment with which to test the hypothesis that such an increase in viscosity should result in a change in the Doppler waveform. A number of studies have now been reported concerning Doppler indices and rhesus disease from the opposite perspective, that is, the use of Doppler to assess the severity of anaemia and to indicate the need for intrauterine treatment.

Chapter 7.2 Doppler and rhesus disease.

Cordocentesis under ultrasound guidance is currently the method of choice not only to evaluate the extent of fetal anaemia but also to provide a route for transfusion (Whittle 1989; Rodeck and Letsky 1989). This method is safer and less invasive than the fetoscopic approach (MacKenzie et al 1987) but a non-invasive method of assessing fetal condition would be clearly desirable and both Rightmire et al (1986) and Copel et al (1988) have studied fetal aortic blood velocities as a means of predicting the severity of haemolytic disease and have produced formulae relating Doppler parameters to fetal haematocrit.

Copel et al also noted a decrease in the systolic/diastolic ratio in the umbilical arteries in babies undergoing intravascular transfusion. This is of course just the opposite of what might be expected, the increase in haematocrit and hence viscosity, being anticipated to cause an increased resistance to flow and therefore an elevated

systolic/diastolic ratio. However, they did not study a group of fetuses undergoing fetal blood sampling alone and consequently the effects attributable to the cordocentesis procedure alone were disregarded. In a prospective study of the accuracy of the formulae which they had previously derived, Copel et al (1989) failed to show an association between Doppler indices and the fetal haematocrit but did nevertheless highlight the evidence supporting the effect of blood viscosity on fetal blood flow.

To determine the effect of acute changes in haematocrit and consequently, of viscosity, on fetoplacental blood flow, as assessed using Doppler velocimetry, it is necessary to compare results from cases undergoing intravascular transfusion with cases undergoing cordocentesis for other reasons. The following section describes such a study.

Chapter 7.3 Methods and patients

Flow velocity waveforms were obtained from the umbilical artery in 20 patients who underwent a total of 35 percutaneous umbilical blood sampling procedures. This was performed in 16 cases to assess the severity of rhesus haemolytic disease, and on 22 occasions intravascular transfusion was indicated by the results obtained; on three occasions blood samples were obtained to provide a rapid fetal karyotype, and in one case to determine the fetal adenosine deaminase activity.

Premedication with lorazepam, papaveretum and fentazine was used in all but three cases. Measurements were made after premedication and immediately before the procedure.

Pre-transfusion and, when possible, post-transfusion haematocrits were recorded. The systolic/diastolic ratio and fetal heart rate were measured from the umbilical artery flow velocity waveform before the procedure and one hour after beginning sampling as described in chapter 4. The systolic/diastolic ratios obtained were corrected for fetal heart rate using the formula reported by Mires et al (1987). Comparisons were made between pre and post procedure values by Wilcoxon test. The values from the transfused fetuses were compared with those who had blood sampling without transfusion, using the Mann Whitney test.

Chapter 7.4 Results.

The mean haematocrit before transfusion was 23.6 (8.7)%, and the mean increase in haematocrit was 17.1 (6.5)% (n=20) following a mean infusion of 49.2 (26) mls of packed cells. The mean percentage increase in fetal haematocrit was 103 (87)%. There was a reduction in fetal heart rate after all but 2 transfusions (mean heart rate 144 (6.8) before and 139 (8.8) at 1 hour: $p<0.03$) but no trend was observed in heart rate in the fetuses who had cordocentesis alone (mean heart rate 143 (6.7) before and 144 (9.9) at 1 hour) (Figures 7.1 and 7.2). This difference in response was significant ($p<0.04$).

Both sampled and transfused groups showed reductions in the systolic/diastolic ratio following the procedure; the corrected systolic/diastolic ratio was 3.65 (1.27) before sampling alone and 3.08 (0.8) at one hour and 3.4 (1.0) before transfusion and 2.95 (0.8) at 1 hour: ($p<0.03$ for

both groups) (Figures 7.3 and 7.4) and there was no significant difference in response between the two groups. Even when the systolic/diastolic ratio was not corrected for heart rate there was a fall in the ratio following sampling alone and a similar reduction following transfusion though this did not reach statistical significance; the uncorrected systolic/diastolic ratio before sampling alone was 3.61 (1.35) and at one hour was 3.03 (0.91) ($p<0.0.03$) and the corresponding figures for transfusion cases were 3.33 (1.05) and 2.96 (0.86) ($p=0.07$).

Chapter 7.5 Discussion.

Although Doppler velocimetry has been used in pregnancies affected by rhesus isoimmunisation to assess the need for fetal intravascular transfusion only two previously reported studies have investigated the effect of intravascular transfusion on Doppler indices. Copel et al (1988) showed a negative correlation between haematocrit and the umbilical artery systolic/diastolic ratio but did not include a group of patients who had blood sampling alone and concluded that this was of questionable clinical significance.

More recently, Weiner & Anderson (1989) studied the effects of cordocentesis with and without fetal curarisation and of intravascular transfusion on the umbilical artery waveform. They noted significant reductions in the systolic/diastolic ratio and the pulsatility index following both blood sampling alone and with transfusion. Their conclusions were limited but they suggested that, if

temporal factors could be excluded, this apparent reduction in vascular resistance was procedure-related. Unfortunately they did not initially comment on any changes in fetal heart rate related to the procedures although they mention that this could in theory have an effect on the Doppler indices.

In this study a reduction in fetal heart rates was observed following transfusion though not after sampling alone. In a subsequent report of their results on heart rate changes following cordocentesis (Weiner 1989) Weiner & Anderson also found that there was a difference in response between their transfused cases and those who underwent cordocentesis alone. The reason for this difference is not known but since a reduction in fetal heart rate might be expected possibly to increase the systolic/diastolic ratio the formula described by Mires et al (1987) was used to correct for heart rate changes. The issue of correcting the systolic/diastolic ratio for changes in fetal heart rate is contentious. In recent studies both Morrow et al (1989) and Mansouri, Gagnon & Hunse (1989) agreed that alterations in fetal heart rate affected the Doppler waveform. Morrow and colleagues felt that in clinical practice correction for heart rate was unimportant whilst recommending that correction be made when using Doppler in the research setting. Mansouri et al felt correction was required for heart rates outside the normal range. Both groups commented that the relationship between these variables may also be influenced by a change in placental vascular resistance in response to heart rate changes. Notwithstanding these observations and the fact that in all cases reported here

the fetal heart rate was in the normal range before the procedure, correction for fetal heart rate was made because of the different heart rate responses between the two groups.

This study has shown that umbilical cord blood sampling is associated with a reduction in the systolic/diastolic ratio whether or not accompanied by intravascular transfusion. However, the fetuses reported here were not representative of the polycythaemic, growth retarded, chronically hypoxic fetus which might be expected to have abnormal Doppler indices. Nevertheless it is concluded that, in the conditions of the study, an increase in haematocrit is not associated with an increase in vascular resistance to flow as detected by Doppler velocimetry. The hypothesis that a humoral vasodilator, perhaps released from the endothelium at the time of umbilical cord puncture, may play a role in controlling fetal blood flow must be investigated. Atrial natriuretic factor (ANF) and 6 keto-prostaglandin F1 alpha are known to increase following intravascular transfusion (Weiner 1989) and ANF in particular may play an important cardioregulatory role in the fetus (McQueen et al 1989; Castro et al 1989). This hypothesis requires further study.

Since cordocentesis had such a clear effect on downstream impedance the hypothesis that a change in blood viscosity alone alters waveform indices has not been ideally tested but while this also awaits further study it is suggested that these findings be considered if umbilical velocimetry is used to assess fetal well being following umbilical blood sampling or transfusion.

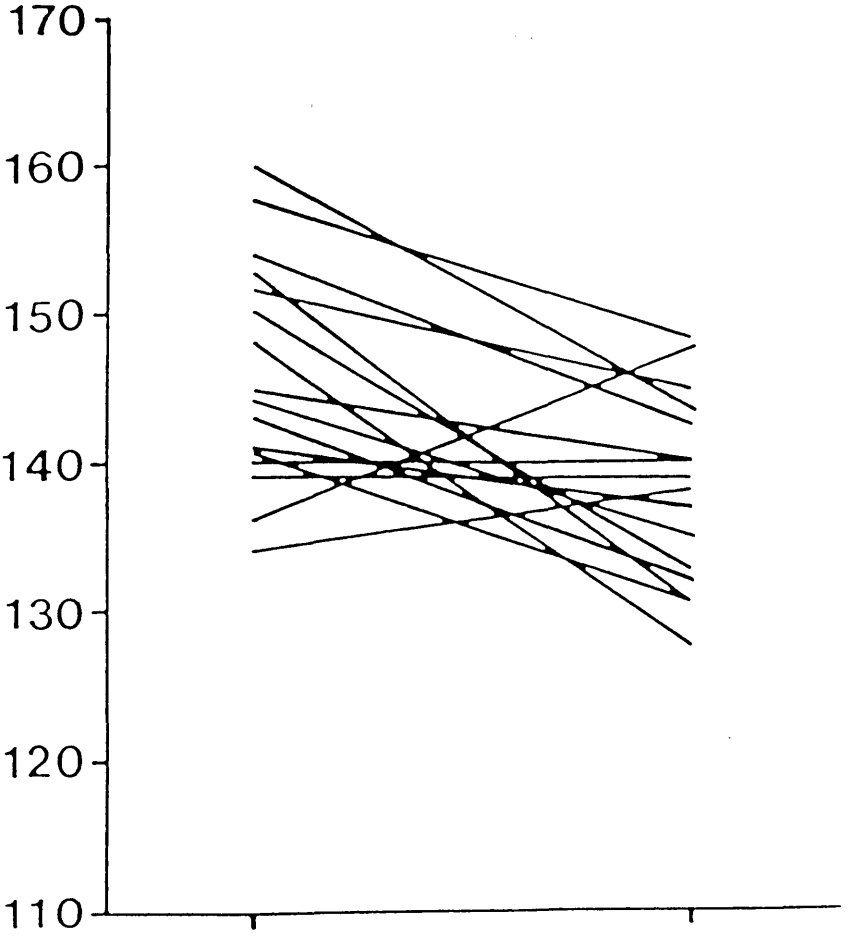


Figure 7.1 Fetal heart rates before and after intravascular transfusion.

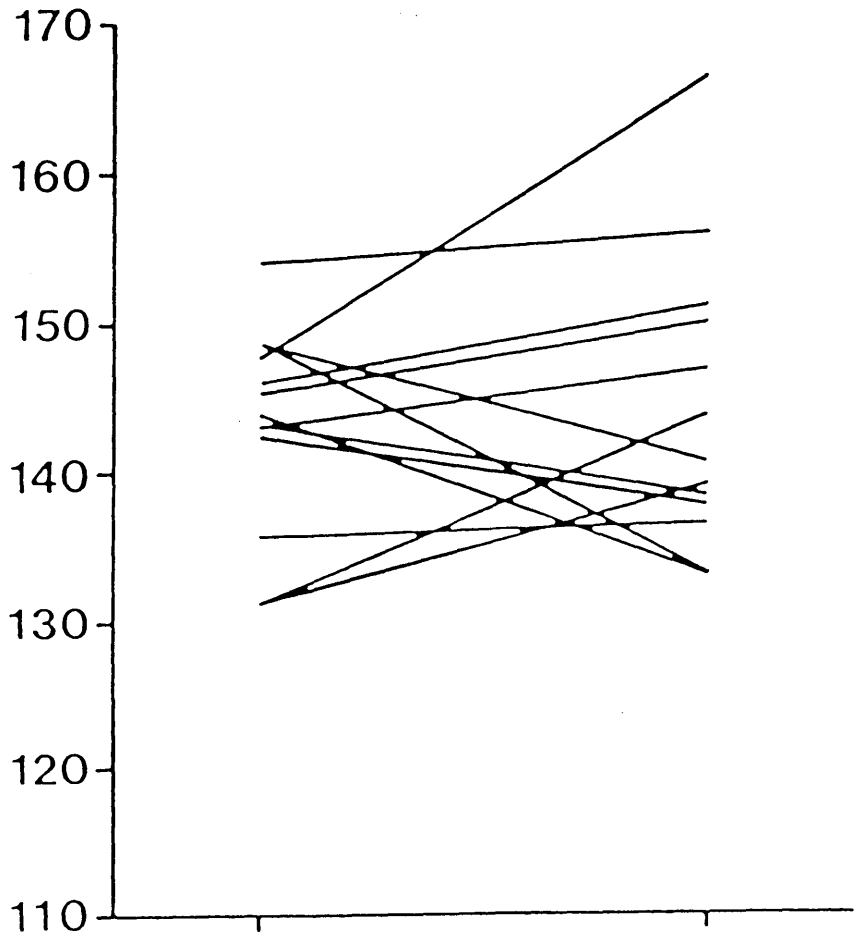


Figure 7.2 Fetal heart rates before and after fetal blood sampling alone.

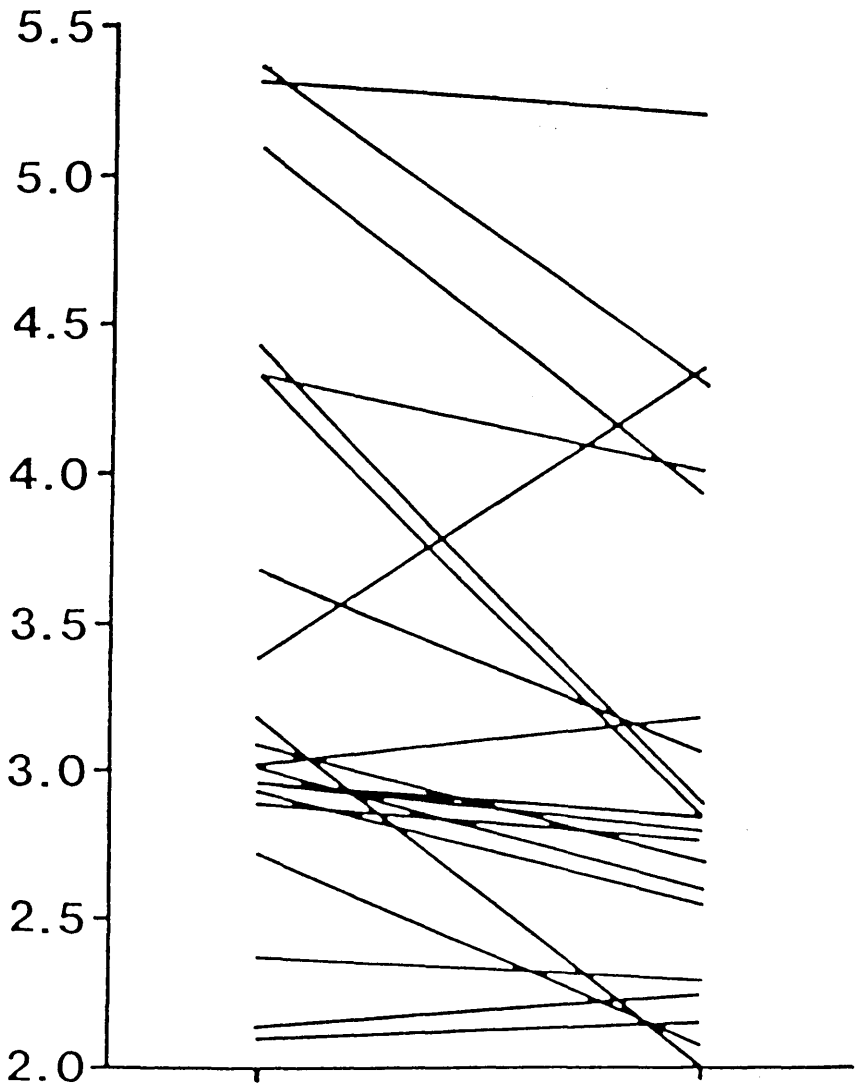


Figure 7.3 Umbilical artery systolic/diastolic ratios before and after intravascular transfusion.

