CARDIOVASCULAR PRESSURES IN THE HUMAN FETUS.

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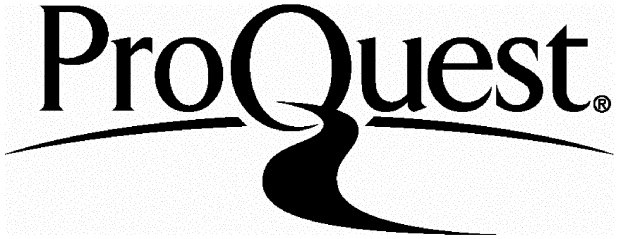

ABSTRACT:

The technique of ultrasound guided fetal blood sampling has been adapted, as herein described, to permit measurement of intra amniotic, intra umbilical vascular and intra cardiac pressures in the human fetus in utero during indicated procedures. 246 pregnancies have been investigated and reference ranges for these pressures established. The effects of fetal disease on these pressures has been examined.

Intra amniotic pressure in the presence of a normal liquor volume is unaffected by fetal abnormality, and increases with gestation. Measurement of intra amniotic pressure in abnormal liquor volumes provides widely varying results and has no proven clinical value.

Umbilical venous pressure does not increase with gestation and is not affected by fetal abnormality unless this involves the fetal heart. In nonimmune hydrops, there is a significant relationship between umbilical venous pressure and cardiac size, providing for the first time direct evidence of intrauterine cardiac failure in some cases of hydrops. Elevation of venous pressure also occurs in congenital heart disease if cardiomegaly is present, and congenital diaphragmatic hernia with associated left ventricular compression.

Umbilical arterial pressure increases with gestation, and

is elevated in the presence of abnormal umbilical artery Doppler blood flow studies and fetal hypoxia.

Left and right atrial pressures do not increase with gestation. Although the pressure in the right atrium is higher than the left, this is not statistically significant. Elevation of atrial pressure occurs in nonimmune hydrops with associated cardiomegaly.

Left and right ventricular pressures are equal and both systolic and end diastolic pressures increase with gestation. The pressure waveforms are similar to those obtained in postnatal investigations. Abnormalities of pressure waveforms and actual values occur in cases of left and right ventricular outflow obstruction, and these measurements provide additional diagnostic and prognostic information.

This study provides new data on umbilical venous pressure in the presence of fetal abnormality and intrauterine cardiac failure. It also provides the results of the first direct measurements of human fetal cardiac pressures in normal and abnormal hearts.

STATEMENT OF ORIGINALITY

The work herein represents the results of a study conducted in the Fetal Medicine Unit, Department of Obstetrics and Gynaecology, in collaboration with the Departments of Paediatric Cardiology and Fetal Cardiology, at Guy's Hospital. The candidate has been responsible for all the pressure measurements and, in the majority of cases, performed the indicated invasive procedures herself.

Publications arising from the work related to this thesis:

Johnson P. and Maxwell D.J. Normal amniotic pressure in oligohydramnios after preterm rupture of membranes. *Am J Obstet Gynecol* 1990; **163**: 1103-1104

Johnson P. and Maxwell D. Intrauterine measurement of fetal cardiac pressures. *Contemp Rev Obstet Gynaecol* 1990; **2**: 141-144

Johnson P. and Maxwell D.J. Nonimmune Hydrops. *Contemp Rev Obstet Gynaecol* 1992 (in press)

Johnson P., Sharland G., Maxwell D. and Allan L. The role of transvaginal sonography in the early detection of congenital heart disease. *Ultrasound Obstet Gynecol* 1992 (in press)

Johnson P., Sharland G., Allan L.D., Tynan M. and Maxwell D.J. Umbilical venous pressure in nonimmune hydrops fetalis: Correlation with cardiac size. *Am J Obstet Gynecol* 1992 (in press)

Maxwell D.J., Johnson P., Hurley P., Neales K., Allan L.D. and Knott P. Pregnancy loss after fetal blood sampling - An evaluation in relation to indication. *Br J Obstet Gynaecol* 1991; **98**: 892-897

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Abbreviations used in this thesis:

AVSD	atrioventricular septal defect
bpm	beats per minute
CHB	congenital heart block
CI	confidence interval
cm	centimetre
CTR	cardiothoracic ratio
dl	decilitre
DORV	double outlet right ventricle
EFE	endocardial fibroelastosis
g	gram
Hb	haemoglobin
HG	mercury
IU	international units
IUD	intrauterine death
KG	kilogram
LSCS	lower segment caesarean section
mg	milligram
MHZ	megahertz
min	minute
ml	millilitre
mm	millimetre
μV	microvolt
NIH	nonimmune hydrops
NND	neonatal death
PROM	premature rupture of membranes
SB	stillbirth
SD	standard deviation

SEM	standard error of mean
SVT	supraventricular tachycardia
SVD	spontaneous vertex delivery
V	volt
VSD	ventricular septal defect

1. INTRODUCTION

1.1 BACKGROUND TO STUDY:

Until recent years, the human fetus has been inaccessible to direct investigation, being protected by amniotic fluid, membranes, the uterus and the maternal abdominal wall. With modern advances in high resolution ultrasound imaging, techniques now exist for accurate prenatal diagnosis of congenital anomalies. Adaptation of procedures used in postnatal life has enabled perinatalogists to offer prenatal therapy in a variety of conditions including congenital cardiac failure and valvular lesions such as critical aortic stenosis.

In spite of advances in surgical technique, postnatal treatment of congenital heart disease still carries a high mortality rate, particularly in severe forms of aortic stenosis presenting in the neonatal period (Balaji et al 1989, Ladusans et al 1989). Such severe congenital heart disease is amenable to prenatal diagnosis by fetal echocardiography, and prenatal examination has greatly enhanced knowledge of the natural history of congenital heart disease (Allan et al 1989 [b], Sharland et al 1991). This has acted as the spur to develop prenatal therapy, which has progressed in the areas of cardiopulmonary bypass (Lee et al 1990, Bradley et al 1990), prenatal insertion of pacemakers (Heinemann et al 1991) and intrauterine balloon valvoplasty (Maxwell et al 1991).

A prerequisite for postnatal treatment is accurate diagnosis, together with information regarding function of the diseased system. For example, in cases of cardiac valvular disease this involves noninvasive and invasive assessments. Echocardiography and Doppler blood flow studies provide structural and limited functional information. This is supplemented by cardiac catheterization studies which offer both radiological examination of anatomy and pressure recordings. Intracardiac pressure measurements not only contribute further functional information, they also offer more accurate prognostic data (Gundry and Behrendt 1986).

In order to select those fetuses which are suitable for prenatal therapy of congenital cardiac abnormalities, and to achieve accurate assessment of the prognosis, direct cardiovascular pressure studies are required. Ultrasound guided needling techniques allow direct access to the fetal cardiovascular system with a low risk of fetal loss, and pressure studies may be performed using this method. However, interpretation of abnormal results requires knowledge of normal findings. No previous data on intracardiac pressures in the human fetus exists, although a small amount of data on other fetal cardiovascular pressures is available. This study was therefore conceived with the following aims.

1.2 AIMS OF STUDY:

i) **to establish a method for the measurement of fetal cardiovascular pressures,**

ii) **to establish reference ranges for amniotic, umbilical venous, umbilical arterial and cardiac pressures in the human fetus,**

iii) **to investigate the changes in these pressures with disease states.**

1.3 HISTORICAL REVIEW:

Investigation of the human fetus has always been difficult, as access is restricted by the liquor, membranes, uterus and maternal abdominal wall. It is only recently that these obstacles have been overcome, permitting direct investigation of the human fetus in utero. However, the fetal cardiovascular system has provided a subject for research over many centuries.

1.3.1 Anatomical studies:

Knowledge of the fetal cardiovascular system was initially extrapolated from information obtained by postmortem dissection. Early theories held that the blood in the fetus did not circulate as cardiac activity did not commence until birth. It was believed that blood vessels within the fetus were kept patent by the forces of 'Mother Nature'.

Harvey, in his treatise published in 1628, stated that blood **did** circulate within the fetus. Although he did not

fully appreciate the differences between pre and post natal circulation, he recognised that there were differences in cardiac anatomy between the fetus and adult, and theorized that the lungs had no function before birth (Barclay A.E. et al 1944).

In 1669 Lower postulated that some blood did circulate through the fetal lungs (Barclay et al 1944), which was an important step in the understanding of fetal physiology. At this time it was believed that the circulation of blood within the fetus was dependent upon maternal forces, until Rouhart in 1718 postulated that the fetal circulation was primarily dependent on fetal forces (Barclay et al 1944).

Knowledge of physiology continued to grow during the next two centuries, though with little practical research. Most physiological concepts were developed by inference from anatomical findings without confirmation by experimentation.

During the early part of the nineteenth century, further suppositions regarding the fetal circulation were made on the basis of anatomical studies (Barclay et al 1944). From fetal anatomy and the theories of Harvey, it was evident to Kilian (1826) that the fetal heart needed to pump blood around the fetal body and placenta, and therefore used both ventricles to provide sufficient force. As both left and right ventricles ejected blood into the aorta he surmised

that the forces, and thus the pressures, exerted by each ventricle must be equal. It was not until the current century that experimental physiology began to confirm and refute previous theories.

1.3.2 Early experimental studies:

1.3.2.1 Umbilical vascular pressure:

The first recording of umbilical blood pressure was reported by Ribemont in 1879. Using a mercury manometer, he measured the pressure within the umbilical artery and vein immediately after birth and before cord pulsations had ceased (Ribemont 1879). Although the experiment was designed to clarify the best time for clamping the umbilical cord after birth, it provided the first record of any attempt to perform a physiological measurement of the human fetal circulation. The values obtained for mean umbilical arterial and venous pressures were 63 mm Hg (range 54 - 75) and 33 mm Hg (range 18 - 61) respectively in 15 neonates in whom the cord was not clamped until after pulsations had ceased. Although these measurements were performed before delivery of the placenta, the fetus was outside the uterus at the time of recording.

Human fetal studies continued to be limited by the inability to gain access to the fetus in utero. Haselhorst (1929) measured umbilical blood pressure at caesarean section immediately after the uterine incision was made and before delivery of the fetus. He recorded an arterial

pressure of 68 mm Hg. While this was the first attempt to perform in utero measurements, the conditions under which these measurements were recorded were not ideal involving the administration of general anaesthetic to the mother and inevitable uterine activity and handling of the cord.

During the 1920's - 1940's, teams under the leadership of Barclay in Oxford and Barcroft in Cambridge produced wideranging work on the study of fetal circulation, using fetal lambs and the newly available cineradiography. Much attention was paid to the changes in the circulation at the time of birth, and also to the changes in hypoxic and acidotic states, using blood gas analysis. A large data base of fetal blood pressure recordings was accumulated. However, little of this data relates to pressures within the umbilical vessels or fetal heart, as the carotid arteries and inferior vena cava were the vessels catheterized in most of these fetal sheep preparations. The majority of the studies were performed on exteriorized fetuses but with the placenta still within the uterus. In others, a loop of cord was lifted out through a small uterine incision and cannulated with the fetus remaining in utero.

This work by Barclay and Barcroft and their respective teams provided evidence in support of a large number of theories regarding fetal circulation. Fetal systemic blood pressure was shown to increase with gestation and fetal

weight (Barcroft 1936). An increase in umbilical venous pressure with advancing gestation was demonstrated by Barcroft and Kennedy (1939).

The concept of blood of differing oxygen concentrations being supplied to different parts of the fetal body, originally put forward by Sabatier in 1774, was supported by this work (Barclay et al 1941). In further study of the course of blood within the fetal circulation, the umbilical venous pressure was recorded in fetal sheep (Barcroft et al 1942), although it is unclear whether the free or intra abdominal portion of the umbilical vein was used. The first reported values ranged from 6 - 15 mm Hg at gestations from 56 - 141 days (term = 147 days).

Further studies by the same teams investigating umbilical arterial pressure at birth gave values of 80 mm Hg (systolic) and 45 mm Hg (diastolic).

It was noted by Barclay et al (1944) that there were marked differences between the blood pressures obtained in human fetuses at birth and fetal lambs. It was thought at this time that the ratio of umbilical arterial to umbilical venous pressure was much higher in the lamb than the human. Although both the human and animal measurements had been recorded in exteriorized fetuses, all the human subjects were term fetuses after either spontaneous or elective caesarean delivery, whereas the animals used were delivered

by caesarean section at varying gestational ages and left attached to the umbilical cord and placenta.

1.3.2.2 Intracardiac pressure:

The first true experiments on fetal cardiovascular physiology were performed by Pohlmann in 1909. He realised that to advance understanding, experiments on live hearts were necessary. He had noticed that if piglets were removed from the uterus of the sow soon after it had been killed, the piglet hearts kept beating for a time. By opening the chests of such piglets to expose the beating hearts, he was able to perform a number of investigations. He demonstrated that left and right ventricular volumes were equal by occluding the atrio-ventricular sulcus at the end of atrial systole and aspirating the blood from each ventricle. He also measured ventricular pressure by inserting 10 cm lengths of fine glass tubing into each ventricle either side of the ventricular septum. When the blood rose to the same level in each tube, he surmised that the pressure exerted by both ventricles was the same. Although there are problems in the methodology adopted in this work, particularly the fact that blood rose in the tubes aided by capillary action, it did mark the beginning of direct experimental cardiovascular research on live animals.

Work on fetal hearts continued to be restricted to animal studies and in 1937 Hamilton, Woodbury and Woods published the results of their study on intracardiac pressures within

the fetal heart (Hamilton et al 1937). They assumed that the right and left ventricular pressures were equal because the ductus arteriosus shunts blood between the two circuits; this also being the reasoning behind Kilian's theories. Using a hypodermic manometer i.e. a needle attached to a manometer, the pressure was measured in the ventricles of dog and rabbit fetuses after they had been delivered through the maternal abdominal wall but before spontaneous respiration had occurred. They discovered that:

1) the earlier the gestation, the lower the pressure

2) right and left ventricular pressures were equal

3) right atrial pressure was equal to or slightly higher then the left

4) there was no change in intraventricular pressures when the cord was clamped.

The question of whether right and left ventricles were of the same size and exerted the same pressure continued to interest investigators. Keen in 1942 stated that:

> "most observers are agreed that the capacities of the two ventricles in the fetal mammal are the same and that the right and left ventricles maintain equal pressures and expel equal volumes of blood".

1.3.2.3 Changes in fetal blood pressure with hypoxia:

The teams of Barclay and Barcroft were the first to use blood gas analysis in the study of the fetal cardiovascular physiology. Reynolds (1954) examined the effect of maternal hypoxia on the fetal circulation and noted that hypoxia exerted a minimal effect on venous pressure until severe

hypoxia occurred when a preterminal fall in venous pressure was noted. Mild hypoxia was associated with an increase in arterial pulse pressure.

1.3.2.4 Amniotic pressure and the effect of uterine activity on fetal pressure measurements:

Following the work of Barclay and Barcroft, it was apparent that there was a need for experimental methods wherein the intact fetus could be investigated still in utero. This was further demonstrated by Reynolds et al (1954) who reported that when amniotic pressure was increased, fetal pressures rose by the same amount. In Reynolds' work on monkeys, umbilical arterial pressure was recorded as 40/32 mm Hg. When intrauterine pressure was increased by the administration of pitocin to the mother, instillation of saline into the amniotic cavity or placing a weight on the uterus, the umbilical arterial pressure increased. Although this study demonstrated that increases in amniotic pressure affected fetal pressures, it was not stated whether fetal pressures were zeroed at amniotic pressure.

Reynolds' work clearly demonstrated interspecies variation and highlighted the difficulty in extrapolating from the animal model to the human fetus. The placentae of monkeys are usually double, and have an intercommunicating artery which was the vessel in which the blood pressure was measured. This arrangement does not exist in the human. Umbilical pressures in the sheep fetus must also be

interpreted with caution, as the sheep fetus has two umbilical veins whereas the human fetus has only one.

In 1958, Reynolds and Paul published further results on cardiovascular pressures in the sheep fetus and the changes which occurred with uterine activity. Normal umbilical venous pressure was recorded as 20-35 mm Hg with arterial pressures of 50-70 mm Hg systolic and 40-50 mm Hg diastolic. Measurement of arterial pressure during delivery implied that the fall in pressure was due to delivery of the fetus into air rather than the loss of amniotic fluid and uterine pressure, although the methodology is unclear and amniotic pressure was not recorded separately.

Subsequently, Reynolds and Mackie (1962) again demonstrated changes in fetal pressures with amniotic pressure. Although the need to record changes in maternal state e.g. breathing movements and amniotic pressure was clearly recognised, fetal pressures were not zeroed at amniotic pressures.

In the studies of Barclay and Barcroft, fetal pressures were recorded with the fetus delivered from the uterus. Fetal cardiovascular pressures recorded by Dawes (1962[a] and [b]), again in exteriorized fetal lambs, were similar to the results obtained by Barclay and Barcroft. These values were consistently lower than Reynolds', a fact probably explained by the failure of Reynolds to zero fetal pressures at amniotic pressure.

1.3.2.5 Umbilical venous pressure in relation to central venous pressure:

The need for precise methods and for amniotic pressure to be recorded separately and subtracted from the total fetal pressures was not appreciated by all workers. However, whether or not amniotic pressure was taken into account, all workers agreed that in the fetal sheep, the umbilical venous pressure was high when compared to central venous pressure as measured in the inferior vena cava or right atrium. It was assumed that this was necessary to keep the flow of blood through the umbilical vein and to prevent that vessel from collapsing (Reynolds et al 1952, Reynolds 1954). The source of pressure was suggested to be the anatomical sphincter in the ductus venosus (Chacko and Reynolds 1953).

1.3.3 STUDIES ON THE INTACT FETUS IN UTERO:

The methods and technology used in cardiovascular pressure measurements continued to become more sophisticated, with silicone strain transducers being more widely used. Advancement in surgical and pharmacological techniques meant that, in animal studies, fetuses could be returned to the uterus after catheters and transducers had been inserted into various cardiovascular sites. Measurements of physiological parameters could then be made with the mother in a resting state, unaffected by anaesthetic agents.

The sheep provided an excellent animal model for this type

of chronic physiological investigation (Assali et al 1974) as the sheep fetus is similar in weight to the human fetus at corresponding gestational ages, and the ovine uterus demonstrates minimal uterine activity in response to surgical manipulation. The rate of spontaneous abortion following such experiments on primates is very much higher.

Since the 1960's, Rudolph and Heymann in the USA have performed a large amount of basic investigation in chronically instrumented fetal animals in utero. Early studies by this team provided data on normal intraventricular pressures in the hearts of fetal goats and lambs from gestational ages 65 to 135 days (Heymann and Rudolph 1966). In this work, fetal pressures were zeroed at amniotic pressure, therefore giving a more accurate assessment of fetal intravascular pressures than previously available.

The same team examined the effect of exteriorization of the sheep fetus on cardiovascular function (Heymann and Rudolph 1967). They noted that, although there was little alteration in blood gases, major changes in the haemodynamics of the fetus occur after exteriorization. This supported the concept that investigation of the fetal cardiovascular system should be performed on the intact fetus in utero.

Having established methods and techniques for investigating

the cardiovascular system in the intact fetus (Rudolph and Heymann 1967), a large data base of normal physiological measurements has been, and is still being, produced by these two workers and their teams. With a successful system established for chronic measurements, they have performed longitudinal studies on the changes in the cardiovascular system with increasing gestational age (Rudolph and Heymann 1970, Lewis et al 1976). These studies have demonstrated a steady increase in cardiac output and umbilical artery mean pressure with age and fetal weight.

Chronic studies have also permitted further examination of the changes in the fetal cardiovascular system with maternal hypoxia and acidemia without the additional influence of maternal anaesthesia (Cohn et al 1972).

Other teams have also studied the intact fetus in utero and been able to investigate changes in the fetal cardiovascular system with growth and maternal activity (Reeves et al 1972, Lawler and Brace 1982).

1.3.4 STUDIES ON THE HUMAN FETUS:

Following the early work of Ribemont (1879) and Haselhorst (1929), few studies were performed on the human fetus until during the 1950's and 60's when termination of pregnancy by hysterotomy became a relatively common surgical procedure. Many investigators used this opportunity to gain access to midtrimester human fetuses. Inevitably these fetuses were

not in utero, although attempts to create an artificial uterine environment were made. Westin et al (1958) developed a technique for the perfusion of the human fetus in an artificial uterus, keeping the fetus at 25° centigrade in order to minimise metabolic rate and therefore extend the length of survival. They reported umbilical arterial systolic pressures of 25-50 mm Hg in fetuses weighing 200 - 375 g, although the pressures are difficult to interpret as the umbilical vessels were artificially perfused. The pressure in the surrounding liquid bath was not recorded.

In a later study using the same technique (Nyberg and Westin 1962) fetal arterial blood pressures of 24/17 - 60/53 mm Hg were recorded. In this experiment, no relationship between blood pressure and fetal weight was demonstrated. The effect of amniotic pressure on fetal blood pressure was also examined, but there is neither information on the method chosen to measure pressure within the artificial amniotic fluid, nor on how the pressure was increased. No effect of amniotic pressure on blood pressure was found.

These studies, apart from the ethical questions raised, provided no information which can be applied to the healthy fetus in utero. The conditions under which the fetuses were kept were not physiological, being cooled to 25°C and perfused with glucose solutions.

Rudolph et al also performed studies on human fetuses after termination of pregnancy by hysterotomy (1971). After the fetuses were delivered, but before the placenta had separated, umbilical vessels were cannulated. Cannulae were inserted into the carotid arteries from which blood pressure recordings were made. This study demonstrated an increase in systolic, diastolic and mean arterial pressure with fetal weight.

The umbilical vascular pressures of the term, healthy human fetus were studied by Margolis and Orcutt in 1960. The only available access to the umbilical circulation in the human was at the time of caesarean section, after the uterine incision and before delivery of the fetus, which was the method used by Haselhorst in 1929. The mean systolic blood pressure recorded was 53 mm Hg (range 50 - 56) and mean diastolic pressure was 42 mm Hg (range 36 - 46). Mean venous pressure was 24 mm Hg (range 17 - 32). One infant was 'depressed' at birth, and died after 32 hours with hyaline membrane disease. In this case, the arterial blood pressure was higher (60-85/30-40 mm Hg). The authors acknowledged that their measurements were not recorded in an undisturbed uterine environment, but used the results of Reynolds and Paul (1958) to support their study, as Reynolds and Paul had found that the opening of the uterus did not affect fetal pressures. However, this was not a reasonable comparison to make as Reynolds' work was performed on sheep, an animal whose uterus is far less

likely to contract in response to handling than the human uterus.

Access to the intact human fetal circulation remained impossible until the advent of fetoscopy and ultrasound. Using fetoscopy to visualise the umbilical vessels, Castle and MacKenzie measured the blood pressure in the umbilical vessels of the human fetus in utero (1986). They were the first workers to report a low umbilical venous pressure in the human fetus (2.2 +/- 1.7 mm Hg), with no increase with gestation. Mean arterial pressure was also recorded, with a range of 6.5 - 26.5 mm Hg, but with no demonstrable correlation with fetal age or weight. In this study, amniotic pressure was recorded separately and fetal pressures were zeroed at amniotic.

The technique of cardiac puncture, aided by real time ultrasound, was first described by Aberg et al in 1978 in a case of selective feticide in a twin pregnancy with one fetus affected with Hurler's disease. In 1982, Bang et al utilised ultrasound to guide a needle into the fetal heart in order to perform intravascular transfusion in a case of severe Rhesus haemolytic disease. With continuing advances in ultrasound imaging, ultrasound guided fetal blood sampling from the umbilical cord became a technique widely applied following the publication of the first large series by Daffos et al (1985). Fetal blood sampling, or cordocentesis, was then adapted for intravascular pressure

measurements by teams in the UK (Nicolini et al 1989 [b]) and the USA (Weiner et al 1989 [a]). Both teams used fluid filled systems and produced similar results to each other, which were in accordance with Castle and Mackenzie's work.

1.4 CARDIAC ASSESSMENT OF THE HUMAN FETUS IN UTERO:

High resolution B and M mode ultrasound, together with continuous wave, pulsed wave and colour Doppler studies, permits detailed examination of the structure of the fetal heart from 18 weeks gestation using abdominal scanning techniques (Allan et al 1980) and as early as 12 weeks gestation if a vaginal transducer is employed (Johnson et al 1992 [a]). Some functional information can be gleaned from Doppler interrogation of cardiac valves, and normal ranges exist for such flow (Allan 1986).

In postnatal life, Doppler studies can provide information regarding pressure gradients across abnormal heart valves. These noninvasive techniques allow much greater diagnostic information to be gained than by B and M mode echocardiography alone, but there are limitations to the quantitization of lesions such as aortic stenosis by Doppler interrogation of the valve. Some of these problems may be overcome by the use of nonimaging continuous wave Doppler in postnatal examinations (Wilde 1989). However, this is not appropriate to fetal examination.

Moreover, the pressure waveform obtained during cardiac

catheterization studies provides additional functional information (Fontana and Lewis 1985). It is valuable to obtain exact pulse and end diastolic pressure recordings prior to cardiac intervention. This information is not available from Doppler studies alone. In addition, catheterization studies allow accurate diagnosis of valvular lesions, provide baseline data and give prognostic information. Hitherto, such information has not been available prenatally.

Details of Patient Groups:

Procedure:		Number of patients:
Amniocentesis		90
Diagnostic fetal blood sampling		91
Failed	***6***	
Cord	***76***	
Heart	***9***	
Termination of pregnancy		59
Abnormal fetus	***17***	
Normal fetus	***42***	
Failed cardiac puncture	*20*	
1 chamber sampled	*18*	
2 chambers sampled	*18*	
3 chambers sampled	*3*	
Cardiac procedures		6
Total		**246**

2. METHODS:

All pressures recorded for the establishment of the data base on which this thesis is founded were performed during indicated procedures. These included amniocentesis, ultrasound guided fetal blood sampling and midtrimester termination of pregnancy. All procedures were performed in the Fetal Medicine Unit at Guy's Hospital, London and the work had been granted approval by the local Ethical Committee.

2.1 PATIENTS:

A total of 246 patients were studied. Informed consent was obtained in each case after explanation of the procedure and reasons for measuring pressures by myself or my supervisor, Mr D Maxwell.

Patients were referred to the Fetal Medicine Unit from the antenatal clinic at Guy's Hospital, other hospitals within the South East Thames region and from further afield. Whilst the majority of referrals were directly to the Fetal Medicine Unit, a large number of patients were seen at the request of the South East Thames Regional Genetics Centre and the Department of Fetal Cardiology at Guy's Hospital.

Invasive procedures were performed for a number of indications. The main indication for amniocentesis was investigation of fetal karyotype because of raised maternal age (35 years and above). Fetal blood sampling was

performed for rapid karyotyping in cases of structural abnormality, failed amniocentesis and women aged 35 or more who booked for antenatal care late in the second trimester. Other indications included family history of genetic diseases for example fragile X syndrome, cysteinosis etc. Midtrimester termination of pregnancy was performed in cases of fetal abnormality and where section 13B of the Abortion Act 1967 was satisfied (Form HSA4, appendix I).

In ongoing pregnancies, only one fetal site was sampled in addition to measuring amniotic pressure. The site chosen in these cases was always the easiest for access into the fetal circulation, being the placental insertion of the umbilical cord in the vast majority.

2.1.1.a Amniocentesis:

Amniotic pressure was recorded in 90 women undergoing diagnostic amniocentesis, where liquor volume was assessed as being normal. Amniotic pressure was also recorded in all women undergoing fetal blood sampling or termination of pregnancy.

In addition, a small number of women whose pregnancies were complicated by abnormalities of liquor volume were investigated. The presence of polyhydramnios or oligohydramnios alone was not the indication for an invasive procedure. However, in some cases amniocentesis to reduce and amnioinfusion to increase the liquor volume were performed. 14 cases of polyhydramnios were investigated. The cases of oligohydramnios were divided into those with evidence of ruptured membranes (n = 4) and intact membranes (n = 10).

2.1.1 Fetal blood sampling - Venous puncture:

We recorded the umbilical venous pressure during fetal blood sampling or termination of pregnancy in 22 fetuses with no abnormality, and in 14 with a structural abnormality which was not anticipated would exert an effect on venous pressure. All fetuses had structurally normal hearts on ultrasound examination. The indications for the procedure in the structurally normal fetuses are shown in Table 2.1, and the underlying structural abnormalities of

Table 2.1

Indication for Umbilical Vein Puncture in Structurally Normal Fetuses.

Investigation of growth retardation (nonhypoxic, normoacidaemic)	5
Investigation of oligohydramnios	4
Investigation of Rhesus affected fetus (nonhydropic, Hb > 8g/dl)	3
Midtrimester termination of pregnancy	2
Failed amniocentesis culture	2
Karyotype for suspected abnormality, (later shown to be normal)	2
Investigation of genetic disease	2
Fragile X	1
Cysteinosis	1
Elevated maternal serum alphafetoprotein	1
Late booking, raised maternal age	1
Total	**22**

the abnormal fetuses in Table 2.2. The indication for fetal blood sampling in the abnormal fetuses was rapid karyotyping.

Table 2.2

Structural Abnormalities		
Abnormality of urinary tract		9
Hydronephrosis	6	
Multicystic kidney	3	
Hydrocephalus		2
Pleural effusion		1
Microcephaly		1
Congenital cystic adenomatoid malformation of the lung		1
Total		**14**

In addition, we recorded umbilical venous pressure in 12 fetuses with structural congenital heart disease, the details of which are shown in Table 2.3.

In 15 cases of nonimmune hydrops, fetal blood sampling and measurement of umbilical venous pressure were performed. Nonimmune hydrops is defined as the presence of excess fluid in two or more fetal compartments in the absence of circulating antibodies to red cell antigens (Romero et al 1988). The indications for fetal blood sampling in the investigation of nonimmune hydrops include rapid karyotype,

Table 2.3

Congenital Heart Disease Underlying diagnosis	
Ventricular septal defect	2
Atrioventricular septal defect	2
Coarctation of aorta	2
Pericardial effusion	2
Absent pulmonary valve syndrome	1
Ectopia cordis	1
Double outlet right ventricle, ventricular septal defect	2
Total	**12**

full blood count and viral studies, particularly parvovirus. The underlying pathology of these cases is provided in Table 2.4.

Umbilical venous pressure was also recorded in three cases of congenital diaphragmatic hernia when fetal blood sampling performed for rapid karyotyping.

Table 2.4

Nonimmune Hydrops - Venous Puncture:
Underlying pathology.

Patient no:	Gestation	Pathology
1	33	SVT
2	30	SVT
3	29	CHB
4	33	SVT
5	32	SVT
6	31	Intermittent tachyarrhythmia
7	29	Twin-twin transfusion
8	20	Fallot's. Intrauterine infection
9	24	Anaemia
10	22	Unknown
11	29	Apert Syndrome
12	30	SVT. Multiple anomalies
13	18	Partial deletion chrom 10.
14	34	SVT
15	26	Meconium peritonitis

SVT supraventricular tachycardia. CHB congenital heart block. Fallot's = tetralogy of Fallot. chrom = chromosome.

2.1.2 Fetal blood sampling - Arterial puncture:

Umbilical arterial pressure was recorded in 13 cases, of whom two had cardiac malformations, five nonimmune hydrops and one abnormal umbilical artery Doppler blood flow studies with absent end diastolic flow. Details of these cases are provided in Table 2.5.

Table 2.5

Indication for Fetal Blood Sampling Arterial Puncture

Normal fetus			**3**
Mosaic on amniocentesis		1	
Late booked, raised maternal age		1	
Placental abnormality		1	
Abnormal fetus			**10**
Nonimmune hydrops		5	
Cardiac abnormalities		2	
Tricuspid incompetence	1		
Unspecified	1		
Intrauterine growth retardation - absent end diastolic flow		1	
Trisomy 13		1	
Diaphragmatic hernia		1	
Total			**13**

2.1.3 Cardiac puncture:

Of 29 fetuses investigated by left ventricular puncture, 16 were normal and five had noncardiac anomalies. Details of the fetuses in whom left ventricular pressure was recorded are provided in Table 2.6. Seven cases of cardiac malformation were investigated, but in one case of aortic atresia the pressure was not zeroed correctly, and this

case has therefore been excluded from the results.

