

"I ask you now to turn your thoughts to the future and to
consider where further progress is most wanted....
We want in medicine more of the knowledge that can
only be gained through research"

Elizabeth Garrett Anderson 1903

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DOPPLER INVESTIGATION OF PLACENTAL BLOOD FLOW

IN THE SECOND TRIMESTER:

A SCREENING STUDY FOR PRE-ECLAMPSIA AND GROWTH RETARDATION

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Original work submitted for the degree of Doctor of Medicine,
University of London 1989.

I declare that the work contained in this thesis is original work carried out by myself at Kings College Hospital, Denmark Hill, London unless otherwise stated in the text. All the work was carried out between September 1986 and October 1988. Women were recruited for the screening study between 17.2.87 and 27.8.87.

Signed..... Date..... 16/12/88

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ABSTRACT

In a cross-sectional study of 977 women recruited from the booking ultrasound clinic at 16-24 weeks gestation, the resistance index (RI) in the uteroplacental circulation and umbilical artery were measured by continuous wave Doppler ultrasound. Reference ranges for these indices were constructed and their relation to maternal social factors and morphometry established. Pregnancies with high values had a higher incidence of pre-eclampsia, abruptio, small-for-gestational age babies, and fetal wastage. Cut-off levels for sensitivity and specificity for the prediction of complications were produced.

Additional studies were made. The RI varied with uterine site and placental location so a new methodology for insonation was developed. Confirmation of the vessel studied was supplied by colour flow mapping and in-vivo studies at laparotomy. The intra-observer error was established. The feasibility of the screening study and methodology were tested in a pilot study of 21 women. The hospital computer provided pregnancy and delivery details in 832 cases. The reliability of the data was assessed in a comparative study of 50 cases. In the remaining 145 cases information was collected after a series of searches including 2 postal requests to GPs and subjects. Follow-up was successful in 96.5% of cases. In 237 cases where pregnancy complications were recorded the medical notes were retrieved and 3 independent

observers coded the diagnoses. The changes in RI with gestation observed in the cross-sectional study were confirmed in a longitudinal study of 33 women from 16-40 weeks. A postpartum study of 21 women suggested the restitution of the uteroplacental circulation to its non-pregnant state does not occur immediately after delivery. Predictions of pregnancy complications by Doppler parameters were compared to one another and to an obstetric risk score. Furthermore, in 183 women, the maternal serum AFP, HPL, BHCG, PAPP-A, SP1 and PP12 were poorer predictors than Doppler ultrasound.

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1. LITERATURE REVIEW

1.1 INTRODUCTION

Although pre-eclampsia (PET) and intrauterine growth retardation (IUGR) are major causes of maternal and perinatal mortality and morbidity, the conditions are poorly defined and the underlying pathology ill-understood. Furthermore, screening tests for these conditions are impractical and have low sensitivity and specificity. Doppler ultrasound appears promising for prediction of outcome in pregnancies complicated by hypertension or a small baby. On the assumption that the underlying pathology may be impaired placental perfusion, the aim of the present study was to determine if assessment of the utero- and feto-placental circulations in the second trimester by Doppler ultrasound was useful as a screening test for these conditions. A review of the literature was undertaken. Section 13 contains a glossary and definitions of the terms used.

1.1.1 Historical perspective

Hippocrates, living on the island of Cos, circa 460 BC, might have been referring in his Aphorisms to eclampsia when he said that "If a woman with child is attacked by one of the acute diseases, it is fatal", and to the problems of placentation when he described "those who have the womb over-dry and very hot do

not conceive, for the seed perishes through lack of nourishment". Aristotle (384-322 BC) recognized the relationship between mammalian mother and fetus via the umbilical circulation; "the vessels join onto the uterus like the roots of plants and through them the embryo receives its nourishment. This is why the embryo remains in the uterus".

Further understanding of the pathophysiology of pregnancy was slow although the consequences were well-known. "No disease is more dreadful and alarming in appearance than convulsions... the disease is always attended with the utmost hazard and frequently kills the woman... the membranes should be broken and the delivery assisted whenever the circumstances of the case will admit of it" (Hamilton 1751).

In 1843 both Lever and Simpson reported the presence of albuminuria prior to and with convulsions (Lever 1843, Simpson 1843). Lever noted "the coincidence of an albuminous condition of the urine" with puerperal convulsions in 14 women and found little or no albuminuria in catheter specimens from 50 normal parturients. Simpson commented that this was "probably granular renal disease" and likened the illness to Brights disease. Pre-eclampsia remained ill-understood and the "disease of theories" (Zweifel 1895).

John Hunter and Colin Mackenzie performed experiments injecting the umbilical vessels of twins of a dead mother, showed that maternal and fetal circulations did not mix and concluded that fetal nourishment was derived from absorption (Radcliffe 1967). The first careful postmortem analysis of the causes of stillbirth was made by Spencer who concluded that trauma alone was the chief factor, but he did not examine the fetuses who were macerated (50 of 180) and had died before labour (Spencer 1891). Young was the first to suggest that the placenta caused stillbirth and that fetal villi were nourished by maternal blood (Young 1914). He stated that placental infarction liberated toxins, finding "recent autolytic changes in the affected area... that generate the poison". He speculated that small accidental haemorrhages might precede toxæmia but that large ones led to the death of the mother or fetus before the development of symptoms or obvious changes of infarction in the placenta. This laid the foundations for the concepts of uterine ischaemia and placental anoxia.

Using radioactive sodium (^{24}Na) to measure uterine blood flow, Browne and Veall (1953) demonstrated a fall in blood flow in cases of PET, confirming the association of 'uterine ischaemia' if not the underlying pathology. Robertson et al (1967) described characteristic abnormalities in the placental bed vasculature of pregnancies complicated by hypertension irrespective of the association with IUGR.

With the development of expectant treatment, which, in the Rotunda hospital in 1896, consisted of morphia, venesection, purgation, oxygen, nil by mouth, lying the woman on her side and minimal interference (Tweedy 1896), mortality from eclampsia had begun to fall at the turn of the century. In Britain in 1922, maternal mortality was reported to be 22.1% following eclampsia (Eden 1922). By 1924, in Leningrad, it had fallen to 2.4% of a series of 253 eclamptic patients (Stroganoff 1924). In 1940 the maternal death rate from eclampsia was 0.4 per 1,000 total births, out of a total maternal mortality rate of 3.28 per 1,000 (Browne 1954).

The association of eclampsia with increased blood pressure and proteinuria led to attempts at detection at an early stage by serial clinical examinations. Visiting pregnant women with 'outdoor antenatal clinics' started in the 1900s but was superseded by the development of hospital antenatal clinics where women were seen regularly. The first was set up in Adelaide, Australia, in 1910 (Browne 1954). The regular monitoring of blood pressure and testing of urine remain the cornerstone of antenatal care and the detection of pre-eclampsia.

This strange, progressive, multi-system disease of pregnancy, which is reversed by delivery of the products of conception, still has an unknown aetiology, but very serious sequelae for mother and fetus and still no specific modes of treatment or

prevention (Redman 1987). Hypertension in pregnancy is still a leading cause of maternal mortality in Britain (DHSS 1989). The remote prognosis of eclampsia, however, is good and it is not a sign of latent hypertension nor causes hypertension (Chesley et al 1976).

The goal of obstetric care has moved on from avoiding maternal death to producing a healthy baby, both physically and mentally intact, and a happy mother. It is recognised that antenatal factors can damage babies and underlying abnormalities of the reproductive process were often present well before labour and delivery (Illingworth 1979). In Illingworth's own series of 762 cases of cerebral palsy, 30% had been delivered prematurely, 7.5% had congenital anomalies and 5% had an affected sibling suggesting that social and genetic factors play a large role.

Although in the last 20 years an ever-expanding range of methods have been developed to assess the condition of the fetus in PET and IUGR pregnancies there is a paucity of reports on early prediction. There are a variety of techniques for assessment of fetal well-being. Reduced fetal movements preceding fetal death (Sadovsky and Yaffe 1973) led to the development of kick-count charts, KCC (Pearson and Weaver 1976). These simple tests of fetal well-being have been supplemented with cardiotocography, CTG, (Visser and Huisjes 1977, Lavery 1982) and the biophysical profile, BPP (Manning et al 1980).

Ultrasound (Donald et al 1958) has allowed structural study of the fetus (Nicholaides and Campbell 1987) and its growth in utero (Campbell and Thoms 1977). Antenatal fetal blood sampling (Daffos et al 1984) has resulted in even closer access to the fetus and a comprehensive understanding of fetal physiology.

With perinatal mortality falling, there is a need for "a non-invasive and repetitive technique that would achieve diagnostic precision in prenatal diagnosis of fetal hypoxia" (Symonds 1987). There is an even more acute need for a non-invasive technique for screening and the early detection of complicated pregnancies that may have an environment hostile to the fetus. Concentration on the accurate early identification of the high risk pregnancy potentially leads to early intervention and prevention of damage.

1.2 ANATOMY OF THE PLACENTAL CIRCULATION

1.2.1 Anatomy of the uteroplacental circulation

The pregnant uterus is supplied by the two uterine arteries with a small contribution from the ovarian arteries (Smout et al 1953). There are extensive ipsilateral and contralateral collateral anastomoses although they may not be functional in normal pregnancy (Itskovitz et al 1980). The uterine arteries divide into arcuate arteries that traverse the uterine surface and give off radial arteries that penetrate the myometrium at right angles (Boyd and Hamilton 1970). These branch into basal arteries, supplying the myometrium and decidua, and two or more spiral arteries that communicate with the intervillous space (IVS). There are about 100 functional openings of spiral arteries into the IVS in a mature placenta (Boyd and Hamilton 1970) but maternal blood enters the IVS in discrete spurts from only a few spiral artery orifices (Ramsey et al 1963). Three dimensional plastic polymer injections have shown the asymmetric origins of the arcuate arteries and their marked tortuosity (Itskovitz et al 1980) (Figure 1).

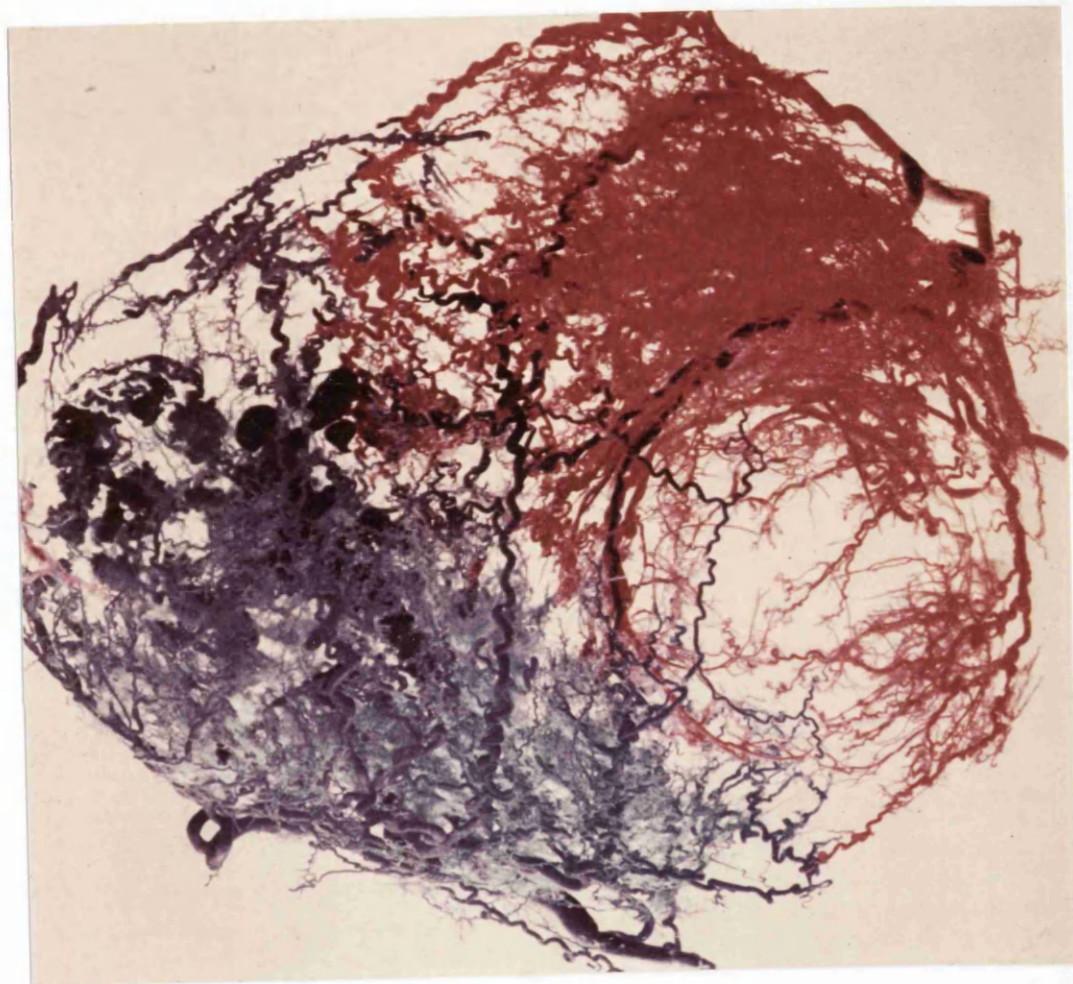


Figure 1 Polymer injection of uterine arteries of a pregnant uterus demonstrating the anatomy of the uteroplacental circulation (with permission, *Obstet Gynecol* 1980;55:67-71)

1.2.2 Anatomy of the fetoplacental circulation

The umbilical cord contains two arteries and a vein that branch into chorionic vessels which pass through the chorionic plate and are continuous with the cotyledonary arteries and veins. These branch into villous arteries, veins and capillaries of the fetal cotyledons and are situated in the stroma and in the terminal villi (Boyd and Hamilton 1970). During pregnancy there is a progressive change in the type of villi found predominantly. In the first trimester they are largely stem villi, in the second, intermediate, and in the third, terminal villi budding off from the intermediate villi (Kaufmann et al 1979). These small terminal villi have a large surface area to volume ratio for efficient gas and nutrient exchange. The placenta has an initial reparative response to ischaemia. Reduced maternal blood supply leads to a proliferation of cytotrophoblastic cells and a thickening of the basement membrane (Fox 1983).

1.2.3 Histopathology

1.2.3.1 Findings in normal pregnancy

These have been divided into findings using light and electron microscopy.

1.2.3.1.1 Light microscopy

Brosens and co-workers (1967) obtained "several hundred" placental bed biopsies from normal women in late pregnancy, taken directly at Caesarean section (CS). A smaller number were taken blindly at vaginal delivery. They found that, in pregnancy, basal arteries showed no changes but spiral arteries were invaded by cytotrophoblast and underwent marked changes to become uteroplacental arteries. These uteroplacental arteries have a dilated and tortuous lumen, a complete absence of muscular and elastic tissue, no continuous endothelial lining, mural thrombi and fibrinoid deposition. Large cytotrophoblast cells were seen in the walls. Although the authors postulated that the changes in the vessel wall were a consequence of trophoblast invasion, the study was purely descriptive and no gestation related sequence was described. The diameter of these vessels increased from 15-20 to 300-500 (Brosens et al 1972) suggesting that this conversion of spiral arteries to uteroplacental arteries allows a great volume of blood to flow to the uterus.

Pijnenborg et al (1980) studied trophoblastic invasion of decidua in 48 intact uteri removed for therapeutic reasons from normal women at eight - 18 weeks' gestation. Cytotrophoblast invades both the distal ends of the spiral arteries and the decidual interstitium. The invasion and conversion of spiral arteries had started before eight weeks and although the study was not

continued beyond 18 weeks the conversion to uteroplacental arteries seemed to have been completed by that time.

1.2.3.1.2 Electron microscopy

De Wolf et al (1973) examined placental bed biopsies taken from six normal women at or near term having CS for obstetric reasons and made the same observations as Brosens et al (1967). The fine structure of fetal and maternal cells in the placental bed corresponded to their ultrastructure. This study confirmed the presence of trophoblast cells in the vessel wall and gives strong support to the view that they cause the normal physiological changes rather than appear there as a consequence.

1.2.3.2 Abnormal findings in complicated pregnancies

There has been dispute as to whether the lesions found in PET and IUGR are distinct from one another.

1.2.3.2.1 Qualitative studies: Pre-eclampsia

Robertson et al (1967) examined "more than 100" placental bed biopsies from hypertensive women at CS. In those with PET they found acute necrosis of the small vessel wall, most clearly seen in the basal arteries, with foam cells or 'acute atherosclerosis'. The most severe changes were seen in the decidual segments and

although the same changes were observed in the spiral arteries, they were complicated by the normal physiological changes. In contrast, in essential hypertension hyperplastic lesions, fibroblast and smooth muscle proliferation in the intima and media were seen most clearly in the basal arteries, but also in the spiral arteries, which assumed the appearance of longstanding arteriosclerosis. In cases of essential hypertension with superimposed PET, a combination of necrotising and hyperplastic lesions were found. This study suggests that there is different pathology in different types of hypertension and emphasizes the heterogeneity of the underlying causes of this particular abnormal sign in pregnancy.

1.2.3.2.2 Qualitative studies: Growth retardation

Sheppard and Bonnar (1981) challenged the view that there was a specific lesion in hypertension when they performed light and electron microscopy on placentae and placental bed biopsies taken from 80 women at CS. 45 women had hypertension and 30 IUGR (<10th centile). Normal physiological changes were found when the birthweight was >10th centile in normotensive women (23/24) and when the birthweight was >50th centile in pre-eclamptic women (11/11). In contrast, in pregnancies with IUGR babies, atheromatous-like lesions with complete or partial occlusion, lipid laden cells and fibrin deposition were seen in decidual spiral arteries whether there was pre-eclampsia ("majority"/11)

or not (8/11). There were no babies in this study weighing between the 25th and 50th centiles and the results were presented differently in each subgroup. These findings did not agree with Brosens et al (1977) where an absence of normal physiological changes was seen in all cases of PET, whether accompanied by appropriate-for-gestational-age (AGA) (8/8) or small-for-gestational-age (SGA) (15/15) babies, all cases of essential hypertension with SGA babies (10/10) and most cases of normotensive SGA (10/18). Acute atherosclerosis was only seen in patients with proteinuric hypertension. Whatever the discrepancies, it would appear that there is an overlap of histopathology in PET and IUGR.

1.2.3.2.3 Quantitative studies

Gerretsen et al (1981) tried to resolve the controversy by examining 277 placental biopsies taken at CS and transcervically without knowledge of the clinical condition. Only 93 specimens contained a portion of the spiral artery at the site of the decidua-myometrial junction, and the rest were rejected. Even with the assumption that one spiral artery represented the whole uteroplacental bed they found a strong association between PET and the absence of physiological changes. Thus, in 22 of 23 normal pregnancies there were physiological changes. In contrast, 29 of 30 pre-eclamptic women had absent physiological changes. In a mixed group of 40 women with other complications,

17 of 19 with AGA babies had normal changes, and 13 of 21 with SGA babies had normal changes. Furthermore, increasing absence of physiological changes was associated with increasing severity of IUGR. This more carefully selected work resolves the discrepancy, in that there is not a specific lesion for PET. There is a strong association of absence of physiological changes and PET and a less constant association with IUGR.

Khong et al (1986) reviewed some of the archived biopsies of Brosens et al. Without clinical information, they assessed the proportion of spiral arteries converted to uteroplacental arteries in 94 central zone placental bed biopsies and 65 placentae. There was no evidence of trophoblast induced physiological change in the myometrial segments of all cases of PET (Blood pressure [BP] > 140/90mm Hg and >500mg proteinuria) and 2/3 of the SGA, but they also noted an absence of trophoblastic invasion in the decidual segments in about half the cases of PET and SGA.

Spiral arteries were also be seen in some basal plates. Among 50 such placentae, 18 showed either no change or a mixture of altered and unaltered spiral arteries and all these pregnancies were abnormal. This suggests that there is an inadequate physiological response both qualitatively and quantitatively in PET and SGA.

1.2.3.2.4 Fetoplacental changes

Using latex injection and corrosion cast techniques, Lee and Yeh (1986) examined the placentae from seven women delivered, all but one at term, of SGA fetuses (<10th centile) and compared light microscopy and electron microscopy of the capillary network. They found a dense capillary network, 'H' shaped anastomoses, budding projections and less branching of the arteries and veins. Light microscopy showed numerous syncytial knots in the chorionic villi with fibrinoid deposits. The diminished branching was postulated to represent an arrest of development and the neovascularization a compensatory response. This lends support to the view that an interrupting event occurring early in blood vessel development leads to alterations in both the macro and microcirculation.

1.2.4 Summary

In pregnancies complicated by PET and IUGR there are characteristic pathological findings in the placental bed vasculature. However, the changes are not specific for these diseases.

1.3. UTERINE BLOOD FLOW

1.3.1 Techniques of assessment

A variety of experimental techniques have been employed to study the uteroplacental circulation in the pregnant human.

Winkelbauer and Tatum (1960) described a technique of auscultation for placental localization and noted two distinct uterine artery and placental souffle sounds (the 'bruit placentaire'). The uterine artery could be heard all along the uterine borders and was modified by dextrorotation of the uterus. Bercovici and Palti (1967) used a reflected light and a photoelectric cell attached to a speculum and obtained pulse waves from vaginal and uterine arteries. It was supposed that a more triangular shape and lack of a dicrotic notch might indicate a vessel supplying a vascular bed rich in terminal arterioles. This study is of interest as it raised the possibility that the shape of the supplying waveform reflects pathology downstream.

Most other early work was more invasive. Browne and Veall (1953) described a method for determining placental blood flow. In term patients with anterior placentae, a needle was injected directly into the chorio-decidual space, determined by withdrawal of blood. ^{24}Na was injected and a Geiger counter used to draw decay curves as the blood removed the radioactivity. There were many

technical failures and only 25 blood-flow curves were obtained from 274 women. Of these, ten were rejected for being too fast or too slow and therefore thought to be in the wrong space.

Assali et al (1960) measured uterine and umbilical blood flow directly using electromagnetic flowmeters in 12 women undergoing termination by hysterotomy. 20 other cases were discarded as the studies were complicated by excessive blood loss during dissection of the uterine blood vessels. Oxygen consumption was calculated using arterio-venous differences in blood gas samples from the uterine artery and vein. Even peri-operative sampling of the intervillous space (IVS) with direct vision during hysterotomy and CS proved extremely difficult. Fuchs et al (1963) found that there was liable to be a confusion of vessels when withdrawing blood from the supposed IVS, packed with chorionic villi, and blood gas samples were very variable, casting doubt on the correct placement of needles and injected isotopes by other workers.

Borell et al (1965) used an arteriographic method to study the uteroplacental circulation. In women with fetuses with lethal malformations, a catheter was passed into the aorta via a percutaneous puncture of the femoral artery and urografin was injected before serial radiographs were taken. Only small numbers of women could be studied by this technique.

Direct injection of isotope was replaced by peripheral intravenous injection of a variety of labelled isotopes, such as ^{113}In (Lunell et al 1979) and $^{99\text{Tc}}$ (Suonio et al 1976). These are nondiffusible tracers and the accumulation of radioactivity over the placenta was measured with gamma cameras to produce a time-activity curve. Blood flow was only measured qualitatively with a relative 'blood flow index', which is maximum activity/rise time and proportional to uteroplacental blood flow. Another technique that could be used repetitively involved peripheral injection of ^{113}Xe , the woman holding her breath for 20 seconds while the bolus reached the placenta, and then measurement of the clearance of the isotope using a scintillation detector (Rekonen et al 1976). This gave flow per unit volume of IVS, not total placental flow, but provided quantification of intervillous blood flow (IVBF). All these techniques were confined to cases with anterior placentae and exposed mother and fetus to radioactivity.

1.3.2 Normal pregnancy

Using the above techniques, much useful information on uterine blood flow has been collected. Uterine blood flow in the term pregnant human uterus is estimated to be 600ml/min (Browne & Veall 1953). Assali et al (1960) showed that uterine and umbilical blood flow and oxygen consumptions increase with gestation. The increased flow in both the uterine and umbilical

arteries suggests improved vascularization on both sides of the placenta.

Angiography has shown that the spiral arteries supply the IVS. During uterine contractions their diameter decreases, or the blood flow stops in an irregular pattern (Borell et al 1965). A decrease in blood flow precedes contractions and recovers over half a minute while the uterine veins empty. Flow then falls and recovers again with the peak and completion of contractions (Brotanek et al 1969).

Ultrasonic measurements of placental length and thickness made during contractions showed that they both increase (Bleker et al 1975). These findings support the idea that the IVS becomes distended during contractions. First maternal venous outflow is halted and eventually arterial inflow. Using a ^{99m}Tc accumulation method and special tilting table, a non-significant fall in placental blood flow was found when changing from the left lateral to supine positions, but there was a significant fall from the left lateral to upright position (Suonio et al 1976)

1.3.3 Complicated pregnancy

Browne and Veall (1953) injected ^{24}Na tracer directly into the choriodecidual space, and found a decreased placental blood flow

in the intervillous space in 15 third trimester hypertensive women (both PET and chronic hypertension); in three of the cases the maximum BP was only 140/80mm Hg. Nevertheless, this was a direct demonstration of 'placental insufficiency'.

IVBF was reduced in pregnancies complicated by severe PET, diabetes, cholestasis, and some cases of IUGR (Kaar et al 1980). Lumbar extradural block had no effect on IVBF of nine normal women undergoing CS (Jouppila et al 1978), but markedly increased the reduced IVBF of nine women with severe PET (Jouppila et al 1982). In labour, IVBF was significantly lower in PET than essential hypertension but the difference disappeared after segmental epidural analgesia (Jouppila et al 1979). Caffeine ingestion by drinking two cups of coffee led to a non-significant fall in IVBF in eight normal and 12 complicated pregnancies (Kirkinen et al 1983b). Increases and decreases in IVBF (but not absolute values) were significantly correlated with long term measures of fetal heart rate variability after smoking a cigarette (Raumaro et al 1983). Oxygen inhalation in a group of 22 women with hypertension and IUGR led to a significant decrease in IVBF (Jouppila et al 1983). This may have been due to vasoconstriction. Labetolol infusion had no effect on IVBF in pre-eclamptic women despite a fall in BP (Jouppila et al 1986).

Sub-maximal exercise (six minutes on a cycle ergometer) has been found to have no effect on IVBF in normal women (Raumaro and

Forss 1988a). In pregnancies complicated by PET, diabetes and cholestasis, initially low levels of IVBF are markedly decreased by exercise (Raumaro and Forss 1988b). IVBF measured by ^{113}Xe techniques is significantly correlated with maternal weight (Raumaro et al 1988a) but no investigators have made corrections or allowances for this finding.

The blood flow index was found to be lower in eight cases of IUGR (Lunnell et al 1979) than 11 normals, although with a great range of variation and overlap which makes it less reliable. The blood flow index increases with gestation and is lower in the supine than left lateral positions (Nylund et al 1982). It has been found to be higher in diabetic pregnancies and is unrelated to fetal weight (Nylund et al 1982). It was significantly reduced by 50% in 25 hypertensive pregnancies compared with 20 normals, and this reduction was more marked for severe hypertension than mild (Lunnell et al 1984). Nylund et al (1983) also found it to be reduced by about 50% in a group of IUGR fetuses (six with, and 24 without fetal malformations), although the controls were not normal pregnancies.

1.3.4 Relation of intervillous blood flow and histology

In one of the few papers to compare blood flow and histopathology, prelabour ^{133}Xe clearances in 23 normal pregnancies and 21 pregnancies with fetal distress or stillbirth

were compared with placental histometry, using this as an approximate measure of villous surface area (Clavero et al 1973). All the distressed fetuses fell outside the normal range of blood flows, with either the IVBF being much greater than the fetal blood flow or vice versa. Distressed fetuses had hypermature or senescent placentae (with grouping or crowding of villi). Those with high flows had hypermature placentae, suggesting that the increased flow might represent a compensatory mechanism before the development of low flow placentae, which had similar histology and histometry but a poorer prognosis.

1.3.5 Animal work

Animal work has been beset by the two problems of interspecies variation in placentation and the lack of good animal models for PET and IUGR. No laboratory species spontaneously develops hypertension in pregnancy (Ahokas et al 1987). A condition with similar haemodynamic changes to PET, with increased BP and peripheral resistance and decreased uterine blood flow and glomerular filtration rate, has been induced by carbohydrate withdrawal in sheep (Thatcher and Keith 1986). Carbohydrate overfeeding of the spontaneously hypertensive rat prevented the normal fall in BP at term (although this may only be a model for nonproteinuric pregnancy induced hypertension [PIH] or 'essential' hypertension).

Repetitive embolization of the uterine circulation of ewes, using radio-labelled microspheres, provided a model of growth retardation (Clapp et al 1980). There was generalised destruction of the vasculature which is similar to PET, but no other features of PET were mimicked. The insult was late in pregnancy and relatively acute compared to another animal model for IUGR which was provided by pre-pregnancy removal of endometrial caruncles in sheep (Owens et al 1986). Nevertheless, animal work has provided important data complementing the human.

In Rhesus monkeys, who have a haemochorial placenta like humans, the contribution of ovarian blood flow to uteroplacental perfusion was minimal. Acute and chronic aortic occlusion led to a dramatic fall in uterine blood flow and no change in the ovarian component (Abitol et al 1980). This suggests that an increase from the ovarian supply cannot compensate for impaired uterine blood flow.

In the gravid ewe, Griess (1966) found a straight line relationship between uterine blood flow and the arterio-venous pressure gradient, suggesting that the uterine vascular bed is normally vasodilated with no tendency to autoregulate when BP falls. However there was no data about the change with a rise in BP. Oxygen consumption rose with gestation in goats, and was high in relation to the blood flow during early gestation (Cotter et al 1969).

Repetitive embolization of the uterine circulation of ewes led to some lambs becoming growth retarded. In those that did, a persistent increase in umbilical vascular resistance and a decrease in umbilical blood flow was observed without significant changes in fetal blood gases (Clapp et al 1980). This suggests that limitation of absolute blood flow can cause growth retardation, but not in all cases, and that the fetal growth rate is limited by factors other than gas exchange. After embolization the uterine blood flow was decreased, uterine vascular resistance increased and the weight of the uterus and its contents decreased (Clapp et al 1982). Reduction of blood flow using a compression balloon around the cord led to a marked increase in oxygen extraction (Iskovitz et al 1983). This demonstrates that the fetus has a capacity to withstand some reduction in umbilical blood flow.

After pre-pregnancy removal of endometrial caruncles in sheep, all experimental animals showed a decrease in placental weight, number of placental cotyledons and fetal brain weight. All fetuses were hypoxaemic, hypercapnicaemic and acidotic. The fetuses were then divided into normal and small by birth weight. Small fetuses had a disproportionately smaller fall in brain weight compared to body and liver weights and a marked decrease in uterine blood flow and normal umbilical blood flow (Owens et al 1986). These results would suggest that the restriction of placental growth limits umbilical and uterine blood flow.

Alternatively, the uterine blood supply is crucial and the small fetuses were compensating more for their shortage of substrate by maintaining umbilical blood flow and redistributing it around different fetal organ beds. However, sheep have a syndesmochorial placenta, unlike the human.

Rats have haemochorial placentae and have also been used as models. In rats, hexoprenaline has been shown to increase placental blood flow, probably by vasodilatation (Lipshitz et al 1986). After carbohydrate overfeeding of spontaneously hypertensive rats, placental blood flow was reduced and systemic vascular resistance increased. There was a negative correlation between placental blood flow, litter size and mean arterial pressure, although the lack of growth retardation may indicate a functional overcapacity (Ahokas et al 1987).

Rat mesenteric artery has shown a decrease in vessel wall stiffness and loss of vascular contractility in pregnancy (Mclaughlin and Keve 1986), so the fall in resistance seen during pregnancy may not only be mediated by vasodilation. Bell reviewed animal evidence and found that two mechanisms for the increased blood flow in pregnancy existed: a dilator action of oestrogen on uterine vessels and depression of the capacity of uterine vasculature to be constricted (Bell 1974).

1.3.6 Human placental perfusion studies

Perfusion pressure changes of placentae or isolated cotyledons in vitro can reflect changes in vascular resistance. Angiotensin II infusion increases placental vascular resistance and this can be reversed by terbutaline and isoprenaline (Soares de Moura 1981). The vasodilation induced when there is basal tonus is mediated through beta-adrenoreceptors as it is blocked by propranolol (Soares de Moura 1981). In isolated human cotyledons there was a reversible fetoplacental vasoconstriction in response to hypoxic perfusate, and the cotyledons that were most sensitive to maternal hypoxia transferred oxygen most effectively (Howard et al 1987). These findings suggest that there is a potential for local redistribution of placental blood flow.

1.3.7 Summary

All the techniques described are imperfect measures of uterine blood flow in humans, as they are invasive or unreliable. However, they do suggest that an increase in uteroplacental blood flow parallels fetal growth. Although there is a margin of placental reserve, chronic underperfusion appears to be associated with PET and some cases of IUGR. What is required is an improved non-invasive method of assessing placental blood flow that is accurate, reliable and cheap and can be used repetitively.

Animal and in vitro work support the model of a normally vasodilated uterine circulation that has overcapacity. Decreased blood flow leads to an increased vascular resistance and eventual IUGR, with later development of hypoxia. There is also some suggestion of autoregulation within the uteroplacental unit.

1.4. DOPPLER ULTRASOUND

1.4.1. Historical considerations

Johann Christian Doppler (Figure 2) was born in Salzburg in 1805, the son of a stone mason. He graduated from the Polytechnic Institute of Vienna and was appointed Professor of Elementary Mathematics and Practical Geometry at the State Technical Academy in Prague in 1841. He published his paper "On the Coloured Light of Double Stars and Some other Heavenly Bodies" (Doppler 1843) and received an honorary doctorate in 1847. He eventually returned to Vienna to receive the prestigious appointment of Professor of Experimental Physics at the Royal Imperial University of Vienna in 1850 but died only three years later of a pulmonary illness (White 1982).

Doppler suggested that the frequency of light and sound can change with movement. Experimental proof was provided by Buys Ballot in 1845. Musicians with perfect pitch compared the trumpet note played by a stationary horn player and one on a moving train, playing before and after passing a station. The musicians scored the tones in eighths of a note and the results compared well with those expected on theoretical grounds (Jonkman 1980).



Figure 2 Daguerreotype of Johann Christian Doppler, the only known photograph (Eden 1986, with permission)

The erroneous conclusion of Doppler's original paper was that blue and red stars were moving towards and away from the earth respectively. Although the effect he described was correct, he made a false assumption that every star emitted white light. In his lifetime his work was generally discredited. It was not until 1929, when Hubble discovered that the more distant a galaxy the greater the Doppler spectral shift towards the red, that the belief in the expanding universe was cemented and the value of the Doppler effect in astronomy confirmed (White 1982).

1.4.2 The Doppler shift effect

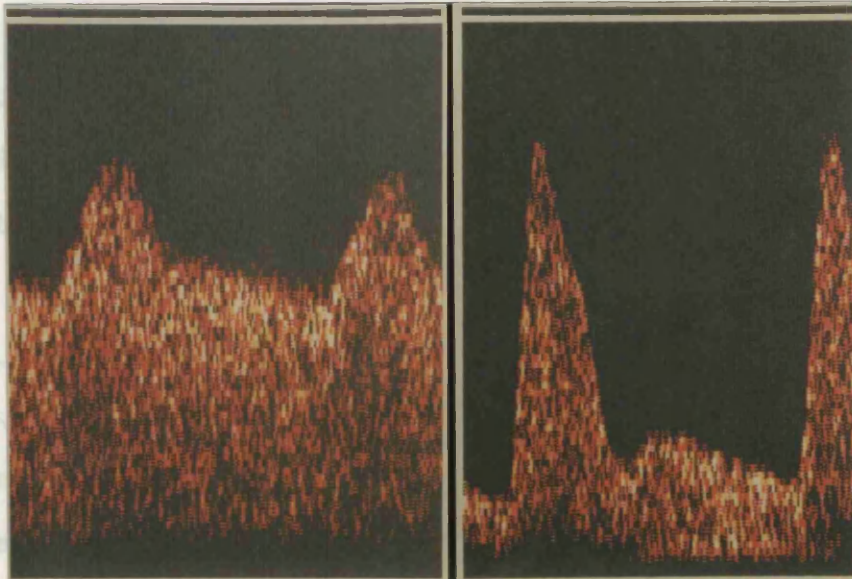
When a sound wave, with frequency f , strikes an object moving with velocity v , and is backscattered, the reflected wave will have undergone a shift in frequency, f_d , known as the Doppler shift:

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

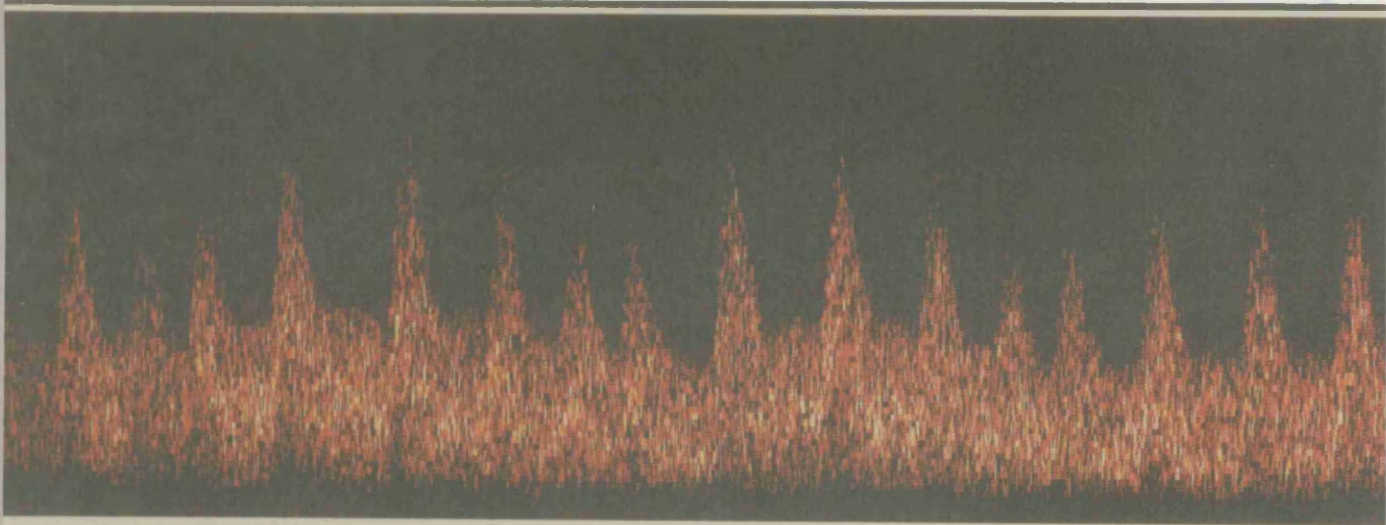
c

where θ is the angle between the direction of travel of the object and the incident sound wave, c is the speed of the wave in the medium, and the source and receiver are very close.

The Doppler effect has been employed to measure blood flow in vessels using ultrasound. The graphical presentation of Doppler shifted frequencies by time over a cardiac cycle is called a flow velocity waveform (FVW) (see Figure 3).



(a) (b)



(c)

Figure 3 a) Low resistance arcuate waveform $RI = 0.29$
 b) High resistance arcuate waveform $RI = 0.79$
 c) Strip of recording of uterine artery showing the effect of sinus arrhythmia on waveform

Satomura (1958) was the first to apply Doppler techniques to describe movements of the cornea and blood vessels and progressed to obtaining Doppler signals from blood vessels.

1.4.3 The difference between pulsed and continuous wave

Continuous wave ultrasound (CW) is emitted continuously at a constant frequency from a ceramic crystal. A second crystal receives the ultrasound which is backscattered by moving blood. Thus, Doppler shifted frequencies can be received from several vessels at once and the waveforms superimposed. A number of vessels in the pathway of the beam cannot therefore be distinguished. In addition, the location, or depth, from which signals are received is not known, even if an imaging system is used concurrently.

Pulsed wave ultrasound (PW) is emitted in short bursts from one crystal which is also used to receive signals. A delayed time gate sets constraints on the reception of echoes, whereby the time delay determines the depth from which echoes will be received. Thus, the depth of the vessel from which the echo originates can be calculated. As the time (range) gate can be superimposed upon the screen of a real-time imaging (duplex ultrasound) system, the vessel producing the Doppler shifted waveform is known precisely. The disadvantage of duplex, PW Doppler equipment is that it is expensive and has limited

resolution because of the time needed to listen for echoes. There is a tradeoff in depth selectivity and resolution. Some PW equipment emits much higher levels of ultrasound and great care must be taken to ensure that the recommendations for obstetric ultrasound are not exceeded.

Using a duplex system, the angle θ can be measured and velocity calculated. However there is a compromise between the best angle for an adequate real-time imaging signal (ideally at 90° to a vessel) and the best angle for a maximal Doppler signal (ideally at 0° to the vessel). In practice, angles less than 60° give adequate Doppler signals ($\cos \theta = 0.5$). Higher angles cause the Doppler shift frequencies to fall markedly with consequent risk of losing end-diastolic flow signals.

Colour flow mapping (Switzer and Nanda 1985) is based on sampling the Doppler shifts at multiple levels from each radial line in the sector plane. The signal is written into a digital scan converter and then a colour converter. A moving colour image is superimposed on the conventional scan picture and shows the direction of flow, velocity and turbulence. Vessels that are too small for visualization using real-time ultrasound may be seen as a colour flash on colour flow mapping (Figure 4). It has similar limitations to pulsed wave but is much more expensive and requires extensive validation.

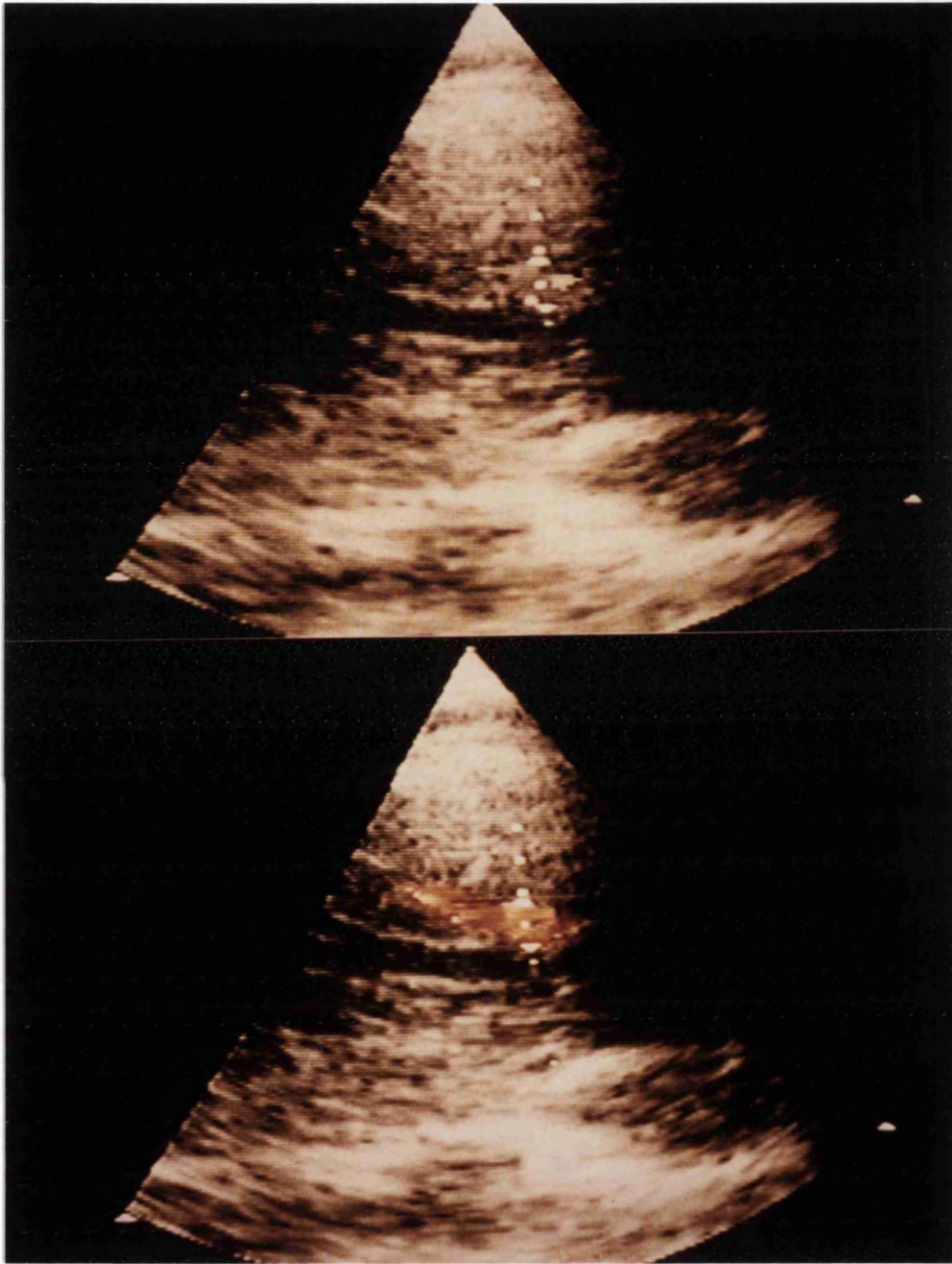


Figure 4 Colour flow mapping

a) Side wall of uterus. Doppler image off

b) Doppler image superimposed. Colour flash shows flow in uterine artery which was not visualised in conventional scan

1.4.4 Flow velocity waveforms versus blood flow

If the mean velocity of blood (v) is known then the flow (Q) can be calculated from the formula:

$$Q = v \times \text{Area}$$

$$Q = v \times \pi r^2$$

where r = radius of the internal diameter of the vessels. v can be estimated as half the maximum velocity but this only holds for parabolic flow in a circular tube which probably only exists in vivo in long non-branching vessels (McDonald 1974). Adding the problems of measuring a non-circular, pulsating vessel diameter to the estimation of mean velocity when flow is spiralling or turbulent leads to large combined errors (Eik-Nes et al 1982). Any error in measurement of vessel radius (usually only millimetres in the uterine and fetal circulations) is magnified as the measurement is squared.

