MASTER OF MEDICINE (OBSTETRICS AND GYNAECOLOGY)

DISSERTATION

UNIVERSITY OF CAPE TOWN

STUDENT: Martin Stanley Puzey, MBChB (UCT) (Honours and Distinction)

FCOG (SA)

SUPERVISOR: Stephen Lindow, MBChB, M Med (O&G), MRCOG

FCOG (SA)

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TITLE:

THE INVESTIGATION OF THE CALCIUM ANTAGONIST NIFEDIPINE ON FETAL UMBILICAL ARTERY DOPPLER WAVEFORMS.

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INDEX

	PAGE
Introduction:	6
Literature Review:	8
A. Utero-Placental Circulation	10
B. Nifedipine	17
C. Doppler Ultrasound	22
Clinical Studies:	35
Stage I : The Effect of Nifedipine on Fetal Umbilical Artery Doppler Waveforms in Pregnancies complicated by Hypertension	36
Stage II : The Effect of Nifedipine on Fetal Umbilical Artery Doppler Waveforms in Pregnancies complicated by Abnormal Waveforms	48
Discussion:	67
Conclusion:	75
Acknowledgements:	76
References:	77

MASTER OF MEDICINE (OBSTETRICS AND GYNAECOLOGY)

DISSERTATION

INTRODUCTION:

The following thesis will describe the investigation of the effect of nifedipine (a calcium antagonist) on the Doppler flow velocity waveform of the umbilical artery.

The thesis is divided into two parts. The first section is a literature review of the three main aspects of the thesis namely:

1. The uteroplacental circulation in humans and the pathophysiology related to this circulation in hypertension and intrauterine growth retardation (IUGR).

2. The biokinetics of nifedipine and a review of the experiments that have been performed using the drug in human and animal models.

3. The principles of Doppler ultrasound and the literature pertaining to its use in the study of the uteroplacental circulation.

The second part of the thesis is devoted to the effect of nifedipine on fetal umbilical artery Doppler waveform analysis. In the first stage of the investigation the effect of the drug on hypertensive mothers has been examined, and in the second stage the effect on fetuses that have an increased resistance index of the umbilical artery Doppler waveform.

LITERATURE REVIEW

INDEX:

A. PLACENTAL CIRCULATION

(i) ANATOMY - FETAL SIDE OF PLACENTA
- MATERNAL SIDE OF PLACENTA

(ii) PHYSIOLOGY - FETAL
- MATERNAL

(iii) PATHOPHYSIOLOGY - PRE-ECLAMPSIA
- IUGR/CHRONIC HYPERTENSION

B. NIFEDIPINE

(i) BIOKINETICS

(ii) ANIMAL STUDIES

(iii) HUMAN STUDIES - IN VITRO
- IN VIVO

C. DOPPLER ULTRASOUND

(i) PHYSICS OF ULTRASOUND

(ii) CLINICAL METHODS OF MEASUREMENT OF THE UMBILICAL ARTERY WAVEFORM

(iii) SAFETY ASPECTS

(iv) CLINICAL STUDIES IN IUGR AND HYPERTENSION

A. PLACENTAL CIRCULATION

(i) ANATOMY

Fetal Side of the Placenta: The fetal blood passes to the placenta through two umbilical arteries which spiral around the umbilical vein in the umbilical cord. Shortly before reaching the placenta the two arteries are connected by one or more anastomosing vessels and may even merge into a single trunk. On reaching the placenta the arteries run in the chorion, usually being of equal size and each supply one half of the organ. The arteries divide into primary stem branches and each primary stem is called a cotyledon (Turnbull 1989(A). The cotyledon is made up of a varying number of lobules. Each lobule consists of tertiary stem villi. The centrally placed cotyledons may contain as many as five lobules while those placed peripherally may only have one or two lobules.

By the end of the first trimester the placenta attains its definitive architecture (Panigel 1986) and the maternal and fetal circulations are separated by a placental barrier.

Maternal Side of the Placenta: The maternal circulation is formed by the uterine arteries which divide into anterior and posterior branches. These further divide into arcuate vessels that terminate in the spiral arteries. A definite relationship exists between the maternal vessels and the fetal lobules probably because the lobules tend to develop preferentially around flow from the eroded maternal vessels (Reynolds 1966). By the third trimester the number of cotyledons correlate with the number of spiral arteries (Ducey 1989). The invading trophoblast effects free communication between the maternal system and the developing intervillous space of the placenta. The spiral arteries undergo a marked dilatation in two phases (Brosens 1967). In the first trimester there is a transmural colonisation of the spiral artery walls by trophoblast and migration of cytotrophoblast into the lumen of the arteries.

The cells migrate down the inner walls of the arteries to almost the myometrial segments. Initially the vascular endothelium is involved then the media of the arteries become invaded by cytotrophoblast and finally the bulk of the musculoelastic tissue of the wall of the artery is replaced by fibrinoid tissue.

At 14-16 weeks there is a similar process with the myometrial portion of the spiral arteries (second wave of invasion) as far as their origin from the parent radial arteries.

(ii) PHYSIOLOGY:

Fetal: The fetal blood flow through the placenta is about 500ml/min. The cardiac output is mainly dependent on the fetal heart rate : The cardiac output (CO) = Heart Rate (HR) x Stroke Volume (SV). The blood flow is derived from the ventricles pumping in parallel into a largely passive umbilical bed. It is possible however that there may be contractions by the myofibroblasts in the placenta: smooth muscle fibres are present in the stem and anchoring villi (Krantz & Parker 1963) and it has been suggested that contraction of these fibres help pump blood from the placenta back to the fetus. More recently it has demonstrated that the fetal vessels in the placenta are embedded in myofibroblastic cells (Feller and Schneider 1985), and contractions of these cells may generate a villous contraction.

The umbilical artery flow accounts for 57% of

fetal cardiac output and is acutely sensitive to oxygen tension in the umbilical venous and arterial blood (Dawes 1969).

Maternal relationship: The regulation of the uteroplacental circulation appears to be under neuroendocrine and environmental factors. Oestrogen increases uterine blood flow by vasodilation and a study by Greiss and Gobble (1967) showed that adrenergic stimulation decreased uteroplacental blood flow. Using pregnant normotensive and unilaterally nephrectomised sheep, Lieb et al (1980) showed that uterine blood flow decreased markedly with the development of hypertension and that the response to angiotensin II depended upon dosage given.

Maternal blood enters the intervillous space in arterial inlets in the basal plate. The driving head of maternal pressure is gradually dissipated, a process aided by the baffling effect of the villi, and lateral dispersion of the blood occurs. This forces the blood already present in the intervillous space out through basally sited venous outlets in the endometrial venous network. The physiologic basis is a series of pressure differentials. The entire system is however a low

pressure one, and in contrast to the general circulation, the utero-placental vessel diameters increase as the vessels approach the intervillous circulation. There is therefore a considerable drop in pressure as the spiral artery widens before the intervillous space, and a low resistance high conductance circulation results. The pressure difference is however enough to prevent mixing of neighbouring arterial flows and to drive blood towards the chorionic plate (Turnbull 1989(B).

Contractions and uterine tone cause decreased venous outflow, and decreased arterial blood supply to the placenta. This is a function of the resting tone and the contraction amplitude and frequency (Harbert 1982). This is probably due to occlusion of the veins of the intervillous space interfering with the pressure differentials. Ultrasonic studies have shown that during a myometrial contraction the intervillous space distends (Bleker et al 1975) and thus the fetus is not deprived of oxygen during maternal contractions.

(iii) PATHOPHYSIOLOGY:

Gestational Proteinuric Hypertension: In gestational proteinuric hypertension as defined by Davey (1986) the second wave of trophoblastic invasion of the spiral arteries fails to occur. (This patho-physiology of decreased uteroplacental blood flow must be differentiated from that which occurs in chronic hypertension or intrauterine growth retardation). In this model the progressive loss of muscular-elastic tissue in the media of the spiral arteries does not extend beyond the deciduo-myometrial junction. (Robertson et al 1975). In addition a process of acute atherosis occurs in the proximal segments of these arteries. Similar atherosis occurs in the smooth muscle cells with necrosis, fibrous vasculosis and infiltration of the damaged wall by macrophages. These pathological processes result in decreased uteroplacental blood flow. The blood flow is further inhibited by decreased intra-vascular volume and an increase in systemic vascular resistance (Ducey 1989).

Intrauterine Growth Retardation (IUGR)/Chronic Hypertension: Experimental studies in fetal lobules have demonstrated a redistribution of blood flow in growth retarded fetuses. Acute asphyxia in fetal lambs causes an increased release of catecholamines and a redistribution of blood flow (Jensen et al 1978). These vasoactive agents cause a constriction of the peripheral vessels, thus lowering the blood flow to the gut, kidneys, lungs, liver and placenta. Simultaneously there is an increase of blood flow to the brain, heart muscle and adrenals. The same pattern of redistribution of blood flow was found in fetal lambs subjected to long-term hypoxia of various degrees. Using pulsed Doppler ultrasound, Laurin et al (1987) confirmed that the blood flow in the fetal aorta and in the umbilical vessels was lower in IUGR (defined as gestational age related birth weight of 2SD or more below the population mean.)

On the maternal side of the placenta abnormal trophoblastic invasion was also found in pregnancies complicated by chronic hypertension and growth retardation (Pijnenborg et al 1991).

NIFEDIPINE

(i) BIOKINETICS

Nifedipine is a pyridine derivative and is an antagonist of the calcium influx through the slow channel of the cell membrane. This direct action on the calcium-ion flux affects the action potential and therefore contraction of smooth muscle. Given sublingually anti-hypertensive effects occur within 5-10 minutes (Erbel et al 1983). It has a half life of 4-6 hrs probably associated with its wider tissue binding and distribution in comparison to the other calcium antagonists (Rogers et al 1981).

The dose of nifedipine is 10-20mg 6-8 hrly. The main effect is to cause a drop in blood pressure in hypertensive patients. It is interesting to note that nifedipine does not result in hypotension in normotensive subjects (Naeijie et al 1982), and it appears that the drug re-establishes the patients "normal" blood pressure. Nifedipine is particularly effective in Prinzmetal angina, presumably because of its coronary vasodilation effect which counteracts the coronary artery spasm that underlies this condition. Additional actions of nifedipine are that cardiac output is maintained or increased and there may be

preferential vasodilation of cerebral vessels (Payen et al 1984). Nifedipine has also been found to cause a decrease in platelet aggregation (Dale et al 1983) which may be mediated by calcium transport across the platelet membrane. Side-effects of nifedipine are most commonly, headache, flushing and dizziness.

(ii) **ANIMAL STUDIES IN PREGNANCY**

Animal studies in pregnant sheep have confirmed the vasodilatory effect of decreasing transiently the maternal blood pressure and increasing maternal heart rate. Veille et al (1986) showed that true uterine blood flow did not fall significantly. An experiment to investigate the effect of nifedipine infusion to pregnant catheterized ewes yielded interesting results (Harake et al 1987). Significant plasma levels of the drug were found in both the maternal and fetal circulations. There was a 30-50% increase in fetal cerebral blood flow without a significant change in fetal oxygenation or cardiac output. Increasing the dose of the drug resulted in decreased uterine blood flow.

(iii) HUMAN STUDIES IN PREGNANCY

In vitro: Using small chorionic plate cultures and umbilical arteries (Maigaard et al 1984) showed that placental vessels utilize multiple sources of calcium for contractile responses. The vessels contracted strongly to both 5-hydroxy-trytophan (5-HT) and prostaglandin F2α. Nifedipine was able to interfere with these contractions and Maigaard et al (1984) postulated that nifedipine was able to theoretically decrease fetal placental resistance. A further study by Allen et al (1988) confirmed a similar inhibitory effect on intramyometrial vessels taken from 10 women with pregnancy induced hypertension. The paper compared the effects of dihydrallazine, prazosin and labetalol in inhibiting agonist effect on isolated vessels in organ baths. Nifedipine inhibited responses to all agonists tested, hydrallazine failed to inhibit any response and the other two drugs gave variable results.

In vivo: In a statement concerning Adalat^{R} (nifedipine) in 1983 the Bayer AG pharmaceutical company noted that there was no information about the use of Aldalat in pregnant women during clinical trials as women of child bearing age were

excluded from the trials. They noted that the drug was contra-indicated throughout pregnancy. However animal studies had shown that a dose of nifedipine of 10mg/kg/day proved to be a "no-effect" dose in respect of fetal development.