Table 2.6

Left Ventricular Puncture:
Underlying Diagnosis

Normal fetus		16
Abnormal fetus, normal heart		5
Sickle cell disease	1	
Spina bifida	1	
Glutaricaciduria type II	1	
Trisomy 13	1	
Hydrocephalus	1	
Nonimmune Hydrops		2
Cardiac malformation		6
Critical aortic stenosis	3	
Mitral atresia	1	
Coarctation of aorta	1	
Ventricular disproportion	1	
Total		**29**

Right ventricular pressures were obtained in 19 fetuses with normal hearts. Details are given in Table 2.7. In three cases of cardiac malformation right ventricular pressures were recorded, two of these also having left ventricular pressure measured.

The pressure within the left atrium was recorded in 10 normal fetuses and four with structural abnormalities but normal hearts on ultrasound examination. The details of these cases are provided in Table 2.8.

Table 2.7

Right Ventricular Puncture:
Underlying Diagnosis

Normal fetus		**12**
Abnormal fetus, normal heart		**7**
Hydrocephalus	2	
Trisomy 13	1	
Glutaricaciduria type II	1	
Urethral agenesis	1	
Spina bifida	1	
Adult polycystic kidney disease	1	
Nonimmune Hydrops		**1**
Cardiac malformation		**3**
Mitral atresia, DORV	1	
Ventricular septal defect, DORV	1	
Ventricular disproportion	1	
Total		**23**

DORV = Double outlet right ventricle

Table 2.8

Left Atrial Puncture:
Underlying Diagnosis

Normal fetus		**10**
Abnormal fetus, normal heart		**4**
Urethral agenesis	1	
Hydrocephalus	1	
Spina bifida	1	
Glutaricaciduria type II	1	
Total		**14**

In 10 cases right atrial pressures were recorded and clinical details are shown in Table 2.9. Eight normal hearts were investigated, four being in fetuses with other structural abnormalities.

Table 2.9

Right Atrial Puncture:
Underlying Diagnosis

Normal fetus		**4**
Abnormal fetus, normal heart		**4**
Sickle cell disease	1	
Trisomy 13	1	
Urethral agenesis	1	
Camptomelic dysplasia	1	
Nonimmune hydrops		**1**
Cardiac malformation		**1**
Ventricular septal defect, DORV		
Total		**10**

DORV = Double outlet right ventricle.

2.2 SCANNING PROTOCOL:

All patients, apart from those undergoing amniocentesis, had a detailed fetal anomaly scan using a 3.5 MHz (sector or linear) or 5 MHz (linear) transducer on an Acuson 128 high resolution ultrasound scanner (Acuson, Mountain View, California) or 5 MHz curvilinear or 3.5 MHz linear transducer on an Aloka 620 (Aloka Co. Ltd., Tokyo, Japan). Patients undergoing amniocentesis had fetal biometry performed to confirm dates, but a formal anatomical survey was not carried out. In other patients, all fetal anatomy was examined, including the heart for which the four chamber view and origin of the great vessels were identified (Allan et al 1980). Doppler blood flow studies of the umbilical artery, middle cerebral and descending aorta were performed in some cases. When a fetal cardiac defect was suspected, detailed fetal echocardiography was performed in the Department of Fetal Cardiology using a 5 MHz transducer on an Ultramark 4 (Advanced Technical Laboratories, Washington, USA) or Hewlett Packard 77020 AC Ultrasound system (Hewlett Packard Ltd, Uxbridge, Middlesex). If the fetal heart appeared to be larger than normal, filling more than one third of the chest at the level of the four chamber view, fetal cardiac size was measured and the cardiothoracic ratio estimated (Paladini et al 1990). This requires measurement of the cardiac and thoracic circumferences at the level of the four chamber view of the fetal heart (Figure 2.1). The cardiothoracic ratio obtained was compared with the normal range (Figure

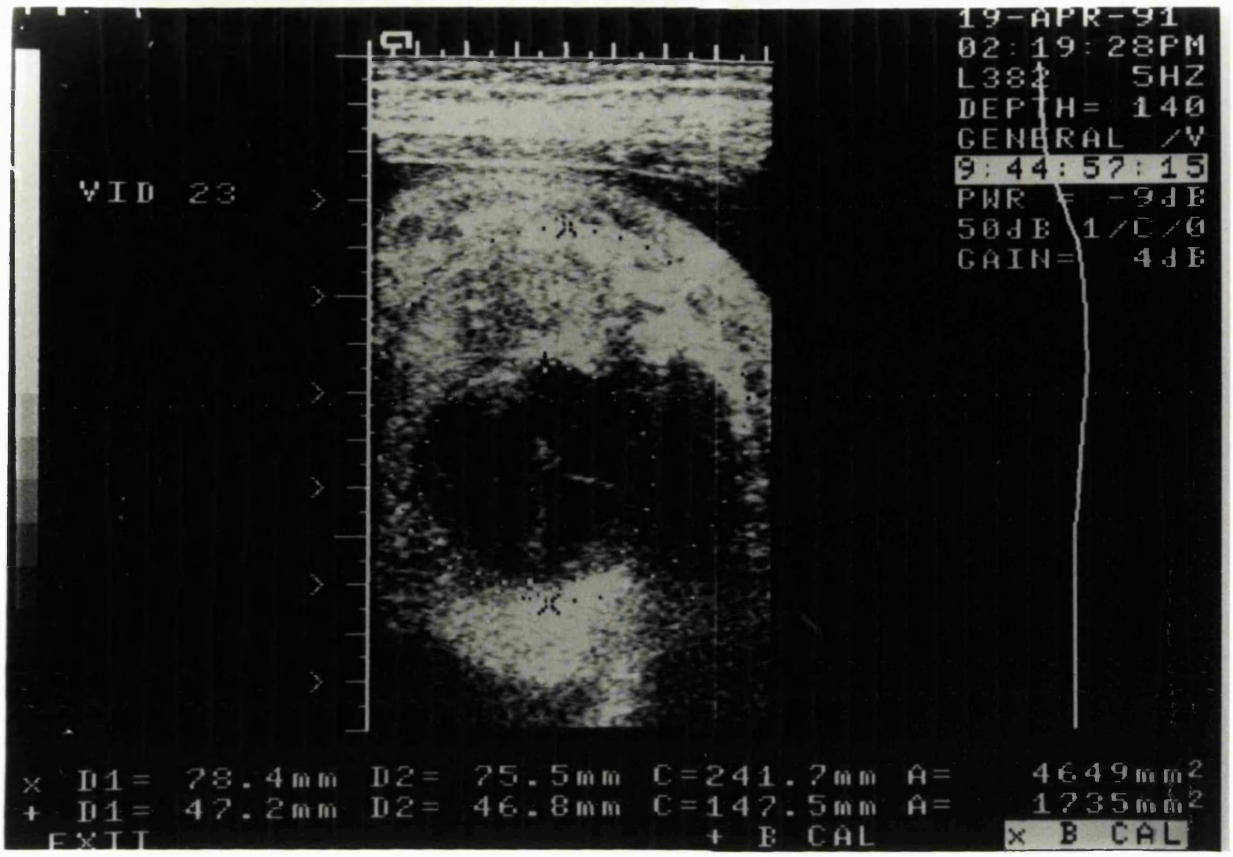


Figure 2.1 Ultrasound picture of measurement of cardiothoracic ratio.

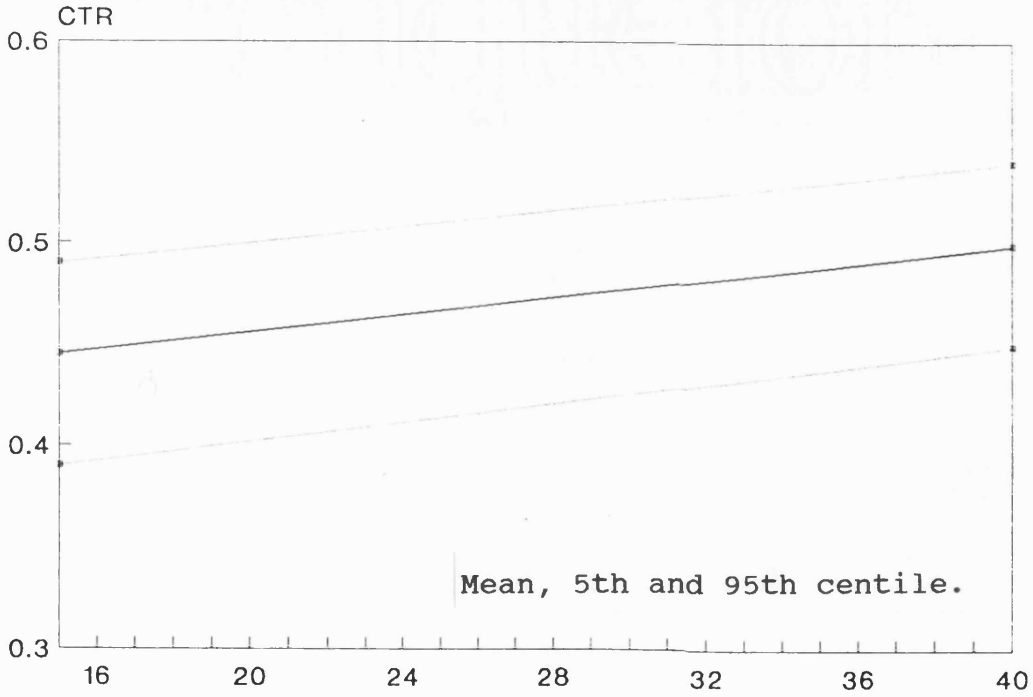


Figure 2.2 Reference range for cardiothoracic ratio

2.2) to assess whether cardiomegaly was present.

Gestational age was assessed from the date of the last menstrual period. Ultrasound measurement of biparietal diameter, head circumference, abdominal circumference and femur length were performed and compared to standard charts (Campbell and Newman 1971 [biparietal diameter], Campbell unpublished data [femur length], Campbell and Thoms [unpublished data, head circumference and abdominal circumference]). If there was a discrepancy of greater than seven days between the menstrual dates and ultrasound assessment of gestation, the pregnancy was redated according to the ultrasound assessment unless menstrual dates had been confirmed by an earlier scan (Hadlock 1990).

Liquor volume was assessed visually during the scan. If it appeared increased or decreased an objective assessment was made using the four quadrant amniotic fluid index (Phelan et al 1987[a]). This method of liquor assessment has little interobserver error (Rutherford et al 1987) and is therefore the standard procedure in our unit. The vertical depth of the maximum liquor pool in each of the four quadrants of the uterus was measured, and added together. Polyhydramnios was defined as an amniotic fluid index exceeding 16 cm below 24 weeks and 20 cm at gestations greater than 24 weeks (Phelan et al 1987[b]). Oligohydramnios was defined as the presence of a single pool of liquor measuring 1 cm or less.

2.3 PROCEDURES:

Following initial ultrasound examination and explanation of the planned procedure, all investigations were carried out using aseptic technique, the operator wearing sterile surgical gloves. The maternal skin was cleansed with aqueous povidone iodine solution (Betadine) or ethyl alcohol. Local anaesthetic (10 ml 1% lignocaine) was infiltrated into the skin and subcuticular tissues prior to fetal blood sampling and termination of pregnancy. Holding the ultrasound transducer in one hand, the operator inserted a 22 gauge single use 9 or 17 cm spinal needle (Becton Dickinson) into the uterus under continuous ultrasound guidance. The needle was guided into the compartment under investigation. Once the needle was in place, the stilette was withdrawn, a syringe attached to the hub of the needle and the appropriate sample aspirated. Pressures were measured after the diagnostic sample had been taken and prior to the needle being withdrawn as it was felt unethical to carry out the research procedure before the clinically indicated investigation. However, at the beginning of the project, pressures were recorded both before and after diagnostic samples had been obtained in ten termination cases, with no demonstrable difference in pressure recorded (see appendix II). If the needle became dislodged before pressure measurements were obtained, on ethical grounds it was not resited once diagnostic samples had been obtained unless the pregnancy was being terminated. At the end of diagnostic procedures, the mother

was shown the fetal heart movement.

If the mothers blood group was Rhesus negative, anti D 250 IU was given intramuscularly after amniocentesis and 500 IU following fetal blood sampling in order to prevent Rhesus immunization.

2.3.1 Amniocentesis:

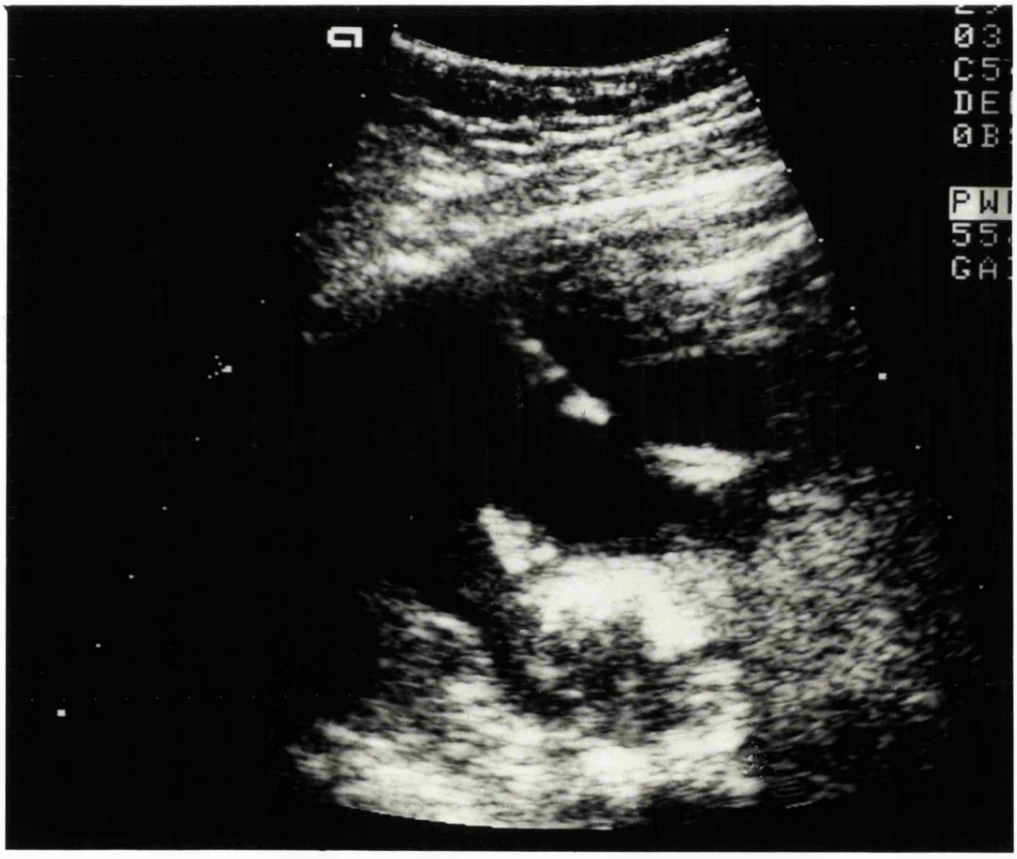


Figure 2.3: Ultrasound picture of needle free in pool of liquor during amniocentesis.

2.3.1.a Subtraction Manometry:

In ten cases, subtraction manometry was employed in order to assess any change in amniotic pressure over time during fetal blood sampling. Two pressure transducers were connected to the Mingograf and calibrated. One 22 gauge needle was inserted into a pool of amniotic fluid, and connected to the first pressure transducer. Intramniotic pressure was measured continuously. A second needle was then used to take the blood sample. Once the fetal blood sample had been taken, the second transducer was connected to this needle and vascular and amniotic pressure recorded simultaneously.

The main indication for amniocentesis in the group of patients studied was karyotyping for raised maternal age. After initial scan for dating and explanation of the procedure to the patient, a suitable pool of liquor was selected by ultrasound examination, avoiding the placenta if possible. Once the needle was in place, Figure 2.3, and the stilette withdrawn, a 10 ml syringe was attached to the hub of the needle and 20 ml of liquor aspirated with continuous ultrasound visualisation.

The risk of pregnancy loss following amniocentesis is estimated to be 0.5 - 1.5% (Canadian Medical Research Council 1977, NICHD Study 1978, MRC Study 1978, Tabor et al 1986).

2.3.2 Fetal Blood Sampling:

Fetoscopy was initially employed for fetal blood sampling but has been superseded by ultrasound guidance due to a lower complication rate. The loss rate after fetoscopy was 7% (Whittle 1989). Ultrasound guided fetal blood sampling was first described by Bang et al in 1982, taking blood from the fetal heart. The preferred technique of puncture of the umbilical cord at the placental insertion was described by Daffos et al in 1985. Other workers employ the intrahepatic portion of the umbilical vein (Nicolini et al 1988). In uncomplicated cases, 1-2% of pregnancies will be lost following ultrasound guided fetal blood sampling (Daffos et al 1985, Maxwell et al 1991).

The indications for fetal blood sampling include rapid karyotyping, blood gas analysis, haematological and virological studies. These may be indicated by family history, raised maternal age, the presence of fetal structural abnormality, fetal hydrops and intrauterine growth retardation.

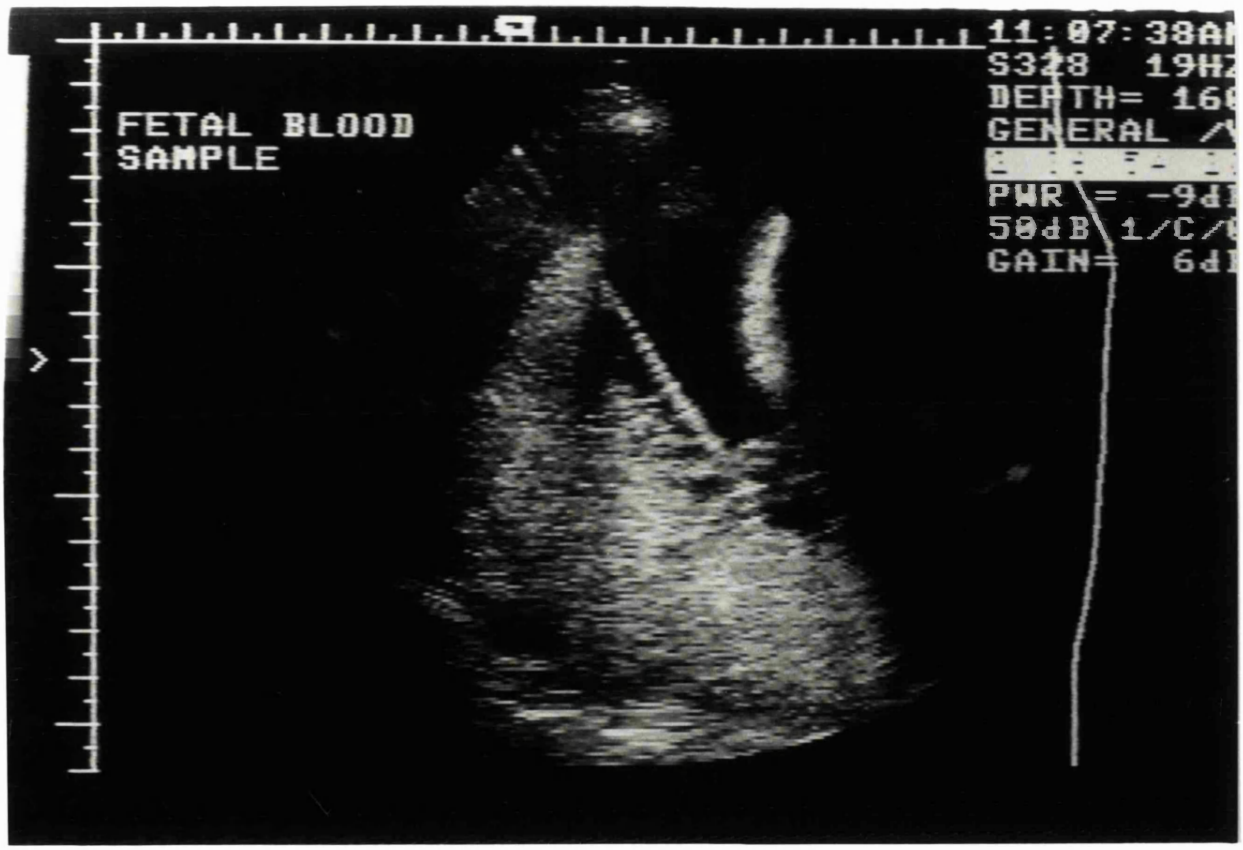


Figure 2.4: Needle in cord insertion during cordocentesis

In our unit, the preferred site for fetal blood sampling is the placental insertion of the umbilical cord (Figure 2.4). If this cannot be accessed due to fetal lie or poor visualisation, alternative sites are the fetal insertion or a free loop of the cord, the intrahepatic portion of the

umbilical vein or the fetal heart. In our experience, there is no increased risk whichever route is chosen (Maxwell et al 1991). We do not attempt to select an individual vessel for sampling; however, the vein is most commonly sampled.

Blood was aspirated using heparinised 1 ml syringes, the volume required usually being 1.5-2.0 ml. Table 2.10 shows the volume of blood required for the tests performed.

Table 2.10

Tests performed on fetal blood:

Test	Volume required (ml)
Karyotype	0.3-0.5
Full blood count	0.2-0.4
Blood gases	0.2
Biochemistry -	
electrolytes and urea	0.3-0.5
protein and albumin	0.2-0.4
Virology	0.5-1.0
Blood group	0.2-0.4
Drug levels	0.5

Following removal of the needle from the cord, the puncture site was observed for bleeding. Once the procedure was complete, the mother was shown the fetal heart movement for reassurance.

2.3.3 Midtrimester termination of pregnancy:

Midtrimester termination of pregnancy can be performed in a number of ways. Dilatation of the cervix and evacuation of products of conception is inappropriate in cases of fetal abnormality where postmortem information is required. Intra or extra amniotic administration of prostaglandins are the alternatives, with administration of intra amniotic prostaglandin being the routine procedure at Guy's Hospital for termination of pregnancies exceeding 16 weeks gestation.

In all cases prior to termination, an attempt was made to enter the fetal heart. Ideally, access was obtained through the anterior chest wall, entering the right or left ventricle at the apex. Figure 2.5 shows an ultrasound picture of a needle in the right ventricle of the fetal heart with this approach. The fetal lie sometimes meant that the only approach available was through the posterior chest wall and atria or laterally through the lung fields. Once the tip of the needle was in situ, the stilette was removed and a 1 ml heparinised syringe attached to the hub of the needle. Blood was aspirated to ensure that the tip of the needle was free within the cardiac chamber under study. Pressure was recorded and, if possible, the needle resited to measure pressures in more than one chamber. The needle was then withdrawn into the amniotic cavity, intra amniotic pressure measured and 10 mg Prostin E2 (Upjohn Ltd, Crawley, West Sussex) instilled under continuous ultrasound guidance. At the end of the

procedure, the needle was withdrawn from the maternal abdomen.

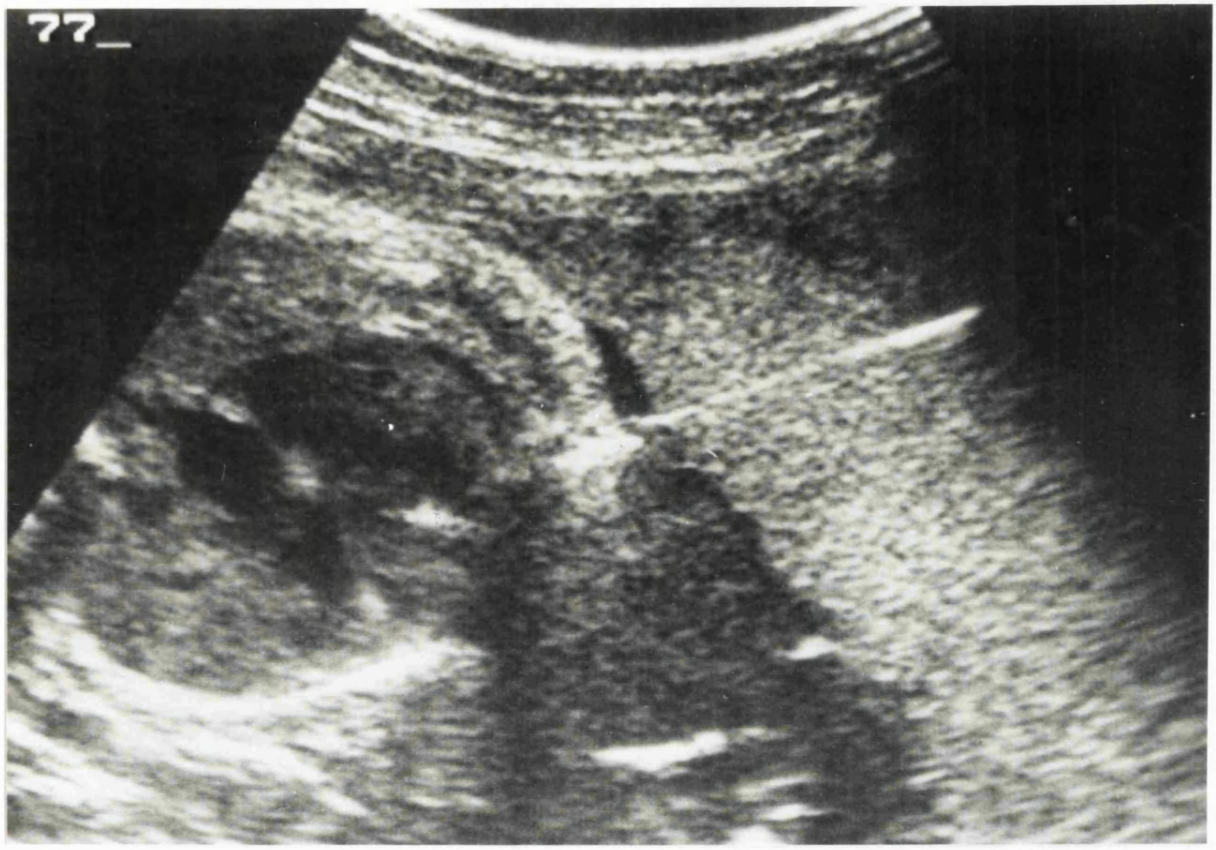


Figure 2.5: Ultrasound picture of needle inserted into the right ventricle of fetal heart.

2.4 FOLLOW UP:

2.4.1 Abnormal pregnancies:

When a fetal anomaly was diagnosed prenatally, postnatal or postmortem examination was sought as appropriate. If a pregnancy was terminated for fetal cardiac abnormality, most fetuses were sent to the Department of Pathology at Guy's, where they underwent detailed cardiac examination. When no cardiac lesion was present, postmortem examination was sought as appropriate at the referring hospital or at Guy's. Postmortem reports were obtained from the relevant Pathology Department in all cases.

In pregnancies which were not interrupted, both the patient and referring doctor were asked to complete and return standard follow up forms after delivery and postnatal examination (see appendix III). The majority of babies with congenital cardiac abnormalities where the pregnancy continued to term were delivered at Guy's, or attended the Department of Paediatric Cardiology for postnatal echocardiography.

2.4.2 Normal pregnancies:

In cases of termination of pregnancy where there was no evidence of fetal abnormality, post mortem examination was not performed on the abortuses. However, the fetal heart was examined for structural abnormality using ultrasound before the termination. Allan et al (1980) and Davis et al (1990) demonstrated excellent correlation between the

accuracy of prenatal echocardiography and post natal examination in normal and abnormal hearts.

All patients in whom there was no evidence of fetal abnormality and the pregnancy continued to term were asked to complete a standard follow up form and return it after delivery.

2.5 EQUIPMENT:

Intrauterine and intrafetal pressures were measured using a fluid filled system. This is the only system available at the present time, as there is not a catheter tip transducer small enough for our purposes. The technique employed was an adaptation of one well established in paediatric and adult cardiology. The measuring system consisted of a solid state pressure transducer connected to a recording device.

A standard 100 cm manometer tube filled with sterile heparinised normal saline (1 unit/ml) was connected at one end to the hub of the needle. The other end was connected via a three way tap to one aperture of a disposable plastic pressure dome. The other aperture was connected by a second three way tap to a 20 ml syringe full of sterile heparinised normal saline (Figure 2.6). The pressure dome screwed on to the transducer with an interface of water.

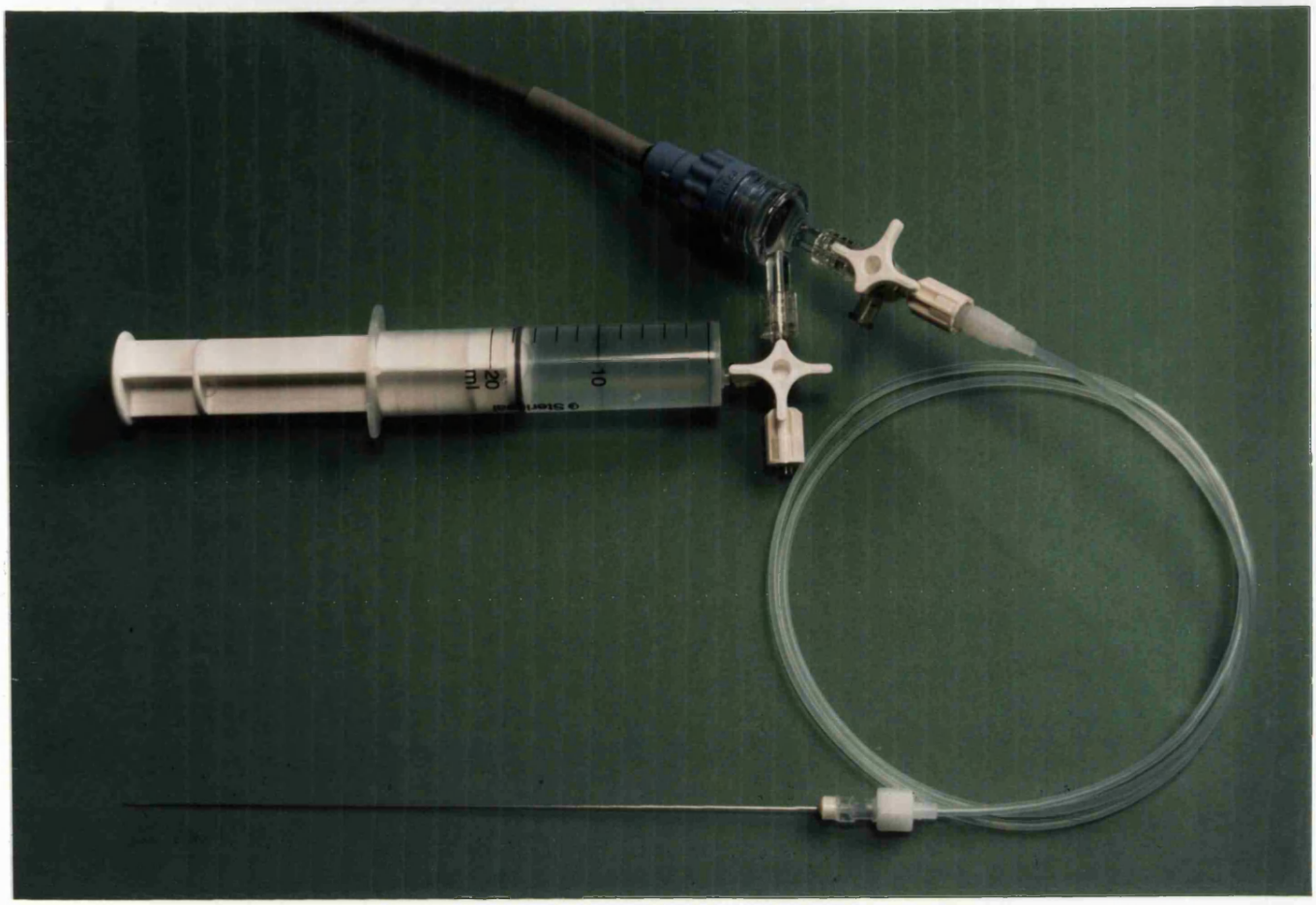


Figure 2.6: P23-XL Solid state pressure transducer, with GB001 disposable dome, manometer tube and 22 gauge needle.