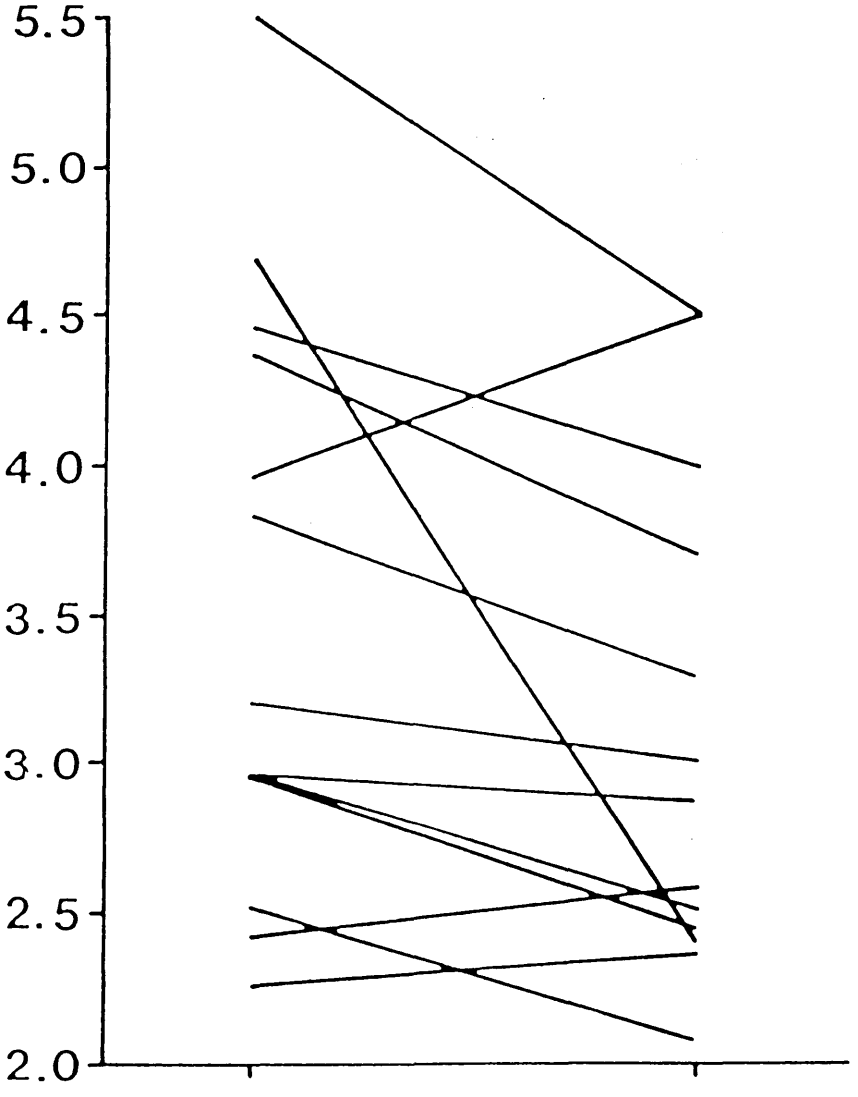


Figure 7.4 Umbilical artery systolic/diastolic ratios before and after fetal blood sampling alone.

Chapter 8 Umbilical and uteroplacental artery flow velocity waveforms in pregnancies with high maternal serum alphafetoprotein (AFP) measurements.

8.1 The clinical significance of high maternal serum AFP levels.

8.2 Methods.

8.3 Results.

8.4 Discussion.

Chapter 8

Umbilical and uteroplacental artery flow velocity waveforms in pregnancies with high maternal serum alphafetoprotein (AFP).

Chapter 8.1 The clinical significance of elevated maternal serum AFP.

Alphafetoprotein is an alpha globulin synthesised by the yolk sac and fetal liver.

Its measurement in pregnancy to screen for neural tube defect is well established but the first proposal for the use of maternal serum AFP in obstetrics was the identification of pregnancies at high risk of fetal distress and intra-uterine death (Seppalla & Ruoslahti 1972).

In the absence of fetal abnormality or multiple pregnancy, elevated levels of AFP have been associated with a number of pregnancy complications: the delivery of low birth weight babies is significantly commoner in women with high AFP levels (Brock, Barron & Jelen 1977; Wald et al 1977) and this reflects a higher incidence both of intra-uterine growth retardation (Purdie et al 1983) and premature delivery (Purdie et al 1983; Hamilton, Abdalla & Whitfield 1985). Placental abruption and pre-eclampsia are also associated with this finding (Hamilton et al 1985; Walters et al 1985). A recent study which reviewed the outcome of over 13,000 singleton pregnancies screened between 15 and 20 weeks (Milunsky et al 1989) reported relative risks of 4.0 for low birth weight and 3.0 and 2.3 for placental abruption and pre-eclampsia respectively. The

association of high levels of AFP and pre-eclampsia is particularly interesting since fetomaternal haemorrhage has been implicated in the aetiology of pre-eclampsia (Jones, McNay & Walker 1969) and it has been hypothesised that the antigenic load to the mother precipitates an abnormal immune response. The mechanism whereby AFP is elevated in these pregnancies is unclear. Fetomaternal haemorrhage has been strongly implicated since Los, De Wolf & Huisjes (1979) suggested that evidence of fetomaternal haemorrhage, demonstrated by the Kleihauer method, made amniocentesis for identification of neural tube defect in pregnancies with high AFP, unnecessary.

Abnormalities of placentation may result either in increased permeability of placental vessels to AFP or a predisposition to fetomaternal bleeding. A recent controlled study has shown an increase in placental volume, villous surface area and placental infarcts in a small series of women with high AFP levels (Boyd & Keeling 1986). Although these women had had uncomplicated pregnancies the authors suggested that high AFP levels in the absence of recognised anomalies was associated with placental lesions which may contribute to fetomaternal haemorrhage.

Salafia et al (1988) reported an association between elevated AFP levels in mid-trimester and chronic villitis in pregnancies complicated by growth retardation, suggesting that a specific lesion may be associated with high AFP levels.

High maternal AFP levels at 16 weeks gestation are associated with a high risk of PIH and IUGR and it has been

suggested that Doppler velocimetry might identify these pregnancies before the onset of clinically obvious disease.

The aim of the study presented here was to establish whether elevated maternal serum AFP in the presence of a structurally normal fetus is associated with abnormal Doppler waveforms from the uteroplacental and umbilical arteries.

Chapter 8.2 Methods.

Patients were recruited who had maternal serum AFP screening performed as part of the West of Scotland screening programme and had been referred for detailed ultrasonography following the finding of a single elevated sample, defined as one greater than two multiples of the median. Patients were excluded from study if one of the following was found:-

Threatened abortion
Multiple pregnancy
Fetal abnormality
Subchorionic haematomas
Maternal hypertension

Forty patients met the selection criteria. Doppler waveforms from the uteroplacental and umbilical arteries were obtained as described in chapter 4.

A control group of patients was recruited from women undergoing detailed ultrasonography because of past obstetric or family history, or women undergoing scanning for confirmation of gestational age. Each of the high AFP

patients was matched to within one week for gestational age with a patient in the control group.

Comparisons were made using unpaired tests as other variables could not be excluded as contributing to the variation in values obtained. Student's T test was used for parametric data and the Mann Whitney test when the data were non-parametric.

Chapter 8.3 Results.

The mean gestational age at the time of study was 19.5 (1.6) weeks in the high AFP group and 19.5 (2.3) in the controls. As a result of the matching these were not significantly different.

The mean gestation at delivery in the AFP group was 38.0 (3.2) weeks and in the control group was 39.1 (1.3) weeks $t=1.96$, $p=0.05$). The birth weights were 3.08 (0.6) Kg and 3.52 (0.55) Kg in the same groups respectively ($t=3.46$, $p<0.001$).

Table 8.1 summarises the outcomes in the pregnancies studied. Complications were significantly commoner in the high AFP group.

The mean umbilical artery pulsatility index was 1.48 (0.34) and was not significantly different from the control group value of 1.44 (0.39). The resistance index was 0.79 (0.07) and 0.76 (0.07) for the same groups and were again not significantly different.

Similarly, the mean uteroplacental pulsatility index was 0.64 (0.42) and 0.63 (0.62) in the AFP and control groups respectively and were not different. The resistance index in

these vessels for the same groups were 0.40 (0.12) and 0.39 (0.14) and again were not significantly different. These values are within the normal limits described for the gestation of study by Pearce et al (1988).

Chapter 8.4 Discussion.

Normal placentation, in particular the invasion of cytotrophoblast into the maternal spiral arteries to convert them into low resistance vessels, begins as early as 12 weeks gestation and is well established in the second trimester. Theoretically, therefore Doppler methods could identify pregnancies at high risk of developing the sort of complications characterised by failure of this mechanism, such as IUGR and PIH (Campbell et al 1986).

The study presented here has utilised the recognised association between high maternal serum AFP levels and later pregnancy complications. Uteroplacental waveforms were similar in both groups and the possible reasons for this are discussed in chapter 2. The work of Campbell et al (1986) is yet to be substantiated by other workers and although the evidence is strongly suggestive, there are no convincing data that uteroplacental perfusion is already compromised early in pregnancies destined to be complicated. An alternative hypothesis is that although there are anatomical differences in the uteroplacental vasculature at delivery between complicated cases and normal pregnancy, perfusion and function may be maintained until the latter weeks of pregnancy, when, as shown by radioisotope methods, perfusion may fall below normal.

It is not surprising if this latter hypothesis is correct, to find no difference in umbilical artery waveforms in early pregnancy. Another possibility, which requires further study, is that the measurements were obtained before spiral artery invasion by trophoblast was completed in either group. A study performed at 24 to 26 weeks gestation should establish whether this factor played a role. Unfortunately since many of the patients in the present study were referred for detailed ultrasonography from elsewhere follow-up throughout pregnancy was not possible.

The hypothesis that elevation of maternal serum AFP might be associated with a placental lesion identifiable between 16 and 24 weeks gestation using Doppler ultrasound is rejected.

This study does add further support to the previous studies showing the value of AFP estimation as an indicator of later complications but does not support the use of Doppler in early pregnancy screening for later complications.

Table 8.1 Complications occuring in the high AFP and control groups.

	High AFP	Controls
Pregnancy induced hypertension	5	3
Small for dates fetus	4	1
Premature labour	6	1
Intra-uterine death	1	0
Total complication	16 (40%)	5 (12.5%)

CHI squared = 6.46, $p<0.02$

Chapter 9 The use of Doppler velocimetry in developmental pharmacology.

Chapter 9

The use of Doppler in developmental pharmacology.

Knowledge of the haemodynamic effects of maternally administered drugs on the uteroplacental and fetoplacental circulations has been hindered by inaccessibility and, until recently, human developmental pharmacology has relied on extrapolation from animal studies. Since human placentation differs radically from most animal models there is a need for a technique which can readily be applied in humans. Furthermore, since our understanding of fetal cardiovascular physiology has previously been based on the invasive techniques discussed in chapter 2, the development of Doppler methods has provided a safe and repeatable method of studying fetal cardiovascular physiology in continuing pregnancies.

Recent advances in instrumentation now permit detailed study of vessels within the fetus as well as the umbilical artery and afford opportunities for the safe study of drug induced changes within the fetal cardiovascular system.

Interest in the use of Doppler in human developmental pharmacology has thus far been directed at the aorta, intra-abdominal part of the umbilical vein and the umbilical artery and whilst the studies described here are limited to the umbilical and uteroplacental arteries the potential effects of drugs on other vessels must also be considered.

Fetal Aorta

Antihypertensives

The linear nature of the fetal aorta and its easy visualisation make it suitable for both quantitative and qualitative assessment of blood flow. Montan et al (1987) have recently reported their findings in 14 patients with pregnancy induced hypertension who received either 50 or 100mgs of the selective beta blocker, atenolol. This drug is of interest since, in the compromised sheep fetus beta blockers have been associated with hypoxia. Patients were studied before treatment and after one and three days. The mean volume flow of 224mls/minute before treatment was no different from the mean values of 238 and 227 mls/minute obtained after treatment. Interestingly, a significant increase in the pulsatility index in the aorta was seen after atenolol which, it was suggested, was an adverse effect. which may represent a redistribution of fetal blood flow secondary to changes in peripheral resistance. However, since each patient acted as her own control interpretation of the study is difficult although it does demonstrate the feasibility of using Doppler ultrasound as a tool in the evaluation of antihypertensives in pregnancy.

Analgesia

Lindblad, Bernow & Marsal (1987) studied the effect of different methods of analgesia on fetal aortic velocities in labour. A reduction in velocities was seen following pethidine but not after epidural anaesthesia when an increase similar to the physiological changes seen in labour was observed.

Newer, more controversial therapies have also been evaluated using Doppler velocimetry. Nicolaides et al (1987) have shown an increase in aortic blood velocity associated with the administration of oxygen by face mask to the mothers of severely growth retarded fetuses. It is tempting to speculate that this finding reflects improved tissue perfusion but it awaits confirmation in larger controlled studies.

In addition to studying possible therapies, Doppler ultrasound has been used to investigate the effect of cigarette smoking. Eriksen & Marsal (1987) have shown a transient increase in fetal central circulation following the smoking of one cigarette and have suggested that this effect is dose related to nicotine content.

Umbilical Vein

Like the aorta, the intra-abdominal part of the umbilical vein is suitable for volume studies. Jouppila et al (1985a) have investigated the effect of the vasodilator, dihydrallazine, on the umbilical circulation. They showed an increase in umbilical venous flow, suggesting for the first time that this agent can cause dilatation of the umbilical vein.