Over the last few years however the Obstetric & Gynaecological literature has published many trials of aspects of nifedipine use in clinical practice. The majority of work has examined the role of nifedipine on hypertensive women in pregnancy. The most dramatic therapeutic intervention of lowering blood pressure in acute hypertensive emergencies has been examined thoroughly both in the United Kingdom and in South Africa (Walters & Redman 1984), (Seabe et al 1989). Both trials noted that the drug was efficacious and had the advantage of oral administration and no fetal effects were noted. The authors stressed that further work was necessary to examine the effect on the feto-maternal circulation. Nifedipine has also noted to be a useful adjunct or second line anti-hypertensive drug in pregnancy (Constantine et al 1987) and recently a paper revealed that it was safe (despite theoretically competing with magnesium channels) to be used with magnesium sulphate (Fenakel et al 1991). There have however

been isolated case reports (Waisman et al 1988) and studies on rats (Overlack et al 1987) showing that nifedipine potentiates the hypotensive effect of magnesium sulphate. Nifedipine has also been used to suppress preterm labour (Read & Wellby 1986). The drug was found to be more effective than ritodrine and/or placebo. The authors also noted it was virtually devoid of side effects.

In view of the animal and in vitro models suggesting that the drug may modify placental resistance, studies have examined the effect on the uteroplacental circulation using radio-nucleotide or pulsed Doppler as a means of investigating blood flow. A study from Cape Town (Lindow et al 1988) showed that the drug lowered the maternal blood pressure but did not reduce utero-placental blood flow. Rizzo et al (1987) showed that there was a transient improvement in Doppler umbilical artery waveform after administration of nifedipine to healthy mothers and fetuses. Work from Nottingham (Hanretty et al 1989) and from Tennesse (Moretti et al 1990) which was done at the same time as phase I of our study, confirms that nifedipine administration in hypertensive mothers both chronically or acutely does not detrimentally alter Doppler waveform

patterns in the fetus.

In a randomised study between nifedipine and hydrallazine in severe pre-eclampsia (Fenakel et al 1991), the nifedipine group had less fetal distress and the infants delivered at a more advanced gestational age, weighed more and tended to have fewer mainly minor complications.

To date no study has attempted to investigate whether the drug may beneficially change the umbilical artery Doppler waveform and hence improve fetal wellbeing. Phase II of this thesis will examine this aspect of uteroplacental blood flow manipulation.

DOPPLER ULTRASOUND

(i) Physics:

The Doppler effect is created by making the sound source immobile and moving the echo-producing interface towards or away from the source in the path of the ultrasound beam.

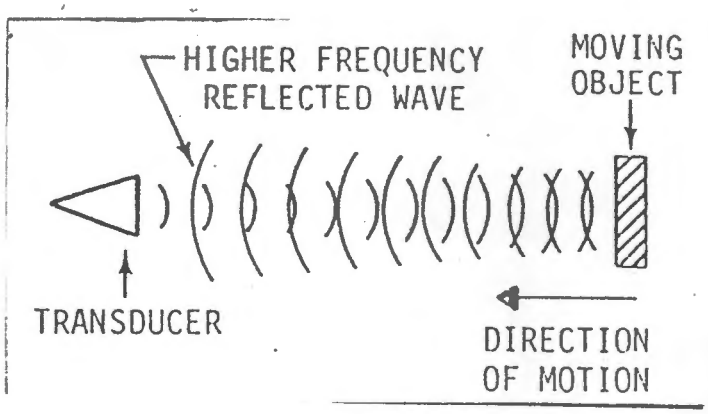

FIG. 1 Doppler echo returns from immobile sound source reflected off a moving echo producing interface.

The reflected wave will be either higher or lower in frequency than the original transmitted frequency depending upon the direction of motion of the moving object. The amount of frequency (Doppler) shift is in proportion to the velocity of the object.

The sound is created by exciting a crystal with an electrical voltage called the piezoelectric effect. The crystal resonates at a desired frequency 3MHz or 5MHz which is released as a short burst; the returning echoes are compared to the original burst, and the detected difference is the Doppler shift. The Doppler shifts are complex

in nature and are divided into their component sine waves by a flow analyser. The analyser uses a Fast Fourier Transformation technique to analyse the Doppler shifts and display the results in real time.

In practice, the physician usually does not wish to analyse the echoes returning from all points along the radiated ultrasound beam. Thus the receiver is turned off except during receipt of echoes returning from the specific site under examination. This system is called Gated Pulsed Doppler and this was the system used in the studies of Part II of this dissertation.

The most common mode for displaying the data is the real time spectral trace and this can be shown on page 25.

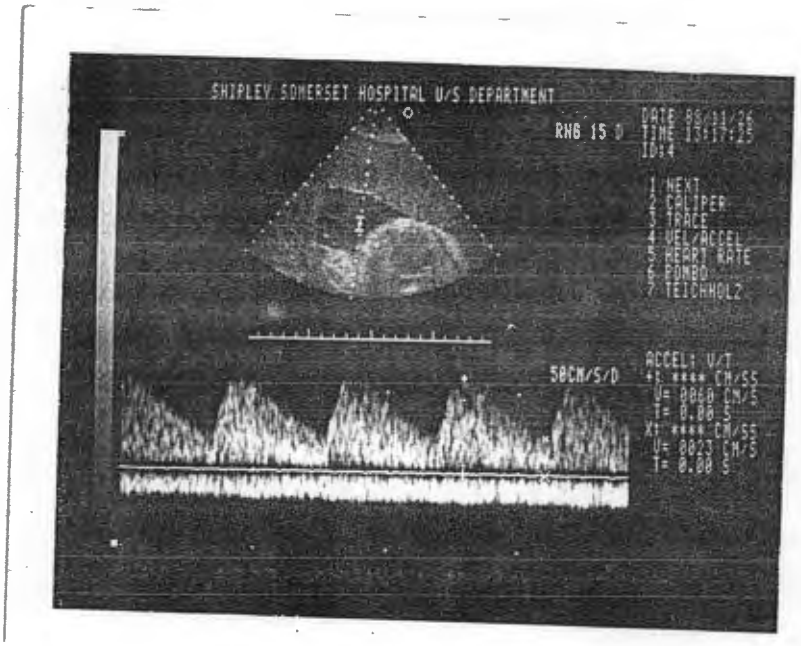

FIG. 2 Gated pulsed Doppler trace from the umbiical artery and vein obtained from a real time spectral image.

The factors affecting the Doppler shift can be summarized in the following equation:

$$\Delta f = \frac{2 V f_o \cos\theta}{C}$$

Δf = Doppler shift

V = velocity of blood flow

θ = angle of beam to direction of flow

C = 1540 um/sec = velocity of sound in body tissue

f_o = carrier frequency (3mHZ or 5mHZ)

(Erskine & Ritchie 1985)

If $\theta = 90^\circ$ then COS $\theta = 0$ so there is no Doppler shift.

If $\theta = 0^\circ$ then flow is towards the probe and there is maximum Doppler shift.

In order to measure the actual blood flow in a given vessel per gram of tissue a further equation is used:

$$\frac{Q = v \pi r^2}{EFW}$$

Q = volume of flow

v = velocity of blood flow

r = radius of vessel

EFW = estimated fetal weight

(Erskine & Ritchie 1985)

(ii) CLINICAL METHODS OF MEASUREMENTS

The inaccuracies of measuring the actual blood flow are obvious and are mostly caused by errors in measurement of θ, estimation of vessel diameter and difficulty in measuring fetal weight (Erskine and Ritchie 1985). Nevertheless Doppler signals from the umbilical artery provide the best estimation of blood flow (Erskine and Ritchie 1985).

In clinical practice ultrasonographers measure the doppler waveform and not the blood flow, and in our study the umbilical artery Doppler waveform shift was measured. The waveform can be measured by 3 different indicies viz A/B ratio; pulsatility index and the Pourcelot ratio or resistance index.

A/B ratio = systolic/diastolic ratio

Resistance index (RI) = Pourcelot ratio = $\frac{A-B}{A}$

Pulsatility index (PI) = $\frac{A-B}{mean}$

(Thompson et al 1988)

The resistance index was chosen as the ratio in the following studies because it is easily calculated and does not approach infinity as the diastolic shift (B) approaches zero as occurs with the A/B ratio.

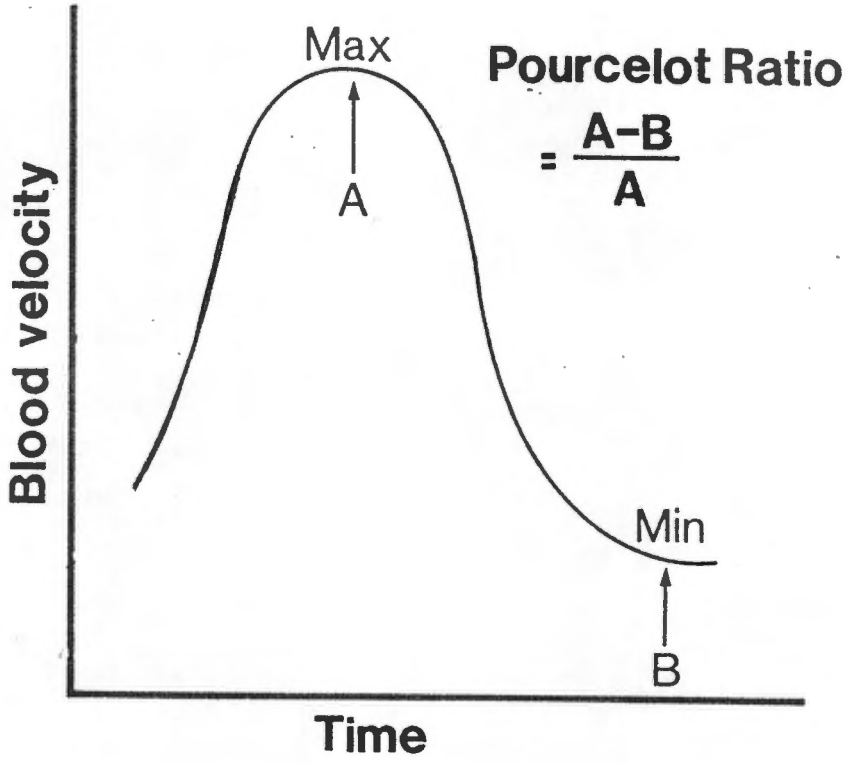

FIG. 3 Pourcelot ratio or resistance index $\frac{A - B}{A}$

Definition of resistance index from one umbilical artery waveform

The waveform characteristics are not constant for changes in the fetal heart rate or gestational age. In the following studies we will use the Pourcelot ratio as our index of Doppler shift. The ratio has to be corrected for these two factors (Thompson et al 1988).

1. A decrease in ratio with advancing gestation age; using a regression formula where the constant is 0,625, the linear coefficient is $6,25 \times 10^{-3}$ and the quadratic coefficient is $- 0,247 \times 10^{-3}$ (Pearce et al 1988)

2. A decrease in ratio with an increase in fetal heart rate:
   corrected RI = OBS RI -0,00 266 (140-OBS FHR)
   (Mires et al 1987).

The waveform shift has therefore to be corrected for these variables to obtain meaningful results and this has been done in the following thesis.

The daily variability of Doppler umbilical artery waveforms has an acceptable range for clinical and research applications (Hastie et al 1988) and both the inter and intra observer error was showed not to be statistically different for analysis of the the umbilical artery (Pearce et al 1988).

Pathological Correlation:

Fetal umbilical artery waveforms have been correlated with placental pathology in an elegant study (Giles and Baird 1985). Pregnancies with a high A/B ratio showed a statistically significant decrease in the modal small artery vessel count in the tertiary stem villi of the placenta Fig. (4 & 5).

Therefore abnormal Doppler waveforms can identify a specific microvascular lesion in the placenta characterised by obliteration of small muscular arteries in the tertiary stem villi that occur in patients with fetal growth retardation and/or hypertension.