2.5.1 System characteristics:

2.5.1.1 Needle. The 22 gauge single use spinal needle used was made of stainless steel. It had a quincke type point, and was provided with a stilette. The needles used for intrafetal measurements were always 17 cm, although for simple amniocentesis the 9 cm needle was more commonly used. The volume of the 17 cm needle was 0.1 ml.

2.5.1.2 Manometer line. 100 cm long sterile manometer tubes with an internal diameter of 1.5 mm and capacity of 2.00 ml with Luer fittings at each end were used. (Vygon,

85440 Ecouen, France).

2.5.1.3 Pressure dome. GB001 sterile, single use pressure domes were used (MDS. Ltd, West Sussex, UK). These have two apertures with Luer fittings, and a silicone diaphragm. They connect to the pressure transducer by a screw fitting, with an interface of water.

2.5.1.4 Pressure transducer. The P23-XL pressure transducer (Viggo Spectramed, California, USA) is a solid state pressure transducer with silicone chip. It has a volume displacement of 0.04 mm^3/100 mm Hg and pressure range of -50 to +300 mm Hg. The transducer sensitivity is 5μV/V/mm Hg +/- 1% with reproducibility of +/- 0.6 mm Hg (manufacturer's technical data).

2.5.1.5 Recording device. The Siemens Mingograf 7 (Siemens PLC, Sunbury on Thames, Middlesex) is an eight channel recording device with simultaneous paper and oscilloscope display (Figure 2.7). Signals from the pressure transducer were amplified by a Siemens pressure amplifier 863, with a high pass filter of 160 Hz, and ranges from 20 to 200 mm Hg. Mean pressures were recorded by electrical integration.

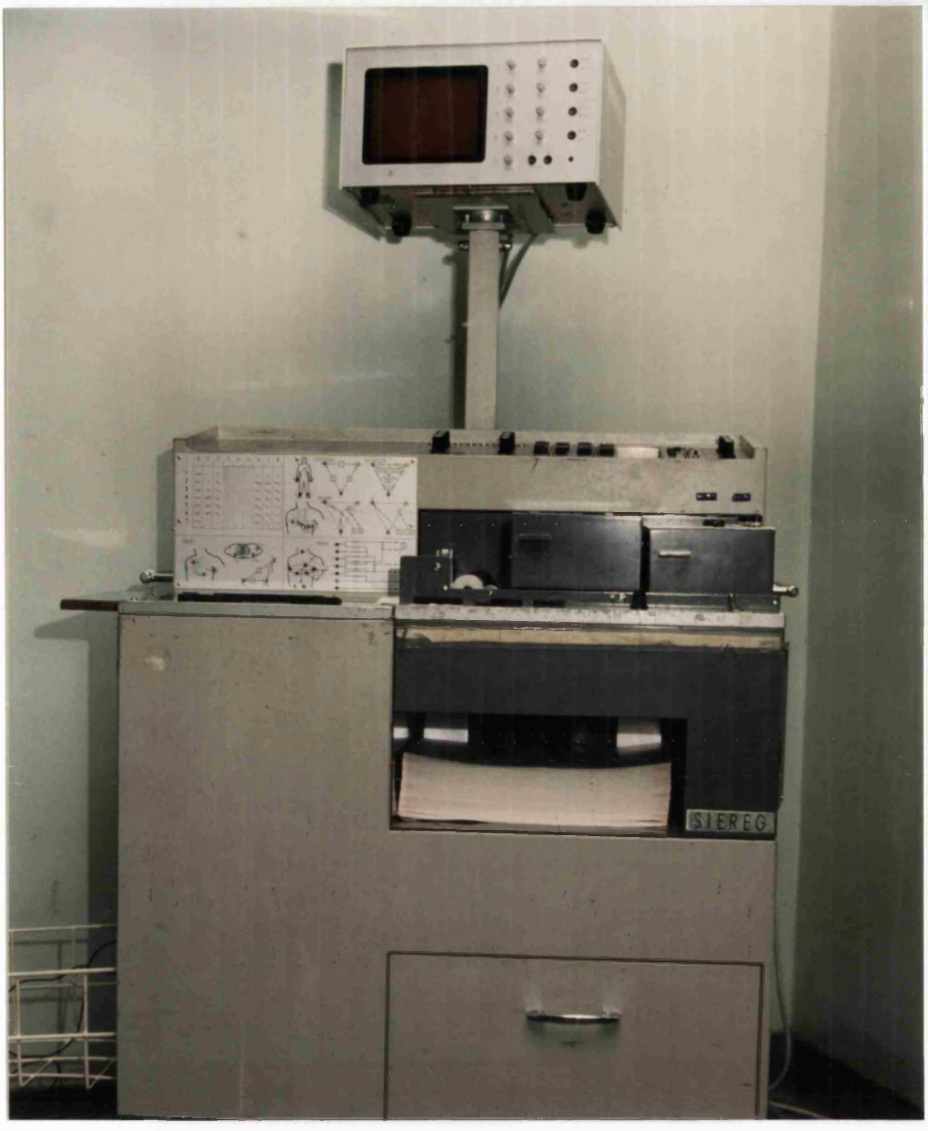


Figure 2.7: Siemens Mingograf.

2.5.1.6 Total system characteristics: The frequency response of the system was measured by generation of a square wave fall in pressure (the 'pop' test - Butler and Oldershaw 1986). After calibration of the system, the end of the needle was inserted into a bung on the end of an adapted syringe which contained 2 ml of saline. The plunger was set at a fifteenth of the remaining volume of the syringe. With the system set ready to record pressure at 100 mm Hg range, the syringe plunger was smoothly and rapidly withdrawn. This applied a negative pressure of approximately 1/15 atmosphere (50 mm Hg). The waveform obtained is shown in Figure 2.8. There is almost no overshoot, being less than 3% of the pressure applied.

Calculation of frequency response was performed as below:

$$f_o = \frac{1}{2\pi\Im} \qquad \text{where } f_o = \text{frequency response}, \quad \Im = \text{time constant}$$

The time constant $\Im$ is the time taken to decay to 0.3678 of the step function, where 0.3678 = 1/e.

For the trace in Figure 2.8:

$$f_o = \frac{1}{2 \times 3.142 \times 0.02} = 7.94 \text{ Hz}$$

The 'pop test' was repeated 23 times over four occasions. There was no discernible difference between waveforms obtained in these tests.

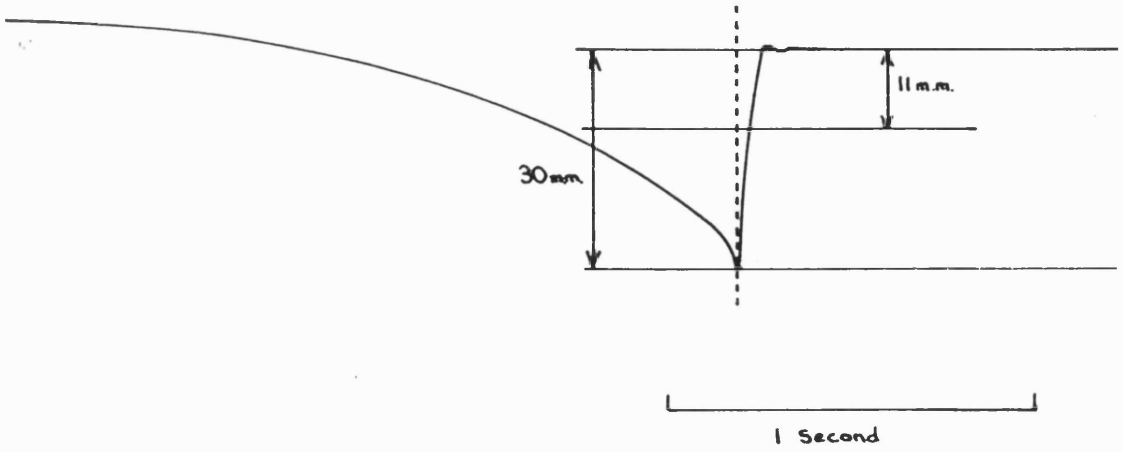


Figure 2.8: Waveform obtained in "pop" test, for calculation of frequency response.

2.6 SETTING UP AND CALIBRATION:

The Mingograf was switched on at least 30 minutes prior to recording to allow time for calibration and stabilising of thermal drift. 500 units of heparin were added to 500 ml of sterile normal saline. 20 ml of heparinised saline was then aspirated into a 20 ml syringe. This was connected to a three way tap, which was then attached to the side aperture of the GB001 pressure dome. A second three way tap was attached to the upper aperture of the dome. With the three way taps turned so that the syringe communicated to air across the dome and second three way tap, heparinised saline was flushed through the dome, ensuring that no air bubbles were present (Figure 2.9). The dome was then left

open to air only, at the sidearm of the upper three way tap (Figure 2.10).

A small volume of water was placed on the pressure transducer, and the dome screwed firmly and securely onto the transducer which was placed in a specially designed holder. The transducer was then connected to one of the pressure amplifiers of the Mingograf. The system was balanced, using the button which balances the Wheatstone bridge within the pressure transducer. The paper transport was turned on and the baseline adjusted, using the shift control, to a suitable line on the paper. The system was balanced every few minutes until the baseline was stable. With the amplifier range set to 100 mm Hg, the test button was depressed. The deviation of the inkjet was checked, and if it did not correspond to 50 mm, the inkjet was adjusted while the test button was depressed using the gain control. The transducer was balanced again, and turned off to air. The side arm of the lateral three way tap was then attached to a mercury sphygmomanometer dedicated to the purpose. The cuff was inflated to a pressure of 100 mm Hg, and connected to the dome (Figure 2.11). The deflection on the paper record should be 50 mm. If this was not so, fine adjustments were made using a screw above the test button on the pressure amplifier. The sphygmomanometer was disconnected, and the system opened to air again and balanced. If there was marked electrical drift, the system was recalibrated.

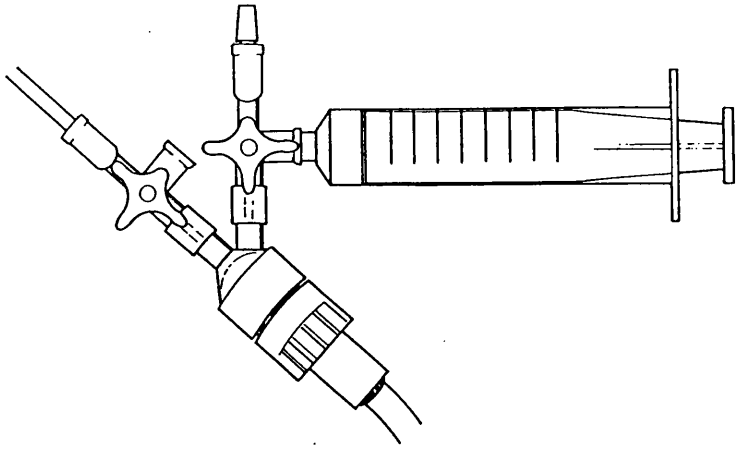


Figure 2.9: Arrangement of system for initial flushing.

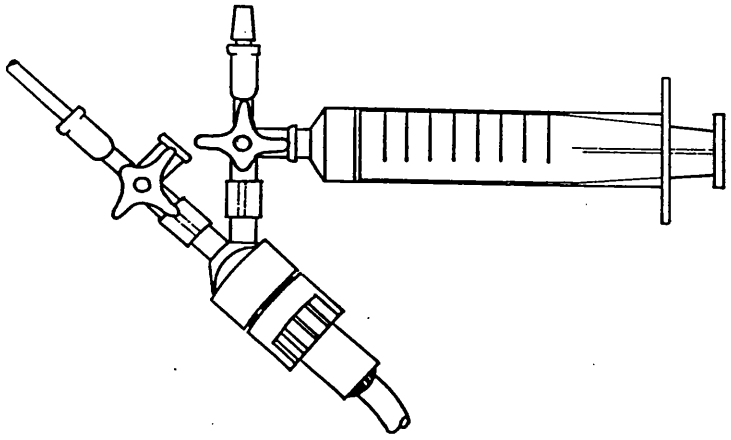


Figure 2.10: System left open to air.

Once the system was calibrated, the manometer tube was attached to the forward aperture of the dome via the three way tap, and the system flushed with heparinised normal saline, again ensuring that no air bubbles were present. The system was left open to air only at the forward three way tap until ready for use. The manometer tube was kept sterile.

2.7 PRESSURE MEASUREMENTS:

Prior to the investigative procedures being performed, the pressure system was calibrated, and the pressure transducer placed at the level of maternal midabdomen. Once diagnostic samples had been obtained, and after balancing the transducer to air, the manometer tube was attached to the hub of the needle. The system was purged, by flushing a small volume (0.1-0.2 ml) of heparinised normal saline, so that the blood/saline interface was at the tip rather than the hub of the needle. The system was then left open to the fetal compartment under review and pressures recorded on the Mingograf (Figure 2.12). All pressures were recorded with the tip of the needle lying freely in the compartment under review, with the mother lying quietly. Most amniotic and venous pressures were measured with the amplifier range at 20 mm Hg, but for fetal hearts, the range was either 40 mm Hg or 100 mm Hg as appropriate. Pressures were recorded for 20 - 30 seconds, and the mean pressure was recorded by electrical integration by depressing the '*mean*' button on the pressure amplifier. Once a satisfactory recording had

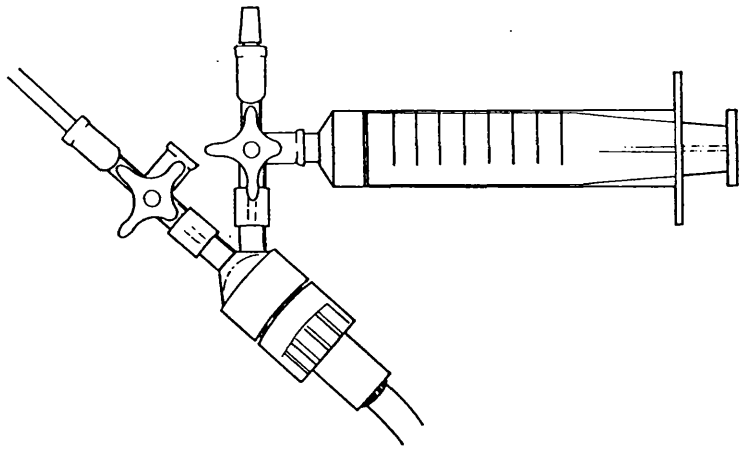


Figure 2.11: Calibration of system.

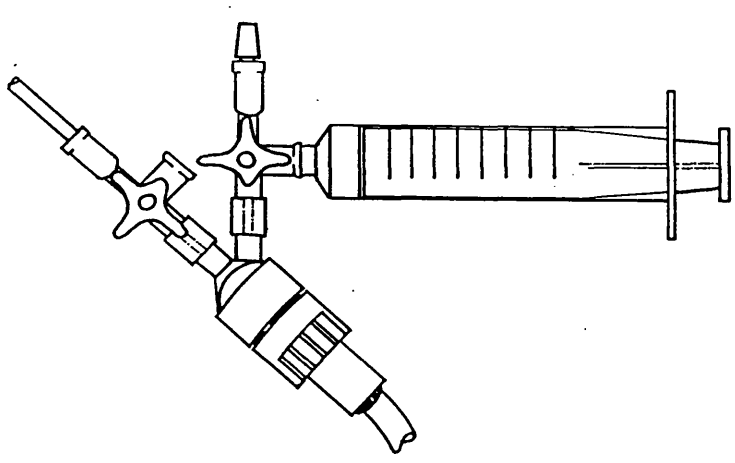


Figure 2.12: Measuring pressure.

been obtained, the needle was resited, either into another fetal compartment or into the amniotic cavity. The transducer was balanced to air between each recording and the system again flushed before stable pressures were recorded. Once all pressures had been obtained, the needle was withdrawn. Baseline recordings were made with the end of the manometer tube placed on the top of the maternal abdomen, at midabdomen and on the table top, for zeroing purposes.

2.8 CALCULATION OF PRESSURES:

2.8.1 Amniotic pressures:

Stable amniotic pressures were recorded in all cases, the pressure tracing showing minimal variation with time (<0.5 mm Hg). The mean pressure was noted, and the pressure calculated from the height of the recording above that obtained with the end of the manometer tube on the top of the maternal abdomen and the amplifier range used (Figure 2.13).

On average, amniotic pressure stabilised within 30 seconds.

If amniotic pressure was recorded before and after fetal blood sampling, the mean of the two readings was taken. In most cases there was no difference. Amniotic pressures were recorded with the amplifier range set at 20 or 40 mm Hg.

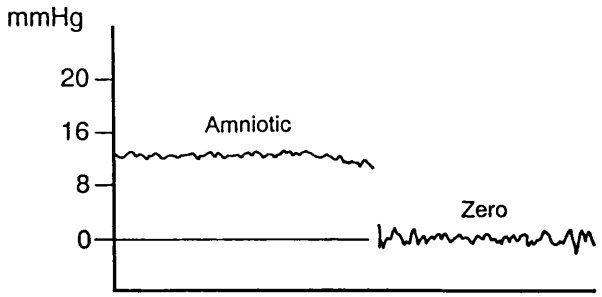


Figure 2.13: Calculation of amniotic pressure.

2.8.2 Umbilical venous pressure:

In order to identify the umbilical vessel entered with the needle, a small volume of heparinised saline was injected and the direction of flow in the vessel noted on ultrasound. If flow was away from the placenta, the needle was in an umbilical vein. The umbilical venous pressures recorded were nonpulsatile. Venous pressures were recorded with the amplifier range set at 20 or 40 mm hg. Amniotic pressure was subtracted from the total pressure recorded to give the umbilical venous pressure.

2.8.3 Umbilical artery pressure:

Pulsatile pressure waveforms were obtained from the umbilical artery. The siting of the needle in an artery was

confirmed when heparinised saline was injected under ultrasound visualisation and flow seen to be towards the placenta. Arterial pressures were recorded with the amplifier range set at 20 or 40 mm Hg. The mean pressure was recorded using the facility on the amplifier. For calculation of systolic and diastolic pressures, the best ten waveforms were examined and the mean of systolic and diastolic values for these calculated. Amniotic pressure was again subtracted to give the umbilical arterial pressure.

2.8.4 Cardiac pressures:

Pulsatile waveforms were obtained from all chambers of the heart. Pressure tracings were accepted as satisfactory when the waveform was similar on subjective comparison to those obtained in postnatal life. Depending upon gestation, the amplifier range was set at 40 mm Hg (<20 weeks) or 100 mm Hg (> 20 weeks). Calculation of the mean systolic and end diastolic values from ten waveforms were calculated and zeroed to amniotic pressure as above. The systolic pressure was measured as the highest point, and the end diastolic at the commencement of the rapid upsweep of the waveform (Figure 2.14). Mean pressures were measured employing the facility on the pressure amplifier.

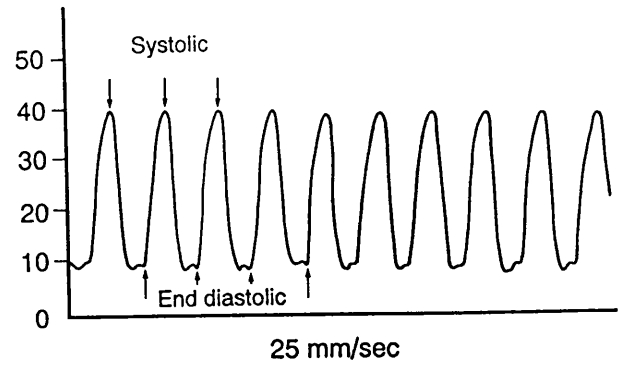


Figure 2.14: Calculation of systolic and end diastolic pressure in a trace from the right ventricle of a normal fetus at 25 weeks gestation.

2.9 STATISTICS:

Statistical analyses were performed using Minitab Statistical Software, Release 7 (Minitab Inc., Philadelphia USA) on IBM compatible hardware. Logarithmic transformation of amniotic and venous data was required as these pressure measurements are not normally distributed.

3. RESULTS:

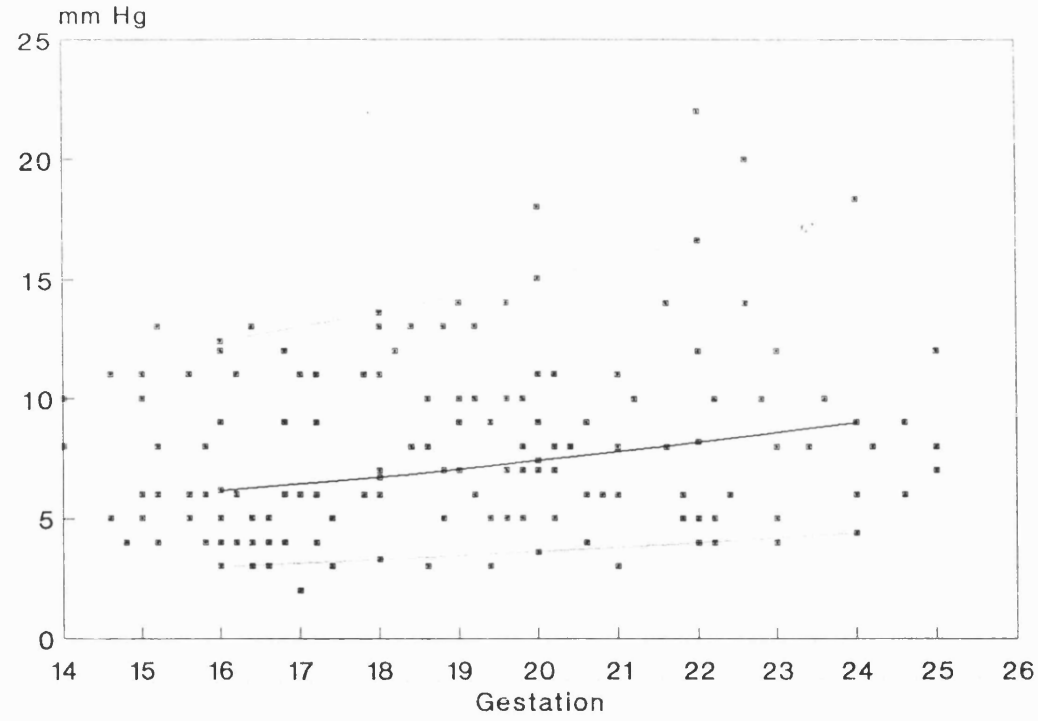
All results obtained are tabulated in Appendix IV to XIV.

3.1 AMNIOTIC PRESSURE:

There was minimal variation over time in the amniotic pressure recorded in the absence of maternal movement, and the pressure was therefore measured while the mother was lying quietly. During measurement, uterine activity was only seen in one case when the procedure was particularly prolonged. An example of an amniotic pressure trace has been provided in Figure 2.13.

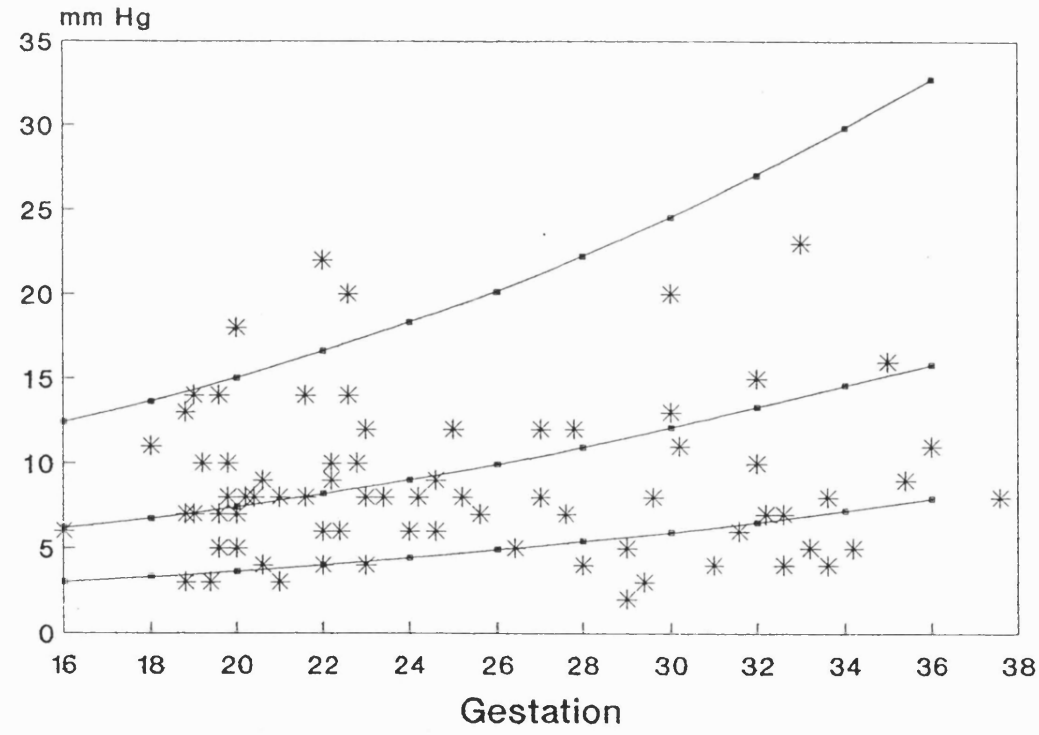
3.1.1 Normal liquor volume:

Intra amniotic pressure was measured in 117 pregnancies with a normal fetus and normal liquor volume, and 82 where there was a fetal structural or karyotypic abnormality but normal liquor volume. Intra amniotic pressure was not normally distributed, but logarithmic transformation of pressure was employed to normalise the distribution for statistical analysis. Figure 3.1 shows the intra amniotic pressure in cases with normal liquor and no fetal abnormality, and figure 3.2 the cases of normal liquor and fetal anomaly. The geometric mean pressure in the normal group was 6.58 mm Hg and in the group with fetal abnormality 7.69 mm Hg. Applying Student's t-test, there was apparently a significant difference in amniotic pressure between the two groups ($p = 0.023$, 95% CI -1.34, -1.02)). However, the majority of pressures in the normal



Mean, 5th and 95th centile

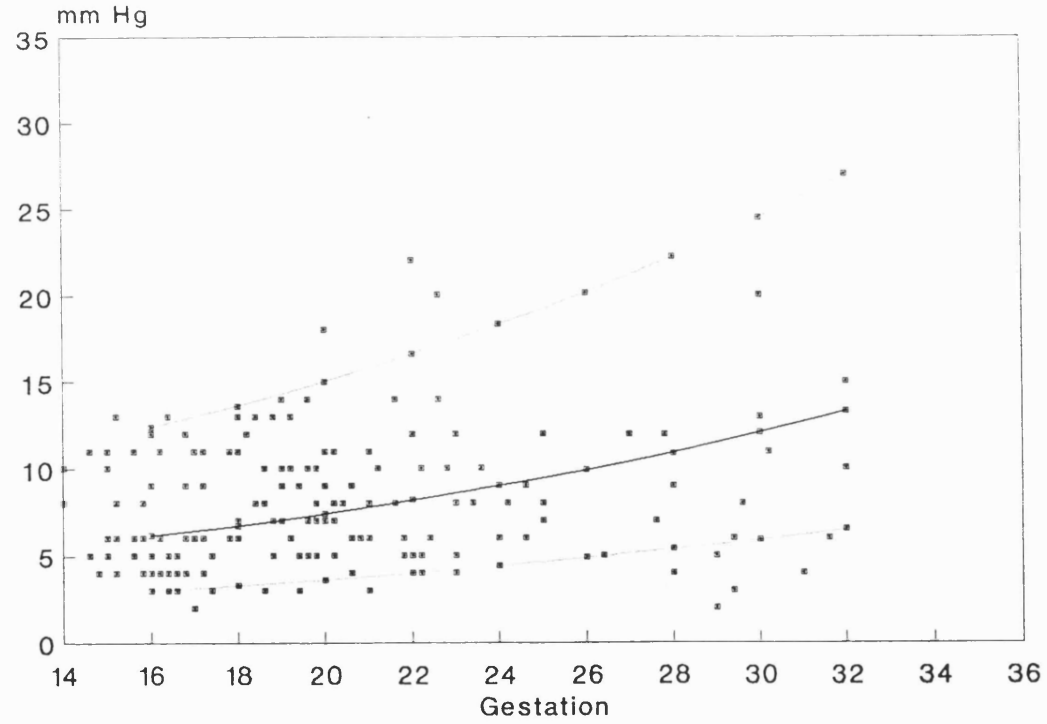
Figure 3.1: Amniotic pressure in normal pregnancies.



Mean, 5th and 95th centile.

Figure 3.2: Amniotic pressure with fetal abnormality

group were recorded at earlier gestations than the abnormals. It was therefore necessary to establish whether the difference between amniotic pressure in the two groups was due to gestational age or an increase in pressure secondary to the fetal abnormality. Multiple regression analysis of log pressure, gestational age and fetal state demonstrated no significant difference between these two groups and that intra amniotic pressure was independently related to gestational age (p=0.04). Accordingly, both groups were used to establish the reference range shown in figure 3.3. There is an increase in amniotic pressure with gestation (p=0.004, regression equation: **log pressure = 0.445 + 0.0212 x gestational age**). Mean amniotic pressure (geometric mean) rises from 5.9 mm Hg at 16 weeks to 12 mm Hg at 34 weeks.



Mean, 5th and 95th centile

Figure 3.3: Reference range for amniotic pressure.

3.1.2 Polyhydramnios:

Intra amniotic pressure was recorded in 14 cases of polyhydramnios. Where the volume of liquor was increased, the pressure recorded depended upon the vertical depth of the needle tip within the amniotic cavity. In three cases of polyhydramnios, the intra amniotic pressure was recorded with the needle tip at varying depths. The vertical distance was measured on the ultrasound image from the top of the maternal abdomen to the needle tip. This distance included the thickness of maternal abdominal and uterine walls and the depth of the needle tip within the amniotic cavity. When this depth was increased by 5 cm or more, the pressure increased by 2 - 4 mm Hg. Therefore, in all cases of polyhydramnios the intra amniotic pressure was taken as that recorded when the needle tip was within 6 cm of the top of the maternal abdomen, i.e. no more than 5 cm vertical distance within the amniotic cavity, allowing for maternal tissues.

Two populations of patients with polyhydramnios were identified; those with normal and those with increased intra amniotic pressure (Figure 3.4). Four patients had intra amniotic pressure above the 95th centile for gestation. The other ten cases had amniotic pressures within the reference range. There was no correlation between amniotic fluid index and intra amniotic pressure. There were no significant differences between the groups in respect to gestation at diagnosis or maternal age. The

patient details are given in Table 3.1.