The same group have also shown a correlation between levels of 6 keto PGF1 alpha, a metabolite of the potent vasodilator prostacyclin, and umbilical venous blood flow. In a further report (1985b) of a study to determine if exogenous prostacyclin administered intravenously to the mother affected umbilical flow no such effect was seen despite an increase in maternal levels of metabolites and a

significant reduction in blood pressure.

Umbilical venous blood flow has also been studied in patients receiving beta mimetics (Jouppila et al 1985c) which are widely used in the management of premature labour. Ritodrine, the most commonly used tocolytic in this class of drugs appears to have no effect on umbilical blood flow but as the fetal levels are only 2 to 3 percent of maternal concentrations this finding is not too surprising. Absence of an adverse effect is nevertheless re-assuring.

Umbilical Artery

Although qualitative assessment of the umbilical artery waveform can be made using relatively inexpensive equipment and this has been the most extensively studied vessel, data on drug effects are limited. Montan et al (1987) showed no difference in waveforms following atenolol when compared to pretreatment values. There is however surprisingly little information on other antihypertensives and their effects.

The effects of regional anaesthesia on the umbilical artery have been studied. Giles, Lah & Trudinger (1987) have shown a reduction in the systolic/diastolic ratio following epidural administration of bupivicaine and suggested that this represented an improvement in perfusion.

A major limitation of these studies and one which will be discussed in later chapters is the interpretation of drug induced changes in the umbilical artery flow velocity waveform. Since drugs are only administered when there is a disease process it seems possible that there may be some degree of fetal compromise. Thus apparent improvements in the umbilical artery waveform pattern, as indicated by a

lower systolic/diastolic ratio, may not reflect possible adverse changes in other parts of the fetal circulation; an increase in fetoplacental perfusion, demonstrated by a reduction in umbilical artery systolic/diastolic ratios, may possibly be associated with a general reduction in visceral blood flow and cerebral perfusion may in particular be compromised.

However, now that it is possible to study the fetal cerebral vasculature with Doppler (Arbeille et al 1987) this problem of interpretation may soon be resolved.

From another perspective, the proposal that umbilical artery velocimetry will be a useful adjunct in fetal assessment must take into account the possibility of drug effects on the waveforms; this is similar to the requirement for knowledge of drug affects on cardiotocography for adequate interpretation of fetal heart rate patterns (Wood & Dobbie 1989).

The uteroplacental circulation

Antihypertensives

Obstetricians have been traditionally concerned that antihypertensive treatment might adversely affect an already compromised pregnancy complicated by hypertension. This anxiety was supported by the initial radioisotope studies of the uteroplacental circulation by by Dixon, Browne & Davey (1963) although later work by Lunell et al (1983) and Jouppila et al (1985a) using Indium 113 and Xenon 133 respectively failed to support the view that significant changes in uteroplacental blood flow occurred despite

showing a reduction in blood pressure following intravenous dihydrallazine infusion.

Montan et al (1987) did however show an increase in uteroplacental pulsatility index, which implied an increased vascular resistance, in seven patients who received atenolol for hypertension in pregnancy.

Beta mimetics

Brar et al (1988) have shown a significant reduction in vascular resistance in the uterine vessels which they attributed to the use of ritodrine. This observation was associated with an increase in maternal heart rate and it seems likely therefore that volume blood flow to the uterus was significantly increased.

Epidural Anaesthesia

The increasing use of conductive anaesthesia in labour has led to concern that haemodynamic changes associated with its use might affect uterine blood flow. The results of Doppler studies have been conflicting: Giles, Lah & Trudinger (1987) found that epidural anaesthesia for elective caesarean section improved uteroplacental perfusion although in a more recent report Long, Price & Spencer (1988) found no change in uteroplacental perfusion in the absence of maternal hypotension.

It seems likely that the uteroplacental blood supply remains remarkably resistant to drug induced changes and that locally active factors are responsible. The limitations of Doppler studies of the uteroplacental vessels have already been discussed. As previously mentioned the technique examines the uteroplacental vessels with the

lowest resistance, essential when using a continuous wave system (Hanretty, Whittle & Rubin 1988). High resistance vessels which are diseased and atheromatous may be found in PIH and are presumably less capable of responding to potential drug induced changes. It is possible therefore that important actions of antihypertensive agents will relate to alterations in perfusion pressure effects and vascular resistance in the non-diseased low resistance vessels. Two studies will now be described in the following chapters, which investigate the effects of two antihypertensive agents, atenolol and nifedipine, on Doppler uteroplacental and umbilical artery waveforms.

Chapter 10 Effect of established therapy with the beta blocker, atenolol, given for pregnancy induced hypertension on umbilical and uteroplacental artery flow velocity waveforms.

10.1 Drug therapy of pregnancy induced hypertension.

10.2 Pharmacology of atenolol.

10.3 Methods.

10.4 Results.

10.5 Discussion.

Chapter 10

Effect of established therapy with the beta blocker atenolol, for pregnancy induced hypertension on uteroplacental and umbilical artery flow velocity waveforms.

Chapter 10.1 Drug therapy in the management of PIH.

The question of how best to manage pregnancies complicated by hypertension generates "strongly held views" (Rubin 1986) which are far from dispassionate. They centre on the role of antihypertensives in the haemodynamically stable woman with pregnancy induced hypertension and are based often on personal experience or anecdote. There is very little substantial evidence in the literature justifying the use of antihypertensive treatment in mild or moderate PIH. The available studies have usually only compared one agent against another and there have been few placebo controlled studies. Nevertheless there are some data concerning the outcome of hypertensive pregnancies managed without the use of specific antihypertensive medication.

The definitive treatment of PIH is delivery and studies have aimed to reduce the need for this intervention without compromising maternal or fetal wellbeing. Andersen & Herbert (1977) had this intention in their study of 259 cases of pre-eclampsia and eclampsia in which all but two received phenobarbitol and sixty-five percent magnesium sulphate. The uncorrected perinatal mortality rate in their series was 7%.

Whilst these treatments are not antihypertensive, the

approach is far from being conservative in terms of drug administration. Hauth, Cunningham & Whalley (1976) in a study of 346 nulliparous hypertensive women used no drug therapy, with the exception of iron supplementation. This approach, which entailed intensive maternal and fetal supervision, produced excellent results with a perinatal mortality rate of 9 per thousand which compared favourably with that of the then current rate of 29 per thousand in the general obstetric population of that centre.

The use of antihypertensives has always been controversial because of the theoretical risk of reducing uteroplacental perfusion with antihypertensives and many obstetricians avoided their use (De Swiet 1985).

Redman et al (1976) attempted to answer the problem by comparing two groups of hypertensive pregnant women, one on specific antihypertensive treatment and the other receiving only standard obstetric care. In this study those receiving methyldopa, which was the antihypertensive used, had an improved outcome compared with the untreated cases.

The study, whilst leading the way in assessing antihypertensives in pregnancy was in retrospect, seriously flawed. The entry criteria did not allow classification into pregnancy induced or chronic hypertension and the outcome was not known for all patients recruited into the study. Most importantly, the obstetric management was determined by obstetricians who were aware of those patients receiving drug treatment. This does not, however, exclude a beneficial effect of treatment since the better outcome in the treated group was a result of fewer mid trimester abortions and not

of a reduction in the number of women developing pre-eclampsia.

Leather et al (1967) had also used methyldopa but in combination with bendrofluazide in a randomised open trial. Though they showed some benefit, interpretation of their data is limited by the sub group analyses which were performed (Fletcher & Bulpitt 1988).

The conclusions and recommendations by these authors were valuable and justifiable but unfortunately these studies lacked a placebo control group. Nevertheless the lack of adverse effect was reassuring and coupled with the apparent improvement in outcome prompted further studies comparing methyldopa with newer therapies.

In a small pilot study Lamming & Symonds (1979) showed better blood pressure control with labetolol when compared with methyldopa and showed it also to be of value in the acute situation and this has also been shown by Walker, Greer & Calder (1983) when comparing this drug with hydralazine which is the accepted therapy under these circumstances. The role of therapy in the management of acute severe hypertension will be discussed further in chapter 11.

Other beta blockers have been compared with methyldopa and Gallery et al (1979) showed a better outcome in terms of birth weight in oxprenolol treated babies compared with methyldopa but the inclusion criteria invalidated any attempt to classify the type of hypertension being treated. The 'improvement' in birth weight in the oxprenolol patients might also be explained by the relatively low birth weight

in the methyldopa group which was not a finding in other studies and for which the explanation remains unclear.

Fidler et al (1983) in a similar study using identical entry criteria showed no advantage of beta blockade over methyldopa which remains the drug of first choice of therapy (de Swiet 1985) because of the reassurance given by prolonged paediatric follow up. Nevertheless these studies did enlarge upon the evidence supporting the use of beta blockade in pregnancy which hitherto had been characterised by poorly controlled studies.

Furthermore, the lack of careful definition and classification of hypertensive disease in these studies limits their relevance and interpretation. Studies of newer therapies are required although unfortunately there is a lack of adequately controlled studies. Thus Sibai et al (1987), comparing the effect of labetolol with hospitalisation against hospitalisation alone for the treatment of early onset pre-eclampsia found a higher incidence of small-for-dates fetuses, coupled with a reduction in platelet count in the labetolol group. These data conflicted with the results obtained by Walker et al (1982) who, in a similar open study showed no adverse maternal or fetal effect and suggested a beneficial effect related to a reduction in platelet aggregation posssibly secondary to a promotion of prostacyclin production.

A more recent study (Plouin et al 1988) compared labetolol and methyldopa with inclusion criteria similar to those of Fidler et al and Gallery et al but with the objective of determining whether differing cardiorespiratory

effects on the fetus and newborn were produced. They found no differences between groups.

In summary, it is difficult to draw conclusions from these studies because of the poor definition of the hypertensive groups studied, the lack of adequate study designs, the various drugs used and a non-uniformity of outcome parameters. Nevertheless all of these studies have shown that antihypertensive therapy is effective in reducing blood pressure in pregnancies complicated by hypertension. However, the issue of adverse effects cannot be resolved without adequate placebo controlled trials and there are only three such studies which have been of sufficient power to show a benefit of treatment to the fetus.

Rubin et al (1983a) performed the first of these studies to determine if atenolol, a beta 1 selective blocker, was of value in improving the maternal and fetal outcome in pregnancy induced hypertension. Since the routine approach in managing such patients in their centre was non-pharmacological this justified a placebo controlled trial. One hundred and twenty patients who met the following criteria were studied:- systolic blood pressure between 140 and 170 mmHg or diastolic blood pressure between 90 and 110mmHg on two occasions 24 hours apart during the third trimester in women with previously uncomplicated pregnancies. Data were complete for 39 women in the placebo group and 46 in the atenolol group. Data were analysed where appropriate on an intention to treat basis.

Proteinuria developed in fewer atenolol treated cases (3) than controls (10). All cases of respiratory distress

syndrome occurred in placebo treated cases. Atenolol treated mothers were less likely to be re-admitted to hospital before the onset of labour. Babies in the atenolol group had lower heart rates but this was not associated with any other adverse effect.

In a subsequent report (Rubin et al 1984) the obstetric aspects of the use of atenolol were examined. The effect of treatment on uric acid, platelet count, urinary oestriol and human placental lactogen were assessed since changes in laboratory indices of disease progression could alter management. Antepartum cardiotocography was also investigated.

Only human placental lactogen was significantly different, being lower in the treated compared with control cases and the explanation was unclear. The authors concluded that, given the weight of evidence in support of beneficial outcome with atenolol that this finding was not relevant as an indicator of fetal compromise. However, the interpretation, clinically, of drug induced changes in biochemical, or biophysical, parameters used in the assessment of fetal wellbeing is of obvious importance to clinical practice.

Many claims have been made for labetolol and advantages it may have over atenolol in improving outcome (Walker et al 1982) but only one study has investigated its use in a randomised placebo controlled double blind study. Pickles, Symonds & Broughton-Pipkin (1989) in their study of 70 treated and 74 control cases concluded that labetolol may have possible advantages over non-pharmacological treatment.

This interpretation might be a little over optimistic since there were no significant differences in fetal outcome between the treated and untreated cases. There were twice the number of babies born below the tenth centile in the labetolol group (10) compared with controls but this did not reach statistical significance and was attributed to the chance recruitment of babies who were already small to the treatment group. The same ratio, 2 to 1, was seen in cases of jaundice although in this case with the lesser number in the labetolol group. This was interpreted as showing a biological advantage of treatment.

Wichman et al (1984) in their study of metoprolol versus placebo demonstrated no difference in fetal outcome between groups. They did show, however, a higher incidence of bradycardia in treated infants.

There was no difference in the overall incidence of proteinuric preeclampsia, 6 of 26 women in each group being defined as such.

On average, treated babies were 262g lighter than controls and most studies of drug treatment versus non-drug treatment have shown lower mean bith weights in treated cases.

Fletcher and Bulpitt (1988) have suggested that this may reflect either a treatment specific effect on fetal growth or improved survival in the treated cases born at an earlier gestational age. Whilst these authors state that their review leads them to believe that there is a clear case for antihypertensive treatment in pregnancies complicated by hypertension they also conclude by mentioning that adverse

effects of treatments must be considered and that these may only be detectable in large trials.

An important finding in two of these three studies has been of smaller babies in treated cases compared with controls. Consequently, although the original study by Rubin et al was re-assuring, further studies must be performed.

Doppler velocimetry can now be used to study potential adverse effects of treatment on fetoplacental and uteroplacental blood flow. Furthermore, since it has been suggested that Doppler velocimetry may be of value in assessing high risk pregnancy (Trudinger et al 1987b) the effects of drugs on Doppler waveforms must be known for the proper use of this technique as a method of assessing fetal wellbeing.

Chapter 10.2 The pharmacology of atenolol.

Atenolol is a hydrophilic selective Beta 1 adrenoreceptor blocker which has been widely and successfully used in non-obstetric hypertension. It is rapidly absorbed orally and maximum concentrations are reached within 2 to 4 hours. The elimination half life is between 6 and 9 hours in non-pregnant subjects (Johnsson & Regardh 1976).

Transplacental passage of atenolol was further confirmed by Melander et al (1978). who calculated a maternal/fetal serum concentration ratio of 1.13 suggesting that during steady state conditions blood levels were similar in mother and fetus. In one patient who withdrew from their study 24 hours before delivery there was no detectable atenolol in

maternal or fetal serum suggesting rapid clearance and lack of accumulation in the fetal circulation.

The remainder of this chapter describes a study to determine the effect of atenolol on uteroplacental and umbilical artery Doppler flow velocity waveforms in patients who had been established on atenolol treatment for PIH and were presumed to be in a pharmacologically steady state.