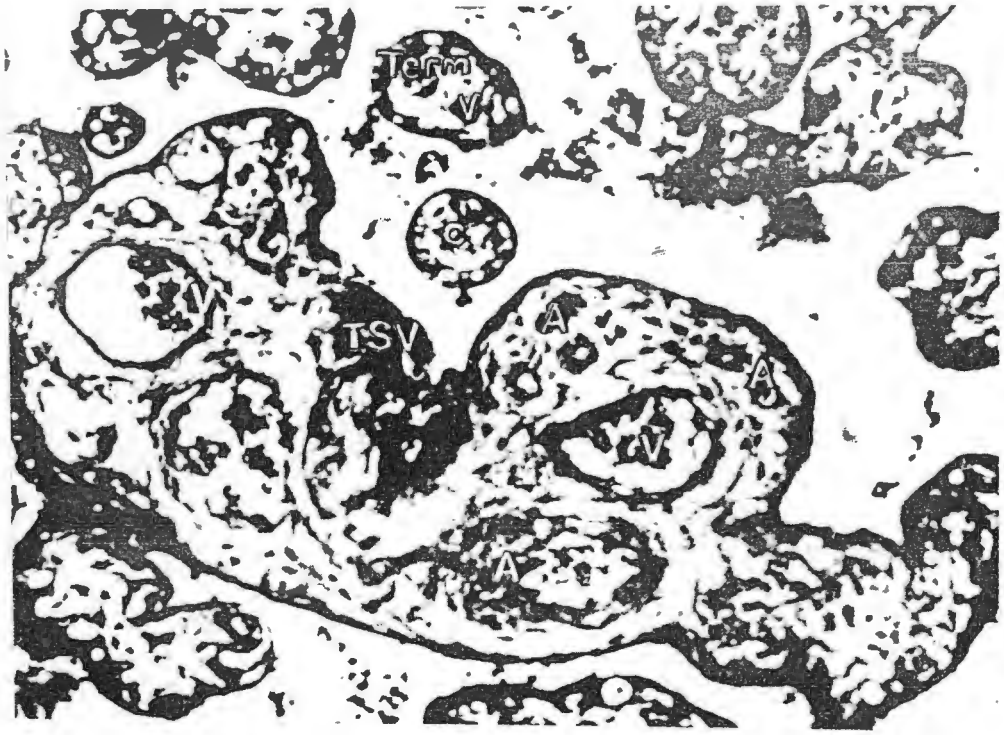

FIG. 4 Placental micrography from a placenta with normal pracental blood flow resistance.

TSV = Tertiary stem villous

Term V = Terminal villous

A = Small arterial vessel

V = Venous channel

C = Capillary

FIG. 5 Placental micrograph from a placenta with raised umbilical placental blood flow resistance. (Index as for Fig. 4.)

(iii) SAFETY

Ultrasound has the potential to cause harmful effects in biological tissues by various effects:- either by absorption of energy by tissue with resultant over-heating; or by formation growth and activity of microbubbles that cause sheer stress near the oscillating bubbles, this mechanism called cavitation has only clearly been shown using agar-gel phantoms; or

by acoustic streaming. (ter Haar G et al 1987). These above theoretical dangers of ultrasound examination have not been reproduced in vitro or in vivo.
A clinical study (Mannor et al 1972) showed that 1,050mW/cm at 2,2 mH2 for 60 mins (far in excess of current levels in diagnostic ultrasound) caused no increase in temperature in animal models, no increase in abnormalities, and no pathological findings on the macroscopic or microscopic examinations in mothers, fetuses and neonates. An examination of levels of either sister chromatid exchanges or chromosome breakage in cord blood from exposed fetuses showed no increase over controls. (Henderson et al 1986).

(iv) **CLINICAL STUDIES IN IUGR AND HYPERTENSION**

The Tygerberg Hospital Perinatal Mortality Research Unit examined the correlation between fetal outcome and abnormal waveforms in severe proteinuric hypertension. They found (Pattinson et al 1989(A) that fetuses with abnormal waveforms in the umbilical artery had more neonatal morbidity, late decelerations, perinatal deaths and growth retardation than the control group. A further study by Pattinson (personal communication) had to be terminated on ethical grounds because the group that was not managed with the Doppler information had a significant increase in perinatal mortality over the patients that were managed with the Doppler

information. The abnormal Doppler waveforms tend to precede the CTG changes for up to two weeks (Trudinger et al 1985).

Studying the effects of IUGR on umbilical artery waveforms is more difficult to show a positive correlation with perinatal mortality due to the multi-factoral nature of IUGR.

A paper from New York (Divon et al 1988) showed the best predictor of IUGR was estimated fetal weight on ultrasound below the tenth percentile for gestational age (sensitivity = 87%), this was nearly twice as good as all the other parameters including Doppler analysis. In this paper it appears that Doppler is better in predicting the non-IUGR infant (sensitivity = 87-98%).

PART II

CLINICAL STUDY IN TWO STAGES

STAGE I: The effect of nifedipine on fetal umbilical artery doppler waveforms in pregnancies complicated by hypertension

STAGE II: The effect of nifedipine on fetal umbilical artery doppler waveforms in pregnancies with abnormal waveform indices.

STAGE I

OBJECTIVE:

To observe whether the administration of nifedipine or placebo changed the umbilical artery waveform characteristics in pregnancies complicated by hypertension.

DESIGN:

A double blind prospective study run in parallel. Both the patient and the ultrasonographer did not know if placebo or nifedipine was administered.

DRUG:

Placebo: Capsule containing multivitamin syrup.

Active drug: Capsule containing nifedipine (Aldalat^{R}:Bayer) 5mg. (The lowest dose of nifedipine was chosen

1. Due to the paucity of studies pertaining to the use of nifedipine in pregnancy.
2. In the current 1992 MIMS Desk Reference, Bayer Miles (Pty) Ltd states under the heading contra-indications, that Adalat^{R} (nifedipine) safety has not been established in pregnancy.)

SETTING:

Somerset Hospital, Green Point

Groote Schuur Hospital, Observatory

INVESTIGATORS:

Drs M.S. Puzey; S.W. Lindow : Hypothesis and Study Design

Dr K.L. Ackovic : Doppler Waveform Analysis

Dr R. Gonin : Biostatistics, Medical Research Council

SUBJECTS AND METHODS:

Nineteen hypertensive pregnant women who were > 28 weeks pregnant were studied. All patients gave written, informed consent to the study, which was approved by the University of Cape Town Ethics Committee. The inclusion criteria required that singleton pregnancies with reactive non-stress tests were studied. Hypertension was defined as a mean diastolic blood pressure, taken over four 6-hourly readings with a standard mercury sphygmomanometer, > 90 mmHg. The patients were then randomly allocated to receive either nifedipine 5mg or a placebo by virture of the last digit of their folder number.

The nifedipine was administered sublingually as a single 5 mg dose, the placebo capsule was a similar size and contained vitamin syrup. The ultrasonographer and patient were unaware which capsule had been given.

Patients were examined supine on the ultrasound couch with 30^{o} lateral tilt. Ten minutes were allowed before starting the study to reassure the patient. Blood pressure recordings were taken at 5-minute intervals from 0 to 60 minutes using the Critikon Dinamp Vital Signs Monitor (18465X). Nifedipine/placebo was administered 30 min after the commencement of recordings. (This is shown graphically in the results figures by an arrow at the 30 min time period labelled with nifedipine/placebo.) Fetal umbilical artery waveform patterns were measured using the Aloka Doppler Unit (UGR-34) with a 100 Hz filter at 10-minute intervals from 0

to 60 minutes. The umbilical artery was identified with a B-mode scanner and the sample volume placed over the vessel; each Doppler trace had an umbilical vein tracing throughout. The Doppler trace was observed until a constant signal was obtained and the A and B values were measured from one representative waveform. The waveform was one of five waveforms that were uniform and a photograph was taken to check that it was representative. Adjacent waves were subsequently sampled to ensure uniformity. The Pourcelot ratio was calculated from the A and B values (Fig. 3) using standard calipers; it was not corrected for fetal heart rate, since the rate was in the normal range (120-160/min) in every patient except case 3 in the nifedipine group and there was no shift > 20/min in any patient. Normalisation of the ratio for heart rate was unnecessary under these circumstances (Murrow et al 1989). No correction for gestational age was necessary because there was an insignificant change in ratio in patients less than thirty seven weeks.

RESULTS:

The characteristics of the two groups of patients are shown in Tables I and II. The Mann-Whitney non-parametric U-test showed no significant difference between the two groups (P> 0,05) with the respect to gestational age, height and weight.

TABLE I

TABLE I. NIFEDIPINE GROUP COMPARED WITH PLACEBO GROUP FOR GESTATIONAL AGE, WEIGHT AND HEIGHT (MEAN ± SD)

	Nifedipine group (N = 9)	Placebo group (N = 10)	Mann-Whitney non-parametric U-tests between means
Gestational age (wks)	**34,5 ± 2,7**	**35,1 ± 3,6**	**NS**
Height (cm)	**159,2 ± 3,4**	**157,4 ± 4,7**	**NS**
Weight (kg)	**72,2 ± 6,5**	**79,7 ± 11,0**	**NS**

Maternal Diastolic Blood Pressure:

Maternal diastolic blood pressure is shown in Fig. 6. Repeated measurement analysis was carried out on diastolic blood pressure using the repeated measurements taken at 5-minute intervals. From 0 - 30 min no significant difference in blood pressure occurred between the two groups. From 35 to 60 minutes a significant treatment X time interaction was found ($p < 0,001$). This implies that the profiles of mean diastolic blood pressures over time do not lie parallel to one another. Differences at each point can therefore be tested. Univariate tests were carried out at each point and a significant fall in diastolic blood pressure was noted at 60 minutes (30 minutes after administration of the drug).

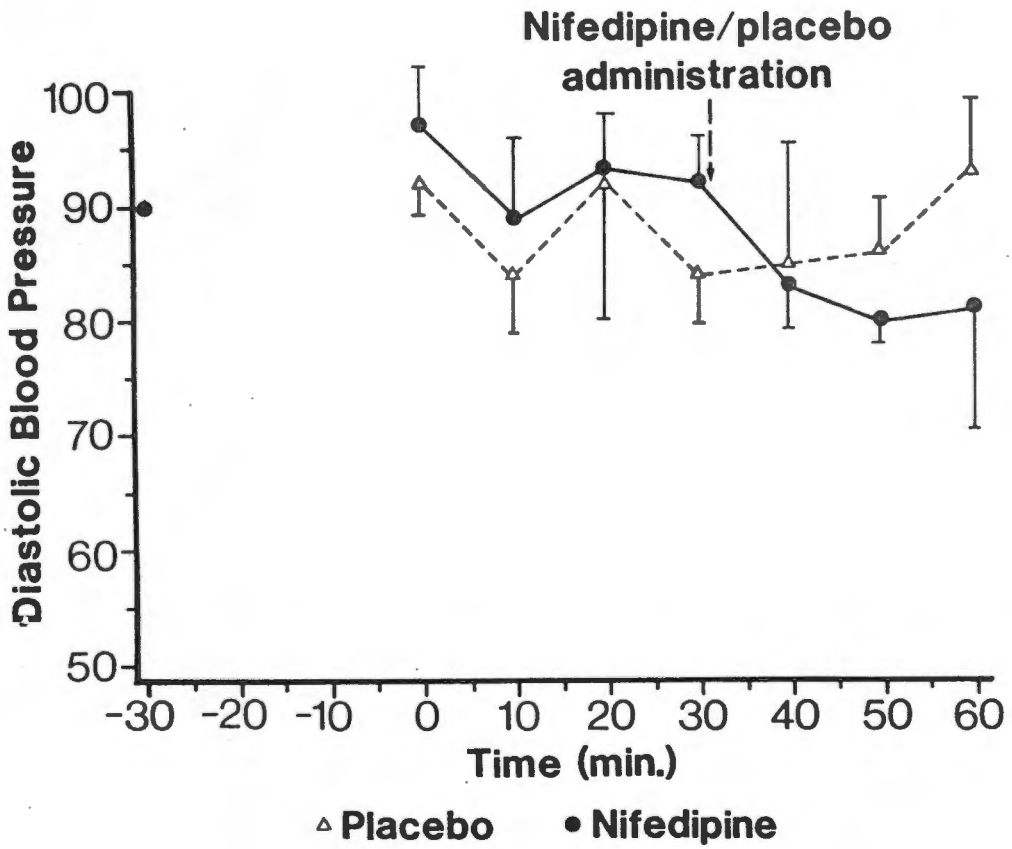

FIG. 6 Mean diastolic blood pressure (mmHg) and standard error of the mean plotted against time (min) for placebo (▲) and nifedipine (●).

Maternal Pulse Rate:

Maternal pulse rate is shown in Fig. 7. Repeated measurement analysis of variants showed a significant difference ($p < 0,001$) for treatment by time interaction. The decrease in maternal pulse rate in the nifedipine group 20 mins after commencing the study was not significant. It is difficult to explain the apparent decrease but it may be due to the small number of patients studied, and thereby be a chance finding.