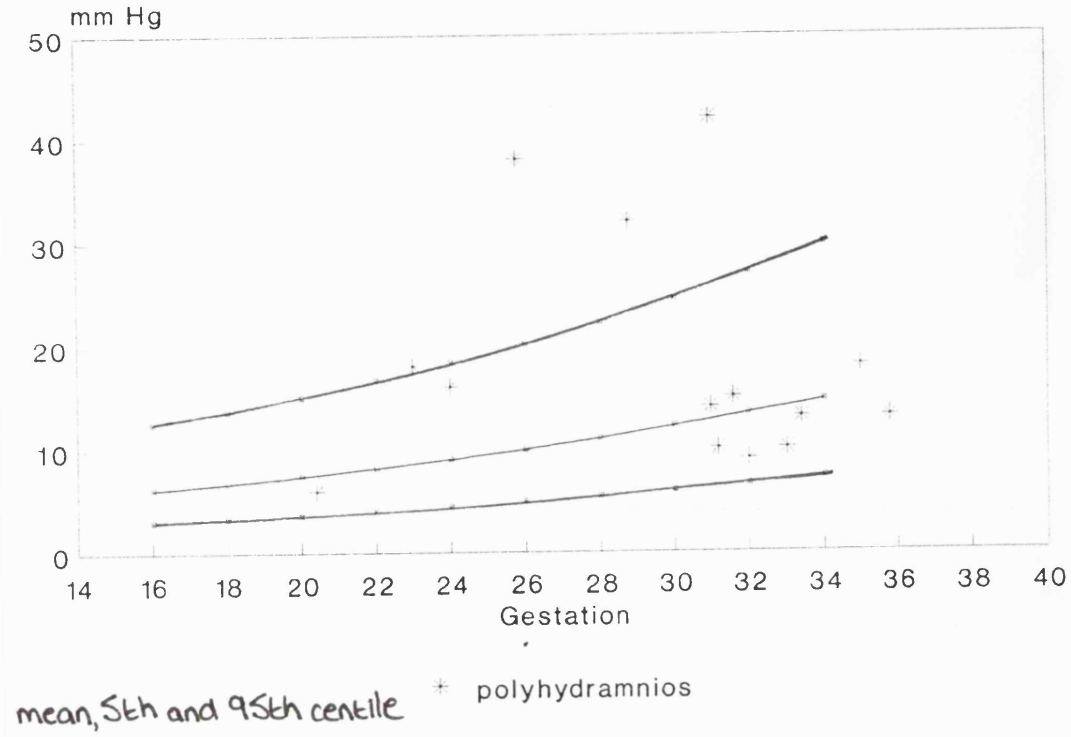


Figure 3.4: Amniotic pressure in polyhydramnios.

Two pregnancies were terminated because of fetal abnormality. Of the pregnancies that continued, the diagnosis-delivery intervals appeared to be greater in the normal pressure group than the high pressure group, but the numbers are too small for statistical analysis.

In seven cases, amniocentesis was performed to drain liquor in the hope of alleviating maternal discomfort and possibly reducing the risk of premature labour. In all cases where amniocentesis was performed, intra amniotic pressure was reduced following the procedure, regardless of volume aspirated (250 - 1500 ml) (Table 3.2).

Table 3.1

Polyhydramnios: Patient details.

No:	Pathology	Gestation	Amniotic Fluid Index	Pressure	Outcome
29	SVT	32+3	40	42	Drained SVD 39+3
33	NIH	23	24	18	TOP
42	SVT	31+2	37	9	Drained SVD 39+1
47	SVT	33+1	32	18	Drained SVD 36+3
57	Rubella	20+2	18	6	Resolved
59	Hydroceph	24+1	20	16	TOP
65	SVT	32+6	27	10	Drained SVD 34+3
91	CHB	30+1	28	14	IUD 31+1
99	Aperts	38+6	34	32	SB 29+1
178	SVT	30+2	25	10	SVD 31+2 NND
193	CHB	31+5	29	15	Drained SVD 32+1 NND
209	Diabetes	35+6	59	13	LSCS 36+3
212	Urinary ascites	35+5	20	11	SVD 37+1
227	Meconium peritonitis	25+6	28	38	PROM SVD 29+3

SVT - supraventricular tachycardia, NIH - nonimmune hydrops, CHB - congenital heart block, SVD - spontaneous vertex delivery, TOP - termination of pregnancy, IUD - intrauterine death, SB - still birth, NND - neonatal death, LSCS - lower segment caesarean section, PROM - premature rupture of membranes, Hydroceph - hydrocephalus.

Table 3.2

Intra amniotic pressure in cases of polyhydramnios, before and after amniocentesis:

Case no:	Pre amnio:	Post amnio:	Volume drained:
29	42	20	450
42	9	5	350
47	18	10	350
73	10	6	500
99	32	14	1000
193	15	8	1000
209	13	6	3000

Resolution of polyhydramnios occurred in three cases. Case 29 was complicated by polyhydramnios and fetal hydrops secondary to supraventricular tachycardia. The intra amniotic pressure was elevated at 42 mm Hg. Drainage of 450 ml of liquor was performed after control of the fetal tachycardia had been achieved with flecanide; the polyhydramnios did not recur and the pregnancy continued for 50 days.

Two further cases, in whom the intra amniotic pressure was within the reference range, also demonstrated resolution of polyhydramnios; one (case 57) spontaneously and one (case 42) following amniocentesis. In both of these cases, the

fetus was hydropic. In case 57, the underlying cause was intrauterine rubella infection and the hydrops and polyhydramnios resolved without treatment. The fetal hydrops in case 42 was secondary to an intermittent fetal tachyarrhythmia, and the polyhydramnios did not recur after drainage of 250 ml of liquor following spontaneous resolution of the hydrops.

3.1.3 Oligohydramnios:

Intra amniotic pressure was recorded in 13 cases of oligohydramnios with intact membranes and four where there was evidence of premature membrane rupture. The pressures obtained are shown in Figure 3.5. In the presence of intact membranes, intra amniotic pressure was within the reference range in nine cases and below the 5th centile in four. In five cases, infusion of warm Hartmann's solution into the amniotic cavity was performed in order to improve ultrasound visualisation (Gembruch and Hansmann 1988). In each case, amnioinfusion was associated with an increase in intra amniotic pressure (Table 3.3).

Following premature rupture of membranes, the intra amniotic pressure was below the 5th centile in one case, normal in one and above the 95th centile in two cases. Amnioinfusion caused further elevation of the pressure in these last two cases.

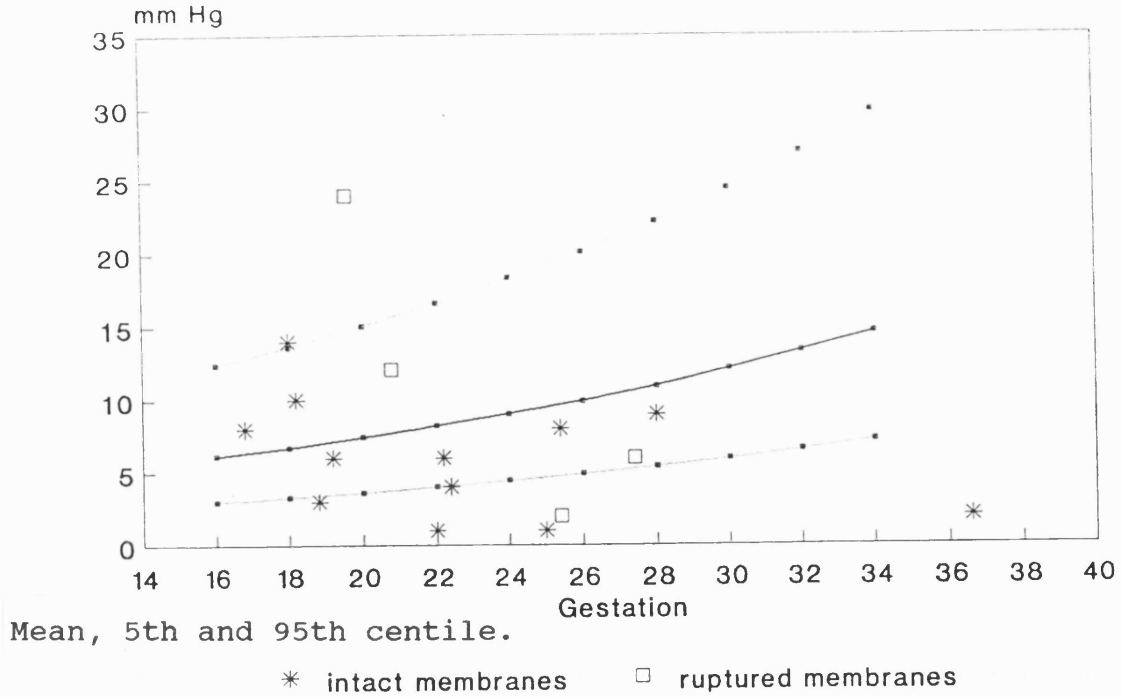


Figure 3.5: Amniotic pressure in oligohydramnios.

Table 3.3

Intra amniotic pressure in oligohydramnios, before and after amnioinfusion.

Case no:	Pre:	Post	Volume:
6	1	9	150
15 *	24	27	150
16 *	12	26	130
18	1	3	180
19	8	8	100
53 *	2	7	300
142	4	7	100
215	9	9	120

*** - premature rupture of membranes**

3.1.4 Multiple pregnancies:

In twin pregnancies (n = 4), the intra amniotic pressure was identical in both sacs, regardless of differences in liquor volume. The patient details are given in Table 3.4.

Table 3.4

Intra amniotic pressure in twin pregnancies: patient details.

No:	Gestn	Indication	Sac 1 Pressure	Sac 2 Pressure
13	30	Hydrops and polyhydramnios twin 1	11	11
49	24	Discordant growth, normal liquor volume	4.5	4.5
100	23	Anhydramnios twin 2, Potter's	4	4
229	26	Polyhydramnios twin 1	6	6

3.2 UMBILICAL VENOUS PRESSURE:

3.2.1 Reference range:

The reference range has been established from 22 normal fetuses and 14 in whom an abnormality was present which was not believed to affect venous pressure e.g. hydrocephalus, hydronephrosis etc. The mean pressure in the normal group was 4.59 mm Hg (SEM 0.56) and in the abnormal group 4.07 mm

Hg (SEM 0.62). There was no statistical difference between these two groups (Students t-test, p=0.70). Data from both groups was therefore combined to compile the reference range.

Umbilical venous pressure is not normally distributed, and therefore log transformation was performed prior to further statistical analysis. The reference range of umbilical venous pressure is shown in Figure 3.6. The geometric mean for venous pressure was 3.726 mm Hg and standard deviation 1.820. There was a trend towards increase in pressure with gestation but this did not reach statistical significance.

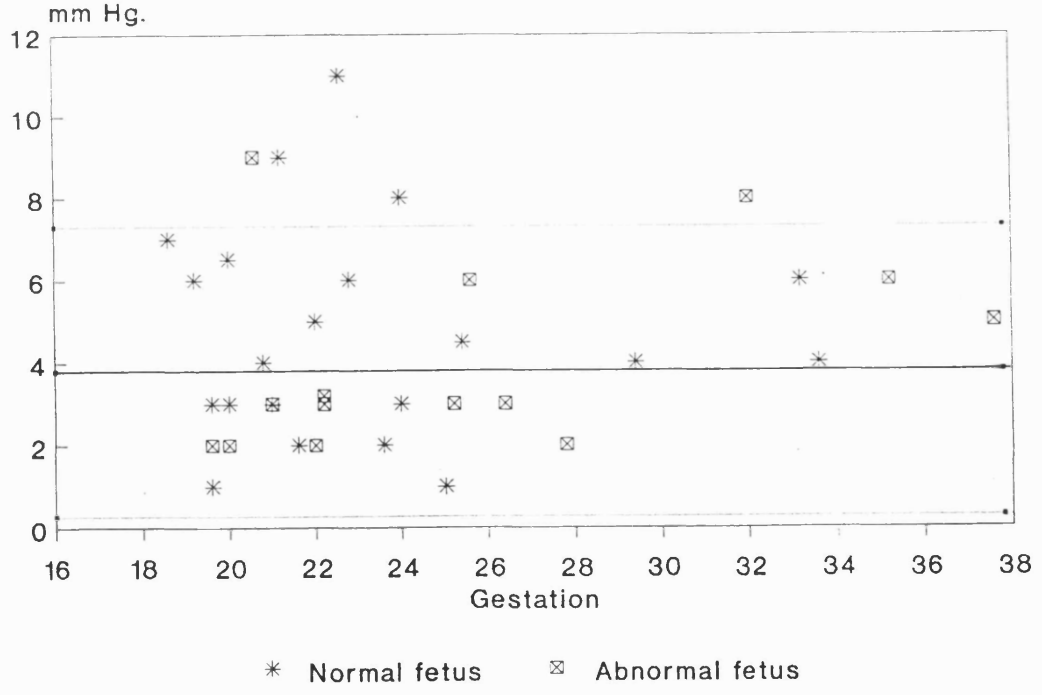


Figure 3.6: Reference range of umbilical venous pressure.

3.2.2 Venous pressure in congenital heart disease:

In 12 fetuses with structural congenital heart disease, the venous pressure was within the reference range apart from two where there was evidence of cardiomegaly as assessed by measurement of the cardiothoracic ratio (Paladini et al 1990). In these two cases the cardiothoracic ratio was greater than 2 S.D. above the mean for gestation and the umbilical venous pressure was also greater than the 95th centile (Figure 3.7). Details of the pathology are given in Table 3.5.

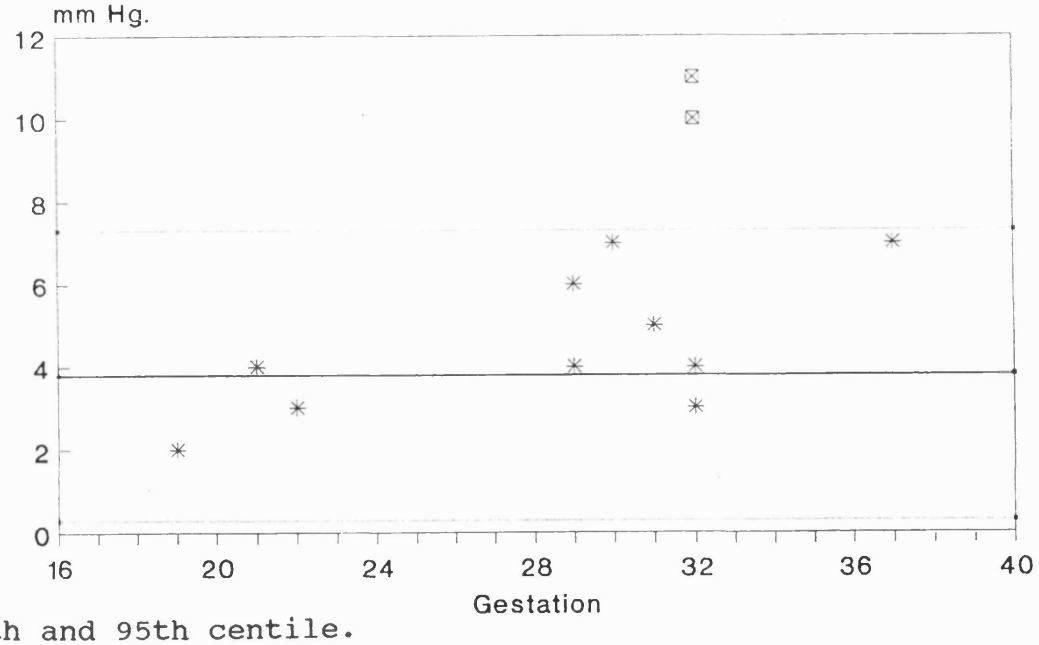


Figure 3.7: Umbilical venous pressure in congenital heart disease.

Table 3.5

Umbilical venous pressure in congenital heart disease.

Case No:	Defect:	Pressure:	Cardiomegaly:
7	VSD	3	-
10	Absent pulmonary valve syndrome	10	+
56	VSD, DORV	8	-
75	Ectopia cordis	2	-
76	AVSD	6	-
97	AVSD	5	-
184	VSD, DORV	4	-
196	Coarctation of aorta	4	-
241	Coarctation of aorta	7	-
243	Pericardial effusion	11	+

3.2.3 Venous pressure in nonimmune hydrops:

Fetal blood sampling is essential in the investigation of nonimmune hydrops. Umbilical venous pressure was measured in 15 such cases. In the presence of ascites, the umbilical venous pressure was elevated to more than the fifth centile (Figure 3.8).

In a series of 12 patients, both umbilical venous pressure and cardiac size were measured. On examination of the standard normal deviate (z test), there was a significant

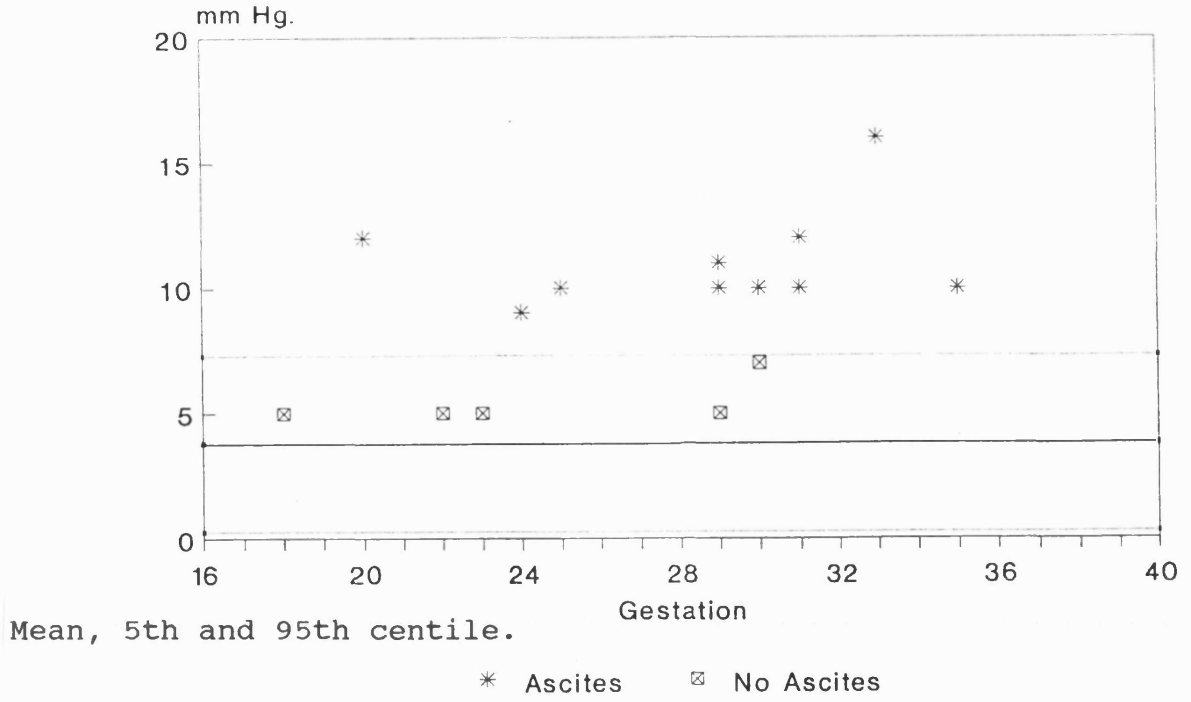


Figure 3.8: Umbilical venous pressure in nonimmune hydrops.

increase in cardiac size in those fetuses with elevated umbilical venous pressure, p=0.02 (Figure 3.9). These fetuses also had ascites. In the absence of ascites, both umbilical venous pressure and cardiothoracic ratio fell within the reference range.

There was a significant correlation between cardiac size and umbilical venous pressure (r=0.75, p=0.003) (Figure 3.10).

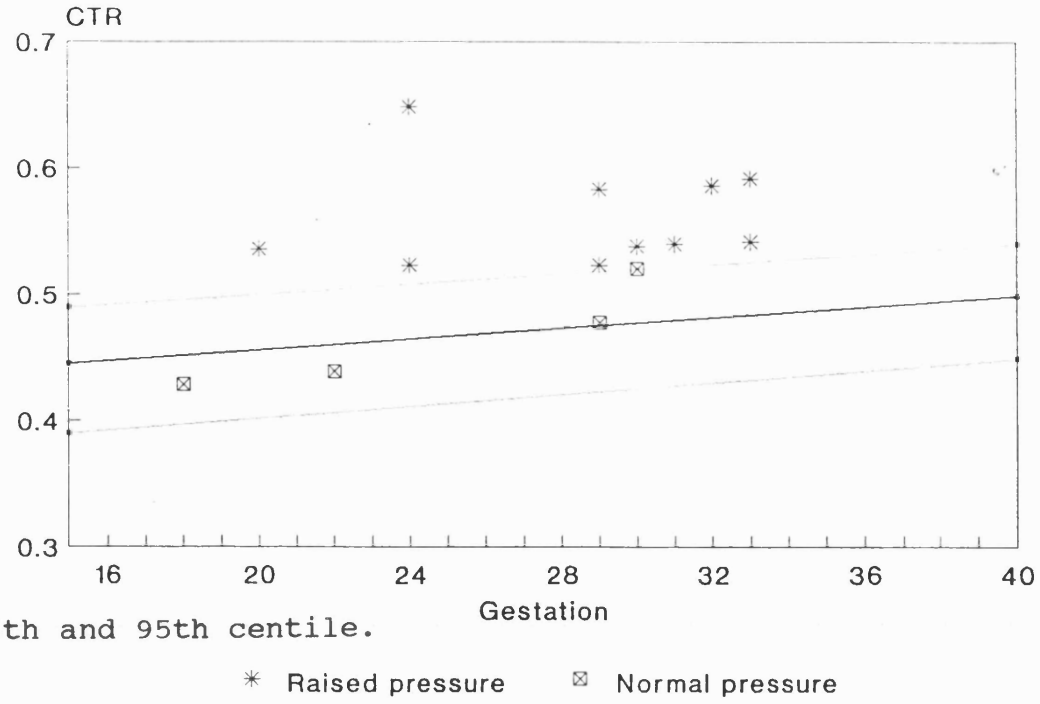
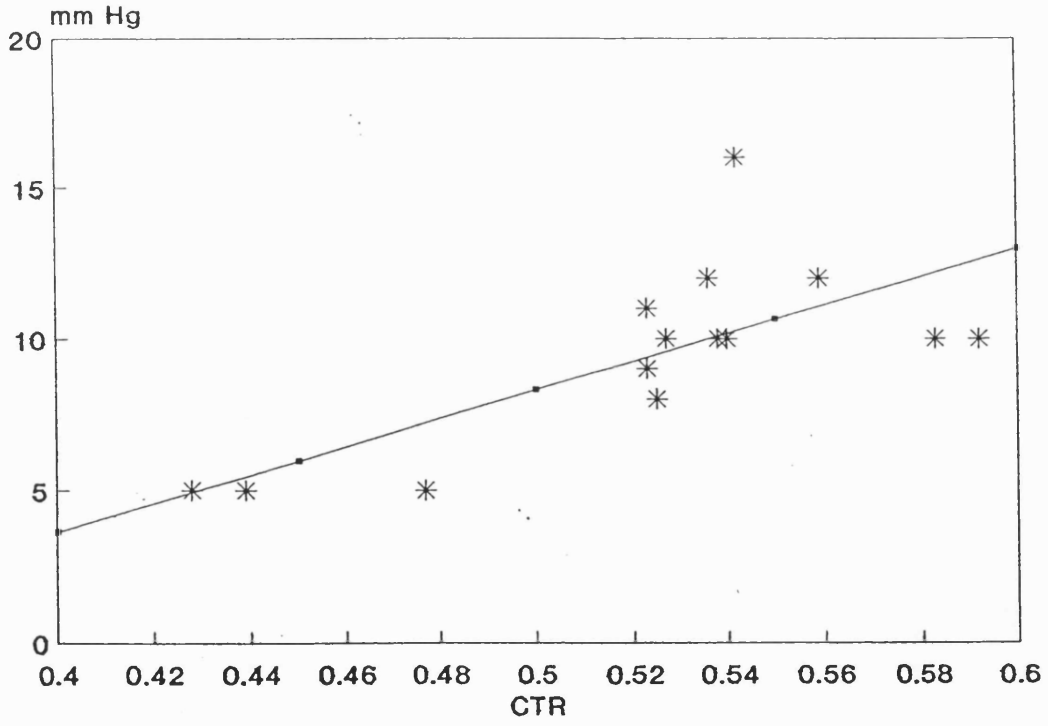


Figure 3.9: Cardiothoracic ratio in nonimmune hydrops.



r = 0.75, y = -15.1 + 46.8x

Figure 3.10: Correlation of CTR and umbilical venous pressure.

3.2.4 Umbilical venous pressure in congenital diaphragmatic hernia:

Three cases of diaphragmatic hernia had fetal blood sampling performed for rapid karyotype and their umbilical venous pressures were measured. The pressure fell well within the reference range in the two fetuses with no evidence of ventricular compression on ultrasound assessment. In one of these, the pregnancy was terminated but in the other the neonate underwent surgery and is alive and well. However, in the third, moderate ventricular compression was noted and the umbilical venous pressure was 8 mm Hg which is just greater than the 95th centile (Figure 3.11). This case resulted in a neonatal death.

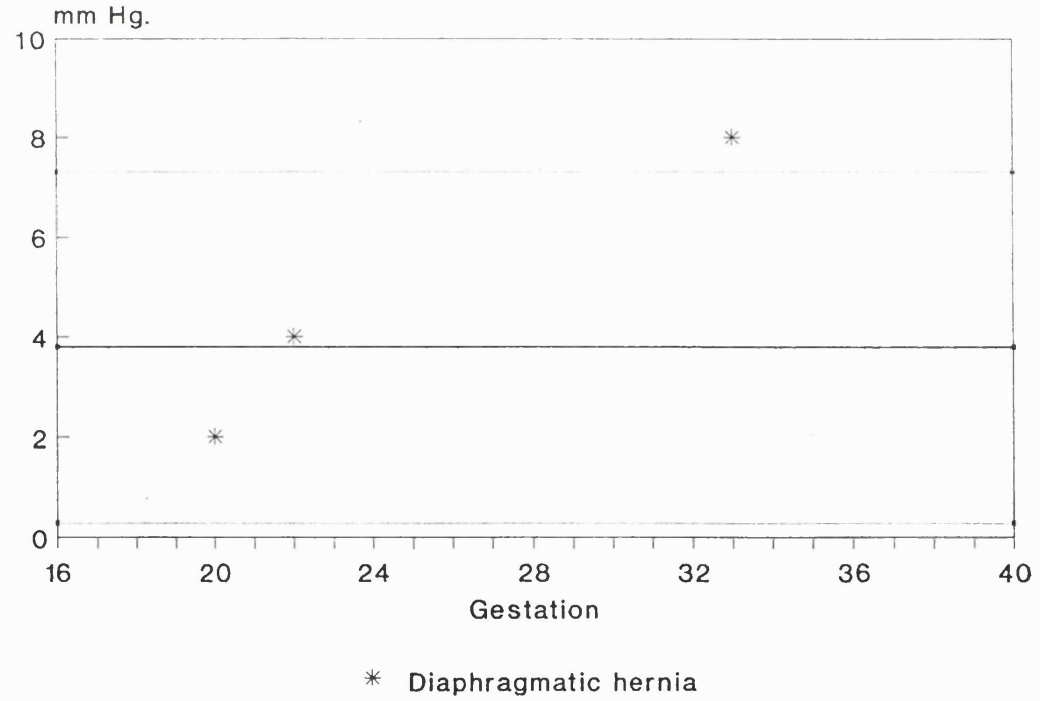


Figure 3.11: Umbilical venous pressure in congenital diaphragmatic hernia.

3.3 UMBILICAL ARTERIAL PRESSURE:

Arterial puncture during fetal blood sampling is fortuitous, and the umbilical vein is the vessel entered most frequently. This accounts for the small number of observations made in this group (n=13). When the arterial pressure was recorded, a typical arterial waveform was seen (Figure 3.12) with a definite dicrotic notch corresponding to the closure of the aortic valve.

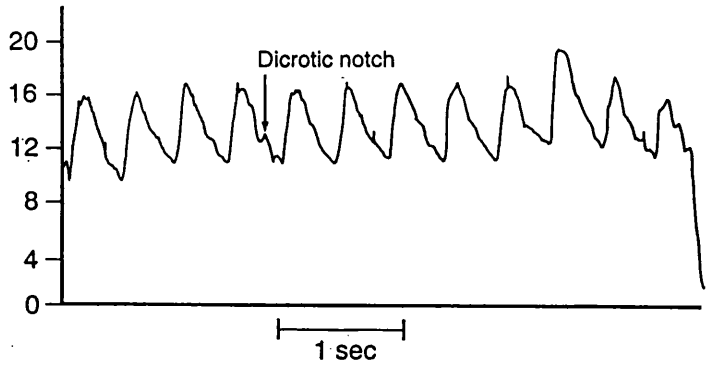


Figure 3.12: Arterial pressure trace.

3.3.1 Reference range:

There appears to be an increase in systolic, diastolic, mean and pulse pressures with advancing gestation (Figure

3.13).

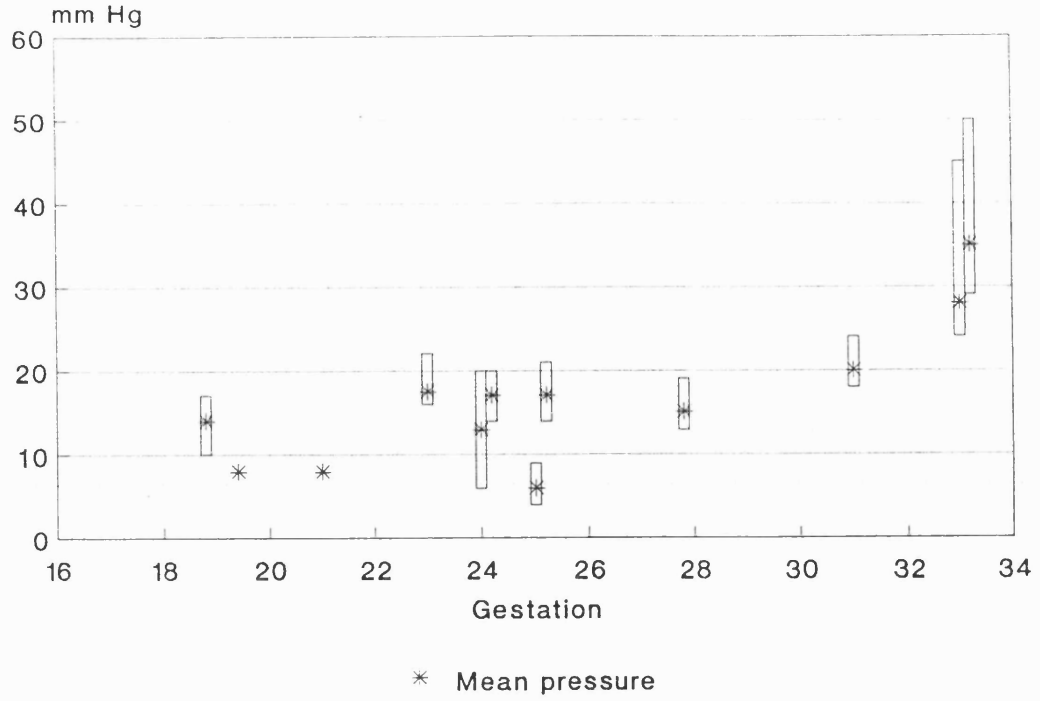


Figure 3.13: Umbilical arterial pressure

3.3.2 Arterial pressure with abnormal Doppler flow studies:

In one case, fetal blood sampling was performed for blood gas analysis in a case of intrauterine growth retardation with absent end diastolic flow on umbilical artery Doppler blood flow studies. The fetus was both hypoxic and acidotic. The umbilical arterial pressure (70/50 mm Hg, mean 54) was higher than the systemic blood pressure measured postnatally in normal infants of equal gestational age and birthweight (57/30 mm Hg, CI 66-43/42-22, mean 41 mm Hg (51-32)) (Versmold et al 1981). The arterial waveform is shown in figure 3.14.