Chapter 10.3 Methods.

The effect of atenolol on uteroplacental and umbilical artery flow velocity waveforms was studied in ten patients treated with 50 or 100mg given orally for pregnancy induced hypertension

Eight patients were studied before treatment and after treatment had been established for between 6 and 7 days. A further 2 women were studied after treatment was established. In all cases the gestation was reliably known from menstrual dates and ultrasound examination in the first trimester. All patients met the criteria for diagnosis of pregnancy induced hypertension mentioned in chapter 3.

The maternal pulse, fetal heart rate, uteroplacental and umbilical artery flow velocity waveforms were obtained as previously described. Blood pressure was measured using an automatic sphygmomanometer. The pulsatility index and resistance index were measured in both circulations following at least 20 minutes rest in the semi-recumbent position.

The same measurements were repeated after treatment was established. There was no deterioration in the clinical

state of any of the cases studied over the treatment period.

Comparisons were made between measurements obtained before and after treatment. The results from these ten patients were also compared with those obtained from ten women who also met the inclusion criteria for the study but who, because of variations in the practice of treating PIH within the hospital, did not receive drug treatment. Though this method of recruitment is clearly not random these patients have been selected as untreated controls and were matched for maternal and gestational age. There was no difference in the disease severity between the untreated group and treated groups at the time of recruitment.

Chapter 10.4 Results.

The mean maternal age was 27.4 (5.5) years for the treated group and 26.2 (4.8) in the untreated cases ($p>0.5$) The gestation at recruitment was 33.1 (2.2) weeks in the atenolol group. The gestation at study following establishment of treatment was 34.0 (1.8) weeks and was the same in the untreated cases (34.0 (2.1) weeks).

The effects of treatment: Indices before and after atenolol.

Figures 10.1-10.7 illustrate the changes following treatment in the parameters studied. There were statistically significant reductions in systolic and diastolic blood pressure ($p<0.02$) but there was no apparent effect on uteroplacental or umbilical artery Doppler indices. There was a mean reduction in fetal heart rate of 7.4 (11.3) beats per minute which did not reach statistical

significance.

Effects of treatment: comparison with controls.

Figures 10.8-10.14 show comparisons between the variables for the ten treated and untreated cases. There was no difference in Doppler indices between groups although fetal heart rates were lower in the atenolol treated group (138 (8.6)bpm versus 146 (6.7)bpm: p=0.032).

For the reasons discussed in chapter 7 it was thought prudent to correct for fetal heart rate in comparing the treated and untreated cases by converting the resistance index to systolic/diastolic ratio and then using the formula of Mires et al. as described in chapter 7. Although there was no significant difference in heart rate before and after treatment in the atenolol group this analysis was also performed. The mean corrected systolic/diastolic ratio before treatment, 3.91 (2.5), was not significantly different from the value of 3.12 (1.1) obtained after treatment (p> 0.38).

Similarly, this last value was not different from the corrected systolic/diastolic ratio in the untreated cases of 3.85 (2.5).

Although there was no change overall in Doppler indices before and after treatment, one patient had absent end diastolic flow, a finding which has been associated with a poor fetal or neonatal prognosis (Woo, Liang & Lo 1987; Hsieh et al 1988). Absent end diastolic velocity was detected immediately before starting atenolol treatment and a resistance index value of 1.0 obtained. The patient was a twenty-nine year old primigravida who required treatment for

PIH at 29 weeks gestation. Doppler studies were repeated on the 6th day of treatment when flow throughout the cardiac cycle was observed; the resistance index was 0.77 (see figure 10.4). Despite the return of normal diastolic flow velocities the clinical condition continued to deteriorate , something which has not previously been described (Hanretty, Whittle & Rubin 1988c). Delivery became necessary in the fetal interest after 2 weeks of treatment although the waveform remained entirely normal until delivery.

This observation raises the possibility that, in cases in which blood flow distribution is already altered, treatment may apparently produce a result which masks the underlying problem.

Nevertheless, the lack of any overall effect of treatment on umbilical artery waveform indices is very reassuring and suggests that no major adaptive mechanisms are influenced by treatment with atenolol. The lack of any effect on maternal waveform indices suggests that diastolic flow in the normally adapted spiral arteries are not influenced by reductions in blood pressure.

Chapter 10.5 Discussion.

This study, which was open and comparative, was designed to evaluate the effects of an antihypertensive medication on Doppler flow velocity waveforms. It failed to show any difference between treated and untreated cases. This suggests that there is no alteration in fetal and uteroplacental haemodynamics following treatment with atenolol. Possibly in the already compromised fetus

some change might occur. This possibility requires further study. Interpretation of the study reported here is obviously limited by its open nature and the non-random prospective allocation of patients. The lack of a uniform approach to the pharmacological treatment of pregnancy induced hypertension in the unit did however permit a form of 'random' allocation insofar as patients were assigned randomly to consultants with different approaches to the value of drug treatment.

One other study, that of Montan et al (1987) has investigated the effects of atenolol on maternal and fetal Doppler waveforms. In their study, increases in the pulsatility index were described in the uteroplacental vessels in the 7 cases in which this was studied. In the 8 cases in which the umbilical artery waveform was studied no change was seen although there was a significant increase in fetal aortic pulsatility index. Interestingly, volume flow in the fetal aorta was not altered and the suggestion was made that the change in qualitative flow represented a differential vasoconstrictor effect on fetal arterioles which was not matched in the umbilical artery. It is not clear in the paper if there was any deterioration in the clinical condition or disease progression over the study period, although some patients were delivered between day 1 and day 3 of the study.

The cases presented in the current study were clinically stable and Doppler indices were no different after treatment and similar to those obtained from untreated cases. The study by Montan et al lacked any comparative group other

than the treated cases themselves.

Under the conditions of this study atenolol has no effect on Doppler uteroplacental and umbilical artery Doppler waveforms. In patients with previously normal waveforms changes in such waveforms seen in treated cases might be attributable to a deteriorating maternal or fetal condition. In patients with abnormal waveforms, who may already have some redistribution of fetal blood flow, the finding of a normal umbilical artery waveform following the onset of treatment should not be considered as necessarily indicating fetal wellbeing.

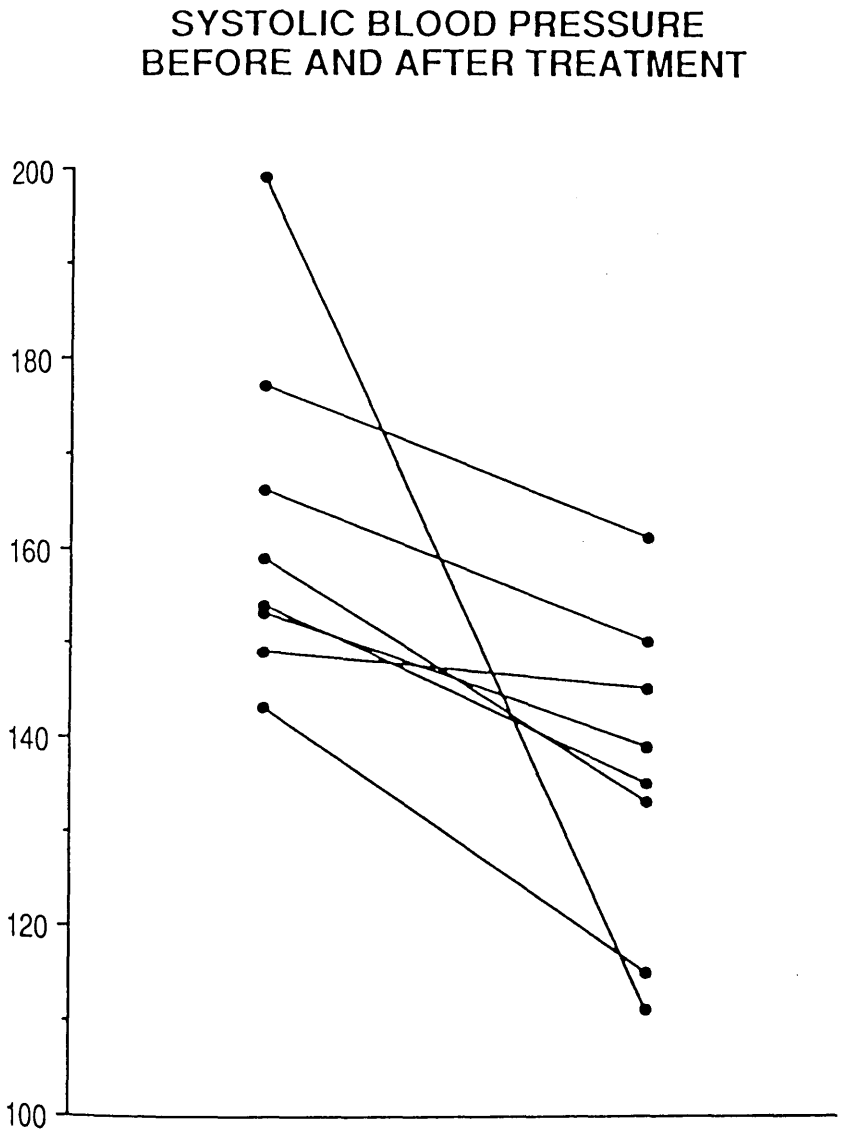


Figure 10.1 Systolic blood pressure before and after establishment of therapy with atenolol.

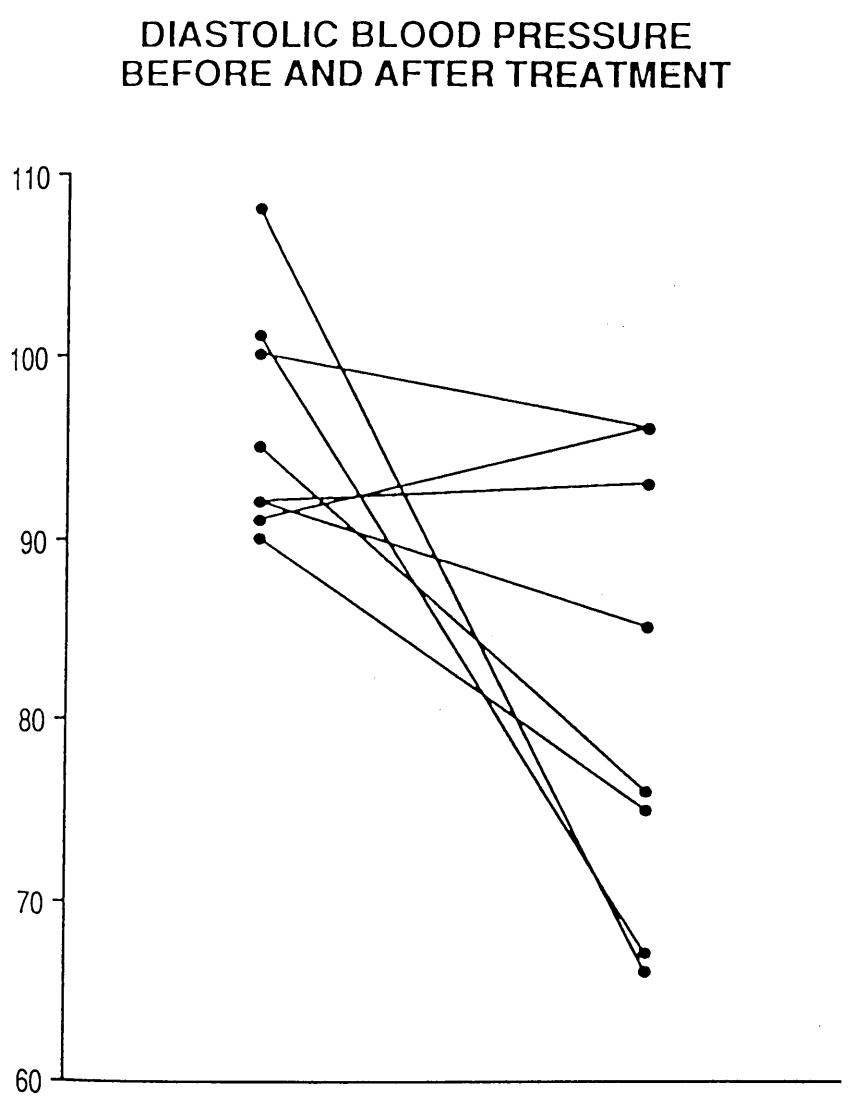


Figure 10.2 Diastolic blood pressure before and after establishment of therapy with atenolol.

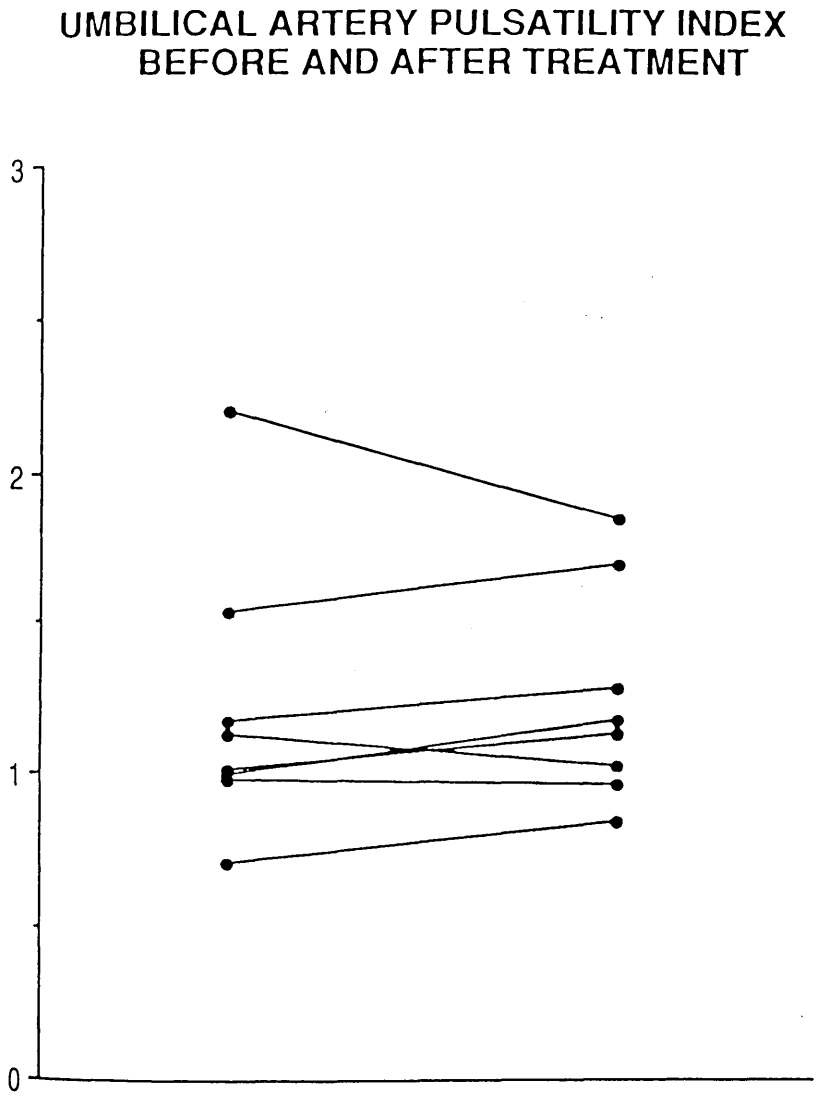


Figure 10.3 Umbilical artery pulsatility index before and after establishment of therapy with atenolol.