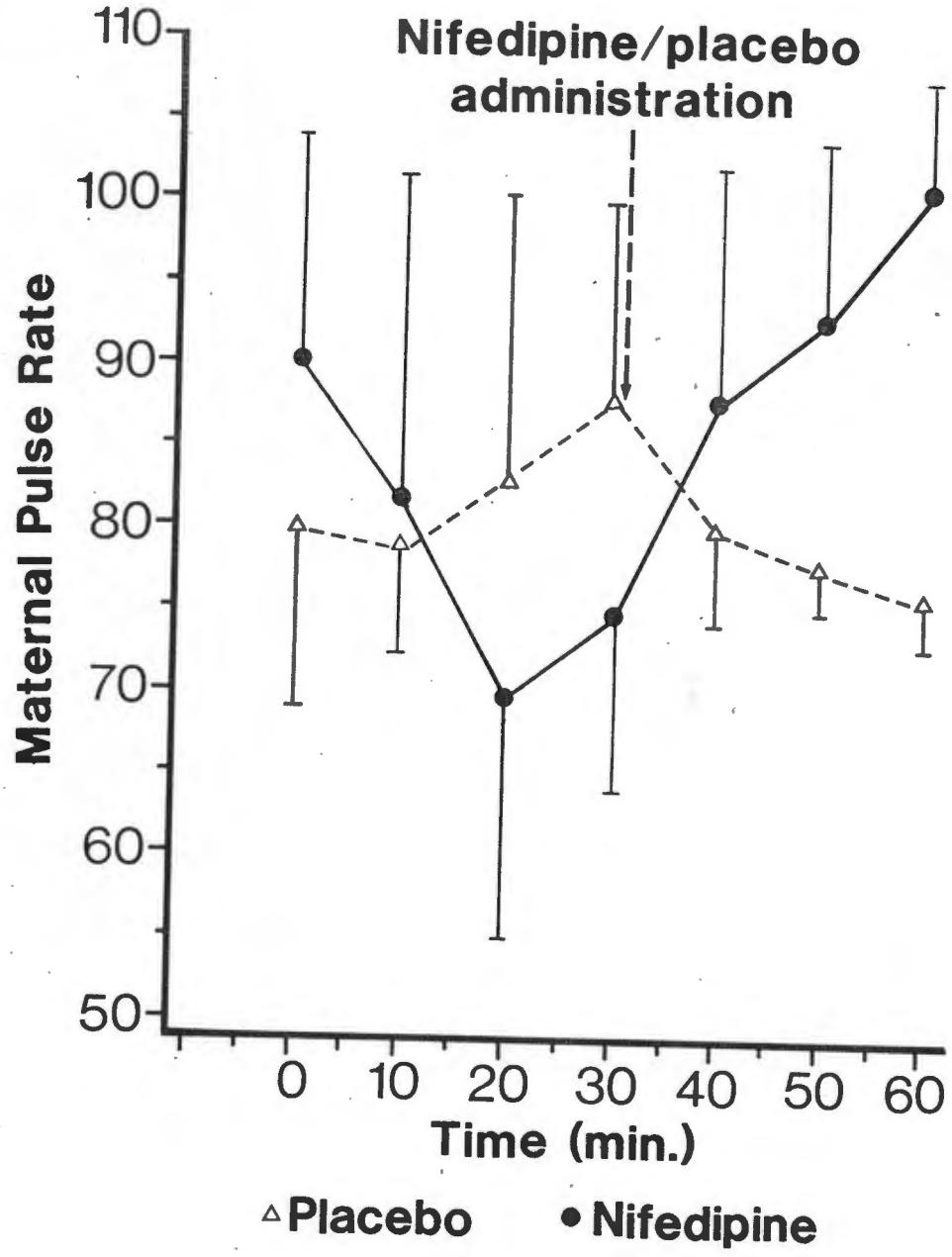

FIG. 7 Mean maternal pulse rate and standard error of the mean plotted against time (min) for placebo (△) and nifedipine (•).

Fetal Heart Rate:

Fetal heart rate, as recorded with a cardiotocograph before and after administration of nifedipine or placebo, is shown in Table II. The Mann-Whitney non-parametric U-test showed no significant change in the fetal heart rate.

TABLE II

TABLE II. INDIVIDUAL MEAN MATERNAL AND FETAL MEASUREMENTS BEFORE (0-30 MIN) AND AFTER (35-60 MIN) ADMINISTRATION OF NIFEDIPINE 5 mg OR PLACEBO

		Mean diastolic blood pressure (mmHg)		Mean maternal pulse rate (/min)		Mean fetal heart rate (/min)		Gestational age (wks)	Mean Pourcelot ratio	
	Patient	Before	After	Before	After	Before	After		Before	After
Placebo	1	85	81	88	105	128	137	40	0,56	0,61
	2	97	85	68	85	145	145	34	0,68	0,67
	3	91	86	69	81	168	168	34	0,62	0,62
	4	85	78	101	124	150	155	36	0,57	0,61
	5	93	75	76	100	140	145	36	0,58	0,56
	6	109	101	100	110	140	155	33	0,60	0,44
	7	95	79	81	100	130	128	30	0,70	0,73
	8	98	81	63	66	128	148	37	0,61	0,57
	9	93	87	72	82	125	125	37	0,64	0,58
	10	88	84	79	83	160	155	34	0,55	0,62
Nifedipine	1	83	82	60	55	150	150	31	0,73	0,71
	2	92	90	110	110	145	145	38	0,52	0,47
	3	105	105	79	78	145	140	36	0,59	0,59
	4	105	107	76	74	160	160	32	0,58	0,60
	5	93	90	100	100	135	140	38	0,55	0,61
	6	87	91	60	59	125	125	31	0,70	0,69
	7	83	79	83	84	145	145	41	0,66	0,65
	8	83	78	80	79	145	155	33	0,64	0,64
	9	84	78	96	99	135	135	36	0,66	0,62

Doppler Waveform Data/Pourcelot Ratio

There were 5 missing values in this set of data due to fetal breathing movements. A missing value was replaced by either an interpolated value or the mean of the adjacent values. Fig. 8 gives the Pourcelot ratio v.time. Of note is that in both groups all the Pourcelot ratios were normal at the time of testing. No significant difference between the mean Pourcelot index in the two groups was detected ($p > 0,05$). In the nifedipine group the Pourcelot ratio measured at each time interval before and after administration of the drug showed no statistical change.

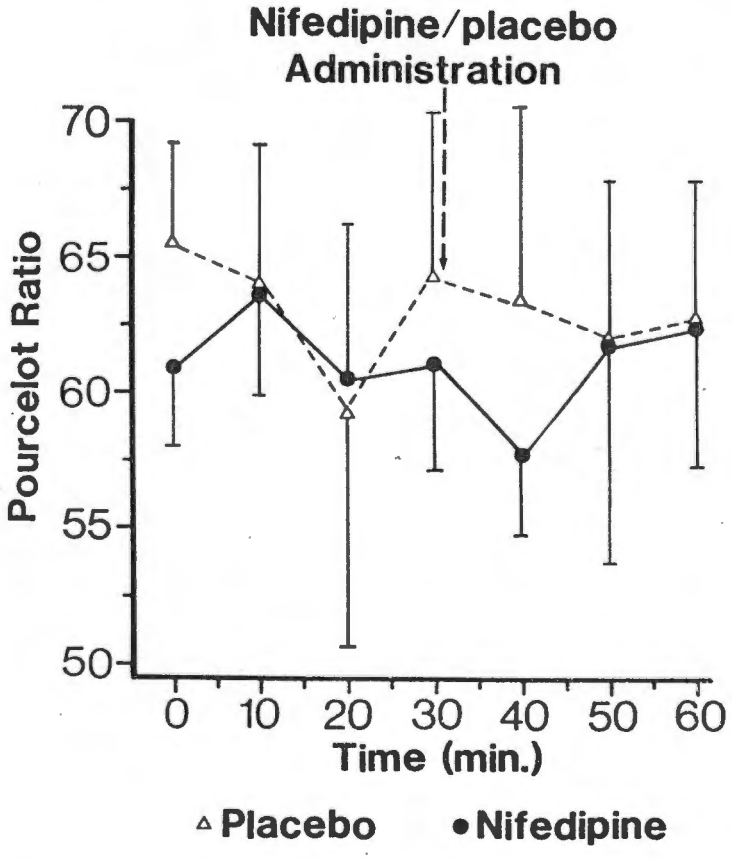

FIG. 8 Pourcelot ratio (Resistance Index) and standard error of the mean v time; (▲) = placebo (•) = nifedipine.

Side Effects

There were no maternal side-effects in either group. The continuous cardiotocograph recordings did not show any evidence of fetal distress.

CONCLUSION

Nifedipine 5mg, when given sublingually, does not cause any detrimental changes in the Doppler waveform analysis expressed as the Pourcelot ratio. This dose effected a drop in maternal diastolic blood pressure and an increase in maternal heart rate which was significant at 60 min (30 min after nifedipine administration).

STAGE II

OBJECTIVE:

To observe the effect of nifedipine on the Doppler umbilical artery waveform in fetuses with an abnormal (> 2SD from the mean) waveform. (Pattinson et al 1989(B).

DESIGN:

Prospective study using patient as her own control ie using the four readings prior to drug administration as control.

DRUG:

Nifedipine 10mg administered by expressing the contents out of the capsule under the tongue for one minute then swallowing the capsule with water. Ten mg dose was used in the second study:

1. The investigators had noted no adverse effects with the smaller dose in stage I.
2. This is the dose that is used in clinical practice.

SETTING:

Groote Schuur Hospital Maternity Centre, Observatory

INVESTIGATORS:

Dr M.S. Puzey } Study Design and Doppler Waveform
Dr S. W. Lindow } Analysis

Dr. T. Dunne : Department of Mathematical Statistics, UCT. Statistical Analysis.

SUBJECTS:

Twenty patients were recruited into the study over a two year period. All patients gave informed written consent, which was approved by the University of Cape Town Ethics Committee. The inclusion criteria required that the fetuses had abnormal velocity waveform in that the Doppler umbilical artery resistance was more than 2SD greater than the mean for that gestational age (Thompson et al 1988) (Pattinson et al 1989(B). Only singleton pregnancies were studied and it was decided that the fetuses should be greater than 28 weeks to provide more practical impact to the experiment. The patients were a heterogenous group as regards the aetiology of the increased placental resistance and no one pathology was used as an entrance criteria. Congenital abnormalities were excluded on Level III Ultrasound examination. Type II cardiotocograph decelerations (i.e. where the decelerations takes time to return to the baseline and does not mirror a contraction) (Turnbull et al 1989(C) were exclusion criteria in this study.

METHODS:

Patients were placed in the supine position at 30 degree lateral tilt for the entire 90min of the study. Their bladders were emptied before the investigations began to ensure that they were not uncomfortable. Fetal monitoring was commenced with a Hewlett Packard 8040A cardiotocograph machine running at a paper speed of 1 cm/s. Accurate

placement of the Doppler receiver over the heart was ensured using real time ultrasound. Maternal pulse rate, systolic blood pressure and diastolic blood pressure were measured at 10min intervals using a Critikon Dinamp Vital Signs Monitor (18465 X) with the correct size cuff measuring at least 2/3 of the anatomical arm. Doppler measurements were taken using a Siemens Sonoline S2 unit with a 100Hz filter at 10 minute intervals. The umbilical artery was identified with real time scanning and the sample volume of the pulsed Doppler was placed over the artery (Fig. 2). Each Doppler trace had the umbilical vein and artery visible throughout to ensure that the umbilical cord was sampled. The Doppler trace was observed until there was a constant trace devoid of the effects of fetal breathing. The trace was stopped when at least five uniform waves appeared and the A and B values were calculated from three waves. The average of the three waves was used as point A and B. (In most traces all three waves had exactly the same A and B values). The Pourcelot ratio was calculated as described in Fig. 3. The fetal heart rate was accurately measured between the peaks of alternate waves and the heart rate was calculated by the system computer. After 30min of recordings (i.e. 4 recordings) nifedipine was administered and a further 6 sets of recordings for the next one hour were obtained. Throughout the period the patient was asked if she experienced any side-effects from the drug.

RESULTS:

1. General

Twenty patients were studied at Groote Schuur Hospital Maternity Centre over a two year period. The mean ages and weights of the patients are shown in Table III. Five black patients and fifteen coloured patients consented to the study. Nine of the patients studied had proteinuric hypertension using the classification described by Davey et al (1986.)

TABLE III

GENERAL CLINICAL CHARACTERISTICS

Number of Patients	N = 20		
Mean Age	28,05 yrs	Standard Deviation	5,25
Mean Weight	70,55 kgs	Standard Deviation	12,92
Proteinuric Hypertensive Patients	N = 9		
Mean Parity	1,8	Standard Deviation	1,58

2. Maternal Heart Rate

The mean maternal pulse rate change measured with a Dinamp Vital Signs Monitor is shown in Fig. 9. At points (*) repeated measurement analysis of variance showed a significant difference for treatment by time interaction. ($p<.05$).