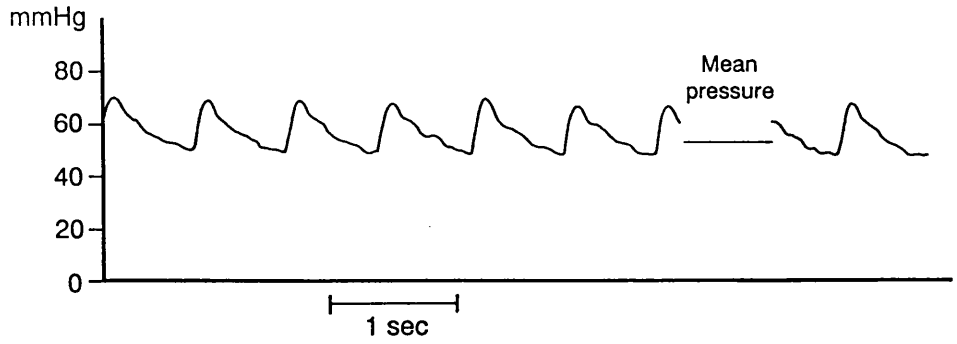


Figure 3.14: Arterial waveform in 37 week fetus with abnormal Doppler blood flow studies.

3.4 VENTRICULAR PRESSURES:

Intraventricular pressures were measured at midtrimester termination of pregnancy and diagnostic fetal blood sampling. The reference ranges have been established from recordings made from normal fetuses and those with structural abnormalities which were not believed to affect the cardiovascular system. All fetuses had structurally normal hearts on ultrasound examination.

3.4.1 Left ventricular pressure in the normal heart:

21 recordings were made from the left ventricle in normal hearts. The waveform obtained was similar to that seen in postnatal life and examples at different gestations are

given in Figures 3.15-16. There is a small atrial component and rapid increase followed by a fall in pressure during ventricular systole.

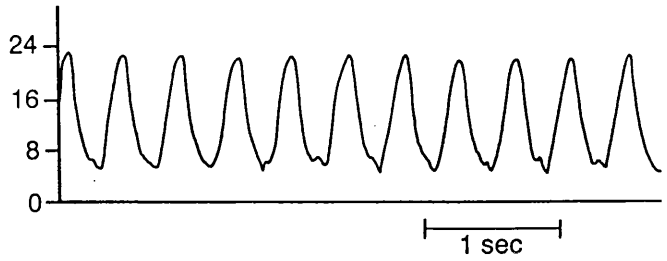


Figure 3.15: Left ventricular pressure in normal fetus at 16+2 weeks gestation

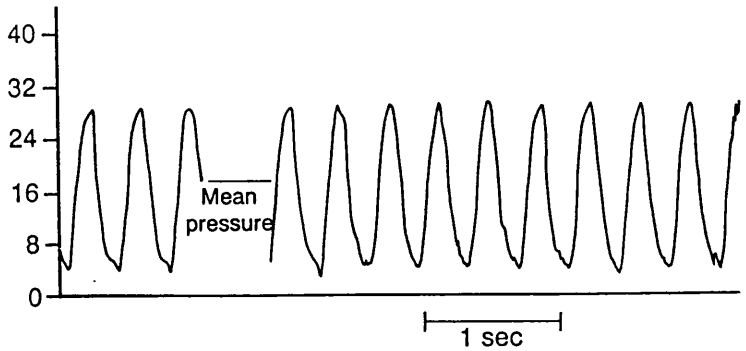


Figure 3.16: Left ventricular pressure in normal fetus at 22 weeks

Systolic pressure increased with gestational age. The regression equation for systolic pressure in the left ventricle is -16.4 + 1.94 x gestation. Standard deviation is 7.519 and p = 0.007. The end diastolic pressure increased with gestation, reaching statistical significance (pressure = -9.23 + 0.745 x gestation, S.D = 2.979, p = 0.008). Figure 3.18 shows the reference ranges for left ventricular systolic and end diastolic pressures.

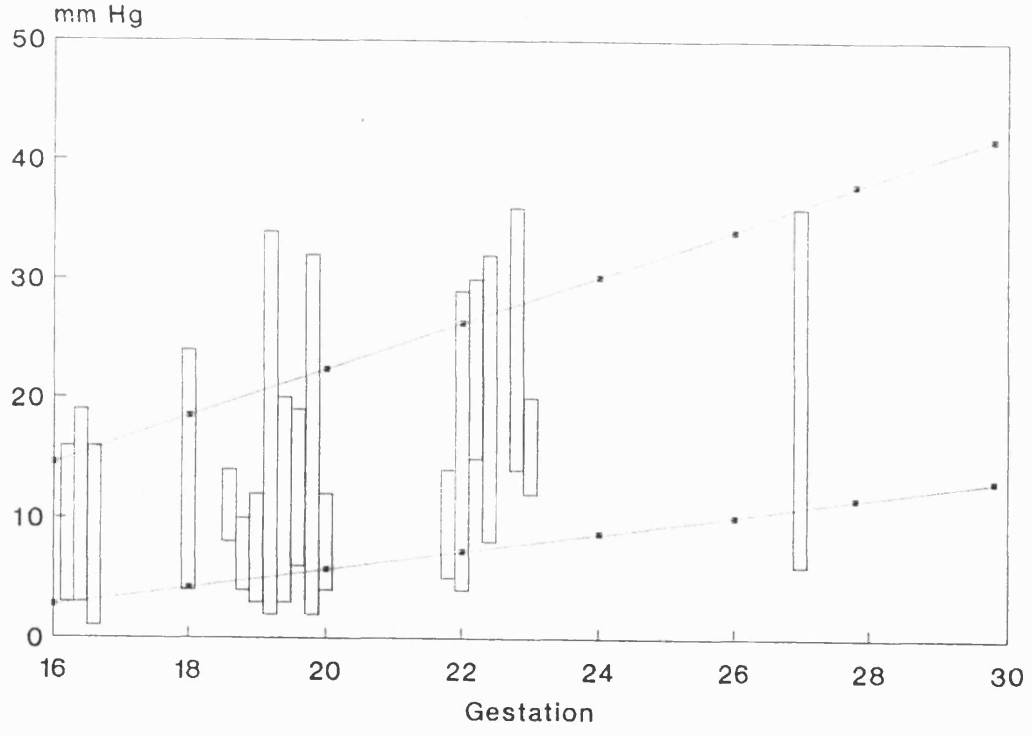


Figure 3.17: Left ventricular pressure in normal hearts.

3.4.2 Left ventricular pressure in abnormal hearts:

Abnormalities of the pressure waveform and values were identified in cardiac disease, for example critical aortic stenosis. Figure 3.18 shows the right and left ventricular pressure tracings from a fetus with critical aortic stenosis at 28 weeks gestation, with an abnormal waveform and gross elevation of end-diastolic pressure with a reduced pulse pressure in the left ventricle. The fetus suffered intrauterine death 24 hours after an attempt at intrauterine balloon valvoplasty and on postmortem was shown to have severe endocardial fibroelastosis.

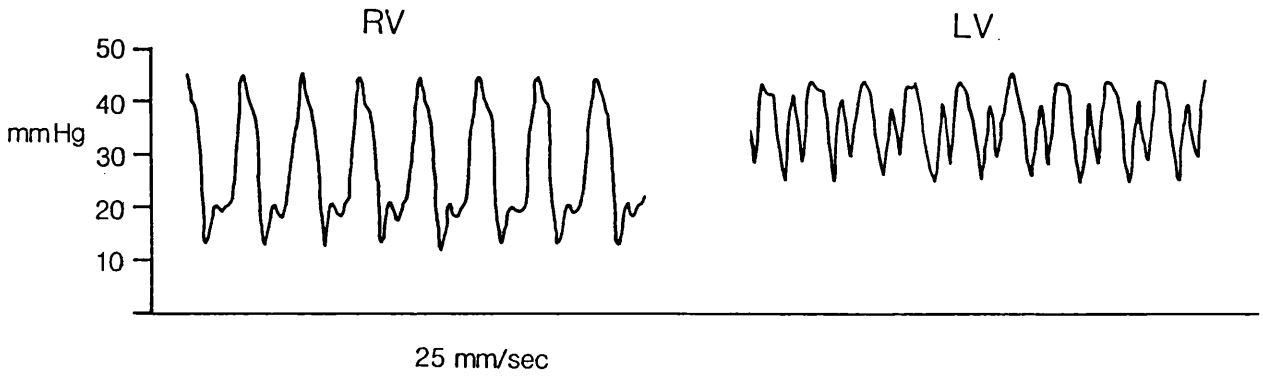


Figure 3.18: Left and right ventricular pressures in critical aortic stenosis at 28 weeks.

The second case of critical aortic stenosis investigated by measurement of cardiac pressures was diagnosed at 32 weeks. The left ventricular pressure tracing obtained is shown in Figure 3.19. In this case, the pulse pressure was

maintained, although there was elevation of end diastolic pressure. This fetus underwent two attempts at intrauterine balloon valvoplasty. After delivery at 36 weeks, the baby died at one month of age, and post mortem revealed severe EFE.

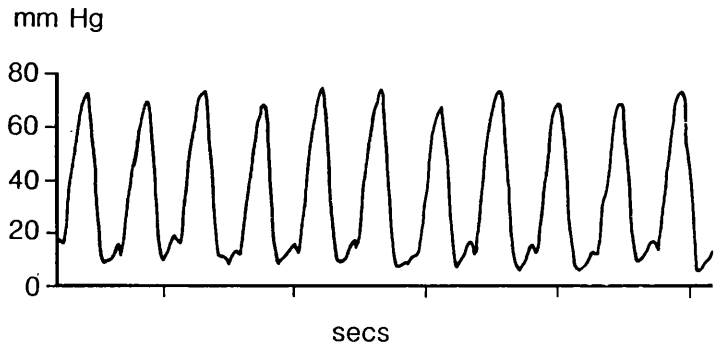


Figure 3.19: Left ventricular pressure in critical aortic stenosis at 32 weeks

The tracing in Figure 3.20 was recorded from the left ventricle of another fetus with critical aortic stenosis at 32 weeks gestation. Although there was ultrasound evidence of endocardial fibroelastosis in this fetus, it was less severe, and following intrauterine balloon valvoplasty the female infant was delivered at term and is well at six months of age.

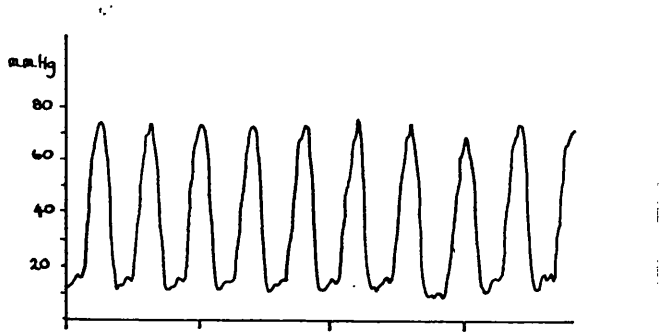


Figure 3.20: Left ventricular pressure in critical aortic stenosis at 32 weeks

Figure 3.21 shows the pressure tracing from a fetus at 31 weeks with critical aortic stenosis. This tracing was not correctly zeroed, but the pulse pressure can be calculated.

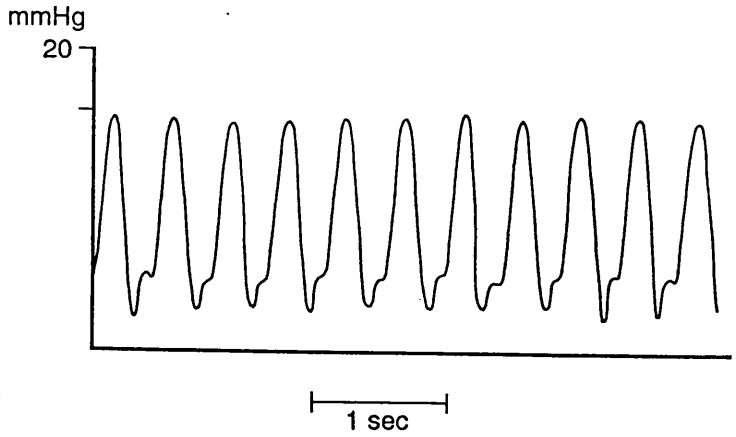


Figure 3.21: Left ventricular pressure in critical aortic stenosis at 31 weeks

3.4.3 Right ventricular pressure in the normal heart:

Right ventricular pressures were obtained in 19 fetuses with normal hearts. The waveforms obtained from a normal heart (Figure 3.22) were similar to those from the left ventricle.

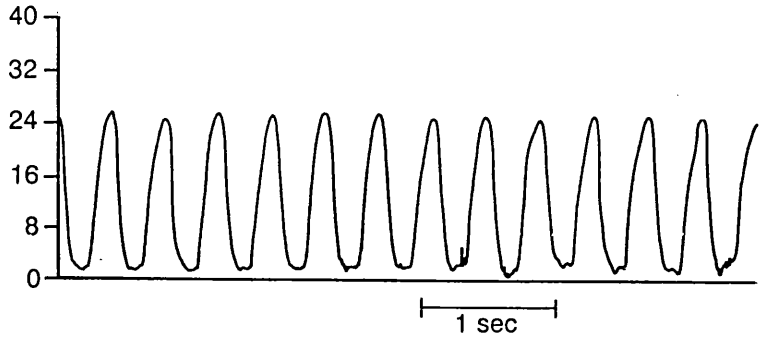


Figure 3.22: Right ventricular pressure in normal fetus at 20+4 weeks gestation

There was an increase in systolic and end diastolic pressure with advancing gestation. The regression equation for systolic pressure = -29.6 + 2.58 x gestation, S.D. = 4.354, p = <0.001. End diastolic pressure appeared to increase with gestation as shown by the equation pressure

= -5.62 = 0.542 x gestation, S.D. = 2.993, p = 0.023. These reference ranges are shown in Figure 3.23.

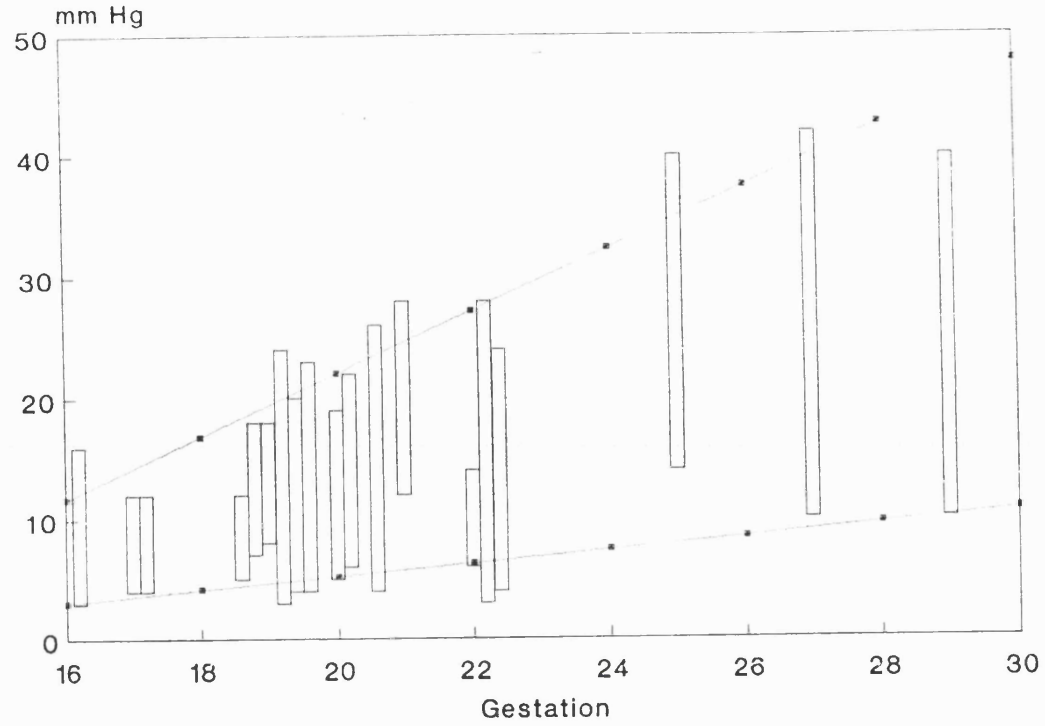


Figure 3.23: Right ventricular pressure in normal hearts.

3.4.4 Right ventricular pressure in abnormal hearts:

One case of mitral atresia and double outlet right ventricle at 25 weeks gestation is shown in Figure 3.24. Whilst the right ventricular pressure profile looks normal, it was not possible to enter the left ventricle.

Figure 3.25 shows the pressure profile from a case with a ventricular septal defect and double outlet right ventricle, with pulmonary atresia, investigated at 24 weeks gestation.

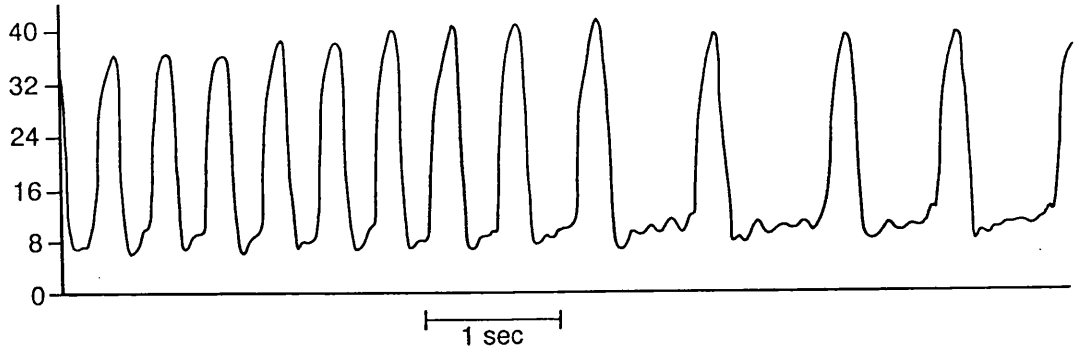


Figure 3.24: Right ventricular pressure in a case of mitral atresia and double outlet right ventricle at 25 weeks gestation.

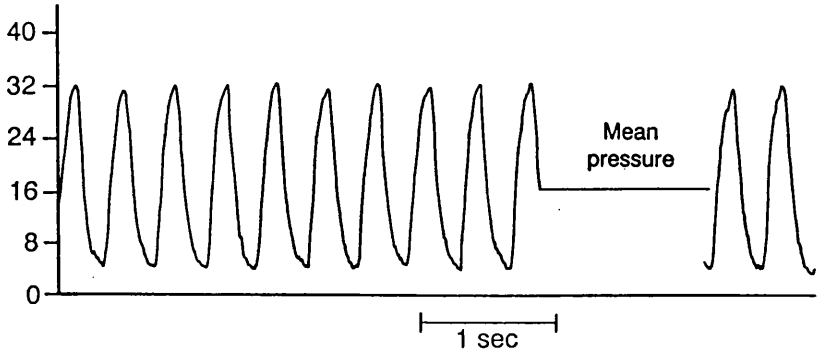


Figure 3.25: Right ventricular pressure in a fetus with VSD, pulmonary atresia and double outlet right ventricle at 24 weeks gestation.

One case of pulmonary stenosis was investigated by measurement of right and left ventricular pressures. The pressure profiles are shown in Figure 3.26. The left ventricular pressure tracing is slightly damped, but the systolic and end diastolic pressures appear to be within our reference range. The right ventricular end diastolic pressure is elevated, as are the systolic and pulse pressures.

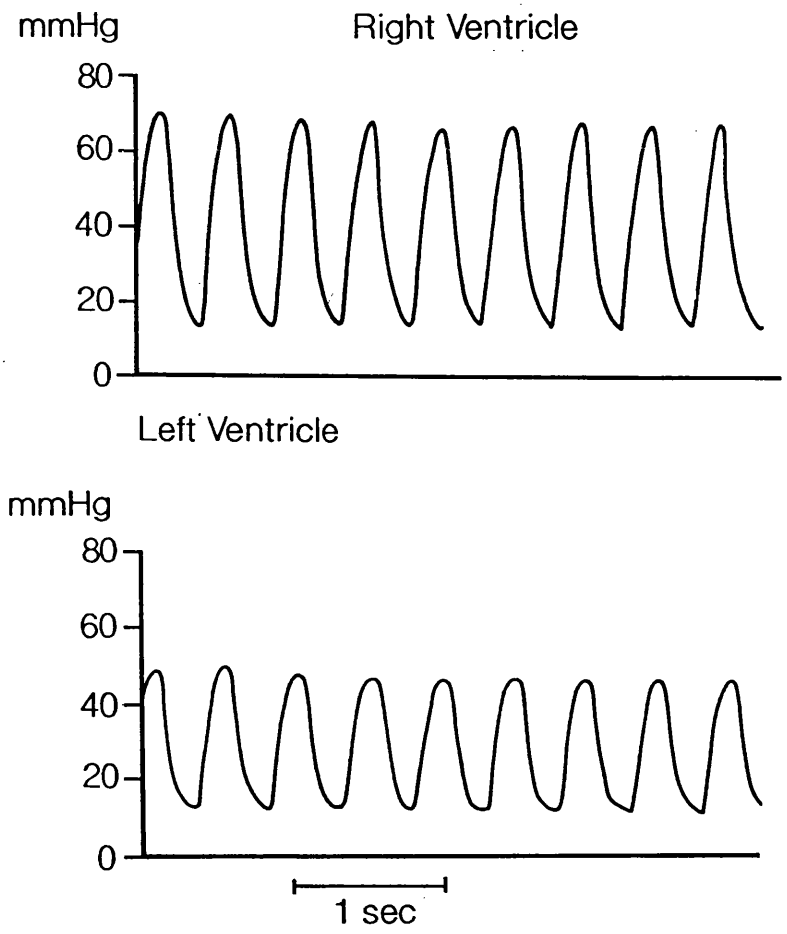


Figure 3.26: Right and left ventricular pressures in a fetus with pulmonary stenosis at 32 weeks gestation.

3.4.5 Left and right ventricular pressure differences in normal hearts:

In five fetuses with structurally normal hearts, pressures were obtained from both left and right ventricles. There was no difference between the pressures obtained from each chamber (Table 3.6).

Table 3.6

Ventricular pressures in right and left ventricles measured in the same fetus.

Gestation weeks	Left Ventricle mm Hg	Right Ventricle mm Hg
18	10/4	11/4
19	20/6	21/5
20	17/4	18/5
22	29/4	28/3
22	25/6	26/6

The pressure tracings from the left and right ventricles of a normal fetus at 22 weeks gestation are shown in Figure 3.27.

3.4.6 Left and right ventricular pressure in the abnormal heart:

In one case of ventricular disproportion, left and right ventricular pressures were recorded. The underlying pathology was a mosaic trisomy 13, and post mortem

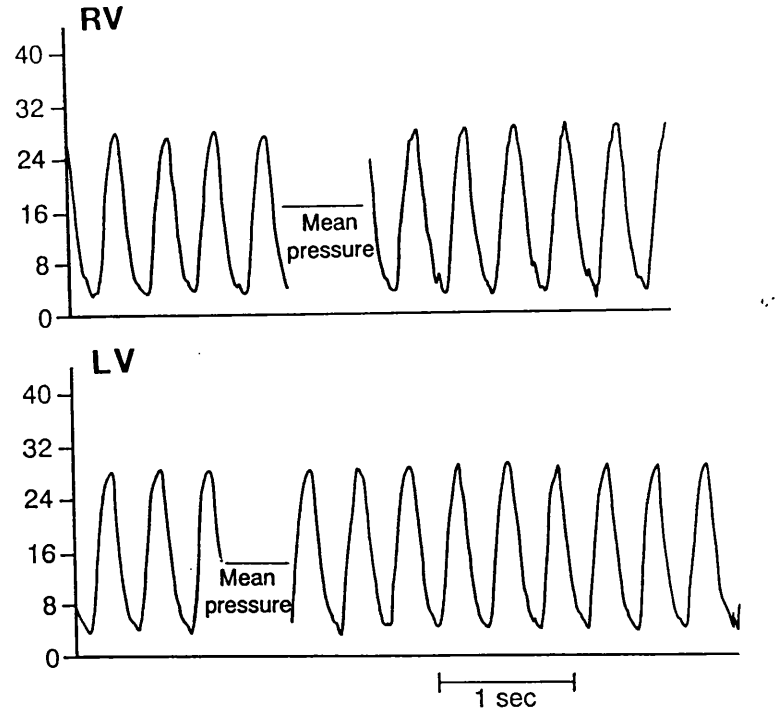


Figure 3.27: Left and right ventricular pressures recorded from a normal fetus at 22 weeks gestation.

demonstrated isthmal hypoplasia. There was a small difference in the pressures in both chambers. The pressure in the left ventricle was 32/3 mm Hg whereas in the right it was 36/4 (Figure 3.28).

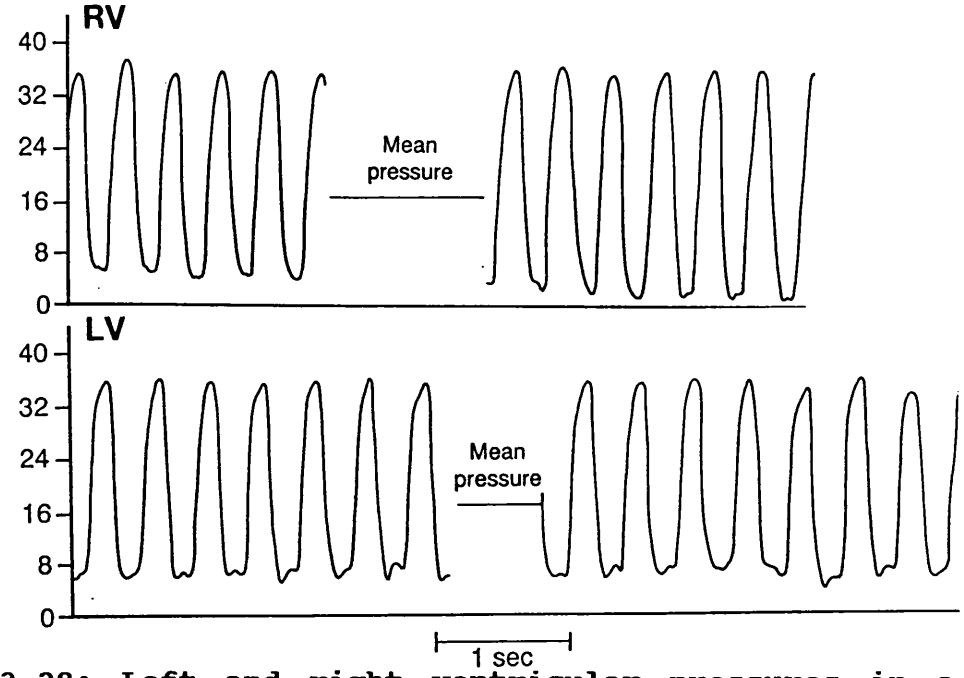


Figure 3.28: Left and right ventricular pressures in a fetus with ventricular disproportion at 27 weeks.

3.5 ATRIAL PRESSURE:

A pulsatile waveform was not always obtained from the atria, almost certainly due to sampling problems in the small chamber. However, in some cases a clear waveform was recorded as shown in Figure 3.29. It is not possible to identify a and v waves without simultaneous electrocardiogram or Doppler studies. In view of the difficulties in obtaining good quality, undamped waveforms, mean atrial pressures have been analyzed.

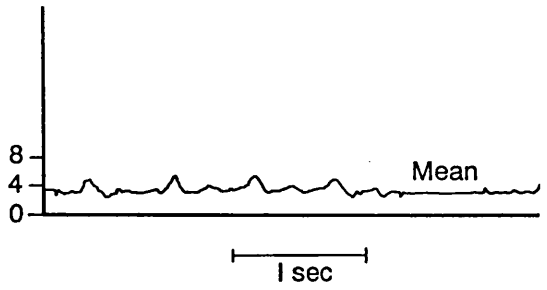


Figure 3.29: Atrial pressure waveform in a normal fetus at 19 weeks gestation.

3.5.1 Left atrial pressure:

The pressure within the left atrium was recorded in 10 normal fetuses and four fetuses with structural abnormalities but normal hearts. Mean left atrial pressure was 3.357 mm Hg and standard deviation 1.865. (Figure 3.30) There was no significant change in left atrial pressure with advancing gestation (p=0.116).

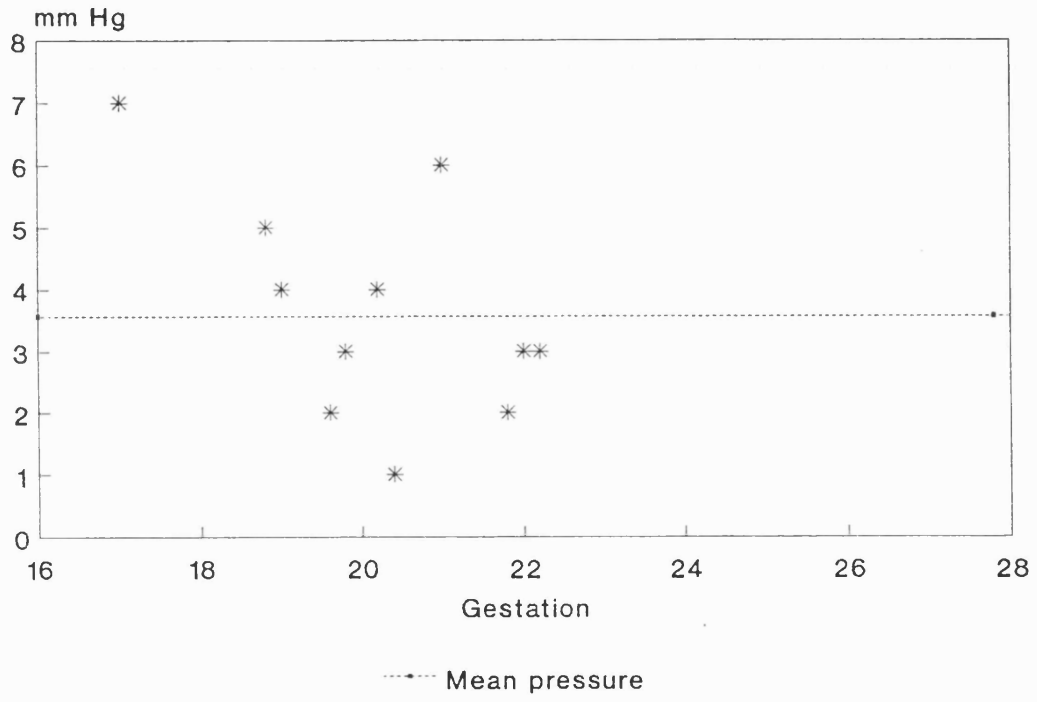


Figure 3.30: Left atrial pressure.

3.5.2 Right atrial pressure:

Right atrial pressure was recorded in 10 cases. Details of right atrial pressures in normal hearts are shown in Figure 3.31. The mean pressure was 3.66 mm Hg and standard

deviation 1.118. There was no change in right atrial pressure with increasing gestational age (p=0.446).

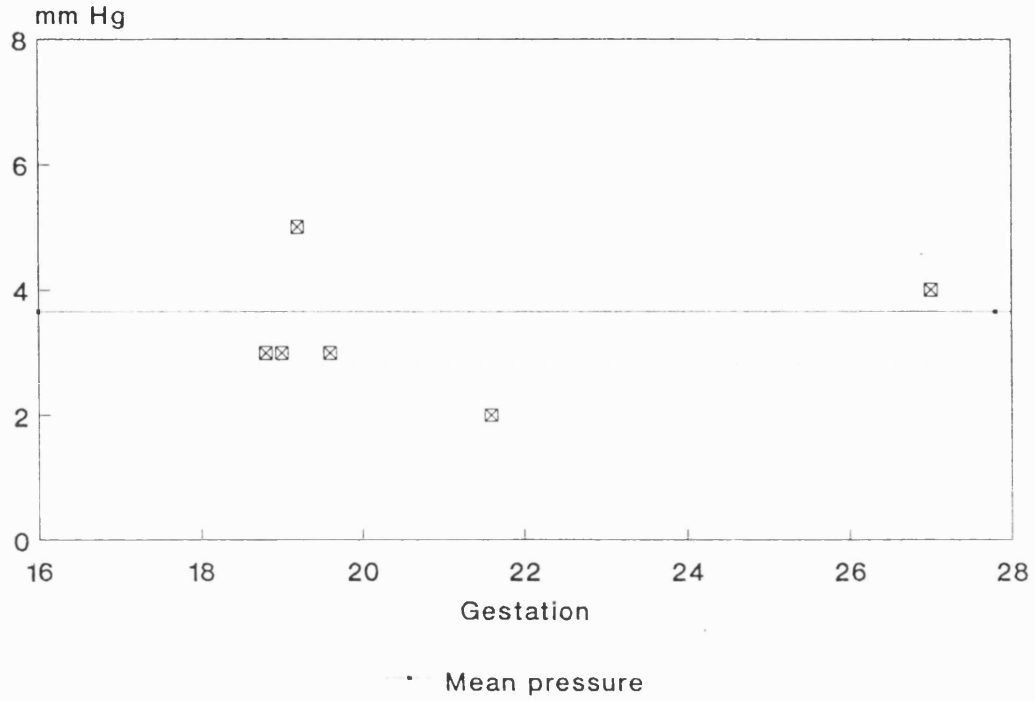


Figure 3.31: Right atrial pressure.