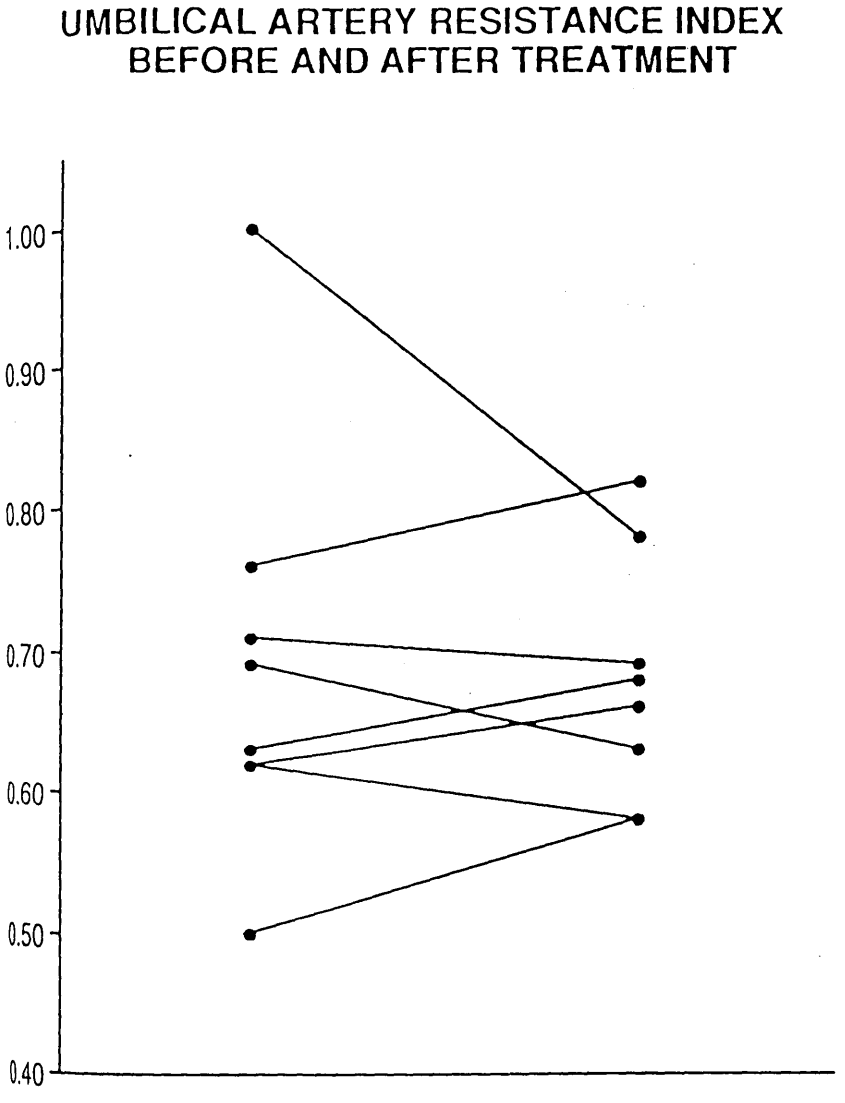


Figure 10.4 Umbilical artery resistance index before and after establishment of therapy with atenolol.

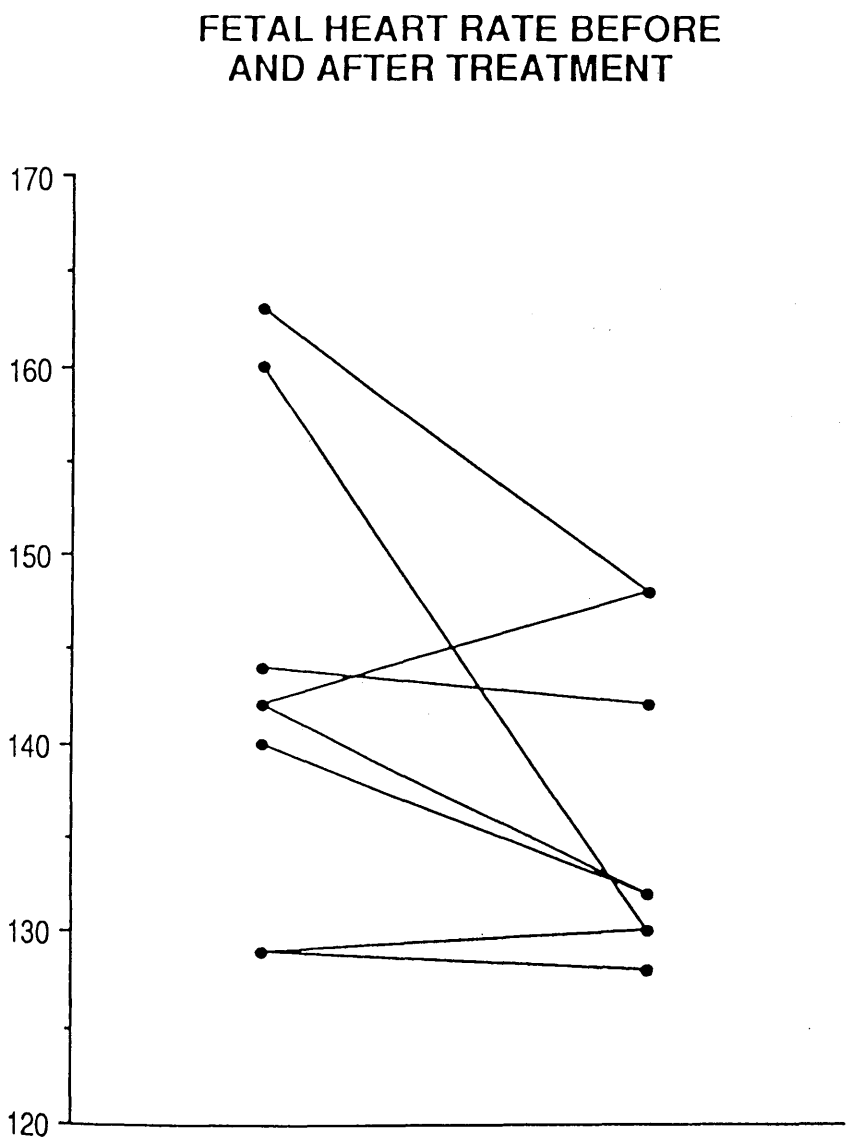


Figure 10.5 Fetal heart rate before and after establishment of therapy with atenolol.

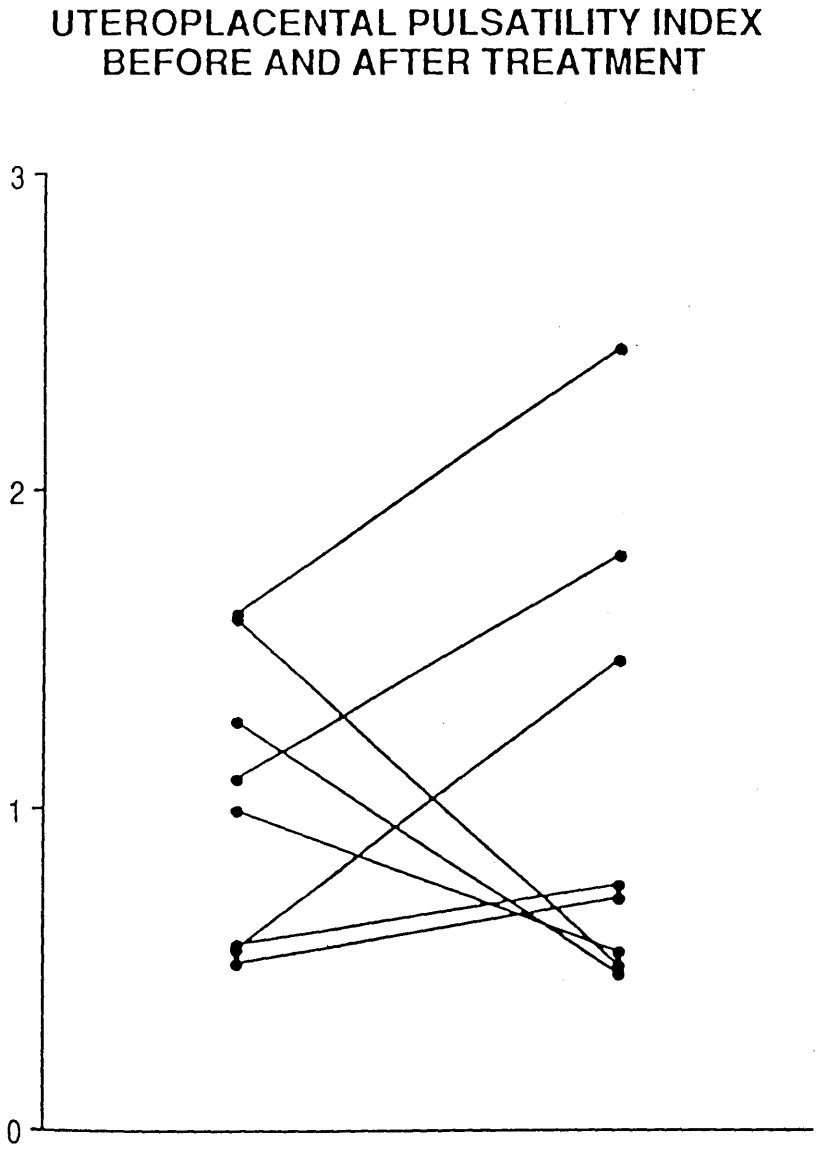


Figure 10.6 Uteroplacental pulsatility index before and after establishment of therapy with atenolol.

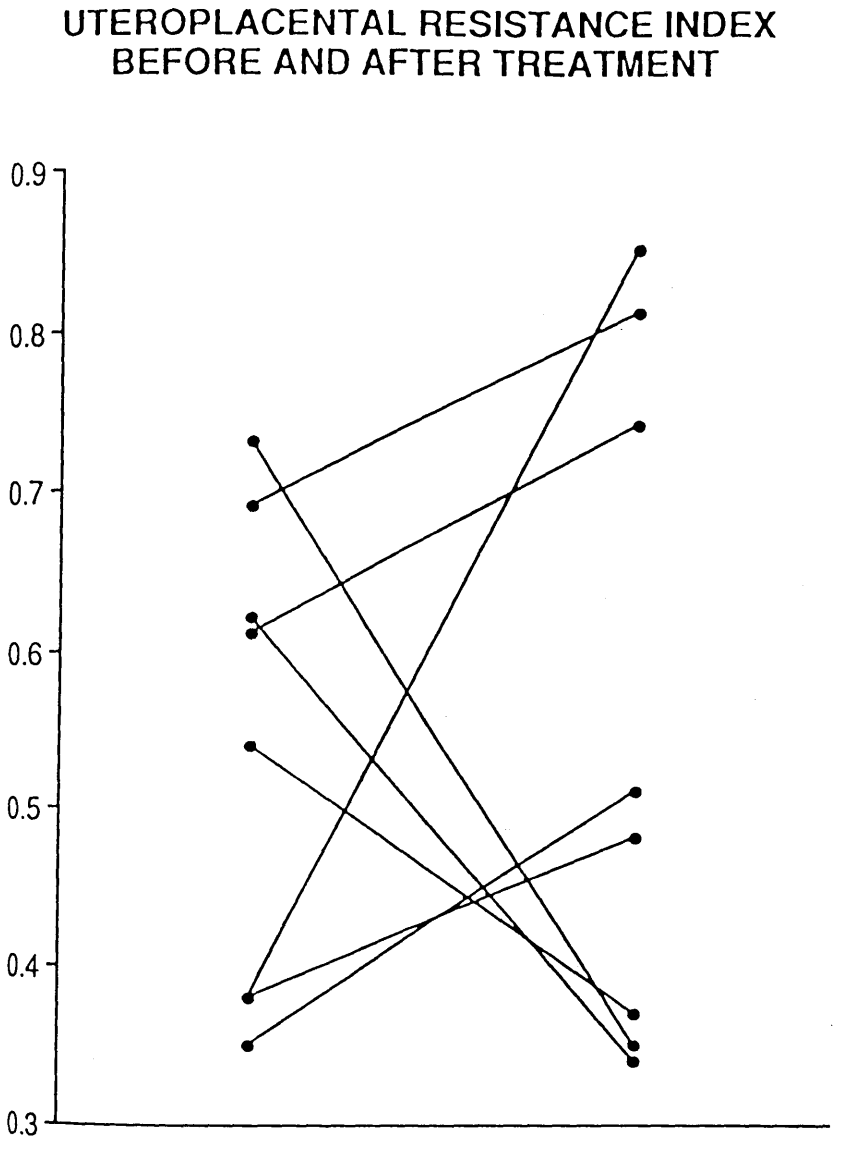


Figure 10.7 Uteroplacental resistance index before and after establishment of therapy with atenolol.