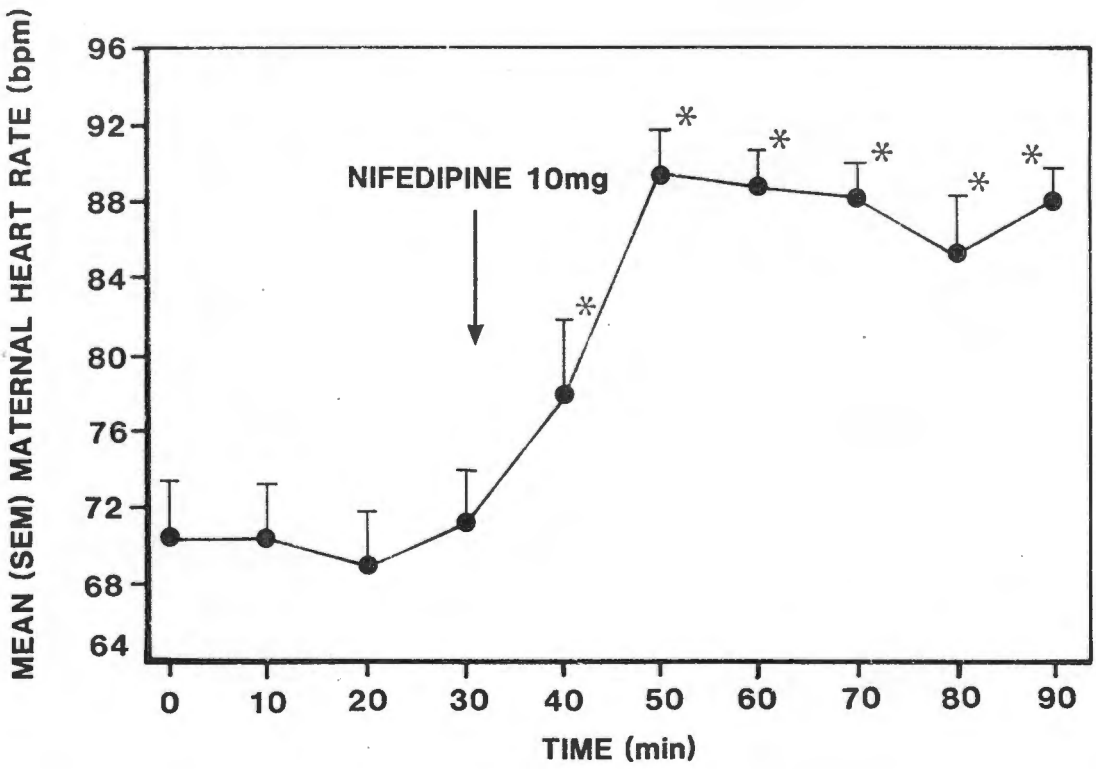

FIG. 9 Maternal heart rate and standard error of the mean plotted against time (min); before and after sublingual nifedipine administration.

3. Maternal Diagnostic Blood Pressure

The mean maternal blood pressure taken at 10 minute intervals with a Dinamp Vital Signs Monitor is shown in Fig. 10. Univariate tests were carried out at each time point and a significant fall in diastolic blood pressure ($p<.05$) was found after nifedipine administrations at points marked by an *.

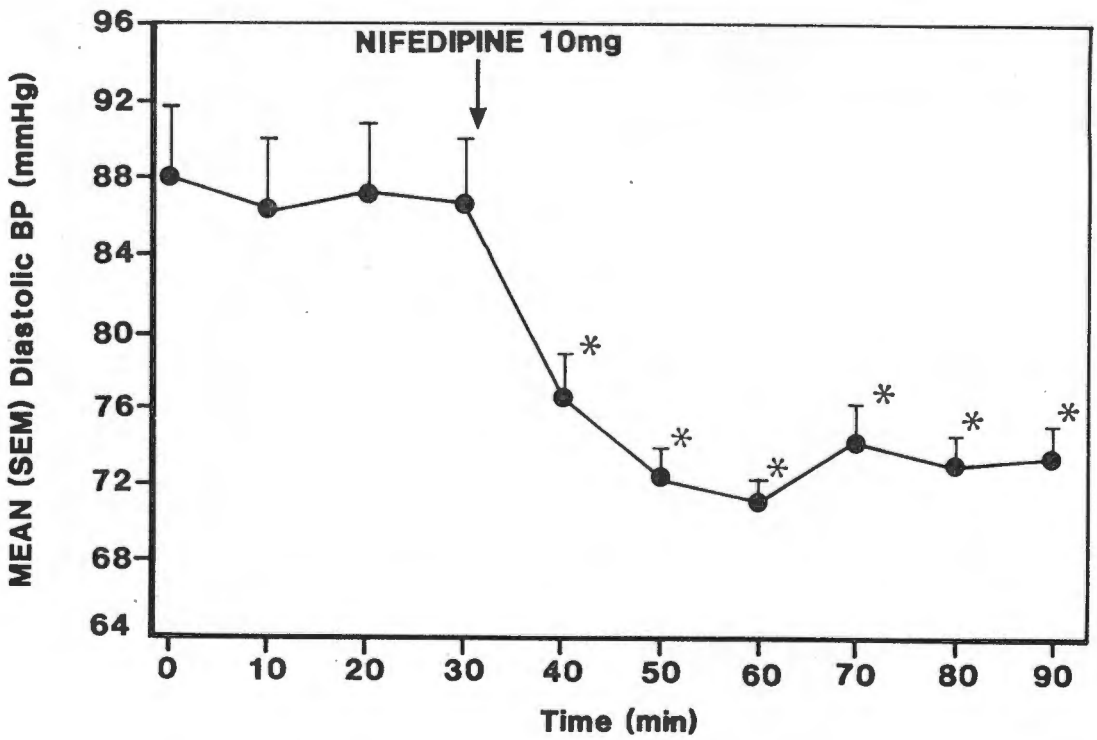

FIG. 10 Mean maternal diastolic blood pressure (mmHg) and standard error of the mean plotted against time (min); before and after sublingual nifedipine administration.

TABLE IV

DIASTOLIC BLOOD PRESSURE (BP) BEFORE AND AFTER NIFEDIPINE ADMINISTRATION

	PATIENT NUMBER	DIASTOLIC (BP) mmHg BEFORE NIFEDIPINE AT 30 MIN	DIASTOLIC (BP) mmHg AFTER NIFEDIPINE AT 60 MIN
HYPERTENSIVE GROUP	1	102	65
	2	90	76
	3	95	72
	4	96	75
	5	109	75
	6	106	70
	7	94	78
	8	109	75
	9	105	88
NON-HYPERTENSIVE GROUP	1	70	66
	2	72	69
	3	86	68
	4	82	72
	5	65	59
	6	80	66
	7	67	71
	8	67	67
	9	83	74
	10	88	64
	11	74	73

4. Fetal Heart Rate

The fetal heart rate was obtained by computer analysis of each alternate "A" value on the Doppler waveform trace. Correlation with the CTG recording was ensured in every reading. The mean fetal heart rate plotted against time is shown in Fig. 11. No significant change in fetal heart rate occurred before or after nifedipine administration. No subjective detrimental change in CTG tracing as observed by the clinician occurred in any patient examined and in one individual the abnormal trace improved after nifedipine administration. (See Discussion. Fig. 16).

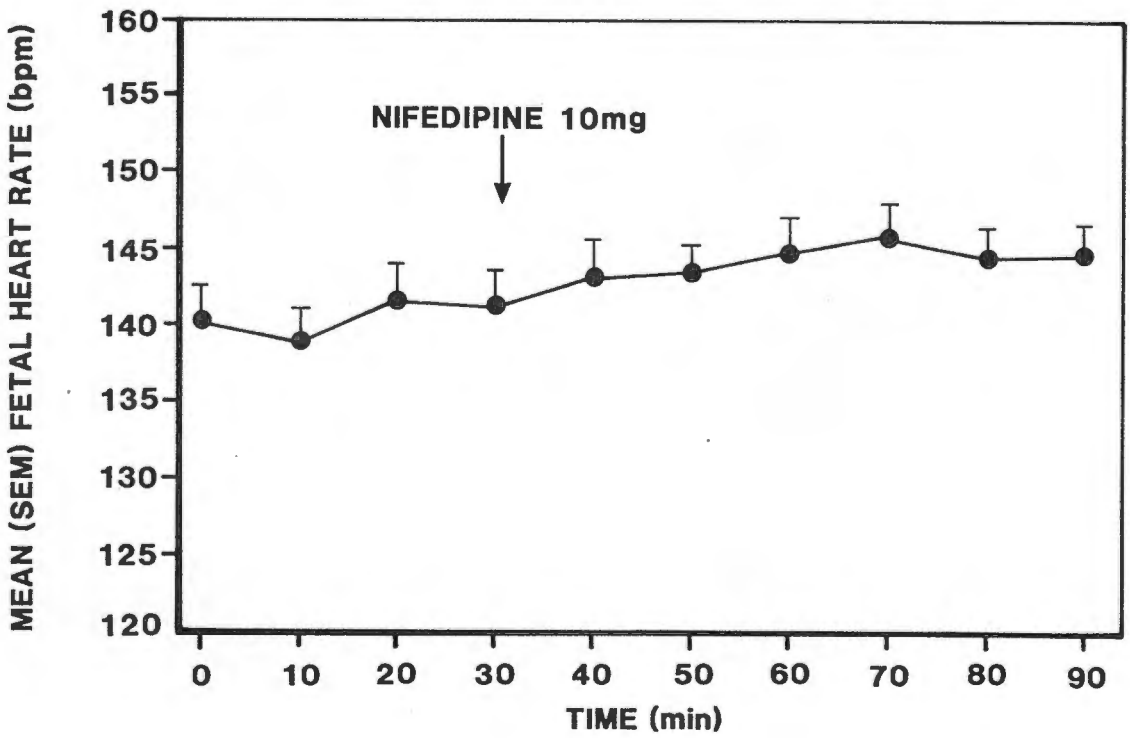

FIG 11 Mean fetal heart rate and standard error of the mean plotted against time (min); before and after sublingual nifedipine administration.

5. Resistance Index (RI)/Doppler Waveform Analysis

Before testing for any change in the ratio after drug administration 3 factors were addressed (see Literature review p 29)

i) The ratio was corrected for fetal heart rate at each measurement using the formula.

Corrected R.I. = Observers R.I. - 0,00266 (140 - observed FHR)

(Mires et al 1987)

ii) The effect of gestational age on the corrected RI was examined by plotting the mean change in corrected RI for each individual against the gestational age. No significant difference could be found between the change in RI through the gestational ages of patients examined; thus analysis of the mean change in RI could be conducted (Fig. 12).

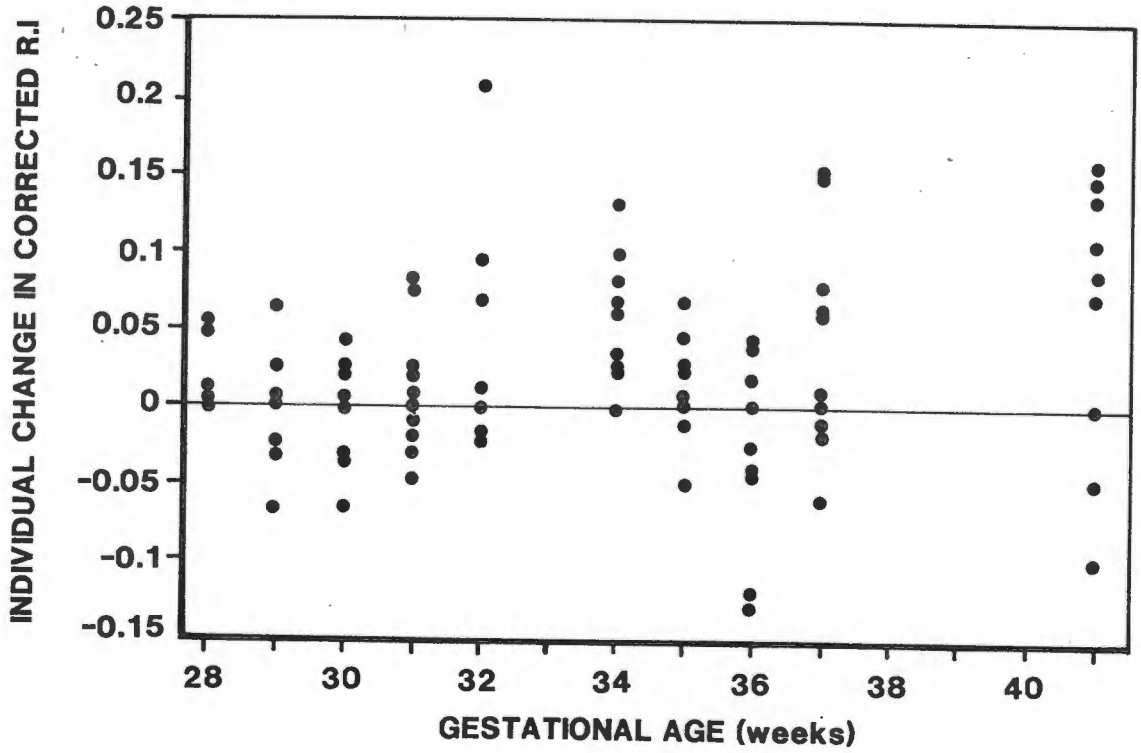

FIG 12. Relationship of change in corrected resistance index and gestational age (weeks) for each individual patient.

iii) There was no significant change in the mean "A" value before or after nifedipine administration (Fig. 13). This meant that the Doppler probe was not deviated to alter the angle of insonation of the artery to improve the umbilical artery waveform "B" value. (See p 26 of literature review). As the "A" value is unchanged any change in the Resistance Index can be attributable to an improvement in the "B" value.