There are a variety of ways to process Doppler shifted signals. Spectrum analysers utilise the entire Doppler spectrum and perform a fast-Fourier analysis on samples of the signal. A three-dimensional picture is constructed. The sonogram represents time (on the x-axis), frequency (on the y-axis) and intensity (shown as grey or colour scaling in place of the z-axis) (Figure 3). A 'thump' filter is generally added to remove

low frequency high amplitude Doppler signals from tissue movement, particularly from the vessel walls. These are generally set at 150 Hz but, if higher, can result in the loss of end-diastolic frequencies and errors in velocity calculation.

Theoretically, even assuming that blood flow is laminar and axisymmetrical and that the ultrasound beam is rectangular, the only way to obtain velocities proportional to instantaneous volumetric flow is with a mean frequency processor and an ultrasound beam uniform over the whole vessel (Evans 1982a). In practice, spectrum analysers with this capacity produce maximum velocity waveforms with overall agreement with mean velocity waveforms from electromagnetic flow meters in pulsatile arteries (Evans 1982b). Spectrum analysers, although more complex and expensive, have replaced zero-crossing detectors.

Doppler ultrasound is a useful non-invasive technique for assessing blood flow. It has been found to compare well with angiography in assessment of arteriosclerosis obliterans in the extremities (Strandness et al 1966) and the carotid artery (Hames et al 1985). There is a high correlation between electromagnetic flow meters and Doppler calculated flow in pig aorta (Eik-Nes et al 1984).

Four main sources of error in the measurement of flow have been identified: measurement of vessel diameter (increased to the

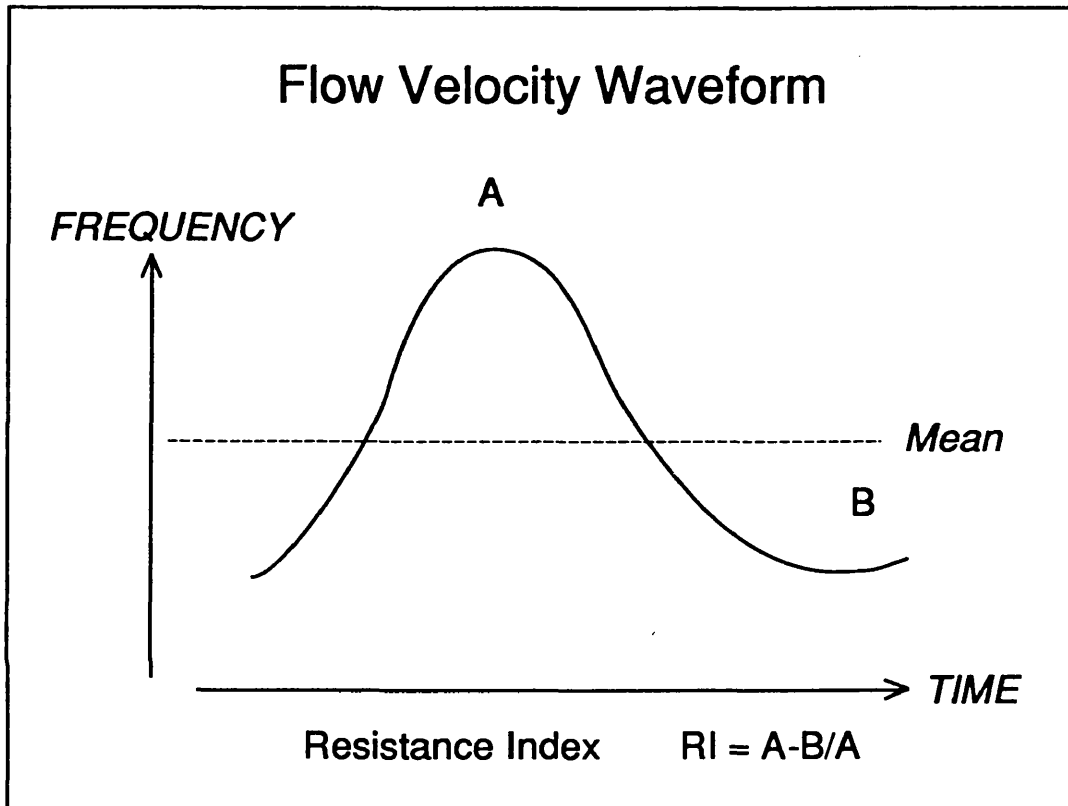
power 2) which worsens as the vessel gets smaller because scanner calipers only resolve to 1mm; the high pass filter, which eliminates vessel wall thump and overestimates mean velocity by excluding low velocities; inclusion of other vessels if the sample volume is too high; and a high angle subtended to the vessel will increase errors when it is over 45° (Eik-Nes 1984). The overriding limitation is, however, the difficulty of measuring cross-sectional area of the vessel and investigators have therefore been driven to analysing the qualitative information contained within the frequency waveform which has also allowed a much wider use of the cheaper, CW, systems.

1.4.5 Indices

A variety of indices that characterise the maximum frequency outline have been developed to describe the waveform. They all essentially relate one part of the waveform to another and are therefore independent of the angle of insonation.

The maximum frequency envelope is the outline drawn from the maximum Doppler shifted frequencies at each point of time in the cardiac cycle. The maximum systolic peak (S or A) and the end-diastolic frequency (D or B) are shown in Figure 5, along with the commonly used indices. The y-axis represents frequency and the x-axis time.

Figure 5 Flow velocity waveform (FVW) indices



S/D or A/B ratio = A/B (Baskett 1977, Stuart & Drumm 1980)

Resistance Index, RI = $A - B/A$ (Pourcelot 1974)

Pulsatility Index, PI = $A - B/Mean$ (Gosling & King 1975)

Impedance Index, ImI = $A \times Mean / B^2$ (Erskine and Ritchie 1985b)

PI is actually defined as $(F_{max} - F_{min})/Mean = (Peak\ to\ Peak)/Mean$. It is only equivalent to $(A - B)/Mean$ when B is the minimum of the cardiac cycle, which is usually the case in the uterine and umbilical circulations. Baskett's A/B ratio (1977) defined B as the secondary peak rather than the end-diastolic value.

As the waveform shape becomes more pulsatile then all the indices increase. If the end-diastolic value is zero then RI becomes 0 and S/D and ImI become infinity, and they lose any usefulness. RI varies linearly between 0 and 1. It is connected to S/D by the equation $S/D = 1/(1-RI)$. The pulsatility index requires the ability to calculate the mean Doppler shifted frequency, or rather, the mean of the maximum envelope. PI was described largely for bi- and tri- phasic waveforms and has value when end-diastolic flow (EDF) is lost.

Waveforms have been analysed using a 'frequency index profile' (FIP) (Campbell et al 1983) which normalised waveforms for heart rate, and other information is contained in further indices such as R (relative flow index) and RS (average rising slope) (Thompson et al 1985), but these are generally laborious to calculate and have not been taken up by other workers. As a variety of different umbilical artery FVW indices had similar detection of fetal compromise, it has been suggested that there should be standardisation to one of the simpler indices such as

RI or PI (Hoskins et al 1989). There is no consensus yet as to the FVW index of preference.

1.4.6 Problems with waveform analysis

In practice, the indices are all crudely assessing the waveform shape and are closely correlated (Thompson et al 1988a). For any particular set of waveforms the indices cannot all be normally distributed at the same time (Thompson et al 1988a). A study of 6 European centres analysing identical taped FVWs found that different methods for determining the maximum frequency envelope and mean fd were being used with consequent variability in the measurement of PI (Ruissen et al 1988). Doppler flow signals can be tape recorded with minimal loss of signal provided the forward and reverse components are recorded separately (Smallwood 1985).

Erskine and Ritchie (1985b) compared the percentage error for RI, PI, A/B and ImI as the number of umbilical artery waveforms sampled increased from one to 100. They found that the error was markedly less for RI than the other indices (5.5% when $n = 1$, as compared with 8.3% for PI, 7.5% for A/B and 18.2% for ImI) and did not decrease greatly after five waveforms.

In the umbilical artery (UA) there is a slight tendency for A/B to increase with a long cycle but 11 other indices were not significantly affected by variations in heart rate (Thompson et

al 1986a). Poor waveform quality is more critical in the classification of waveforms than the type of waveform (maximum velocity, minimum velocity or first moment), and there is a serious loss of data when the power spectra are low or there is little EDF (Thompson et al 1986b). For the Doptek spectrum analyser (as used in the studies reported in this thesis) the smallest errors in calculation were when the maximum frequency envelope was traced with a light pen by hand (Gilbert et al 1988) rather than when calculated by an inbuilt computer which was affected markedly by artefactual errors from dropout, background noise and an uneven outline.

1.4.7 Validation of pattern recognition in the abdomen

In order to validate vessel patterns, Taylor et al (1985a) performed PW Doppler examinations in 20 nonpregnant women undergoing diagnostic laparotomy and ten volunteers. Signals were taken from many abdominal and pelvic arteries; the aorta, bifurcation, common iliac, internal iliac, coeliac trunk, hepatic, renal, ovarian and uterine arteries. The uterine arteries were sampled in the paracervical region and, by moving the gate, flow in two directions could be found. Each vessel had a different and characteristic Doppler signature. This work was extended to include pregnant women and a study of 45 women having PW Doppler studies of the iliac, ovarian and uterine arteries validated at laparotomy and vaginal termination of pregnancy

again showed that each had a typical pattern and pulsatility index (Taylor et al 1985b). The internal iliac artery in the nonpregnant woman is of high pulsatility with a dicrotic notch and low flow throughout diastole (Taylor et al 1985a).

1.4.8 Physiological meaning of Doppler waveforms

That Doppler shifted waveforms reflect downstream pathology has been investigated for both umbilical (Giles et al 1985a, McCowan et al 1987b) and uteroplacental circulations (Pearce 1987).

Histopathological associations with umbilical artery (UA) Doppler waveforms have been found. Placentae from normal pregnancies, complicated pregnancies with normal UA FVWs and matched complicated pregnancies with abnormal FVWs were compared, blind to clinical details. A significant decrease was found in small arterial counts in the third group with similar tertiary stem villi counts (Giles et al 1985a). This suggests that the increased A/B ratio was due to occlusion of these resistance vessels. A highly significant difference in uteroplacental RI was found between patients with pathological and physiological invasion assessed from placental bed biopsies (McParland and Pearce 1988).

FVWs are also affected by cardiac output, blood viscosity and the elasticity of vessel walls (MacDonald 1974). From a study of

three fetuses with arrhythmias, the PI varied inversely with heart rate and changed from beat to beat showing that a raised PI need not only be due to increased impedance to flow (Erskine 1987). Maternal blood viscosity variables explained only a small variation in the uteroplacental RI in a group of normal and complicated pregnancies (Steel et al 1988c). Babies with abnormal UA FVWs also have a higher haematocrit and whole blood viscosity but this is probably an effect following hypoxaemia rather than causal (Giles et al 1986b) as clinical outcome was not predicted by the blood viscosity. It is assumed that, in the presence of a regular heart beat, changes and differences in FVWs reflect downstream resistance and pathology.

This is confirmed theoretically by a computer model of uterine artery waveforms which suggested that the FVW shape abnormalities found in PIH were caused by high vascular resistance and decreased arterial diameter (Adamson et al 1989)

1.4.9 Safety

There is a large body of literature on the bio-effects of ultrasound. The American Institute of Ultrasound in Medicine (AIUM 1982) and the Royal College of Obstetricians and Gynaecologists (RCOG 1984) have reviewed the potential mechanisms and the evidence of possible hazards. They concluded that the present benefits are great, no adverse effects have been proven

and the chance of long term hazard is remote considering the lack of effect on the genetic material of somatic or maternal or fetal germ cells.

Ultrasonic energy is propagated as a pressure wave and the energy crossing a unit per second is called the intensity, expressed as watts/cm². A major problem with the investigation of possible harm from Doppler ultrasound is that a variety of measures of intensity exist, especially for PW, and there is no agreed international definition of exposure conditions (Meire 1987). The American Institute of Ultrasound in Medicine (AIUM) advises an upper limit for obstetric ultrasound of 100mW/cm² SPTA (spatial peak temporal average) (Wells 1987).

The biological effects of ultrasound demonstrable in vitro that would be relevant to its safe use in vivo include inherited changes, increased sister chromatid changes and membrane permeability changes (Dyson 1986). Ultrasound does not seem to damage DNA of somatic cells which might lead to chromosome aberrations, cell death or mutagenesis. Although Macintosh and Davey (1970,1972) reported that diagnostic ultrasound was capable of causing chromosome aberrations under experimental conditions others have failed to confirm their findings under more rigorous conditions in vitro (Buckton and Baker 1972, Abdulla et al 1972) and in vivo (Abdulla et al 1971, Lucas et al 1972).

Ultrasound could exert a biological effect by heating tissue due to absorption of sound in the medium. The temperature rise depends on the heat generation at a particular site (related to the absorption coefficient) and the heat conduction away from it (related to the tissue vascularity). Ultrasound of diagnostic intensity did not significantly raise the temperature of mammalian tissue (Nyborg et al 1983). In vivo exposure of a thermocouple with Doppler ultrasound during a second trimester termination did not increase amniotic fluid temperature (Soothill et al 1987b).

Ultrasound can cause mechanical effects on tissue, including cavitation (the oscillation of gaseous bubbles due to the pressure of the acoustic wave), microstreaming (an eddying motion) or radiation force (a steady force on cells that moves them, seen with standing waves) (RCOG 1984). These do not seem to occur to a significant degree in human tissues with diagnostic ultrasound (Kremkau 1983). However, pre- and post-delivery erythrocyte osmotic fragility testing showed a marginal increase in fragility in women exposed to continuous heart monitoring for over seven hours with Doppler ultrasound (Bause et al 1983).

Ultrasound exposure during pregnancy of 1114 women did not lead to an increase in fetal abnormalities (Hellman et al 1970). One year follow-up of 297 fetuses exposed in utero to ultrasound and amniocentesis revealed no difference in neurological or physical

examination compared to groups having amniocentesis alone or no testing (Scheidt et al 1978). A study of 381 exposed fetuses and unexposed matched controls found no difference in a variety of birth and behavioural variables (Stark et al 1983). Although no adverse effects arising from the use of diagnostic ultrasound have been identified in practice, epidemiological investigations are not able to give a clear reassurance. This is because they have had difficulty matching exposed and non-exposed controls and they may not pick up small changes in the rate of occurrence of a common abnormality. It would be possible to miss subtle effects such as minor behavioural change or long term delayed effects.

The fetus is certainly aware of insonation as ultrasound increases fetal movement compared with sham exposure (David et al 1975), although there is no way of knowing if this is perceived as a painful stimulus (Richards 1985). It is important to remember that the fetus is exposed to ultrasound for only a short time during a PW examination and that actual patient exposure time is much less than the consultation time (Andrews et al 1987).

In obstetrics, the awareness of the vulnerability of the fetus and the potential for effects to be delayed makes caution in introducing new treatments particularly trenchant. Constant checks should be kept on the ultrasound equipment in use. Despite the paucity of evidence of harm, with the advent of much

higher power machines and the use of serial scanning and blood flow, it would seem prudent to use minimum power levels and to keep exposure as short as possible.

1.4.10 Summary

Doppler offers an exciting, non-invasive method of assessing the circulation. Although volume flow can be measured, it is beset by problems of errors, especially in small vessels, such as those found in the pregnant uterus and fetus. Colour flow mapping has not yet found a role. CW is cheap, easy and lower power but only provides a FVW. Pattern recognition has been validated and a variety of indices described that analyse the FVW. RI is simple, varies linearly and has small errors. We should continue to be wary about safety.

1.5 FETOPLACENTAL DOPPLER

1.5.1. Introduction

The first investigators used a combination of imaging, PW and CW ultrasound to obtain waveforms from the umbilical artery and found a clear difference in the reproducible signals obtained from the artery and vein (Fitzgerald & Drumm 1977). High UA PI, indicating greater placental impedance, was noted in some complicated pregnancies (McCallum et al 1978). In the first description of non-invasively measuring human fetal blood flow (Eik-Nes et al 1980), the investigators measured velocity and flow using PW in the fetal aorta and intra-abdominal portion of the umbilical vein. Later, realtime scanners were interlaced with PW Doppler and real-time spectral analysers (Griffin et al 1984, Teague et al 1985).

Technical difficulties have prevented measurement of UA flow as the two arteries are highly coiled and of small diameter. Flow measurements in the aorta and umbilical vein are prone to considerable errors (Erskine and Ritchie 1985a, Griffin et al 1985) and have largely been replaced by velocity measurements and qualitative analysis of the FVWs. Now colour flow mapping (Kurjak et al 1987) can show the two umbilical arteries clearly and it is theoretically possible to measure the diameter and angle of the arteries. Although flow measurements may become

possible in the future, at present UA FVWs are universally used.

1.5.2 Normal pregnancy

1.5.2.1 Normal data and reference ranges

The shape of the UA FVW changes during pregnancy with an increasing diastolic component and falling A/B ratio (Stuart et al 1980). Longitudinal and cross-sectional normal ranges for umbilical artery parameters have been established (Schulman et al 1984, Trudinger and Cook 1985, Trudinger et al 1985b, Gerson et al 1987b, Thompson et al 1988b, Al-Ghazali et al 1988, Pearce et al 1988).

All investigators have used essentially the same technique to obtain UA FVWs. The probe is placed on the abdomen (with or without prior location of the cord using real-time ultrasound) and the UA FVW is recognized using visual recognition (see Figure 6). It is important when measuring UA FVWs to specify that readings were taken during fetal apnoea and that the umbilical vein was seen in the opposite channel to confirm it. Few of the investigators have provided ranges below 28 weeks.

Schulman et al (1984) described a group of 89 women who had 162 examinations between 15 and 41 weeks. It was not specified that readings were taken during apnoea, nor with umbilical vein in the

opposite channel. Indeed, one of the figures (on p 986) shows an umbilical vein FVW superimposed on the UA FVW. No outcomes were available for the 56 readings from under 25 weeks, whereas the others delivered AGA babies. A regression line was drawn from 25 weeks to give a normal range. This was neither a clear cross-sectional nor longitudinal range. The mean error between successive measurements was 6% (SD 5). The authors did not use this normal range for subsequent definitions of normality (Fleischer et al 1985).

The same workers produced another reference range based on the UA S/D values of 110 women in a monthly screening study from 20 weeks' gestation onwards who had normal perinatal outcomes and no significant maternal disease (Schulman et al 1989).

Trudinger et al (1985b) provided a normal range from 28 weeks' gestation based on serial two-weekly studies of 15 women with a normal outcome and delivery of AGA babies at term. The intra-observer error was quoted as <15% (Trudinger and Cook 1985).

Gerson et al (1987b) used PW duplex Doppler equipment to locate the range gate in a section of umbilical cord and provided mean values of S/D ratios for four weekly gestation periods for a sample of 209 retrospectively defined normal women at 19 to 43 weeks' gestation. The mean error between successive measurements was 7.5% (intra-observer 9.3%)

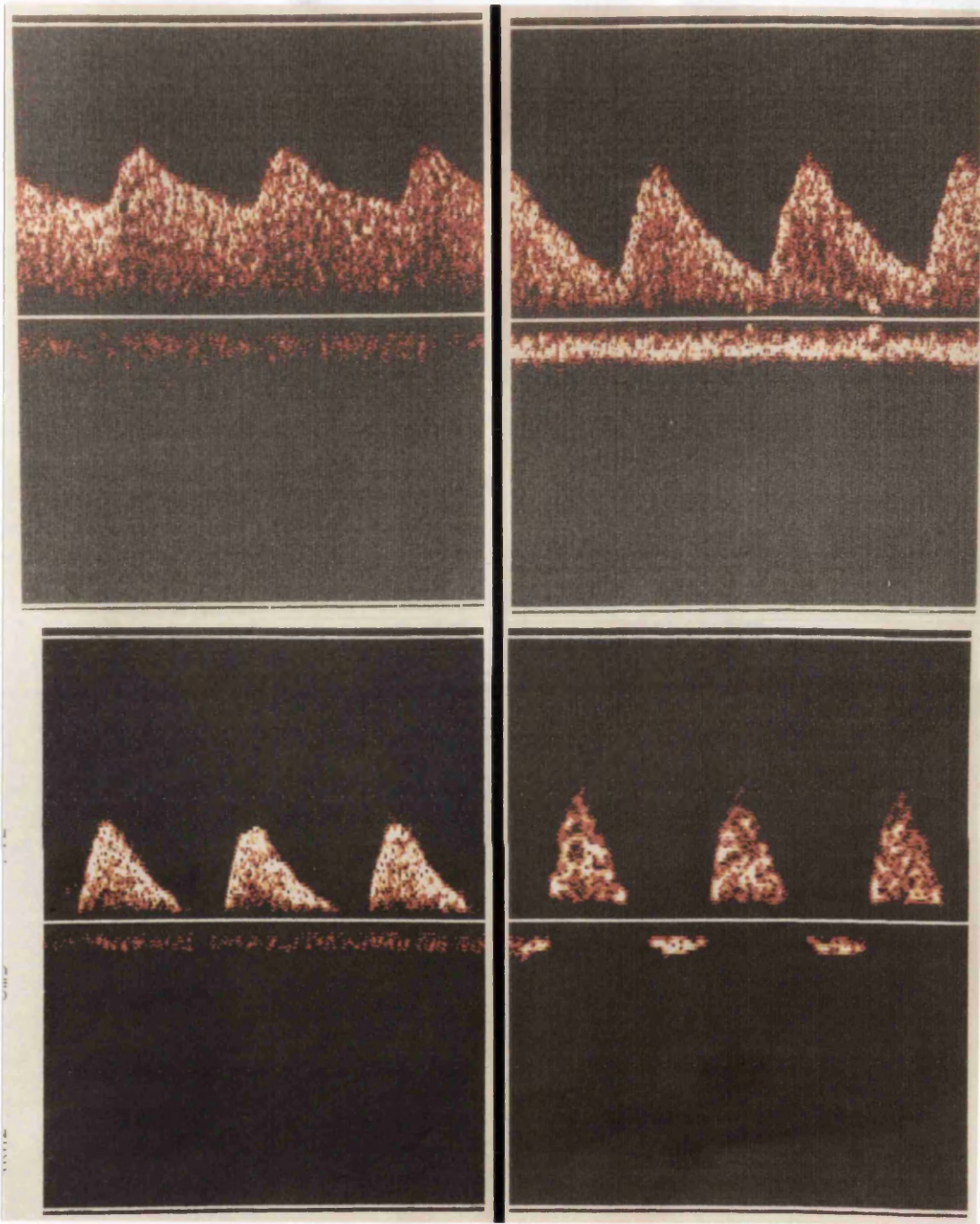


Figure 6 Umbilical artery flow velocity waveforms, umbilical vein seen in lower channel

- a) Normal third trimester FVW
- b) Normal second trimester FVW
- c) Absent end-diastolic frequencies
- d) Reverse flow in the umbilical artery

Thompson et al (1988) reported a series of 35 normal patients studied serially at two-week intervals. 15 and 18 women had studies at 20 and 24 weeks respectively. They noted that A/B ratios were not normally distributed although RI values were, but still plotted centiles assuming a normal distribution, justifying this on the basis of the error being small (<10%).

Al-Ghazali et al (1988) defined a normal range from 271 normal pregnant women between 16 and 42 weeks' gestation recruited from the antenatal and fetal echocardiography clinics. The umbilical artery was insonated using duplex Doppler equipment during fetal apnoea (Al-Ghazali et al 1987). No error estimation was described.

Pearce et al (1988) studied 34 women longitudinally at four weekly intervals who were retrospectively defined as normal. Waveforms were normalized by dividing into 256 points to overcome the dependence on the cardiac cycle length before the indices were calculated. All their reference ranges are lower than other published ranges, probably because of this correction for heart rate, but are not comparable unless other workers also use the 'frequency index profile' (FIP) computer programme. There was no significant difference between the readings taken by three observers.

Table 1 Normal ranges for umbilical artery RI

| Author | Year | Index | Doppler | RI equivalent (20 weeks) | Error % |
|------------|------|--------|---------|-----------------------------|------------|
| Schulman | 1984 | S/D | CW | 0.72 (approx) | 6 (SD 5) |
| Schulman | 1989 | S/D | CW | 0.77 (approx) | |
| Gerson | 1987 | S/D | PW | 0.76 | 7.5 |
| Thompson | 1988 | A/B,RI | CW | 0.75 | not given |
| Al-Ghazali | 1988 | A/B | PW | 0.76 (approx) | not given |
| Pearce | 1988 | RI | PW | 0.68 | "no diff" |

(Values are approximate if extrapolated from graphs in the publication rather than from supplied formulae)

1.5.2.2 Factors affecting the flow velocity waveform

1.5.2.2.1 Fetal behavioural state

Umbilical artery Doppler measurements are influenced by fetal behavioural states. During apnoea there is regular pulsatile flow while complicated patterns are found during breathing. Umbilical vein velocity changes with movement of the fetal abdominal wall (Chiba et al 1985) and thus the flat venous pattern is used to define apnoea. There was no significant change in UA PI, in 37 normal fetuses, between the fetal

behavioural states of quiescence and frequent movements (Van-Eyck et al 1987).

In normal pregnancies a negative correlation between UA RI and fetal heart rate (FHR) has been established (Mires et al 1987), although correction for heart rate is thought to be unnecessary (Kofinas et al 1989). External vibratory acoustic stimulation was followed by a decrease in S/D in 12 term fetuses compared with controls and this was related to fetal tachycardia (Gagnon et al 1988)

1.5.2.2.2 Maternal position

In a group of 20 normal primigravidae in labour the UA A/B ratio was lower in the semilateral than supine position (Marx et al 1986). There was a drop of 14% in A/B ratio with a maximum error between readings of 16%. A percentage change in A/B has no mathematical significance as the ratio varies non-linearly but nevertheless, this work suggests that there is a significantly higher resistance when the mother is supine.

1.5.2.2.3 Drugs

A moderate dose of ethanol (weight adjusted equivalent to 17.5gms/70kg) had no effect on the PI of six normal fetuses (Erskine and Ritchie 1986). Caffeine had no effect on the umbilical vein blood flow in a group of normal and complicated

pregnancies (Kirkinen et al 1983b). Smoking one cigarette led to an increase in FHR and increased S/D ratio in a group of 15 normal smokers (Morrow et al 1988). The effect had disappeared by 30 minutes. This suggests a change in placental vascular resistance. Treatment of hypertensive women with atenolol had no effect on umbilical volume flow or PI but the FHR decreased at the same time (Montan et al 1987)

1.5.2.2.4 Labour

The UA A/B ratio and acceleration slope before and after contractions were unaltered in ten normal labouring women (Stuart et al 1981). UA S/D was unchanged in 12 normal term labours before, during and after contractions; between the latent and active phases; and after rupture of the membranes and institution of syntocinon (Fleischer et al 1987). UA PI did not alter with progress of labour in 103 parturients, although it did increase during contractions only if FHR decelerated (Fairlie et al 1989). Whatever disruption contractions cause to the uterine inflow, it does not seem to affect the fetoplacental circulation in normal women.

1.5.2.2.5 Fluid loading and epidural anaesthesia

Giles et al (1987a) studied the effects of fluid loading with one litre of Hartmann's solution and epidural anaesthesia in eight

women prior to elective CS. Both led separately to significant decreases in the UA A/B ratio. Marx et al (1986) found that, in 16 labouring women, there was not a consistent decrease in UA A/B after fluid loading and epidural anaesthesia.

1.5.2.2.6 Diurnal variation

There were neither circadian changes in UA FVWs nor differences before and an hour after meals (Pearce et al 1988). There was no significant variation of UA A/B with time over one week (Hastie et al 1988). This suggests a relative stability of the fetal circulation but small differences might not have been noticed.

1.5.2.2.7 Maternal exercise

Umbilical S/D ratios in 15 term women undergoing five minutes of exercise on a bicycle ergometer were unchanged (Morrow et al 1989) suggesting that maternal exercise in normal pregnancies has no effect on fetoplacental resistance.

1.5.3 Complicated pregnancy

1.5.3.1 Growth retardation and hypertension

McCallum et al (1978) first noted that some fetuses of complicated pregnancies had high placental impedance, assessed by

a high UA PI. Arterial waveforms in SGA pregnancies have different characteristics suggesting increased impedance to flow in the umbilical artery (Griffin et al 1983, Erskine and Ritchie 1985b). Alongside a high resistance arterial circulation a low venous flow is found. Low umbilical venous flow/kg values have been found in complicated pregnancies and predict SGA (<10th centile) more accurately than low biparietal diameter (BPD) (Gill et al 1984). In 11 SGA babies with abnormal CTGs all had small vein diameter and, when measurable, the flow was below the tenth centile (Jouppila and Kirkinen 1984a).

When 189 women attending a high risk pregnancy clinic were divided retrospectively by birthweight centiles, the sensitivity and specificity of antenatal UA S/D estimates predicting a weight below the 10th centile were 78 and 83% respectively (Fleischer et al 1985). S/D ratios were higher in the groups <25th and <10th centile. This suggests that some babies may have been growth retarded and at risk but not appeared in the smallest birthweight groups.

When CW assessment of the umbilical artery was compared to duplex assessment of the aortic and umbilical vein volume flows in five normal and 37 complicated pregnancies, the UA FVW was the most sensitive index in the prediction of SGA fetuses (Giles et al 1986a). Umbilical vein volume blood flow/kg of fetus remained unchanged while the percentage of the fetal aortic flow to the

placenta decreased. This suggests that, to maintain placental perfusion in the face of increased resistance in the umbilical vascular tree, fetuses increased their cardiac output rather than increased the resistance of their other vascular beds. However, there was a great deal of overlap between normal and small (10) fetuses. In pregnancies complicated by SGA babies, morbidity was seen in those with abnormal UA A/B ratio whether or not the uterine D/S (diastolic/systolic ratio) was abnormal or not (Al-Ghazali et al 1988).

1.5.3.2 Maternal diabetes and medical problems

Fetuses of diabetic mothers had high umbilical venous flow values (Gill et al 1984) which conforms, as they are usually macrosomic. A positive correlation between S/D ratios and blood sugar was found in 43 diabetic pregnancies studied serially (Bracero et al 1986). This may reflect the influence of poor early carbohydrate regulation on the placenta with immature chorionic villi leading to mild hypoxaemia. A high A/B ratio has been reported in a normal baby of a diabetic mother (Friedman et al 1985). Landon et al (1989) longitudinally followed 35 diabetic pregnancies and found that the UA S/D was usually normal and independent of glycemic control. However, four out of five diabetics with vasculopathy had SGA babies and elevated S/D ratios before decreased ultrasound growth. Doppler may help detect at risk fetuses of diabetic mothers.

High UA A/B ratios have been found in two SGA fetuses whose mothers had systemic lupus erythematosus (Friedman et al 1985). UA FVWs have been used to monitor women with poor obstetric histories who were positive for lupus anticoagulant in order to decide on time of delivery (Trudinger et al 1988)

1.5.3.3 Rhesus incompatibility

Very high umbilical venous flow rates have been found in Rhesus affected pregnancies (Kirkinen et al 1983a, Gill et al 1984). Flow was higher in fetuses with severe, rather than moderate or mild, disease (Kirkinen et al 1983a, Jouppila and Kirkinen 1984b), and was inversely related to haemoglobin (Kirkinen et al 1983a). Umbilical vein diameter and mean velocity (Vm) were increased as well (Jouppila and Kirkinen 1984b). UA PI was inversely related to fetal haematocrit (Rightmire et al 1986). Mean velocity in the aorta and inferior vena cava were increased in affected fetuses, but the UA PI was only high in the hydropic fetuses (Rightmire et al 1986). All these results suggest that the fetoplacental circulation is hyperdynamic.

1.5.3.4 Maternal bleeding and anaemia

Jouppila and Kirkinen (1984b) found no correlation between anaemia (<10g/dl Hb) and umbilical venous flow in seven cases of maternal anaemia. They also found high umbilical flow rates in

13/19 cases of antepartum haemorrhage.

High UA A/B ratio has been found in an SGA fetus whose mother had sickle cell disease (Friedman et al 1985). Significantly more fetuses had abnormal UA S/D if their mothers had sickle cell disease (6/10) rather than sickle cell trait (3/40) (Anyaegbunam et al 1988). This is probably secondary to the effect of sickling in the maternal circulation.

1.5.3.5 Fetal well-being

High A/B ratios can precede intrauterine death (IUD) (Friedman et al 1985). Absent UA EDF and oligohydramnios were noted at 21 weeks in a fetus of a sickle cell mother, one week before fetal death. High UA A/B ratios in a small, growing fetus of a mother with systemic lupus erythematosus at 27 and 28 weeks preceded IUD at 29 weeks. Abnormal UA A/B ratios preceded CTG changes in a high risk group of in-patients and were slightly better at predicting the abnormal outcomes of SGA and low Apgar score than a scored antenatal CTG (Trudinger et al 1986).

Trudinger et al (1987) have reported on the only randomised controlled trial (RCT) of the use of UA Doppler velocimetry. In a group of 300 high risk pregnancies the UA FVW results were available to clinicians in half the cases and were concealed for the other half. They found a lower emergency CS rate for fetal

distress in the revealed group but no other differences. More babies in the control group were admitted to the special care baby unit (SCBU) which, although not making a significant difference to the mean gestation of the two groups, might indicate more cases of severe prematurity and thus higher risk in the control group. No range or SD was given of gestational age. Other RCTs are awaited.

1.5.3.6 Loss of end-diastolic frequencies (EDF)

Increasing placental resistance results in loss of forward flow in diastole, or loss of EDF. Absent EDF (AEDF) and reverse flow are the most extreme abnormalities found in the UA (see figure 6c). 15 high risk fetuses who demonstrated AEDF had a 40% mortality rate, and all but the four pregnancies with congenital anomalies were accompanied by hypertension (Rochelson et al 1987). This very high perinatal mortality and morbidity was confirmed in a study of 14 fetuses with AEDF who also had increased volume flow on the right side of the heart and combined cardiac output (Reed et al 1987). 12 high-risk fetuses with reverse EDF had a 50% perinatal mortality rate (Brar and Platt 1988). Johnstone et al (1988) found 24 cases of AEDF in a group of 320 complicated pregnancies, and no cases in 160 uncomplicated pregnancies. Of the 24 fetuses with AEDF, there were four deaths, 22 were <5th centile weight and 20 developed other evidence of antenatal compromise up to 24 days later.

AEDF can precede delivery by weeks although it was invariably followed by IUD (3) or an operative delivery for fetal distress (ODFD) (16) when it was found in an IUGR pregnancy (Reuwer et al 1987). In eight cases of congenital anomaly where UA FVWs were obtained whilst anticipating IUD, AEDF preceded death by one to seven days, and even reverse flow by seven days (Hsieh et al 1988). These data suggest that AEDF and reverse EDF have a poor prognosis.

This poor outlook continues into extra-uterine life. McCowan et al (1987a) studied 15 women being delivered electively preterm for severe IUGR, of whom 14 had a high UA PI and eight had AEDF. All three neonatal deaths (NND) occurred in the AEDF group. A very high PI (>2) was strongly associated with poor neonatal outcome (5/6), defined as NND, neurological or chromosomal abnormality.

In SGA fetuses, UA AEDF correlates well with hypoxaemia and acidaemia in umbilical venous blood samples obtained by cordocentesis (Nicholaides et al 1988). However, even with normal gases a case of AEDF has been followed by fetal distress (Warren et al 1989). Improvement in FVWs has been seen in five of a group of 31 fetuses with AEDF (Brar and Platt 1989). At present, AEDF has a sinister prognosis but does not precisely predict fetal distress or demise, or the optimal time for delivery.

1.5.3.7 Twins

UA FVWs have been utilized in the surveillance of twins where conventional methods such as fetal movements, symphyseal-fundal height (SFH) and CTGs are less easily applied. Mean UA S/D was higher in twin pregnancies than singleton pregnancies (Farmakides et al 1985), but no correction was made for gestational age.

In a study of 71 sets of twins the UA A/B showed close agreement with normal singleton values where both twins were AGA. Of 33 sets, where at least one of the twins was small, 23 had one or both abnormal UA A/B, which is a positive predictive value of 70% for discordant weight (Giles et al 1985b). In 43 pairs of twins an S/D difference of >0.4 was used to predict discordance of >350 grams with a sensitivity and specificity of 73% and 82% (Farmakides et al 1985). A similar study of 71 twins found values of 80% and 85% (Saldana et al 1987). In 56 multiple pregnancies assessed monthly the S/D ratio was superior to umbilical vein blood flow for predicting discordance in fetal weight. When the first Doppler parameters were used in addition to BPD and estimated fetal weight (EFW) differences the sensitivity and specificity of detecting discordance were 82% and 98% respectively (Gerson et al 1987a). When looking at the percentage differences of a range of Doppler parameters, AEDF and difference in volume flow were found to be the sensitive indicators of adverse outcome in twins (Nimrod et al 1987).

Delta S/D was very high in two cases of twin-twin transfusion (Farmakides et al 1985). Out of ten sets of twins where one was SGA and both had normal UA FVWs five had twin-twin transfusion, suggesting that normal UA FVWs in the presence of ultrasound discrepancy in size should lead to the suspicion of twin-twin transfusion (Giles et al 1985b). Cyclically changing PI, in the smaller twin of a discordant pair that later died in utero, was explained by postpartum proven UA-UA arterial anastomosis. The smaller twin was 'giving way' during cardiac cycles and died of a high cardiac workload (Erskine et al 1986a). The dependence of blood flow and Doppler parameters on the nature and number of anastomoses has not been established. A double layer FVW has been reported with different pulse rates in conjoint twins with a single cord (Woo et al 1987).

Although Doppler ultrasound potentially provided an improved means of monitoring twins, the picture remains confused. There is also a technical difficulty of knowing which cord supplies which fetus unless it is seen at the abdominal insertion with duplex equipment.

1.5.3.8 Fetal anomaly

13 of 26 fetuses with a major structural (11) and/or chromosomal (4) abnormality had abnormal UA FVWs (Trudinger et al 1985a). The two structurally normal fetuses with chromosome anomalies had

trisomy 21 and triploidy. 17 of 32 fetuses between 26 and 41 weeks with a major structural fetal abnormality had a high UA S/D ratio (Meizner et al 1987). There was no obvious difference in the anomalies that were or were not associated with abnormal UA FVWs. A fetal mechanism may result in changes in the fetoplacental circulation.

Al-Ghazali et al (1987) investigated 244 pregnancies for fetal cardiac anomaly. Of the 34 with congenital heart disease 17 had an abnormal UA FVW. In the ten cases with consistent AEDF there was a poor immediate outcome; termination (3), IUD (5) and NND (3) within three weeks, and three of these also had chromosomal anomalies (trisomies 18 and 21, and XO).

In ten extremely small babies with oligohydramnios, the four with normal UA and internal carotid PI values all had structural anomalies including two with an abnormal karyotype (trisomy 18 and 69XXX) (Wladimiroff et al 1986). This leads to the conclusion that an anomaly should be suspected in an apparently growth retarded fetus whose UA FVW is normal, and, conversely, in the structurally normal fetus whose UA FVW is abnormal.

1.5.3.9 Postmaturity

No published ranges exist for normal FVW indices after 42 weeks. Rightmire and Campbell (1987) found that the UA RI was higher in

eight postterm fetuses with signs of fetal compromise (operative delivery for fetal distress or 1-min Apgar <7) than 24 fetuses with an acceptable outcome. In contrast, Guidetti et al (1987) found that the umbilical S/D was the same for 20 compromised fetuses (abnormal stress test, oligohydramnios, meconium, fetal acidosis or 5-min Apgar <7) and 26 fetuses of uncomplicated prolonged pregnancies.

1.5.10 Summary

There has been much work on the UA FVW in health and disease. The reference ranges are in approximate agreement although they have largely been established using small numbers, with mixed longitudinal and cross-sectional data and with retrospectively defined normal pregnancies. There is no agreement as to the need to correct indices for FHR. Biological variance of the FVW has been studied. There is a clear increase in PI related to SGA and other complications of pregnancy, and AEDF is a sinister sign which can be present before other signs of fetal compromise. Although abnormal UA FVWs are associated with a poor outcome the exact place for the investigation in the armamentarium of antenatal tests has not been established.

1.6 UTEROPLACENTAL DOPPLER

1.6.1 Introduction

Maternal arterial sounds from outside the uterus were first heard using Doppler ultrasound by Goodman (1980). PW was used initially (Campbell et al 1983) to insonate the uteroplacental circulation and then the use of CW with pattern recognition was described (Schulman et al 1986). Colour flow mapping has been used but not yet evaluated in the uteroplacental circulation (Campbell et al 1987). Standardising the technique of obtaining FVWs has proved much more difficult than in the umbilical circulation.

1.6.2 Normal pregnancy

1.6.2.1 Normal data and reference ranges

The use of PW Doppler ultrasound to obtain 'arcuate' artery waveforms was first described by Campbell et al (1983). External and internal iliac signals were obtained after identification of the common iliac artery and its bifurcation. Small vessels were identified in the uterine wall from which 'arcuate' signals were obtained (method 1). Although this technique is the only one where there is exact placement of a range gate and therefore the source of the signals is visualized (Pearce et al 1988), the

vessel itself is not always visualized when an appropriate FVW is obtained and indeed, some echoes considered to be arcuate arteries may even be artefacts. Pearce et al (1988) created reference ranges (see Section 1.5.2.1) using this method. 34 women, retrospectively defined as normal, were followed longitudinally and measurements made on normalized FVWs using FIP. Separate ranges were created for placental and non-placental sides of the uterus.

Trudinger et al (1985c) described a simple method (method 2), using CW Doppler ultrasound, where the probe was pointed at the subplacental bed after location using realtime ultrasound. The method was validated by using a PW Doppler facility directed along the same line in 15 pregnancies and obtaining identical waveforms from the subplacental bed. However, if the placenta was posterior, then a reading from the edge sufficed. A normal range was derived from serial readings from 12 normal women.

A third method (method 3) was described by Schulman et al (1986). A CW Doppler transducer was directed into the parauterine area in the region of the lower uterine segment and moved until a waveform, previously described from duplex studies as the uterine artery pattern, was identified. They started using duplex scanning and performing studies at CS but changed to CW. They confidently stated that all other vessels in the pelvis had no diastolic component and that the uterine and arcuate arteries

could easily be identified by pattern recognition. Under 28 weeks S/D ratios obtained abdominally were lower than those obtained by the vaginal route. There was a fall in S/D ratio in the second trimester, that continued until 26 weeks' gestation, and the early diastolic notch disappeared between 20 and 26 weeks.

Baumann et al (1989) studied 21 normal pregnancies from 16 weeks' gestation to six weeks postpartum using duplex PW. There was a dramatic rise in RI to very high levels by one week postpartum.

The normal ranges that have been published vary considerably. Three show a fall in impedance in the second trimester and a levelling off in the third trimester (Schulman et al 1986, McCowan et al 1988, Pearce et al (1988), whereas two show a continuing fall throughout the last two trimesters (Trudinger et al 1985c, Al-Ghazali et al 1988), and one shows a continuing fall and then slight rise at term (Baumann et al 1989). Schulman (1987a) stated that the resistance fell earlier on the placental than nonplacental (or antiplacental) side, but quoted no figures to support this.

A summary of the methods, index used and mean RI at 20 weeks are shown in Table 2.

Table 2 Normal ranges for uteroplacental RI

| Author | Year | Doppler | Method | Index | RI equivalent (20 weeks) |
|-----------|-------|---------|-------------------|-------|-----------------------------|
| Trudinger | 1985c | CW | (2) Subplacental | D/S | 0.39 |
| Schulman | 1986 | CW | (3) Lower uterine | S/D | 0.57 |
| McCowan | 1988 | CW | (2) and (3) | S/D | 0.31 |
| Alghazali | 1988 | Colour | ? | D/S | 0.41 |
| Pearce | 1988 | PW | (1) Arcuate | RI | 0.41(P) 0.46(NP) |
| Baumann | 1989 | PW | ? | RI | 0.46 |

1.6.2.2.1 Errors

Many papers do not quote an error estimation and those that do often do not give details as to the method. A summary of the estimates is given in Table 3. Mulders et al (1988) carefully analysed the intra-patient, intra-observer and inter-observer errors from the most proximal part of the uterine artery using PW. The errors may be even larger. For example, although Pearce et al (1988) found no significant differences between three observers, large intra-observer errors were present. Calculated coefficients of variation (COV) for each observer range from 12.5% to 36%. It must be assumed that authors often quote their best (or lowest) errors.

Table 3 Quoted errors in uteroplacental FVW measurement

| Author | Year | Type | Method | No patients | Error |
|-----------|-------|------|------------------------------|-------------|---------------|
| Trudinger | 1985c | CW | 2 observers | 10 | no diff |
| Schulman | 1986 | CW | 'Intraobserver' | ? | 4% (SD 2.3) |
| McCowan | 1988 | CW | Comparison 5,10,20 FVWs | 5 | minimal diffs |
| Pearce | 1988 | PW | 3 observers, 10 FVWs | 10 | no sig diff |
| Fleischer | 1986 | CW | 'Intraobserver' | ? | about 6% |
| Arduini | 1987b | PW | 'Repetitive determinations'? | ? | 14.5% max |
| Rightmire | 1987 | PW | 'Inpatient variability' ? | ? | 16.9% |
| Steel | 1988a | CW | RI every minute for 1/2 hr | 7 | 9% COV |
| Stabile | 1988a | PW | 3 FVWs by 1 observer | ? | 15% COV |
| | | | 1 FVW by 4 observers | ? | 12% COV |
| Gagnon | 1988 | CW | Separate analysis 4 FVWs | 11 | 6.1% COV |
| Long | 1988 | CW | 3 records, mean of 6 PI | 20 | 6% COV |
| Mulders | 1988 | PW | 8 consecutive FVWs, PI | 21 | 6.4% COV |
| | | | 8 FVW at 2 min intervals | 21 | 11.7% COV |
| | | | 8 FVW, moving probe | 16 | 12.5% COV |
| | | | 2 observers | 13 | 11.1% COV |

1.6.2.2 Factors affecting the flow velocity waveform

1.6.2.2.1 Maternal behavioural state

Maternal heart rate (MHR) was negatively correlated to uterine PI in 19/21 women (Mulders et al 1988). However, the large intra-patient variance suggested that correction for MHR was unnecessary. External vibratory acoustic stimulation did not alter uterine S/D ratios in 12 term women (Gagnon et al 1988).

1.6.2.2.2 Drugs

Smoking of one cigarette had no effect on uterine S/D in 15 healthy women at term despite an increase in heart rate (Morrow et al 1988) although the number studied was small. This is not surprising as rhesus monkey experiments have shown that maternal smoking caused fetal hypoxia without disturbance in maternal blood gases or haemodynamics (Socol et al 1982).