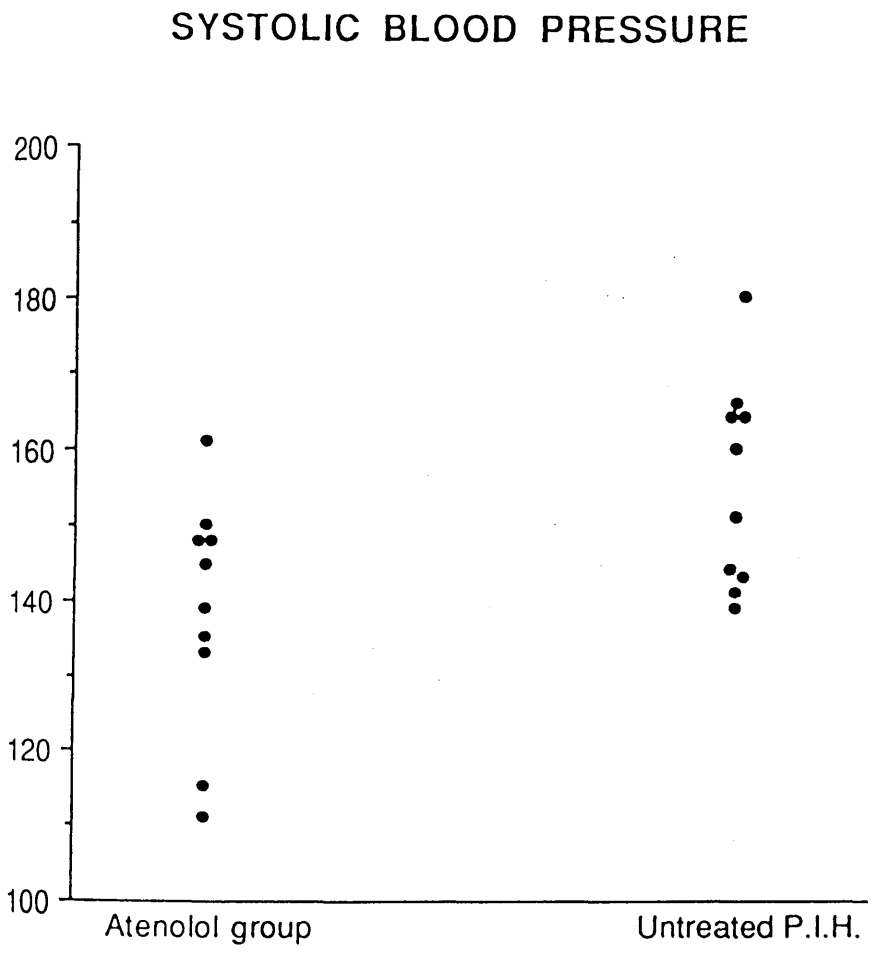


Figure 10.8 Systolic blood pressure in treated and untreated cases of PIH.

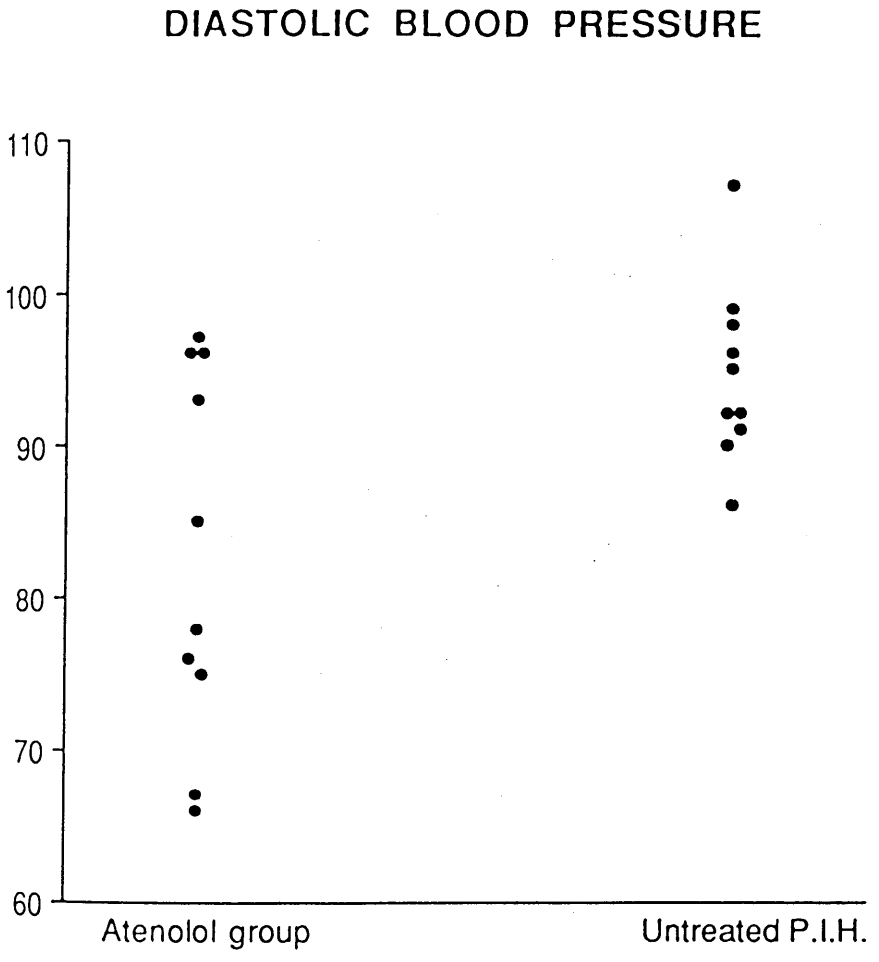


Figure 10.9 Diastolic blood pressure in treated and untreated cases of PIH.

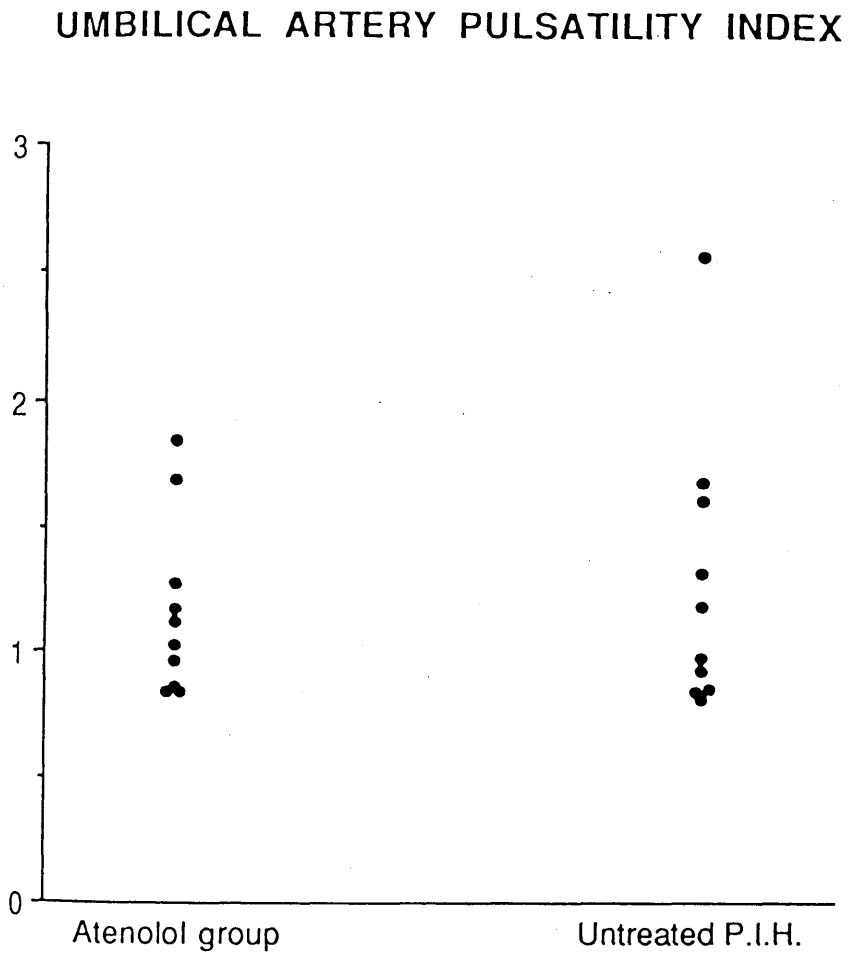


Figure 10.10 Umbilical artery pulsatility index in treated and untreated cases of PIH.

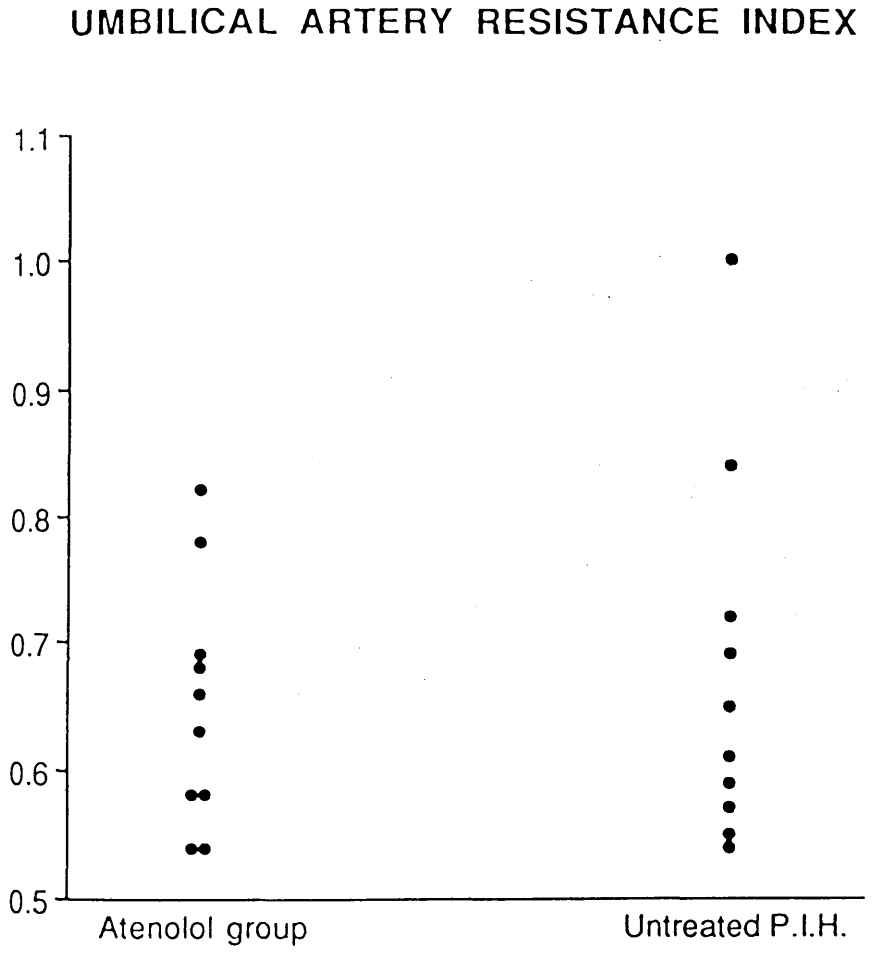


Figure 10.11 Umbilical artery resistance index in treated and untreated cases of PIH.

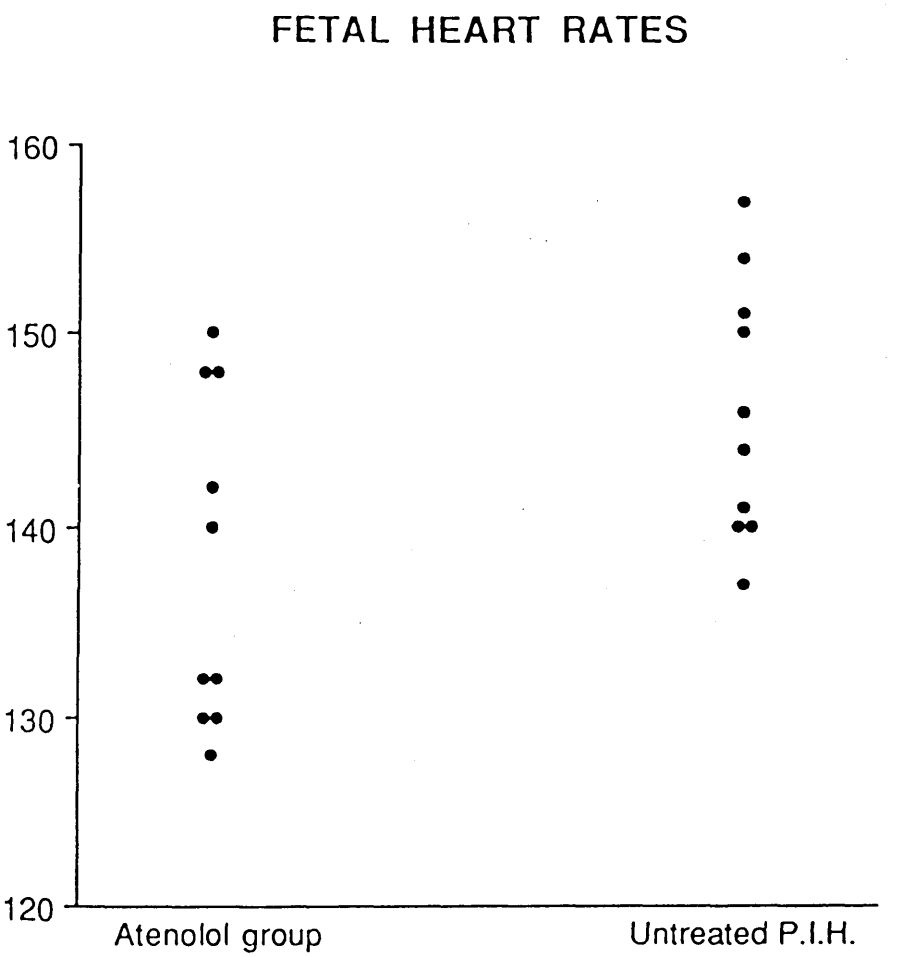


Figure 10.12 Fetal heart rates in treated and untreated cases of PIH.

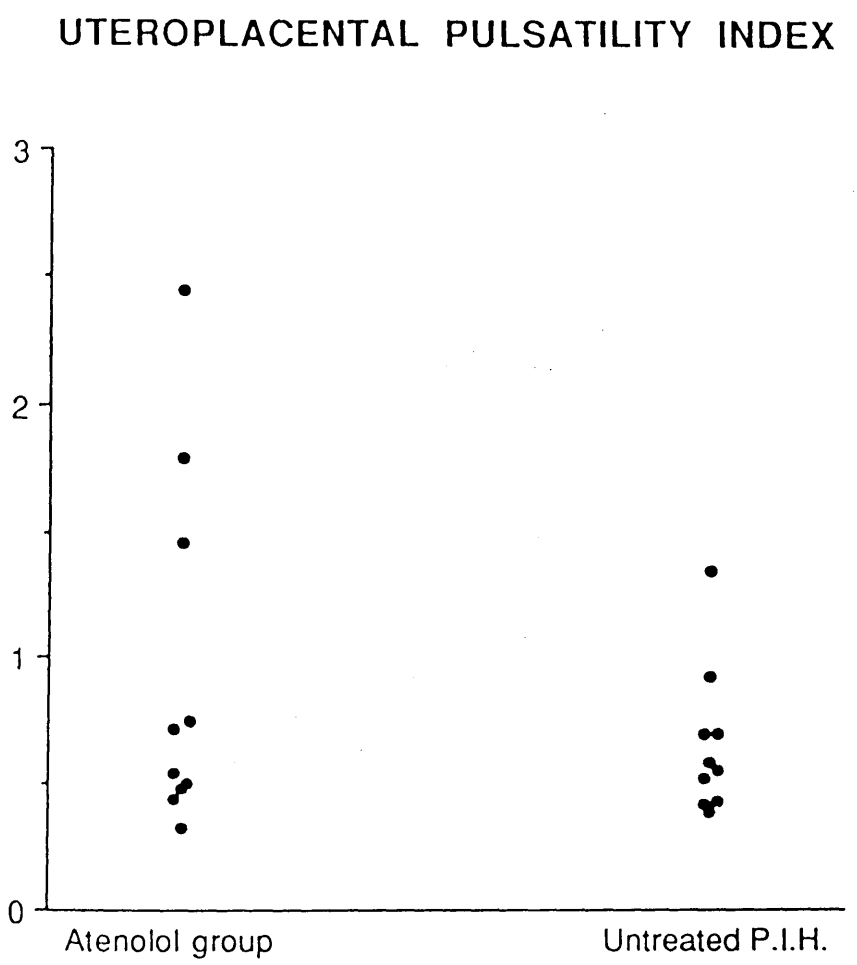


Figure 10.13 Uteroplacental pulsatility index in treated and untreated cases of PIH.