3.5.3 Relationship of left to right atrial pressure in normal fetal hearts:

The left and right atrial pressures were not significantly different (Student's t test, p=0.86) and did not show any increase with gestational age (Figure 3.32). Mean atrial pressure, combining data from left and right, was 3.478 and S.D. 1.620 mm Hg.

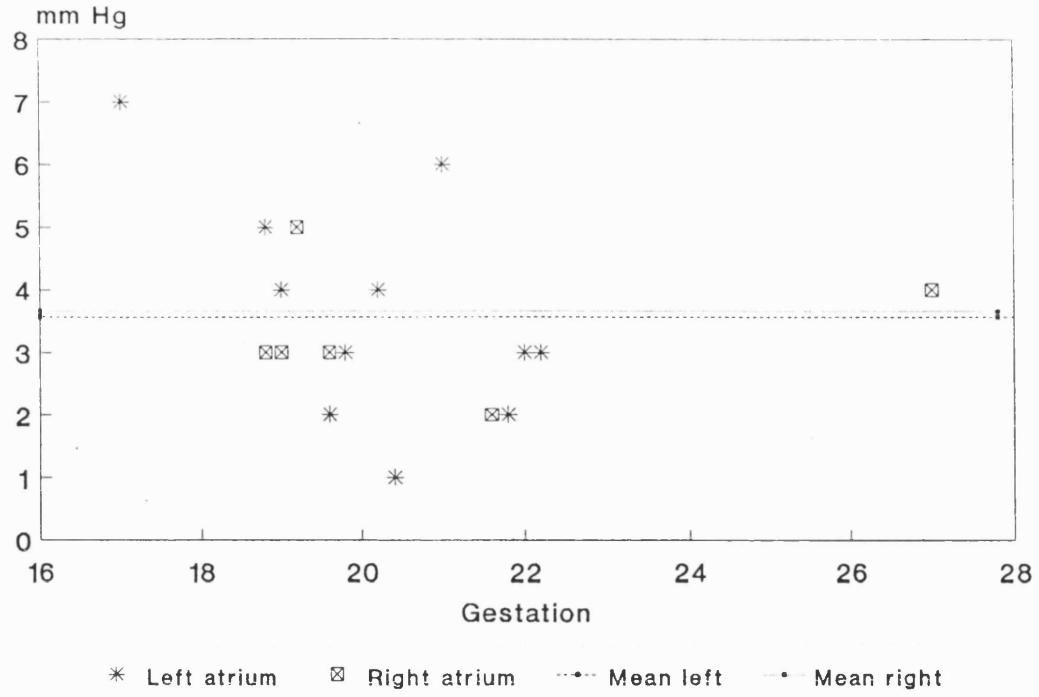


Figure 3.32: Atrial pressure in left and right atria in normal hearts

3.5.4 Atrial pressure in abnormal hearts:

Atrial pressure was recorded at diagnostic fetal blood sampling in one fetus with nonimmune hydrops, associated with cardiomegaly and ascites. In this case the atrial pressure was 9 mm Hg, greater than 2 S.D. above the mean. The pressure tracing from the right atrium of a fetus with a VSD, DORV and pulmonary atresia is shown on figure 3.33.

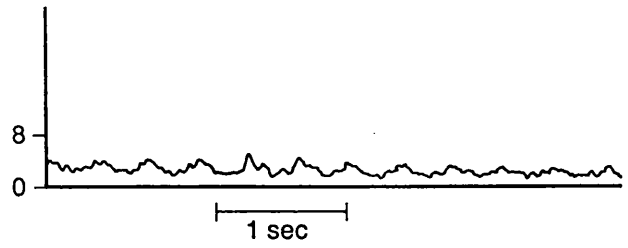


Figure 3.33: Right atrial pressure in a fetus with VSD, pulmonary atresia and DORV at 24 weeks.

4. DISCUSSION:

4.1 METHODOLOGY:

4.1.1 Gestational age assessment:

In any study of a variable which changes with gestational age, an accurate assessment of the age of the fetus is required. Pregnancy duration is usually calculated from the first day of the last menstrual period, this being a date which most women can remember whereas few know the date of ovulation or conception. However, there are many reasons why menstrual dates may be inaccurate including irregular cycle length and delayed ovulation. Ultrasound measurement of various fetal parameters has been shown to be accurate in assessing gestational age, the accuracy depending on the age of the fetus and the number of parameters measured. During the second trimester, measurement of biparietal diameter, head circumference, abdominal circumference and femur length will provide an assessment of gestational age within an error of less than seven days (Hadlock 1990). It is our practice, therefore, to perform fetal biometry by ultrasound during the second trimester and adopt the ultrasound estimate of gestational age if this differs from the menstrual dates by seven days or more, unless a previous scan has confirmed dates.

4.1.2 Ultrasound assessment of fetal anatomy:

With the advent of high resolution ultrasound, our ability to examine fetal anatomy has developed and led to an increase in the number of congenital abnormalities which

can be diagnosed in utero. Careful follow up of all diagnostic cases is essential to ensure continuing diagnostic of the techniques employed. It is our practice to perform postmortem examination of all fetuses when the pregnancy has been terminated because of fetal anomaly and where the parents give consent for such examination. We also make considerable efforts, as stated above, to obtain follow up information of all babies born after anomaly scanning in our unit, whether normal or abnormal.

The majority of cardiac pressures obtained in this study were recorded during midtrimester termination of pregnancy in cases where there was no evidence of fetal abnormality. Postmortem study of these fetuses was not performed because of problems in obtaining consent. However, full examination of the heart using ultrasound was always achieved, in order to confirm structural normality. Previous studies by workers in the field of fetal echocardiography have confirmed the reliability of prenatal echocardiography in excluding abnormality and diagnosing congenital cardiac defects (Achiron et al 1992, Allan et al 1980, Allan 1985, Allan et al 1989, Davis et al 1990, DeVore et al 1982, Lange et al 1980). Ultrasound examination of the fetal heart at 18 or more weeks gestation with confirmation of a normal four chamber view and great vessel connections excludes major heart malformations, and this was the method employed in this study.

4.1.3 Liquor volume assessment:

Liquor volume can be assessed clinically by palpation and by ultrasound visualisation. Noninvasive precise measurement of liquor volume is not possible, but various techniques have been developed using ultrasound measurement. These include vertical measurement of the single deepest pool of liquor (Chamberlain et al 1984 [a]), and the four quadrant amniotic fluid index (Phelan et al 1987[a] and [b]). Definitions of polyhydramnios vary, particularly with a single column measurement (Chamberlain et al 1984[b], Hill et al 1987, Lange et al 1989, Fisk et al 1990). We have employed the four quadrant method as it is apparently a more accurate assessment of intrauterine volume (Jeng at al 1990) and the measurement has good reproducibility with little interobserver error (Rutherford et al 1987).

4.1.4 Uterine activity during manometry:

The fact that fetal pressures increase in line with amniotic pressures was recognised by early workers in the field of fetal physiology (Reynolds et al 1954). Nicolini (1989[b]) advocated the technique of subtraction manometry, simultaneously measuring intra amniotic and intrafetal pressures, in order to allow the increases in uterine pressure which occur during maternal movement and uterine activity to be recorded. Subtraction manometry carries the disadvantage of requiring the insertion of two needles into the amniotic cavity, whereas diagnostic invasive techniques

rarely involve more than one uterine puncture. In our experience there is no increased risk of fetal loss with repeated needle insertions although the more needle insertions performed, the greater the maternal discomfort and the higher the theoretical risk of introducing infection into the amniotic cavity.

At the start of our study, we employed the technique of subtraction manometry in ten cases. We did not note rhythmic increases in intra amniotic pressure in any case, and we therefore reverted to a single needle technique. Normal maternal breathing did not produce an increase in intra amniotic pressure, and all measurements were taken with the mother lying quietly. Uterine activity during invasive procedures was only noted on one occasion later in our study. This was a case of bladder outflow obstruction at 18 weeks, where the bladder was aspirated following ultrasound guided fetal blood sampling. Intra amniotic pressure was recorded throughout and uterine contractions lasting 60 - 70 seconds were noted on the pressure tracing. The mother was aware of the uterine activity. On no other occasion was uterine activity noted during manometry. We do not believe that subtraction manometry is necessary, particularly in the quick, routine procedures of amniocentesis and fetal blood sampling. The time taken to complete these procedures is usually less than five minutes, although fetal blood sampling may take up to fifteen minutes.

4.1.5 Pressure measurement technique:

Invasive pressure measurements have been performed for many years. Early workers employed a simple mercury manometer (Ribemont 1879), attaching this to a fluid filled tube usually inserted into the blood vessel or compartment by a needle. In recent years, catheter tip transducers have become available which permit measurement of pressure without the problems of a fluid filled system. However, catheter tip transducers suitable for human fetal work are not yet available.

Fluid filled measuring systems are relatively cheap and easy to adapt to different techniques, but their use is accompanied by a number of problems. The combination of a transducer and catheter will always give rise to oscillations due to the natural elasticity of the tube, which results in distortion of the signal. However, friction within catheter tubing causes damping, which reduces this signal distortion (Butler and Oldershaw 1986).

Cardiovascular pressure waveforms are complex when assessed by Fourier analysis, and there may be significant contributions up to the tenth harmonic. Therefore, for the accurate measurement of pulsatile pressures, the system used should have a flat frequency response up to 20 Hz (Butler and Oldershaw 1986), although this is only adequate to heart rates of up to 200 bpm (Rudolph and Heymann 1980). However, because the high frequency components contribute

most to the fast changing part of the waveform, if changes in the pressure profile such as dP and dT are **not** examined, reliable pressure values can be recorded with a system with a lower frequency response, provided that it is at least that of the frequency of the signal. In the recording of fetal cardiac and arterial pressures, both of which have a biphasic waveform, the frequency response should be at least 4 Hz.

The frequency response of the system used in this study conforms with this requirement, although it is not adequate for measurement of dP and dT. Frequency response, and the degree of distortion of pressure signals, are affected by the stiffness, length and internal diameter of the catheter and needle, and the displacement of the transducer membrane. Reducing the length of needle and manometer tube would have made the technique of fetal vascular puncture and pressure measurement cumbersome and difficult. Increasing the diameter of the needle to 17 gauge resulted in an improvement in the frequency response (from 7.9 Hz to 15.9 Hz). This is due to the fact that the resistance to flow in a tube is inversely proportional to the radius of the tube raised to the power 4. There was less natural damping with the larger needle, which could result in distortion of the signal.

At early gestations, the small size of vessels and cardiac chambers means that it is very difficult, even with a 22

gauge needle, to ensure that the whole of the needle tip lies within the compartment under study. In addition, it is our experience that bleeding after puncture is increased if a larger needle is used, and as many procedures were performed on ongoing pregnancies, it was felt unethical to increase the risk of the procedure by using a larger needle. For clear comparison of results across the gestational range studied, it was essential to use the same system throughout the study. The needle size chosen (22 gauge) was the safest for the procedures, whilst allowing accurate recordings.

The transducer used in this study has a membrane displacement of 0.04 mm^3/100 mm Hg. This is a satisfactory characteristic for this study, in which all the pressures recorded are of low values (less than 100 mm Hg) .

The presence of any air bubbles in a fluid filled system will markedly distort the signal and result in overdamping, as well as introducing the risk of air embolus, and it can be difficult to ensure that the system is free from air. However, this can be achieved by paying meticulous attention to detail whilst setting up the equipment, and regular visual checks to ensure no air bubbles are present.

When a catheter is placed with its open end facing into the blood flow, pressure recorded will be higher than when the tip is away from the blood flow (Barcroft 1946, Brown and

Smallwood 1981). This problem is reduced if a side opening catheter is used, and minimised by the use of a catheter tip transducer. The needle we used had a bevelled end. Biopsy needles are available with a side opening as well as a bevelled end. Unfortunately these could not be used as, in order for both apertures to be freely within the blood stream, the length of needle required to be in the compartment under review was greater than the maximum diameter of some chambers.

Early workers reported greater spasm in the umbilical vessels when a catheter rather than needle was inserted (Barcroft 1946), although Reynolds et al (1952) noted considerable spasm following insertion of a needle into the umbilical vessels. We have employed Doppler ultrasound to examine flow in a vessel during fetal blood sampling. No change was seen in the flow velocity signal and no obvious change in the diameter of the vessel was demonstrated when a needle was inserted. Access to all fetal compartments had to be with a needle in our study, and pressure measurements through a small catheter inserted down the needle lumen would have lead to greater distortion of the pressure signal, through noise and altered frequency response (Fry 1960).

During in utero studies, fetal pressures are traditionally zeroed at amniotic pressure. The siting of the pressure transducer has been a subject of controversy amongst

current workers. With a fluid filled system, the transducer should be placed at the same level as the compartment under study in order to minimise increases or decreases in the pressure recorded due to the effect of hydrostatic pressure (Brown and Smallwood 1981, Butler and Oldershaw 1986). Placing a transducer level with the fetal heart for measurement of umbilical venous pressure was advocated by Weiner et al (1989[a]). This is very difficult to achieve particularly with an active fetus. The siting of the transducer only affects the pressure values recorded if they are zeroed to the level of the transducer. The maternal midabdomen approximates to the level of the fetus, and is much more reproducible. It is also suitable for measurement of the intra amniotic pressure, although zeroing pressures at the top of the maternal abdomen was the most accurate and reproducible method (Nicolini et al 1989[b]). In the current study, the transducer was placed at the mid level of the maternal abdomen, although pressures were zeroed to the top of the abdomen. Fetal pressures were zeroed to amniotic pressure and therefore unaffected by transducer level. Sideris and Nicolaides (1990) attempted to solve the problem of an accurate zero for amniotic pressure by having the transducer above the patient and correcting for the angle of the needle. This technique is reproducible, although pressures recorded would be lower than those using the technique adopted in this study. All of these problems would be solved using a catheter tip transducer.

The use of an inkjet recorder provides for less error than any other paper recording system (Butler and Oldershaw 1986). Digitalized recording of the signal on to magnetic tape or computer would have allowed future analysis of various pressure characteristics e. g. dP/dT. However, the characteristics of the recording system used are not adequate for this type of analysis. If such studies were to be performed, a catheter tip transducer would be required.

4.1.6 Left ventricular puncture:

In previous studies on cardiovascular pressures in humans and animals, access to the heart chambers has generally been via a catheter inserted into a peripheral artery or vein. This is not possible in the human fetus in utero. However, the technique of direct left ventricular puncture is used in both adult (Mendel and Oldershaw 1986) and paediatric cardiology (Rudolph and Cayler 1958). There are theoretical hazards in using this technique, including puncture of the coronary arteries and bleeding into the pericardial and pleural spaces. Nevertheless, the technique appears to be safe, and with minimal complications (Brock et al 1956). The problem of extrasystoles at the time of puncture described in postnatal life (Mendel and Oldershaw 1986) has not been seen during our study. Dysrhythmias (in the form of bradycardias) have only been seen when the needle crossed the intraventricular septum, and they have always been transient.

On occasions, due to fetal lie, it was necessary to approach the heart through the posterior chest wall. This approach has also been used in postnatal life, but carries a higher rate of complication particularly that of inadvertent vascular puncture (Fisher 1955). Transthoracic access to the heart during fetal life, using ultrasound guidance, can be more difficult than direct ventricular puncture through the anterior chest wall, but in our experience has not been associated with an increase in complications.

The quality of waveforms obtained from ventricular puncture was generally very good, when compared with postnatal waveforms. Damping of the signal was a problem. When this occurred, the needle was flushed and the system thoroughly checked to ensure that no air bubbles were present. In most cases where poor quality waveforms were obtained, it was due the tip of the needle catching against the wall of the ventricle or the chordae tendineae. In approximately 30% of cases where ventricular puncture was attempted, adequate waveforms were not obtained. Accurate siting of the needle could not be achieved in all cases, often due to excess fetal activity or poor lie.

All waveforms were examined visually and compared with those obtained in postnatal catheter investigations. If the appearances of the fetal waveforms were similar to postnatal ones, they were accepted for the study.

4.1.7 Atrial puncture:

Obtaining high quality pressure recordings from the atria was extremely difficult. This was due to the small size of the chamber. In order to obtain a satisfactory pressure tracing, it is essential to have the needle tip free in the chamber under investigation. The atrium of the fetal heart measures only three to five millimetres in the largest diameter at the gestations under study. Also, in the left atrium the flap of the foramen ovale must be avoided. In 50% of cases where the atrium was entered, it was not possible to obtain a pressure recording, even though blood could be aspirated. In most cases, it was not possible to resite the needle in order to obtain an adequate pressure recording. This was due to poor fetal lie, excess fetal activity or maternal discomfort. At all times in this study, attention was paid to the ethical considerations of the procedures, and this usually limited us to measuring pressure in one, or at most two, compartments.

4.2 AMNIOTIC PRESSURE:

4.2.1 Normal liquor volume:

The literature on intrauterine pressure during labour is substantial. However, there has been little interest expressed in the changes in intrauterine pressure during pregnancy until the last few years. The increase in intra amniotic pressure with gestational age is well established (Nicolini et al 1989[b], Weiner et al 1989[a], Fisk et al 1990). By investigating pregnancies in the first trimester, Sideris and Nicolaides (1990) have shown that intra amniotic pressure falls from 9 to 14 weeks, before rising with further increase in gestational age. No workers have previously examined the effect of fetal abnormality on intra amniotic pressure, although Sideris and Nicolaides excluded pregnancies with major fetal abnormality from their study. This study has specifically examined the effect of fetal abnormality on intra amniotic pressure in the presence of normal liquor volume, and has thus provided new information. Whilst the fetus plays an active role in the production of liquor, and certain fetal abnormalities are known to be associated with altered amniotic fluid volume, the present study fails to produce evidence that, in the population studied, fetal abnormality *per se* exerts any effect on intra amniotic pressure when liquor volume is normal.

4.2.2 Intra amniotic pressure in abnormal liquor volumes:

Abnormalities of liquor volume are associated with various

complications of pregnancy, both fetal and maternal. In the presence of fetal abnormality, liquor volume may be increased e.g. tracheo-oesophageal fistula, or decreased e.g. renal agenesis (Thomas and Smith 1974). Maternal conditions are associated with changes in liquor volume: polyhydramnios occurs in diabetes, and oligohydramnios is common in pregnancies complicated by proteinuric hypertension and intrauterine growth retardation. Polyhydramnios can lead to maternal discomfort, dependent oedema, premature labour, unstable lie and malpresentation. Oligohydramnios on the other hand, whether related to intact or ruptured membranes, is associated with pulmonary hypoplasia and compression deformities. Both abnormalities are accompanied by an increase in perinatal morbidity and mortality (Chamberlain et al 1984(a) and 1984(b), Hill et al 1987).

Published work has demonstrated an increase in pressure with severe polyhydramnios and a reduction in pressure in oligohydramnios with intact membranes (Nicolini et al 1989 (b), Weiner et al 1989[a], Fisk et al 1990). However, all these studies suffer from small numbers and variable definitions of polyhydramnios and oligohydramnios. Our results demonstrate that these changes occur in some, but not all, patients with abnormal liquor volumes.

The relationship of intra amniotic pressure to abnormalities of liquor volume and the associated increase

in perinatal mortality and morbidity is of clinical interest, as therapeutic options exist which could improve outcome. This relationship is not straightforward, and we have been unable to elucidate the nature of any correlation between amniotic volume and intra amniotic pressure. It may be related to speed of onset of polyhydramnios. However, this is very difficult to establish in most cases. Some women are aware of a sudden increase in abdominal distension which may represent so-called 'acute hydramnios', but in the absence of a documented rapid increase in liquor volume, speed of onset is impossible to establish. The speed of onset appears to vary even when the underlying pathology is the same. In our own experience, some women whose pregnancy is complicated by polyhydramnios secondary to fetal tachyarrhythmia complain of a rapid increase in abdominal size, whereas others report a slow increase or remain asymptomatic.

Methods of diagnosing polyhydramnios and oligohydramnios vary. At Guy's Hospital, we have employed the four quadrant amniotic fluid index for polyhydramnios (Phelan et al 1987[a]) as this measurement carries little interobserver error (Rutherford et al 1987). A single pool of less than 1 cm depth represents severe oligohydramnios, mild to moderate cases being associated with normal intra amniotic pressure (Fisk et al 1990).

Fisk et al (1990) demonstrated a linear relationship

between intra amniotic pressure and the size of the largest pool of liquor assessed by ultrasound linear measurement. In his paper, however, the depth of the needle tip in the amniotic cavity is not described. We have shown that increasing the depth of the needle in the uterine cavity increases the measured amniotic pressure, presumably by hydrostatic effect. If amniotic pressure is zeroed to the top of the maternal abdomen, the vertical distance from the top of the maternal abdomen to the needle tip must be standardized. We have failed to demonstrate a correlation between amniotic fluid index and intra amniotic pressure in the presence of a stable fluid volume. However, a relationship does exist between intra amniotic pressure and liquor volume as amniocentesis resulted in a fall, and amnioinfusion was associated with an increase, in intra amniotic pressure in each case. This may be related to speed of onset or the rate of change in muscle tone which accompanies an increase or decrease in intra uterine volume. Further work is required to elucidate the nature of this relationship.

Early work involving amniocentesis in cases of polyhydramnios had given the impression that the intrauterine pressure was not always elevated. Whilst liquor was observed to flow from the needle with considerable force in some cases, in others the liquor did not drain freely and required aspiration (Rivett 1933). The possibility of there being two types of polyhydramnios,

high and normal pressure, was first suggested by Caldeyro-Barcia et al (1957), and our results support this. We have not demonstrated any difference between these two populations in liquor volume, but it would appear that the time from diagnosis to delivery and gestational age at delivery are longer in the normal pressure group, although our numbers are too small to permit statistical analysis. This was also demonstrated by Fisk et al (1990). If this is substantiated in further studies, measurement of intra amniotic pressure may become a useful clinical tool in helping to predict those pregnancies complicated by polyhydramnios at risk of preterm delivery. Whilst amniocentesis to reduce maternal discomfort in both high and normal pressure leads to a reduction of intra amniotic pressure, there is no evidence that draining lengthens the pregnancy.

Low amniotic pressure in oligohydramnios has been suggested as the mechanism whereby pulmonary hypoplasia develops. Amnioinfusion to restore intra amniotic pressure into the normal range has been suggested as a therapeutic measure to improve pulmonary development (Nicolini et al 1989 [a]). Whether the low pressure alone is responsible for lung hypoplasia is open to debate (Johnson and Maxwell 1990). Certainly, lung hypoplasia can develop in cases of oligohydramnios with normal or elevated amniotic pressure. Fetal breathing movements are reduced in some cases of oligohydramnios (Blott et al 1987). This may be due to

restriction of space for movement, and alterations in surrounding pressure (Pringle 1986). Such breathing movements are believed to exert a beneficial effect on lung growth, and their absence may therefore be associated with a failure of lung development although some workers have noted that breathing movements are not predictive of lung hypoplasia (Moessinger et al 1988).

In cases where there is evidence of premature rupture of membranes amnioinfusion may not be beneficial in reducing the risk of lung hypoplasia, as fluid added to the amniotic sac may leak away. Our study has shown that in cases of oligohydramnios with rupture of membranes, intra amniotic pressure may be elevated (n=1), normal (n=2) or low (n=1). Elevation of intra amniotic pressure was not seen in any case of oligohydramnios with intact membranes. Therefore, if intra amniotic pressure is measured in a case with reduced liquor and found to be low, this measurement may help differentiate between intact and ruptured membranes.

4.2.3 Multiple pregnancies:

Multiple pregnancies are often associated with abnormalities of liquor volume, particularly polyhydramnios. We have measured the pressure in both sacs in four cases of diamniotic twins and in each case the pressure in both sacs was the same. Intra amniotic pressure was within the reference range for singleton pregnancies, even though polyhydramnios was present in one of the sacs

in three cases. This may be a reflection of the greater diameter of the uterine sphere in relation to wall thickness (Laplace's law [pressure = 2 x wall tension/radius]) and the fact that the membranes are so compliant that pressure from one sac is transmitted to the other. Fisk et al (1990) recorded high pressure in three sets of twins, but did not comment on whether polyhydramnios was present in both sacs, and whether both sacs had identical pressures. The value of measuring intra amniotic pressure in multiple pregnancies awaits further clarification.

4.2.4 Clinical applications of intra amniotic pressure measurement:

In the presence of normal liquor volume, there is no clinical advantage gained in measuring the intra amniotic pressure. Abnormalities of liquor volume are often associated with abnormal intra amniotic pressure, which may help in the diagnosis of ruptured membranes or identifying those at risk of preterm labour.

There is evidence to suggest that reducing the pressure to within the normal range in cases of polyhydramnios may be beneficial. In cases with abnormal umbilical artery Doppler studies, and abnormal blood gas analysis on fetal blood sampling, reducing intra amniotic pressure into the normal range has been shown to reverse fetal hypoxia and acidosis (Fisk et al 1990). The risk of preterm labour may be

reduced by amniocentesis in cases of polyhydramnios.

The use of amnioinfusion in cases of oligohydramnios to restore intra amniotic pressure into the normal range has also been recommended as a therapeutic measure to minimise the risk of pulmonary hypoplasia (Nicolini et al 1989[a]). Fetal compromise can occur during amnioinfusion (Tabor and Maier 1987) which may be due to an excessive increase in intra amniotic pressure. This could be avoided by monitoring intra amniotic pressure during the procedure.

If intrafetal pressures are to be recorded, it is essential to measure the intra amniotic pressure. The wide range of pressures in cases with normal liquor, compared to the low intrafetal pressures recorded, makes it necessary to measure each case. The variation in intra amniotic pressure in abnormal liquor volumes is even greater, and it is impossible to predict the intra amniotic pressure in any case.

The importance of intra amniotic pressure within this thesis is that it cannot be assumed, and must therefore be measured.

4.3 UMBILICAL VENOUS PRESSURE:

The umbilical vein is a relatively large vessel and provides a low resistance route for blood from the placenta to the fetus. The volume of flow has been estimated by many workers to be 180-220 ml/Kg/min, using a variety of techniques and with little inter-species variation (Dawes 1968, Scopes 1977). This is approximately 50% of cardiac output in primates.

The single umbilical vein enters the fetal abdomen at the umbilicus and runs for a short distance in the free margin of the falciform ligament before running cranially through the liver. The majority of blood within the intrahepatic portion of the vein bypasses the liver sinusoids and flows into the ductus venosus. The ductus venosus enters directly into that part of the right vitelline vein which becomes the inferior vena cava. It has a wide diameter and is believed to act as a low resistance shunt, allowing oxygenated blood from the placenta to bypass hepatic sinusoids and enter the inferior vena cava. Within the ductus venosus, some poorly oxygenated blood from the left branch of the portal vein is mixed with oxygenated blood from the umbilical vein, although over 98% of the blood flowing through comes from the umbilical vein (Edelstone et al 1978).

There is a sphincter or lip at the beginning of the ductus venosus (Chacko and Reynolds 1953), the role of which still

requires further elucidation. Recent work examining the blood flow within the ductus venosus with colour and pulsed wave Doppler in human fetuses has suggested that this short vessel has a high flow in order to ensure that the jet of well oxygenated blood from the umbilical vein is directed towards the foramen ovale on entering the heart (Kiserud et al 1991), and it may be that the sphincter mechanism is responsible for the control of this. In the experimental animal the ductus venosus does not appear to be particularly sensitive to changes in PO_2, PCO_2 or pH (Edelstone et al 1980). Minimal constriction occurs with very large concentrations of noradrenaline and it appears to accommodate its circumference passively to changes in venous return.

It is thought that, in the human fetus, umbilical venous pressure reflects central venous pressure (Weiner 1989[a]). Measurement of the umbilical venous pressure may therefore have clinical applications in the diagnosis and management of fetal cardiac failure. The aim of this part of the thesis was to establish a reference range for umbilical venous pressure, and investigate the changes that occur in cardiac failure.

4.3.1 Umbilical venous pressure in the normal fetus:

Initial attempts to measure umbilical venous pressure directly were limited to studies on fetuses at the time of birth or instrumented fetal animals, particularly the fetal

lamb (Barcroft et al 1942, Crosby et al 1970, Dawes 1962[a], Haselhorst 1929, Margolis and Orcutt 1960, Reynolds and Paul 1958, Ribemont 1879). Results of these early studies varied widely and also gave little information on the changes with gestation. The umbilical venous pressure in the fetal sheep was reported by Barcroft and Kennedy (1939) to be less than 10 mm Hg at 56 days, 10 mm Hg at 110 days and 18 mm Hg at 140 days (term = 147 days), thus demonstrating an increase with advancing gestation. Barcroft had previously reported a single recording of 20 mm Hg (1936). Reynolds reported varying venous pressures in the fetal sheep, with values from 4-30 mm Hg in one study (1951). Dawes reported results similar to those of Barcroft, with umbilical venous pressure recorded as 8-14 mm Hg in lambs near term (1962[a]). These results are higher than the pressures recorded directly in human fetuses in utero.

There are fundamental differences in the circulatory systems in fetal sheep and humans. The main difference is that fetal sheep generally have two umbilical veins outside the abdomen (Dawes 1962[a]), whereas the human has only one. There are also differences in regional blood flow. Measurements of venous pressure in chronically instrumented sheep have often been made from the abdominal portion of the umbilical vein, rather than the cord, which may account for the difference in pressure. In addition, true intra uterine measurements were rarely made. Most workers

exteriorized the fetus, or lifted a loop of cord from the amniotic cavity before making their observations. In a review of the literature, Assali et al (1974) noted that exteriorization of the fetus has little effect on blood pressure as long as amniotic pressure is taken into account. However, it has since been shown that, even with the feto-placental circulation intact, exteriorization of a fetus results in alteration of fetal vascular pressures (Rudolph and Heymann 1980).

The need to take amniotic pressure into account in the measurement of fetal pressures was illustrated by Reynolds et al (1954), when they investigated the effect of increasing uterine pressure on fetal cardiovascular pressures. However, despite demonstrating that fetal arterial pressure increased with increases in intra amniotic pressure, and by similar amounts, they failed to take this into account and give no details on how fetal pressures were zeroed.

Other studies by the same team gave similar, high values for umbilical venous pressure (Reynolds et al 1952, Reynolds and Paul 1958) although no account was taken of intra amniotic pressure. They suggested that the umbilical venous pressure in the fetal sheep was high in order to maintain a large diameter, and thus high flow, in the long vessels. It was thought that this high pressure was produced by the activity of the sphincter in the ductus

venosus (Reynolds and Paul 1958, Reynolds 1961). The method of zeroing fetal pressures is not mentioned in this, or other, work by the same team and it may be that fetal venous pressures were high because they were not zeroed at amniotic pressure.