Treatment of 14 hypertensive women with 50-100mg of atenolol increased arcuate PI but the MHR decreased at the same time (Montan et al 1987). The increase may have been due to an increase in resistance in the uteroplacental circulation or just be an effect of lengthening the cardiac cycle. Unfortunately, the sample was also heterogeneous containing 5 multigravidae and only 5 women with proteinuric hypertension.

Tocolysis with magnesium sulphate had no effect on uterine artery S/D in the treatment of 40 women with premature labour although ritodrine infusion in 20 women was followed by a decrease in S/D (Brar et al 1988a). However, this may have been secondary to increased maternal heart rate rather than an effect on uteroplacental resistance.

Prostacyclin infusion in two cases of severe early onset IUGR had no effect on uteroplacental FVWs (Steel and Pearce 1988)

1.6.2.2.3 Labour

In 12 normal women in labour the UA S/D remained unchanged during contractions while the uterine FVWs showed a fall in EDF whilst intrauterine pressure increased. Despite the rise in S/D there was no appearance of any notching (Fleischer et al 1987). This was confirmed in a study of 27 women in active labour where AEDF was noted in the uterine artery during the peak amplitude of the uterine contraction (Brar et al 1988c). Velocity in the uterine artery has been estimated, without knowing the angle of estimation, and found to decrease during contractions (Janbu et al 1985) in ascending branches and branches penetrating the myometrium, and remain constant in descending branches to the vagina (although the identification of the different branches was based on the velocity in the first instance). Both the PI and velocity in the uterine artery have been shown to increase during

contractions of eight normal women in labour and seven antenatal women with Braxton Hicks contractions. Intrapartum intrauterine pressure monitoring showed a linear inverse velocity/pressure relationship (Janbu and Nesheim 1987). These findings and those in Section 1.5.2.2.4 suggest that, during contractions, reduction in uterine blood flow is dependent on the intensity of the contraction whilst fetoplacental blood flow is uninterrupted.

Elevated S/D ratios in either the umbilical or uterine artery were associated with failure of tocolysis in premature labour (Brar et al 1988b). This finding could be explained in a number of ways. It might be postulated that, in the more well-established premature labours, contractions were influencing waveforms, and the authors do not state that readings were made between contractions. The other possibility is that the more abnormal the pregnancy (as assumed by the high S/D) the more established the labour and thus the failure of tocolysis. These findings support the hypothesis that intrauterine growth retardation leads to premature labour.

1.6.2.2.4 Fluid loading and epidural anaesthesia

In one study of eight women undergoing elective CS a decrease in A/B ratio was found after fluid loading and insertion of an epidural with no change in maternal pulse but a fall in BP (Giles et al 1987a). This was postulated to be due to increased

perfusion subsequent to plasma volume expansion. A similar study of 20 women showed no change in PI of the placental FVW (Long et al 1988) although no change in BP was noted either, so the A/B changes may just be related to the fall in BP. Petrikovsky et al (1988) confirmed the stability of S/D ratios with achievement of epidural anaesthesia in 22 women undergoing elective CS, but extended the observations by making intraoperative recordings. They showed a rise in S/D ratios after opening of the abdomen and before incision of the uterus.

1.6.2.2.5 Diurnal variation

No significant day to day variability was found in mean A/B of FVWs (Hastie et al 1988) when assessed by three recordings over a week in 57 complicated and 46 normal subjects grouped into three unequal gestation groups. There were no circadian changes or differences before and an hour after meals (Pearce et al 1988). However, with the small numbers of subjects any differences in waveforms may have been hidden by the large minute to minute variation.

1.6.2.2.6 Exercise

No changes in uterine A/B ratios were found after graded stationary bicycle exercise of up to 20 minutes in 11 normal women between 16-28 weeks' gestation (Moore et al 1988).

However, this is in contrast to another study of 15 term women undergoing five minutes of exercise on a bicycle ergometer in whom uterine S/D ratios became significantly elevated (Morrow et al 1989). The studies are not comparable in subjects or type of exercise. Another problem with both of them is that CW equipment was used and the FVWs of great vessels supplying the exercised legs may have been mistaken for uterine vessels. The studies were performed on normal women without complications and the exercise was of low intensity and short duration (Shangold 1988).

1.6.3 Complicated pregnancy

Initially mixed groups of complicated pregnancies were studied. Campbell et al (1983) examined 30 normal and 31 complicated pregnancies and found a significant increase in proteinuric hypertension and decreased birthweight ratio in the 14 of 31 complicated pregnancies where the frequency index profile (FIP) fell outside the nomogram constructed from 30 normal pregnancies as compared to the 17 complicated pregnancies where waveforms were normal. However the patients had a mixed group of complications with a low percentage of primigravidae in both groups. In a study of 53 women with hypertension and growth retardation, using arcuate and umbilical Doppler studies, an increased amount of proteinuric hypertension, and decreased birthweight ratio, was found in the group with both circulations abnormal, and fetal asphyxia was increased in the group with loss

of EDF in the UA (Campbell et al 1984).

1.6.3.1 Hypertension

High resistance uterine FVWs have been found to be associated with hypertension, especially when accompanied by proteinuria (Griffin et al 1983, Campbell et al 1983, Trudinger et al 1985c). In a group of 71 hypertensive women, higher S/D ratios were found in women with PET than in those with chronic hypertension. Higher ratios were also associated with higher CS rate, premature delivery, stillbirth and growth retardation. The sensitivity and specificity of an abnormal outcome to the pregnancy (delivery <37 weeks or baby <2.5kg) were 93% and 91% respectively if a notch was also present. High S/D ratio and the presence of a notch were found to predict outcome more accurately than BP or uric acid level (Fleischer et al 1986).

In a further study of 136 hypertensive women, classification by the S/D of the uterine waveform clearly separated the pre-eclamptic from the chronically hypertensive women. All four perinatal deaths were in the group with abnormal uterine and umbilical FVWs. The two patients with eclampsia had normal uterine artery FVWs (Ducey et al 1987). Severe pregnancy induced hypertension can be found with normal uterine FVWs (Al-Ghazali et al 1988).

Doubt has been cast on the association of high resistance waveforms with PET by Hanretty et al (1988) in a case-control study of the lowest resistance waveforms found in a group of 32 women with PIH and 32 matched controls. No significant difference was found in the PI of the two groups but the cases were a mixed group including late onset mild nonproteinuric hypertension. The search for waveforms was made from all over the uterus and not from a consistent place in relation to the uterine circulation or placenta (Campbell et al 1988). Internal iliac artery and uteroplacental waveforms may also have been confused (Pearce and McParland 1988).

Schulman et al (1987b) found a high correlation between high S/D ratio and high delta S/D (the left-right difference). Delta S/D is calculated by subtracting one S/D ratio from the other. High delta S/D was also found in some poor outcome pregnancies where S/D was normal. This was postulated as evidence for unilateral placental blood flow as a pathophysiological event in hypertension. However, S/D is a non-linear ratio that varies between one and infinity. Identically small changes in diastolic frequencies will lead to a larger delta S/D as the absolute value of S/D increases. By definition, delta S/D would be expected to be highly significantly correlated with S/D. Delta S/D is a non-linear difference between two non-linear ratios and has no physiological meaning. The conclusion that a large delta S/D reflects unilateral flow is erroneous.

Atenolol treatment in hypertension led to an increase in arcuate PI, suggesting an increase in peripheral resistance (Montan et al 1987). However, with a concomitant fall in maternal pulse, the change in PI might have been due to lengthening of the diastolic portion of the FVW.

There has been one case report of a woman with Takayasu's aortitis and hypertension, who had stenosis of the aorta in the lumbar region, whose uterine and femoral FVWs showed a dampened systolic acceleration (Giles et al 1987b). There is one case report of uterine velocimetry performed during cardiac surgery when the mother was on a by-pass pump. There was still pulsatile flow in the uterine arteries and a temporary increase in resistance (Farmakides et al 1987). These two cases demonstrate the influence that downstream circulation may exert on FVWs.

1.6.3.2 Growth retardation

In many studies of mixed complicated pregnancies, abnormal uteroplacental waveforms have been associated with SGA babies (Griffin et al 1983, Campbell et al 1983, Trudinger et al 1985b,c), and a poorer neonatal outcome (Trudinger et al 1985c).

By contrast, Gudmussion and Marsal 1988 found that the arcuate artery PI, from the subplacental bed, had no significant relationship to fetal distress or IUGR, in a study of 129 small

fetuses suspected of being <15th centile weight on a routine 32 week ultrasound scan. This may be because a different part of the uteroplacental circulation was being studied.

Of 12 growth retarded pregnancies, six out of seven with PET had abnormal FVWs, most with notching, and only one out of five when there was chronic hypertension or unknown cause (McCowan et al 1988). Severe SGA has been associated with normal maternal waveforms (Al-Ghazali et al 1988). This supports the concept of some growth retardation being secondary to reduced uterine blood flow, especially in PET, rather than the underlying pathology in all cases.

1.6.3.3 Sickle cell haemoglobinopathy

Anyaegbunam et al (1988) compared 48 women with sickle cell haemoglobinopathy (eight with SS and 40 with AS haemoglobin) with 48 controls. 88% of women with SS, 3% of women with AS and none of the controls had elevated uterine S/D ratios. SGA and fetal distress were found in pregnancies with both abnormal uterine and UA FVWs. None of the women had hypertension. The process of intravascular sickling, vaso-occlusion and infarction may have taken place in the uteroplacental bed leading to increased vascular resistance, with the fetoplacental response determining growth retardation and the UA S/D.

1.6.3.4 Early onset oligohydramnios

A group of 41 pregnancies, complicated by severe second trimester oligohydramnios and with a retrospective definition of the underlying cause, showed that 90% of cases with renal agenesis or dysplasia or preterm premature rupture of the membranes had normal arcuate FVWs. 12 out of 14 of the cases of idiopathic IUGR had abnormal arcuate and aortic FVWs, and only two (of which one was a partial mole) had normal arcuate FVWs, suggesting that uteroplacental Doppler can distinguish the underlying pathology in these cases where ultrasound is particularly difficult (Hackett et al 1987).

1.6.3.5 Fetal well-being

Absent EDF in the UA is associated with an abnormal uterine waveform in 88% of cases, suggesting that decreased uterine blood flow is the cause of both findings (Rochelson et al 1987). Uterine FVWs have been correlated directly with fetal blood gases for a group of 32 IUGR fetuses who were structurally normal and having cordocentesis for karyotyping. There was a positive correlation between uterine RI and pO₂, pCO₂ and lactate and a negative correlation between RI and pH (Soothill et al 1987a).

1.6.3.6 Fetal anomaly

Trudinger and Cook (1985) found normal uterine FVWs in a group of 16 fetuses with chromosomal or structural abnormality. Meizner et al (1987) confirmed this in a study of 32 fetuses with severe structural abnormalities. All but two with equivocal results had normal uterine FVWs (Meizner 1987). This suggests that the abnormal UA FVWs found in fetal abnormality are determined by some fetal mechanism.

1.6.3.7 Postmaturity

Arcuate RI using PW did not correlate with birth weight or outcome of labour in 35 postmature pregnancies >42 weeks (Rightmire et al 1987). This absence of a relation was confirmed in a CW study of 149 pregnancies >41 weeks where no differences were found in uterine S/D regardless of the outcome (Farmakides 1988). This suggests that the 'placental insufficiency' of postmaturity is not primarily of maternal origin.

1.6.4 Summary

There is more disparity and confusion in the Doppler assessment of the uteroplacental circulation compared to the fetoplacental circulation. The normal values are different, the errors larger

and the techniques variable. Abnormal FVWs are found in association with hypertension (especially proteinuric), growth retardation (although not all cases), sickle cell disease and early onset oligohydramnios. There is an association with abnormal UA FVWs, abnormal fetal blood gases and failed tocolysis of premature labour. Abnormal uteroplacental FVWs may reflect the underlying pathology of PET and some growth retardation but not the 'placental insufficiency' of postmaturity.

1.7 SCREENING

1.7.1 Introduction

The major problem affecting both the diagnosis and prediction of PET and IUGR is one of definition. Pregnancies complicated by hypertension and/or small babies have many causes, and without a clear understanding of the underlying pathology any screening tests for prediction will always be indirect and inadequate. Screening tests to detect disease or predict its development are different. In antenatal care the distinctions are blurred as the final diagnosis may have to wait until after delivery.

1.7.2 Problems of definition

So far in the text, the terms used have been those used by the investigators. The definitions of disease used for the experiments described in the thesis are found in Section 13.2.

1.7.2.1 Growth retardation

Small-for-gestational-age and growth retardation are not synonymous. The first refers to the end result with respect to some standard and the second term is used with the implication that some process has been at work that limits the attainment of genetic potential. The purpose of screening the placental

circulations can only be to predict growth retardation of placental origin.

A small baby can be defined by a cut-off point, either of absolute weight or weight for gestation (or even a corrected cut-off weight for gestation taking sex and birth order into account). This still only defines a group of small babies, not all those who have failed to grow to their maximum potential. The weights of 'failed to grow' babies overlap with those that are genetically small.

There is a heterogeneous group of causes and associations of smallness including fetal chromosome and structural anomalies, multiple pregnancy, PET, chronic renal disease, diabetes, viral infections (rubella and cytomegalovirus), drugs (smoking, alcohol and opiates) and maternal factors (race, weight, height, parity, social class, malnutrition and obstetric history) (Beischer et al 1983). Low birth weight at term is associated with primigravidity, low social class, low maternal height and weight, smoking, previous low birth weight infant, threatened miscarriage and PET (Fedrick and Adelstein 1978). There is a small genetic effect on birth weight (Carr-Hill et al 1987). Birth weight can be adjusted for maternal height and weight, gestational age, pregnancy number and fetal sex (Thomson et al 1968). However, whichever charts are used they may only be valid for their own population.

A biometric test for size, such as SFH measurement or ultrasound, might be expected to predict smallness, whereas tests of uterine function, such as obstetric risk scores or Doppler ultrasound might relate more to adverse outcome. However, whilst any new test of placental function test is compared with the 'gold standard' of weight it always has to contend with the problem of overlap of normal and abnormal. Chard and Klopper (1982) have described the 'submerged two-thirds' of growth retarded babies that cannot be identified as such on the basis of birth weight.

1.7.2.2 Pre-eclampsia

Pre-eclampsia is a pregnancy specific disease characterised by generalised vaso-constriction (Gant et al 1973). Hypertension develops because cardiac output is maintained despite increased peripheral resistance (Assali et al 1964). It is only a sign, not a diagnosis in itself. Pregnancy induced hypertension refers to the development of this sign in pregnancy, and the cause is sometimes pre-eclampsia.

It is important to try and distinguish the different underlying causes of hypertension, because, as with SGA, it is a condition with a variety of causes. None of the signs of PET define the underlying disease and so all criteria have their limitations (Redman 1987).

Hypertension can be defined by a threshold BP, a rise in BP, or a combination of both. Recently, the International Society for the Study of Hypertension in Pregnancy (ISSHP) published a classification system (Davey and MacGillivray 1986). Redman and Jeffries (1988) studied defining parameters to see which ones selected out other features of PET, such as primigravidity, perinatal mortality and proteinuria. They then suggested a revised definition of the cut-off for hypertension which depended entirely on the diastolic component (Redman and Jeffries 1988). A problem with many of the studies on PET is that proteinuric and nonproteinuric hypertension are not distinguished, and that the definitions are not comparable.

BP and fetal growth are connected in a complex way. No difference in birth weight or placental weight was found between 3369 normals and a group of 364 women with two of the classical triad of hypertension ($> 140/90$ mm Hg), proteinuria and oedema. Differences were seen, however, between those who were delivered prematurely because of worsening maternal condition and those who "responded favourably" to bedrest (De Souza et al 1976). In a study of over 11,000 women, birth weight increased with BP up to a diastolic BP of $/90$ mm Hg and fell with proteinuria. There was no evidence of fetal growth retardation with non-proteinuric hypertension (Naeye 1981).

Therefore, in this thesis, emphasis has been placed on the

difference between proteinuric and non-proteinuric hypertension, and the classification systems of the ISSHP and Redman have been used.

1.7.3 Traditional methods of screening

The non-Doppler methods of predicting and detecting IUGR and PET are described. Some, such as the roll-over test, are pure screening tests attempting to predict the later development of PET, whereas others, such as ultrasound, attempt to detect small fetuses.

1.7.3.1 Clinical suspicion

Clinical suspicion from abdominal palpation, reduced weight gain or a previous SGA baby led to a suspicion of growth retardation (less than 10th centile) in 50% of cases and action in only one third of those suspected (Rosenberg et al 1982a).

1.7.3.2. Obstetric risk score

An obstetric risk score (ORS) has been developed to predict low birth weight at term in nulliparae and multiparae with a sensitivity of 35-46% and a specificity of 94-80% (Adelstein and Fedrick 1978). This has not been universally incorporated into routine antenatal care although it is very simple. A risk score

for prematurity (and thus low birth weight) that is assessed at every antenatal visit has been developed (Papiernik 1969) and used clinically as part of a programme for prevention of preterm births, but in an uncontrolled way with many confounding variables (Papiernik et al 1985).

1.7.3.3 Symphyseal-fundal height

Symphyseal-fundal height (SFH) can be measured easily (Belizan et al 1978) and predicted low birth weight with a sensitivity and specificity of 86% and 90% in a study that excluded more than half of the women entered into it. In a study of high risk pregnancies with certain menstrual dates and early ultrasound examinations the results were 79% and 92% (for the worst patterns of catch-up and low growth SFH curves) and 86% and 79% (for static curves) (Cnattingius et al 1984). When the use of SFH curves was examined in actual practice with different observers the values fell to 56% and 85% (Rosenberg et al 1982b).

1.7.3.4 Ultrasound

Different patterns of growth have been distinguished using SFH and ultrasound. Symmetrically growth retarded fetuses have a consistently low growth profile whilst asymmetrical growth retardation is demonstrated by a late flattening of the SFH (Cnattingius et al 1984), or fetal biparietal diameter (BPD)

(Campbell and Dewhurst 1971). The ratio of fetal head to abdominal circumference is said to distinguish between wasted small babies, with uteroplacental insufficiency as a presumed underlying cause, and genetically small or congenitally abnormal babies (Campbell and Thoms 1977). Abdominal circumference (AC) is better at predicting SGA babies than BPD, particularly the very small babies (sensitivity and specificity for <10th and <2.5th centile babies were 62% and 93%, and 82% and 92% respectively) (Rosendahl and Kivinen 1988). AC alone at a routine second stage ultrasound examination at 34-36 weeks detects SGA babies under the 5th centile with a sensitivity and specificity of 83% and 90% (Neilson et al 1980). Even when this is improved to 94% and 90% in a randomised controlled trial using crown rump length x trunk area no beneficial effect on fetal outcome or obstetric management could be demonstrated (Neilson et al 1984).

1.7.3.5 Roll-over test

The roll-over test is performed between 28 and 32 weeks of pregnancy and is positive if there is a rise in diastolic BP of ≥ 20 mm Hg between BP measured in the left lateral and supine position. Gant et al (1974) reported a sensitivity and specificity of 88% and 95% in a group of 38 primigravidae, but with a prevalence of disease of 45%. Other studies using more subjects did not reach these high levels of sensitivity and

specificity (Marshall and Newman 1977, Degani et al 1985). It is not clear that results were concealed from the clinicians or from the investigators making the diagnosis of pregnancy induced hypertension. Although the test is simple, it is performed relatively late in pregnancy and its validity has not been confirmed.

1.7.3.6 Infusion of Angiotensin II

Pregnant women are relatively refractory to the pressor effect of intravenous infusion of angiotensin II (Abdul-Karim and Assali 1962). This insensitivity is lost in pre-eclamptic women (Chesley 1966). Gant et al (1973) serially infused pregnant women with angiotensin II and showed that, whereas all of 192 randomly selected primigravidae were refractory to the pressor effects under 20 weeks gestation, 45/50 who developed pregnancy induced hypertension had a positive test between 28 and 32 weeks of pregnancy. However, the population studied were very young and 80% black and so the validity to other populations uncertain. Studies confirming the validity of the test have largely used small numbers and different definitions of pregnancy-induced hypertension (Morris et al 1978, Nakamura et al 1986). The largest contained 231 subjects and reported a sensitivity and specificity of 76% and 83% for predicting a BP of $\geq 140/90$, found in 15% of subjects, (Oney and Kaulhausen 1982) but did not state whether a double-blind design was used. The test is complicated

and time consuming and, like the roll-over test, predicts hypertensive disease relatively late in pregnancy.

1.7.3.7 Summary of present screening methods

These studies demonstrate that, clinically, IUGR is often missed. Although the prediction can be improved using SFH and ultrasound, there is a tradeoff in sensitivity and specificity. When the criteria are made more stringent the false negative rate falls but more cases are missed. When put into clinical practice tests may have a lower efficiency than in a research setting (see Section 1.7.3.3).

Although the underlying pathological changes of PET have been present from early on in pregnancy the clinical signs appear late, and the disease runs a short time course in the more severe and early onset cases. Present screening methods are applicable late in pregnancy and are complicated and time-consuming. If there is to be effective prevention, PET has to be detected earlier when it is in the subclinical phase (or at-risk women identified even before they become pregnant).

1.7.4 Screening of the placenta

1.7.4.1 Placental morphology

Placental weight was related to birth weight and was lower in cases of PET, antepartum haemorrhage (APH) and perinatal death, but was an inaccurate predictor of birth weight and a poor indicator of function (Thomson et al 1969). No-one has tried to predict complications of pregnancy using estimates of placental mass. Ultrasonic measurements of placental volume can be made (Bleker et al 1977). Grannum grading of the placenta has been associated with pulmonary maturity (Grannum et al 1979) smoking, low maternal age, low parity, being white, fetal distress and low birthweight (Proud and Grant 1987). A significant decrease in perinatal death has been shown in a randomised controlled trial where half of the results of placental grading were available to clinicians (Proud and Grant 1987).

1.7.4.2 Placental function tests

Placental function can be assessed indirectly by a host of blood and urine placental function tests (PFTs) whose aim is to assess fetal well-being in early or late pregnancy (Chard and Klopper 1982). They have not generally been used in the second trimester for prediction of complications.

1.7.4.2.1 Alphafetoprotein (AFP)

Alphafetoprotein (AFP) is of fetal origin and levels in pregnancies ending in delivery of babies <2.5 kg were higher than controls (Brock et al 1980). The birth weight among pregnancies with raised AFP was over 300g lower than among those with normal levels (Wald et al 1980a). The increased risk of low birth weight has been found to be independent of maternal weight (Haddon et al 1987). Although raised AFP has been associated with prematurity, IUGR and low birth weight, the prospective sensitivities and specificities were too low to use for screening in the second trimester (Chard et al 1986). If oligohydramnios was present as well as a raised AFP the prognosis for the pregnancy was very poor (Dyer et al 1987). Women with high unexplained AFP levels had a greater incidence of proteinuric PET than controls (Walters et al 1985).

1.7.4.2.2 Oestriol (E3)

Oestriol is a fetoplacental steroid. A low 24hr urinary E3 measurement at 34-36 weeks gave a sensitivity of 32% and 43% for the prediction of IUGR or perinatal death (Beischer et al 1984). Falling serial measurements in diabetics predict stillbirth (Gabbe et al 1977). The test has fallen into disuse (Chamberlain 1984).

1.7.4.2.3 Human placental lactogen (hPL)

Human placental lactogen, hPL, human chorionic gonadotrophic (hCG) and Schwangerschaftsprotein 1 (SP1) are trophoblastic proteins with hormonal function. Their levels are controlled by uteroplacental blood flow and the trophoblastic mass. Since they reflect the pathology of the placenta they have been used in clinical practice as biochemical markers of fetal well-being.

Depressed levels of hPL, were found in SGA pregnancies but the predictive properties were not high (Westergaard et al 1984a, Obiewke et al 1984). Even when 51 small babies under the 10th centile were subdivided into dysmature (with thin extremities, dry skin etc) and normal but small, although the hPL and SP1 levels were significantly lower for the first group, the predictive value of a low hPL rose only to 45% (Westergaard et al 1985b). However, hPL was distinguishing the genuinely deprived fetus. Low hPL was more closely associated with SGA than SP1 and pregnancy associated plasma protein A (PAPP-A) was the least closely associated (Westergaard et al 1984a). At the other extreme, hPL was the PFT most closely correlated with birth weight and placental weight in twin pregnancies (Westergaard et al 1985a).

hPL levels were significantly lower in primigravidae with severe PET and not multigravidae (Obiekwe et al 1984) but the test was

most predictive in multigravidae with IUGR. hPL levels were lower in hypertensive pregnancies in late pregnancy (Westergaard et al 1984b) but this may be because of the association with growth retardation.

1.7.4.2.4 Schwangerschaftsprotein 1 (SP1)

Depressed levels of SP1 were related to IUGR but the association was not strong (Westergaard et al 1984a). There was no relation to hypertension (Westergaard et al 1984b). Low SP1 levels preceded spontaneous premature labour (Westergaard et al 1984c).

1.7.4.2.5 Pregnancy associated plasma protein A (PAPP-A)

PAPP-A and plasma protein 5 (PP5) arise from trophoblast and are thought to have a local function involving immune and coagulation systems.

PAPP-A levels have been found to be higher in PET (Hughes et al 1980). However, Westergaard et al have shown it is of no value in the prediction of growth retardation (1984a), hypertensive pregnancies (with or without proteinuria) (1984b) or premature labour (1984c). The discrepancies may be explained by the use of anticoagulants (Westergaard 1984b). The major application of PAPP-A estimation is probably in the first trimester (Stabile et al 1988b)

1.7.4.2.6 Placental protein 5 (PP5)

The role of PP5 seems to relate to the coagulation system within the IVS (Salem et al 1980). Elevated PP5 levels have been found in five out of 12 women with abruptio often before clinical signs developed (Salem et 1981) which suggests a possibility of its use for prediction of this complication.

1.7.4.2.7 Placental protein 12 (PP12)

The source of PP12 is endometrium and decidua. It is thought to be involved in the maternal response to pregnancy and to be under the control of placental oestrogens and progesterone. In a series of 501 pregnant women at term PP12 was inversely related to hPL and was raised in cases of SGA (Howell et al 1985). The predictive properties of a high test were similar to a low hPL.

1.7.4.3 Summary of placental function tests

A summary of the predictive properties of PFTs performed in the second trimester is given in Table 4. Placental function tests have low predictive properties and have found no clinical application in the second trimester. A raised AFP without structural abnormality may be a fortuitous by-product of neural tube screening that can give clinicians some cause for suspicion.

Table 4 PFT predictions in second trimester

| Author/year | PFT | Gest | Cut-off | | SE | SP | PO | NE |
|----------------------|--------|-------|---------|-------|----|----|----|-----|
| | | | Outcome | Test | | | | |
| Brock 1980* | AFP | 15-22 | Wt<2.5 | >2MoM | (9 | 97 | 19 | 93) |
| Westergaard 1984a | HPL | 20 | SGA<10 | <10 | 39 | 89 | 32 | 87 |
| " | SP1 | " | " | " | 21 | 90 | 29 | 86 |
| " | PAPP-A | " | " | " | 21 | 90 | 29 | 86 |
| Westergaard 1984c | HPL | 18-22 | Prem<37 | <10 | 13 | | 5 | 95 |
| " | SP1 | " | " | " | 13 | | 6 | 95 |
| " | PAPP-A | " | " | >90 | 13 | | 6 | 95 |
| Chard 1986 | AFP | 15-18 | SGA<10 | >90 | 14 | 91 | 14 | |
| " | " | " | Wt<2.5 | " | 16 | 91 | 9 | |
| " | " | " | Prem<37 | " | 13 | 91 | | |

* Results in brackets as this was a retrospective case-control study but extrapolations were made for the Scottish population.

1.7.5 Screening using Doppler

This all leads to an understanding of IUGR and PET as manifestations of failed trophoblast invasion and 'uterine ischaemia'. The disease is exhibited in mothers as PET, with its own mortality and morbidity, and in the fetus as growth retardation, which may be accompanied by hypoxia, neonatal brain

damage and perinatal mortality. The assumption on which Doppler screening is based is that the fall of uteroplacental FVW resistance indices by 22-24 weeks represents the second wave of trophoblastic invasion, and that the uteroplacental FVW reflects the depth of trophoblastic invasion. UA Doppler screening has been largely confined to predicting SGA in the third trimester.

1.7.5.1 Fetal waveforms

As the UA PI can be abnormal weeks, or months, before the birth of an SGA baby (Reuwer et al 1984), UA velocimetry has been used, both to predict outcome in high risk pregnancies, and to predict SGA in unselected populations of pregnant women.

Even in a group of 159 suspected IUGR pregnancies, AEDF predicted SGA (>2SDs below mean for gestational age) with a sensitivity and specificity of 50% and 97% respectively (Laurin et al 1987). However the figures for ODFD were 83% and 90% respectively, illustrating the point that FVWs reflect function rather than absolute smallness.

Many studies confirm these findings. UA S/D can predict SGA in high-risk patients (Gaziano et al 1988). UA S/D predicts IUGR and poor neonatal outcome in pregnancies at risk of IUGR (Berkowitz et al 1988b), but ultrasound predicts IUGR more accurately (Berkowitz et al 1988a). In a comparison of UA S/D

and a variety of ultrasound measurements, the best predictor of IUGR was an ultrasound estimated fetal weight (Divon et al 1988). High A/B was less effective at predicting SGA in clinically high-risk pregnancies than late decelerations in labour (Dempster et al 1988). However, these studies only examined at-risk fetuses late in pregnancy. Arduini et al (1987a) found the ratio of PI in the UA and internal carotid artery at 26-28 weeks' gestation useful in predicting IUGR in high-risk pregnancies, but this is a complex test to contemplate using in practice.

A trial of routine UA Doppler screening in 2097 low-risk women at 28, 34 and 38 weeks' gestation showed that a high A/B at 34 weeks predicted SGA <5th centile with a sensitivity of 40% and specificity of 84%. A sensitivity of only 43% was achieved for any abnormality of the FVW to predict SGA (Beattie and Dornan 1989). All three unexplained stillbirths and one of two caused by placental abruption had an abnormal waveform antenatally, which might suggest that the underlying pathology in unexplained stillbirth is disturbance of placental function. However, there has been a report of a late unexplained stillbirth one day after a normal ultrasound scan, normal UA FVW and cardiotocograph suggesting that not all unexplained stillbirths are related to placental function (Erskine et al 1986b). Sijmons et al (1989) also were unable to obtain a sensitivity of >42% for the prediction of SGA in 400 hospital population women studied at 28 and 34 weeks' gestation.

In a study of 543 third trimester women from the antenatal clinic, no differences were found between normal and abnormal UA A/B groups (Hanretty et al 1989). However, although there was no difference in the percentage of SGA babies, high A/B was associated with lower mean birth weight. This supports the hypothesis that Doppler ultrasound identifies fetuses who have not fulfilled their growth potential whilst not necessarily ending up below the lowest weight-for-gestation centiles.

1.7.5.2 Uterine waveforms

Five papers have reported on screening the uteroplacental circulation in the second trimester to predict complications of pregnancy, three with PW and three with CW Doppler ultrasound.

Campbell et al (1986) reported on a single study performed at 16-18 weeks' gestation on consecutive attenders for a booking ultrasound scan. The results were concealed from the clinicians. 126/149 (85%) cases were available for analysis. A cut-off of RI of 0.58 from either side was used to define an abnormal FVW, this value representing two SDs from the mean of a normal range (of FVWs that had been transformed by a FIP). However, 40% (50 women) of this apparently unselected group had an RI above the 95th centile of the normal range.

The criteria for definition of abnormality were: PIH, a rise in systolic BP > 30/ or diastolic BP /15 with proteinuria or generalised oedema (as defined by Chesley [1978]); IUGR, a birth weight <10th centile corrected for sex and parity; and birth asphyxia, all three features of abnormal non-stress test antepartum CTG, scalp or cord pH <7.20 and 5-min Apgar score <7.

Of these women with abnormal FVWs, ten developed PIH (2 accompanied by IUGR and one by an IUD), ten pregnancies were complicated by IUGR alone and one fetus was asphyxiated at birth. Of the 76 with normal FVWs, five developed PIH (one accompanied by IUGR) and five pregnancies were complicated by IUGR alone. A total of 31 women developed pregnancy induced hypertension, growth retardation or asphyxia in labour (Campbell et al 1986), giving the test a sensitivity and specificity of 68% and 69%. The positive and negative predictive values were 42% and 87%.

With 15% of subjects lost to follow up and a high complication rate of 25% in the remainder it seems as though the study group may not have been randomly selected and representative. With such a high prevalence of disease, the predictive values would be expected to be lower when applied to a normal pregnant population (Grant and Mohide 1982).

Another screening study of a normal pregnant population was reported by Steel et al (1988b). A CW study of primigravidae

only was made at 18-20 weeks, and repeated at 24 if the result was abnormal. They were repeated 2-4 weekly until delivery or until no abnormal result could be found. The results were not made available to the clinicians but this study design means that both the woman and the clinicians could extrapolate from the mere performance of the studies to the deduction that the results were abnormal. 200/252 (79%) cases were available for analysis. However, failure to attend at 24 weeks was considered a reason for exclusion and since only those with abnormal results were recalled this must have biased the analysis.

An unspecified number of "waveforms on either side of the uterus" were obtained and if any had an RI > 0.58 the test was considered abnormal. A FIP was not used so this cut-off is now arbitrary. 75 women (37%) were found to have abnormal FVWs.

The criteria for definition of abnormality were: Hypertension, a BP >140/90mm Hg in the second half of pregnancy; IUGR, an AC >2SDs below the mean on ultrasound measurement or, when there was no third trimester scan, a birth weight <10th centile.

Of the 75 women with abnormal FVWs, 21 were still abnormal at 24 weeks (10% of the total). Five developed hypertension (four accompanied by IUGR), six pregnancies were complicated by SGA alone and one fetus was stillborn. Of the 179 with normal FVWs, 11 developed hypertension, 17 pregnancies were complicated by SGA

and one by eclampsia. A total of 41 women developed hypertension, growth retardation, eclampsia or stillbirth, giving the test a sensitivity of 29% and a specificity of 94%. The positive and negative predictive values were 57% and 84% respectively.

In this study, which was only a preliminary report of a larger series, 21% of the initial subjects were not followed up and there was still a high complication rate of 21% in the remainder. The final study of 1004 women is claimed to show a 100% sensitivity in predicting severe hypertensive disease (McParland and Pearce 1988). The definition of severe hypertensive disease used is that requiring premature delivery, associated with IUGR or significant proteinuria ($>0.5\text{gm}$ or ++). However, this extreme definition must be excluding one patient with eclampsia and another woman with a diastolic BP $>/110\text{mm Hg}$ and ++ proteinuria that were reported in the preliminary series.

Arduini et al (1987) studied a group of 60 women at high risk of developing PIH. 38 (64%) had previous PIH, 15 (25%) had previous PET, four (7%) had renal disease and three (5%) collagen disease. Readings were taken from the lateral uterine wall using PW on a single occasion at 18-20 weeks' gestation. An RI > 0.57 was considered abnormal and the authors do not indicate whether the results were concealed from the clinicians. All 60 pregnancies were followed up.

The criterion for definition of abnormality was: PIH, two BP readings $>140/90$ mm Hg four hours apart. Of the 20 (33%) women with abnormal FVWs, 14 developed PIH, whereas 8/32 with normal FVWs developed PIH. The breakdown of results was only given for PIH. For PIH alone the test has a sensitivity and specificity of 64% and 84%. The positive and negative predictive values were 70% and 80% with a prevalence of 37%. The predictive values are very high as this is a high risk population.

Schulman et al (1989) have recently reported a screening study using CW of both the uterine and umbilical arteries. Studies were performed on 255 women (46% of potential participants) at monthly intervals from 20 weeks' gestation. These volunteers had higher risk scores than the non-volunteers. Results were given to both the women and clinicians. No women appear to have been lost to follow-up.

Nine women (3.5%) had an average 26 week uterine RI > 0.62 , which was considered abnormal. No results were given for the normal FVWs. Seven of the nine had IUGR, PIH or PET (no definitions given) giving the test a positive predictive value of 78%. The UA screening parameters were only given from 30 weeks onwards.

Hanretty et al (1989) have also recently reported a study of the uteroplacental circulation performed on 543 unselected women in the antenatal clinic at 26-30 or 34-36 weeks' gestation. There

were 357 in the earlier and 395 in the later group, whilst 209 women appeared in both. The results were not available to the clinicians. The CW transducer was moved until uteroplacental waveforms representing lowest resistance were obtained. No satisfactory waveform could be obtained from 18% and 19% of cases in the two groups. An A/B ratio of 2.07 (RI = 0.52) or 2.0 (RI = 0.5) was used for the definition of abnormal at the two gestation periods, representing values over the 95th centile of another pilot study of 150 patients. 6.5% and 2.8% of pregnancies had abnormal uteroplacental waveforms in the two groups.

The criteria for definition of abnormality were: PIH, a BP \geq 140/90 if the obstetrician arranged for further investigation or treatment and SGA, a birth weight <5th centile of a locally derived database. They also compared the prematurity, CS, instrumental delivery, elective delivery, low Apgar and SCBU admission rates.

No significant differences in the percentage of women who developed complications in the normal or abnormal groups were found.

Recruitment at an antenatal clinic may have biased collection in favour of high risk pregnancies. 46% of women were admitted or investigated during the pregnancy, 25% developed PIH, 24% of pregnancies were delivered electively and 36% had instrumental

deliveries. With over 18% failure to obtain recordings the study group may have become biased even if the subjects had been randomly selected. The method of FVW collection was not from a defined site, and was designed to find low resistance waveforms, not high, or even standard, ones. There was an eccentric definition of PIH and no breakdown of hypertension by severity or the presence of proteinuria.

1.7.6 Limitations of second trimester Doppler studies

It is difficult to draw general conclusions from the Doppler ultrasound screening studies. They have used varying and different definitions of PET, IUGR and poor pregnancy outcome as well as combining the outcomes in unique ways. There appears to have been a strange selection of "unselected" patients since abnormal FVWs were found in between 2.8% - 37% of the population. There may have been a fault in the normal ranges or the selection process. A large percentage of subjects had failed recordings or were lost to follow-up. Those women who ended their pregnancies as an emergency elsewhere, whose notes were sequestered at some point or who moved may have been a different group than those with known outcomes. No studies have described whether the assessment of outcome was made 'blind', separate from knowledge of the test result.

2. AIMS OF THIS STUDY

The principal aim of this study was to determine the ability of a second trimester CW Doppler examination of the placental circulation to predict PET and IUGR. A descriptive study of the literature was made (Section 1). The methodology is divided into two: the main screening study itself and its validation.

The specific aims of the screening study were:

- a) to define reference ranges for placental FVWs in the second trimester,
- b) to elucidate maternal parameters that affect uteroplacental waveforms in the second trimester,
- c) to define the relationship of complications of pregnancy to early Doppler findings,
- d) to quantify the predictive properties of the test and
- e) to compare the screening properties with obstetric risk score and placental protein estimation.

The specific aims of the validation studies were:

- a) to substantiate the technique used,
- b) to estimate the reproducibility of the test,
- c) to determine whether CW Doppler ultrasound with pattern recognition correctly identifies uteroplacental vessels and
- d) to assess the reliability of the data collection.

3. METHODOLOGY

3.1 CHOICE OF TECHNIQUE

3.1.1 Development of fixed insonation sites

Because the previous investigators had used different techniques, different modes of Doppler ultrasound and studied different parts of the uteroplacental circulation (see Section 1.7.5.2), a technique was devised that incorporated elements of all three published methods. Four fixed points with respect to the uterus were used for insonation. These were designated as left and right 'uterine' (LU, RU) and left and right 'arcuate' (LA, RA) points (see Section 5.1 for the need for fixed points, and Section 3.2.4 for their definition).

3.1.2 Pilot studies

Training in the use of CW and PW Doppler took place between August 1986 and January 1987. The pulsed wave study of Campbell et al (1986) was considered as a pilot for the outcomes, so a full pilot of the whole method, including waiting for deliveries, was not performed. The protocol was written in September 1986. The computer validation study (see Section 5.4) was performed in October 1986. The experiment studying variation around the uterus (see Section 5.1) was performed in November 1986.

Before starting the main screening programme, a pilot was performed in January 1987 to assess the feasibility of the study and equipment, estimate the time taken to perform the test and employ the data form. 21 pregnant women in the second trimester were studied using the four chosen sites (LA, LU, RA, RU) and a first draft of the data collection form (see Section 14.7). There were no failures to obtain waveforms and some questions were modified because of ambiguity (such as the placental location which was divided into three parts).

3.2 SCREENING STUDY

3.2.1 Selection criteria

Every woman who booked for antenatal care at Kings College Hospital (KCH) had a routine ultrasound scan between 18 and 20 weeks' gestation for dating and detection of fetal structural anomalies. The women in the study were recruited consecutively during attendance for this scan. Gestational limits of 16 + 0 to 24 + 6 weeks were set but there were no other selection criteria. The study was cross-sectional, with each subject being examined only once. All studies were performed by the author. Informed consent was obtained from all women who had been given a copy of the letter in Appendix 14.4.

There are two groups of women who booked for antenatal care at KCH who could not be recruited to the study. Firstly, some established insulin dependent diabetics who were participating in another study where the blood flow results were revealed; and secondly, women who had a fetus with a serious congenital anomaly detected at the ultrasound scan who were counselled about termination or continuing care and were not approached.

3.2.2 Booking ultrasound scan

The routine booking scan was performed by doctors (professor,

consultants, senior registrars and registrars), radiographers and midwives trained to carry out this procedure (see Appendix 14.1 for details of routine scan). The gestational age was calculated from the last menstrual period (LMP) using Naegles' rule, and confirmed by biparietal diameter and femur length measurements. Where the LMP was uncertain, or there was a discrepancy of more than ten days between the postmenstrual age and the prediction from ultrasound, then the ultrasound gestation was used (Campbell et al 1985b).

The placental location was determined by scanning the uterus in the transverse and longitudinal planes. All ultrasonographers were asked to note whether the bulk of the placenta was right, left or central in addition to their usual assessment of whether it was anterior, posterior, lateral or fundal; upper, lower or covering the cervix. The information from the ultrasound scan was recorded on a proforma (see Appendix 14.7). For the purposes of this study 'side' is taken to mean left-right (which can then be transformed into placental-nonplacental).

3.2.3 'Doptek' machine

The equipment used in this study was a CW Doptek 9000 Spectrum analyser (Doptek, Chichester) (Figure 7). This was the instrument for all studies unless otherwise indicated.



Figure 7 Doptek spectrascan used for all measurements

A 4MHz transducer was used and the filter level was 150Hz with a facility to decrease to 100Hz in equivocal cases of absent EDF. Ultrasound output levels were measured at King's College Hospital by Roland Blackwell of the Department of Medical Physics, University College Hospital, London, before the start of the screening study described later. The Doptek spectrascan 4MHz transducer had a total power of 6mW, SPTA intensity of 99 mWcm⁻² and peak positive pressure of 0.06 mPa.

3.2.4 Sites of insonation

All mothers were asked to lie in the semi-recumbent position for at least ten minutes prior to the blood flow scan, during which time demographic details were recorded. The maternal pulse and BP were measured automatically using a 'Dinamap' (Critikon Inc., Tampa, Florida). Subsequently, signals from the uteroplacental circulation were obtained at the designated four points on the uterus; left and right 'arcuate' and 'uterine' (LA, LU, RA, RU) (see Figure 8). The UA FVW was obtained from any convenient site.

The uterine artery was insonated near its origin. The technique described by Campbell et al (1983), employing PW was modified. The CW transducer was held at 45° from the perpendicular to the patient with the end halfway along and two cm above the inguinal ligament pointing medially and caudally. If the characteristic

soft pulsatile signal from the uterine vessel was not heard immediately, the external iliac artery was located by making small sliding and tilting movements until a 'pistol shot' pulsatile sound with early reverse flow was found. After localization of the external iliac artery the transducer was pointed slightly more medially and cranially to locate the uterine artery. Identification of the uterine artery was made using the direction of flow and the quality of the sound. The vessel has continuous forward flow and a soft pulsatile quality and the direction of flow is up the side of the uterus.

The arcuate site was defined with relation to the fundus and most lateral point of the uterus. The transducer tip was placed on the lateral wall of the uterus in a transverse plane halfway between the fundus of the uterus and the symphysis pubis and pointed at 45° laterally and caudally. The FVWs were identified by their sound and direction of flow. Readings were taken from both sides of the uterus. See Figure 9 for insonation sites.



Figure 8 Readings being taken by the author, woman in semi-recumbent position

Diagram to show sampling points

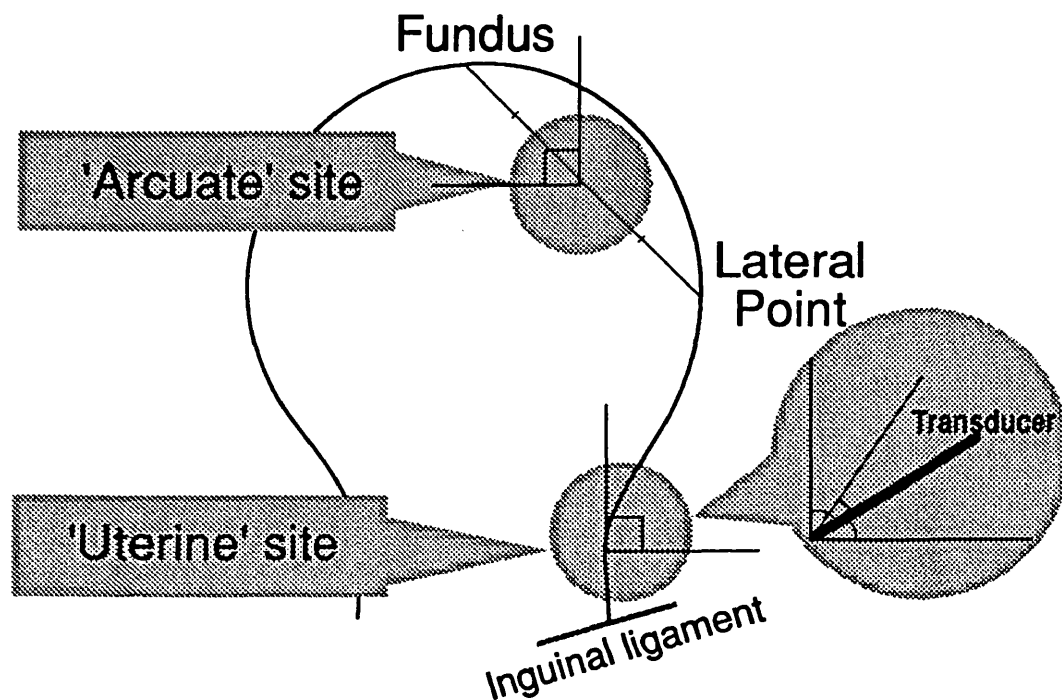


Figure 9 'Arcuate' and 'Uterine' insonation sites of this study

3.2.5 Measurements

Waveforms were obtained from the higher A and lower U sites on both sides of the uterus. FVWs were continuously displayed on the screen. A clear, sharp edge to the waveforms was obtained by small movements of the transducer and adjustments of scale and gain on the machine. The highest quality waveforms were identified both by ear and by eye. When FVWs of maximal clarity (a high signal-to-noise ratio) and maximum height (ie maximal Doppler shifted frequencies and most acute angulation to the vessel) were obtained, the tape recorder was started. At least five FVWs from each site were recorded on magnetic tape for storage. The tape was then stopped, the image frozen on the screen and the last waveform chosen for measurement.