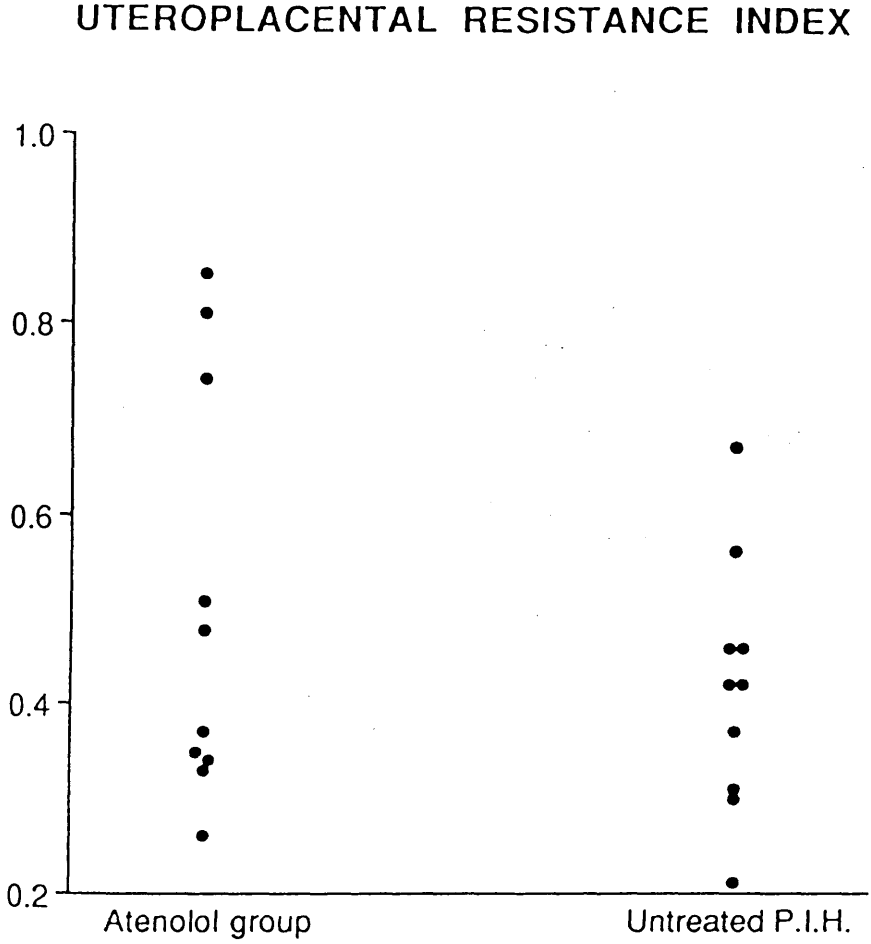


Figure 10.14 Uteroplacental resistance index in treated and untreated cases of PIH.

Chapter 11 Effect of acute therapy with a calcium channel blocker, nifedipine, on umbilical and utero-placental artery flow velocity waveforms in pregnancy induced hypertension.

11.1 Introduction.

11.2 Clinical pharmacology of nifedipine.

11.3 Methods and patients.

11.4 Results.

11.5 Discussion.

Chapter 11

The acute effects of nifedipine on uteroplacental and umbilical artery flow velocity waveforms in severe pre-eclampsia.

Chapter 11.1 Introduction.

The management of severe pre-eclampsia, particularly when of early onset, remains problematical. The control of hypertension in particular remains contentious but there is a clear need for effective antihypertensive drugs which can be easily administered without adverse effect on mother or fetus. A common approach has been to institute single agent therapy with atenolol, labetolol or methyldopa and in the presence of severe disease to add other more potent therapies. Vasodilators such as prazosin have been used successfully in combination with both oxprenolol (Lubbe & Hodge 1981) and atenolol (Rubin et al 1983b) but the success of calcium channel blockers in non-obstetric hypertension (Murphy, Scriven & Dollery 1983) has led to considerable interest in their use in pre-eclampsia. Nifedipine is the most commonly used of these agents has been used as a second line agent in severe early onset pre-eclampsia and the results are promising (Walters & Redman 1984; Rubin, McCabe & Low 1984; Constantine et al 1987). However, the potential adverse effects of such therapy are not known and it is important to determine whether the uteroplacental or umbilical circulations are adversely affected by reduction in blood pressure. Furthermore, for reasons discussed earlier it is important to determine if an effect of such

therapy is seen on Doppler waveforms, particularly if Doppler methods are to be accepted as a method of monitoring fetal wellbeing in high risk pregnancy. Although nifedipine appears to have no acute effect on uteroplacental blood flow (Lindow et al 1988) there are no data concerning effects on umbilical blood flow or intermediate effects on uteroplacental blood flow.

Chapter 11.2 Clinical pharmacology of nifedipine.

The clinical pharmacology of nifedipine has been comprehensively reviewed recently (Sorkin, Clissold & Brogden 1985) and points of relevance to its use in obstetrics will be discussed here. Nifedipine has potent coronary and peripheral arterial dilator properties which are a result of antagonism of calcium influx through the slow channel of the cell membrane. Its hypotensive effects appear to be more pronounced in hypertensive individuals compared to normotensive volunteers (Pedersen et al 1980).

Ninety percent of orally administered nifedipine is absorbed, almost all of this being in the small intestine and peak plasma levels are reached after 0.5 to 2.2 hours in the non-pregnant state (Taburet et al 1983). Some workers have described a wider variation among individuals and there is no information regarding pharmacokinetics of calcium channel blockers in hypertensive human pregnancy. Nifedipine is eliminated in the urine and although concentrations have been found to be higher in patients with renal disease there is no significant reduction in renal plasma flow (Austin, Robson & Bailey 1983).

The effective arterial dilating properties are associated with a reduction in peripheral vascular resistance and an increase in peripheral vascular blood flow.

Nifedipine reduces uterine tone and has been investigated as a potentially useful tocolytic (Ulmsten 1984) In the ewe its tocolytic effects can be achieved with only mild haemodynamic effects (Golichowski et al 1985) and in the human nifedipine has produced satisfactory tocolysis without producing any reduction in blood pressure (Read & Wellby 1986). Its use as an antihypertensive in pregnancy has usually been as a second line agent in severe disease making interpretation of data difficult. The anti-aggregatory effects on platelets make its use in pre-eclampsia particularly attractive. Clearly an adverse effect on uteroplacental perfusion should be excluded insofar as possible before widespread use.

Veille, Bissonette & Hohimer (1986) studied the effect of nifedipine on uterine blood flow in the pregnant pygmy goat and showed no effect on uterine blood flow. However, some animal studies have suggested that calcium channel blockers have an adverse effect on uteroplacental perfusion and fetal oxygenation.

Doppler velocimetry is a method of studying uterine blood flow which remains the only safe and repeatable method of measurement and the study presented here examines the effects of nifedipine on uteroplacental and umbilical artery Doppler waveforms.

Chapter 11.3 Methods and patients.

Nine proteinuric hypertensive women all of whom had been normotensive in early pregnancy were studied. Their mean age was 28.0 (5.5) years and all but one were primigravidae. The gestation at the time of study was 29.4 (4.4) weeks range 24-35 weeks). Doppler uteroplacental and umbilical artery waveforms were obtained after a 30 minutes rest period in the semi-recumbent position. The pulsatility index was calculated individually for each waveform and the mean then recorded. Since there was absent end diastolic flow in the umbilical artery in 4 of the cases the resistance index and systolic/diastolic ratios were not calculated. Blood pressure was measured using an automatic sphygmomanometer. Maternal pulse and fetal heart rate were also noted. Nifedipine retard 20mg was then given orally and all recordings repeated hourly for 8 hours. Differences in the parameters studied were analysed using repeated measures analysis of variance,with Bonferroni multiple comparisons where appropriate.

Chapter 11.4 Results.

Despite a rapid and sustained effect on blood pressure, no effect was seen on either fetal or maternal Doppler indices (Table 11.1). The reduction in systolic blood pressure was significant for the first 5 hours after treatment and an effect on diastolic and mean arterial blood pressure seen throughout the study period. No effect was seen on fetal heart rates although the maternal pulse was slower at 8 hours than immediately following treatment. For

ease of display, Figures 11.1-11.5 show the means and standard errors for the maternal and fetal variables recorded. Although the principal analysis was by non-parametric repeated measures analysis of variance, these figures also show statistically significant changes detected by paired t testing of post treatment to pre-treatment values.

All patients complained of headache over the first three hours of study but this was never severe and required no treatment.

There were two perinatal deaths. Both followed the development of fulminant pre-eclampsia at 24 weeks. In both cases the fetal condition was poor before treatment; there was marked oligohydramnios and absence of any fetal movement. Although nifedipine allowed the continuation of the pregnancies for 2 and 3 days respectively, deteriorating maternal thrombocytopenia necessitated delivery, which was achieved vaginally following extra-amniotic prostaglandin infusion. Of the remaining cases all but one showed evidence of intra-uterine growth retardation and all but one were delivered by caesarean section. Only two of these babies were delivered after 37 weeks gestation. In the other cases delivery was indicated because of deteriorating maternal condition. All these babies have subsequently done well.

Chapter 11.5 Discussion.

The efficacy of calcium channel blockers in controlling blood pressure following oral administration makes their use attractive in severe PIH. However, since experience with

nifedipine has largely been based on its value as a second line agent in pregnancies which are already severely compromised, assessment of possible adverse effects is difficult as the outcome in these pregnancies will often be poor. The high risk nature of the cases presented in this study was also associated with a high perinatal loss rate and although the need for preterm delivery was by no means eliminated the blood pressure control obtained suggests that nifedipine is an effective first line agent in severe pre-eclampsia. Since this study lacks a control group, witholding treatment in this high risk group being ethically unacceptable, our data must be interpreted with caution. Nevertheless, the blood pressure control obtained in our patients was similar to that reported by Walters & Redman (1984) in 8 patients who were also treated with nifedipine alone. Their series also showed a trend towards a reduction in maternal heart rate at 8 hours but the significance of this observation is unclear.

A decrease in uteroplacental blood flow and an increase in maternal heart rate have been described in both the rabbit (Lirette, Holbrook & Katz 1987) and sheep (Harake et al 1987) when calcium channel blockers have been given intravenously in the study of experimentally induced preterm labour. Lirette et al have suggested that this observation may be related to massive peripheral vasodilatation and diversion of blood to other organs. In contrast with this finding is that by Ahokas et al (1988) who studied the effects of nifedipine on uteroplacental perfusion in the spontaneously hypertensive rat at term. These workers

demonstrated a 25% drop in mean arterial blood pressure but, despite this significant reduction, there was no change in uteroplacental perfusion. The animal model used is more appropriate to the evaluation of drug effects in essential hypertension rather than pre-eclampsia (Ahokas et al 1987) but this finding and those presented here do not suggest a major change in uteroplacental perfusion.

Fetal hypoxia has also been described following nicardipine but the results obtained in this study suggest that the fetoplacental circulation remains stable following nifedipine implying that the fetal condition is unchanged although possible changes within the fetus remain uninvestigated.

These findings support a recent controlled study by Lindow et al (1988) who studied acute effects of nifedipine on uteroplacental blood flow using radioisotope techniques and showed no effect on perfusion despite a reduction in blood pressure. Although nifedipine crosses the placenta no effect was seen on umbilical artery blood flow velocity waveform.

In conclusion, the data from this small series suggest that the use of drugs like nifedipine in severe pre-eclampsia may be appropriate. These findings also confirm the findings of more invasive studies of the use of nifedipine which suggest that uteroplacental blood flow is not altered thus confirming the usefulness of Doppler as a non-invasive method of assessing drug effects in pregnancy.

Table 11.1 Maternal and fetal indices following oral nifedipine.

Time (Hrs)	0	1	2	3	4
SBP	157 (18)	142 (9)	141 (13)	143 (9)	148 (14)
DBP	99 (9)	85(5)	84 (6)	84 (7)	85 (7)
PULSE	78(12)	81 (18)	82 (17)	79 (16)	79 (16)
FHR	143 (7)	145 (11)	142 (10)	143 (9)	140 (10)
UMB PI	1.73 (0.61)	1.85 (0.73)	1.90 (0.57)	1.81 (0.55)	1.86 (0.55)
UTR PI	1.20 (0.60)	1.24 (0.80)	1.22 (0.85)	1.41 (1.05)	1.35 (1.10)

Time	5	6	7	8	Significance
SBP	146 (14)	146 (9)	154 (19)	153 (13)	p=0.022
DBP	86 (7)	89 (9)	91 (11)	90 (10)	p<0.001
PULSE	75 (12)	72 (12)	73 (15)	70 (16)	p=0.013
FHR	142 (11)	140 (7)	141 (9)	139 (7)	p=0.878
UMB PI	1.87 (0.50)	1.73 (0.49)	1.82 (0.48)	1.78 (0.45)	p=0.848
UTR PI	1.31 (0.88)	1.26 (0.80)	1.22 (0.83)	1.20 (0.84)	p=0.871

Figures in parenthesis are standard deviations

SBP Systolic blood pressure

DBP Diastolic blood pressure

FHR Fetal heart rate

UMB PI Umbilical artery pulsatility index

UTR PI Uteroplacental pulsatility index

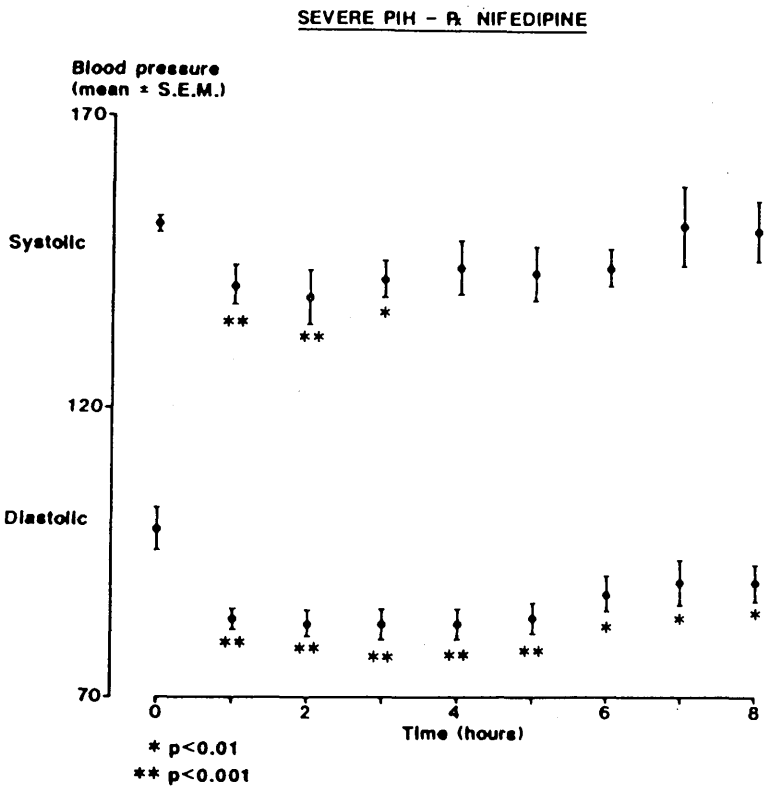


Figure 11.1 Blood pressure changes after oral nifedipine.