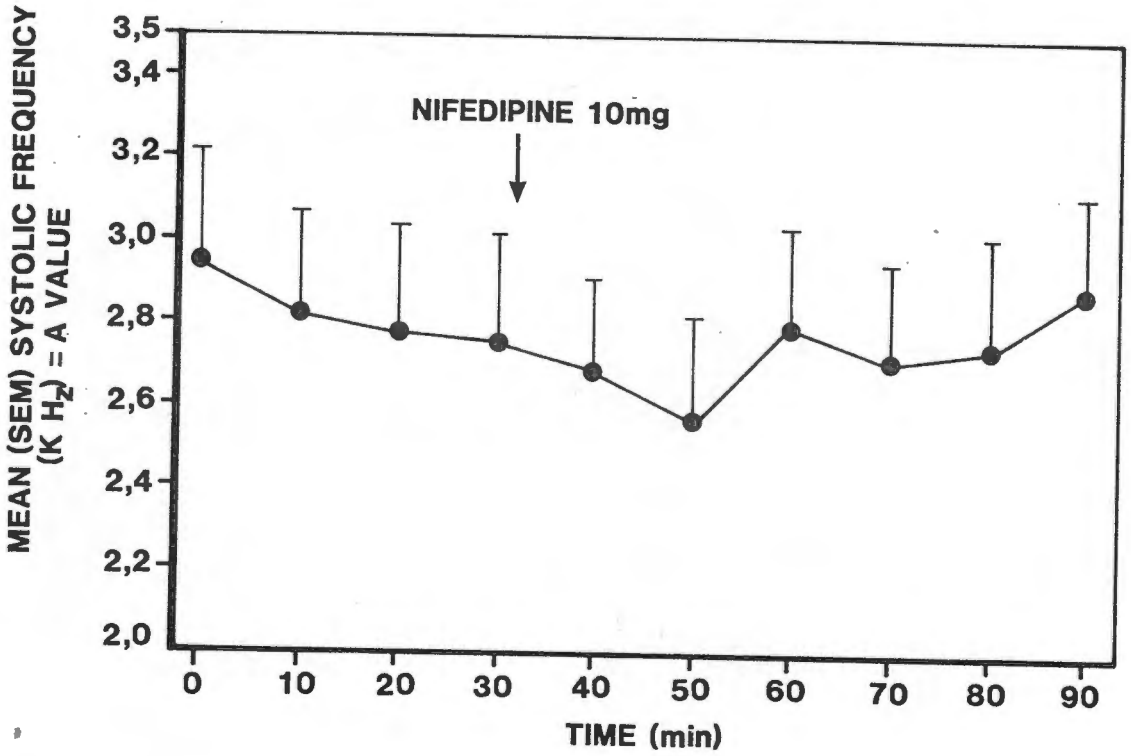

FIG 13 Mean "A" value and standard error of the mean plotted against time (min); before and after sublingual nifedipine administration.

Having ensured that the above factors did not influence the corrected resistance index, the effect of drug administration was examined. The change in corrected RI relative to the 30 min interval (i.e. just before nifedipine administration) was calculated. A significant change occurred at the 40; 50; 60; 70 and 80 min time points but by the 90 min point, that is 60 min after drug ingestion the ratio was not significantly different from the value at 30 min. (Fig. 14).

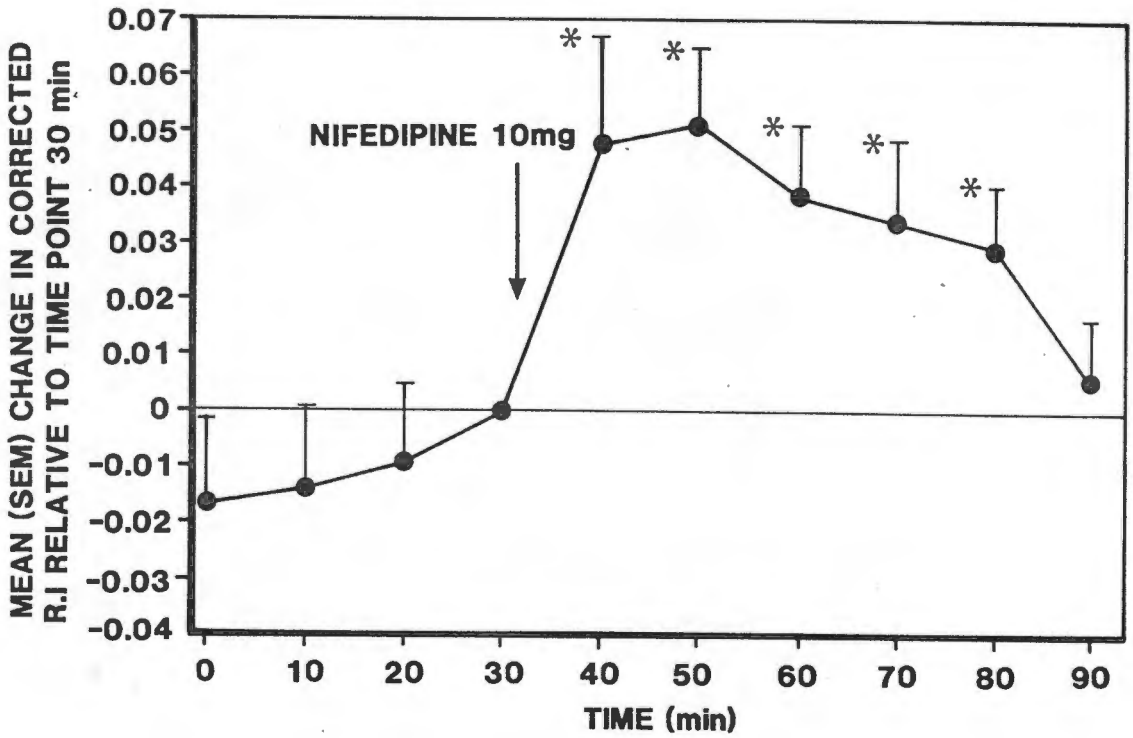

FIG. 14 Mean (SEM) change in corrected R.I. relative to time interval 30 min. plotted against time (min); before and after sublingual nifedipine administration.

The mean corrected resistance index against time also showed a significant decrease in ratio at the time points marked * ($p<.05$) (Fig. 15). This obviously mirrors the results of Fig. 14. The corrected R.I. at each time interval for the twenty patients examined is shown in Table IV. The reason for the resistance index greater than unity in this table is because of the correction factor for fetal heart rate. A fetal heart rate less than 140 increases the resistance index for absent and diastolic flow above unity. A fetal tachycardia in contrast reduces the ratio.

TABLE V

INDIVIDUAL VALUES OF THE R.I. OF THE UMBILICAL ARTERY (CORRECTED FOR FHR) THROUGH TIME FOR THE TWENTY PATIENTS INVESTIGATED

Corrected R.I.

Time (min)

	0	10	20	30	40	50	60	70	80	90
1	.99	1.00	1.05	1.07	.86	.88	1.00	1.07	1.06	1.05
2	.79	.78	.79	.73	.67	.74	.84	.73.	.74	.73
3	.82	.83	.86	.76	.77	.70	.74	.66	.70	.84
4	.65	.66	.68	.66	.59	.51	.60	.62	.59	.67
5	.81	.83	.80	.76	.77	.75	.74	.74	.75	.71
6	.77	.73	.73	.67	.72	.73	.69	.61	.70	.72
7	.79	.86	.81	.78	.74	.77	.79	.74	.82	.82
8	.80	.82	.76	.73	.70	.72	.67	.71	.73	.73
9	.76	.79	.77	.82	.75	.77	.74	.74	.82	.74
10	.76	.71	.70	.71	.72	.64	.68	.66	.68	.70
11	1.03	1.03	1.00	1.03	1.03	1.01	1.01	1.00	.99	1.00
12	1.02	1.01	1.02	1.01	1.05	.91	.93	1.05	1.04	1.03
13	1.03	1.01	1.07	.88	1.00	.85	.90	1.04	.82	1.01
14	.84	.79	.67	.74	.65	.60	.59	.58	.64	
15	.78	.68	.71	.84	.61		.74	.87	.82	.80
16	.69	.69	.79	.79	.77	.76	.72	.67	.66	.71
17	.89	.87	.91	.86	.74	.78	.87	.85	.85	.84
18	.83	.81	.74	.79	.59	.67	.67	.75	.73	.74
19	.79	.86	.81	.78	.74	.77	.79	.74	.82	.82
20	.70	.73	.74	.78	.76	.79	.70	.67	.66	.68

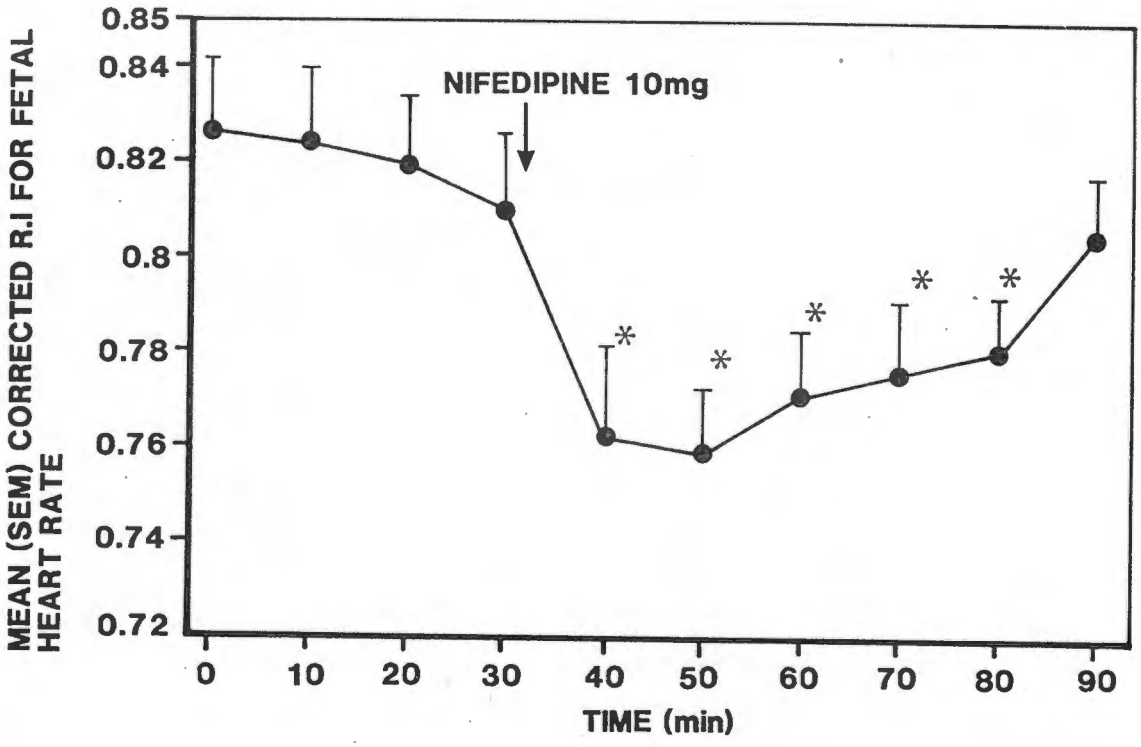

FIG. 15 Mean (SEM)corrected R.I. (for fetal heart rate) and standard deviation plotted against time (min);before and after sublingual nifedipine administration.