Umbilical artery signals were collected and chosen in a similar way. They were only acceptable if taken during fetal apnoea, with a clear steady venous signal in the opposite channel. In cases with minimal or absent end-diastolic frequencies, repeat measurements were made from another part of the uterus. This was to ensure that the AEDF was not artefactual due to a high angle and disappearance of EDF behind the filter.

The peak systolic (A) and end-diastolic (B) frequencies were measured on the screen using a light pen. The resistance index ($RI = A-B/A$) was calculated later by computer for the five sites.

For further analysis the uteroplacental RI values were redesignated according to the side of the placenta (left-right). If the placenta was not centrally placed the values from the sites on the same side as the placenta were called placental and the values for the sites on the opposite side from the placenta were called nonplacental (PA, PU, NPA, NPU).

The averaged uteroplacental RI from the four sites was called AVRI. Other parameters were also calculated. AVA and AVU were the mean of the two arcuate and two uterine readings. WORST RI was the highest value, and BEST RI the lowest. A U:A ratio was calculated (for cases with all four readings) = AVU/AVA .

No results were revealed to the subjects or the clinicians. No action was taken on the basis of any readings. Mothers were simply informed that the uterine FVW represented "the blood supply to the uterus, it was the sound the baby might hear" and that the umbilical FVW was "the babies heartbeat which sounds strong at present". If any women enquired whether the test was normal, it was explained that the normal ranges were unknown and the research was aiming to find what was normal or abnormal.

3.2.6 Repeat testing

157 women who were having a repeat real-time scan for any reason attended for a second blood flow scan at the same time (16.1% of

the total valid population of 977). Reasons for a repeat scan included confirmation of changed dates and failure to see all the fetal anatomy. The latter occurred due to maternal obesity, early gestation, a persistent occipito-posterior fetal position or an upright position due to marked anteversion of the uterus. These subjects were otherwise unselected and there was no consistent time interval between the first and second scan.

3.2.7 Serial testing

A notice, placed in the ultrasound department waiting area for the duration of the screening study, requested volunteers for a serial study. 33 women attended four weekly for Doppler ultrasound examination. For the establishment of normal ranges from 16 - 40 weeks' gestation only those with a normal outcome were used (ie those who had a baby born after 37 weeks' gestation, weighing >2.5 kg, with Apgar score at one and five minutes >7, who had an uneventful antenatal course and a normal delivery, or assisted delivery for mechanical reasons).

3.2.8 Postpartum study

21 women who had had a normal delivery were approached on the postnatal wards. The test was performed in exactly the same way as for the booking scan. The results were divided into three time periods; <24 hrs, 24 - 48 hrs and >48 hrs post delivery.

3.2.9 Comparison with placental function tests

At KCH all women were offered an AFP test for the detection of neural tube defects and other anomalies. This was usually offered after the booking scan. This system prevented unnecessary anxiety caused by falsely high levels due to wrong dates or twin pregnancies, and allowed a smaller number of women to have a high resolution scan promptly. In addition, dating pregnancy by BPD measurement increases the sensitivity of AFP screening as spina bifida babies have a low BPD (Wald et al 1980b).

Women who were having the AFP blood test were asked to give a second blood sample for this study. However, if menstrual dates agreed with uterine size clinically or a first trimester scan had confirmed the dates, then the AFP might have already been taken at the booking clinic. AFP samples were not taken after 22 weeks' gestation as the laboratory did not analyse them. Samples could not be taken on Friday afternoons due to transport problems. The study was not set up and running until halfway through the screening study, after May 1986. All women who were having an AFP estimation were invited to give blood, with the above limitations and were otherwise unselected.

185 samples were taken of which two were lost. The first 40 samples were plasma and the rest serum. Blood samples were

collected into a ten ml glass tube with no anticoagulant using a Vacutainer from the antecubital vein. They were allowed to stand and clot and, within four hours, were centrifuged at 1,500 rpm for ten minutes. Five 1/2 aliquots of serum were placed into plastic tubes, labelled and stored without thawing at -20°C. Bloods were analysed for AFP, human placental lactogen (HPL) and beta-human chorionic gonadotrophin (BHCG) at the Department of Reproductive Physiology at St Bartholomews' Hospital. Pregnancy associated placental protein A (PAPP-A), Schwangerswaft protein (SP1) and pregnancy protein 12 (PP12) results were analysed at the Department of Obstetrics and Gynaecology at the London Hospital. The units used were AFP iu/ml, HPL µg/ml, BHCG iu/ml, PAPP-A miu/ml, SP1 miu/ml and PP12 µg/l. Levels were compared with AVRI values.

3.3 DATA COLLECTION

3.3.1 Outcome data collection

All women booked for delivery at KCH had, at their first visit, a standardised history taken by a midwife and recorded on an interactive computer. Immediately after delivery details were updated onto this system (EIT PDP 11) on labour ward (Appendices 14.2 and 14.3). Computerised booking and delivery details were collected at monthly intervals and the information coded onto forms 20 and 21 (Appendix 14.7). Information about neonatal outcome was obtained from the neonatal unit ledger or the baby notes.

If a woman had a Doppler test and then failed to book at KCH with the name given on data collection form one (either booked elsewhere or change of name), then all the initial booking data was missing. If she booked but subsequently moved, transferred her care or was sent to Dulwich Hospital for delivery (when the labour ward at KCH was full) then the delivery data was missing.

3.3.2 Search for missing data

If a woman did not have a computer antenatal booking form a search was made through the antenatal filing cards manually and

on the computer using the woman's name, hospital number and date of birth. The main hospital microfilm was consulted if there was no hospital number available and then both the KCH and Dulwich Hospital medical records departments were searched. If there were no pregnancy details in the notes the address of the woman and her general practitioner were noted. Where there were no notes, the ultrasound records were scrutinized for an address. Letters were sent to the woman and her general practitioner and if there was no reply by April 1988 (two months after the final EDD) a second postal inquiry was made enclosing a stamped self-addressed envelope (Appendices 14.5 and 14.6).

Some women had booked at KCH but had no delivery recorded. In these cases each hospital number was checked on microfilm, the KCH and Dulwich Hospital medical records departments were searched, and letters were sent to both the women and their GPs. If a woman had transferred her care to another hospital then a letter was sent to that hospital. If she had indicated at the time of the blood flow scan that she might move or have a home confinement her address was noted on the test form. She was given a form to keep in her cooperation card, fill in and return after delivery (see Appendix 14.6). At the end of the study all cases with missing data were put through the above procedure for a second time to try and maximise the yield.

Two groups of missing data were identified, those with no booking or outcome information (group one) and those with booking details but no outcome information (group two). Many records from Dulwich hospital, and details from GPs and mothers were incomplete.

3.3.3 Coding of booking and delivery details

Coding forms were completed with booking and delivery details for each subject by a coder (AS) (Appendix 14.7) using standard coding instructions (Appendices 14.8 and 14.9). The data were then entered into the University of London Computer (Computer centre, Amdahl 5890/300, SSPS statistical package). The data were entered twice and the computer files compared to pick up transcription errors. Validation checks were also performed to pick up obvious coding errors.

Because errors in gestation were crucial, a gestation check was also performed to see if the gestation on the delivery form was correct. A formula (in days) was applied:

$$(280 + \text{actual DOB}) - (\text{Delivery gestation} + \text{EDD at booking scan})$$

This = 0 if the gestation was correctly transferred into the computer by the delivering midwife. If the result was $> \pm 7$, then the notes were reviewed to establish the correct gestation.

3.3.4 Coding of abnormal outcome

Medical notes were retrieved and reviewed in detail if there was any deviation from normal indicated on the computer delivery form (ie all premature deliveries, all hypertension, all antepartum haemorrhage (APH), all antenatal admissions, all emergency CSs, all "abnormal CTG", all operative deliveries for fetal distress (ODFD), all neonatal unit admissions, all maternal disease and anything else suspicious). For practical reasons, the notes had to be collected and reviewed by the author. This process was kept separate from knowledge of the initial test results by leaving the test forms undisturbed in a locked filing cabinet for the duration of the study.

Abnormal outcome forms with distilled details from the notes (see Appendix 14.7) were completed and later coded separately by three coders (SB, KB, BW, all obstetricians) all unaware of the initial CW test results. 237 forms were completed (24.3% of total valid population). Discrepancies in coding were reviewed by all three in conjunction with the coding forms and instructions to decide on the final assignment of diagnoses.

3.3.5 Definitions used

The coding instruction forms can be found in Appendices 14.8, 14.9 and 14.10 and are self-explanatory. The diagnoses of

hypertension, PIH, PET, SGA, APH, fetal distress and induction of delivery were all subdivided into groups rather than aggregated. Thus, they could all be assessed separately, and joined later in any desired combination.

The obstetric risk score was calculated on the basis of Adelstein and Fedricks' score (1978), but features (such as the development of hypertension in the current pregnancy) were omitted as they were not present at booking.

Social class was assessed according to the Registrar General's classification (OPCS 1980). As many women in Camberwell are unsupported or unemployed some extra categories were devised (see Appendix 14.9). Women and men were assigned social class separately and the higher of the two was also calculated.

For assessment of SGA, comparison was made with KCH nomograms. A reference range had been created from consecutive deliveries from 1982-1985. All deliveries were included and the only selection criterion was that dates had been confirmed by ultrasound or the woman had ultrasound derived dates. LMP alone was not considered adequate for dating. The figures are shown in Section 13.2. As there were not many cases under 36 weeks, and as a large proportion of premature deliveries are complicated, premature birth weights were compared to a premature infant weight chart which is used in the KCH neonatal unit (Gairdner and Pearson

1971). This chart is made from smoothed composites of several sets of data and meets the KCH population weights at 36 weeks.

Using weights derived from ultrasound estimated weights was considered and rejected. Ultrasound measurement charts are derived from pregnancies that end normally, whereas it should be recognised that the definition of normal birth weight for a premature infant is complicated by the fact that it is not normal to be premature. However, the ultrasound estimated weights were much greater than the actual KCH population weights at 36 weeks and this would have had the effect of over-diagnosing rather than under-diagnosing SGA. For deliveries under 28 weeks however, estimated fetal weights extrapolated from ultrasound charts were used for an estimation of expected weight (Shepherd et al 1982).

The actual birth weight of each baby was expressed as a number of standard deviations from the mean expected weight for gestation. Three degrees of SGA were defined where the birth weight was below the 3rd, 5th and 10th percentile for gestation (SGA 3, SGA 5 and SGA 10 using the number of SDs from expected birth weight = 1.96, 1.65 and 1.28 respectively).

3.4 STATISTICAL METHODS

3.4.1 Statistical tests

The Kolmogorov-Smirnoff test (K-S) was used to test all variables for normality. Pearson's correlation coefficient was used for normally distributed populations. If populations of variables were not normally distributed, Spearman's non-parametric correlation coefficient was used. If two variables both changed with a third (eg gestation) a partial correlation coefficient controlling for the third variable was used.

Student's t-test was used to test for significant differences between two groups, unless otherwise stated, and a p-value of < 0.05 was considered to be significant. Chi-square testing or analysis of variance was employed to detect differences between more than two groups. The notation used for P values is; $p \leq 0.05$ *, ≤ 0.01 **, ≤ 0.005 ***, > 0.05 NS.

The coefficient of variation (COV) was calculated for the intra-observer error experiment = $SD/mean \times 100\%$.

3.4.2 The construction of reference ranges

The RI for each vessel was related to gestational age and subjected to regression analysis in order to calculate the mean

and 5th to 95th confidence intervals for individual RI values (Draper and Smith 1966). This is equivalent to the 5th and 95th centiles. Having constructed the normal ranges, each RI was expressed as a number of standard deviations from the expected mean for gestation (delta RI). The values were considered to be in the top 2.5%, 5% and 10% of the population if the values of delta RI were more than 1.96, 1.645 and 1.282 SDs from the mean respectively.

3.4.3 Screening characteristics

The numbers of true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) for each complication for a variety of cut-offs were calculated. The following test parameters were calculated:

$$\text{Sensitivity (SE)} = \text{TP} / (\text{TP} + \text{FN})$$

$$\text{Specificity (SP)} = \text{TN} / (\text{TN} + \text{FP})$$

$$\text{Positive predictive value (PO)} = \text{TP} / (\text{TP} + \text{FP})$$

$$\text{Negative predictive value (NE)} = \text{TN} / (\text{TN} + \text{FN})$$

$$\text{Prevalence of disease (PR)} = (\text{TP} + \text{FN}) / (\text{TP} + \text{FP} + \text{TN} + \text{FN})$$

$$\text{Relative risk (RR)} = \frac{\text{TP} (\text{FN} + \text{TN})}{\text{FN} (\text{TP} + \text{FP})}$$

RR is the increased risk of having disease that a test positive subject has compared to a test negative one.

3.5 ETHICAL CONSIDERATIONS

3.5.1 Ethical committee submission and approval

The study protocol was submitted to the Hospital ethical committee and formal approval was received on 18.2.87.

3.5.2 Consent of participants

Notices about the study were displayed in the waiting area. Women were recruited by the person performing the booking scan and gave verbal consent to participate in the study. For women who did not speak English, it was necessary to have an interpreter to make sure they understood the request. These women were usually sent for a real-time scan directly from the booking appointment as they were often accompanied for that initial visit by a friend or relative who could interpret. Girls under 16 were only included if they were accompanied by a parent, and both the girl and parent consented to her participation.

3.5.3 Letter to all participants

A letter was written by the author and included in the ethical committee submission (see Appendix 14.4). This letter was handed to every woman as she entered the blood flow room to read, usually while her BP was being measured, and to take home. Four

copies were also displayed on the walls of the ultrasound waiting room. Women were encouraged to ask questions and to write spontaneously if they were delivering elsewhere. A large notice in the waiting room requested volunteers for the serial study. There was no active recruiting.

3.5.4 Notification of general practitioners

Local general practitioners were notified formally and informally. A letter to all the local general practitioners was sent out on 10.2.87 (Appendix 14.5). It contained brief details of the research, explaining that the results were concealed from the participants. In addition, a presentation of the study was made by the author at a "Meet the Department" evening for local general practitioners held in the medical school. This was followed by discussion.

4. SUBJECTS

4.1 SUBJECT NUMBERS

4.1.1 Subjects entered and exclusions

1022 women were approached in the ultrasound department and 1018 agreed to participate in the study. These women were all assigned a study number. Four exclusions were made before performing a complete Doppler examination. One woman was excluded as there was no UA FVW and a previously undetected intrauterine death was confirmed. One woman was inadvertently entered twice and so the second entry was excluded. Two women were entered into the study but the uterus was impalpable and they were not pregnant.

Nine women were known not to have taken part in the study. There were four refusals and five women could not be entered (three diabetics already entered in a revealed Doppler study and two with newly diagnosed fetal anomaly).

An unknown number of women were not asked to take part when the author was not available or on holiday. Occasionally the ultrasonographer forgot to ask women to wait. As the collected sample appears random (as it is similar to the KCH population, Tables 9 and 10) these missed subjects are probably not significant.

4.1.2 Follow up and missing outcomes

Of the 1014 cases who had a Doppler study, all were followed up for outcome details. Exclusion for being outside the gestation limits at the time of the initial scan was not performed until after the outcome details were collected and the gestation check (see Section 3.3.3) had been performed. 37 proved to be under 16 weeks' gestation or over 25 completed weeks at the time of the Doppler test. These were excluded from all further analysis.

The hospital computer provided pregnancy and delivery details in 832 cases. In the remaining 145 cases information was collected after a series of searches including 2 postal requests to GPs and subjects. In 237 cases where pregnancy complications were recorded the medical notes were retrieved. There were 14 twin pregnancies which were excluded from the outcome analysis (reasons explained in Section 6.2.6.1). See Figure 10 for details of subject numbers.

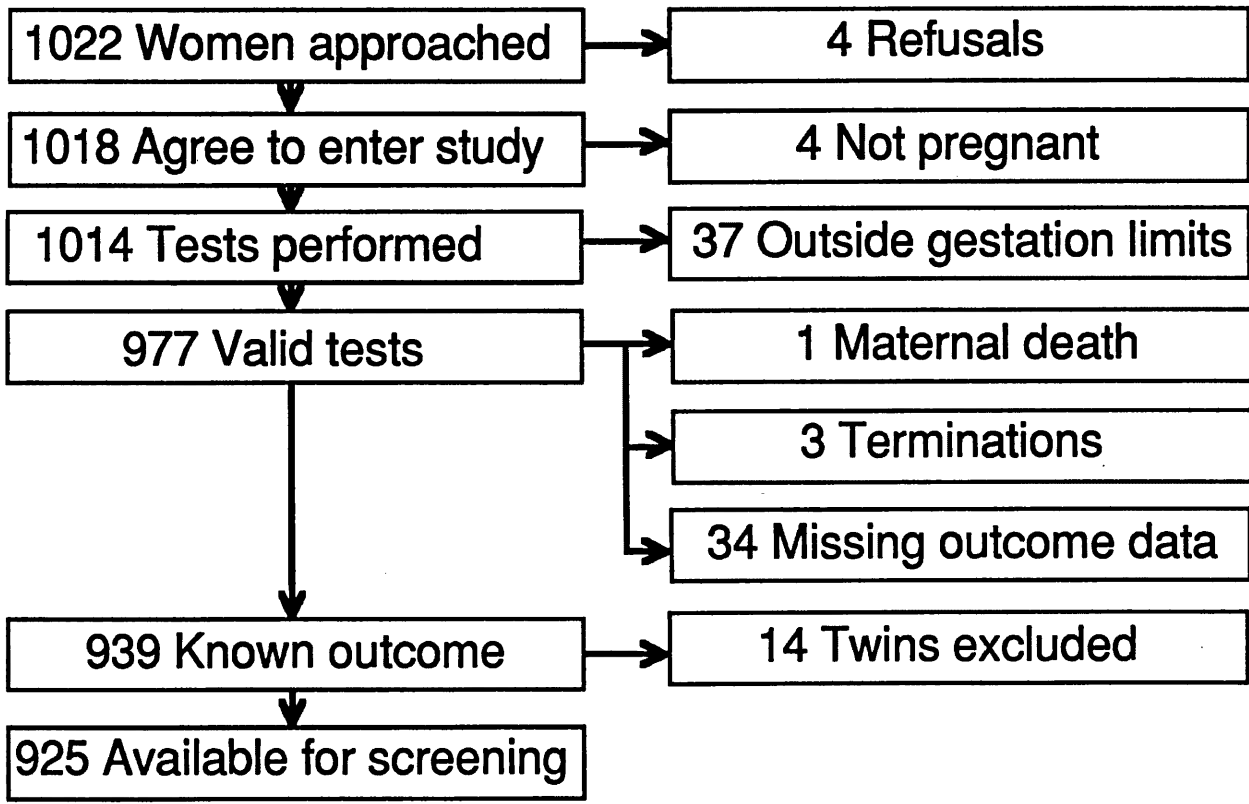


Figure 10 Flow diagram of subject numbers

4.2 DEMOGRAPHIC DETAILS OF STUDY POPULATION

The demographic details of the study population are shown in the Tables 5 - 8 and the findings are discussed in Section 7.1.2.2.

4.2.1 Age

There was a high proportion of teenage pregnancies in the study population (Table 5).

Table 5 The age distribution of the study population

| Age | No | % |
|-------------|-----|------|
| <15 | 1 | 0.1 |
| 15-19 | 117 | 12.0 |
| 20-24 | 267 | 27.2 |
| 25-29 | 323 | 33.1 |
| 30-34 | 171 | 17.4 |
| 35-39 | 72 | 7.3 |
| 40+ | 13 | 1.3 |
| Unspecified | 13 | 1.3 |

4.2.2 Race

The study population was ethnically mixed with a high proportion of Afro-Caribbean women (Table 6).

Table 6 The racial composition of the study population

| Race | No | % |
|------------------|-----|------|
| Caucasian | 589 | 60.3 |
| West Indian | 159 | 16.3 |
| African | 102 | 10.4 |
| Asian | 30 | 3.1 |
| Mixed | 18 | 1.8 |
| Chinese/Far East | 18 | 1.8 |
| Mediterranean | 28 | 2.9 |
| Arab/other | 13 | 1.3 |
| Unspecified | 20 | 2.0 |

4.2.3 Marital status

Nearly a half of the women in the study were unmarried (Table 7).

Table 7 The marital status of the study population

| Marital status | No | % |
|----------------|-----|------|
| Married | 531 | 54.4 |
| Single | 383 | 39.2 |
| Divorced | 20 | 2.0 |
| Separated | 19 | 1.9 |
| Widowed | 1 | 0.1 |
| Unspecified | 23 | 2.4 |

4.2.4 Social class

The total number of households in this study with no steady income (or welfare only) was 286, or 28.2% of the population (Table 8).

Table 8 The social class distribution of the study population

| Social Class | Subject | | Partner | | Highest | |
|--------------|---------|------|---------|------|---------|------|
| | No | % | No | % | No | % |
| I | 17 | 1.7 | 39 | 3.8 | 47 | 4.6 |
| II | 127 | 12.5 | 161 | 15.9 | 202 | 19.9 |
| IIIM | 39 | 3.8 | 234 | 23.1 | 216 | 21.3 |
| IIIN | 201 | 19.8 | 95 | 9.4 | 160 | 15.8 |
| IV | 39 | 3.8 | 107 | 10.6 | 86 | 8.5 |
| V | 24 | 2.4 | 9 | 0.9 | 17 | 1.7 |
| 6A | 301 | 29.7 | | | 120 | 11.8 |
| 6B,6C | 20 | 2.0 | 53 | 5.2 | 25 | 2.5 |
| 7 | 203 | 20.0 | 172 | 17.0 | 113 | 11.1 |
| Unknown | 43 | 4.4 | 144 | 14.2 | 28 | 2.8 |

(6A - Housewife, 6B 6C - Students, 7 - Unemployed)

4.3 OBSTETRIC OUTCOME OF THE STUDY POPULATION

4.3.1 Place of confinement

977 of the 1014 women entering the study were within the gestation limits and therefore had a valid Doppler scan test. Of the 977 confinements, 832 (85.2%) took place at KCH, 80 (8.2%) at Dulwich Hospital, seven (0.7%) at home and 23 (2.3%) in other hospitals. In 34 (3.5%) the outcome was unknown and one woman (0.1%) died at home.

4.3.2 Obstetric outcome

Of the 977 women, 920 (94.2%) were delivered of a live baby (or babies). Three women (0.3%) had a medical termination of pregnancy, five (0.5%) had a miscarriage <24 weeks, three (0.3%) had an intrauterine death 24-28 weeks and seven (0.7%) had a stillbirth >28 weeks. One woman (0.1%) had both a live birth and a neonatal death and three (0.3%) had neonatal deaths. One woman (0.1%) died without giving birth and 34 (3.5%) had missing data.

Of the 991 babies (including twins) studied there were 932 (94.0%) delivered alive, 17 (1.7%) lost before delivery (miscarriage, intrauterine death and stillbirth), three (0.3%) terminated, four (0.4%) had a neonatal death, one (0.1%) died in utero due to death of the mother and 34 (3.4%) had missing data.

Of the 939 cases where sex was known, 451 (48%) were girls and 488 (52%) were boys. Of the 939 cases where gestation at delivery was known, 18 (1.8%) were <28 weeks, 93 (9.9%) 28 - <37 weeks, 822 (87.5%) 37 - <43 weeks and six (0.6%) 43+ weeks.

4.3.3 Mode of delivery

The mode of delivery was known in 933 cases. There were 690 spontaneous vaginal deliveries (73.9%), 135 CSs (14.5%), 96 forceps or ventouse deliveries (10.3%) and 12 vaginal breech deliveries (1.3%). Of the CSs, 80 (8.6% of total) were emergency and 55 (5.9%) elective.

Of those with the available information, 77/925 (7.9%) had an operative delivery for fetal distress, and 104/896 (10.6%) passed meconium before delivery.

4.4 COMPARISON WITH KINGS COLLEGE HOSPITAL POPULATION

In order to demonstrate whether there was any selection bias, the demographic and obstetric details of the study population were compared to the following year of deliveries at KCH (Tables 9 and 10). Detailed breakdown of the annual figures was only available for 1988. Chi-square testing was used. It must be remembered that these are not comparisons of like with like, as the KCH figures are for all women delivering and thus include late bookers who could not have been included in a screening study, and women who transferred their bookings to KCH, a renowned perinatal referral centre, maybe after diagnosis of a high-risk problem.

4.4.1 Demographic details

The study mothers had demographic details similar to the Camberwell population in general, although there were significantly more Caucasians and less Africans (Table 9).

Table 9 Comparison of study population and KCH population-demographic details.

| | Study % | KCH 1988 % | Chi-Sq | p |
|----------------------|------------|----------------------|--------|----------|
| Caucasian | 60.3 | 54.4 | 9.86 | <0.01 ** |
| West Indian | 16.3 | 18.2 | 1.73 | NS |
| African | 10.4 | 13.2 | 4.78 | <0.05 * |
| Asian | 5.0 | 3.6 | 3.4 | NS |
| Married | 54.4 | 53.2 | 0.35 | NS |
| Single | 43.2 | 46.8 | 3.66 | NS |
| Mean age at delivery | 26 | 27 (no SD available) | | |
| Number of mothers | 977 | 2773 | | |

4.4.2 Obstetric details

The study mothers had a similar pregnancy outcome to the Camberwell population in general, although significantly fewer inductions and forceps deliveries.

Table 10 Comparison of study population and KCH population-obstetric details.

| | Study | KCH 1988 | Chi-Sq | p |
|-----------------------|-------|----------|--------|----------|
| | % | % | | |
| Multiple pregnancies | 1.4 | 2.4 | 2.86 | NS |
| Induction | 5.1 | 8.3 | 10.1 | <0.01 ** |
| CS rate | 14.5 | 15.4 | 0.35 | NS |
| Forceps rate | 10.4 | 13.1 | 4.43 | <0.05 * |
| Stillbirth rate (>28) | 0.7 | 0.6 | 0.01 | NS |
| Number of mothers | 977 | 2773 | | |

4.5 MISSING DATA

A meticulous search for missing outcomes was made to ensure the data set was as near complete as possible.

4.5.1 Numbers

Of the 977 valid subjects, 34 had no outcome details at all, either because there was no reply from the postal query or the subject had moved with no knowledge of the forwarding address or hospital of delivery. In 13 cases (group one) there was no booking data or outcome data, and the other 21 cases (group two) had no outcome details only.

There was an excellent response to the postal questionnaire. To 93/115 enquiries (81%), either the subject, the GP or both replied. An unexpectedly high number of women did not book or deliver at KCH. Some of these cases have incomplete outcome data. In the following Tables and the Results Section, calculations are made using the total available data for any parameter unless otherwise specified. The numbers sometimes vary between Tables or outcomes in the Screening Section if the information was only partial.

4.5.2 Missing booking and outcome data

In order to demonstrate that the available data truly represented the whole population a comparison of social measures of subjects with and without booking and outcome data was made (Tables 11 and 12). AVRI was higher for all the missing data groups but the difference was not significant. Apart from a slightly lower average age of leaving school in the no booking data group, there were no significant differences between the groups with and without booking and outcome data. This suggests that the lost data do not significantly skew the results.

Table 11 A comparison of subjects with and without booking data

| Factor | No booking data n = 13 | Booking data n = 964 | p |
|-----------------|---------------------------|-------------------------|---------|
| Age left school | 16.1 (1.5) | 17.6 (2.7) | 0.05 * |
| AVRI | 0.56 (.09) | 0.51 (.09) | 0.06 NS |
| % smoking | 54% | 31% | 0.19 NS |
| % threatened | 18% | 18% | 1.0 NS |

Table 12 A comparison of subjects with and without outcome data

| Factor | Booking data but no outcome data n = 21 | Outcome data n = 943 | p |
|--------------|---|-------------------------|---------|
| Age (yrs) | 24.5 (5.0) | 26.2 (5.5) | 0.17 NS |
| Parity | 0.90 (1.7) | 0.89 (1.2) | 0.99 NS |
| ORS | 0.57 (0.9) | 0.51 (0.8) | 0.72 NS |
| | No outcome data n = 34 | Outcome data n = 943 | p |
| AVRI | 0.52 (.08) | 0.51 (.09) | 0.47 NS |
| % smoking | 47% | 31% | 0.07 NS |
| % threatened | 15% | 19% | 0.73 NS |

5. VALIDATION OF THE METHODOLOGY

5.1 VARIATION AROUND THE UTERUS

5.1.1 Methodology

Waveforms can be obtained from the uterine artery and its branches all over the uterine surface. There can be a large variation in the FVWs obtained from different parts of the same uterus. In order to determine the best sites for insonation of representative vessels, a study of the variation around the uterus was performed. Afterwards four standard points were defined and used for the screening study (see Section 3.2.4).

12 women who were attending the Ultrasound department for a routine booking scan at 18 - 22 weeks' gestation were studied. The same procedure of placental localization, ten minutes rest and location and measurement of the FVWs was undertaken as described in Section 3.2.4.

For this study, however, as well as the arcuate and uterine sites, two other sites on the sides of the uterus were insonated. The sites were defined with relation to the fundus and most lateral point of the uterus.

Position one was the arcuate site described in Section 3.2.4

(halfway between the fundus and most lateral point). Position two was on the lateral wall of the uterus at a level halfway between the fundus of the uterus and the symphysis pubis. Position three was halfway between position two and the symphysis pubis. Position four was the uterine site described in Section 3.2.4. Readings were taken from both sides of the uterus.

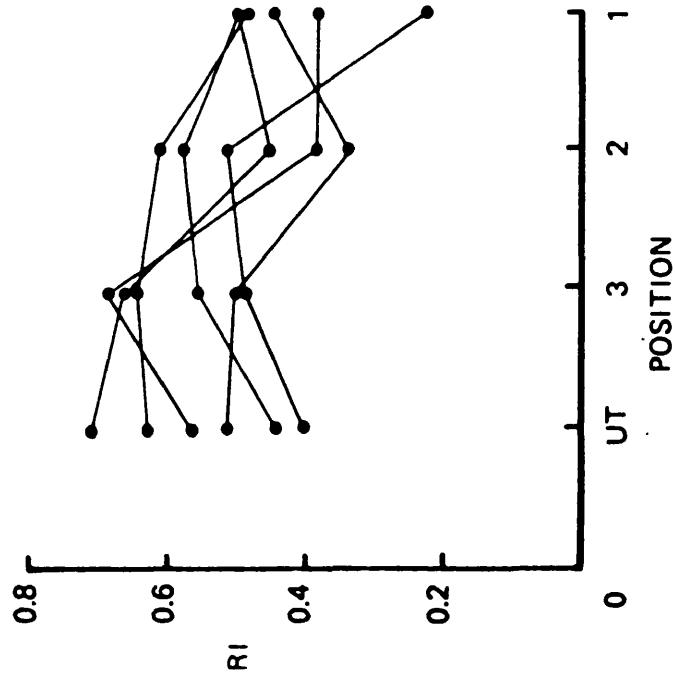
5.1.2 Results

The results are shown graphically, according to placental side (Figure 11). The results for all 12 subjects are presented according to left-right site in Table 13. No statistics are presented for this early observational study which was used to aid the methodological design.

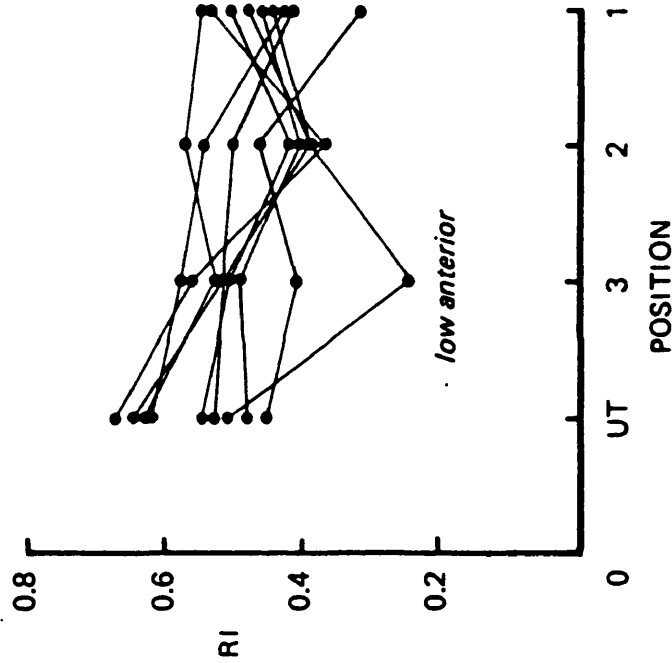
Table 13 Mean RI of 12 subjects at different positions along the sides of the uterus.

| Left | | Right | |
|------|-------------|-------|-------------|
| Posn | mean (SD) | Posn | mean (SD) |
| 1(A) | 0.45 (0.14) | 1(A) | 0.49 (0.11) |
| 2 | 0.47 (0.10) | 2 | 0.48 (0.10) |
| 3 | 0.54 (0.08) | 3 | 0.54 (0.13) |
| 4(U) | 0.58 (0.09) | 4(U) | 0.56 (0.09) |

RI vs POSITION ON UTERINE WALL
CENTRAL PLACENTA



RI vs POSITION ON UTERINE WALL
PLACENTAL



RI vs POSITION ON UTERINE WALL
NON-PLACENTAL

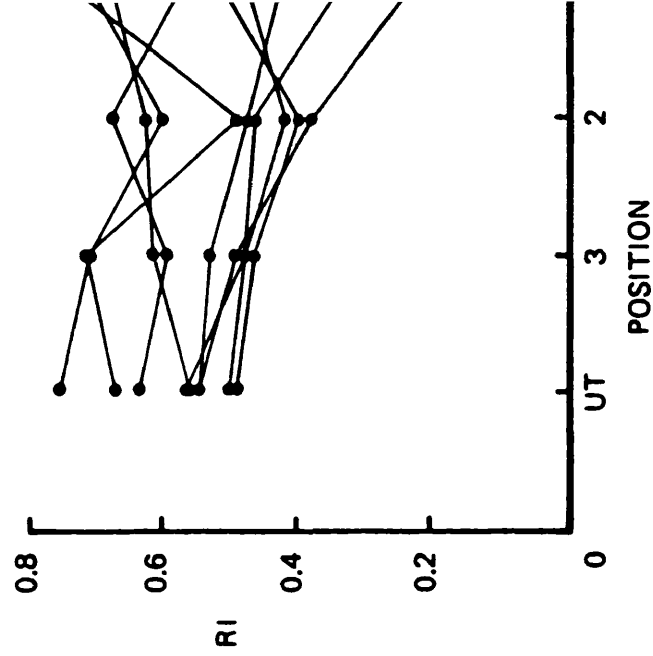


Figure 11 The effect of position of insonation along uterine side-wall depending on side of placenta

This initial study demonstrated that:

- i) RI fell with increasing distance from the origin of the uterine artery (Table 13).
- ii) The RI for the placental side was lower than the nonplacental side (Figure 11).
- iii) In some cases (3/12) the placenta had no obvious laterality.

5.1.3 Development of fixed points

These findings led to the development of the particular study design described in Section 3.2.4. Sampling points that were fixed with respect to the uterine wall were used and the placental location was noted at the ultrasound scan. Points one and four were chosen as they were usually nearest and furthest from the placenta and were referred to as the 'arcuate' and 'uterine' sites (A,U).

5.2 ERRORS

The following experiments were performed in order to assess the intra-observer error for individual sites and AVRI, to assess the reproducibility under 'less than ideal' conditions and to gauge the inter-observer error.

5.2.1 Introduction

The intra-observer error was assessed in two ways, immediately, and after one hour. As with the main study, one FVW was taken at each site as one observation. The inter-observer error was assessed by comparing the author with two other observers.

5.2.2 Intra-observer: Immediate test-retest

11 subjects, all between 16 and 24 weeks gestation, had three sets of measurements taken in no particular order, with no change in conditions. The raw data is displayed in Table 14. Missing data is left blank. Scatter plots were made of tests 1 vs 2, 2 vs 3 and 1 vs 3 for each site. These three graphs were then superimposed and the summary scatter plots are shown for each site in Figures 12 and 13.

Table 14 Raw data for immediate intra-observer test. RI from LA, RA, LU, RU and UA. Three readings in 11 subjects.

| Case | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gest | 19 | 24 | 19 | 19 | 20 | 18 | 18 | 20 | 23 | 17 | 24 |
| LA1 | .54 | .39 | .45 | .45 | .37 | .55 | .69 | .69 | .51 | .52 | .38 |
| LA2 | .41 | .45 | .42 | .38 | .39 | .57 | .56 | .80 | .44 | .61 | .38 |
| LA3 | .44 | .48 | .44 | .37 | .40 | .58 | .68 | .83 | .49 | .43 | .41 |
| RA1 | .57 | .38 | .41 | .69 | .33 | .47 | .54 | .43 | .58 | .55 | .46 |
| RA2 | .51 | .32 | .37 | .61 | .36 | .59 | .53 | .47 | .53 | .59 | .36 |
| RA3 | .63 | .31 | .42 | .69 | .37 | .58 | .55 | .42 | | .60 | .46 |
| LU1 | .51 | .45 | .55 | .62 | .53 | .57 | .64 | .71 | .53 | .59 | .42 |
| LU2 | .44 | .44 | .50 | .64 | .36 | .46 | .66 | .65 | .55 | .59 | .38 |
| LU3 | .56 | .43 | .50 | .62 | .56 | .47 | .67 | .59 | .50 | .57 | .40 |
| RU1 | .66 | .49 | .45 | .73 | .47 | .73 | .58 | .49 | .49 | .50 | .44 |
| RU2 | .63 | .44 | .59 | .67 | .44 | .71 | .58 | .51 | .42 | .44 | .41 |
| RU3 | .71 | .42 | .55 | .69 | .46 | .71 | .54 | .57 | .45 | .53 | .35 |
| UA1 | .84 | .73 | .73 | .80 | .83 | .85 | .82 | .75 | .79 | .89 | .70 |
| UA2 | .84 | .72 | .70 | .83 | | .78 | .84 | .83 | .69 | .94 | .73 |
| UA3 | .80 | .68 | .75 | .82 | .84 | .80 | .84 | .82 | .69 | .89 | .75 |

The means and SDs of all the groups of measurements were calculated. The COVs are shown in Table 15.

Table 15 Coefficients of variation (COV) by vessel. 11 subjects, three sets of measurements, five minutes apart.

| Vessel | UA | LA | LU | RA | RU | AVA | AVU | AVRI |
|--------|-----|-----|-----|-----|-----|-----|-----|------|
| COV % | 3.3 | 8.8 | 7.1 | 7.6 | 7.1 | 6.5 | 5.1 | 3.9 |

5.2.3 Intra-observer: One hour test-retest

Two sets of measurements were performed by the author in similar conditions before and after the ultrasound scan about one hour apart in 23 subjects. The scatter plots of the results for each site are shown in Figures 12 and 13. The raw data is presented in Table 16.

Table 16 Raw data for delayed intra-observer test. RI at each of the sites, LA, RA, LU, RU and UA, measured twice in 23 subjects.

| Case | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gest | 22 | 18 | 17 | 20 | 24 | 22 | 19 | 21 | 21 | 21 | 20 | 20 |
| LA1 | .54 | .35 | .35 | .46 | .46 | .25 | .44 | .52 | .49 | .52 | .35 | .39 |
| LA2 | .40 | .37 | .54 | .32 | .40 | .51 | .56 | .34 | .32 | .46 | .54 | .32 |
| RA1 | .42 | .46 | .42 | .33 | .25 | .57 | .35 | .62 | .46 | .26 | .47 | .38 |
| RA2 | .34 | .25 | .57 | .34 | .50 | .77 | .29 | .38 | .47 | .21 | .39 | .40 |
| LU1 | .66 | .56 | .29 | .32 | .58 | .54 | .40 | .60 | .64 | .48 | .29 | .45 |
| LU2 | .66 | .42 | .23 | .50 | .56 | .70 | .52 | .58 | .70 | .55 | .54 | .44 |
| RU1 | .48 | .61 | .53 | .39 | .40 | .67 | .28 | .63 | .75 | .51 | .31 | .49 |
| RU2 | .50 | .43 | .64 | .60 | .57 | .78 | .56 | .62 | .66 | .50 | .21 | .50 |
| UA1 | .80 | .85 | .93 | .69 | .80 | .78 | .77 | .64 | .81 | .82 | .83 | .73 |
| UA2 | .79 | .83 | .86 | .67 | .79 | .83 | .79 | .65 | .78 | .74 | .84 | .78 |

Table 16 (continued) Raw data for delayed intra-observer test. RI at each of the sites, LA, RA, LU, RU and UA, measured twice in 23 subjects.

| Case | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 |
|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gest | 18 | 19 | 17 | 22 | 20 | 21 | 19 | 19 | 18 | 18 | 23 |
| LA1 | .62 | .51 | .68 | .37 | .45 | .46 | .49 | .44 | .44 | .88 | .57 |
| LA2 | .56 | .55 | .58 | .38 | .41 | .45 | .59 | .41 | .40 | .82 | .53 |
| RA1 | .42 | .44 | .54 | .37 | .65 | .48 | .48 | .49 | .40 | .59 | .42 |
| RA2 | .45 | .47 | .51 | .23 | .52 | .49 | .58 | .46 | .45 | .58 | .33 |
| LU1 | .60 | .49 | .71 | .57 | .53 | .68 | .68 | .51 | .35 | .60 | .47 |
| LU2 | .71 | .55 | .69 | .50 | .33 | .63 | .71 | .35 | .50 | .74 | .53 |
| RU1 | .66 | .50 | .54 | .42 | .37 | .64 | .62 | .44 | .43 | .64 | .65 |
| RU2 | .72 | .40 | .55 | .44 | .41 | .71 | .70 | .52 | .58 | .69 | .35 |
| UA1 | .83 | .84 | .83 | .73 | .80 | .73 | .93 | .75 | .63 | .83 | .80 |
| UA2 | .85 | .76 | .84 | .67 | .76 | .77 | .85 | .76 | .84 | .81 | .75 |

Table 17 Coefficients of variation (COV) by vessel. 23 subjects, two sets of measurements one hour apart.

| Vessel | UA | LA | LU | RA | RU | AVA | AVU | AVRI |
|--------|-----|------|------|------|------|------|------|------|
| COV % | 3.8 | 16.1 | 13.9 | 14.5 | 14.9 | 12.2 | 10.9 | 10.2 |

These COVs are higher than those in the previous Table. This is not just a result of natural inflation as the number of observations decreased from three to two (although this may partially explain the higher figures). This is demonstrated visually in the scatter plots which show wider discrepancy between values taken one hour apart than minutes apart.