The advent of antenatal fetal blood sampling has allowed direct access to the human fetal circulation in utero from early gestations (16-18 weeks to term). Amniotic pressure can also be measured, and fetal pressures zeroed to amniotic pressure. All studies on the human fetus prior to the last ten years were performed on exteriorized fetuses at termination of pregnancy by hysterotomy or on fetuses at the time of birth, when many physiological changes are occurring.

Recent studies published concerning human fetal umbilical venous pressure measured directly and zeroed at amniotic pressure have given very similar results. Castle and Mackenzie (1986), using fetoscopic visualisation of the umbilical vessels, measured mean umbilical venous pressure and found it to be 2.2 +/- 1.7 mm Hg in 15 cases (range 0 - 5.0), with no increase with gestation. Weiner et al (1989[a]) measured umbilical venous pressure during ultrasound guided fetal blood sampling and again showed no increase with gestation, with pressure being 5.3 mm Hg +/- 2.3. Nicolini et al (1989[a]) employed the same technique and found umbilical venous pressure to be 4.5 mm Hg (95th

C.I. 3.2-5.8). Our reference range concurs with these values, and again shows no increase in umbilical venous pressure with gestation. Why human umbilical venous pressure is so much lower than in the sheep is unclear. It may be due to differences in investigative technique, zeroing procedures or inter species physiological differences. It illustrates well the need for caution in extrapolating from animal data to man, which has been the usual practice in fetal physiology to date.

Umbilical blood flow in the normal fetus is nonphasic. This is demonstrated by the continuous flow seen during Doppler interrogation of the umbilical vessels, with constant velocities in the vein. At no time was a pulsatile waveform obtained from the umbilical vein during pressure measurements. Reynolds et al (1952) demonstrated small venous pressure pulsations in the umbilical cord of exteriorized fetal lambs, with the placentae left in situ. They suggested that these pulsations might have been transmitted from the umbilical arteries. No other workers have demonstrated pulsatile flow in the umbilical vein of normal fetuses. The findings of Reynolds et al may have been artefactual due to their methodology.

4.3.2 Umbilical venous pressure in congenital heart disease:

In the presence of structural heart disease, the umbilical venous pressure was within the reference range in all cases

except two where the heart was enlarged. One of these fetuses had the absent pulmonary valve syndrome, and the other an enlarged heart and pericardial effusion.

In postnatal life, cardiomegaly is one of the signs of cardiac failure. Paladini et al (1990) examined cardiac size in normal and abnormal fetal hearts by measuring the cardiothoracic ratio. They found that certain forms of congenital abnormality, particularly Ebstein's anomaly and tricuspid valve dysplasia, were associated with cardiomegaly. Our finding of increased umbilical venous pressure in cases with congenital heart disease and cardiomegaly implies that cardiac failure may be present or imminent (see below). However, in conditions with gross atrio-ventricular valve regurgitation, this interpretation may not be correct since such regurgitation may influence venous pressure. To diagnose cardiac failure, an additional sign such as skin oedema, must be present.

4.3.3 Umbilical venous pressure in nonimmune hydrops:

The antenatal diagnosis of nonimmune hydrops fetalis remains a considerable challenge to the practising clinician. Fetal blood sampling under ultrasound guidance is now an integral part of the investigation of such cases and its use has served to further highlight the wide diversity of fetal and maternal conditions associated with this diagnosis. However, uncertainty with regard to the underlying pathophysiology gives rise to considerable

difficulty in management.

There are numerous causes of nonimmune hydrops including congenital heart disease, arrhythmias (Allan et al 1986), and fetal infections as well as associations with other structural and karyotypic anomalies (Beischer et al 1971, Machin 1989, Janiaux et al 1990). Nonimmune hydrops is associated with high fetal and neonatal loss (Andersen et al 1983), although successful prenatal therapy has been reported in a variety of cases. Such therapy usually involves the treatment of fetal heart failure (Harrigan et al 1981, Maxwell et al 1988, Gembruch et al 1989) or drainage of fluid collections (Schmidt et al 1985, Benaceraff and Frigoletto 1986) but may include intrauterine transfusion of blood (Soothill 1990) or albumin (Shimokawa et al 1988).

The exact pathogenesis of nonimmune hydrops fetalis remains unclear, and is probably a combination of two or more factors in most cases. There are three main mechanisms presently believed to be involved in the development of hydrops:

1. anaemia
2. hypoproteinaemia
3. cardiac failure.

It is unlikely that a single mechanism is active in any one case. Information obtained from invasive fetal investigation has confirmed anaemia and hypoproteinaemia to

be present in a number of cases (Nicolaides et al 1985). In postnatal life, these three processes can be interlinked, with anaemia leading to high output cardiac failure and resultant hypoproteinaemia. The same occurs in fetal life.

The evidence to support cardiac failure as a mechanism underlying fetal hydrops to date has been based on noninvasive assessment of cardiac function and postmortem studies (Harrigan et al 1981, Keeling et al 1983). The diagnosis of intrauterine cardiac failure is often made in the presence of cardiac dysfunction without any hard evidence.

Intrauterine cardiac failure is believed to be the commonest mechanism underlying the development of nonimmune hydrops (Keeling et al 1983). In postnatal life, congestive cardiac failure is associated with an increase in cardiac size, elevation of central venous pressure and fluid retention. Fetal cardiac size can be assessed by measurement of the cardiothoracic ratio (Paladini et al 1990). Fluid collections in the fetus are easily demonstrated using ultrasound, and venous pressure can be measured at the time of fetal blood sampling. Using these techniques, we can therefore now make the diagnosis of intrauterine cardiac failure with confidence.

Depending on the underlying cause, cardiac failure in fetal life is amenable to intrauterine therapy. If a fetus is

anaemic, intrauterine transfusion may be indicated (e.g Rhesus disease, parvovirus infection [Soothill 1990]). The management of the fetus with a tachyarrhythmia and hydrops involves administration of antiarrhythmic agents, either transplacentally or directly to the fetus.

We have measured umbilical venous pressure in 15 patients with nonimmune hydrops. The venous pressure was greater than 2 S.D. above the mean in the presence of ascites. There was also a significant increase in cardiac size in those fetuses with elevated umbilical venous pressure. There was a positive correlation between umbilical venous pressure and cardiothoracic ratio (0.725, $p = <0.01$, Figure 3.10). It is interesting to note that only when ascites was present were cardiac size and venous pressure increased.

Congestive cardiac failure therefore seems to be one of the mechanisms underlying hydrops associated with ascites. In no case without ascites did we find evidence to suggest that cardiac failure was present. Our data shows a high association between ascites and cardiomegaly. Ascites could cause an elevation of venous pressure by compression of the intraabdominal portion of the umbilical vein. This would not result in cardiomegaly. The associated increase in cardiac size in these cases suggests that compression of the umbilical vein is not be the primary mechanism. In addition, in one nonhydropic case (no. 233) with isolated ascites, and no other fluid collections, the heart size and

umbilical venous pressure were normal.

In extrauterine life, congestive cardiac failure is associated with an increase in cardiac size and elevation of central venous pressure. The umbilical venous pressure is thought to reflect central venous pressure in fetal life (Weiner et al 1989[a]). In animal work, umbilical venous pressure has been shown to be higher than pressure in the inferior vena cava (Reynolds and Paul 1958). However, our results show that right atrial pressure is very similar to umbilical venous pressure. In addition, right atrial pressure is increased in hydrops with cardiomegaly and ascites. It would therefore appear that, in the human fetus, umbilical venous pressure does indeed reflect central venous pressure. If this is true, then the cardiac enlargement and elevated pressures that we have demonstrated provide direct evidence of cardiac failure in some cases of fetal hydrops. The statistically significant relationship between umbilical venous pressure and the cardiothoracic ratio has provided validation for the noninvasive diagnosis of congestive cardiac failure, both in initial assessment of the fetus, and in monitoring the effects of therapy.

Other noninvasive methods of assessing fetal cardiac function include Doppler ultrasound. This may be applied to the heart valves, and also to individual vessels. Some workers have reported a pulsatile waveform on Doppler

interrogation of the umbilical vein in cases of fetal hydrops (Gudmundsson et al 1991). These cases also had reduced right ventricular shortening fraction, suggestive of congestive cardiac failure. Doppler interrogation of the ductus venosus in fetal hydrops demonstrated reverse blood flow through the ductus venosus during atrial systole (Kiserud et al 1991). This reverse flow may explain the pulsatile waveform, and may be a further indicator of congestive heart failure as an underlying mechanism in these cases.

Examination of the flow in the inferior vena cava in fetuses with tachyarrhythmias and sinus bradycardias demonstrated increased reverse flow during atrial systole (Reed et al 1990). It is likely that this reverse flow is transmitted to the ductus venosus and thus the umbilical vein.

4.3.4 Umbilical venous pressure in congenital diaphragmatic hernia:

Left ventricular compression in congenital diaphragmatic hernia is a poor prognostic sign (Sharland et al 1992). Fetal blood sampling for rapid karyotype is commonly performed in the investigation of diaphragmatic hernia diagnosed prenatally. On three occasions, umbilical venous pressure was measured during the investigation of such cases. In one fetus, moderately severe left ventricular compression was present. In this case, umbilical venous

pressure was elevated at 8 mm Hg. The infant was born at term, but died in the neonatal period before surgery could be performed. One of the other two fetuses survived postnatal surgery, whilst the pregnancy was terminated in the third case.

Venous pressure is a reflection of ventricular end diastolic pressure. Elevation of umbilical venous pressure in diaphragmatic hernia with evidence of ventricular compression may be a reflection of altered cardiodynamics. Observations in three cases are inadequate for firm conclusions. However, if further studies confirm the relationship between elevated umbilical venous pressure and ventricular compression or poor outcome, this would be another potential clinical application for this investigation.

4.3.5 Clinical applications of umbilical venous pressure measurements:

The main area for clinical application of umbilical venous pressure measurements is in the assessment and management of fetuses with cardiac failure. This is a potentially treatable condition. Umbilical venous pressure measurements have validated a noninvasive assessment of cardiac function (the cardiothoracic ratio). However, in the treatment of fetal cardiac failure, if it is necessary to repeat fetal blood sampling, repeated pressure measurements could aid the accurate assessment of response to treatment in cases where this is in doubt on noninvasive assessment, and

may improve outcome.

In the management of Rhesus disease, intrauterine transfusion is commonplace. This may be intravascular or intraperitoneal. Intraperitoneal transfusion is usually associated with an increase in intraperitoneal pressure (Holt et al 1972). The increase in pressure is not related to the rate of transfusion. In studies on fetal monkeys, death occurred when, due to the increase in intraperitoneal pressure, umbilical venous flow ceased during intraperitoneal transfusion (Crosby et al 1970). This was due to intraperitoneal pressure exceeding venous pressure and therefore obstructing venous return, depriving the fetus of oxygenated blood. Dunnihoo (1982) demonstrated that if the pressure increase was kept below 10 cm H_2O, fetal death was avoided. In human work, complications occurred following intraperitoneal transfusion with a large increase in pressure (Nicolini et al 1989[c]), whereas transfusions accompanied by a small increase in pressure were without complication. Intravascular transfusion of the nonhydropic fetus is accompanied by an increase in venous pressure. However, in the presence of hydrops, umbilical venous pressure falls following transfusion (Weiner et al 1989[b]). In units where intrauterine manometry is available, Monitoring and knowledge of the normal values of the umbilical venous or intraperitoneal pressures is recommended during intrauterine transfusions in order to reduce complications.

4.4 UMBILICAL ARTERY PRESSURE:

4.4.1 Changes with gestation:

Access to the umbilical artery during ultrasound guided fetal blood sampling is fortuitous rather than deliberate. It is therefore more difficult to systematically measure umbilical arterial than venous pressure in the human fetus. With small numbers of recordings, detailed statistical analysis is inappropriate. In addition, the frequency response of the system used is insufficient for detailed analysis of waveforms. However, by comparison with previous data and extrapolation from the cardiac pressures obtained in this study, it is possible to draw some conclusions from our results.

Our data demonstrates an increase in systolic, mean and diastolic umbilical arterial pressures with gestation. This is in agreement with all published data with the exception of the work of Castle and Mackenzie (1986). Most human studies in the past have been limited to a small gestational age range. Margolis and Orcutt (1960) recorded arterial blood pressure in a loop of cord at caesarean section prior to delivery of the fetus in term pregnancies. Nicolini et al (1989[b]) measured mean umbilical arterial pressure in four fetuses, with no comment on changes with gestation. When arterial blood pressure is measured postnatally, there is a linear increase with gestational age at delivery and birth weight (Versmold et al 1981).

There are numerous reports of studies of umbilical arterial pressure in animals, all of which demonstrate an increase in pressure with gestation and fetal weight. The increase in umbilical arterial pressure is not linear, there being an accelerated phase in the third trimester (Barcroft and Kennedy 1939).

4.4.2 Umbilical arterial pressure and placental resistance:

Barcroft and Kennedy (1939) suggested that the increase in blood pressure in the third trimester of pregnancy occurred in order to increase the rate of blood flow through the placenta. Dawes (1962[b]) noted that arterial pressure increased with gestation in all species but questioned whether umbilical arterial pressure reflects primarily myocardial performance or downstream resistance and the need to maintain umbilical blood flow. On vascular pressure data obtained in fetal lambs, he assessed the total vascular resistance to be 85% placental and 15% liver and ductus venosus. From this, he concluded that umbilical blood flow was determined mainly by the level of myocardial performance and resistance of umbilical vessels in the fetal side of the placenta. He demonstrated that umbilical blood flow increased throughout gestation and that the mechanism whereby this occurred was an initial fall in placental resistance followed by an increase in myocardial performance in the third trimester.

The relationship between placental resistance and umbilical

arterial pressure was also questioned by Reynolds (1960) and Brace and Brittingham (1986), who suggested that transient increases in placental resistance occur during uterine contractions which are reflected in increases in arterial pressure.

4.4.3 Umbilical arterial pressure and abnormal umbilical artery Doppler blood flow studies:

The finding of elevated umbilical artery pressure in a growth retarded fetus with hypoxia and acidosis, accompanied by loss of end diastolic flow in the umbilical artery, warrants further consideration. Intrauterine growth retardation is associated with abnormalities of trophoblast invasion (Brosens et al 1977) and abnormal fetal (Giles et al 1985) and uterine (Pearce and MacParland 1991) Doppler blood flow studies. In those cases where umbilical artery Doppler studies are abnormal, there is a decrease in the number of small arterioles in the tertiary stem villi (Giles et al 1985). This leads to an increase in downstream resistance which might therefore require an increase in arterial pressure in order to maintain an adequate blood flow to the placenta (Dawes 1962[b]). When end diastolic flow in the umbilical artery is absent, adequate blood flow to the placenta is no longer maintained. In our single case study, the elevation of umbilical arterial blood pressure to a level higher than the expected neonatal value implies considerable physiological adaptation of the fetus. The mechanism whereby this occurs is unclear. Moderate hypoxia

causes an increase in fetal blood pressure and an increase in umbilical blood flow, but severe, prolonged hypoxia leads to a fall in umbilical blood flow (Dawes 1962[a]). The vessels in the umbilical cord are believed to be free from neural control and therefore increases in umbilical artery flow must occur as a result changes in cardiac output (Pearce 1987). These may be mediated through the release of catecholamines (Comline and Silver 1961). Further studies on the stress axis in human fetuses are required. Fetal survival in utero with absent end diastolic frequencies on umbilical artery Doppler blood flow studies is variable. The relationship of maximal increase in blood pressure to eventual decompensation and fetal demise warrants further investigation.

4.4.4 Clinical applications of umbilical artery pressure measurements:

It is well established that umbilical arterial pressure increases with gestation and fetal weight. Further work is required to establish a satisfactory reference range of arterial pressures in the human fetus.

Doppler interrogation of the umbilical circulation is widely applied in modern clinical obstetrics. However, in abnormal cases, the full implications of the Doppler findings remain unclear. Measurement of umbilical artery pressure at the time of fetal blood gas analysis may assist in identifying the time of fetal decompensation and thus

allow better identification of the optimum time of delivery in severe intrauterine growth retardation.

4.5 VENTRICULAR PRESSURES IN NORMAL FETAL HEARTS:

There have been no previous studies on the pressure profiles within the developing human fetal heart. Details of human fetal cardiac anatomy have been well established on postmortem specimens, but knowledge of cardiac physiology is limited to extrapolation from animal and human paediatric data. Extrapolation from paediatric data to the fetus is extremely difficult because of the changes that occur in the heart at birth. The left and right ventricles work in parallel in the fetal heart, and both eject blood into the aorta, the left directly and the right via the ductus arteriosus. Fetal physiologists always consider the cardiac output in the fetus as the combined output from right and left ventricles. In postnatal life, the ventricles work in series with the left ventricle becoming dominant. Discussions on cardiac output involve left ventricular output.

4.5.1 Left ventricle:

The pressure waveform obtained in the left ventricle is similar in shape to that obtained in catheterization studies of the postnatal heart (Rudolph and Cayler 1958). The similarity of fetal cardiac pressure waveforms to those of the adult has been previously noted in animal work (Clark 1990). There is a small atrial component, followed by the rapid increase of ventricular pressure in systole. The waveforms are comparable at all gestations, although damping of the trace is a problem at earlier gestational

ages. This is due to the small size of the chamber in relation to the tip of the needle used in our method. It is necessary to have the complete bevel of the needle free within the chamber for a good pressure waveform recording. At early gestations (16 - 18 weeks) the ventricle is so small that it is very common for the needle to abut the side wall or chordae tendineae, or for part of the bevel to remain within the myocardium. A catheter tip transducer would solve this problem.

Systolic and end diastolic pressure increase with gestation. This is reflected by the changes in arterial blood pressure in the fetus. The increase appears to be linear, although the limited data available must be interpreted with caution.

4.5.2 Right Ventricle:

The pressure tracings obtained from the right ventricle are similar to those from the left side. There is an increase in systolic and end diastolic pressure with gestation. That end diastolic pressure increases with advancing gestation without a similar increase in venous pressure requires further consideration. The "a" wave of atrial contraction is a reflection of ventricular end diastolic pressure. The "a" and "v" waves change during gestation, but may not affect the mean pressure which we have been measuring.

4.5.3 Comparison of right and left ventricular pressures in the developing fetal heart:

The question of whether left and right ventricular pressures are equal in the fetal heart has been a subject of much debate. On an anatomical basis, the pressures should be equal as both ventricles expel blood into the same vessel. As early as 1909, Pohlmann designed an experiment on fetal pigs to establish whether there was any difference, and found that left and right pressures were the same. This has been supported by the work of Hamilton et al (1937) and Rudolph (1970). Many workers have suggested right ventricular dominance to be present in fetal life. This has not been supported by pressure studies, and postmortem anatomical investigations have given conflicting results. Keen (1942) demonstrated that left and right ventricular dimensions were similar in the fetal heart. Emery and MacDonald (1960) noted a change with gestation. Before 24 weeks, the left ventricle was heavier than the right. After this time, both ventricles were similar in size until the middle of the third trimester when there was evidence of right ventricular dominance. This is supported by echocardiographic studies (Allan, unpublished data). However, from 39 weeks onwards, this was reversed and the left ventricle became dominant as in postnatal life. These findings were disputed by a further anatomical study (St John Sutton et al 1984) in which no significant difference was detected in ventricular wall thickness between left and right ventricles. This study

also noted that both right and left ventricular wall thickness increased linearly with gestation.

In this study, there appear to be differences between left and right ventricular pressures. However, on each occasion when pressures within both ventricles of one fetus were recorded they were the same. These differences therefore probably reflect individual variances. In addition, the increases seen with gestation in systolic and end diastolic pressure with advancing gestation are similar in both right and left ventricles. It is difficult to measure end diastolic pressure accurately without simultaneous ECG for timing of events in the cardiac cycle and therefore there is inevitably some degree of error in the assessment of end diastolic pressure, which may also explain the apparent differences between left and right ventricles.

4.6 ATRIAL PRESSURES IN NORMAL FETAL HEARTS:

As with ventricular pressure, there is no previous data available concerning atrial pressures in the human fetus. Data from atrial pressures obtained in the neonate cannot be extrapolated to the fetus because of the circulatory changes which occur at birth, particularly with the closure of the foramen ovale. In the neonate, left atrial pressure is consistently higher than the right (Arcilla et al 1966, Rudolph and Cayler 1958). During fetal life, blood flows across the foramen ovale from the right atrium into the left. In order for this to occur, right atrial pressure must be at least equal to, if not greater than, that in the left.

In our study, mean atrial pressure did not increase with gestation. There was no significant difference between left and right atrial pressures, although the mean right pressure was slightly higher than the left. However, we were not able to record both atrial pressures in the same fetus. In animal work where left and right atrial pressures were recorded simultaneously, the pressures were not equal in individual animals but the differences varied from preparation to preparation (Anderson et al 1981).

Fetal atrial pressure waveforms show the "a" and "v" waves seen in postnatal life. However, without synchronous electrocardiogram or Doppler studies, it is impossible to ascertain which is which. We have been able to record a

direct cardiac electrocardiogram in some patients, by attaching one lead of a 12 lead ECG to the needle. The mother acts as reference. Problems encountered have included patient refusal to be connected to the ECG, as this involves four limb leads and a chest reference on the mother. As most of our cardiac pressures have been recorded during midtrimester termination of pregnancy, this refusal is perfectly understandable: the ECG recording involves the mother in the procedure to a far greater extent. When a direct fetal cardiac ECG has been recorded, it has not been easy to interpret as the vectors are not known. Synchronous Doppler studies have not been performed during pressure recordings. While this would be possible with the ultrasound equipment used, it would have required another experienced fetal echocardiographer to be available which was not possible during the time of this study. In addition, the effect of the presence of a needle within a cardiac chamber on the Doppler examination is unknown. Echo interference from the needle would be likely, and could make the Doppler display difficult to interpret. As it was extremely difficult to obtain atrial pressures, and particularly a good waveform, due to the problems of access to, and signal damping in, such a small cardiac chamber, no further effort was made to clarify these areas. If a catheter tip transducer is available in the future, the quality of pressure recordings should be such that suitable interpretations of the waveform can be made.

4.6.1 The relationship of umbilical venous pressure to atrial pressure:

Previous workers have assumed that umbilical venous pressure reflects central venous pressure (Weiner 1989 [a]). In animal work, there is a marked discrepancy between these two values, umbilical venous pressure being much higher (Dawes 1962[a]). However, in this study, there is only a small difference between atrial and venous pressures in the human fetus. The haemodynamic effects of the ductus venosus are still unclear, but there is evidence that this acts as a sphincter, controlling blood flow from the umbilical vein to the inferior vena cava. There is postnatal data available on the pressure changes between the portal sinus, ductus venosus and right atrium but this is not applicable to fetal life (Arcilla et al 1966). The finding that umbilical venous pressure is elevated in association with cardiomegaly implies that changes in the umbilical venous pressure do reflect changes in central venous pressure. Furthermore the presence of venous pulsations in the umbilical vein in some cases of fetal hydrops (Gudmundsson et al 1991), with associated reverse flow in the ductus venosus and inferior vena cava (Kiserud et al 1991), again supports the notion that there is a direct relationship between umbilical venous and atrial pressures. Thus, the weight of evidence suggests that the ductus venosus is just a conduit but further studies are required. It should be possible to feed a catheter tip transducer along the umbilical vein into the ductus venosus

in fetal life. It is certainly possible in the neonate, both premature and at term (Arcilla et al 1966, Kitterman et al 1970), and future studies using such a technique would provide detailed and accurate information on the precise function of the ductus venosus.

4.7 INTRACARDIAC PRESSURES IN THE PRESENCE OF STRUCTURAL HEART DISEASE IN THE HUMAN FETUS:

The clinical applications of the measurement of intracardiac pressures in the human fetus lie in the interpretation of the abnormal pressure values and waveforms obtained in cases of congenital heart disease. This data provides additional information regarding cardiac function, which will be of value in the assessment of prognosis and likely benefit of intrauterine treatment. For example, measurement of ventricular end diastolic pressure in postnatal life provides valuable prognostic information (Gundry and Behrendt 1986). However, interpretation of abnormal results is only possible with knowledge of the normal expected values, the establishment of which has been the main aim of this thesis. Some cases of congenital heart disease have been investigated and abnormal results obtained. This has allowed the opportunity to assess directly the value of these investigations.

4.7.1. Critical aortic stenosis:

Congenital critical aortic stenosis is a rare condition, accounting for just 28 referrals to a national centre of Fetal Cardiology in a ten year period. In our experience, the outcome is universally fatal, either in utero or in early postnatal life, when the diagnosis is confirmed prenatally. This poor outcome is due to irreversible left ventricular damage, exemplified by endocardial fibroelastosis (EFE). In critical aortic stenosis, fetal

echocardiography demonstrates a poorly contracting, globular left ventricle with the echogenic appearance of EFE (Veille and Sivakoff 1988) and reduced or absent flow across the small aortic valve. The diagnosis of critical aortic stenosis is not easy, and the differential diagnoses include aortic atresia and hypoplastic left heart syndrome (Sharland et al 1991). Valvular stenoses in postnatal life can be relieved by percutaneous balloon valvoplasty (Lababidi and Jium-Ren 1983, Lababidi and Weinhaus 1986, Wren et al 1987). Prior to postnatal cardiac surgery, pressure studies are performed in order to maximise diagnostic information (Gundry and Behrendt 1986, Hammon et al 1987) and these techniques have now been adapted for intrauterine application (Maxwell et al 1991).

Critical aortic stenosis diagnosed in utero appears to be a progressive disease (Allan et al 1989[b]) in which correction, if performed early, could restrict the damage to the myocardium with resultant improvement in outcome. Present techniques of assessing cardiac function in utero are limited to B and M mode echocardiography with Doppler studies. By measuring intracardiac pressures in the fetus, additional information regarding function can be obtained which is essential if intrauterine therapy is to be considered.

In four cases of critical aortic stenosis, attempts at intrauterine valvoplasty have been made. In the first, at

28 weeks, a commercially available coronary angioplasty balloon catheter was used (USCI), with a purpose made 3 mm balloon catheter (NuMed) being employed in the other three cases. The technique of intrauterine balloon valvoplasty involved inserting an 18 gauge needle through the maternal abdomen, after the infiltration of local anaesthetic, into the amniotic cavity and thence into the apex of the fetal left ventricle under continuous ultrasound control. After recording the intraventricular pressure, the balloon catheter was passed down the needle until the balloon lay across the aortic valve when it was inflated with normal saline.

In the first case, diagnosed at 20 weeks by fetal echocardiography and treated at 28 weeks gestation, a highly abnormal waveform was obtained (Figure 3.18). The left ventricle was small and contracting very poorly. The pulse pressure was reduced, and end diastolic pressure grossly elevated. The fetus died in utero 48 hours after the procedure and postmortem confirmed aortic stenosis and severe EFE. The valve had been split during the attempted valvoplasty.

The second patient was 32 weeks when critical aortic stenosis was diagnosed in the fetus and valvoplasty performed. In this case, the severity of the EFE on ultrasound assessment was less than case 1. At the initial attempt, we were unsuccessful in crossing the valve with

the balloon, and the balloon burst during the procedure. The left ventricular systolic pressure was elevated to approximately 170% of normal and the end diastolic pressure was mildly elevated (Figure 3.19). A second procedure carried out ten days later was successful, with an increase in flow across the aortic valve on colour Doppler flow studies. Following spontaneous labour one week later, the male infant underwent formal balloon valvoplasty at the age of 18 hours. He died after one month, and again postmortem demonstrated the success of the valvoplasty. EFE was present.

The third case was referred for fetal echocardiography at 31 weeks because of an abnormal four chamber view of the fetal heart. Critical aortic stenosis was diagnosed, and successful intrauterine balloon valvoplasty performed. The systolic pressure was above our reference range (Figure 3.20). The valvoplasty was followed by a reduction in the velocity across the valve, and an increased flow. After delivery at term, the neonate underwent percutaneous balloon valvoplasty and is alive and well at the age of twelve months.

The fourth case was diagnosed at 30 weeks gestation, and intrauterine balloon valvoplasty attempted. Unfortunately, the pressure recording was not correctly zeroed, and it is therefore not possible to make any calculations as to end diastolic pressure values. However, the waveform was

similar to that seen in case 2 above (Figure 3.21), and the pulse pressure was approximately 150% that of normal. There was mild to moderate echogenicity in the left ventricle (evidence of EFE) and the chamber was poorly contracting. The attempt was unsuccessful, it proving impossible to cross the valve with either the guide wire or the balloon. The infant was delivered at term, but died a few days after birth. Postnatal echocardiography confirmed the diagnosis of critical aortic stenosis. Post mortem information is not available. The fact that left ventricular systolic and pulse pressures were elevated implies that the contractile function of the left ventricle was maintained at the time of investigation, although the pulse pressure was higher than expected for the gestation. Further deterioration would have been expected during the subsequent time until delivery.

The differences between the pressure recordings from the first case and the others are marked. Case 1 demonstrated gross elevation of end diastolic pressure and a markedly reduced pulse pressure. In the other three cases, the waveforms obtained from the left ventricle were similar to those obtained in a normal heart, although all had increased systolic pressure and in case 2 end diastolic pressure was elevated. The increased intraventricular pressures demonstrate that the ventricle is stressed, and therefore intervention should be of benefit. Intracardiac pressures increase the information available to us

regarding cardiac function and help to differentiate between irreversible ventricular damage associated with severe EFE and that where some degree of recovery may be expected if an obstructed valve is relieved. Reduction of afterload alone will improve ventricular performance. The fact that left ventricular end diastolic pressure, when taken in isolation, was not of value in predicting outcome has been noted in previous postnatal studies (Hammon et al 1988).

4.7.2 Ventricular pressure and the development of endocardial fibroelastosis:

The presence of endocardial fibroelastosis signifies severe cardiac disease. The exact pathogenesis of this rare condition remains obscure, as it has been documented in association with valvular disease (Veille and Sivakoff 1988) and is also reported to occur as an isolated lesion (Carceller et al 1990). Spontaneous resolution has been reported (Pearl 1989).

It is believed that EFE occurs in valvular stenosis due to abnormal pressures in the ventricle (Anderson and Kelly 1956), which increases myocardial oxygen demand. Coronary arteries show pathological changes (Sauer et al 1989) and this leads to reduced perfusion of the endocardium. The resultant ischaemia predisposes to the development of EFE. The underlying abnormality must be long term, as short term experimental aortic stenosis in fetal lambs is not

associated with such disruption of myocardial structure (Bical et al 1990). The severity of EFE in the four cases reported above was assessed by ultrasound, and postmortem examination in two, and was reflected by the degree of abnormality of the pressure waveform and absolute values. Measurement of the left ventricular pressure in cases of critical aortic stenosis therefore provides additional diagnostic information and allows better assessment of the severity of the disease than echocardiography and Doppler alone.

An additional finding was that of altered function related to the severity of EFE. In case 1, with very severe EFE, the ventricular systolic pressure was not elevated implying loss of systolic (contractile) function. The high end diastolic pressure demonstrated that diastolic function (compliance) was reduced. Case 3, on the other hand, had less severe EFE and systolic function was maintained, demonstrated by ventricular hypertension. That EFE is associated with poor cardiac function is demonstrated by the association with cardiac failure (Bovicelli et al 1984). Potential for improvement in function is the reason behind attempts at intrauterine therapy. In animal work, experimental aortic stenosis in lambs over a period of 45 days (term = 145) did not lead to the development of abnormal tissue, and prenatal repair was therefore not associated with any reduction in tissue damage. However, prenatal repair did result in better heart weights and

would therefore appear to have been beneficial (Bical et al 1990).

4.7.3 Mitral atresia, double outlet right ventricle:

Congenital cardiac disease that does not affect cardiac function should be associated with normal pressure profiles. With no evidence of an obstruction to outflow from a cardiac chamber, as in this case, both the waveform and absolute pressure values would be expected to fall within the normal range. The finding of a normal waveform and pressure measurements in this case supports this.

4.7.4 VSD, DORV, Pulmonary atresia:

This case also demonstrated normal pressure waveforms and absolute values. Because there was no obstruction to the flow through the VSD or aortic valve, normal right ventricular pressures for the fetus were maintained.