The change in corrected R.I. was not significantly different between the hypertensive and non-hypertensive groups.

6. Side Effects

13 patients had no side effects that they could attribute to the drug. Four individuals developed a frontal headache that occurred 10 min after taking the capsule and lasted for approximately 30 min. Three patients described the headache as "mild" and one as "severe". Two patients felt "dizzy" after drug administration and one patient described a marked increase in fetal movements.

CONCLUSION

Sublingual administration of 10 mg of nifedipine to patients with fetuses with an abnormal umbilical artery waveform caused a significant increase in maternal heart rate and decrease in maternal diastolic blood pressure. These results reflected the findings in Stage I of this thesis. As expected the fetal heart rate did not respond to maternal drug ingestion and this rate was accurately measured in this second study.

The second study however found that the abnormal (> 2 SD from normal) resistance index improved significantly after drug administration to within the normal range for this population group (Pattinson et al 1989(B). This improvement in waveform lasted 50 min, and reverted to the abnormal ratio 60 min after taking the capsule. The change in ratio occurred both in the hypertensive and non-hypertensive patients.

Six patients experienced adverse side effects in this study. These side effects were "mild" in 5 patients and did not result in any patient asking the investigator to stop taking recordings and abandon the study.

DISCUSSION

The results of this thesis have confirmed the safety and effectiveness of a single dose of nifedipine in the treatment of hypertension in pregnancy. In addition the second study has raised the exciting possibility of pharmacologically manipulating the fetus in utero to improve fetal wellbeing.

In stage 1 the value of the drug in lowering maternal blood pressure was demonstrated, and no adverse maternal or fetal effects were noted. This has been confirmed by two other authors who were researching the drug at the same time as our study was in progress (Rizzo et al 1987, Hanretty et al 1989). The first study did however show a transient improvement in doppler waveform and this led us to postulate that the drug may improve the resistance index. Animal work (Veille et al 1986) has shown that the drug crossed into the fetal circulation to preferentially vasodilate organ systems. In vitro work (Maigaard et al 1984) showed that vasodilation of placental arteries occurred, and together with the evidence that myofibroblasts were a major cellular constituent of the human placenta (Feller and Schneider 1985); pointed towards possibilities in manipulation of the feto-placental circulation.

Individual mention must be made of a single hypertensive patient (Patient 1) with a compromised fetus. This patient

was included because the cardiotocograph was normal prior to the commencement of the study. We were excited to note a subjective improvement in CTG after drug administration. Fig. 16 is a trace of the cardiograph at the time of drug administration. This shows decelerations, (these cannot be classified due to absence of the tocograph recording) that revert to an equivocal trace. Subsequently the trace became reactive. Furthermore the abnormal Doppler waveform returned to the normal range! (Figs. 17 & 18). (Table IV). This was the only patient who demonstrated any CTG improvement.

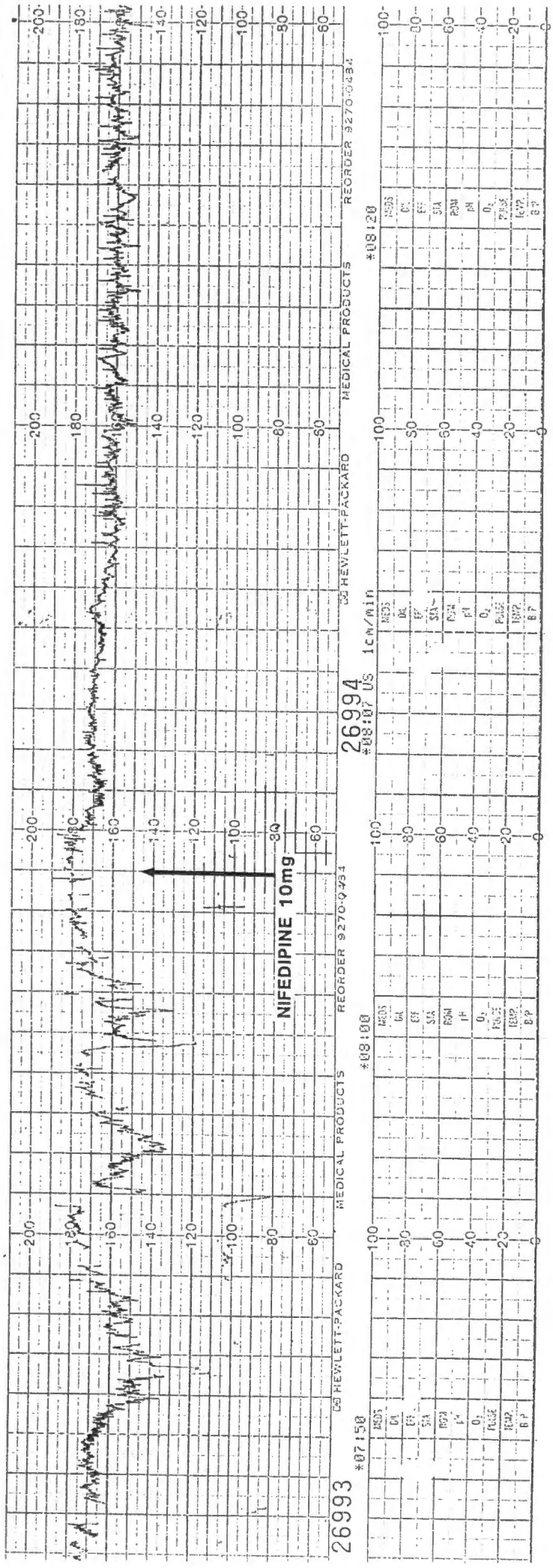

FIG. 16 Cardiotocograph of patient 1 before and after receiving sublingual nifedipine.

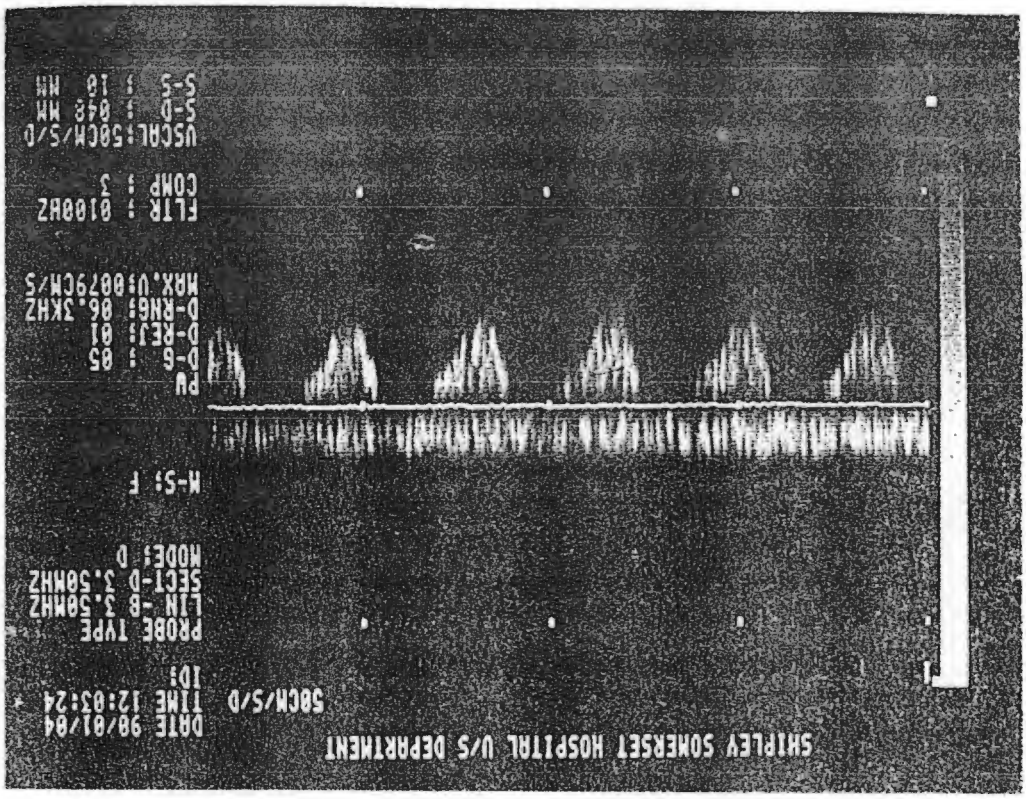

FIG. 17 Pulsed Doppler waveform pattern of the umbilical artery and vein of patient 1 at time interval 10 min before sublingual nifedipine administration.

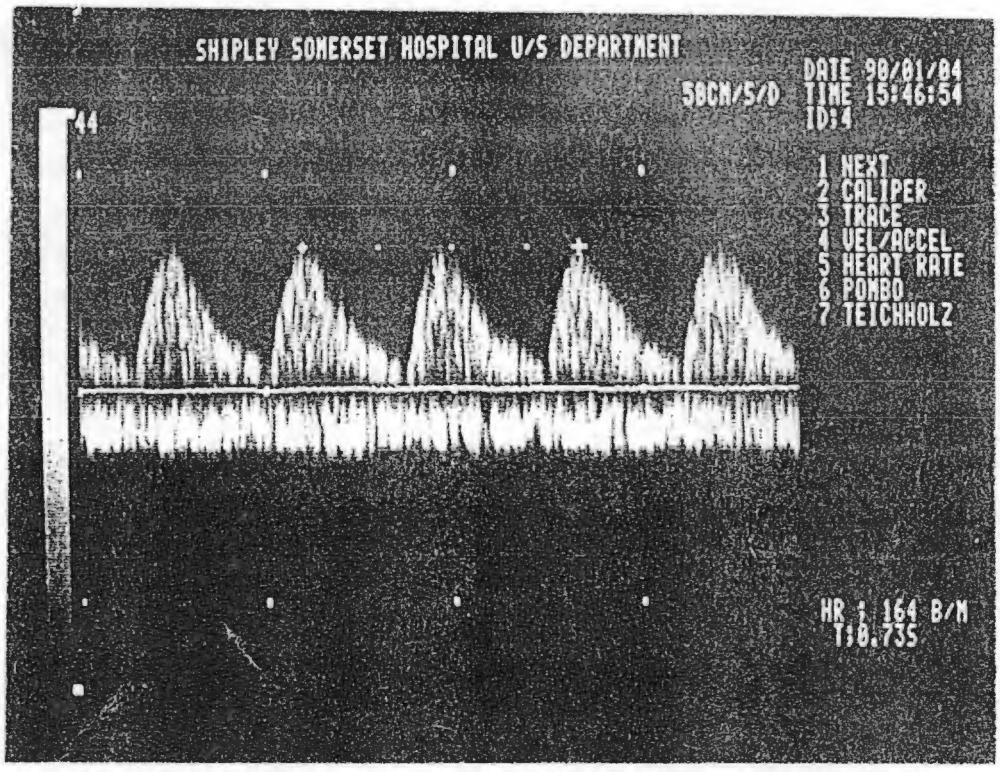

FIG. 18 Pulsed doppler waveform pattern of the umbilical artery and vein of patient 1 at time interval 50 min i.e. 20 min after sublingual nifedipine administration.

In phase 2 of this thesis the drug improved the Doppler waveform for up to 50 min after administration.
Why the drug improves the Doppler ratio may be difficult to explain, when referring to the following equation.

$$\Delta P = CO \times PR$$

ΔP = Change in Pressure

CO = Cardiac output

PR = Peripheral resistance

If the peripheral resistance changes (drug effect) then the same pressure change must occur in both diastole and systole - so that there will be no change in ratio of these parameters and the Doppler waveform ratio. In addition it is unlikely that the CO will be affected because our study study showed no change in fetal heart rate which is an important determinant of CO as expressed by the formula:

$$CO = SV \times FHR$$

CO = Cardiac Output

SV = Stroke Volume

FHR = Fetal Heart rate

The answer as to why the ratio is changed must lie in preferential organ perfusion. A preferential feto-placental perfusion could be caused by 2 mechanisms:

1. The uterus may be preferentially perfused because of the tocolytic action of nifedipine (Read and Wellby 1986). The "relaxed" uterus may therefore allow an improved fetal circulation. This may be a too

simplistic view of the physiological changes after drug administration.

2. Another explanation is based on the animal experimental models: the drug crosses into the fetal circulation and preferentially vasodilates the fetal cerebral and feto-placental circulations (Harake et al 1987). Relaxation of the chorionic plate arteries (Maigaard et al 1984) and promotion of the placental myofibroblast contractions (Feller and Schneider 1985) occur promoting blood flow in diastole. Increased blood flow in diastole will change the "B" value of the doppler waveform and improve the resistance index.