Figure 12 Intra-observer error of uterine RI, immediate and delayed

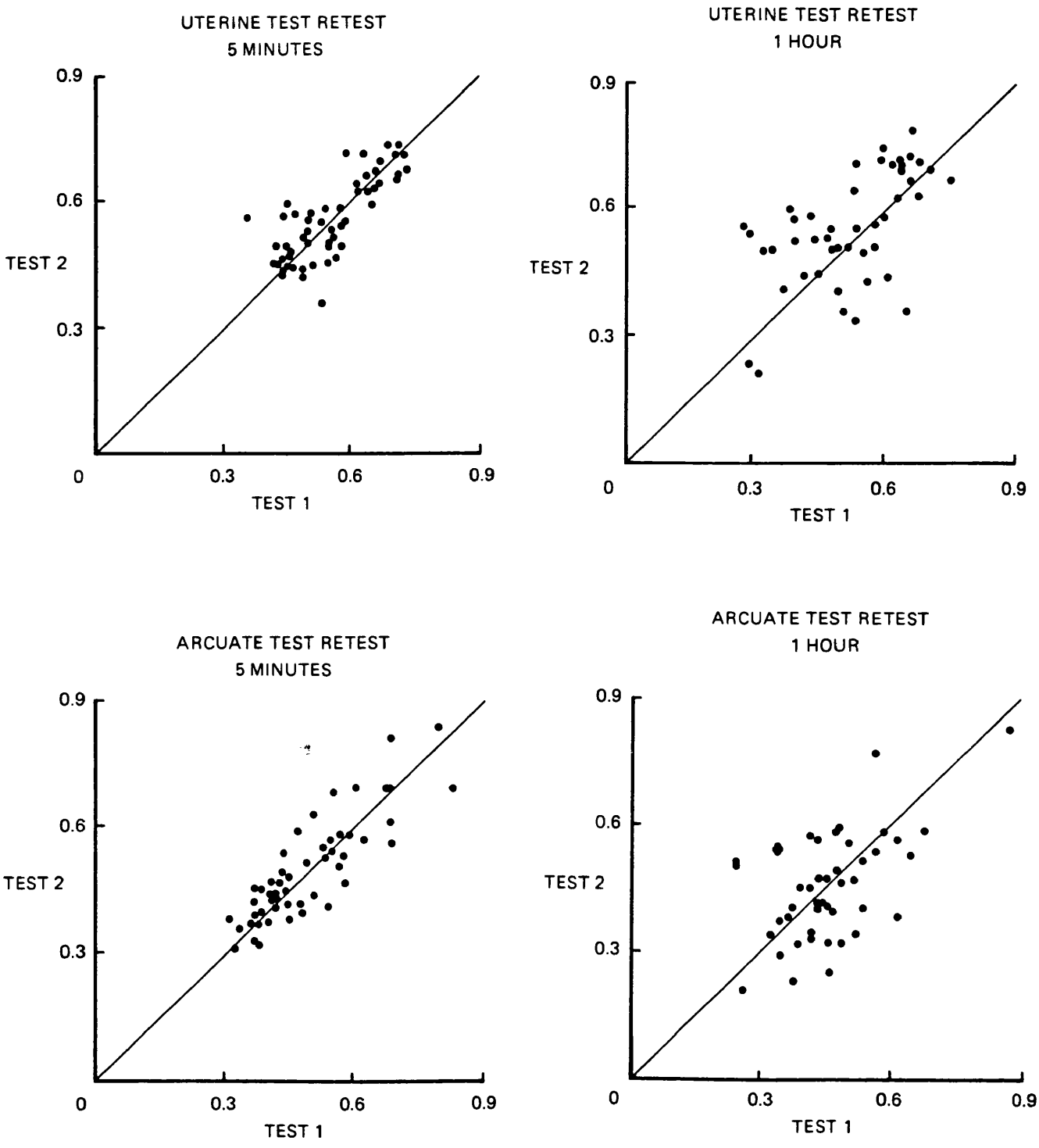
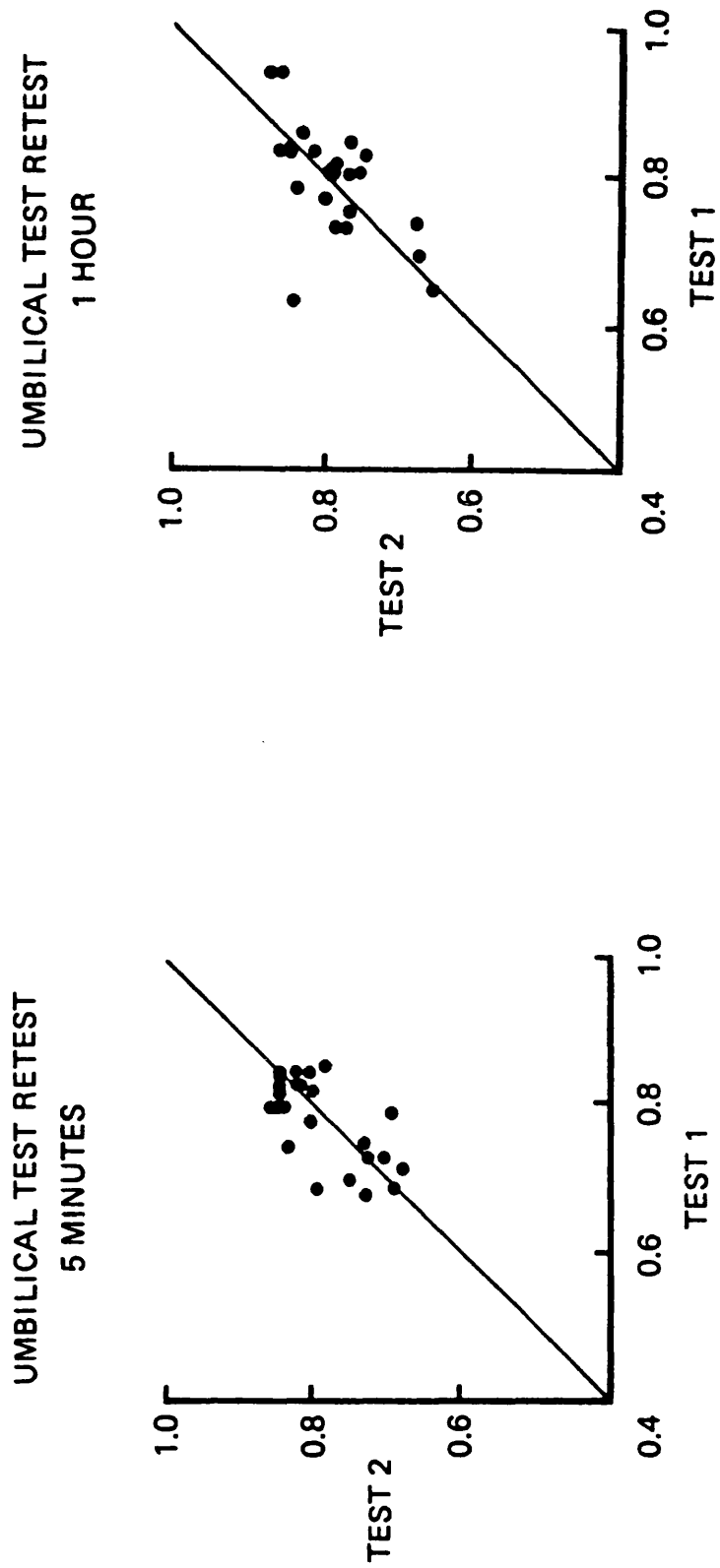


Figure 13 Intra-observer error of umbilical RI, immediate and delayed



5.2.4 Inter-observer error

The inter-observer error was assessed by comparing RI readings from the four sites and the UA in 19 subjects, taken by the author and one of two other observers (a radiographer and a scientist who had been trained in the technique).

Table 18 Raw data for inter-observer test. RI at each of the sites, LA, RA, LU, RU and UA, measured twice. SB vs observer one (9 cases) and SB vs observer two (ten cases). SB's results first.

| Case | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Observer | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 1 | 2 |
| Gestation | 23 | 20 | 20 | 17 | 19 | 20 | 21 | 18 | 20 | 20 |
| LA1 | .64 | .76 | .35 | .67 | .41 | .67 | .54 | .50 | .26 | .36 |
| LA2 | .71 | .87 | .55 | .67 | .50 | .63 | .50 | .43 | .33 | .26 |
| RA1 | .58 | .57 | .69 | .66 | .49 | .66 | .26 | .47 | .34 | .48 |
| RA2 | .76 | .71 | .38 | .66 | .31 | .41 | .40 | .43 | .46 | .55 |
| LU1 | .64 | .75 | .42 | .72 | .69 | .72 | .59 | .55 | .53 | .53 |
| LU2 | .77 | .79 | .40 | .73 | .55 | .51 | .45 | .45 | .49 | .44 |
| RU1 | .67 | .65 | .62 | .46 | .65 | .46 | .54 | .56 | .37 | .45 |
| RU2 | .76 | .69 | .67 | .46 | .49 | .43 | .51 | .28 | .59 | .48 |
| UA1 | .83 | .75 | .81 | .86 | .89 | .86 | .76 | .89 | .79 | .85 |
| UA2 | .74 | .76 | .78 | .87 | .81 | .85 | .79 | .86 | .68 | .79 |

Table 18 (continued) Raw data for inter-observer test. RI at each of the sites, LA, RA, LU, RU and UA, measured twice. SB vs observer one (9 cases) and SB vs observer two (ten cases). SB's results first.

| Case | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Observer | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 1 |
| Gestation | 23 | 22 | 19 | 18 | 17 | 16 | 21 | 20 | 18 |
| LA1 | .42 | .71 | .39 | .71 | .69 | .45 | .62 | .48 | .45 |
| LA2 | .26 | .41 | .36 | .64 | .60 | .53 | .44 | .47 | .41 |
| RA1 | .52 | .59 | .49 | .49 | .35 | .44 | .53 | .30 | .40 |
| RA2 | .33 | | .27 | .61 | .54 | .37 | .35 | .51 | .33 |
| LU1 | .53 | .75 | .40 | .52 | .59 | .40 | .45 | .55 | .35 |
| LU2 | .68 | .69 | .45 | .53 | .61 | .40 | .41 | .46 | .50 |
| RU1 | .42 | .61 | .46 | .61 | .64 | .42 | .57 | .33 | .43 |
| RU2 | .31 | .63 | .48 | .41 | .56 | .69 | .34 | .49 | .61 |
| UA1 | .82 | .86 | .83 | .85 | .87 | .88 | .88 | .74 | .63 |
| UA2 | .67 | .77 | .78 | .83 | .77 | .85 | .77 | .69 | |

The inter-observer error was calculated as a mean percentage error between the author and each of the two observers and the results are presented in Table 19. The inter-observer mean percentage difference in any individual uteroplacental reading was 19.6% and 24.6%. The inter-observer mean percentage difference in AVRI was 11.9% and 14.1%

Table 19 Mean percentage difference in RI measured by two observers

| Vessel | UA | LA | LU | RA | RU | AVA | AVU | AVRI |
|--|-----|------|------|------|------|------|------|------|
| % error SB vs observer one (N = 9) | 6.7 | 10.7 | 13.4 | 31.4 | 17.0 | 16.1 | 13.5 | 11.9 |
| % error SB vs observer two (N = 10) | 8.3 | 23.2 | 13.2 | 31.9 | 30.1 | 16.5 | 16.1 | 14.1 |

5.3 VALIDATION OF PATTERN RECOGNITION

Identification of the uteroplacental FVW with CW relies on pattern recognition of the appropriate vessel. Two experiments were established to verify that the correct vessels were being insonated.

5.3.1 In vivo

A study of FVWs obtained by placing a probe directly on the uterine artery during CS showed that they were identical to those obtained with CW Doppler ultrasound (Schulman et al 1986) and this has been used as justification for pattern recognition. To determine if this was also true for the second trimester, two women who were having second trimester laparotomies were investigated.

5.3.1.1 Methodology

The first subject, CD, was a 28 year old having an abdominal cervical suture inserted at 16 weeks' gestation for cervical incompetence. The second, GB, was a 32 year old having a total abdominal hysterectomy and oophorectomy at 21 weeks' gestation for a malignant ovarian tumour with ascites. Both gave written consent to the procedure.

In the first case LA, LU, RA, RU readings were taken pre-operatively. They were repeated after induction of anaesthesia but before opening of the abdomen, and then, after opening of the peritoneum. In the second case readings were taken after induction of anaesthesia, before and after opening of the abdomen. Whilst access to the higher arcuate point was not possible, readings from the internal iliac (II) arteries were obtained in both women. Identification was made by palpation. The transducer was held at 45° pointing medially, caudally and posteriorly to replicate the angle used for the U points. As the author and transducer head were gowned and sterile, fine tuning of the spectrum analyser had to be undertaken by the anaesthetist and measurements were made later from tape recordings.

5.3.1.2 Results

In case one the uterine vessels all had forward flow in diastole and the internal iliacs had none. When the uterine artery was intermittently compressed for ten cardiac cycles, end-diastolic flow ceased and the waveform became indistinguishable from that of the internal iliac. The CW uterine FVW had a similar shape and sound to the directly obtained FVW.

In case two the uterine arteries were insonated and had continuous forward flow throughout the cardiac cycle. The CW uterine FVW had a similar shape and sound to FVW obtained

directly. Each internal iliac was identified and showed no flow in end-diastole. It was difficult to obtain a good quality signal for tapping.

In both cases the internal iliac artery flowed in the opposite direction to the uterine. It was impossible to locate and confidently identify either internal iliac artery using CW in the unanaesthetised women. Table 20 shows the RI of the vessels.

Table 20 RI of vessels using CW. Preoperative and intra-abdominal readings.

| Patient 1 | LA | LU | RA | RU | LII | RII | Pulse |
|------------------|-----|-----|-----|-----|-----|-----|-------|
| Pre anaesthetic | .67 | .67 | .47 | .83 | | | 73 |
| Post anaesthetic | .51 | .54 | | .67 | | | 113 |
| In abdomen | | | | .72 | 1.0 | 1.0 | 89 |
| Patient 2 | | | | | | | |
| Post anaesthetic | | .72 | | .43 | | | 111 |
| In abdomen | | | | | 1.0 | | 101 |

Although this was a limited qualitative study, these experiments confirmed: a) that the uterine artery could be identified by pattern recognition; b) that the internal iliac artery is of high

pulsatility (RI=1); c) that the two vessels flow in opposite directions.

5.3.2 Colour flow mapping

Colour flow mapping allows blood vessels to be visualised non-invasively. The vessels can be traced from the external iliac to the internal iliac to the uterine artery. Again, it was extremely difficult to visualise the internal iliac artery as it lies posterior to the pregnant uterus and was often overlaid with bowel that obscured it ultrasonically. The course of the uterine artery can be traced up the side of the uterus branching at variable intervals.

5.3.2.1 Methodology

An examination of the uterine arteries using CW and colour flow mapping (Accuson 128, linear array transducer imaging frequency 3.5 MHz, Doppler 2.5 MHz) was made after completion of the main study. Initial observations were made by Dr S Vyas that showed that there was a constant finding of a point medial to the external iliac artery where the uterine artery can be visualised, and where the two arteries appeared to cross-over (see Figure 14). The colour flow transducer was usually held at about 45° when the uterine artery was found. This cross-over point and the U point of the main study were compared.

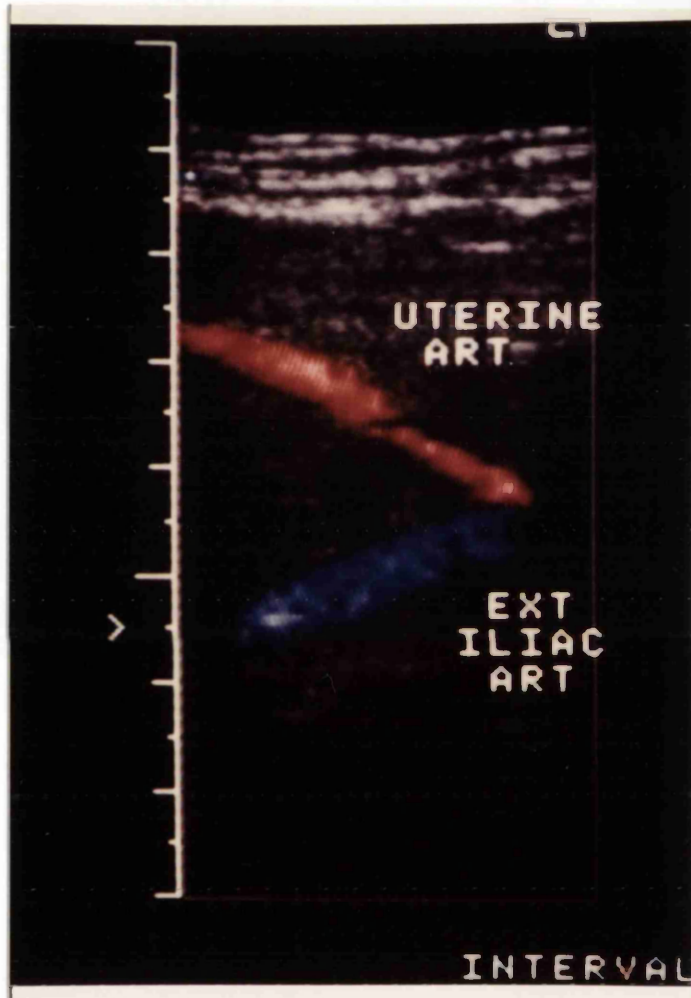


Figure 14 'Crossover' point of uterine and external iliac arteries shown with colour flow mapping

Five women, with normal pregnancies between 20 and 32 weeks' gestation, were studied in March 1988 by two independent observers. Ten measurements of RI from each side of the uterus were made using colour flow (SV). This was repeated using CW (SB). All FVWs were analysed using the Doptek spectrum analyser.

5.3.2.2 Results

Table 21 CW and Colour flow measurement of the uterine artery

| No | Gest | Pl | | RI mean(SD) | | |
|----|------|----|---|-------------|-----------|----|
| | | | | Colour | CW | |
| 1 | 20 | = | R | 0.54(.07) | 0.50(.07) | NS |
| | | | L | 0.47(.07) | 0.46(.06) | NS |
| 2 | 32 | L | R | 0.50(.06) | 0.47(.03) | NS |
| | | | L | 0.47(.04) | 0.49(.06) | NS |
| 3 | 28 | R | R | 0.50(.04) | 0.53(.08) | NS |
| | | | L | 0.60(.04) | 0.57(.06) | NS |
| 4 | 32 | = | R | 0.41(.04) | 0.39(.03) | NS |
| | | | L | 0.42(.04) | 0.39(.04) | NS |
| 5 | 32 | = | R | 0.52(.04) | 0.61(.07) | ** |
| | | | L | 0.45(.04) | 0.45(.04) | NS |

Apart from one reading, there was no significant difference in the mean RI values obtained by each of the two methods (t-test).

5.4 COMPUTER VALIDATION

As the coded outcomes depended heavily on the computerised notes, a study was undertaken to validate the quality of the information before the start of the main screening study. The antenatal booking details were taken in an interactive way and reviewed with the mother from a video display unit before becoming the medical records. The accuracy was probably higher than the outcome data but could not be assessed in a similar computer validation study.

5.4.1 Methodology

Details of 50 consecutive deliveries in the first week of October 1986 were collected on a standard data form by two separate observers, the author (who examined the medical records) and the computer midwife (Fiona Richards, who examined the computer generated notes).

5.4.2 Results

There were 157 confirmed discrepancies between 1464 possible items of information (10.7%). These were further arbitrarily divided into serious - 5% (eg Apgar Score, gestation, level of anaemia > 1gm haemoglobin difference) and trivial - 5.7% (eg missing details of the ward the infant was discharged to,

spelling mistake of delivery attendant, missing rubella status). The fault could not be ascribed to one or other set of notes with certainty in many cases. Missing data occurred in both sets of notes.

The serious discrepancies were all reviewed to assess their harm. No discrepancies of sex of infant, birthweight, parity, placental completeness or onset of labour were found. There was one discrepancy in each of the following; date of delivery (one day different), rupture of membranes, time of delivery, blood group, electrophoresis, estimated blood loss, method of delivery of the placenta, perineal injury and type of delivery (CS rather than CS plus Wrigley's forceps).

There was one major error in gestation (46 weeks not 40+2) and four minor (eg 39+3 not 39+4). Sometimes the medical notes had less information than the computer, especially the neonatal examination, head circumference and cord pH, although some information, such as amniocentesis, was missing from the computer records. Admissions to hospital were recorded on computer but medical information was imprecise (eg in the computer questionnaire no distinction was made for different severity of hypertension).

Following the validation of computer records study a list of recommendations was drawn up and circulated including: redesign

and internal validation of certain questions; only the midwife who performed the delivery should complete the record keeping before the mother left labour ward; the status of computer records should be raised; the records were to be signed by the attending midwife and filing in the antenatal clinic should be improved. These changes took place gradually over the time period of the study and the anticipated improvement in accuracy was not assessed.

The overall agreement between the medical notes and computer records was acceptable for simple data (5% serious errors). However, for precise diagnosis of medical conditions occurring during pregnancy it was necessary to use the medical records. To improve precision a gestation check was included in the coding validation.

A check was performed (by SB) on one in 20 delivery forms to confirm the accuracy of the coder. Only three minor errors were found in 825 items (0.36%).

5.5 SUMMARY OF METHODOLOGY

Over 1,000 consecutive women attending for a booking scan had a screening Doppler ultrasound scan. 977 were within the gestation limits of 16-24 weeks. They were otherwise unselected, and, after the outcome data was collected, found to be representative

of the local population. A thorough search for missing data was made and outcome data was available for 96.5% of the population. Four fixed points with respect to the uterus were chosen for study as RI is affected by placental site and position on the side of the uterus. Under ideal conditions the intra-observer COV for AVRI was 3.9% but in practice, errors are higher. In-vivo and colour flow mapping confirm that pattern recognition identifies uteroplacental vessels.

6. RESULTS

In this Section, the test characteristics are given, followed by the correlations of RI with place, placental position and gestation, including reference ranges. The associations of AVRI and UARI with pregnancy complications are described. The screening properties of the test are then calculated.

6.1. TEST CHARACTERISTICS

6.1.1 Time taken

The average time taken to perform the examination in a sample of 420 was 6.6 minutes (SD 2.0). The range was from three to 15 minutes.

6.1.2 Difficulty of test

Analysis of variance (ANOVA) showed mean AVRI was related to the subjective difficulty of the test (Table 22; $p = 0.015, *$).

Table 22 The relationship of mean AVRI to the difficulty of the test.

| Test | Mean AVRI | SD | n |
|-----------|-----------|-----|-----|
| Easy | 0.51 | .09 | 806 |
| Moderate | 0.52 | .10 | 111 |
| Difficult | 0.58 | .11 | 11 |

6.1.3 Failed test data

The failure rate per vessel varied between 0.2 and 1.9% and was marginally higher for the right sided vasculature (Table 23).

Table 23 The failure rate per vessel

| Vessel | LA | LU | RA | RU | UA |
|----------------|-----|-----|-----|-----|-----|
| Number missing | 5 | 2 | 8 | 3 | 19 |
| % failure | 0.5 | 0.2 | 0.8 | 0.3 | 1.9 |

These cases were reviewed to see if the inability to obtain a waveform indicated abnormality. 15 out of 16 women with missing uteroplacental data had normal weight babies at term, one had a

stillbirth at 29 weeks. The mean AVRI of the remaining vessels in cases where some result was missing (RI = 0.53; SD = 0.09; n = 16) was not different from cases where there were no missing measurements (RI = 0.51; SD = 0.09; n = 961; p = 0.63, NS).

The mean RI of the case of stillbirth was 0.70. It was therefore decided to ignore missing data rather than ascribe a particular, or high, RI value.

Missing data for the UA was entirely due to persistent fetal breathing patterns throughout the examination.

6.1.4 Wrong dates

The mean AVRI of cases where ultrasound agreed with dates (RI = 0.51; SD = 0.09; n = 638) was not different from cases where there was a discrepancy (RI = 0.51; SD = 0.09; n = 339; p = 1.0, NS).

6.2 RESISTANCE INDEX

6.2.1 Correlations

The RIs of all vessels were highly significantly correlated with one another although the Pearson correlation coefficients were low (Table 24). The pairs of correlations in order of size were:

NPU NPA; PU PA; NPU PU; NPU PA; PU NPA followed by the umbilical correlations to PA; PU; NPU; NPA. The correlations were highest between the U and A on the same side of the uterus, followed by the same vessel on opposite sides. The UA was most highly correlated with the placental arcuate, ie the vessel nearest the intervillous space.

Table 24 Correlation coefficients of RIs of uteroplacental vessels compared with one another (n = 977).

| | UA | PA | NPA | PU |
|-----|---------|---------|---------|---------|
| PA | .17 *** | | | |
| NPA | .10 ** | .32 *** | | |
| PU | .14 *** | .36 *** | .21 *** | |
| NPU | .12 *** | .26 *** | .46 *** | .35 *** |

6.2.2 Effect of gestation

At all gestations and for all sites on the uterus the frequency distribution of RI values approximated to a normal distribution.

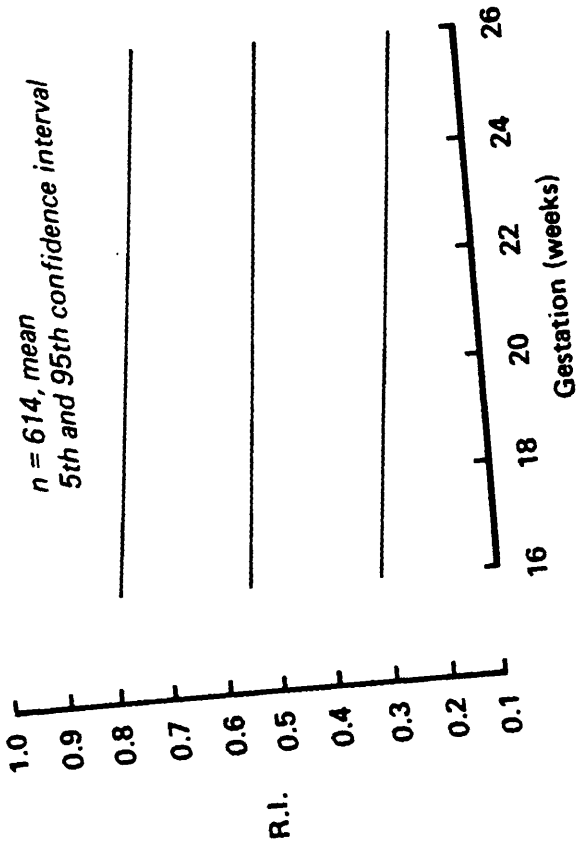
The RI for each vessel was related to gestational age and subjected to regression analysis in order to calculate the mean and 5th to 95th confidence intervals for individual RI values, which is equivalent to the 5th and 95th centiles. Quadratic regression analysis did not explain significantly more variation in the data than linear regression analysis, so the latter was employed.

The reference ranges are shown in Figures 15-17. The regression equations are in Table 25. With advancing gestation the resistance index of the uterine and arcuate arteries fell significantly. Multiple regression analysis was performed to compare each site as a pair with each other site and there was a highly significant amount of extra variation explained ($p < 0.005$ for every pair of sites). Placental side values were lower than nonplacental side and arcuate values were lower than uterine (ie distal values were lower than proximal values).

Figure 15 Reference ranges of uterine and arcuate RI, demonstrating the effect of placental site

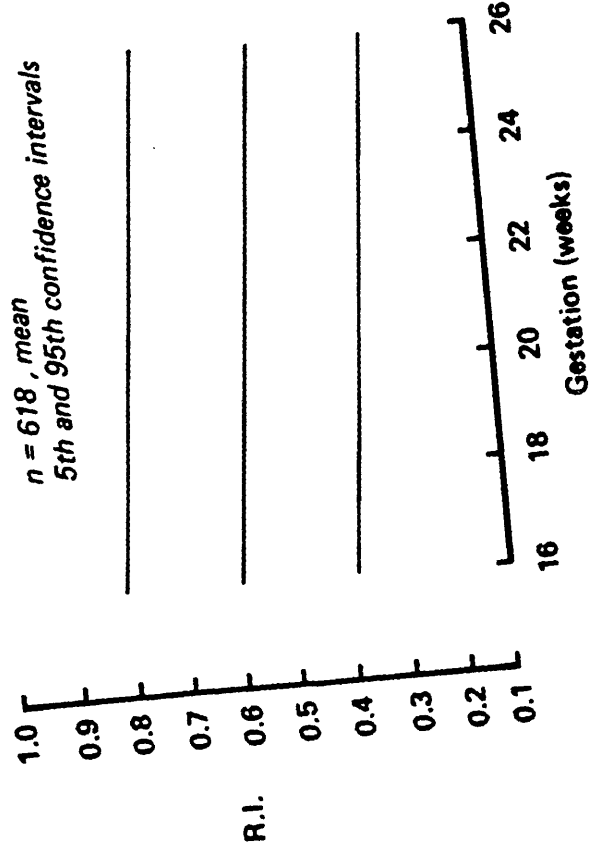
NONPLACENTAL ARCUATE

n = 614, mean
5th and 95th confidence interval



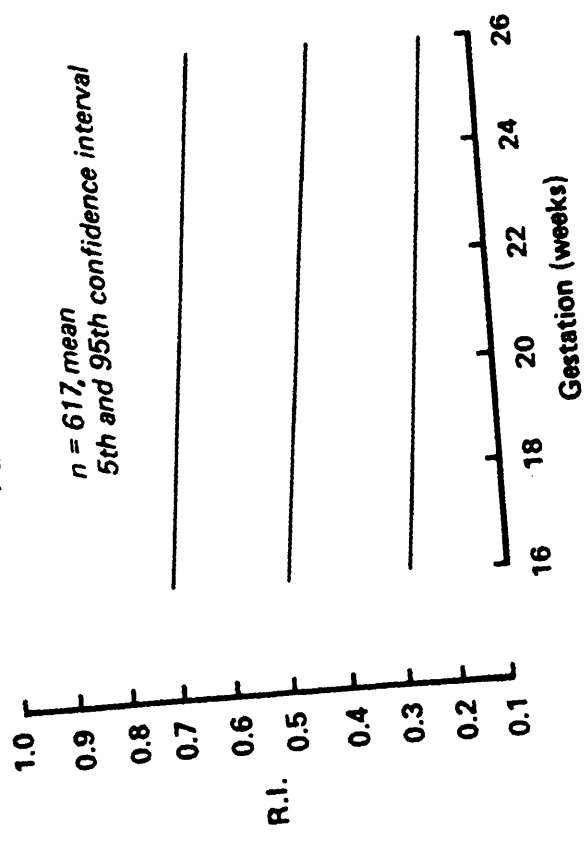
NONPLACENTAL UTERINE

n = 618, mean
5th and 95th confidence intervals



PLACENTAL ARCUATE

n = 617, mean
5th and 95th confidence interval



195

PLACENTAL UTERINE

n = 619, mean
5th and 95th confidence intervals

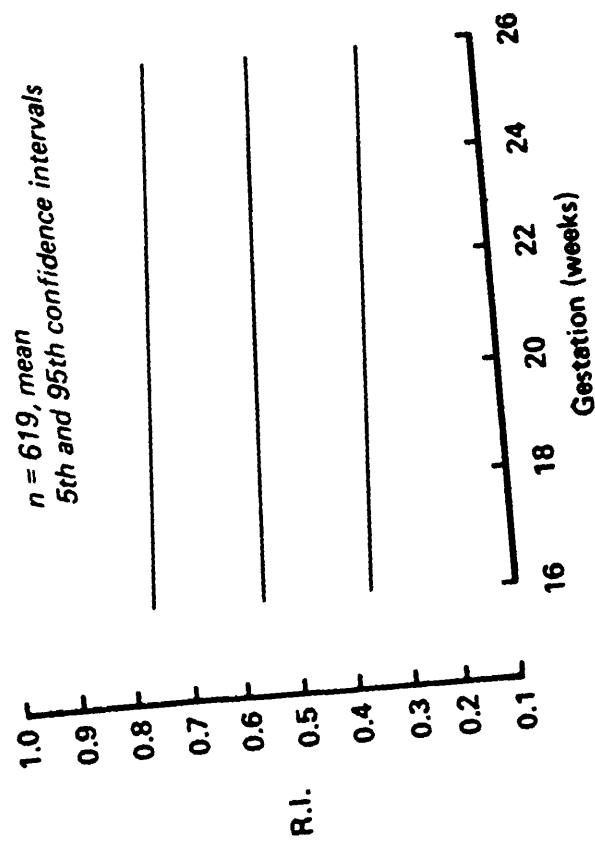


Figure 16 Difference between mean RIs by site of insonation

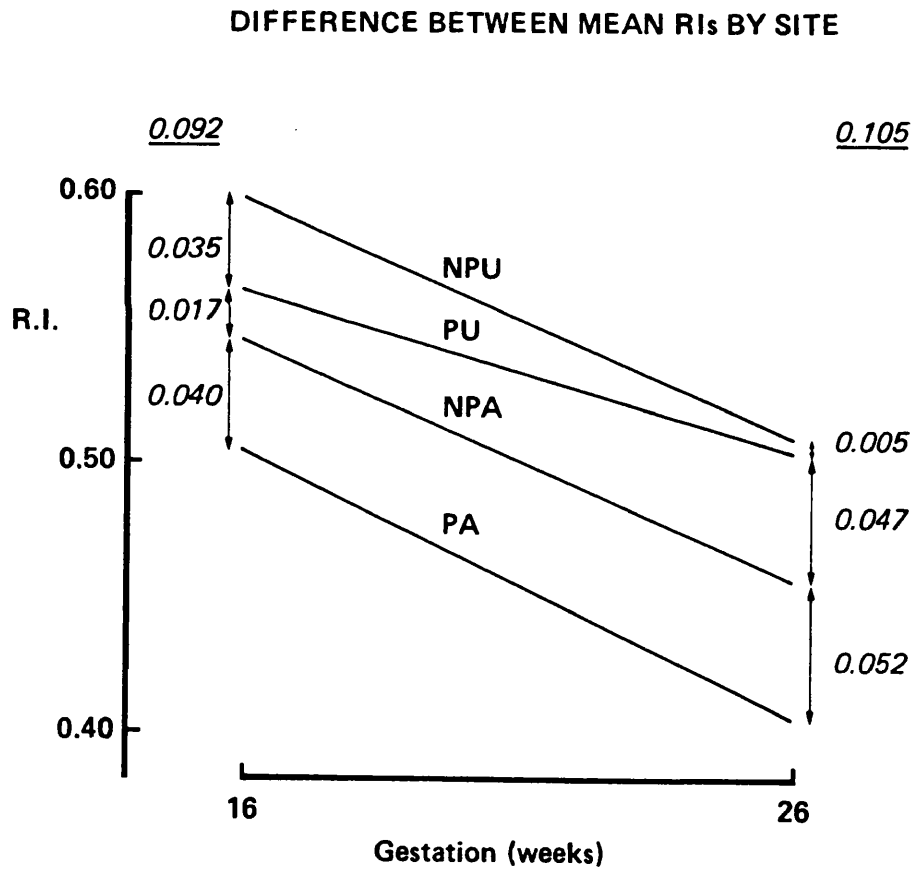
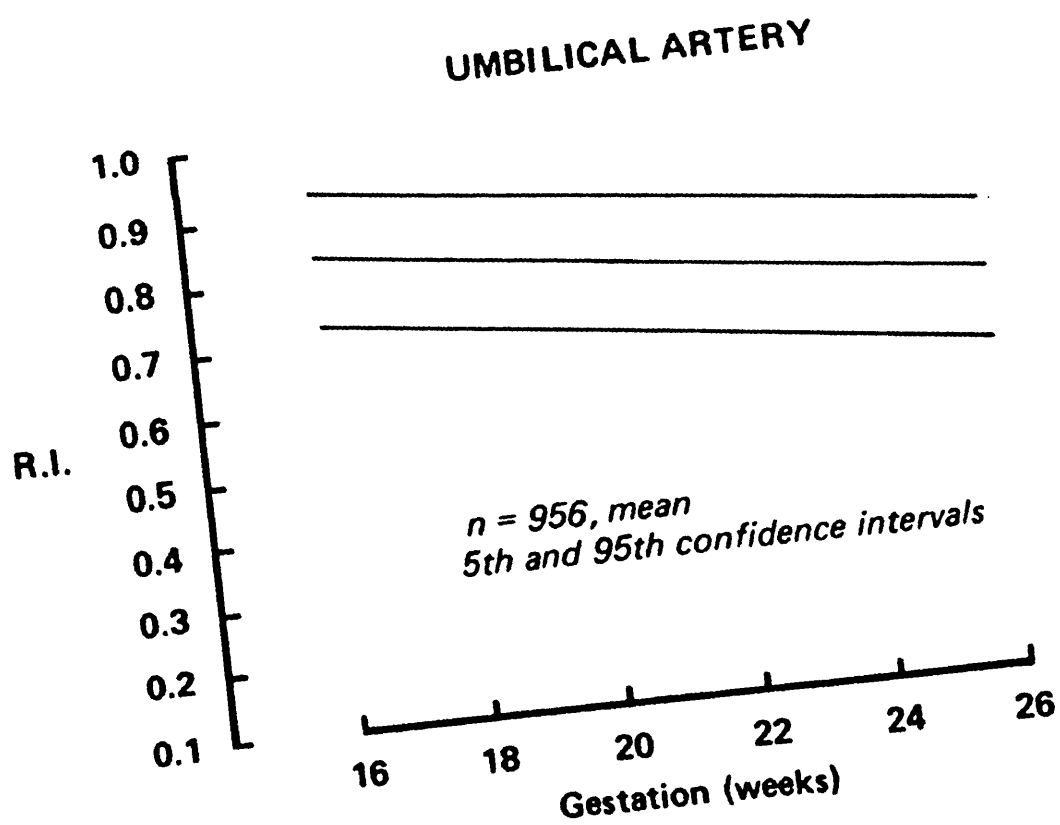


Figure 17 Reference range of umbilical RI



6.2.2.1 Reference ranges

The regression equations for the uteroplacental vessels are shown in Tables 25 and 26. They have been calculated for the placental and non-placental sides. The ranges for 'worst' and 'best' vessels have also been calculated

Table 25 The regression equations for mean RI with gestation. Placental and nonplacental arcuate and uterine arteries.

| Vessel | Slope x 10^{-3} | Constant | Corr coeff | RMS x 10^{-3} | Sign |
|--------|----------------------|----------|---------------|--------------------|--------|
| | S | C | R | | P |
| NPU | 1.318 | 0.746 | -0.13 | 16 | <0.001 |
| PU | 0.881 | 0.662 | -0.09 | 15 | 0.013 |
| NPA | 1.310 | 0.693 | -0.11 | 20 | 0.003 |
| PA | 1.490 | 0.673 | -0.14 | 17 | <0.001 |
| UA | 1.573 | 1.006 | -0.31 | 4 | <0.001 |

$$y = S \times \text{Gestation (in days)} + C$$

Table 26 The regression equations for RI for calculated parameters with gestation.

| Vessel | Slope x 10^{-3} | Constant | RMS x 10^{-3} | Number cases |
|----------|----------------------|----------|--------------------|-----------------|
| | S | C | | N |
| WORST A | 1.405 | 0.750 | 16 | 960 |
| WORST U | 0.927 | 0.728 | 11 | 968 |
| WORST RI | 1.070 | 0.779 | 11 | 975 |
| AV A | 1.420 | 0.685 | 13 | 963 |
| AV U | 0.787 | 0.655 | 10 | 970 |
| AVRI | 1.090 | 0.669 | 8 | 975 |
| BEST RI | 1.030 | 0.543 | 11 | 975 |

6.2.2.2 Longitudinal ranges

AVRI falls sharply in the second trimester and less in the third (see Table 27 and Figure 18). No statistics were performed on the longitudinal data as not all the subjects appear in all 6 gestation groups.

Table 27 Mean AVRI values of longitudinal, serial study subjects

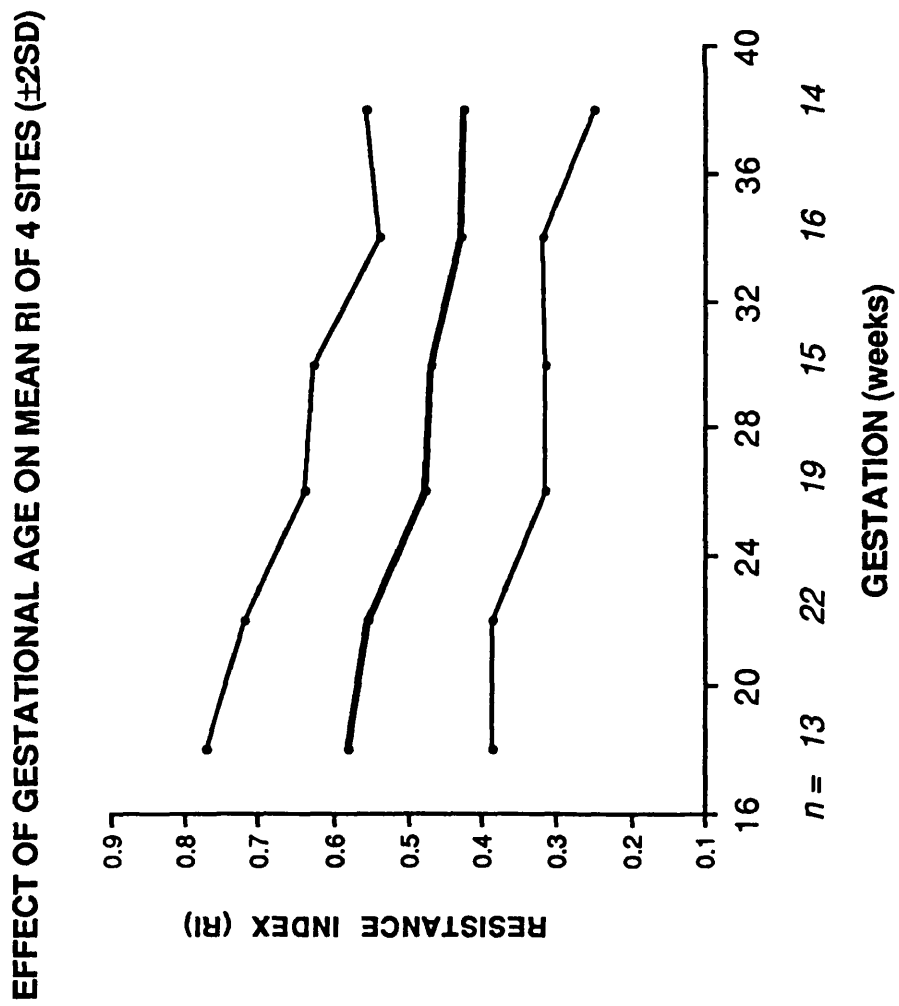
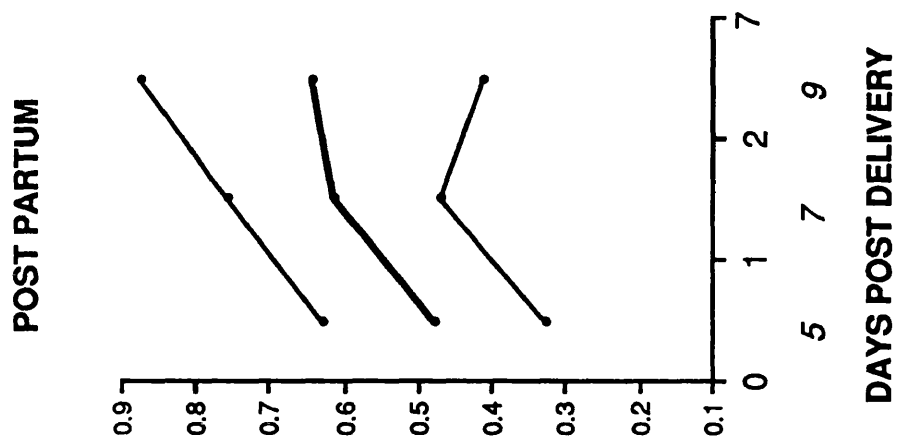
| Gest | 16-<20 | 20-<24 | 24-<28 | 28-<32 | 32-<36 | 36+ |
|-----------|--------|--------|--------|--------|--------|------|
| n | 13 | 22 | 19 | 15 | 16 | 14 |
| Mean AVRI | 0.58 | 0.55 | 0.48 | 0.47 | 0.43 | 0.43 |
| SD | 0.10 | 0.08 | 0.08 | 0.08 | 0.06 | 0.09 |

AVRI does not change suddenly immediately after delivery but increases from the term pregnant levels slowly over the few days post delivery (see Table 28 and Figure 18). There is a significant rise in RI from the first day post delivery to the second day and first week values, but the numbers in the groups are very small.

Table 28 Mean AVRI values of postpartum study subjects

| Days post delivery | 0 - <1 | 1 - <2 | 2 - 7 |
|----------------------|--------|---------|--------|
| n | 5 | 7 | 9 |
| Mean AVRI | 0.48 | 0.61 | 0.64 |
| SD | 0.08 | 0.07 | 0.12 |
| p (t-test vs <24hrs) | | <0.02 * | 0.02 * |

Figure 18 Longitudinal range of AVRI and postpartum values



6.2.3 Effect of placental location

The difference in uteroplacental RI values depending on placental location was explored.

6.2.3.1 Anterior/posterior

Mean RI values were consistently higher when the placenta was posterior than when it was anterior, whatever the vessel under study (Table 29). The values for fundal placentae were higher than either anterior or posterior placentae.

Table 29 Mean RI for uterine vessels compared by placental location.

| Vessel | RI mean(SD) by placental location | | | | ANOVA | |
|--------|-----------------------------------|-----------|-----------|-----------|-----------|--------------|
| | n | Anterior | Posterior | Fundal | Lateral | Significance |
| LU | 461 | 0.54(.12) | 0.56(.11) | 0.59(.13) | 0.55(.08) | 0.001 *** |
| RU | 460 | 0.51(.13) | 0.55(.12) | 0.56(.12) | 0.55(.12) | <0.001 *** |
| PU | 296 | 0.52(.13) | 0.55(.11) | 0.59(.14) | 0.52(.10) | 0.01 ** |
| NPU | 297 | 0.54(.13) | 0.57(.11) | 0.58(.09) | 0.58(.10) | 0.04 * |
| MEAN U | 460 | 0.52(.11) | 0.56(.09) | 0.58(.11) | 0.55(.08) | <0.001 *** |

6.2.3.2 Left/right

The effect of the side of the placenta on the left and right values of RI is shown in Table 30. The U and A values were significantly lower on the ipsilateral side. When there was a centrally placed placenta the mean right RI was significantly lower than the left.

Table 30 The effect of the side of the placenta on RI. t-test of pairs of RI when placenta R, L or R=L.

| Placenta | n | Mean(SD) | Mean(SD) | p | |
|----------|-----|-----------|-----------|--------|-----|
| | | LA | RA | | |
| Right | 323 | 0.51(.14) | 0.45(.14) | <0.001 | *** |
| Left | 289 | 0.47(.13) | 0.50(.14) | 0.004 | *** |
| Central | 308 | 0.50(.14) | 0.47(.14) | 0.006 | ** |

| Placenta | n | LU | RU | p | |
|----------|-----|-----------|-----------|--------|-----|
| | | LU | RU | | |
| Right | 327 | 0.57(.12) | 0.53(.13) | <0.001 | *** |
| Left | 291 | 0.55(.11) | 0.55(.13) | 0.66 | NS |
| Central | 309 | 0.55(.12) | 0.53(.13) | 0.004 | *** |

6.2.4 Uteroplacental resistance index and maternal factors

The relation between AVRI and BP, pulse, early pregnancy symptoms

and various social factors was investigated.

6.2.4.1 Relation to maternal blood pressure and pulse

Mean RI was inversely related to pulse and BP (Table 31). Partial correlation coefficients controlling for gestation are shown. There was a highly significant negative correlation between heart rate and RI but the coefficient was very low. BP was significantly correlated to AVU but not AVRI or AVA.

Table 31 Effect of BP and heart rate on maternal RI

| Vessel | Parameter | Partial corr coefficient | n | p | |
|--------|---------------|-----------------------------|-----|--------|-----|
| AVRI | Sys BP | -0.03 | 958 | 0.15 | NS |
| | Dias BP | -0.04 | 958 | 0.10 | NS |
| | Heart rate(M) | -0.18 | 957 | <0.001 | *** |
| AVU | Sys BP | -0.08 | 953 | 0.01 | ** |
| | Dias BP | -0.09 | 953 | 0.002 | *** |
| | Heart rate(M) | -0.20 | 952 | <0.001 | *** |
| AVA | Sys BP | 0.01 | 946 | 0.35 | NS |
| | Dias BP | 0.01 | 946 | 0.37 | NS |
| | Heart rate(M) | -0.11 | 945 | <0.001 | *** |

6.2.4.2 Smoking, 'flu-like illness, threatened miscarriage

There were no significant differences in mean AVU, PA, NPA, PU or NPU in cases where there had or had not been a threatened miscarriage (18%). Nor were any differences found between smokers (32%) and nonsmokers, however heavy their intake. Mean AVRI was not significantly different in either group (see Table 32). Mean AVRI was lower in cases where there had been a 'flu-like illness in early pregnancy (16%).