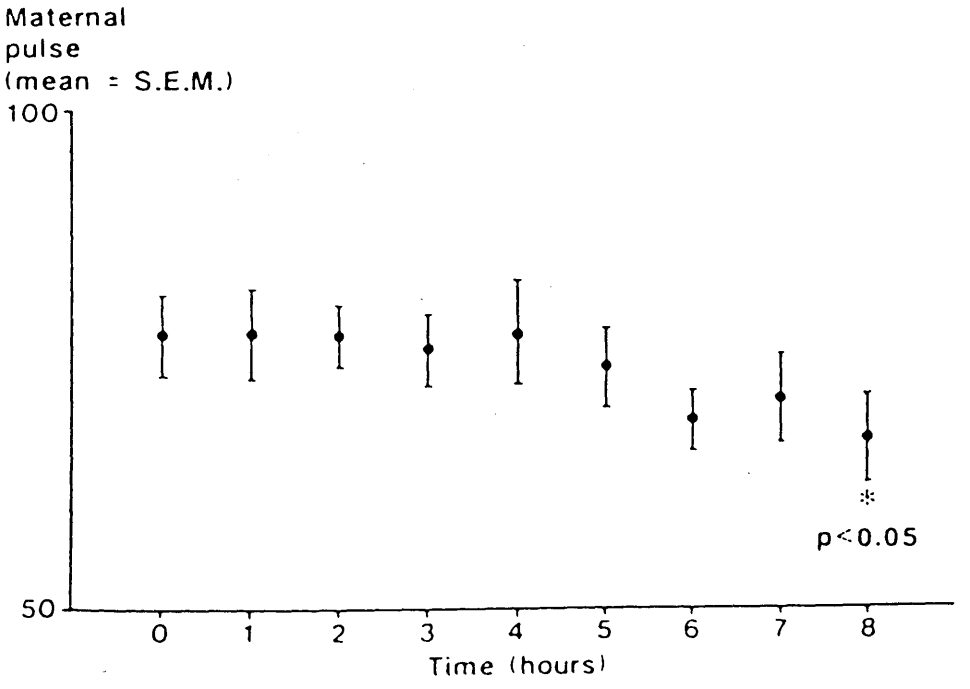


Figure 11.2 Maternal pulse after oral nifedipine.

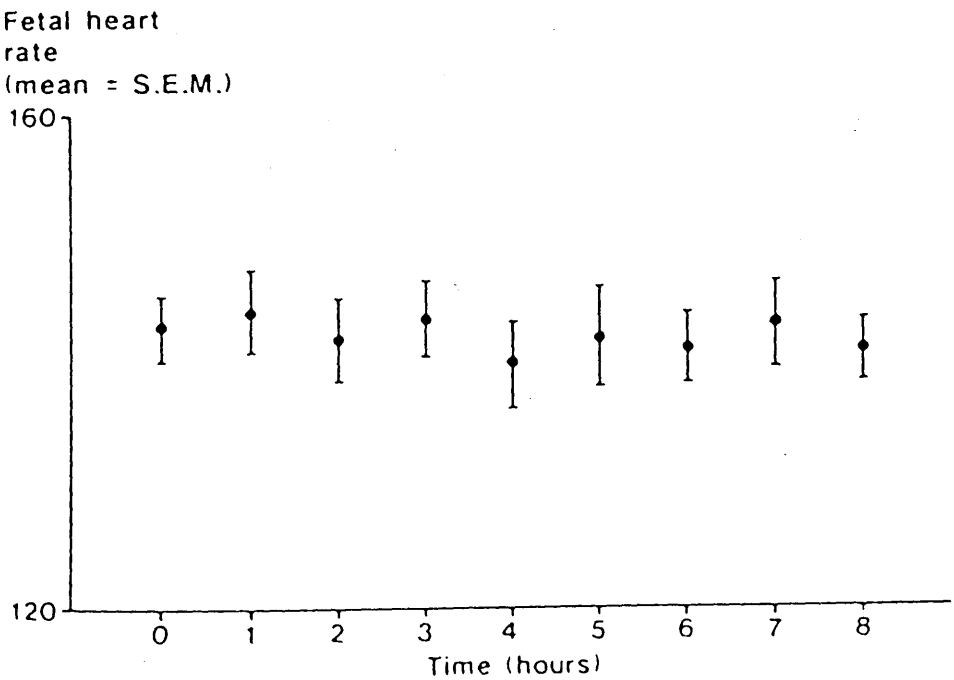


Figure 11.3 Fetal heart rates following oral nifedipine.

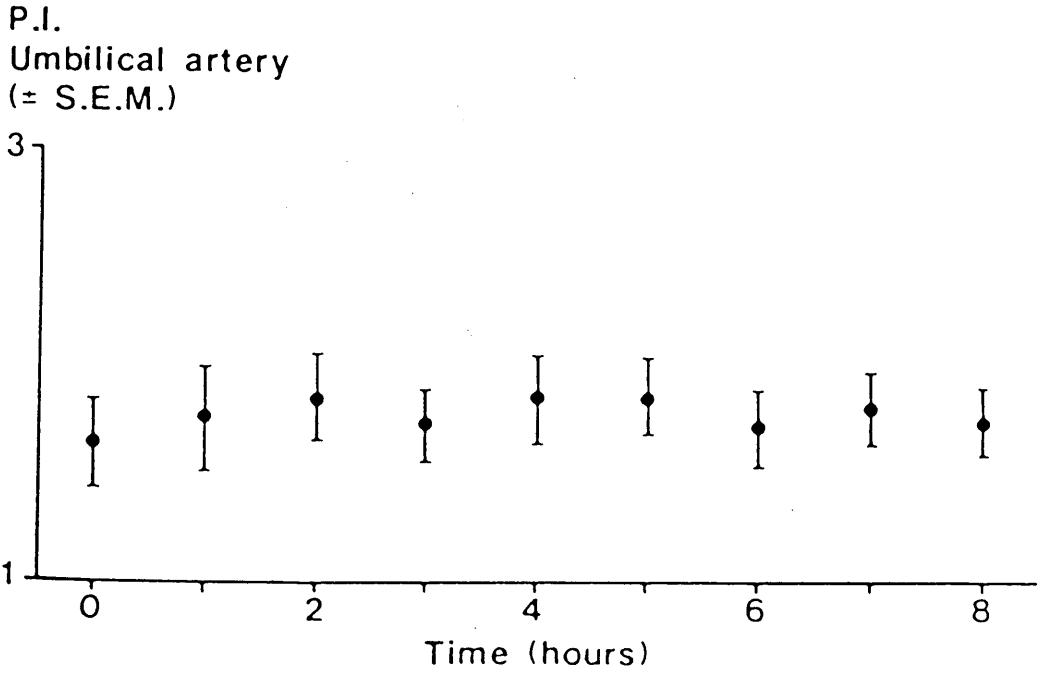


Figure 11.4 Umbilical artery pulsatility index following oral nifedipine.

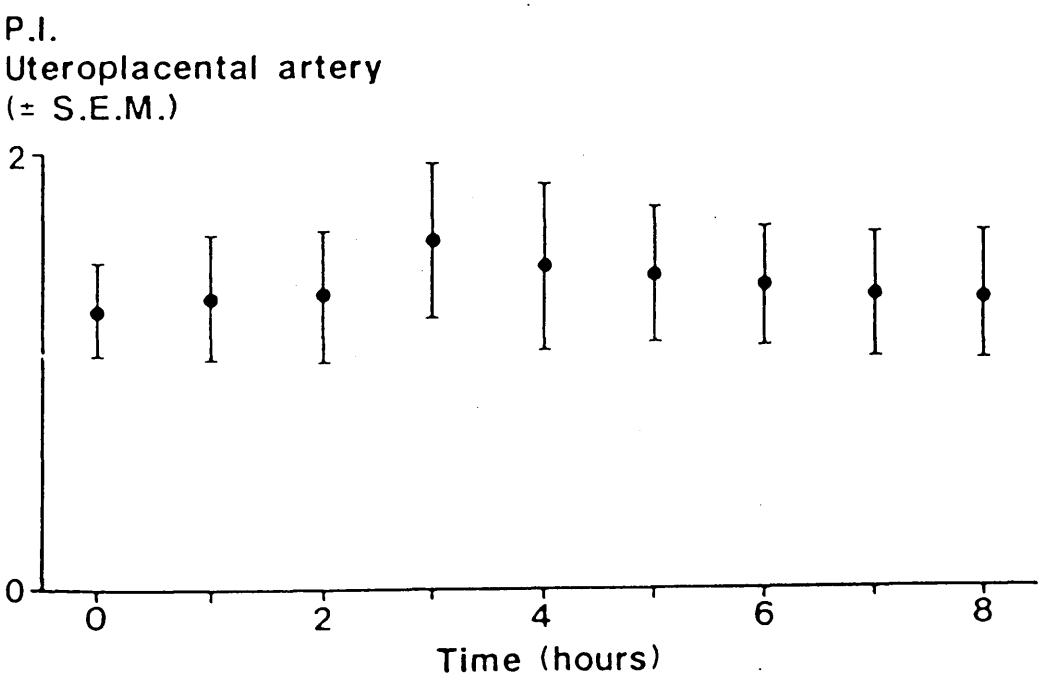


Figure 11.5 Uteroplacental pulsatility index following oral nifedipine.

Chapter 12 Conclusions.

Chapter 12 Conclusions.

The potential role of Doppler velocimetry in obstetrics necessitates an understanding of the determinants of such waveforms. In this chapter the factors studied in this thesis and their effects on uteroplacental and umbilical artery waveforms are discussed.

Determinants of uteroplacental flow velocity waveforms.

The studies described in this thesis permit the following conclusions about determinants of uteroplacental waveforms to be drawn:

a) In contrast with the only published controlled study of uteroplacental waveforms, PIH is associated with Doppler patterns of higher resistance than control cases (Chapter 5). There was no association between the levels of hypertension observed and Doppler indices. The clinical value of this observation may be limited by the overlap between normal and abnormal cases but the observation confirms the value of Doppler methods in assessing the pathophysiology of the disease.

b) Uteroplacental waveforms were not different from controls in pregnancies associated with small-for-dates fetuses (Chapter 6). This suggests that the vascular pathology which results in some cases of growth retardation is not sufficiently profound to influence waveforms and that Doppler uteroplacental waveform analysis will not aid the identification of the small-for-dates fetus.

c) Despite the high rate of complications in patients with elevated maternal serum alphafetoprotein, no difference in

uteroplacental waveforms was seen in these patients compared with controls (Chapter 8). It was not possible therefore to identify, using Doppler, a placental vascular lesion which might be associated with high risk for certain later complications. This finding contrasts with earlier uncontrolled studies.

d) The effect of lowering blood pressure using two agents with different modes of action was investigated. Although both drugs reduced blood pressure significantly this had no effect on uteroplacental waveforms (Chapters 10 & 11).

Atenolol had no effect on uteroplacental waveforms when given orally for one week. Against the background of concern for possible effects of antihypertensive medication in reducing placental perfusion this is a reassuring finding. This is particularly so since, from the results of the study described in chapter 5, there is a pre-existing increase in resistance to flow in the uteroplacental circulation.

Acute reduction in blood pressure achieved with a calcium channel blocker, nifedipine, did not alter waveforms. The use of this agent has hitherto been limited to high risk pregnancies often with an inevitably poor prognosis. The lack of any change in uteroplacental vascular resistance, as detected by Doppler, is also reassuring.

Determinants of umbilical artery flow velocity waveforms.

a) In a controlled study of the effect of PIH on umbilical artery waveforms no effect was seen overall contrasting with the results of uteroplacental waveform changes (Chapter 5).

In the sub-group of patients with significant proteinuria there was significantly increased resistance to flow. This finding suggests that alterations in vascular resistance on the fetal side of the placental circulation are secondary to those on the maternal side.

b) In contrast, in the study of fetuses which were small-for-dates, waveforms were obtained showing increased resistance to flow compared with controls despite no detectable difference in uteroplacental waveforms. This suggests that the placental vascular pathology in the pregnancies occurred despite apparently normal uteroplacental perfusion (Chapter 6).

c) The hypothesis that umbilical artery Doppler waveforms would be altered by intravascular transfusion was tested and the results obtained were surprising; instead of showing increased resistance to flow as might be expected from the increase in blood viscosity, a reduction was seen (Chapter 7). Since this was also seen following cordocentesis it seems likely that another mechanism, situated within the vessel wall was operative in these cases. Consequently the primary hypothesis was not tested but information was obtained which indicates the need for further study of the effects of cordocentesis on fetal physiology.

d) As with the uteroplacental waveforms, the finding of elevated maternal serum alphafetoprotein did not influence umbilical artery waveforms despite a higher incidence of later complications in this group (Chapter 8).

e) Although atenolol has been shown to cross the placenta and has effects on the fetal cardiovasculature, it does not

influence umbilical artery waveforms. Similarly nifedipine, despite having significant effects on reducing maternal blood pressure, did not influence umbilical artery waveforms (Chapters 10 & 11).

In summary the studies described in this thesis have identified a number of determinants of changes in Doppler waveforms in the uteroplacental and umbilical circulation. These findings must be considered in interpreting the results of further studies directed at determining the clinical value of Doppler velocimetry in obstetric practice.

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