Perhaps this effect can even be amplified in gestational proteinuric hypertension. The spiral arteries with "intact" musculature (Robertson et al 1975) will respond to the vasodilator and increase their blood flow. This "expansion" of the maternal compartment may lead to increased water exchange over the placenta and "volume expand" the fetal circulation and improve the fetoplacental circulation.

An alternate possibility is that <u>the Doppler waveform characteristics are improved without a concommitant improvement in feto-placental blood flow.</u> It is acknowledged that without the simultaneous measurement of the umbilical artery diameter and the angle of insonation that blood flow cannot be determined. In those cases where absent diastolic blood flow returned after nifedipine

improved.

If diastolic blood flow has been regenerated in some cases at least, nifedipine could have new therapeutic indications. As a single dose intervention, practical implications of such therapy could be applied in emergency therapy, possibly as an emergency measure in supporting the fetal circulation in cases of fetal distress prior to caesarean section.

This thesis provides a new insight into fetal intra-uterine pharmacological manipulation. This is the only study to date examining the effect of a calcium antagonist in compromised fetuses, and hopefully further research will provide more insight into the pharmacological and physiological action of these drugs.

New calcium antagonists such as nimodipine (Langley et al, Sorkin 1989) appear to have a selective action on the cerebral circulation. This has obvious implications in the future treatment of eclampsia. It is hoped that a new generation of calcium channel blockers that are "target specific" may be the treatment of choice to enhance both maternal and fetal wellbeing.

CONCLUSION

1. Nifedipine as a single dose is a safe and effective anti-hypertensive agent in pregnancy.

2. Nifedipine administration in the third trimester of pregnancy results in no adverse fetal effects to the umbilical artery Doppler waveforms and the CTG pattern in patients with both normal and abnormal umbilical artery Doppler waveforms. The possibility exists for an improvement in waveform characteristics theoretically indicating beneficial fetal perfusion of the placenta.

ACKNOWLEDGEMENTS

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Miss Jill Artlett }
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Mr Dave Levin for preparing the Figures for publication.

Dr T Dunne for assisting with statistical analysis.

REFERENCES

Allen J, Maigaard S, Forman A, Anderson K E. (1988) Nitrendipine inhibits contractile activation of intra-myometrial arteriers from women with pregnancy induced hypertension. Abstracts XII World Congress of Ostetrics & Gynaecology. Rio De Janeiro FIGO. 183.

Bleker O P, Kloosterman G J, Mieras S J. (1975) Intervillous space during uterine contractions in human subjects. Am J Obstet Gynecol. 123; 697-699.

Brosens I, Robertson W B, Dixon H G. (1967) The physio-logical response of the vessels in the placental bed to normal pregnancy. J Pathol, Bacteriol. 93; 569-579.

Constantine G, Beeuers D G, Reynolds A Z, Luesley D M. (1987) Nifedipine as a second line antihypertensive drug. Br J Obstet Gynaecol. 94; 1 136-1 142.

Dale J, Landmark K H, Mhyre E. (1983) The effect of nifedipine, a calcium antagonist on platelet function. Am Heart J. 105; 103-105.

Dawes G S. (1969) Fetal and Neonatal Physiology Year Book. Medical Publishers Chicago. 66-77.

Davey D A, MacGillivray I. (1986) The Classification of Hypertensive Disorders of Pregnancy. Clin & Exper Hyper B5; 97-133.

Divon M Y, Guidetti D A, Braverman J J, Oberlander E, Langer O, Merkatz I R. (1988) Role of Doppler ultrasound in predicting IUGR. Obstet Gynecol. 72; 611-614.

Ducey J. Velocity waveforms in hypertensive disease. (1989) Clin Obstet Gynecol. 32; 679-686.

Erbel R, Brand G, Meter J, Effert S. (1983) Emergency treatment of hypertensive crisis with sublingual nifedipine. Postgrad Med J. 59; 134-136.

Erskine R L A, Ritchie J W K. (1985) Quantitative measurement of fetal blood flow using Doppler ultrasound. Br J Obstet Gynaecol. 92; 600-604.

Feller A C, Schneider H. (1985) Myofibroblast as a major cellular constituent of villous stroma in human placenta. Placenta. 6; 405-415.

Fenakel K, Fenakel G, Appelman Z, Lurie S, Katz Z, Shoham Z. (1991) Nifedipine in the treatment of severe pre-eclampsia. Obstet Gynecol. 77; 331-337.

Giles W B, Baird P J. (1985) Fetal umbilical artery flow velocity waveforms and placental resistance = a pathological correlation. Br J Obstet Gynaecol. **92**; 31-38.

Greiss F C, Gobble F C. (1967) Effect of sympathetic nerve stimulation on the uterine vascular bed. Am J Obstet Gynecol. **97**; 962-967.

ter Haar G, Duck F A, Mortimer A J, McKinney P A. (1987) Proceedings of The British Institute of Radiology. Br J Radiol **60**; 207-208.

Hanretty K P, Whittle M J, Howic C A, Rubin P C. (1989) Effect of nifedipine on Doppler flow velocity waveforms in severe pre-eclampsia. Br Med J. **299**; 1205-1206.

Harake B, Gilbert R, Ashwal S, Power G. (1987) Nifedipine : Effects on fetal and maternal haemodynamics in pregnant sheep. Am J Obstet Gynecol. **157**; 1003-1008.

Harbert G M. (1982) Uterine and placental blood flow Masson Publishing New York. Edited by Moaward AH, Lindheimer MG. 193-199.

Hastie S J, Howie C A, Whittle M J, Rubin P C. (1988) Daily variability of umbilical and lateral uterine wall artery blood velocity waveform measurements. Br J Obstet Gynaecol. 95; 571-574.

Henderson L M, Aghamohammad S Z, Arlett C F, Cole R J. (1986) Lack of discernible effect of diagnostic ultrasound on the chromosomes of cord blood lymphocytes exposed in utero. Br J Radiol. 59; 499-503.

Jensen A, Kunzel W, Hohmann M. (1978) Dynamics of fetal organ blood flow redistribution and catecolamine release during acute asphixia. The physiological development of the fetus and newborn. Edited by Junes CT, Nathanielsz PW. London Academic Press. 405-410.

Krantz K E, Parker J G. (1963) Contractile properties of the smooth muscle in the human placenta. Clin Obstet Gynecol. 6; 26-38.

Langley M S, Sorkin E M. (1989) Nimodine : A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cerebrovascular disease. Drugs. 37; 669-699.

Laurin J, Lingman G, Marsal K, Persson P H. (1987) Fetal blood flow in pregnancies complicated by intra-uterine

growth retardation. Obstet Gynecol. 69; 895-902.

Lieb S M, Cabalum T, Zueaibm M, Erkkola R, Tabsh K, Ushioda E, Nuwayid BS, Brinkman CR, Assali NS. (1980) Vascular reactivity to angiotension II in the normotensive and hypertensive ewe. Am J Physiol. 238; H209-H213.

Lindow S W, Davies N, Davey D A, Smith J A. (1988) The effect of sublingual nifedipine on uteroplacental blood flow in hypertensive pregnancy. Br J Obstet Gynaecol. 95; 1276-1281.

Maigaard S, Forman A, Anderson K E. (1984) Effects of nifedipine on human placental arteries. Gynaecol Obstet Invest. 18; 217-224.

Mannor S M, Serr D M, Tamari I, Mestharer A, Frei E. (1972) The safety of ultrasound in fetal monitoring. Obstet Gynecol 72; 653-658.

Meire H B. (1987) Proceedings of the British Institute of Radiology : Safety of diagnostic ultrasound. Br J Radiol. 60; 707-708.

Mires G, Dempster J, Patel N B, Crawford J W. (1987) The effect of fetal heart rate on umbilical artery flow velocity waveforms. Br J Obstet Gynaecol. 94; 665-669.

Moretti M M, Fairlie F M, Akl S, Khovry A D, Sibai B M. (1990) The effect of nifedipine therapy on fetal and placental Doppler waveforms in pre-eclampsia remote from term. Am J Obstet Gynecol. **163**; 1 844-1848.

Murrow R J, Adamson S L, Lewin M, Bill S, Ritchie J W. (1989) The influence of spontaneous accelerations of fetal heart rate on the umbilical artery velocity waveforms. Am J Obstet Gynecol. **160**; 995-997.

Naeijie R, Melot C, Mols P, Hallemans R. (1982) Effects of vasodilators on hypoxic pulmonary vaso-constriction in normal man. Chest. **82**; 404-409.

Overlack A, Zenzen J G, Nessel C, Muller H M, Stumpe K D. (1987) Influence of magnesium on blood pressure and effect of nifedipine in rats. Hyperten. 9; 139-143.

Panigel M. (1986) Anatomy and Morphology. Clinics Obstet Gynecol. 13:3; 421-445.

Pattinson R C, Kriegler E, Odendaal H J, Muller L M M, Kirsten G. (1989(A) Increased placental resistance and late decelerations associated with severe proteinuric hypertension predicts poor fetal outcome. S Afr Med J. 75; 211-214.

Pattinson R C, Theron G B, Thompson M L, Lai tung M. (1989(B) Doppler ultrasonography of the fetoplacental circulation - normal reference values. S Afr Med J. 76; 623-625.

Payen D M, Penaud M L J, Lampron N, De Kersant, Gilly A, Nicolas F M. (1984) Common carotid haemodynamic and metabolic effects of acutely administered nifedipine in human subarachnoid haemorrhage. Cardiovas Res. 18; 626-631.

Pearce J M, Cambell S, Cohen-Overbeck T, Hackett G, Hernandez J, Royston J P. (1988) Reference ranges and sources of variation for indices of pulsed doppler flow velocity from the uteroplacental circulation. Br J Obstet Gynaecol. 95; 248-256.

Pijnenborg R, Anthony J, Davey D A, Rees A, Tiltman A, Vereruysse L, van Assche A. (1991) Placental bed spiral arteries in the hypertensive disorders of pregnancy. Br J Obstet Gynaecol. 98; 648-655.

Puzey M S, Ackovic K L, Lindow S W, Gonin R. (1991) The effect of nifedipine on fetal umbilical artery Doppler waveforms in pregnancies complicated by hypertension. S Afr Med J. 79; 192-194.

Read M D, Wellby D E. (1986) The use of a calcium antagonist (nifedipine) to suppress preterm labour. Br J Obstet Gynaecol. 93; 933-937.

Reynolds S R M. (1966) Formation of fetal cotyledons in the hemochorial placenta : a theoretical consideration of the functional implications of such an arrangement. Am J Obstet Gynecol. 94; 425-439.

Rizzo G, Ardunini D, Mancusos S, Romanini C. (1987) Effects of Nifedipine on umbilical artery velocity waveforms in healthy fetuses. Gynecol Obstet Invest. 24; 151-154.

Robertson W B, Brosens I, Dixon G. (1975) Uteroplacental vascular pathology. Eu J Obs Gynaecol Reproductive Biology. 5(1-2); 47-65.

Rogers H J, Spector R G, Trounce J R. (1981) A textbook of clinical pharmacology. London, Hodder and Stroughton. pg. 382.

Seabe S J, Moodley J, Becker P. (1989) Nifedipine in acute hypertensive emergencies in pregnancy. S Afr Med J. 76; 248-250.

Thompson R S, Trudinger B J, Cook C M. (1988) Doppler ultrasound waveform indices : A/B ratio, Pulsatility index and Pourcelot ratio. Obstet Gynecol. 95; 581-588.

Trudinger B J, Giles W B, Cook C M, Bombardieri J, Collins L. (1985) Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. Br J Obstet Gynaecol. 92; 23-30.

Turnbull A, Chamberlain G. (1989(A) Obstetrics. London: Churchill Livingstone; 70-76.

Turnbull A, Chamberlain G. (1989(B) Obstetrics. London: Churchill Livingstone; 72.

Turnbull A, Chamberlain G. (1989(C) Obstetrics. London: Churchill Livingstone; 376-380.

Veille J C, Bissonnette J M, Hohimer A R. (1986) The effect of a calcium channel blocker (nifedipine) on uterine blood flow in a pregnant goat. Am J Obstet Gynecol. 154; 1160-1163.

Waisman G D, Mayorga C M, Camera M I, Vignolo C A, Martionotti A. (1988) Magnesium plus nifedipine : Potentiation of hypotensive effect in pre-eclampsia? Am J Obstet Gynecol. 59; 308-309.

Walters B N J, Redman C W G. (1984) Treatment of severe pregnancy associated hypertension with the calcium antagonist nifedipine. Br J Obstet Gynaecol. 91; 330-336.