Table 32 The association of smoking, 'flu-like illness and threatened miscarriage with mean AVRI.

| | Mean AVRI(SD) | n | p |
|------------------------|---------------|-----|---------|
| 'Flu-like illness | 0.50 (.09) | 154 | 0.02 * |
| No 'flu-like illness | 0.52 (.09) | 819 | |
| Threatened miscarriage | 0.52 (.09) | 179 | 0.42 NS |
| No threat miscarriage | 0.51 (.09) | 794 | |
| Smoking (any amount) | 0.51 (.09) | 307 | 0.38 NS |
| Non smoking | 0.51 (.09) | 664 | |

6.2.4.3 Social factors

The relationships of maternal social factors and AVRI are shown (Table 33). Although the coefficients were low, there were highly significant correlations between AVRI and height and ORS. AVRI was not related to maternal age, weight, social class, smoking or parity. Height and weight were correlated to one another, but only height was significantly correlated to AVRI.

Table 33 The relation of maternal social factors and AVRI.

| Maternal factor | Corr coefficient (Spearman) | n | p |
|-----------------|--------------------------------|-----|------------|
| Age | <0.01 | 964 | 0.48 NS |
| Height | -0.10 | 953 | 0.001 *** |
| Weight | -0.04 | 955 | 0.12 NS |
| Social class | 0.02 | 949 | 0.26 NS |
| Smoking | -0.01 | 971 | 0.38 NS |
| Parity | 0.01 | 962 | 0.35 NS |
| ORS | 0.13 | 977 | <0.001 *** |

6.2.4.4 Race

There was no difference in mean AVRI between racial groups (Table

34) (ANOVA $p = 0.48$, NS).

Table 34 The relation of race to mean AVRI.

| Racial group | Mean AVRI (SD) | | n |
|------------------|----------------|-----|-----|
| Caucasian | 0.51 | .09 | 589 |
| West Indian | 0.51 | .09 | 159 |
| African | 0.53 | .10 | 102 |
| Asian | 0.53 | .10 | 30 |
| Mixed | 0.51 | .08 | 18 |
| Chinese/Far East | 0.53 | .05 | 18 |
| Mediterranean | 0.51 | .08 | 28 |
| Arab | 0.53 | .13 | 13 |
| Unspecified | | | 20 |

6.2.4.5 Parity

There was no significant difference in mean AVRI between primigravidae (RI = 0.51; SD = 0.09; $n = 471$) and multigravidae (RI = 0.51; SD = 0.09; $n = 491$; $p = 0.60$, NS). Nor was there any difference in mean AVRI, for women with no previous delivery, between those with (RI = 0.51; SD = 0.10; $n = 145$) and without any previous miscarriages or abortions (RI = 0.52; SD = 0.09; $n = 326$; $p = 0.39$, NS).

6.2.5 Umbilical resistance index and maternal factors

The relation of UARI to the same maternal factors was examined.

6.2.5.1 Smoking, 'flu-like illness, threatened miscarriage

Mean UARI was not different in pregnancies complicated by a 'flu-like illness in early pregnancy or a threatened miscarriage. Differences were found between smokers and non-smokers (Table 35).

Table 35 The association of smoking, 'flu-like illness and threatened miscarriage with mean UARI (statistical test = ANOVA).

| | Mean UARI(SD) | n | p |
|------------------------|---------------|-----|---------|
| 'Flu-like illness | 0.78 (.07) | 151 | 0.35 NS |
| No 'flu-like illness | 0.78 (.07) | 803 | |
| Threatened miscarriage | 0.78 (.06) | 174 | 0.60 NS |
| No threat miscarriage | 0.78 (.06) | 780 | |
| Smoking (any amount) | 0.79 (.06) | 301 | 0.04 * |
| Non smoking | 0.78 (.06) | 651 | |

6.2.5.2 Social factors

The relationships of maternal social factors and UARI are shown in Table 36. There was a significant positive correlation of UARI with low social class and ORS, and a negative correlation with age and height, although the coefficients are small. No relation between UARI and maternal weight or parity was found.

Table 36 The relation of maternal social factors and UARI

| Maternal factor | Corr coefficient (Spearman) | n | p |
|-----------------|--------------------------------|-----|-----------|
| Age | -0.83 | 946 | 0.005 *** |
| Height | -0.08 | 935 | 0.006 ** |
| Weight | -0.02 | 937 | 0.30 NS |
| Social class | 0.08 | 958 | 0.006 ** |
| Parity | -0.01 | 944 | 0.40 NS |
| ORS | 0.08 | 958 | 0.007 ** |

NB. Social class is represented by a number here. Low social class had a higher number and was correlated with high UARI.

6.2.5.3 Race

There was a difference in mean UARI between different racial

groups (ANOVA = 0.02, *).

Table 37 The relation of race to mean UARI.

| Racial group | Mean UARI (SD) | | n |
|------------------|----------------|-----|-----|
| Caucasian | 0.78 | .06 | 580 |
| West Indian | 0.78 | .06 | 155 |
| African | 0.80 | .07 | 98 |
| Asian | 0.77 | .07 | 30 |
| Mixed | 0.80 | .05 | 18 |
| Chinese/Far East | 0.79 | .06 | 18 |
| Mediterranean | 0.77 | .07 | 27 |
| Arab | 0.79 | .06 | 13 |
| Unspecified | | | 38 |

6.2.6 Uteroplacental resistance index and fetal factors

The relation between AVRI and twins and fetal sex was investigated.

6.2.6.1 Twins

The AVRI in 14 twin pregnancies was compared to that of singleton pregnancies (Table 38). Twins had a lower AVRI than singleton

pregnancies.

Table 38 The effect of twins on mean AVRI

| Group | n | Mean AVRI (SD) | p |
|------------|-----|----------------|---------|
| Singletons | 963 | 0.51 (.09) | 0.011 * |
| Twins | 14 | 0.46 (.07) | |

The gestation at which the test was performed was not significantly different for singletons (mean gestation = 20.3, SD = 12.3, n = 961) and twins (mean = 19.4, SD = 17.3, n = 14, p = 0.07). If anything, an earlier gestation on testing in twins would be expected to increase AVRI. Because of this marked difference in RI, the difficulty in definition of complications in twins, and the confused analysis of twin Doppler results (see Section 1.5.3.7), twins were excluded from further screening analysis.

6.2.6.2 Fetal sex

There was no significant difference in mean AVRI between female fetuses (Table 39).

Table 39 The effect of fetal sex on mean AVRI

| Sex | n | Mean AVRI(SD) | p |
|--------|-----|---------------|---------|
| Female | 445 | 0.51 (0.09) | 0.74 NS |
| Male | 482 | 0.51 (0.09) | |

6.2.7 Umbilical resistance index and fetal factors

The relation between UARI and fetal heart rate (FHR) was examined, as was the relation of FHR and fetal sex.

6.2.7.1 Fetal heart rate

There was a highly significant partial correlation of fetal heart rate and UARI (Table 40).

Table 40 Effect of fetal heart rate on UARI.

| Vessel | Parameter | Partial corr coefficient | n | p |
|--------|---------------|-----------------------------|-----|------------|
| UARI | Heart rate(F) | -0.24 | 950 | <0.001 *** |

6.2.7.2 Fetal sex

There was a highly significant difference in mean UARI between female and male fetuses (Table 41).

Table 41 The effect of fetal sex on mean UARI

| Sex | n | Mean UARI(SD) | p |
|--------|-----|---------------|------------|
| Female | 432 | 0.79 (.06) | <0.001 *** |
| Male | 465 | 0.77 (.06) | |

6.2.7.3 Fetal heart rate and fetal sex

Fetal heart rate at 16 to 24 weeks was not significantly different for female (FHR = 148.4; SD = 7.6; n = 432) and male fetuses (FHR = 148.6; SD = 7.5; n = 464; p = 0.80, NS), suggesting that the sex difference in UARI was not related to a difference in heart rate.

6.3 MATERNAL FLOW VELOCITY WAVEFORMS AND OUTCOME

Mean AVRI was compared for pregnancies with normal outcomes and complications. 925 singleton pregnancies were considered.

6.3.1 Uteroplacental resistance index and obstetric outcome

A normal pregnancy was considered to be one ending in a live birth after 37 weeks of a baby over 10th centile weight where there were no antenatal complications and no operative delivery for fetal distress. Only 573 subjects fulfilled these criteria. All the abnormal outcomes were considered separately and have been grouped into pregnancy loss, antepartum haemorrhage, hypertension, obstetric outcomes, neonatal outcomes and fetal distress for convenience. Section 13.2 contains the details of the definitions of outcomes. Appendix 14.10 contains the coding instructions.

6.3.1.1 Pregnancy loss

Mean AVRI was higher in pregnancies ending in pregnancy loss (IUD or NND) (Table 42).

Table 42 A comparison of mean AVRI for normals vs pregnancy loss

| Outcome | n | Mean AVRI | SD | p |
|-------------------|-----|-----------|-----|--------|
| Normals (vs rest) | 573 | .50 | .09 | |
| IUD | 12 | .54 | .11 | .13 NS |
| IUD OR NND | 15 | .55 | .10 | .04 * |

6.3.1.2 Antepartum haemorrhage

Abruptio placentae was associated with a high RI in the second trimester (Table 43).

Table 43 A comparison of mean AVRI for normals vs APH

| Outcome | n | Mean AVRI | SD | p |
|-------------------|-----|-----------|-----|--------|
| Normals (vs rest) | 573 | .50 | .09 | |
| Placenta praevia | 10 | .51 | .08 | .66 NS |
| Definite abruptio | 8 | .58 | .13 | .01 ** |
| Probable abruptio | 1 | .53 | | |
| Local causes | 5 | .46 | .03 | .26 NS |
| Unknown | 12 | .55 | .10 | .05 * |
| APH (all causes) | 36 | .53 | .10 | .03 * |

The groups 'all APH' and 'APH of unknown cause' were associated with a high RI possibly because they contained cases of abruptio.

6.3.1.3 Hypertension

Mean AVRI was significantly higher for all grades of proteinuric hypertension. It was not elevated in non-proteinuric hypertension (Table 44).

Table 44 A comparison of mean AVRI for normals vs hypertension

| Outcome | n | Mean AVRI | SD | p |
|----------------------|-----|-----------|-----|-----------|
| Normals (vs rest) | 573 | .50 | .09 | |
| Hypertension (any) | 100 | .55 | .11 | <.001 *** |
| Nonproteinuric: mild | 18 | .54 | .11 | .07 NS |
| mod | 17 | .50 | .09 | .92 NS |
| severe | 9 | .52 | .12 | .49 NS |
| (All) | 44 | .52 | .11 | .17 NS |
| Proteinuric: mild | 11 | .56 | .11 | .04 * |
| mod | 9 | .58 | .12 | .005 *** |
| severe | 20 | .58 | .12 | <.001 *** |
| (All) | 40 | .57 | .11 | <.001 *** |

6.3.1.4 Obstetric complications

AVRI was significantly higher in pregnancies ending in prelabour preterm CS but not induction of labour (IOL), nor a variety of other complications (Table 45).

Table 45 A comparison of mean AVRI for normals vs obstetric complications

| Outcome | n | Mean AVRI | SD | p | |
|-----------------------|-----|-----------|-----|-------|-----|
| Normals (vs rest) | 573 | .50 | .09 | | |
| Premature labour < 37 | 53 | .51 | .11 | .70 | NS |
| IOL <42 | 33 | .53 | .10 | .08 | NS |
| IOL >42 | 12 | .51 | .07 | .67 | NS |
| Prelabour CS <37 | 20 | .60 | .11 | <.001 | *** |
| PPROM | 18 | .51 | .09 | .66 | NS |
| Diabetes | 5 | .54 | .15 | .35 | NS |
| Polyhydramnios | 6 | .49 | .08 | .62 | NS |

PPROM = Preterm premature rupture of membranes

6.3.1.5 Neonatal outcome

The mean AVRI was higher in SGA babies and those admitted to the

SCBU (Table 46).

Table 46 A comparison of mean AVRI for normals vs SGA and SCBU admission

| Outcome | n | Mean AVRI | SD | p |
|-------------------|-----|-----------|-----|-----------|
| Normals (vs rest) | 573 | .50 | .09 | |
| SGA 5 - <10th | 66 | .55 | .10 | <.001 *** |
| SGA 3 - <5th | 22 | .55 | .11 | 0.02 * |
| SGA <3rd centile | 29 | .58 | .11 | <.001 *** |
| Baby to SCBU | 36 | .57 | .11 | <.001 *** |

6.3.1.6 Parameters of fetal distress

For parameters of fetal distress, a t-test was performed comparing all subjects, not just normals versus each outcome, because the particular parameters of normal pH and Apgar score were not included in the definition of normals. Mean AVRI was not related to five minute Apgar, low cord pH or operative delivery for fetal distress, ODFD (Table 47).

Table 47 Comparison of mean AVRI to parameters of fetal distress

| Outcome | n | Mean AVRI | SD | p |
|-----------------|-----|-----------|-----|--------|
| 5 Min Apgar > 7 | 847 | .51 | .09 | .32 NS |
| 5 Min Apgar < 7 | 21 | .53 | .10 | |
| Cord pH > 7.1 | 358 | .51 | .09 | .90 NS |
| Cord pH < 7.1 | 65 | .51 | .09 | |
| No ODFD | 837 | .50 | .07 | .25 NS |
| ODFD | 73 | .51 | .09 | |

6.3.2 Degree of smallness or delta birth weight

A correlation was made between delta RI and delta Bwt (delta = number of SDs from mean expected for gestation) for a variety of vessels (Table 48). The distributions of the variables were normal. There were highly significant correlations between uteroplacental RIs and delta birthweight although the coefficients are small. The correlations may be partly affected by the different number of readings in the different groups (which could be one, average of two, average of four, worst of two or worst of four) but still, arcuate readings had higher correlation coefficients than uterine. The placental arcuate,

which is the nearest to the intervillous space, had the highest value for a single vessel. However, the UA correlation coefficient was almost the lowest.

Table 48 Correlation of delta RI and delta Bwt in rank order of Pearson correlation coefficient

| Vessel | n | Corr coeff | p | |
|----------|-----|------------|--------|-----|
| AVRI | 926 | -0.26 | <0.001 | *** |
| AVA | 914 | -0.25 | <0.001 | *** |
| WORST A | 913 | -0.22 | <0.001 | *** |
| WORST RI | 926 | -0.22 | <0.001 | *** |
| PA | 587 | -0.21 | <0.001 | *** |
| NPA | 584 | -0.21 | <0.001 | *** |
| WORST U | 919 | -0.19 | <0.001 | *** |
| AVU | 921 | -0.19 | <0.001 | *** |
| NPU | 588 | -0.15 | <0.001 | *** |
| UA | 910 | -0.15 | <0.001 | *** |
| PU | 589 | -0.14 | <0.001 | *** |

6.3.3 Uterine to arcuate ratio

The RI value for the U site is higher than the A value (Figure 16). U:A ratio is defined as AVU/AVA if all four RI results are

available. The study population was divided into High U ($U:A \geq 1$) and High A ($U:A < 1$). The same outcomes as above were compared vs normals (using chi-square). There were no significant differences for any outcomes except the complications of SGA, prelabour CS and IOL for postmaturity (which are shown in Table 49).

Table 49 The distribution of High U and High A cases for outcomes that are significantly different from normals

| Outcome | High U | High A | % U:A<1 | p |
|------------------|--------|--------|---------|--------|
| Normals | 425 | 138 | 25 | |
| SGA 5 - 10 | 45 | 19 | 30 | .60 NS |
| SGA 3 - 5 | 15 | 7 | 32 | .45 NS |
| SGA <3 | 16 | 13 | 45 | .03 * |
| IOL postmaturity | 10 | 10 | 50 | .02 * |
| Prelabour CS <37 | 5 | 8 | 62 | .01 ** |

Although a higher rate of low U:A ratio is seen in all the SGA groups it was only significant in the SGA <3 group.

Nevertheless, a trend can be seen, suggesting that, with increasing degrees of growth retardation, there is an increasing distortion of the uteroplacental vasculature. This seems to be a continuous rather than an 'all-or-nothing' phenomenon.

6.4 FETAL FLOW VELOCITY WAVEFORMS AND OUTCOME

Mean UARI was compared between pregnancies with normal outcomes and those with complications.

6.4.1 Umbilical resistance index and obstetric outcome

The abnormal outcomes were examined separately and are grouped, for convenience, as for the maternal FVWs into pregnancy loss, antepartum haemorrhage, hypertension, obstetric outcomes, neonatal outcomes and fetal distress. The same definitions of a normal pregnancy and the complications were used (Section 6.3.1).

6.4.1.1 Pregnancy loss

There was no difference in mean UARI in cases that ended in stillbirth or neonatal death (Table 50).

Table 50 A comparison of mean UARI for normals vs pregnancy loss

| Outcome | n | Mean UARI | SD | p |
|-------------------|-----|-----------|-----|--------|
| Normals (vs rest) | 563 | .79 | .06 | |
| IUD | 12 | .80 | .09 | .26 NS |
| IUD OR NND | 15 | .82 | .09 | .09 NS |

6.4.1.2 Antepartum haemorrhage

Mean UARI was no different in cases which were complicated by antepartum haemorrhage (Table 51).

Table 51 A comparison of mean UARI for normals vs antepartum haemorrhage

| Outcome | n | Mean UARI | SD | p |
|-------------------|-----|-----------|-----|--------|
| Normals (vs rest) | 563 | .79 | .06 | .31 NS |
| Placenta praevia | 10 | .77 | .05 | .31 NS |
| Definite abruptio | 8 | .78 | .05 | .95 NS |
| Probable abruptio | 1 | .79 | | |
| Local causes | 5 | .78 | .06 | .88 NS |
| Unknown | 11 | .79 | .08 | .55 NS |
| APH (all causes) | 35 | .78 | .06 | .89 NS |

6.4.1.3 Hypertension

Mean UARI was significantly higher in pregnancies complicated by severe proteinuric hypertension (Table 52).

Table 52 A comparison of mean UARI for normals vs hypertension

| Outcome | n | Mean UARI | SD | p |
|----------------------|-----|-----------|-----|--------|
| Normals (vs rest) | 563 | .79 | .06 | .31 NS |
| Hypertension (any) | 97 | .79 | .06 | .31 NS |
| Nonproteinuric: mild | 18 | .80 | .05 | .15 NS |
| mod | 17 | .78 | .08 | .80 NS |
| severe | 8 | .77 | .08 | .78 NS |
| (All) | 43 | .79 | .07 | .53 NS |
| Proteinuric: mild | 11 | .78 | .06 | .81 NS |
| mod | 9 | .77 | .07 | .87 NS |
| severe | 19 | .81 | .05 | .02 * |
| (All) | 39 | .79 | .06 | .18 NS |

6.4.1.4 Obstetric complications

Mean UARI was significantly higher for cases that ended in preterm, prelabour CS (Table 53). It was significantly lower for cases of spontaneous premature labour. This appears to be a purely fetal circulation phenomenon as there was no difference in AVRI (Table 45).

Table 53 A comparison of mean UARI for normals vs obstetric complications

| Outcome | n | Mean UARI | SD | p | |
|-----------------------|-----|-----------|-----|------|-----|
| Normals (vs rest) | 563 | .79 | .06 | .31 | NS |
| Premature labour < 37 | 51 | .75 | .07 | .005 | *** |
| IOL <42 | 32 | .79 | .06 | .56 | NS |
| IOL >42 | 12 | .78 | .06 | .90 | NS |
| Prelabour CS <37 | 20 | .82 | .07 | .005 | *** |
| PPROM | 18 | .80 | .10 | .28 | NS |
| Diabetes | 5 | .82 | .05 | .12 | NS |
| Polyhydramnios | 6 | .79 | .08 | .67 | NS |

6.4.1.5 Neonatal outcome

There was a significant increase in UARI in SGA babies <3rd centile (Table 54).

Table 54 A comparison of mean UARI for normals vs SGA and SCBU admission

| Outcome | n | Mean UARI | SD | p | |
|-------------------|-----|-----------|-----|------|----|
| Normals (vs rest) | 563 | .79 | .06 | .31 | NS |
| SGA 5 - <10th | 66 | .79 | .06 | .25 | NS |
| SGA 3 - <5th | 22 | .80 | .06 | .25 | NS |
| SGA <3rd centile | 29 | .81 | .05 | .009 | ** |
| Baby to SCBU | 36 | .79 | .08 | .35 | NS |

6.4.1.6 Parameters of fetal distress

Mean UARI was unrelated to parameters of fetal distress (Table 55).

Table 55 Comparison of mean UARI to parameters of fetal distress

| Outcome | n | Mean UARI | SD | p |
|-----------------|-----|-----------|-----|--------|
| 5 Min Apgar > 7 | 832 | .79 | .06 | .74 NS |
| 5 Min Apgar < 7 | 21 | .79 | .07 | |
| Cord pH > 7.1 | 353 | .78 | .07 | .89 NS |
| Cord pH < 7.1 | 64 | .78 | .07 | |
| No ODFD | 822 | .78 | .06 | .81 NS |
| ODFD | 72 | .78 | .06 | |

6.5 SCREENING CHARACTERISTICS

The screening characteristics of the test were calculated. Delta AVRI was used to predict outcomes. >95th centile AVRI is referred to as AVRI 5 (ie top 5%). The notation used in the Tables is explained in Section 3.4.3.

6.5.1 Prediction using top 5%

Table 56 The prediction of different separate complications using Doppler test AVRI 5 as cut-off for abnormality.

| Outcome | n | PR % | TP | FN | FP | TN | SE % | SP % | PO % | NE % | RR |
|-----------|-----|---------|----|-----|----|-----|---------|---------|---------|---------|-----|
| IUD | 925 | 1.3 | 3 | 9 | 51 | 862 | 25 | 94 | 6 | 99 | 5.4 |
| APH (all) | 922 | 4.0 | 5 | 32 | 48 | 837 | 14 | 95 | 9 | 96 | 2.6 |
| Abruptio | 922 | 1.0 | 3 | 6 | 50 | 863 | 33 | 95 | 6 | 99 | 8.2 |
| BP (all) | 922 | 10.7 | 19 | 80 | 34 | 789 | 19 | 96 | 36 | 91 | 3.8 |
| Prot BP | 925 | 4.3 | 10 | 30 | 44 | 841 | 25 | 95 | 19 | 97 | 5.4 |
| SGA 3 | 913 | 3.2 | 6 | 24 | 46 | 837 | 20 | 95 | 12 | 97 | 4.0 |
| SGA 5 | 913 | 5.6 | 10 | 42 | 42 | 819 | 19 | 95 | 19 | 95 | 4.0 |
| SGA 10 | 913 | 12.8 | 18 | 100 | 34 | 761 | 15 | 96 | 35 | 88 | 3.0 |

Table 56 shows that the sensitivity of AVRI 5 varies between 15% and 33%. The relative risk of a test positive woman developing complications as opposed to a test negative woman ranged from 2.6 to 8.2 and was higher for more severe disease.

6.5.2 Combinations of complications

To define the risk to any particular pregnancy of developing complications the outcomes were amalgamated in groups. MILD represented a wider definition of abnormal (SGA <10th or any BP or any APH or IUD or ODFD). SEVERE represented severest disease and a narrower definition of abnormal (SGA <3rd or severe proteinuric hypertension or abruptio or IUD). Women with severe complications are also included in the MILD group. The positive predictive value of an AVRI 5 test was 67% of developing a mild complication and 25% of developing a severe complication.

Table 57 The prediction of combinations of complications using AVRI 5 as cut-off for abnormality.

| Outcome | n | PR % | TP | FN | FP | TN | SE % | SP % | PO % | NE % | RR |
|---------|-----|---------|----|-----|----|-----|---------|---------|---------|---------|-----|
| MILD | 912 | 30.2 | 35 | 241 | 17 | 619 | 13 | 97 | 67 | 72 | 2.4 |
| SEVERE | 889 | 7.0 | 13 | 49 | 38 | 789 | 21 | 95 | 25 | 94 | 4.3 |

6.5.3 Comparison of mean, highest and umbilical tests

Screening characteristics were compared using different parameters (Table 58). AVRI was more accurate than WORST RI and BEST RI in prediction of complications. The UARI predictions were similar to chance.

Table 58 The prediction of complications using different 95th centile Doppler tests as cut-off for abnormality.

| Delta RI | SGA 10 | | PROT BP | | MILD | | SEVERE | |
|-------------|--------|-----|---------|-----|------|-----|--------|-----|
| | SE% | SP% | SE% | SP% | SE% | SP% | SE% | SP% |
| AVRI 5 | 15 | 96 | 25 | 95 | 13 | 97 | 21 | 95 |
| WORST 5 | 14 | 95 | 22 | 95 | 11 | 96 | 13 | 94 |
| BEST 5 | 10 | 95 | 17 | 95 | 10 | 96 | 16 | 95 |
| UARI 5 | 3 | 95 | 5 | 95 | 4 | 95 | 5 | 95 |

6.5.4 Comparison using different cut-offs

The test can be used with any cut-off (Table 59), but the specificity falls to below 73% before the sensitivity reaches 50% for severe complications.

Table 59 The prediction of complications using different centiles of delta AVRI as cut-off for abnormality.

| Delta AVRI | SGA 10 | | PROT BP | | MILD | | SEVERE | |
|---------------|--------|-----|---------|-----|------|-----|--------|-----|
| | SE% | SP% | SE% | SP% | SE% | SP% | SE% | SP% |
| 2.5 | 11 | 98 | 15 | 97 | 8 | 99 | 13 | 97 |
| 5 | 15 | 96 | 25 | 95 | 13 | 97 | 21 | 95 |
| 10 | 22 | 92 | 30 | 91 | 17 | 93 | 29 | 91 |
| 15 | 32 | 89 | 35 | 87 | 23 | 90 | 37 | 88 |
| 20 | 36 | 83 | 47 | 82 | 28 | 85 | 44 | 82 |
| 25 | 42 | 78 | 52 | 77 | 34 | 80 | 45 | 77 |
| 30 | 47 | 74 | 55 | 72 | 38 | 75 | 50 | 73 |

6.5.5 Screening at earlier and later gestation

In Table 60 the population was divided into two gestation periods, 16-20 weeks, and >20-24 weeks. The screening characteristics were all higher for the later gestation period, although the predictive values only improved slightly. Predictive value depends on the prevalence of disease but, for the milder complications, where the prevalence was lower in the later gestation group, all parameters were higher. Nevertheless, the predictive properties are still low throughout.

Table 60 The screening characteristics of the Doppler test (AVRI 5) for lower and higher gestation populations.

| Gestation | 16 - ≤20 (n=452) | | | | | >20 - 24 (n=472) | | | | |
|-----------|------------------|-----|-----|-----|-----|------------------|-----|-----|-----|-----|
| | PR% | SE% | SP% | PO% | NE% | PR% | SE% | SP% | PO% | NE% |
| SGA 10 | 11.4 | 14 | 96 | 33 | 96 | 14.4 | 16 | 95 | 35 | 87 |
| PROT BP | 5.5 | 20 | 96 | 23 | 95 | 3.2 | 33 | 94 | 16 | 98 |
| MILD | 31.1 | 10 | 97 | 64 | 71 | 30.0 | 16 | 97 | 71 | 73 |
| SEVERE | 6.7 | 14 | 96 | 19 | 94 | 7.3 | 27 | 95 | 30 | 94 |

6.5.6 Comparison with risk score

An ORS > 1.5 defined 41 out of 925 (4.4%) of cases as high-risk. An ORS of >1 defined 83 out of 925 (9.0%) as abnormal. Virtually all screening parameters were lower than those of AVRI > 95th centile (Table 61).

A direct comparison of AVRI and ORS as predictors of outcome is shown in Table 62. Although ORS was designed only to predict low birth weight it predicted all the outcomes to some extent, but the Doppler test had a higher combination of sensitivity and specificity than either of these two ORS cut-offs.

Table 61 The prediction of complications using a high ORS (> 1.5) as cut-off for abnormality.

| Complication | n | TP | FN | FP | TN | SE | SP | PO | NE |
|--------------|-----|----|-----|----|-----|----|----|----|----|
| | | | | | | % | % | % | % |
| IUD | 925 | 3 | 9 | 38 | 875 | 25 | 96 | 7 | 99 |
| APH (all) | 922 | 4 | 33 | 37 | 848 | 11 | 96 | 10 | 96 |
| Abruptio | 922 | 2 | 7 | 39 | 874 | 22 | 96 | 5 | 99 |
| Prot BP | 925 | 2 | 38 | 39 | 846 | 5 | 96 | 5 | 96 |
| SGA 3 | 913 | 4 | 26 | 35 | 848 | 13 | 96 | 10 | 97 |
| SGA 5 | 913 | 6 | 46 | 33 | 828 | 12 | 96 | 15 | 95 |
| SGA 10 | 913 | 9 | 109 | 30 | 765 | 8 | 96 | 23 | 88 |

Table 62 A comparison of the prediction of complications using a high ORS or AVRI 5 as cut-off for abnormality.

| ORS | SGA 10 | | PROT BP | | MILD | | SEVERE | |
|--------|--------|-----|---------|-----|------|-----|--------|-----|
| | SE% | SP% | SE% | SP% | SE% | SP% | SE% | SP% |
| > 1 | 21 | 93 | 13 | 91 | 14 | 93 | 24 | 92 |
| >1.5 | 8 | 96 | 5 | 96 | 5 | 96 | 13 | 96 |
| AVRI 5 | 15 | 96 | 25 | 95 | 13 | 97 | 21 | 95 |

6.5.7 Separating out by parity

The Doppler test was marginally more accurate in predicting severe pre-eclampsia in primigravidae (n= 448) than multigravidae (n= 476), and much more accurate for SGA (Table 63). It was equivalent for mild disease, but the sensitivity in multigravidae was higher for severe complications.

Table 63 A comparison of the prediction of complications in primigravidae and multigravidae using AVRI 5 as cut-off for abnormality.

| Parity | SGA 10 | | | | PROT BP | | | |
|--------|--------|-----|-----|-----|---------|-----|-----|-----|
| | PR% | SE% | SP% | PO% | PR% | SE% | SP% | PO% |
| 0 | 16.4 | 19 | 96 | 47 | 6.0 | 26 | 95 | 23 |
| ≥ 1 | 9.6 | 9 | 96 | 18 | 2.7 | 23 | 95 | 13 |

| Parity | MILD | | | | SEVERE | | | |
|--------|------|-----|-----|-----|--------|-----|-----|-----|
| | PR% | SE% | SP% | PO% | PR% | SE% | SP% | PO% |
| 0 | 38.3 | 13 | 97 | 76 | 7.8 | 18 | 94 | 20 |
| ≥ 1 | 23.2 | 13 | 97 | 58 | 6.2 | 25 | 97 | 33 |

6.5.8 Separating out by race

The prevalence of complications was higher in black than white women. The prediction of severe proteinuric hypertension and severe complications of pregnancy was markedly higher for black women than white women (Table 64). For the purposes of this Table, White = Caucasians (n = 564) and Black = West Indians and Africans (n = 254).

Table 64 A comparison of the prediction of complications in blacks and whites using AVRI 5 as cut-off for abnormality.

| Race | SGA 10 | | | | PROT BP | | | |
|-------|--------|-----|-----|-----|---------|-----|-----|-----|
| | PR% | SE% | SP% | PO% | PR% | SE% | SP% | PO% |
| Black | 13.7 | 15 | 95 | 31 | 5.1 | 46 | 95 | 35 |
| White | 11.9 | 10 | 96 | 26 | 4.4 | 8 | 95 | 7 |

| Race | MILD | | | | SEVERE | | | |
|-------|------|-----|-----|-----|--------|-----|-----|-----|
| | PR% | SE% | SP% | PO% | PR% | SE% | SP% | PO% |
| Black | 33.2 | 14 | 97 | 71 | 10.7 | 27 | 95 | 41 |
| White | 29.5 | 10 | 97 | 62 | 5.1 | 11 | 96 | 12 |

6.5.9 Repeat test study

The prediction of the test improved if performed later in pregnancy on the same woman (Table 65). 157 women in the repeat study had two screening tests. The same normal range of AVRI was used. The average gestation of performing test one was 18, and test two, 23 weeks. The prevalence of complications in the repeat study group was higher than the study population. The number of abnormal tests decreased from 13 (8%) to 8 (5%). The prediction of all (MILD) complications worsened, while the prediction of severe complications improved (even though the severe complications are included in the MILD group).

Table 65 A comparison of the prediction of complications using AVRI 5 as the cut-off for abnormality for a first and second test (n = 157).

| | PR% | First test | | | | Second test | | | |
|---------|------|------------|-----|-----|-----|-------------|-----|-----|-----|
| | | SE% | SP% | PO% | NE% | SE% | SP% | PO% | NE% |
| SGA 10 | 17.3 | 15 | 93 | 31 | 84 | 15 | 97 | 50 | 84 |
| PROT BP | 5.1 | 25 | 93 | 15 | 96 | 13 | 95 | 13 | 95 |
| MILD | 34.8 | 15 | 96 | 67 | 68 | 9 | 97 | 63 | 67 |
| SEVERE | 7.8 | 17 | 92 | 15 | 93 | 17 | 96 | 25 | 93 |

6.5.10 Comparison with old cut-off

A comparison was made with the cut-off used by Campbell et al (1986) and Steel et al (1988b) of 0.58 in any vessel (Table 66). This is not quite an exact comparison as WORST RI in this study was the worst of four sites, whereas the other studies used the worst of two sides of the uterus. Although the sensitivities were high, 65% of the population was defined as abnormal using this cut-off.

Table 66 Comparison of WORST RI with old absolute cut-off of RI \geq 0.58.

| Complication | n | TP | FN | FP | TN | SE % | SP % | PO % | NE % |
|--------------|-----|-----|----|-----|-----|---------|---------|---------|---------|
| SGA 10 | 913 | 97 | 21 | 494 | 301 | 82 | 38 | 16 | 93 |
| Prot BP | 925 | 33 | 7 | 568 | 317 | 82 | 36 | 4 | 99 |
| MILD | 915 | 204 | 75 | 389 | 247 | 73 | 39 | 34 | 77 |
| SEVERE | 889 | 48 | 14 | 525 | 302 | 77 | 37 | 8 | 96 |

6.6 PLACENTAL FUNCTION TESTS

The correlations between PFTs and the RIs of the maternal and fetal circulations were examined. Normal ranges for the PFTs were devised and then the predictions of abnormal outcome were compared.

6.6.1 Testing for normality

The PFT results were tested for normality. If the distribution of results did not significantly differ from normal then the test result was employed, otherwise the results were logarithmically transformed. The transformed data was checked for normality.

6.6.2 Placental function tests and resistance index

As RI changes with gestation, and also some of the PFTs, partial correlation coefficients correcting RI and PFT for gestation were employed. Only BHCG had a significant positive correlation with AVRI (Table 67).

Although the coefficients were smaller still, BHCG, PAPP-A and HPL appeared to be significantly correlated to umbilical RI (Table 68).

Table 67 Partial correlation coefficients, correcting for gestation, of AVRI with PFT.

| Test | Log trans | n | Corr coeff | p | |
|--------|-----------|-----|------------|-------|-----|
| AFP | yes | 179 | 0.07 | 0.17 | NS |
| HPL | yes | 179 | -0.04 | 0.30 | NS |
| BHCG | yes | 179 | 0.21 | 0.002 | *** |
| PAPP-A | yes | 139 | -0.05 | 0.28 | NS |
| SP1 | no | 139 | 0.07 | 0.19 | NS |
| PP 12 | no | 139 | 0.09 | 0.15 | NS |

Table 68 Partial correlation coefficients, correcting for gestation, of UARI with placental function test

| Test | Log trans | n | Corr coeff | p | |
|--------|-----------|-----|------------|------|----|
| AFP | yes | 172 | <0.01 | 0.5 | NS |
| HPL | yes | 172 | 0.16 | 0.02 | * |
| BHCG | yes | 172 | 0.15 | 0.03 | * |
| PAPP-A | yes | 133 | 0.16 | 0.03 | * |
| SP1 | no | 133 | 0.22 | 0.17 | NS |
| PP 12 | no | 133 | -0.01 | 0.13 | NS |

6.6.3 Construction of reference ranges

The population was divided into 'totally normal outcomes' and 'some complication'. The definition of normals was the same as previously (Section 6.3.1). Normal ranges were then derived for this normal population. Only AFP, HPL and PAPP-A changed significantly with gestation between 16 and 24 weeks (Table 69).

Table 69 The regression equations of placental function tests with gestation (for normals only).

| PFT | Slope | Constant | Corr Coeff | RMS | N | Sign |
|------------|----------|----------|---------------|------|-----|-----------|
| | S | C | R | | | P |
| Log AFP | 0.021 | 1.195 | 0.48 | 0.23 | 103 | <0.001*** |
| Log HPL | 0.018 | 0.777 | 0.49 | 0.24 | 103 | <0.001*** |
| Log BHCG | -0.00469 | 10.00 | -0.09 | .008 | 103 | 0.18 NS |
| Log PAPP-A | 0.017 | 7.516 | 0.27 | .071 | 82 | 0.008 ** |
| SP1 | 228.9 | 4085 | 0.13 | .017 | 82 | 0.12 NS |
| PP12 | 0.0735 | 109.5 | 0.01 | .006 | 82 | 0.45 NS |

6.6.4 Prediction of complications

Using the whole population again, those with a placental function

test >95th centile were used to predict complications compared to AVRI 5. The sensitivity and specificity of the PFTs were all low (Table 70). However, several approached the Doppler screening test in ability to predict abnormal outcomes. High AFP predicted SGA and mild complications of pregnancy, but not the severest cases. High PP 12 also predicted SGA. High BHCG and PAPP-A predicted the severest complications of pregnancy. SP1 and HPL were similar to chance.

Table 70 Prediction of complications using high placental function tests (n = 183).

| PFT >95th centile | SGA 10 | | MILD | | SEVERE | |
|----------------------|--------|-----|------|-----|--------|-----|
| | SE% | SP% | SE% | SP% | SE% | SP% |
| AVRI 5 | 15 | 95 | 13 | 96 | 40 | 95 |
| Log AFP | 15 | 94 | 15 | 96 | 10 | 93 |
| Log HPL | 4 | 97 | 2 | 96 | 0 | 97 |
| Log BHCG | 8 | 97 | 5 | 96 | 20 | 97 |
| Log PAPP-A | 6 | 97 | 7 | 97 | 43 | 98 |
| SP1 | 0 | 96 | 2 | 96 | 0 | 86 |
| PP 12 | 17 | 93 | 9 | 92 | 0 | 92 |
| Prevalence % | 14.9 | | 34.7 | | 6.0 | |

Low levels of these PFTs have extremely low predictive properties in the same group of pregnancies (Table 71).

Table 71 Prediction of complications using low placental function tests.

| PFT <5th centile | SGA 10 | | MILD | | SEVERE | |
|---------------------|--------|-----|------|-----|--------|-----|
| | SE% | SP% | SE% | SP% | SE% | SP% |
| Log AFP | 0 | 93 | 8 | 96 | 0 | 94 |
| Log HPL | 0 | 97 | 2 | 97 | 0 | 97 |
| Log BHCG | 8 | 97 | 7 | 98 | 0 | 97 |
| Log PAPP-A | 6 | 91 | 13 | 93 | 0 | 90 |
| SP1 | 6 | 99 | 2 | 99 | 0 | 99 |
| PP 12 | 0 | 95 | 4 | 96 | 0 | 96 |

6.7 SUMMARY OF RESULTS

AVRI is a simple, quick test and missing values can be ignored in its calculation. Reference ranges were created. AVRI is related to gestation, A or U site, left or right side and the placental implantation site. It correlates with maternal heart rate, height and ORS and is lower in twin pregnancies.

UARI is related to gestation, fetal heart rate and sex. It

correlates with maternal age, height, race, ORS and smoking habit. PFTs are related to AVRI and UARI.

Pregnancies complicated by fetal wastage, APH, proteinuric hypertension, SGA <10th centile and neonatal morbidity have significantly higher mean AVRI. Mean UARI was higher in pregnancies complicated by SGA <3rd centile, severe proteinuric hypertension and premature prelabour CS.

AVRI predicts complications more accurately than other Doppler tests, ORS or PFTs. AVRI 5 has a positive predictive value of 67% for any complication, and of 25% for severe complications. Sensitivity is low, however, but reached 45% in blacks and 26% in primigravidae for the prediction of proteinuric hypertension. Lowering the cut-off produced unacceptably high specificities without producing > 50% sensitivity.

7. DISCUSSION

7.1 REVIEW OF THE METHODOLOGY

In this Section the limitations of the methodology are presented first and then the interpretation of the results is discussed (Section 7.2).

7.1.1 Technique

The continuous wave test is discussed and then the screening study itself.

7.1.1.1 Justification of the use of fixed points

There was a fall in resistance from the uterine to the arcuate vessels (see Section 5.1). This has also been documented in the first trimester (Stabile et al 1989). It was therefore decided to take readings from fixed points with reference to the uterus rather than uterine or subplacental readings. The CW Doppler test was not performed at the same time as the booking scan and there was no spare real-time machine available. Therefore the CW transducer could not be directed at the subplacental region under ultrasound guidance. As there seemed to be a fall in RI along the sides of the uterus, it was also possible that the fall continued from the edge of the placental bed inwards. Thus the

technique described by Trudinger et al (1985b) did not compare like with like when the centre of the placental bed was used for anterior placentae and the edge for posterior placentae. The virtue of the technique described here is that the points of insonation are fixed with respect to the uterus, although the position of the placenta varies. Points one and four (A and U) were chosen as they were maximally different and represented different parts of the uterine circulation. Choosing these sites allowed a comparison to be made with the previous techniques.

The four points may be no more representative of the total circulation than the previously described techniques and AVRI may not have any physiological meaning, but this does not really matter if they give an indication of abnormal placentation.

The four points and the angles subtended by the transducer were not absolutely fixed, as, for example, by using a tape measure, and the operator had to judge where they were, so there is some margin for error.

Whether the points actually insonate the uterine artery and arcuate arteries will only be established using colour flow mapping. However, in human pregnancy, arcuate arteries undergo a marked increase in diameter and some become as large as the internal iliac artery (Burchell 1967). This suggests that arcuate arteries can be insonated.

7.1.1.2 Pattern recognition

As this study was set up to assess screening using CW, it was considered that the waveforms would have to be identified only by site, sound quality and direction (see Section 5.3). Pattern recognition alone was used as CW relies on locating the vessels 'blind'. Checking of abnormal waveforms using PW Doppler was not performed. Firstly, it would have been time consuming when the essence of CW is that it is quick and convenient. Secondly, the exact definition of screening cut-offs awaited the results of the study. Also, if only high resistance waveforms were checked this would have introduced a bias into the study.

As readings were obtained from these four fixed locations, there was no element of choice of higher or lower RI waveforms and this was intended to reduce observer bias. There was a choice in picking a representative waveform for measurement of systolic and diastolic frequencies, but this was governed by choosing a waveform of maximum height (and thus minimum insonation angle).

The reliance on pattern recognition may have meant that some very abnormal uteroplacental waveforms were missed as they were not recognised as such. Also, internal iliac artery waveforms may have been included, mistaken for abnormal arcuate arteries. It is not possible to be absolutely sure that this did not occur. It was assumed that there is little or no flow in diastole in the

internal iliac artery and that the direction of flow could not be parallel to and up the side of the uterus.

7.1.1.2.1 In-vivo experiment

The intra-abdominal experiment was limited and only two cases became available. Case two must also be treated with caution because of the unknown effect of the ovarian tumour on the uterine blood supply. CW FVWs from the patient when awake and FVWs taken directly from arteries when anaesthetized may not be comparable.

Nevertheless, the uterine vessels all had forward flow in diastole and the internal iliac arteries none. This concurs with earlier work performed at the time of third trimester CS (Schulman et al 1986) validating the pattern recognition of the uterine artery.

The fall in RI after induction of anaesthesia may have been related to the effect of drugs on maternal cardiac contractility, an effect on the uterine circulation or just the increased pulse rate.

When the uterine artery was intermittently compressed for ten cardiac cycles, end-diastolic flow ceased and the FVWs became indistinguishable from that of the internal iliac. This directly

confirms that the diastolic portion of a FVW decreases with increasing distal impedance to flow. It also illustrates the possibility that when the uterine waveform is abnormal it may become indistinguishable from an internal iliac FVW. For a screening study, that would not matter if the abnormal uterine FVW was missed and the case was still correctly classified as abnormal, albeit on the basis of an internal iliac FVW. It would matter if a normal uterine FVW was missed and the internal iliac FVW was chosen.

There is no information about the normal range of internal iliac FVWs. No-one has studied how they vary in the various pregnancy complications. It is quite conceivable that internal iliac impedance indices change in IUGR and PET. There is a rise in total systemic vascular resistance (Gant and Pritchard 1987) and increased resistance in the placental bed could be transmitted back upstream to the supplying vessel.

Although there are very few descriptions of the internal iliac artery waveform, the external iliac artery FVW is obviously different from the uterine, with very high pulsatility and early reverse flow. There is a notable exception, after tensing and relaxing of the quadriceps muscle, when forward flow occurs and makes it indistinguishable temporarily from a uterine artery. This was one reason that an exercise study was not undertaken as it would have been appropriate only with PW or colour flow.

Further reassurance that pattern recognition of the umbilical and uterine arteries is possible comes from a comparative study of PW and CW in 85 women showing consistency between measurements, although the correlation coefficient for the uterine S/D was only 0.58 (Mehalek et al 1988). No difference was found between umbilical S/D ratios obtained by CW or PW (Brar et al 1989). No comparison was made in this thesis between CW and PW as PW was not used at any stage and small vessels are difficult to visualise. However, with the advent of colour flow mapping it is possible to visualise vessels and so a comparison study was performed.

7.1.1.2.2 Colour flow experiment

The RI of the uterine artery was not significantly different when identified by CW and pattern recognition or by colour flow mapping (Section 5.3.2). This does not indicate agreement or lack of agreement of individual values but does support the contention that the vessels insonated by the two techniques were the same. The limitations were that it only involved a small number of normal women who were not all in the second trimester.

The standard deviation from the mean RI was no different between the two methods, suggesting, that so long as the vessel is correctly identified, there is no increased accuracy by using colour flow mapping.

A potential advantage of duplex scanning or colour flow mapping is that the internal iliac will not be insonated. However, the manoeuverability of the transducers are limited by their larger size. Also, the equipment is expensive and the power outputs are higher.

Pattern recognition of the uterine artery relies on the fact that there is always forward flow in diastole. If there are situations where end-diastolic flow disappears then it would be virtually impossible for identification by CW. Only lower RI waveforms would be picked up, minimising the abnormality.

7.1.1.3 The choice of resistance index

In the measurement of impedance to flow, RI, rather than PI, was chosen. This is the index used in previous studies and it is unambiguous. There are different methods of calculating mean fd for the PI. The most precise measurement of PI, using a light pen to outline the waveform, is laborious. It is also not easy to make comparisons between centres. The author had participated in a multicentre European study on PI variability, which found a large difference between different centres working on uniform tapes of FVWs (Ruissen et al 1988). A/B is directly related to RI but has the disadvantage of varying in a non-linear fashion. Only one RI measurement was taken from each site. Other investigators have averaged a number of waveforms. Here, the

COV was satisfactorily low when AVRI was calculated from the four sites.

7.1.1.4 Errors

In the measurement of RI of individual FVWs of the uterine and umbilical circulation the intra-observer COV varied between 3.3% and 8.8% (Section 5.2.2). The mean COV for any uteroplacental vessel was 7.6%. The errors in the test were high. Calculation of AVRI brought the COV down to 3.9% which is very acceptable. These results are not very different from previous reports (see Section 1.6.2.1.1). Calculating the COV was chosen to establish the real error in measurement. Only systematic errors can be picked up by t-testing paired sets of measurements.

When the same test was performed an hour later the COVs of the uterine vessel increased (Section 5.2.3). This finding could be a consequence of a shrewd operator being able to return to the exact same spot immediately, or the increased error could represent biological variance. The Doppler test itself is not necessarily unreliable, but the system under test may be very variable.

One source of variation may have been the difference in maternal heart rates. Even though the mothers were rested, they had very different resting pulse rates, and pulse is not stable anyway.

Whether correction of the FVW by maternal heart rate, or the beat to beat time, would substantially improve accuracy remains to be proven. Certainly, for the UA, a correction formula for beat-to-beat length did not improve the COV (Hoskins et al 1989b). The variation of uterine and fetal FVWs with smoking, exercise, position, meals and diurnal rhythm were not studied as these effects have been reported (see Section 1.6.2.2).

Biological variance in uterine blood flow has also been described in some of the earlier works. When relative blood flow was measured indirectly using a cervical thermistor method it was shown that blood flows in frequent and irregular waves of 5-10 cycles per minute independent of contractions (Brotenek 1969). This is important and might explain some variation in resistance indices as the system is not a static one. Ramsey et al (1963) showed directly that the spiral artery supply of the IVS was constantly and randomly changing. Serial and cine-radioangiographic studies in Rhesus monkeys showed maternal blood entering the intervillous space in high pressure streams as funnel shaped jets, curtailed during contractions, but when successive contractions were studied the spiral artery spurts appeared and disappeared independently of one another. Also, successive series of angiograms without contractions showed differences in the pattern of arterial entries (Martin et al 1964), a 'winking and blinking' phenomenon. This suggests that there may be constriction or dilatation of vessels, irregular

localized myometrial contractions, or regulation of blood flow within the placenta.

7.1.1.5 Placental location

There was a difference in measurement of RI dependent on placental location (Section 6.2.3). This demonstrates the importance of accurate determination of placental position by real-time ultrasonography. In this study it was assumed that localization was unequivocal. However, it is recognized that this may not be the case and no reproducibility study was performed. The intra-observer variation in assignment of placental location has been quoted as 13% (Kofinas et al 1989). Apart from noting whether the placenta was left, right or central the rest of the localisation formed part of the routine scan. The definition of placental location was loose. Ultrasonographers were merely asked to describe where the bulk of the placenta was. However, despite potential inaccuracy, highly significant associations were discovered between placental location and uteroplacental FVWs.

7.1.1.6 Failure to obtain result

In 0.2% - 0.8% of cases there was a failure to obtain a uteroplacental FVW (Table 23). This is inconsistent with previous studies which have not reported failure rates. This

might be because the number of tests performed here was much higher. Other investigators may have disregarded failures or just moved to another site on the uterus. Only Hanretty et al (1989) have quoted a failure rate of 18% and 19% at 26-30 and 34-36 weeks. This seems surprisingly high, especially as their method involved moving the transducer around the uterus, but may have been due to pressure of time as examinations were performed in the antenatal clinic.

Since the CW method depended on pattern recognition a uteroplacental vessel with extremely high impedance mimicking an internal iliac artery could have falsely been described as 'not found'. If that was the case then the incidence of complications would be expected to be higher in these women. This may well have been the case for the one out of 16 who had a stillbirth (Section 6.1.3). However, the other vessels in the case of stillbirth had a high RI whereas the other vessels were normal in the other 15 cases with normal outcomes. Rather than missing high impedance vessels these cases seem to represent a genuine failure. Possibly some areas of the normal uterus do not have vessels from which signals can be obtained.

In 1.2% the test was subjectively difficult and these women had a higher mean RI (Table 22). So, although the missing test women did not have higher RIs, higher RI did relate to the difficulty of test (Section 6.1.2). High RI vessels might be harder to

locate because their diameter is narrower and there is also a reduction in the absolute number of uteroplacental arteries accompanying failed trophoblastic invasion (Khong et al 1986).

A recommendation that emerges from these findings is that, if there is difficulty in finding vessels, it is important to persist as the circulation is more likely to be abnormal. When it is impossible to find a particular vessel the remaining vessels are relevant.

The failure rate was higher on the right than the left which matches the subjective impression that it is harder to find right sided signals and can be attributed to dextrorotation of the uterus.

7.1.2 Screening procedure

7.1.2.1 Selection of gestation

The Doppler scan test was performed at the same time as the routine booking structural ultrasound scan as it was the only consistent gestation that pregnant women were seen in early pregnancy. The KCH policy is for every woman booking for antenatal care to have a booking scan and refusal is rare. It was not possible to estimate the cases lost due to refusal or booking at another hospital if a woman objected to this policy.

The choice of testing at the booking ultrasound scan allowed maximal recruitment to the study (supported by the findings in Sections 4.2 and 4.3) and would be an ideal time for applying the test in practice. Preselection of subjects has coloured the results of previous studies (Section 1.7.6). This method of selection may be a major reason for differences in results between this and the other screening studies.

The range of 16-24 weeks was chosen although it was wider than the intended scan timing of 18-20 weeks. If dates are changed it is rarely by more than four weeks. Other studies have had more limited ranges of 16-18 or 18-20 weeks or have done a two stage test at 20 and 24 weeks (see Section 1.7.5.2). Earlier gestation would have the advantage of allowing possible earlier intervention. However, CW assessment of the four sites is difficult under 16 weeks as the uterus is small. The upper limit was chosen as trophoblastic invasion is normally complete. If screening proved to be useful it would have to be performed in time for treatment or intervention. It is possible that the ideal time for screening might be earlier, if prophylactic treatments were to be considered that ameliorated failed trophoblastic invasion, or, later, after the demands of the fetoplacental unit have increased, when pregnancies with and without placental insufficiency have more clearly separated. The choice of gestation may explain the low predictive values of the test.

It might be postulated that the fetuses that were smaller than expected at the first booking scan were not wrongly dated but already suffering early growth retardation. If they were all redated they might be missed as small-for-dates at delivery and the results become biased. That it was valid to assume wrong dates with a discrepancy of more than ten days on ultrasound size is supported by the prediction of date of delivery (Campbell et al 1985b) and the finding of no difference in the mean AVRI between the groups where dates and scan agreed or disagreed. This suggests that they were not a different population of pregnancies.

7.1.2.2 Selection of subjects

The high prevalence of teenage pregnancies (12.1%), unmarried mothers (43.2%) and households with no earned income (28.2%) in the study group (Tables 5,7 and 8) reflects the social deprivation encountered in Camberwell, as in many inner London districts. There is a large Afro-Caribbean population (26.7% of the total, Table 6) in the area that is served by KCH. Overall, the study population is a heterogeneous one, and it must be emphasised that the results of this study apply to this population only. Care should be taken before extrapolating the results to similar or different populations.

There is evidence that the sample was unselected. By trying to

recruit everyone attending for a booking scan the study looked at as representative a population as possible. The outcome totals in Table 10 show that the study population was indeed very similar to the population delivering at KCH in a consecutive time period, even though the KCH population includes late bookers. The comparability of the study and KCH population (Table 9) suggests that it was a random sample. The loss of diabetics and abnormal fetuses is not serious and does not affect the overall conclusions.

7.1.2.3 Reduction of bias

Minimal bias was ensured by not giving the mothers or their clinicians any information about the screening study. This was to prevent the screening test from affecting the outcome. A revealed test can potentially affect the outcome in either direction. For example, knowledge of an 'abnormal' test might worry a mother or her clinician and lead to repeated and high BP readings, converting an otherwise false positive test to a true positive one. Conversely, increased surveillance in a similar woman might lead to earlier delivery and avoidance of a late stillbirth, converting an otherwise true positive test to a false positive one (and vice versa for 'normal' tests). Of course, if a study woman had a late Doppler scan as part of her clinical management the outcome might have been affected but she would have had an indication for it unrelated to the screening test.

The test result was strictly confidential and women were not asked to return on the basis of the result, so one can be confident that it was truly unbiased.

This is different for the repeat and placental function test study populations. They were not randomly selected but were volunteers, having a repeat scan for some clinical indication or recruited after the Doppler test. Indeed, the prevalence of complications was higher in these groups (Tables 65 and 70).

Observer bias was also reduced by not asking about the obstetric history at the time of the scan. Only three enquiries about smoking, bleeding and school-leaving age were made. Smoking was recorded at the time of the scan as the intake might have changed since booking. Bleeding might also have occurred in the intervening period. Age on leaving full-time education was recorded as a potential discriminator of social class in single unemployed women, but was not eventually required. It was also used to detect differences between subjects with and without booking information.

7.1.2.4 Data collection

In this study the past obstetric history and demographic details were taken from the computer. It might perhaps have been more accurate to take the booking history at the time of the screening

test, but it was a deliberate policy to avoid potentially influencing the observer in the search for waveforms. The validation exercise showed that the data collected by the computer was accurate enough.

For practical reasons, all the medical notes of complicated cases had to be reviewed by the author. It is possible that bias was introduced at this stage, but it was minimised by keeping the initial test results locked away and by obtaining an independent assessment of the diagnoses. The coding of all the medical diagnoses was cross-checked with two other obstetricians.

7.1.2.5 Definitions

To avoid some of the problems of definition, hypertension and SGA were divided into degrees of severity. This also enabled an analysis of a type of 'dose response', comparing different degrees of severity of SGA.

The use of a mixture of local KCH weight nomograms and premature nomograms was a necessary compromise to be able to calculate standard deviations of birth weight from the mean expected for gestation. The mean and SDs of birth weight were calculated directly from the Gairdner and Pearson graphs as there were no figures in the original paper. This was considered valid as the charts are those used in the hospital, and as the weights meet

the KCH population at 36 weeks. Other nomograms did not match the KCH population. The premature charts were constructed in 1971 and the KCH nomogram was derived from data from 2 - 5 years prior to the study. It is possible that demographic changes might have occurred and made them inapplicable for the local population. However, the percentage of SGA <3rd, <5th and <10th centiles was 3.3%, 5.7% and 12.9% respectively, which suggests that the charts used were appropriate.

Birth weights were not adjusted for parity, sex, race or maternal height and so the categories of SGA are imprecise. Despite this, differences in RI in SGA babies were found, and predictions could be made. The predictions might be improved if one could accurately assess each individual baby's expected birth weight or underlying potential, but this is impossible at present.

7.1.2.6 Missing data

The very high response rate to the postal enquiry and small number of lost outcomes (34/977, 3.5%) indicate that the search for missing data was thorough, especially when the number of women who moved during their pregnancies is considered.

Group one (no booking data) left school younger than the rest of the population and their average uterine RI was slightly higher, but not significantly (t-test). There was no significant

difference in smoking habit or incidence of threatened miscarriage (chi-square). There was no significant difference between the cases with outcome data and those in group two (no outcome data), when compared on the basis of age, parity or mean uteroplacental RI (t-tests), or race or social class (chi-square). The obstetric risk score, ORS (Adelstein and Fedrick 1978), for the group two was not significantly higher than that for the rest of the population. The ORS is always one when booking data is missing so it was not compared for group one cases.

In summary, although there is some evidence that the cases for whom all data was not available may be more socially disadvantaged, the cases that were lost between performing the test and delivery are comparable to those with full information. The missing data do not appear to belong to a socially disadvantaged group. By showing minimal differences between the women with and without booking or outcome data, the results can be confidently assumed to represent the whole population.

7.2 INTERPRETATION OF THE RESULTS

The results are discussed in the order: factors affecting the test, findings in complicated pregnancies and then the screening results.

7.2.1 Parameters affecting the test

These were divided into maternal and fetal factors.

7.2.1.1 Maternal factors

7.2.1.1.1 Blood pressure and pulse

Mean uterine RI was inversely related to pulse and BP (Table 31). The significant effect of BP was present for the uterine arteries (AVU) but had disappeared when the arcuate values were included (AVRI) (Table 31). This could represent a dampening effect as the pulse wave travels into the uterine circulation.

Despite a highly significant effect of pulse (Tables 31 and 40), RI values were not corrected for maternal or fetal heart rate. This was partly because the correlation coefficients were so low and heart rate accounted for less than 4% of the variation in RI (correlation coefficient²). Also, it should probably be performed on-line on a waveform analysis programme (thus the

advantage of complicated indices such as FIP). There is such disagreement and disarray it is not clear at the present moment which indices will survive and contain maximal information, nor which method should be used for correction of heart rate.

7.2.1.1.2 Smoking, 'flu-like illness, threatened miscarriage

Smoking is known to have an effect on fetal size (Butler and Alberman 1969). It might be postulated that maternal smoking decreased uterine blood supply by arteriosclerosis or a vasoconstrictive effect of nicotine. No differences were found between smokers and non-smokers, however heavy their intake (Table 32). It would seem that the effect of smoking is not mediated through the uteroplacental circulation, but must be a direct one on the fetus or placenta. This is supported by the finding of higher UARI in smokers (Table 35)

Mean AVRI was lower in cases where there had been a 'flu-like illness in early pregnancy (Table 32), although there was no difference in UARI (Table 35). The question was asked to identify possible early infections such as cytomegalovirus that could be associated with SGA. If a 'flu-like illness is related to viral infection and SGA, this finding might represent a successful attempt to compensate for placental damage. It could be a spurious 'significant' finding.

Defective placentation is associated with recurrent miscarriage (Khong et al 1987). Therefore one might expect to find a difference in RI in cases of miscarriage or threatened miscarriage. Minor differences in the rate of fall of uteroplacental RI have been found in first trimester threatened miscarriages (Stabile et al 1988a). However, there were no significant differences here in AVRI or UARI values in cases with or without a threatened miscarriage (Tables 32 and 35). As an episode of threatened miscarriage was not followed by a difference in RI in the maternal circulation, it is not analogous to the later APH (where an association with AVRI was found, see Table 43).

7.2.1.1.3 Social factors

The only maternal social factor significantly, and negatively, correlated to AVRI was height (Table 33). The explanation possibly lies in the attenuation of the waveform from the heart downstream. There is a known dampening of FVW shape with distance from the heart (MacDonald 1974). The length of vessel from the heart to the uterine artery is longer in tall women than short women which may explain this finding. However, UARI was also negatively correlated to height. It is possible that UARI was lower secondary to AVRI, if another factor common to tall women, such as better nutrition or social class, had an effect on trophoblast invasion.

AVRI was not related to maternal weight or age. UARI was negatively correlated to maternal age. This is surprising and unlikely to be a reflection of increasing parity with age, as UARI was unrelated to parity.

AVRI was highly significantly positively correlated to ORS (Table 33). This might be due to the effect of height as one factor in the calculation of ORS, or to the effect of a previous stillbirth or low birth weight baby, leading to a high AVRI in the studied pregnancy. UARI was also positively correlated to ORS (Table 36). Although the ORS was devised to predict SGA at birth, it seems to be related to both maternal and fetal blood flow in the second trimester. This also lends support to the theory of reduced blood flow causing growth retardation.

Although the association of lower social class with higher perinatal mortality and with lower birth weight is well established (Chamberlain 1975, Macfarlane and Mugford 1984) the present study found no relationship between social class and AVRI (Table 33). This suggests that the mechanism by which social factors have an adverse effect on pregnancy is not mediated through the uteroplacental circulation. This is supported by the association of lower social class and higher UARI (Table 36). Improvement in social factors (maternal age, parity and social class) have been estimated to account for only a quarter of the fall in perinatal mortality between 1950 and 1973 (Hellier 1977).

7.2.1.1.4 Race

Other screening studies have not mentioned the racial distribution of subjects nor differences found between races. There is known to be a poorer perinatal outcome in women from Africa, the Indian subcontinent and the West Indies (Macfarlane and Mugford 1984) with strikingly higher perinatal mortality rates amongst women from Pakistan (Balarajan 1989). The study population had few women of Asian descent. No differences in AVRI were found between races (Table 34) although there were differences in UARI (Table 37). African women had fetuses with slightly higher mean UARI. This might reflect a genetic difference or some concurrent social factor that contributes to the worse perinatal outcome.

7.2.1.1.5 Parity

There is a 'J' shaped association of parity with perinatal mortality (Chamberlain 1975). First babies weigh less than subsequent ones (Thomson et al 1968). This study found no relation of AVRI to parity (Table 33). This suggests that the mechanism again lies outside the uteroplacental circulation. Unless each fetus somehow 'knows' where it is in the birth order, the explanation has to lie in the interaction of placenta and uterine supply, increased efficiency of transfer of nutrients or a direct effect on the fetus related to maternal age (for

example, to do with growth or insulin like hormones). The other possibility is, that, as resistance can be the same for different volume flows to the uterus, with increasing parity blood flows into the uterus with an increased 'head of pressure'. This may be due to different circulatory characteristics that change with age.

No difference in AVRI between women of parity 0 + 0 and 0 + 'any' was found. This might have been expected because of the relation of primigravidity with PET, although a first trimester abortion does not necessarily confer 'immunity' to severe PET in a subsequent pregnancy (Campbell et al 1985a).

7.2.1.2 Fetal factors

7.2.1.2.1 Twins

In the 14 twin pregnancies mean AVRI was significantly higher than in singletons (Table 38). Perhaps, if resistance was only determined by trophoblastic invasion, the explanation is that there is more trophoblastic invasion in twins (or the development of even more low resistance vessels related to a greater amount of trophoblast) or the process was completed earlier. It could be that some other factor in twin pregnancies, such as higher hormone levels, determines the lower resistance. Greater volume flow to the larger uterus in twin pregnancies might be achieved

by this decreased resistance, in anticipation of greater nutritional requirements.

Twin pregnancies were left out of further analysis because they are associated with an increased rate of pregnancy complications, they are different physiologically and their mean AVRI was so different. Although there is a normal range for UA S/D (Gerson et al 1987a) there is no normal range for uteroplacental FVWs in twin pregnancies.

7.2.1.2.2 Fetal sex

Although the gap is narrowing, there is a male excess of stillbirths and neonatal deaths over females (Macfarlane and Mugford 1984). Even in very premature babies, males have a worse prognosis than females (Brothwood et al 1986). One might therefore expect to find worse uterine and umbilical Doppler parameters in males. Even at five months of fetal life a sex difference in fetuses is observable (see Table 41), but it is female fetuses who have a small but significantly higher UARI than male fetuses. AVRI was not related to fetal sex (Table 39), suggesting that this is a primary fetal phenomenon, rather than secondary to poor placentation. There might be slight histopathological differences between male and female placentae. The finding of higher UARI in female fetuses may therefore represent a slight stress to which females adapt, making them

less vulnerable or developmentally more mature.

Second trimester FHR and sex were not related (Section 6.2.7.3). This finding refutes an 'old wives' tale' that fetal sex can be predicted from FHR.

7.2.2 Reference ranges

7.2.2.1 Variation around the uterus

The RIs from the fixed points have highly significant correlations with one another (Table 24). This is not surprising as they are all part of the same circulation. This lends support to the concept of an average resistance, or overall RI, incorporated in AVRI, and to the concept of a complex uteroplacental circulation (Bewley et al 1989) rather than a single supply point.

The differences between the placental and nonplacental side and the U and A sites demonstrate the value of using standardized insonation sites as there can be up to 50% difference in the mean RI between a 16 week NPU and the 24 week PA (Figure 16). The second trimester is the time of maximum change in resistance (Schulman et al 1986, Pearce et al 1988, Cohen-Overbeek et al 1985) and the differences will be most marked at this time.

The statistics and reasoning for the construction of the reference ranges has been discussed in the methodology. RI was chosen because it varies linearly. It was found to be normally distributed which enabled the use of parametric statistical tests. It also has the advantage of varying only between nought and one and thus the waveform of any value is easily visualised.

The value of all the calculated reference ranges is that small differences in technique, and choice of vessel may be crucial in the assignment of normality in a screening programme.

The fixed points chosen standardize the method of insonation and enable a detailed understanding of the effect of the placental location on RI values. The lower point examines the uterine artery near its origin from the internal iliac artery. The distal point is specific in relation to the uterine wall and insonated distal branches of the uterine artery or arcuate arteries. These would have been at a variety of distances from the centre of the subplacental bed, depending on the position of the placenta.

The rapid fall in resistance in the gestation period studied provides support for the hypothesis of trophoblastic invasion of the spiral arteries and their conversion to low resistance uteroplacental arteries in normal pregnancy, although this is thought to be complete well before 24 weeks (Pijeneborg 1980) and

only takes place in placental spiral arteries. Resistance continues to fall throughout the period studied. Another factor may be a continuing hormonal effect on elasticity of arterial walls, such as is seen in the mesenteric artery in animal studies (McLaughlin & Keve 1986) and this may explain why resistance falls in all sites. Also, the uterine circulation has many collaterals and a fall in resistance in the placental bed may be transmitted to all parts of the uterine circulation. The fall in resistance with placental location and with distance from the origin of the uterine artery can be explained by the nature of the complex and branching circulation. There is an increasing total cross-sectional area as the uterine artery branches from its origin and pressure and resistance fall continuously from the uterine artery to the intervillous space.

When the placenta is posterior, RI values are higher (Table 29). The U and A sites are not on the lateral border of the uterus, but on the anterolateral wall and so will be nearer the centre of the placental bed when it is anterior and further when it is posterior.

When the placental location appears central on the ultrasound scan, right sided RIs were lower (Table 30). These findings can be explained by dextrorotation of the uterus. Although dextrorotation means that a placenta that looks 'central' on the scan is actually slightly nearer the left uterine vasculature,

the effect is cancelled out by the rotation bringing proximal branches of the left uterine artery nearer the fixed LU and LA insonation points on the abdominal surface and more distal branches of the right uterine artery towards the RU and RA points. This adds support to the concept of a uteroplacental circulation 'tree', with a fall in RI from trunk to twigs.

7.2.2.2 Serial and postpartum study

The serial values (Table 27) are based on several measurements from normal subjects rather than cross-sectional data. The ranges concur with other studies. As the numbers of women in each four week period varies, no statistics were performed on the results. The graph (Figure 18) shows a steeper fall in resistance in the second than the third trimester.

The postpartum study can clearly be criticised as it incorporates very small numbers, the time intervals are not equivalent, the latest study was made at only one week postpartum and the standard deviations are wide (Table 28). However, tentative information can be gleaned. Contraction and retraction of the oblique fibres of the myometrium compress the blood vessels supplying the placental site after placental separation. If RI was related to the total organ resistance or was inversely related to volume flow through the uterus, then one might expect this sudden event to be followed by a sudden increase in AVRI.

However, the mean AVRI immediately postpartum is similar to the term pregnant value (Figure 18). This finding has not been reported before. Thus, this study illustrates the point that RI and resistance are not equivalent to flow. It also begs the question how RI and resistance are related in the postpartum uterus.

AVRI rises over the next few days, bringing it towards the high impedance non-pregnant FVW (Long et al 1989). Uterine artery RI has been found to be higher than mid and late pregnancy values by one week postpartum (Baumann et al 1988), but the study did not look at women immediately post delivery. More work is required in the puerperium.

7.2.2.3 Comparison with other normal ranges

The reference ranges described in this thesis (Tables 25 and 26) differ from the previously published normal ranges (Trudinger et al 1985b, Schulman et al 1986, McCowan et al 1988, Pearce et al 1988, Al-Ghazali et al 1988) but contain many more cases and were not derived from retrospectively defined normal patients. Nevertheless they may not be representative of all populations. When the previously published data were compared on the basis of what part of the uteroplacental circulation was studied than they corresponded with one or other of these ranges. Trudinger et al (1985b) using CW, serially studied uteroplacental waveforms from

under the placental location, or the edge of the placenta if it was posterior, in 12 normal women. Their mean RI for the second trimester was lower than the PA value but they were insonating centrally under the placenta whereas PA is a fixed position on the lateral uterine wall. If resistance continued to fall, as expected, from the edge of the placenta inwards then this would explain the discrepancy. McCowan et al (1988), using the same CW technique, reported an even lower normal range.

Schulman et al (1986) described a technique using CW, for obtaining uterine artery FVWs and averaged left and right readings. Between 16 and 26 weeks they had only 38 readings made by the abdominal route but these were similar to the mean NPU values. Only one normal range had the impedance index corrected for maternal heart rate (Pearce et al 1988), but it was still similar to the U ranges, and was probably insonating the uterine artery near the origin with PW (Campbell et al 1988). Al-Ghazali et al (1988) provided a range for the uteroplacental bed that demonstrated a fall in impedance, as assessed by a rise in D/S ratio up to term, but the exact method was not described.

Three of the four normal ranges were parallel (Figure 15), but the RI in the PU falls at a slower rate with gestation than the others (Figure 16). It is unclear why this should be so.

The work showing the effect of placental position and uterine

site is important as it demonstrates just how complex the circulation is, and gives an important clue as to the reason for variation in results and apparent inaccuracies in the test.

7.2.3 Uteroplacental flow velocity waveforms and outcomes

There were highly significant associations between mean AVRI and abruptio placentae, proteinuric hypertension, premature delivery by CS and SGA (Section 6.3). There was also a significant association with perinatal mortality (though the numbers were small) and neonatal morbidity.

7.2.3.1 Abruptio

The association of RI with abruptio (Table 43) is possibly of value as, at present, there are no routine methods to predict it apart from clinical suspicion. The finding also suggests a common underlying pathology for abruptio with PET and IUGR. There has only been one case report of this association of abruptio and high uterine RI (Morrow and Ritchie 1988).

7.2.3.2 Hypertension

There was a difference in the association of uteroplacental FVWs with proteinuric and nonproteinuric hypertension (Table 44). This suggests that, even at this gestation, they are quite

different diseases pathologically.

The clear distinction between proteinuric and nonproteinuric hypertension suggests that defining PIH on the basis of increased BP alone (eg Hanretty et al 1988) will include two different disease entities. This may not matter in the clinical management of patients but it has been suggested (Chesley 1985) that, for research purposes, PET should only be diagnosed in primigravidae with proteinuria. However, the need to confine the diagnosis to primigravidae contrasts with the finding here of equivalent prediction of PET whatever the parity. Possibly the local population had a high rate of change of partner and so the distinction between first and other pregnancies genetically or immunologically can not be assumed.

Pre-eclamptic women did not have a significantly higher proportion of cases of U:A ratio < 1 than normals, in contrast to growth retarded pregnancies (Table 49). This finding differs from an Israeli study (Leiberman et al 1988) showing that waveforms from the fundal region in women with PET were even more pulsatile and of higher resistance than the uterine waveforms.

7.2.3.3 Small-for-gestational-age

The relation of each vessel to SGA showed that AVRI as an overall assessment of uteroplacental flow had the highest correlation to

delta birthweight (Table 48). The arcuate values had higher correlation coefficients than the uterine, suggesting that it is the final supply to the intervillous space that is important in fetal growth.

This observation was supported by the finding that reversal of U:A ratio was associated with the complications of SGA, prelabour CS and induction for postmaturity. The increased proportion of U:A <1 in SGA (Table 49) suggests that not only are the absolute RI values high, but there is also a change in the relative resistance of the arcuate and uterine vessels, or the distal and proximal parts of the circulation in IUGR.

Because the correlations to delta birth weight were for all birth weights, not just those babies < 10th centile, this work supports the concept that some babies can be > 10th centile but still growth retarded, ie have not reached their genetic potential.

If the correlation of SGA and RI improves on approaching the intervillous space, the UA RI might be expected to have the highest correlation coefficient. Although the placental arcuate correlation with delta birth weight was higher than other vessels, the UA RI had a low correlation (Table 48). This might suggest that, at the gestation of the study, the fetoplacental circulation had not yet become impaired.

The absence of significant associations with parameters of fetal distress (Table 47) may be because the cause is often multifactorial. Other stresses apart from reduced blood supply lead to a compromised fetus and some factors can intervene before delivery to prevent it. Although Campbell et al (1986) had one case of birth asphyxia with an abnormal arcuate FVW in their series, Arduini et al (1987) found that the predictions of PIH did not improve when perinatal distress was also considered, and Hanretty et al (1989) found no relation of uterine FVW with low Apgar score. The failure to find an association of AVRI and UARI with parameters of fetal distress is therefore consistent with previous findings in smaller studies.

Mean AVRI was higher as the degrees of SGA increased (Table 46) suggesting either that there is a kind of dose response (higher RI leads to less nutrition) or that other causes of smallness are excluded (ie SGA <3rd centile is a more homogeneous group).

The highly significant associations of AVRI with proteinuric hypertension, abruptio and SGA strongly support the hypothesis that failed trophoblast invasion early on is the common underlying pathology.

7.2.4 Umbilical artery flow velocity waveforms

UARI was significantly associated with only a few abnormal

outcomes (Section 6.4). However, there was a significantly higher mean UARI in severe proteinuric hypertension (Table 52), prelabour premature CS (Table 53) and SGA <3rd centile (Table 54). This suggests that fetuses are largely unaffected by reduced uterine blood supply at this gestation, but that they are affected in the severest cases. The changes in fetal circulation seem to occur after the maternal and this may explain why they seem to be less useful for screening at this gestation than AVRI. The UA waveform is not an accurate screening test for SGA even at later gestation (Beattie and Dornan 1989).

A low UARI was associated with spontaneous premature delivery (Table 53). This was not because the assumption about changing dates was wrong, as the uterine RI would also have been expected to be affected. Maybe low resistance (and by implication high UA flow) is a sign of maturity and, in some way, signals the onset of labour.

7.2.5 Placental function tests

If the peripheral blood level of a placental protein is proportional to its production and the blood flow away from the placenta, then a close correlation between RI and PFTs might be anticipated. The interpretation of the low correlation coefficients of PFTs with both AVRI and UARI (Tables 67 and 68) must be that, either RI does not reflect placental blood flow, or

that the above concept is wrong.

Only BHCG was significantly correlated to AVRI (Table 67). BHCG, PAPP-A and HPL were significantly correlated to umbilical RI (Table 68). It might be suggested that they would increase *pari passu* with appropriate placental growth and development and thus increased flow (and by implication decreased resistance and low RI) would be found with increased levels of PFT. However, increased RI was related to increased hormone. The assumption that high flow is found with low RI may be incorrect or this might suggest that damaged placentae release or leak more hormone, while healthy placentae remain intact and impermeable.

Although both had low sensitivities, the Doppler test was more accurate than the PFTs in the prediction of most complications (Tables 70 and 71). High AFP, PP12 and PAPP-A predict SGA, which corresponds with the third trimester experience. PAPP-A was capable of predicting the most severe complications. Low levels of PFTs had extremely low predictive properties. The results were lower than those documented in Section 1.7.4.3, partly because 5th and 95th centile cut-offs have been used rather than 10th and 90th. Still, the inability of low HPL to predict SGA contradicts the well established findings later in pregnancy. If it is related to placental damage secondary to poor uterine supply, then low levels may be only be found in the third trimester.

7.2.6 Screening results

The screening results were low, even though the top 5% of the screening tests contained 15 - 33% of each complication, and an individual's relative risk increased from 2.8 - 8.2 (Table 56). Any individual woman's risk of having complications was multiplied several times by having a high AVRI.

The predictive values were high when the test result was very high. Thus, in the AVRI 5 group, a woman had a 25% chance of a very serious complication, and a 67% chance of one probably requiring investigation or admission to hospital (Table 57). So, the test defines well a high risk group of women. This may be acceptable for collecting a group for research purposes and for any individual woman who could have increased surveillance or antenatal care, but in routine practice the majority of women with disease would be missed. False reassurance can lull the woman and clinician into complacency and can form the basis for litigation for missed disease.

7.2.6.1 Effect of different cut-offs, parity and race

Despite analysing the data in a variety of ways, the predictions were not greatly influenced. As the numbers were small and the test always poor, statistical comparisons were not made, but indications as to how the test could be improved were gathered.

The test can have an improved sensitivity by use of a lower threshold for the definition of abnormality. However, the specificity fell to below 73% before the sensitivity reached 50% for severe complications (Table 59). This means that over a quarter of the population have to be defined as abnormal even to pick half of those with disease. This would not support the introduction of Doppler on a routine basis.

When the test was repeated in the same population, the sensitivity of predicting proteinuric hypertension and mild complications worsened, in contrast to the findings in Table 65, where the values were higher in the later gestation group. This may be because it was not valid to extend the reference ranges beyond 25 weeks' gestation. However, the average gestation for test two was 23 weeks. It may be the numbers of abnormal tests are too small to make meaningful comparisons. The explanation for different predictive values in the groups above and below 20 weeks could be that the populations are somehow different, but sensitivity and specificity are unaffected by prevalence of disease.

This is an important discrepancy as Steel et al (1988) used a two stage test in their work. However, they only asked women with FVWs with an RI >0.58 to return and based the predictions on the second result. On the basis of the results presented in this study, it is not possible to say whether a two stage test is

better, as the repeat study consisted of women with both normal and abnormal FVWs.

Increasing gestation improved the positive and negative predictive values of the test (Table 60 and 65), as did performing it in Afro-Caribbean women (Table 64), so there are suggestions that changing the exact application might make the test useful. The screening test AVRI 5 was more accurate than ORS in the prediction of problems (Table 62). AVRI was more accurate than WORST RI (Table 58).

There is a large difference in the sensitivity of the test for prediction of PET in Afro-Caribbean women (Table 64), and yet no difference in mean AVRI between any racial groups (Table 34). There are racial differences in PET although they are not apparent at 16-24 weeks' gestation. This might suggest that in Afro-Caribbean women, PET is more severe, with higher AVRI values, and therefore more disease is correctly predicted. Alternatively, more hypertension in Caucasians is labelled PET when it is not associated with abnormal maternal circulation and may be essential hypertension. The World Health Organization (WHO) has found that, in the second trimester, there are similar blood pressures between races despite very different incidences of PIH later (WHO 1988).

The screening test was similar when used in primigravid or

multigravid populations (Table 63). This was surprising as the most strict criteria for definition of PET include primigravidity (Chesley 1985) and severe proteinuric hypertension in a multigravida is regarded as suspicious of other disease.

7.2.6.2 Comparison with other screening studies

The sensitivity and specificity of the test were different from previous reports (Campbell et al 1986, Arduini et al 1987, Steel et al 1988b) but there are possible explanations.

This investigation was performed using CW Doppler rather than PW duplex scanning, and although validation was obtained, blind 'pattern recognition' might have mis-identified vessels.

The test was performed with the observer unbiased to clinical information and a history of previous complications, whereas, in Arduini's study for example, all the patients were known to be high-risk. It was also performed as a part of the ultrasound clinic routine and thus probably took less time, although no paper has reported how long Doppler examinations take. This was a deliberate move to find out how well the test worked in realistic conditions.

The author may have been less skilled than previous investigators in obtaining the correct, highest quality FVWs. However, this CW

test was being performed as a research project by one operator and the cumulative experience was considerable. Therefore, even if the skill was lower than before, the test might be expected to perform more accurately than when applied in an everyday setting.

A different methodology was employed in that an overall average RI was calculated. This had the highest correlation with delta birthweight, suggesting that it gave an indication of the whole uterine circulation. Other investigators have used the average of two uterine FVWs (Schulman et al 1986), the worst FVW (Campbell et al 1986, Arduini et al 1987) or even the best FVW (Hanretty et al 1988) as the marker of abnormality. In this study, there was no marked difference in the screening parameters of AVRI and WORST RI. Other studies have often averaged several consecutive waveforms whereas in this study only one representative waveform was measured, and then the four sites averaged.

The cut-off of >95th centile for gestation was thought to be a suitable cut-off for abnormality, and although the sensitivities are low at this cut-off, the specificities are high. Using the original cut-off of 0.58 gives sensitivities comparable to the other papers although the specificities are lower. Even with a cut-off of 0.58, Campbell et al (1986) defined 30% of the population as abnormal. The AVRI index is made up of arcuate and uterine vessels therefore even more of the population would be

defined as abnormal.

This study had a substantially higher follow-up rate than the other two second trimester population screening studies (Campbell et al 1986, Steel et al 1988b).

In conclusion, although the findings are different from other studies, there is no reason to doubt their validity. The associations with disease fall between the initial optimistic results of Campbell et al (1986) and the entirely negative results of Hanretty et al (1989).

7.3 THE VALUE OF SCREENING

In this Section, only screening of the uteroplacental circulation is discussed as the fetoplacental screening parameters were so poor.

7.3.1 Explanation of screening results

The data demonstrated that the sensitivity and specificity of CW Doppler of the uteroplacental vessels in the prediction of pregnancy complications is lower than previously reported.

The overlap in second trimester AVRI between normal and abnormal outcome pregnancies could be due to a number of reasons:

a) The test has low reproducibility. This has been demonstrated, but when it is most reproducible in the form of AVRI the coefficient of variation at 3.9% is acceptable. It may be that the test is accurate but that uteroplacental resistance itself is not static and is very variable in both normals and abnormal.

b) The definitions of outcome are inadequate. All the diseases or outcomes are actually heterogeneous mixtures of different underlying pathologies. Small-for-dates is a heterogeneous group of pathologies. There was a kind of 'dose response', with increasingly high RI with decreasing centiles of delta

birthweight. This suggests that the Doppler test may be correctly distinguishing the diagnosis of 'starved' (as not all babies end up below the 10th centile) rather than absolute low weight. There is a problem in that there is no assessment of a particular fetus's growth potential, or 'loss of expected weight' that might be more related to uterine blood supply and fetal damage.

c) The mother and fetus may have mechanisms which compensate for or overcome the restricted uterine blood supply. There is a functional reserve capacity of the placenta. Loss of a third of the villous parenchyma can take place without an effect on fetal growth, development or viability (Fox 1983).

d) There is always overlap between normal and abnormal. No obstetric test is 100% sensitive or specific.

7.3.2 The false positive test

A false positive test might be explained by compensatory mechanisms that overcome deficient placentation. The placenta, which has overcapacity, may be able to redistribute blood locally away from scantily supplied and perfused segments and protect fetal growth. Delivery may supervene before the development of a stillbirth or PET. There may be much more overlap of normal and abnormal FVWs at this gestation than later in pregnancy. Some

normal pregnancies may still not have reached their minimum resistance by 20 weeks.

7.3.3 The false negative test

A false negative test might arise during sampling of such a large circulation if there is a mixed population of vessels. Although the previous studies suggest that the FVWs are not greatly influenced by time of day, meals, smoking, exercise and posture (Sections 1.5.2.2 and 1.6.2.2) and that the test is reproducible, there may be erroneous false tests entirely due to biological variance. Only normal pregnancies have been studied in this way and there may be much greater variations or instability in the abnormal pregnancy. Abnormal uterine waveforms may only develop later in pregnancy, after the time of the screening test. In early onset PET, cases of underlying renal disease may be undiagnosed and add to the false negative rate (Ihle et al 1987).

7.3.4 Improvement of the test

To improve both the sensitivity and specificity of the test at the same time, an improvement has to be made in the test itself or in the skill of the test operator or interpreter. Receiver operator curves (ROC) have been used to compare one screening test with another (Richardson et al 1985) but were not used here because all the sensitivity and specificity results were too low

to consider the test for routine practice. A test with a low ROC might be acceptable if it were fast, easy, safe and cheap or the result was not vital. However, the point of screening in early pregnancy for these conditions must be to institute some form of treatment or surveillance and a high ROC would be required.

The test needs to be refined, possibly by the use of the PI, waveform shape or other computerised waveform analyses. It might not be accurate and reliable because resistance is a fluctuating phenomenon, in which case there may be improvements but not enough to make screening worthwhile.

It has been demonstrated that the screening test is quick. An average time of 6.5 minutes is short for a screening test, and it can be assumed to take ten minutes maximum including documentation. By comparison with, for example, the ORS which could be calculated easily by computer, a Doppler screening test is not fast, cheap or easy, although it might take about the same time as a "roll-over" test. Also, with less than 1% failures to obtain readings it does have to be repeated. At 9,500 per machine that should last five years, and 10,000 for a half time radiographer, a screening programme for a unit of 3,500 deliveries would cost under 12,000 a year to run (1988 prices). A screening test has to be easy, cheap, convenient, quick and non-invasive to be useful in clinical practice. Although the Doppler test fulfils these criteria, its accuracy would have to

be improved first.

This study does not support the contention that "the... claim that Doppler study of the arcuate artery at around 18 weeks is a useful screening technique... does not stand up to critical analysis" (Neilson 1987). It has been shown that many complications can be predicted from a very early stage but not with great enough accuracy for widespread adoption. The usefulness may be limited but there is clearly much information available in the uteroplacental FVW.

However, it might be possible to use the screening test to determine an appropriate level of care. If the cut-off is high enough an investigator can collect a very high risk group before clinical signs have appeared. It might be worth treating this group prophylactically with drugs or physical therapies. But at this cut-off there is a low sensitivity, and most cases of disease would be missed. If the cut-off was low, then, with the knowledge of low risk, women could be given decreased routine, or patient-demand antenatal care. This system would have lower cost and facilitate effective use of expensive resources. The problem is that using a high cut-off hardly reduces the risk for the remainder, and they would still require the basic antenatal care they receive at present. Using a low cut-off creates unacceptably high numbers of 'abnormals'.

The test might be useful in limited populations rather than all pregnant women. It performed better in black women than white, for example, and has high predictive values in a high risk population (Arduini et al 1987).

With increasing use of Doppler and more understanding of waveform shapes the operators and their training might become more skilled and thus the usefulness of the test become greater.

7.3.5 Potential hazards of screening

The safety of Doppler ultrasound is not guaranteed, and it would seem prudent to restrict its use to defined clinical situations for the present.

There is certainly a powerful psychological effect and evidence of both anxiety and bonding at an ultrasound scan (Stewart 1986). Although no information was divulged about the Doppler test, many women were clearly relieved and pleased to hear the fetal heart beat, and very concerned about the blood flow. It might be speculated that any suggestion that there is something wrong with the uterine blood flow will fuel great anxiety that the mother is "starving" her fetus. This loss of confidence might create obstetric problems, not least of which could be an inappropriate increased use of medical services and a diminution of bonding consequent to the fear that the baby might be abnormal or die.

Another hazard of injudicious implementation and inappropriate use would be to risk the credibility of Doppler ultrasonography. A few bad experiences on the part of clinicians might lead to it being discredited when there is usefulness in the test.

7.3.6 Implications of this work

The normal ranges will be of particular value in screening for complications related to abnormal development of the maternal uterine circulation. In second trimester complications such as oligohydramnios (Hackett et al 1987b) and early onset IUGR an assessment of uterine blood supply may be valuable in differentiating the underlying cause.

It has been established that valuable information can be gleaned from studying the uteroplacental circulation, but not if the placental location is unknown, or if readings from anywhere are accepted. If, in addition to this, there is a differential ease in obtaining waveforms, from under the placenta, for example, then, by randomly sampling around the uterus, a biased set of non-interpretable waveforms will be obtained. It is not possible to study the uteroplacental circulation using Doppler ultrasound without having a clear definition of the site studied. Serial studies must contain a method that reliably returns to the same standardised fixed points. These may be the uterine origin and the centre of the subplacental bed, or fixed with respect to

uterine landmarks.

Screening the uteroplacental circulation in the second trimester is of great interest, but the accuracy is not high. The fetoplacental circulation is not useful. It is certainly worth continuing the research for determinants of second trimester FVWs and for refining its use

8. FUTURE DIRECTIONS

Colour flow is a very recent innovation and shows very well the limitations of conventional PW for studying the uteroplacental circulation. Branches can be followed all over the uterus and under the placenta. It has the potential to eventually measure velocity, volume and pressure gradients.

Some experiments need to be performed to validate past CW and PW findings. Colour flow could be used to delineate the difference between the normal and abnormal FVWs from the internal iliac and uterine arteries. The effect of insonation place should be studied by making multiple readings along the pregnant and nonpregnant common, external and internal iliac arteries to see if resistance falls in these vessels too, and whether the downstream changes in pathology are reflected here. A study comparing different subplacental regions might find a fall in resistance from the edge inwards. It would be interesting to look at other peripheral arteries in pregnancy, for example the brachial, to see if the fall in resistance in the uteroplacental arteries is paralleled there. It would establish whether the documented fall in resistance was really related to histology rather than vasodilatation. The peripheral resistance in PET is known to be raised (Gant and Pritchard 1987) and the relation to uterine resistance might distinguish the different maternal responses to inadequate trophoblastic invasion.

There is a need for further experiments, in the third trimester, comparing pathology, ultrasound placental grading (Grannum et al 1979) and Doppler findings in normal, SGA and postmaturity cases. Vaginal Doppler scanning (Deutinger et al 1988) may allow screening to take place even in the first trimester.

The findings in this study need to be confirmed. Ways of improving the test so that it has a potential for screening should be explored as suggested above. Before being brought into clinical use, proof of benefit should be established in a randomised controlled trial (RCT).

If an RCT was set up to look at the benefit such a screening test might produce, whether in conjunction with a treatment or not, it would be vital to also look for negative aspects, such as increased anxiety and complications of treatment. A high quality RCT should follow clear guidelines if it is to unambiguously show a difference between different managements (Thacker 1985). It might be possible to use the Doppler test for an assignment of risk. The population could be divided into a variety of high and low risk groups and given different antenatal care regimes. For example, with a normal scan and Doppler test a woman could be given minimal care, such as a kick count chart and four weekly BP checks. With an abnormal test she could have fortnightly traditional visits, scans and Doppler tests. However, to show any effect on traditional measures such as perinatal mortality

would require very large numbers of women and many participating centres.

Many potential treatments have been suggested for preventing and treating PET and IUGR, including bedrest (Laurin and Persson 1987), aspirin (Wallenburg and Rotmans 1987, Beaufils et al 1988), oxygen administration (Nicolaidis et al 1987) and nifedipine (Lindow et al 1988). Doppler ultrasound may provide a way of identifying the at-risk pregnancy and monitoring drug studies when the technique is more accurate.

9. SUMMARY OF CONCLUSIONS

The aims set out in Section two have been fulfilled.

Intrauterine death, proteinuric hypertension, abruption of the placenta and intrauterine growth retardation are associated with abnormal Doppler flow velocity waveforms in early pregnancy, well before the development of symptoms or signs of the diseases. These results lend support to the concept of a unifying pathology, or a common problem of uterine blood supply despite the different presentations of the diseases. There are many diverse causes of stillbirth, hypertension, antepartum haemorrhage and small babies which makes accurate prediction difficult. However, the increasingly high predictions in more severe disease (severe PET, PET in primigravidae and blacks and SGA <3rd centile) suggest that Doppler investigation is differentiating the pregnancies with reduced uterine blood supply or failed trophoblastic invasion from normals.

These diseases of pregnancy can be predicted, with no other clinical information, and can be predicted with similar accuracy to an obstetric risk score and better than placental function tests.

In the second trimester, uterine FVWs are much more accurate indicators of potential problems than umbilical FVWs.

The uterine circulation is a very complex branching structure. RI values are affected by the position of the placenta, the rotation of the uterus, and the branching of the vessels and many maternal and fetal factors.

Doppler screening is easy, cheap, convenient, quick and reliable. To be a useful screening test in practice it would need to have higher accuracy than described in this thesis. It is not suitable yet for introduction for all women, but maybe high risk groups (where the prevalence of disease will be higher and consequently the predictive values higher).

It has been shown that the uterine blood supply determines from an early stage that some women are destined to develop complications. Doppler examination of the fetus is more informative of immediate fetal well-being, and is not predictive at this gestation. The prediction improves with gestation as the overlap of normal and abnormal separates, or as the women succeed or fail to compensate for the problem of failed trophoblastic invasion. More research is needed before the place of Doppler investigation of the fetus, placenta and uterine arteries is firmly established.

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13. GLOSSARY

13.1 Abbreviations used in the text

| | |
|-----------|---|
| A | Arcuate site |
| A | Maximum systolic peak |
| A/B | Systolic/diastolic ratio |
| AC | Abdominal circumference |
| AEDF | Absent end-diastolic frequencies |
| AFP | Alphafetoprotein |
| AGA | Appropriate-for-gestational-age |
| ANOVA | Analysis of variance |
| APH | Antepartum haemorrhage |
| AVA | Average arcuate value |
| AVRI | Average RI value |
| AVU | Average uterine value |
| | |
| B | End diastolic frequency |
| BEST RI | Lowest RI |
| BHCG | Beta human chorionic gonadotrophin |
| BP | Blood pressure |
| BPD | Biparietal diameter |
| bpm | Beats per minute |
| BPP | Biophysical profile |
| | |
| c | Speed of ultrasound in a medium |
| C | Constant |
| oC | Degree Centigrade |
| cm | Centimetre |
| cos | Cosine |
| COV | Coefficient of variation |
| CS | Caesarean section |
| CTG | Cardiotocography |
| CW | Continuous wave ultrasound |
| | |
| D | End diastolic frequency |
| Delta S/D | Difference between left and right S/D |
| Delta Bwt | Number of SDs of Bwt from mean expected for gestation |
| Delta RI | Number of SDs of RI from mean expected for gestation |
| Dias | Diastolic BP |
| DNA | Deoxyribonucleic acid |
| DOB | Date of birth |
| dl | Decilitre |
| D/S | Diastolic/systolic ratio, % |
| | |
| EDD | Estimated date of delivery |
| EDF | End diastolic frequencies |
| EFW | Estimated fetal weight |
| | |
| f | Frequency |
| fd | Doppler shifted frequency |
| FHR | Fetal heart rate |

| | |
|------|---------------------------------|
| FIP | Frequency index profile |
| FN | False negative |
| FP | False positive |
| FVW | Flow velocity waveform |
| g | Gram |
| GP | General practitioner |
| Hb | Haemoglobin |
| Hg | Mercury |
| HPL | Human placental lactogen |
| hr | Hour |
| Hz | Hertz |
| II | Internal iliac artery |
| IOL | Induction of labour |
| ImI | Impedance Index |
| IUD | Intrauterine death |
| IUGR | Intrauterine growth retardation |
| IVBF | Intervillous blood flow |
| IVS | Intervillous space |
| kg | Kilogram |
| KCC | Kick-count chart |
| KCH | Kings College Hospital |
| K-S | Kolgomorov-Smirnoff test |
| l | Litre |
| L | Left |
| LA | Left arcuate |
| LMP | Last menstrual period |
| LU | Left uterine |
| µ | Micron |
| mg | Milligram |
| MHR | Maternal heart rate |
| mHz | MegaHertz |
| min | Minute |
| ml | Millilitre |
| mm | Millimetre |
| mod | Moderate |
| mPa | MilliPascal |
| mW | MilliWatt |
| n | Number of sample |
| NE | Negative predictive value |
| NND | Neonatal death |
| No | Number |
| NPA | Nonplacental arcuate |
| NPU | Nonplacental uterine |
| NS | Not significant |

| | |
|---------|---|
| ODFD | Operative delivery for fetal distress |
| ORS | Obstetric risk score |
| | |
| p | Statistical significance |
| PA | Placental arcuate |
| PAPP-A | Pregnancy associated placental protein A |
| PET | Pre-eclampsia |
| PFT | Placental function test |
| pH | $-\log_{10} [H^+]$ |
| PI | Pulsatility Index |
| PIH | Pregnancy induced hypertension |
| PO | Positive predictive value |
| PP12 | Pregnancy protein 12 |
| PPROM | Preterm, premature rupture of membranes |
| PROT BP | Proteinuric hypertension |
| PU | Placental uterine |
| PW | Pulsed wave ultrasound |
| | |
| Q | Volume flow |
| | |
| r | Radius of the internal diameter of a vessel |
| R | Right |
| R | Correlation coefficient |
| RA | Right arcuate |
| RCT | Randomised controlled trial |
| RI | Resistance Index |
| ROC | Receiver operator curve |
| rpm | Revolutions per minute |
| RU | Right uterine |
| | |
| S | Maximum systolic peak |
| S | Slope |
| S/D | Systolic/diastolic ratio |
| SCBU | Special care baby unit |
| SD | Standard deviation |
| SE | Sensitivity |
| SFH | Symphyseal-fundal height |
| SGA | Small-for-gestational-age |
| SGA3 | Birth weight <3rd centile for KCH population |
| SGA5 | Birth weight <5th centile for KCH population |
| SGA10 | Birth weight <10th centile for KCH population |
| SP | Specificity |
| SP1 | Schwartzwanger protein 1 |
| SPTA | Spatial peak temporal average |
| Sys | Systolic BP |
| | |
| ∅ | Angle |
| TN | True negative |
| TP | True positive |
| | |
| U | Uterine site |
| UA | Umbilical artery |

U:A Average uterine RI/Average arcuate RI

v Velocity

w Watt

WORST RI Highest RI value

13.2 Definitions of terms and outcomes

Antepartum haemorrhage

The definition used was bleeding from the genital tract after 28 weeks' gestation of more than five mls. The causes were divided into placenta praevia (if proven at delivery or on ultrasound scan), definite abruptio (if proven retroplacental clot or if the bleeding was accompanied by clotting disturbances), probable abruptio (if the bleeding was accompanied by pain or CTG abnormalities), probable local cause (if there was a cervical erosion, cervical polyp, vaginal trauma, vaginal infection, or the bleeding was related to sexual intercourse) or unknown.

Birth asphyxia

Birth asphyxia was not defined as such, due to the difficulty in its diagnosis (Sykes et al 1982), the failure to obtain cord pH after every delivery and the low relation of Apgar score and pH to later detection of brain damage (Ruth and Raivio 1988). Although the BPP has accurately predicted acidaemia in fetuses undergoing elective prelabour CS (Vintezileos et al 1987), in practice, there is a problem of distinguishing between babies who were at risk but delivered at a timely moment, and those at no disadvantage antenatally who had long, obstructed labours before becoming compromised. It was decided to examine separately the features of operative delivery for fetal distress (ODFD), cord pH and Apgar score.

Chronic hypertension

If hypertension was noted before 20 weeks' gestation it was defined as chronic hypertension, and the cause was assumed to be essential hypertension in the absence of renal or other known disease.

Fetal loss

Fetal loss was defined as death of a fetus between the blood flow screening scan and delivery (excluding termination of pregnancy). Losses were arbitrarily divided into pre-viable late miscarriages < 24 weeks, intrauterine death 24-28 weeks, and stillbirth > 28 weeks. They were also divided into explained and unexplained. An unexplained loss was one not associated with any fetal or maternal abnormality. An APH was considered an accompaniment but not a cause of fetal loss.

Hypertension

At any stage of pregnancy two recordings of diastolic BP \geq /90mm Hg four hours apart, or one reading of \geq /110mm Hg was defined as hypertension (Davey and MacGillivray 1988).

Induction of labour

Induction of labour was defined as any labour initiated by medical or surgical means for a maternal or fetal reason.

Stimulation of labour after 37 weeks using an oxytocic for premature rupture of the membranes without contractions was excluded. Induction for postmaturity, after 42 weeks, was considered separately. A prelabour CS before 37 weeks was considered as a premature delivery for medical reasons.

Intrauterine growth retardation and small-for-gestational-age

SGA was considered to be a baby under a certain centile weight for gestation. Intrauterine growth retardation refers to the underlying disease process that limits growth of the fetus to its full genetic potential.

The mean and standard deviation of birth weight above 36 weeks' gestation have been calculated for the KCH population. From 28-35 weeks a premature infant chart was used (Gairdner and Pearson 1971). For babies 24-28 weeks an estimated fetal weight was used, using ultrasound growth charts and a calculation from AC and BPD (Shepherd et al 1982). There is a slight gap between the charts at 27-28 weeks, but it was considered to be small.

The actual birth weight of each baby was expressed as a number of standard deviations from the mean expected weight for gestation. Three degrees of SGA were defined where the birth weight was below the 3rd, 5th and 10th percentile for gestation (SGA 3, SGA 5 and SGA 10, number of SDs from expected birth weight = 1.96, 1.65 and 1.28 respectively). A correlation of delta RI versus delta Bwt was made for each vessel of the uteroplacental circulation.

Table 72 Kings College Hospital birth weight normal range and premature range

| Gest Wt(gm) All | SD | n | Gest Wt(SD) Male | Wt(SD) Female |
|--------------------|------|-----|---------------------|--------------------------|
| 36 | 2741 | 420 | 135 | 24 780 (168) Same |
| 37 | 2918 | 428 | 303 | 25 905 (206) Same |
| 38 | 3120 | 416 | 696 | 26 1045 (230) Same |
| 39 | 3275 | 422 | 1130 | 27 1205 (291) Same |
| 40 | 3417 | 432 | 1260 | 28 1100 (273) 1180 (164) |
| 41 | 3553 | 430 | 651 | 29 1310 (313) 1290 (180) |
| 42 | 3668 | 454 | 188 | 30 1530 (336) 1470 (203) |
| 43 | 3623 | 522 | 28 | 31 1780 (367) 1680 (219) |
| 44 | 3883 | 576 | 6 | 32 2030 (398) 1890 (242) |
| | | | | 33 2260 (406) 2100 (297) |
| | | | | 34 2500 (391) 2330 (367) |
| | | | | 35 2750 (430) 2520 (383) |

Neonatal death

Death of the baby in the first week of life.

Normals

A group of women were defined as being entirely normal. The definition of normal was a pregnancy that resulted in a live birth after 37 weeks' gestation of a baby weighing over the 10th centile for gestation. The pregnancy was accompanied by no antenatal complications and did not result in an operative delivery for fetal distress. The RI of the uterine and umbilical artery were then compared for the groups of normals versus abnormal by each complication separately.

Obstetric risk score (ORS)

This was taken from the definition of Adelstein and Fedrick (1978), but modified as APH and PET had not developed by the time of the Doppler scan. (see modified ORS in Appendix 14.11).

Operative delivery for fetal distress

The definition of ODFD was based on the indication for delivery by forceps, or CS, ie the clinical judgement of the operator at the time.

Pregnancy induced hypertension (PIH)

If hypertension was noted in second half of pregnancy, after 20 weeks' gestation, then it was defined as PIH. If there was no proteinuria (urinalysis 0 or trace, 24 hour collection < 150mg/24 hrs) then it was considered non-proteinuric. Nonproteinuric hypertension was divided into mild (BP rise above booking level <30/25mm Hg [Redman 1987]) moderate (rise \geq 30/25mm Hg) and severe (an absolute diastolic level \geq /110mm Hg).

Proteinuric hypertension

Proteinuria that disappeared on repeat testing was considered nonsignificant. Proteinuria was divided into light (150-500mg/24hr, equivalent to + on Albustix analysis) and heavy (>500mg/24hr equivalent to ++,+++ or ++++). Hypertension accompanied by persistent proteinuria in the absence of renal disease or urinary tract infection was considered proteinuric hypertension.

Proteinuric hypertension was divided into mild (rise <30/25mm Hg, protein +), moderate (rise <30/25mm Hg, protein \geq ++ or rise \geq 30/25mm Hg, protein ++ or diastolic \geq /110mm Hg, protein +) and severe (diastolic \geq /110mm Hg and rise \geq 30/25mm Hg and protein \geq ++). If either the BP was \geq 170/110mm Hg or the proteinuria was \geq ++ or \geq 500mg/24hr then it was labelled moderate and if both, severe.

An eclamptic fit, a cerebro-vascular accident, disseminated intravascular coagulopathy (DIC), hepato-renal failure, or the combination of the use of antihypertensives and anticonvulsants,

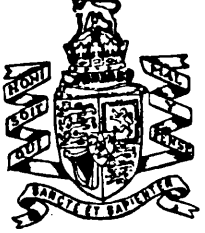
diuresis after delivery and premature delivery precipitated by the deteriorating condition of the patient were all considered diagnostic factors for severe pre-eclampsia.

Social class

As the local population had high rates of unsupported mothers and unemployment, social class was defined separately for both the woman and her partner using the Registrar General's definition (OPCS 1980). A separate code was made for housewives, unemployed and students (see coding sheets in Appendix 14.9). For analysis, the higher code was used.

14. APPENDICES

- 14.1 Routine booking scan
- 14.2 Computer booking history
- 14.3 Computer delivery details
- 14.4 Letter to all participants
- 14.5 Letter and forms sent to General Practitioners
- 14.6 Follow up letter and forms
- 14.7 Data collection forms
 - Main screening study
 - Repeat and serial studies
 - Inter-observer study
 - Intra-observer study five mins
 - Intra-observer study one hour
 - Variation around the uterus
 - Booking details
 - Delivery details
 - Complications form
 - Pilot form
- 14.8 Coding instructions for delivery form
- 14.9 Coding instructions for booking form
- 14.10 Coding instructions for complications form
- 14.11 Modified obstetric risk score



DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY
KING'S COLLEGE SCHOOL OF MEDICINE AND DENTISTRY
DENMARK HILL, LONDON SE5 8RX.

Director: Professor Stuart Campbell
Deputy Director: Mr. Kypros Nicolaides

Telephone: 01-274 6222 Extensions: 2517, 2908
Direct line: 01-326 1042

ULTRASOUND REPORT

DATE.....

Dear

Re: DOB..... HOSPITAL No.

Thank you for referring this patient for an ultrasound scan at.....weeks.....days..... menstrual age.

INDICATION:

FINDINGS: Number of fetuses.....Presentation

Amniotic fluid volume.....Placental localisation.....

| FETAL MEASUREMENTS: |
|--------------------------------------|
| Biparietal diameter |
| Head circumference (HC) |
| Cerebral ventricle (anterior) |
| Cerebral ventricle (posterior) |
| Cerebral hemisphere |
| Abdominal circumference (AC) |
| HC/AC |
| Femur length |

| FETAL ANATOMY: | | |
|----------------|------------------|----------------|
| Brain..... | Thorax..... | Stomach..... |
| Spine..... | Diaphragm..... | Abdo wall..... |
| Face..... | Heart: | Kidneys..... |
| Limbs..... | Rhythm..... | Bladder..... |
| Genitalia..... | 4 cham. view.... | Cord..... |

ULTRASOUND GESTATION weeks

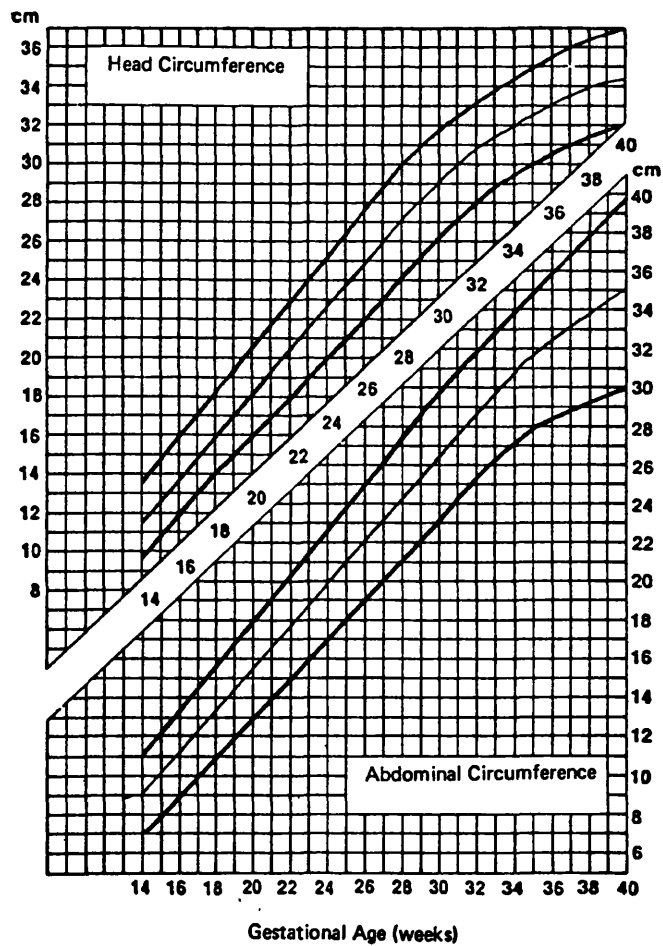
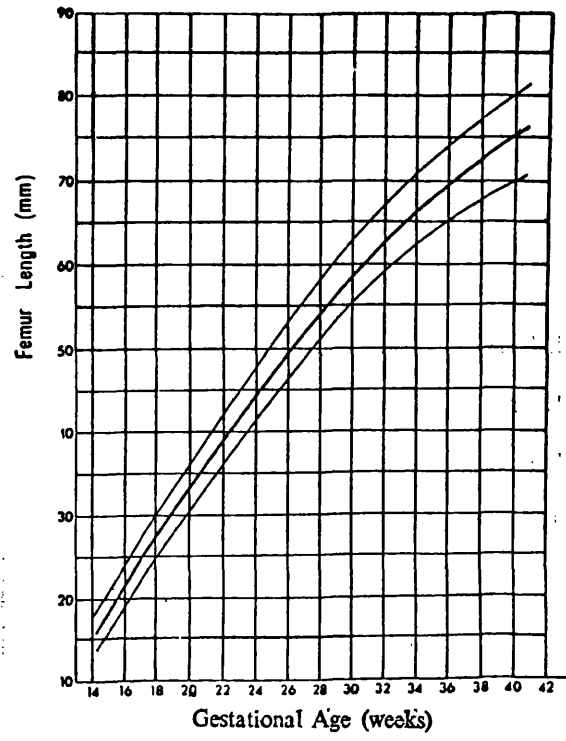
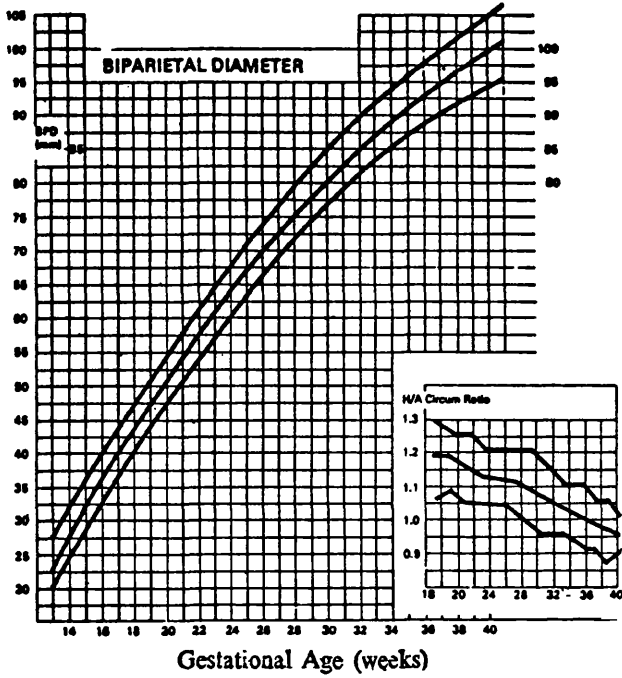
EDD

FETAL WEIGHTKgms

FURTHER INVESTIGATIONS: Cordocentesis/Amniocentesis/Placental Biopsy/Blood Flow Measurements.

COMMENTS:

.....
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.....



Unit no: A295590

Surname:

First names:

D.O.B.: 27/10/61 Age: 25

6

Consultant: Mr. Brudenell

Address:

:

:

:

Marital status: Married

: CHAYLE

Place of birth: ENGLAND

: GP

Change of address:

Patients occupation: HOUSEWIFE

Partners occupation: UNEMPLOYED

GP. (Pregnancy care) :

: DR ALMEIDA
: 296 QUEENS ROAD
: SE14

Next of kin:

(Husband)

GP. (Normal care) :

: DR ALMEIDA
: 296 QUEENS ROAD
: SE14

A295590

booked: 29/01/87

status: Married

D.O.B.: 27/10/61 age: 25

: Caucasian (white)

Height: 159 cms Weight 73400 gm

Con: Mr. Brudenell

Past MEDICAL and SURGICAL History

Migraine
Asthma
Rubella - Vaccinated
Tonsillectomy / adenoids
NO Blood transfusions
Smear: Unknown month-81

FAMILY History

Diabetes - No
Hypertension -
Twins -
Cong. abnormality - No

DRUGS taken during pregnancy

ASPRIN
Pain killers
Allergic to
HAYFEVER

Non smoker
Never drinks alcohol

Past OBSTETRIC History

GRAVIDA 2 Para 1 + 0

| Date | Place | gest wks | pregnancy | labour | puerperium | infant |
|--------|--------|----------|-----------|-------------------------|------------|---|
| MAY-81 | King's | Term | normal | Spont. labour S.V.D. | normal | 3150 gm GIRL Bottle Child alive & well |

Current pregnancy

LMP: 06/10/86 certain
: early/late + abnormal
: bleeding
: TWO DAYS ONLY
: No bleeding since LMP
Cycle: 2-6 / 28-28
: regular
Contraception: Combined pill
Stopped: JUN-86
: 4 periods since stopped
: Planned pregnancy

Referral req: Social worker not required
Health Visitor: NO
Antenatal prep: Discussed but not interested
Diet: Poor protein intake
: Poor vitamin intake
Dentist:

menstrual EDD: 13/07/87

ultrasound EDD:

working EDD:

Full Care

Full Stay

?Bottle ?Breast

Blood group _____ Rhesus _____
ELECTROPHORESIS _____
Mother _____ Partner _____
Normal _____ Normal _____
Carrier state _____ Carrier state _____
Disease _____ Disease _____
Counselling Yes/No _____ Counselling Yes/No _____

Phy Exam Heart _____
Lungs _____
Breasts _____
Abdo. _____
Pelvic _____

Smear Taken/Not taken Result _____
Rubella status Immune/Non Immune _____
VDRL Neg/Pos HIV Neg/Pos Date _____
Hepatitis Neg/Pos Result _____

| HAEMOGLOBIN | | ANTIBODIES | |
|-------------|--------|------------|--------|
| Date | Result | Date | Result |
| Booking | _____ | _____ | _____ |
| 26 wks | _____ | _____ | _____ |
| 36 wks | _____ | _____ | _____ |

Name:
Maternal No: A295590
Consultant: Mr. Brudenell
Ethnic origin: Caucasian

D.O.B.: 27/10/61
Age: 25
Marital status: Married

Booking

Booked for: King's
Date booked: 29/01/87
Booking gest: 16 + 3
E.D.D.: 13/07/87
Calculated by: LMP date = USS date
Delivery gest: 37 + 5
Antenatal care: Full care
Parity: Para 1 + 0

Antenatal

Smokes: Non smoker
Blood group: B Rh Positive
Lowest Hb: 9.9 gm/decilitre
Rubella: Immune
Electrophoresis: Normal

Labour

Admitted: 27-JUN-87 0 hrs 32 mins
Membranes: S.R.O.M.
Cx on admission: 2-3 cms. dilated
Analgesia: Entonox
: Pethidine

Delivery

Delivery: S.V.D.
Presentation: Cephalic O.A.
Delivered by: Agency Staff Midwife
: R U NWIGWE

Third Stage

Oxytocic drug: Syntometrine 1 ml. I.M.
Delivered: C.C.T.
Placenta: Placenta complete
Membranes: Membranes complete
Cord vessels: Three vessels
Placenta weight: 500 gm
Blood loss: 100 mls
Perineum: Intact
Transferred to: Sylvia Henley Ward

Baby

Gestation: 37 + 5
Weight: 3950 gm
Head circum: 36 cms
Sex: Girl
Apgar at 1 min: Response to stimuli Good = 2
: Tone 1
: Heart rate 2
: Colour 1
: Respiration 1
Total at 1 min: 7
Apgar at 5 mins: Colour 1
: Response to stimuli 2
: Tone 2
: Heart rate 2
: Respiration 2
Total at 5 min: 9
First gasp: Immediate
Reg respirations: 1 minute
Oxygen: **Ventilated using mask**
Duration: 1 min or less
Drugs/procedures: Konakion 1 mg
Temperature: 36.4 deg/cen
Cord blood: No cord blood taken
Cord pH: 7.33 pH
Resuscitated by: Agency staff midwife
: R U NWIGWE
Examination: Baby appeared normal
Transferred to: Sylvia Henley Ward
Baby No: A929853

Times

Membranes ruptured: 27-JUN-87 23 hrs 30 mins
Labour started: 26-JUN-87 21 hrs 00 mins
Full dilatation: 0 hrs 15 mins
Delivered: 27-JUN-87 0 hrs 32 mins
Placenta delivered: 0 hrs 40 mins
Duration 1st stge: 3 hrs 15 mins
Duration 2nd stge: 0 hrs 17 mins
Duration 3rd stge: 0 hrs 08 mins
LABOUR DURATION: 3 hrs 40 mins
Dur membrane rupt: -22 hrs 02 mins

BLOOD FLOW SCREENING SCAN

Thank you for having a blood flow scan

We are doing research on the blood flow in the uterus and placenta (womb and afterbirth). It involves having a short 5 minute ultrasound scan where we listen to the blood flow.

We are trying to find ways of telling early on which pregnancies will progress normally and which ones are at risk.

I will listen to the blood flow and take various readings. After your baby is born I will look at your notes and see whether the test relates to your pregnancy, the labour and baby's weight. All the information is confidential. I will be using a computer for analysis but there will be only a number for identification, and no names.

I want to repeat the test in a number of women to see if it changes with time and so we may ask you to return. This does not mean that the result is normal or abnormal - we are asking a mixture of women to return

It is important that if you deliver anywhere else apart from Kings we can find out about your details to make this test more useful in the future for other pregnant women so if you deliver anywhere apart from Kings please write to me. You may get a letter from me asking about your pregnancy, delivery and baby's weight

In some women I also want to take a sample of blood and I can take the alphafetoprotein (spina bifida test) at the same time, so you will have no more needles

If you are admitted to hospital at any stage of the pregnancy I may like to repeat the test so do ask in the scan department

If you do not wish to participate please inform me now as I need to know about the women not being scanned as well as the women who are

Thank you

Dr Susan Bewley
Ultrasound Department, 6th floor New Ward Block
Kings College Hospital
Denmark Hill
London S.E.5.
Daily 9 - 5 (except Mon a.m.)

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY
KING'S COLLEGE SCHOOL OF MEDICINE AND DENTISTRY
DENMARK HILL, LONDON SE5 8RX.



Telephone: 01-274 6222

Dear

re: name:

address:

d.o.b.:

study no:

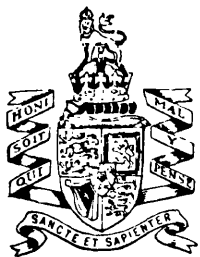
When this woman was about 5 months pregnant she had a booking scan at Kings College Hospital and agreed to participate in a study looking at the value of blood flow screening in early pregnancy with Doppler ultrasound.

As she did not book / deliver at Kings I am unable to obtain her full details and obviously want as complete a record as possible. I would be most grateful therefore if you could fill in the enclosed form and return it to me.

Thanking you in advance,

Dr Susan Bewley

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY
KING'S COLLEGE SCHOOL OF MEDICINE AND DENTISTRY
DENMARK HILL, LONDON SE5 8RX.



Telephone: 01-274 6222

Dear

study no:

When you were about 5 months pregnant you had a booking scan at Kings College Hospital. I was doing research looking at the blood flow in your arteries and the babies cord with Doppler ultrasound. You agreed to help in my study and had a quick blood flow scan.

As you did not book / deliver at Kings I am unable to get your full details and obviously want as complete a record as possible. I would be most grateful therefore if you could fill in the enclosed form and return it to me. Everything is completely confidential.

I am trying to see if we can predict complications of pregnancy and work out if this is going to be a useful test in the future for pregnant women. Whether you had problems or not I really want to know the outcome of the pregnancy.

If you have any queries about the questionnaire please do not hesitate to write to me. Thanking you in advance,

Dr Susan Bewley

GP FORM

study number:

name:

address:

d.o.b:

Has her address changed or have I got the wrong address?

Please amend address:

age:

marital status:

occupation of patient:

occupation of her partner:

race:

height:

weight at booking:

smoking at booking (no of cigs per day):

any bleeding in early pregnancy?:

past obstetric history:

(please list all pregnancies, year, outcome,
gestation at delivery, weight)

hypertension in previous pregnancies?:

previous antepartum haemorrhage?:

no of previous babies < 2.5 kg:

no of previous babies > 4.0 kg:

no of prem babies 24 - 37 weeks:

no of stillbirth > 28 weeks:

no of losses 16 - 28 weeks:

no of neonatal deaths (1st week):

other important medical history:

DELIVERY DETAILS

study no:

name:

Was the delivery booked at a hospital?.....If so, which?.....

Where did the delivery take place?.....

Do you have the hospital number?.....

was she admitted antenatally?:

any medical problems?:

any fetal problems?:

did she have an antepartum haemorrhage in this pregnancy?

amount of largest bleed:

cause:

booking blood pressure:

past history of bp:

family history of bp:

highest bp in this pregnancy:

significant proteinuria:

indication for induction:

study no:

type of delivery? (normal, forceps, Caesarean)

What was the expected date of delivery?

What date was the delivery?

gestation (weeks and days):

meconium stained liquor:

operative del for fetal distress:

placental weight:

weight of baby:

head circumference:

sex:

apgars 1 and 5 min:

cord ph:

normal?:

admitted to a neonatal unit?

any labour problems?

any third stage problems?

thank you again for your help.

study number:

name:

address:

d.o.b:

Has your name or address changed?

Please change address:

how old are you?:

are you single/married/divorced/widowed?:

your occupation:

occupation of your partner:

race:

height:

weight at booking:

smoking at booking (no of cigs per day):

any bleeding in early pregnancy?:

please tell me about your past pregnancies:

(please list all pregnancies, year, outcome, number
of weeks at delivery, weight)

did you have blood pressure in previous pregnancies?:

did you have bleeding in late pregnancy before?:

do you have any other important medical history?:

name:

address:

d.o.b:

Has your name or address changed?

Please change address:

Was the delivery booked at a hospital?.....If so, which?.....

Where did the delivery take place?.....

Do you have the hospital number?.....

were you admitted to hospital during the pregnancy?

any medical problems?

did you have any bleeding late in this pregnancy?

do you know the cause?

did labour start on its own or were you induced?

did you have any labour problems?

any problems with the afterbirth (placenta)?

type of delivery? (normal, breech, forceps, Caesarean)

What was the reason for induction/forceps/caesarean?

What was the expected date of delivery?

What was the actual date of delivery?

was there any fetal distress in labour?

do you know the weight of the placenta?

weight of baby?

head circumference?

girl or boy?

did the baby cry at birth?

was the baby normal?

was the baby admitted to a special care unit?

327

thank you again for your help.

NAME _____
 HOSP NO _____
 D.O.B. ____/____/____
 TEL. NO. _____

STUDY NUMBER

| | | | |
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| 0 | 1 |
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DATE OF TEST

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PROBLEMS:

NO OF FETUSES

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PLACENTAL SITE:

1 - UPPER 2 - LOWER 3 - PRAEVIA
 1 - ANT 2 - POST 3 - FUNDAL 4 - LAT
 1 - RIGHT 2 - LEFT 3 - L=R

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GESTATION

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EDD

DO DATES AGREE WITH SCAN ? 0 - NO 1 - YES
 IS THE SCAN NORMAL ? 0 - NO 1 - YES

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PROBLEM ON SCAN:

CURRENT PREGNANCY

AGE ON LEAVING FULLTIME EDUCATION

ANY BLEEDING IN EARLY PREGNANCY?

ANY 'FLU' OR ILLNESS IN EARLY PREGNANCY?

SMOKING 0 - NONE 1 - <5 2 - 6-10

3 - 11-15 4 - 16-20 5 - >20

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| 0 | 2 |
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READINGS:

BLOOD PRESSURE
 HEART RATE

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UMBILICAL ARTERY

FHR

LEFT ARCUATE

LEFT UTERINE

RIGHT ARCUATE

RIGHT UTERINE

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TIME TAKEN FOR READINGS

WAS EXAM DIFFICULT? 1 - EASY 2 - MOD 3 - DIFF

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TAPE NO/ COUNTER NO...../.....-.....

OTHER STUDIES

BLOODS

ANY OTHER COMMENTS?.....

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INTEROBSERVER STUDY

STUDY NUMBER

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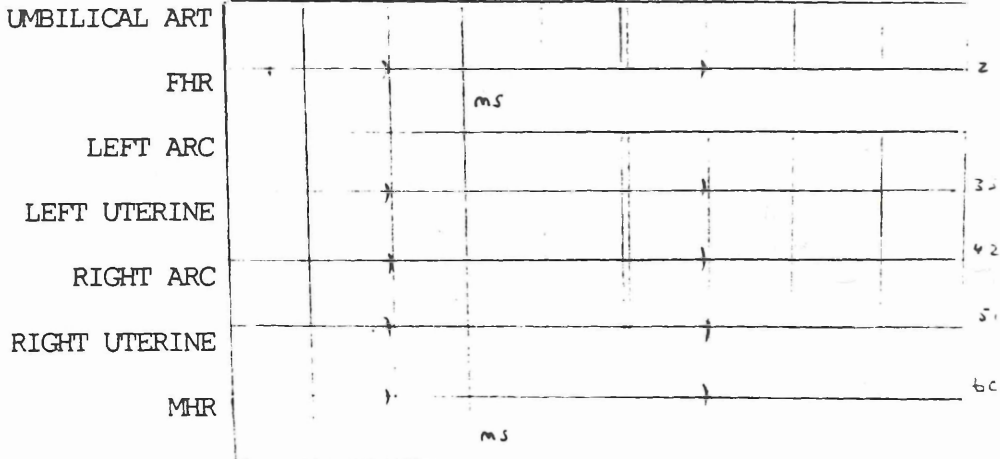
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PATIENT NAME.....
 MAIN STUDY NUMBER

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DATE OF TEST.....
 GEST

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OBSERVER.....

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 64

TAPE NO/.....-

MULTIPLE READING STUDY

STUDY NUMBER

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PATIENT NAME.....
MAIN STUDY NUMBER

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DATE OF TEST.....
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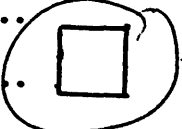
PLACENTAL POSN.....

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| LEFT ARC 1 | | | | | | | | |
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| 3 | | | | | | | | |
| 4 | | | | | | | | |
| LEFT UTERINE | | | | | | | | |
| RIGHT ARC 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| RIGHT UTERINE | | | | | | | | |
| MHR | | | | | | | | |

ms

OBSERVER.....

TAPE NO/.....-.....



placental side

Doptek / Krantz / HP / Other



1=R 2=L 3=L

BOOKING DETAILS

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STUDY NUMBER

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HOSPITAL NUMBER

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FIRST NAME

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SURNAME

POST CODE

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AGE

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MARITAL STATUS

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SOCIAL CLASS

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RACE

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HEIGHT

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WEIGHT

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SMOKING

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BLEEDING EARLY PREGNANCY

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PAST OBSTETRIC HISTORY

PARITY

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BP IN PREVIOUS PREGNANCY

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PREVIOUS APH

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NO OF PREVIOUS BABIES < 2.5 KG

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|--|

NO OF PREVIOUS BABIES > 4.0 KG

| |
|--|
| |
|--|

NO OF PREM BABIES 24+0 TO 36+6 WEEKS

| |
|--|
| |
|--|

NO OF STILLBIRTHS > 28 WEEKS

| |
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| |
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NO OF LOSSES 16 TO 27+6 WEEKS

| |
|--|
| |
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NO OF NEONATAL DEATHS (FIRST WEEK)

| |
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OBSTETRIC RISK SCORE

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OTHER

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FIRST NAME _____

SURNAME _____

DELIVERY

PLACE OF DELIVERY

GESTATION (WKS AND DAYS)

MEC STAINED LIQUOR

MODE OF DELIVERY

OPERATIVE DELIVERY FOR FETAL DISTRESS

| | | |
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PLACENTA

PLACENTAL WEIGHT

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BABY

OUTCOME OF PREGNANCY

WEIGHT

HEAD CIRCUMFERENCE

SEX

APGAR AT 1

APGAR AT 5

CORD PH

ANY ABNORMALITY?

ADMISSION TO FRED STILL OR BABY UNIT

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DATE OF DELIVERY

OTHER

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SB ANTENATAL

ADMITTED ANTENATALLY

MEDICAL PROBLEMS

FETAL PROBLEMS

LABOUR PROBLEMS

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SCREENING TEST

FIRST NAME:.....

SURNAME:.....

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HOSPITAL NUMBER:.....

DATE OF BIRTH:.....

TEL NO.:.....

STUDY NUMBER:

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| P | 0 | 10 |
|---|---|----|

NUMBER OF FETUSES:

PLACENTAL SITE:

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|---|---|
| U | L |
|---|---|

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|---|---|---|---|
| A | P | A | P |
|---|---|---|---|

| | | | |
|---|---|---|---|
| R | L | R | L |
|---|---|---|---|

TEST NUMBER:

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DATE OF TEST:

GESTATION (Weeks and days):

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LMP=USS/USS:

LEFT RI:

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Y N

(Notch?):

RIGHT RI:

| | |
|--|--|
| | |
|--|--|

Y N

(Notch?):

LEFT UTERINE RI:

| | |
|--|--|
| | |
|--|--|

Y N

(Notch?):

RIGHT UTERINE RI:

| | |
|--|--|
| | |
|--|--|

Y N

(Notch?):

UMBILICAL ART RI:

| | |
|--|--|
| | |
|--|--|

Y N

EDF:

BLOOD PRESSURE:

| | | | | | |
|--|--|--|--|--|--|
| | | | | | |
|--|--|--|--|--|--|

SMOKER:

AGE LEAVING FULLTIME EDUCATION:

| | |
|--|--|
| | |
|--|--|

RESULTS REVEALED:

| |
|--|
| |
|--|

BLOODS TAKEN:

Y/N

AFP

HPL

FBC

HIV

URATE

THROMBOXANE

OESTRIOL

U+E

CR CL

GLU

SERUM SAVED

PLASMA SAVED

OPERATOR:

SB /

14.8 Coding instructions for delivery form

| | | |
|---------------------------------------|-------|--|
| place of delivery | k | kings |
| | d | dulwich |
| | h | home |
| | o | other hosp |
| | blank | dont know |
| gestation | | weeks and days at delivery |
| meconium stained liquor | 0 | none |
| | 1 | yes |
| | 2 | no liquor/oligohydramnios |
| delivery | 1 | SVD |
| | 2 | forceps/ventouse |
| | 3 | emergency CS |
| | 4 | elective CS |
| | 5 | breech |
| | blank | dont know |
| operative delivery for fetal distress | 0 | no |
| | 1 | forceps for FD |
| | 2 | CS for FD |
| outcome of pregnancy | 1 | live baby |
| | 2 | intrauterine death 24-28 |
| | 3 | stillbirth 28+ |
| | 4 | neonatal death <1 week |
| | 5 | miscarriage <24 |
| | 6 | TOP |
| | 7 | maternal death |
| | 8 | 1 live/1 dead twin |
| placental weight | | in gms |
| weight | | in gms |
| head circumference | | in cms |
| sex | G | girl |
| | B | boy |
| apgars | | at one and five minutes, leave if dont know C,C if "cried at birth" |
| cord pH | | leave if dont know |
| any abnormality | 0 | none |
| | 1 | yes |

| | | |
|-----------------------------|----------------|-----|
| admission Fred Still (SCBU) | 0 | no |
| | 1 | yes |
| date of delivery | day then month | |

Final instructions

then, if forms all complete put onto list and put form into the "ready for computer" file.

if any queries or missing data pin print-out and coding forms all together for me to chase up.

14.9 Coding instructions for booking form

| | |
|---------------------------------|--|
| study number | main study number |
| age | in years |
| marital status | m married s single d divorced p separated w widow o other blank dont know |
| social class woman, then man | 1 I 2 II 3N III non manual 3M III manual 4 IV 5 V 6A housewife 6B student 6C schoolstudent 7 unemployed 8 army/other/prison 9 dont know 00 no male partner |
| race | 1 caucasian 2 west indian 3 african 4 asian 5 mixed 6 chinese/far east 7 mediterranean 8 arab blank dont know |
| height | in cms 3.05 x ft + 2.54 x inches |
| weight | in gms 454 x lbs + 28.3 x oz |
| smoking | 0 none 1 1-5 /day 2 6-10 /day 3 11-15 /day 4 16-20 /day 5 21-30 /day 6 31+ |

| | | |
|--------------------------|---|--|
| bleeding early pregnancy | 0 | none or "? bleeding" |
| | 1 | yes |
| parity | | box 1 = no of deliveries \geq 28 plus no live births \geq 24 box 2 = no of miscarriages, abortions and stillbirths $<$ 28 |
| bp | | blood pressure/hypertension |
| aph | | antepartum haemorrhage, bleeding after 28 weeks |
| < | | less than |
| > | | greater than |
| <2.5 | | up to 2.499 kgs |
| >4.0 | | 4.000kgs inclusive and over |
| nnd | | neonatal death, death in first week of life |
| term | | = 37 + 0 weeks to 41 + 6 |
| postcode | | 0000 if outside london |

14.10 Coding instructions for complications form

| | | | |
|------------------------------|---------------------------|-------------------------------|-------------------|
| IUD | 0 | none | |
| | 1 | unexplained ie no cause | |
| | 2 | explained | |
| | 3 | TOP | |
| | 9 | dont know | |
| APH \geq 5 mls $>$ 28 | 0 | none | |
| | 1 | praevia (inc CS not bleeding) | |
| | 2 | definite abruptio | |
| | 3 | probable abruptio | |
| | 4 | local (def/prob) | |
| | 5 | unknown origin | |
| | 9 | dont know | |
| hypertension | 0 | none | = 1 x \geq /110 |
| | 1 | yes | or 2 x \geq /90 |
| | 9 | dont know | |
| booking BP ($<$ 20weeks) | 0 | normal booking BP | |
| | 1 | booking \geq /90 essential | |
| | 2 | booking \geq /90 renal | |
| type of increase BP | 0 | none | |
| | 1 | non-proteinuric | mild |
| | 2 | | mod |
| | 3 | | sev |
| | 4 | proteinuric | mild |
| | 5 | | mod |
| | 6 | | sev |
| | 7 | non-proteinuric dont know BP | |
| | 8 | proteinuric dont know BP | |
| 9 | hypertension unknown kind | | |

nonproteinuric = 0 / tr protein, $<$ 150mg/24 hrs

mild BP rise $<$ 30/25
 mod BP rise \geq 30/25
 sev diastolic \geq /110 (and rise \geq 30/25 if high booking)

proteinuric = +, 150-500mg
 ++, \geq 500mg

mild BP rise $<$ 30/25 and prot +
 mod BP rise \geq 30/25 and prot ++ OR,
 BP rise $<$ 30/25 and prot ++ OR,
 sev diastolic \geq /110 and prot +
 diastolic \geq /110 and prot ++
 (and rise \geq 30/25 if high booking)

| | | |
|---------------------|-----------------|---|
| premature delivery | 0 | spontaneous onset/elective CS ≥ 37 |
| | 1 | prem spontaneous <37 weeks |
| | 2 | IOL <42 (exc stimulation PROM >37) |
| | 3 | IOL ≥ 42 |
| | 4 | prelabour CS <37weeks |
| | 5 | IUD |
| other complications | 9 | dont know |
| | 0 | none |
| | 1 | PPROM <37 before contractions |
| | 2 | diabetes |
| | 3 | polyhydramnios |
| 4 | combination 2+3 | |
| admission to SCBU | 9 | dont know |
| | 0 | no |
| | 1 | yes |
| | 9 | dont know |

14.11 Modified obstetric risk score (ORS) (Adelstein and Fedrick 1978)

Start with one and multiply by various factors

For women of all parity:

| Factor | | Multiply by |
|---------------------|------------|-------------|
| Social class | I, II | 0.7 |
| | IV, V, 6,7 | 1.2 |
| Threatened abortion | | 1.7 |
| Cigarette smoking | none | 0.8 |
| | 10+/day | 2.0 |
| Height | < 157 cm | 1.5 |
| | > 167 cm | 0.5 |
| Weight | < 50.8 kg | 2.1 |
| | > 63.5 kg | 0.6 |

If parous:

| | | |
|----------------------------|----|-----|
| Stillbirth, neonatal death | 0 | 0.8 |
| | 1 | 1.1 |
| | 2 | 2.0 |
| Livebirth < 2.5 kg | 0 | 0.6 |
| | 1 | 2.5 |
| | 2 | 2.8 |
| | 3+ | 5.9 |
| Livebirth > 4.0 kg | 1+ | 0.2 |

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