4.7.5 Ventricular disproportion:

The finding of mild ventricular disproportion is associated with karyotype anomalies. Although minimal right ventricular dominance is a normal finding in the term fetus, when seen at earlier gestations it is a marker for coarctation of the aorta and chromosomal anomalies, particularly trisomy 13.

Our results show that, when measured in the same fetus, left and right ventricular pressures are equal. On one

occasion, left and right ventricular pressures were measured in a fetus with ventricular disproportion and a mosaic trisomy 13. On postmortem, there was evidence of arch hypoplasia, although there was not a coarctation shelf present. Although the differences between the left and right pressures were small, and could be due to experimental error, our findings could demonstrate that in early in the development of a coarctation abnormal ventricular function, as assessed by pressure measurements, is apparent. This is an exciting finding which requires further study.

4.7.6 Pulmonary atresia:

Right and left ventricular pressures were obtained from a fetus with pulmonary atresia at 31+5 weeks gestation. The left ventricular pressure values were within our reference range. The right ventricle was small, and there was marked tricuspid regurgitation and a dilated right atrium. The velocities across the tricuspid valve during ventricular systole, measured by Doppler studies, were 4.1 m/sec which implied that the gradient across the valve would be 68 mm Hg, a relection of the systolic pressure within the ventricle. This was indeed the case. Systolic pressure was 70 mm Hg against an expected value of 40 mm Hg.

The pressures were recorded during a diagnostic procedure to differentiate between the possible diagnoses of pulmonary atresia and stenosis. Right ventricular

hypertension was noted, and a contrast echo showed filling of the pulmonary artery only through the ductus arteriosus. Although balloon valvoplasty has been successfully employed in postnatal treatment of pulmonary atresia with intact ventricular septum (Ino et al 1989), it was not attempted here as our own experience is that the atretic valve needs to be perforated with a laser or radiofrequency prior to balloon dilatation (Qureshi et al 1991). The fetus was delivered at 38 weeks gestation, and postnatal investigations confirmed the diagnosis of pulmonary atresia. Laser assisted balloon valvoplasty was successful on the second day of life.

4.7.7 Atrial pressure in nonimmune hydrops:

Nonimmune hydrops is frequently associated with cardiac failure (Keeling et al 1983), although there has not previously been direct evidence of this. The finding of elevated umbilical venous pressure in nonimmune hydrops associated with cardiomegaly (see above) supports the hypothesis that cardiac failure is an underlying mechanism in these cases. However, the exact relationship between umbilical venous pressure and central venous pressure in the human fetus has been unclear. The opportunistic nature of many of the pressure measurements recorded in this thesis is reflected in the small numbers of pressures obtained from certain chambers. Only one atrial pressure was obtained in a case on nonimmune hydrops. This fetus was markedly anaemic (Hb 2.9 g/dl) at 29 weeks gestation

secondary to a parvovirus infection. Cardiothoracic ratio was outside the reference range at 0.61 and gross ascites was present with pleural effusions and skin oedema. The right atrial pressure was measured at fetal blood sampling, and found to be 9 mm Hg, above the 95th centile. Although care must be exercised when dealing with such small numbers, the fact that atrial pressure was markedly elevated in such a case implies a fairly direct relationship between umbilical venous and atrial pressure in the human fetus. Further studies are required to elucidate the exact nature of this relationship.

4.8 FUTURE STUDIES:

This study has produced a data base of amniotic and umbilical vascular pressures and the first recordings of intracardiac pressures in the human fetus in utero. The technique for such measurements has been established and a reference range of pressure values for the four chambers of the fetal heart has been constructed. In addition, cases of congenital heart disease have been investigated.

However, although this data has provided the answers to many questions, examination of the results has also posed many new questions which will provide the basis for future research.

4.8.1 Venous pressures:

The findings of this study have thrown light on the relationship between umbilical venous pressure and central venous pressure in the human fetus, but raised further questions regarding the function of the ductus venosus. With further advances in technology, and the potential development of catheter tip transducers, it might be possible to catheterize the ductus venosus. Such investigation would permit examination of ductus venosus flow in fetal cardiac failure, and also in conditions of altered blood flow such as intrauterine growth retardation.

4.8.2 Arterial pressures:

Further data is required to establish a full reference

range of arterial pressures in the human fetus. Umbilical arterial pressure appears to increase in line with ventricular pressure with advancing gestation. While it is unlikely that pressures will be recorded from normal hearts in the third trimester, fetal blood sampling is performed at all gestations, and further studies of arterial pressures in later pregnancy will elucidate the nature of changes in ventricular pressure in the third trimester.

4.8.3 Cardiac pressures:

This study has clearly shown that additional diagnostic information is gained from measurement of intracardiac pressures in congenital heart disease, and that it is inappropriate to apply data from animal studies to the human fetal heart. With advances in prenatal therapy, this information is essential for correct selection of those fetuses who will benefit from such intervention. Present techniques generally limit pressure measurements to one cardiac chamber, but catheter tip transducers would allow further cardiac catheterization studies. In addition to diagnostic information, such studies would further our understanding of the pathological changes in cardiac disease. This will improve our ability to treat such cases and lead to better management and improved prognosis in congenital heart disease.

REFERENCES:

Aberg A., Mitelman F., Cantz M. and Gehler J. Cardiac puncture of a fetus with Hurler's disease avoiding abortion of unaffected co-twin. *Lancet* 1978; **ii**: 990-991

Achiron R, Glaser J, Gelernter I, Hegesh J, Yagel S. Extended fetal echocardiographic examination for detecting cardiac malformations in low risk pregnancies. *Br Med J* 1992; **304**: 671-674

Allan L.D. Fetal echocardiography: Confidence limits and accuracy. *Ped Cardiol* 1985; **6**: 145-146

Allan L.D. Normal fetal cardiac anatomy - Doppler echocardiography. In: *Manual of Fetal Echocardiography*. MTP Press, Lancaster. 1986; 56-73

Allan L.D., Chita S.K., Sharland G.K., Fagg N.L.K., Anderson R.H. and Crawford D.C. The accuracy of fetal echocardiography in the diagnosis of congenital heart disease. *Int J Cardiol* 1989 [a]; **25**: 279-288

Allan L.D., Crawford D.C., Sheridan R. and Chapman M.G. Aetiology of non-immune hydrops: the value of echocardiography. *Brit J Obstet Gynaecol* 1986; **93**: 223-5

Allan L.D., Sharland G.S. and Tynan M.J. The natural

history of the hypoplastic left heart syndrome. *Int J Cardiol* 1989 [b]; **25**: 341-343

Allan L.D., Tynan M.J., Campbell S., Wilkinson J. and Anderson R.H. Echocardiographic and anatomical correlates in the fetus. *Br Heart J* 1980; **44**: 444-451

Andersen H.M., Drew J.H., Beischer N.A., Hutchison A.A. and Fortune D.W. Nonimmune hydrops fetalis: changing contribution to perinatal mortality. *Brit J Obstet Gynaecol* 1983; **90**: 636-9

Anderson D.F., Bissonnette J.M., Faber J.J. and Thornburg K.L. Central shunt flows and pressures in the mature fetal lamb. *Am J Physiol* 1981; **241**: H60-66

Anderson D.J. and Kelly J. Endocardial fibroelastosis. I. Endocardial fibroelastosis associated with congenital malformations of the heart. *Pediatrics* 1956; **18**: 513-538

Arcilla R.A., Oh W., Lind J. and Blankenship W. Portal and atrial pressures in the newborn period. *Acta Pæd Scand* 1966; **55**: 615-625

Assali N.S., Brinkman C.R. and Nuwayhid B. Comparison of maternal and fetal cardiovascular functions in acute and chronic experiments in the sheep. *Am J Obstet Gynecol* 1974; **120**: 411-425

Balaji S., Keeton B.R., Sutherland G.R., Shore D.F and Monro J.L. Aortic valvotomy for critical aortic stenosis in neonates and infants aged less than one year. *Br Heart J* 1989; **61**: 358-360

Bang J., Bock J.E. and Trolle D. Ultrasound guided fetal intravenous transfusion for severe rhesus haemolytic disease. *Br Med J* 1982; **284**: 373-374

Barclay A.E., Barcroft J., Barron D.H., Franklin K.J. and Prichard M.M.L. Studies of the foetal circulation and of certain changes that take place after birth. *Am J Anat* 1941; **69**: 383-406

Barclay A.E., Franklin K.J. and Prichard M.M.L. *Foetal circulation and cardiovascular system, and the changes that they undergo at birth.* Blackwell Scientific Publications, Oxford 1944.

Barcroft J. Fetal circulation and respiration. *Physiol Review* 1936; **16**: 103-128

Barcroft J. Blood Pressure In: *Researches on Prenatal Life Volume I*, Blackwell Scientific Publications, Oxford. 1946: 112-122

Barcroft J., Barron D.H. and Forsham P. The blood pressure in the umbilical vein of the fetal sheep. *Science* 1942; **96**:

179-180

Barcroft J. and Kennedy J.A. The distribution of blood between the foetus and the placenta in sheep. *J Physiol* 1939; 95: 173-186

Beischer N.A., Fortune D.W. and Macafee J. Nonimmunologic hydrops fetalis and congenital abnormalities. *Obstet Gynecol* 1971; **38**: 86-95

Benaceraff B.R. and Frigoletto F.D. Inutero treatment of a fetus with diaphragmatic hernia complicated by hydrops. *Am J Obstet Gynecol* 1986; **155**: 817-8

Bical O., Gallix P., Toussaint M., Landais P., Gaillard D., Karam J. and Neveux J.Y. Intrauterine versus postnatal repair of created pulmonary artery stenosis in the lamb. *Thorac Cardiovasc Surg* 1990; **99**: 685-690

Blott M., Greenhough A., Nicolaides K.H., Moscoso G., Gibb D. and Campbell S. Fetal breathing movements as a predictor of favourable outcome after oligohydramnios due to membrane rupture in second trimester. *Lancet* 1987; **ii**: 129-31

Bovicelli L., Picchio F.M., Pilu G., Baccarani G., Orsini L.F., Rizzo N., Alampi G., Benenati P.M. and Hobbins J.C. Prenatal diagnosis of endocardial fibroelastosis. *Prenat Diag* 1984; **4**: 67-72

Brace R.A and Brittingham D.S. Fetal vascular pressure and heart rate responses to nonlabour uterine contractions. *Am J Physiol* 1986; **251**: R 409-416

Bradley S.M., Hanley F.L., Jennings R.W., Duncan B.W., Jester J.A. and Verrier E.D. Regional blood flows during cardiopulmonary bypass in fetal lambs: The effect of nitroprusside. *Circulation* 1990; **82**: Supplement III 413

Brock R., Milstein B.B. and Ross D.N. Percutaneous left ventricular puncture in the assessment of aortic stenosis. *Thorax* 1956; **11**: 163-171

Brosens I., Dixon H.G. and Robertson W.B. Fetal growth retardation and the arteries of the placental bed. *Br J Obstet Gynaecol* 1977; **84**: 656-663

Brown B.H. and Smallwood R.H. Vascular measurements. In: *Medical Physics and Physiological Measurement*. Blackwells, Oxford. 1981: 312-339

Butler P.R.E. and Oldershaw P.J. Measurement of Pressure. In: *A Practice of Cardiac Catheterisation* Eds: Mendel D., Oldershaw P. Blackwell Scientific Publications, Oxford. 1986: 164-189

Caldeyro-Barcia R., Pose S.V. and Alvarez H. Uterine contractility in polyhydramnios and the effects of

withdrawal of the excess amniotic fluid. *Am J Obstet Gynecol* 1957; **73**: 1238-1254

Campbell S. and Newman G.B. Growth of the fetal biparietal diameter during normal pregnancy. *J Obstet Gynaecol Br Commonw* 1971; **78**: 513-519

Canadian Medical Research Council 1977. Diagnosis of genetic disease by amniocentesis during the second trimester of pregnancy. A Canadian study. Report No. 5. Supply services, Ottawa, Canada

Carceller A.M., Maroto E. and Fouron J-C. Dilated and contracted forms of primary endocardial fibroelastosis: a single fetal disease with two stages of development. *Br Heart J* 1990; **63**: 311-313

Castle B. and Mackenzie I.Z. *In vivo* observations on intravascular blood pressure in the fetus during mid-pregnancy. In: *Fetal Physiological Measurements* ed. Rolfe P. Butterworths, London 1986; 65-69

Chacko A.W. and Reynolds S.R.M. Embryonic development in the human of the sphincter of the ductus venosus. *Anat Record* 1953; **115**: 151-173

Chamberlain P.F., Manning F.A., Morrison I., Harman C.R. and Lange I.R. Ultrasound evaluation of amniotic fluid

volume. I. The relationship of marginal and decreased amniotic fluid volume to perinatal outcome. *Am J Obstet Gynecol* 1984[a]; **150:** 245-249

Chamberlain P.F., Manning F.A., Morrison I., Harman C.R. and Lange IR. Ultrasound evaluation of amniotic fluid volume. II. The relationship of increased amniotic fluid volume to perinatal outcome. *Am J Obstet Gynecol* 1984[b]; **150:** 250-254.

Clark E.B. Growth, Morphogenesis, and Function: The dynamics of cardiac development. In: *Fetal, Neonatal, and Infant Cardiac Disease*. Eds. Moller J.H. and Neal W.A. Appleton Lange, Connecticut. 1990; 3-23

Cohn H.E., Sacks E.J., Heymann M.A. and Rudolph A.M. Cardiovascular responses to hypoxemia and to acidemia in unanesthetized fetal lambs. *Ped Res* 1972; **6:** 342

Comline R.S. and Silver M. The release of adrenaline and noradrenaline from the adrenal gland of the foetal sheep. *J Physiol* 1961; **156:** 424-444

Crosby W.M., Brobman G.F. and Chang A.C.K. Intrauterine transfusion and fetal death. *Am J Obstet Gynecol* 1970; **108:** 135-138

Daffos F., Capella Pavlovsky M. and Forestier F. Fetal

blood sampling during pregnancy with use of a needle guided by ultrasound: a study of 606 consecutive cases. *Am J Obstet Gynecol* 1985; **153**: 655-660

Davis G.K., Farquhar C.M., Allan L.D., Crawford D.C. and Chapman M.G. Structural cardiac abnormalities in the fetus: reliability of prenatal diagnosis and outcome. *Br J Obstet Gynaecol* 1990; **97**: 27-31

Dawes G.S. The umbilical circulation. *Am J Obstet Gynecol* 1962[a]; **84**: 1634-1648

Dawes G.S. Placental development and umbilical blood flow. *J Obstet Gynaecol Brit Comm* 1962[b]; **69**: 815-817

Dawes G.S. Foetal Circulation. In: *Foetal and Neonatal Physiology* Year Book Publishers, Inc. Chicago 1968; 91-105

DeVore G.R., Donnerstein R.L., Kleinman C.S., Platt L.D. and Hobbins J.C. Fetal echocardiography. I: Normal anatomy as determined by real-time-directed M-mode ultrasound. *Am J Obstet Gynecol* 1982; **144**: 249-260

Dunnihoo D.R. Intrauterine fetal transfusion: monitoring intraperitoneal pressure. *Am J Obstet Gynecol* 1982; **142**: 241-242

Edelstone D.I., Rudolph A.M. and Heymann M.A. Liver and

ductus venosus blood flows in the fetal lamb in utero. *Circ Res* 1978; **42**: 426-433

Edelstone D.I., Rudolph A.M. and Heymann M.A. Effects of hypoxemia and decreasing umbilical blood flow on liver and ductus venosus flows in fetal lambs. *Am J Physiol* 1980; H656-663

Emery J.L. and MacDonald M.S. The weight of the ventricles in the later weeks of intra-uterine life. *Br Heart J* 1960; **22**: 563-570

Fisher D.L. The use of pressure recordings obtained at transthoracic left heart catheterization in the diagnosis of valvular heart disease. *J Thoracic Surg* 1955; **30**: 379-396.

Fisk N.M., Tannirandorn Y., Nicolini U., Talbert D.G. and Rodeck C.H. Amniotic pressure in disorders of amniotic fluid volume. *Obstet Gynecol* 1990; **76**: 210-214.

Fontana M.E. and Lewis R.P. Evaluation of valvular heart disease by invasive methods. In: *Invasive Cardiology* Ed: Speer Schroeder *J Cardiovascular Clinics* 1985; **15/1**: 165-185

Fry D.l. Physiological recording by modern instruments with particular reference to pressure recording. *Physiol Review*

1960; **40**: 753-788

Gembruch U. and Hansmann M. Artificial instillation of amniotic fluid as a new technique for the diagnostic evaluation of cases of oligohydramnios. *Prenat Diag* 1988; **8**: 33-45

Gembruch U., Manz M., Bald R., Ruddel H., Redel D.A., Schelbusch H., Nitsch J. and Hansmann M. Repeated intravascular treatment with amiodarone in a fetus with refractory supraventricular tachycardia and hydrops fetalis. *Am Heart J* 1989; **118**: 1335-1338

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

Gudmundsson S., Huhta J.C., Wood D.C., Tulzer G., Cohen A.W. and Weiner S. Venous Doppler ultrasonography in the fetus with nonimmune hydrops. *Am J Obstet Gynecol* 1991; **164**: 33-37

Gundry S.R. and Behrendt D.M. Prognostic factors in valvotomy for critical aortic stenosis. *J Thorac Cardiovasc Surg* 1986; **92**: 747-754

Hadlock F.P. Sonographic estimation of fetal age and

weight. *Radiol Clin of N America* 1990; **28**: 39-50

Hamilton W.F., Woodbury R.A. and Woods E.B. The relation between systemic and pulmonary blood pressures in the fetus. *Am J Physiol* 1937; **119**: 206-212

Hammon J.W., Lupinetti F.M., Maples M.D., Merrill W,H., Frist W.H., Graham T.P. and Bender H.W. Predictors of operative mortality in critical valvular stenosis presenting in infancy. *Ann Thorac Surg* 1988; **45**: 537-540

Harrigan J.T., Kangos J.J., Sikka A. et al. Successful treatment of fetal congestive heart failure secondary to tachycardia. *N Engl J Med* 1981; **304**: 1527-9

Haselhorst G. Úber den Blutdruck in den Nabelschnurgefässen, die Ausschaltung des Nabelschnurund Plazentarkreislaufs nach geburt des Kindes und úber den Blutstillungsmechanismus. *Z. Geburtsh. Gynäk.* 1929; **95**: 400-426

Heinemann M.K., Sabik J.F., Gambe W.J. and Hanley F.L. Prenatal pacemaker implantation in the fetal lamb. *Circulation* 1991; **84**: Supplement II 513

Heymann M.A. and Rudolph A.M. Physiological observations of the normal fetus in utero. *J Pediat* 1966; **69**: 967

Heymann M.A. and Rudolph A.M. Effect of exteriorization of the sheep fetus on its cardiovascular function. *Circ Res* 1967; **21**: 741-745

Hill L.M., Breckle R., Thomas M.L. and Fries J.K. Polyhydramnios: Ultrasonically detected prevalence and neonatal outcome. *Obstet Gynecol* 1987; **69**: 21-25

Holt E.M., Boyd I.D., Gillmer M.A., Naylor C.J. and Thomas G. Fetal intraperitoneal pressure during intrauterine transfusion. *J Obstet Gynaecol Br Common* 1972; **79**: 225-259

Ino T., Yabuta K. and Tanaka A. Balloon valvuloplasty in pulmonary stenosis with intact ventricular septum. *Lancet* 1989; **334**: 1531

Janiaux E., Van Maldergem L., De Munter C., Moscoso G. and Gillerot Y. Nonimmune hydrops fetalis associated with genetic abnormalities. *Obstet Gynecol* 1990; **75**: 568-72

Jeng C., Jou T., Wang K., Yang Y., Lee Y, and Lan C. Amniotic fluid index measurement with the four quadrant technique during pregnancy. *J Reprod Med* 1990; **35**: 674-677

Johnson P. and Maxwell D.J. Normal amniotic pressure in oligohydramnios after preterm rupture of membranes. (letter) *Am J Obstet Gynecol* 1990; **163**: 1103-1104

Johnson P., Sharland G., Maxwell D. and Allan L. The role of transvaginal sonography in the early detection of congenital heart disease. *Ultrasound Obstet Gynecol* 1992 (in press)

Keeling J.W., Gough D.J. and Iliff P. The pathology of non-Rhesus hydrops. *Diag Histopath* 1983; **6**: 89-111

Keen J.A. A note on the closure of the foramen ovale and the post-natal changes of the ventricles in the human heart. *J Anat (London)* 1942; **77**: 104-109

Kilian H.F. Ueber den Kreislauf des Blutes im Kinde, welches noch nicht geathmet hat. Karlsruhe: *Verlag der Chr. Fr. Müller'schen Hofbuchhandlung*. 1826

Kiserud T., Eik-Nes S.H., Blaas H.K. and Hellevik L.R. Ultrasonographic velocimetry of the fetal ductus venosus. *Lancet* 1991; **338**: 1412-1414

Kitterman J.A., Phibbs R.H. and Tooley W.H. Catheterization of umbilical vessels in newborn infants. *Ped Clin N America* 1970; **17**: 895-912

Lababidi Z. and Jium-Ren W. Percutaneous balloon pulmonary valvoplasty. American Journal of Cardiology 1983; 52: 560-562

Lababidi Z. and Weinhaus L. Successful balloon valvuloplasty for neonatal critical aortic stenosis. *Am Heart J* 1986; **112**: 913-915

Ladusans E.J., Parsons J.M., Qureshi S.A., Baker E.J. and Tynan M.J. Results of percutaneous balloon dilatation for critical aortic stenosis in neonates with severe endocardial fibroelastosis. *B Heart J* 1989; **61**: 470

Lange I.R., Harman C.R., Ash K.M., Manning F.A. and Menticoglau S. Twins with hydramnios: Treating premature labour at source. *Am J Obstet Gynecol* 1989; **160**: 552-557

Lange L.W., Sahn D.J., Allen H.D., Goldberg S.J., Anderson C. and Giles H. Qualitative real-time cross-sectional echocardiographic imaging of the human fetus during the second half of pregnancy. *Circulation* 1980; **62**: 799

Lawler F.H. and Brace R.A. Fetal and maternal arterial pressures and heart rates: histograms, correlations, and rhythms. *Am J Physiol* 1982; **243**: R433-444

Lee F-Y., Assad R.S., O'Hare R.E. and Hanley F.L. Cardiopulmonary bypass in isolated in situ lamb placenta: Haemodynamic characteristics. *Circulation* 1990; **82**: Supplement III 151

Lewis A.B., Heymann M.A. and Rudolph A.M. Gestational

changes in pulmonary vascular responses in fetal lambs in utero. *Circ Res* 1976; **39**: 536-541

Machin G.A. Hydrops Revisited: Literature review of 1414 cases published in the 1980's. *Am J Med Genet* 1989; **34**: 366-90

Margolis A.J. and Orcutt R.E. Pressures in human umbilical vessels in utero. *Am J Obstet Gynecol* 1960; **80**: 573-576

Maxwell D., Allan L. and Tynan M.J. Balloon dilatation of the aortic valve in the fetus: a report of two cases. *Br Heart J* 1991; **65**: 256-258

Maxwell D.J., Crawford D.C., Curry P.V.M., Tynan M.J. and Allan L.D. Obstetric importance, diagnosis and management of fetal tachycardias. *Br Med J* 1988; **297**: 107-110.

Maxwell D.J., Johnson P., Hurley P., Neales K., Allan L.D. and Knott P. Pregnancy loss after fetal blood sampling - An evaluation in relation to indication. *Br J Obstet Gynaecol* 1991; **98**: 892-897

Medical Research Council. An assessment of the hazards of amniocentesis. *Br J Obstet Gynaecol* 1978; **85**: (suppl 2).

Mendel D. and Oldershaw P. Left Ventricular Puncture In: *A Practice of Cardiac Catheterisation.* Eds: Mendel D. and

Oldershaw P. Blackwells, Oxford 1986: 96-99

Moessinger A.C., Fox E., Higgins A., Rey R. and Alhaideri M. Fetal breathing movements are not a reliable predictor of pulmonary hypoplasia in pregnancies complicated by oligohydramnios. *Lancet* 1988; **331**: 305-306

National Institute of Child Health and Development Amniocentesis Register. The safety and accuracy of mid-trimester amniocentesis. US Department of Health, Education and Welfare, 1978; No.78-100

Nicolaides K.H., Rodeck C.H., Lange I., Watson J., Gosden C.M. Miller D., Mibashan R.S., Moniz C., Morgan Capner P and Campbell S. Fetoscopy in the assessment of unexplained fetal hydrops. *Br J Obstet Gynaecol* 1985; **92**: 671-679

Nicolini U., Santolaya J., Ojo O.E., Fisk N.M., Hubinont C., Tonge M. and Rodeck C.H. The fetal intrahepatic vein as an alternative to cord needling for prenatal diagnosis and therapy. *Prenat Diag* 1988; **8**: 665-671

Nicolini U., Fisk N.M., Rodeck C.H., Talbert D.G. and Wigglesworth J.S. Low amniotic pressure in oligohydramnios - Is this the cause of pulmonary hypoplasia? *Am J Obstet Gynecol* 1989 [b]; **161**: 1098-1101

Nicolini U., Fisk N.M., Talbert D.G., Rodeck C.H.,

Kochenour N.K., Greco P., Hubinont C. and Santolaya J. Intrauterine manometry: Technique and application to fetal pathology. *Prenat Diag* 1989 [b]; **9**: 243-254

Nicolini U., Talbert D.G., Fisk N.M. and Rodeck C.H. Pathophysiology of pressure changes during intrauterine transfusion. *Am J Obstet Gynecol* 1989[c]; **160**: 1139-1145

Nyberg R. and Westin B. An experimental study of the previable human foetus. *J Obstet Gynaecol Br Common* 1962; **69**: 831-835.

Paladini D., Chita S.K. and Allan L.D. Prenatal measurement of cardiothoracic ratio in evaluation of heart disease. *Arch Dis Child* 1990; **65**: 20-23

Pearce J.M. Uteroplacental and fetal blood flow. *Clin Obstet Gynecol* 1987; **1**: 157-184

Pearce J.M. and MacParland P. Predictive role of Doppler waveforms: the uteroplacental circulation. *Contemp Rev Obstet Gynaecol* 1991; **3**: 4-12

Pearl W. Regression of endocardial fibroelastosis. *Am Heart J* 1989; **117**: 1401

Phelan J.P., Ock Ahn M., Vernon Smith C., Rutherford S.E. and Anderson E. Amniotic fluid index measurements during

pregnancy. *J Reprod Med* 1987[a]; **32**: 601-604

Phelan J.P., Vernon Smith C., Broussard P. and Small M. Amniotic fluid volume assessment with the four-quadrant technique at 36-42 weeks gestation. *J Reprod Med* 1987[b]; **32**: 540-542

Pohlmann A.G. The course of the blood through the heart of the fetal mammal, with a note on the reptilian and amphibian circulations. *Anat Record* 1909; **3**: 75-109.

Pringle K. Human fetal lung development and related animal models. *Clin Obstet Gynecol* 1986; **29**: 502-513

Qureshi S.A., Rosenthal E., Tynan M., Anjos R. and Baker E.J. Transcatheter laser assisted Balloon pulmonary valve dilatation in pulmonic valve atresia. *Am J Cardiol* 1991; **67**: 428-431

Reed K.L., Appleton C.P., Anderson C.F., Shemker L. and Sahn D.J. Doppler studies of vena cava flows in human fetuses. *Circulation* 1990; **81**: 498-505

Reeves J.T., Daoud F.S. and Gentry M. Growth of the fetal calf and its arterial pressure, blood gases and haematologic data. *J Applied Physiol* 1972; **32**: 240-244

Reynolds S.R.M. Arterial and venous pressures in the

umbilical cord of the sheep and nature of return from the placenta. *Am J Physiol* 1951; **166**: 25-36

Reynolds S.R.M., Light F.W., Ardran G.M. and Prichard M.M.L. The qualitative nature of pulsatile flow in umbilical blood vessels, with observations on flow in the aorta. *Bull John Hopkins Hosp* 1952; **91**: 83-104

Reynolds S.R.M. Hemodynamic characteristics of the fetal circulation. *Am J Obstet Gynecol* 1954: **68**: 69-80

Reynolds S.R.M., Paul W.M. and Huggett A.St.G. Physiological study of the monkey fetus in utero: A procedure for blood pressure recording, blood sampling, and injection of the fetus under normal conditions. *Bull John Hopkins Hosp* 1954; **95**: 256-268

Reynolds S.R.M. and Paul W.M. Pressures in umbilical arteries and veins of the fetal lamb in utero. *Am J Physiol* 1958; **193**: 257-259

Reynolds S.R.M. Regulation of the fetal circulation: Its relation to fetal distress. *Clin Obstet Gynecol* 1960; **3**: 834-851

Reynolds S.R.M. Cineroentgenographically demonstrated changes in the fetal circulation occurring at birth: a serendipic commentary. *Am J Roentgen* 1961; **86**: 407-414.

Reynolds S.R.M. and Mackie J.D. Umbilical venous pressure and other cardiovascular responses of fetal lambs to epinephrine. *Am J Physiol* 1962; **203**: 955-960

Ribemont A. Recherches sur la tension du sang dans less vaisseaux du fœtus et du nouveau-né. *Arch Tocol Maladies* 1879; 577-599.

Rivett L.C. Hydramnios. *J Obstet Br Emp* 1933; **40**: 522-525

Romero R., Pilu G., Jeanty P., Ghidini A. and Hobbins J.C. Nonimmune hydrops fetalis. In: *Prenatal Diagnosis of Congenital Anomalies* 1988; Appleton and Lange, Connecticut 414

Rudolph A.M. The changes in the circulation after birth: Their importance in congenital heart disease. *Circulation* 1970; **41**: 343-359

Rudolph A.M. and Cayler G.C. Cardiac catheterization in infants and children. *Ped Clin N America* 1958; 907-943

Rudolph A.M. and Heymann M.A. The circulation of the fetus in utero - Methods for studying distribution of blood flow, cardiac output and organ blood flow. *Circ Res* 1967; **21**: 163-184

Rudolph A.M. and Heymann M.A. Circulatory changes during

growth in the fetal lamb. *Circ Res* 1970; **26**: 289-299

Rudolph A.M., Heymann M.A., Teramo K.A.W., Barrett C.T. and Räihä N.C.R. Studies on the circulation of the previable human fetus. *Ped Res* 1971; **5**: 452-465

Rudolph A.M. and Heymann M.A. Methods for studying the circulation of the fetus in utero. In: *Animal Models in Fetal Medicine* Ed: Nathanielsz P.W. Elsevier/North Holland Biomedical Press, Amsterdam. 1980; 1-57

Rutherford S.E., Vernon Smith C., Phelan J.P., Kawakami K. and Ock Ahn M.. Four-quadrant assessment of amniotic fluid volume. *J Reprod Med* 1987; **32**: 587-589

Sauer U., Gittenberger-de Groot A.C., Geishauer M., Babic R. and Bühlmeyer K. Coronary arteries in the HLH syndrome. *Circulation* 1989; **8**: Supplement I 168-176

Schmidt W, Harms E, Wolf D. Successful prenatal treatment of nonimmune hydrops fetalis due to congenital hydrothorax. *Br J Obstet Gynaecol* 1985; **92**: 685-687

Scopes J.W. The fetal circulation. In *Scientific Foundations of Obstetrics and Gynaecology* Eds.Philipp E, Barnes J, Newton M. 1977 Heinemann, London. 369-375.

Sharland G.K., Chita S.K., Fagg N.L.K., Anderson R.H.,

Tynan M., Cook A.C and Allan L.D. Left ventricular dysfunction in the fetus: relation to aortic valve anomalies and endocardial fibroelastosis. *Br Heart J* 1991; **66**: 419-424

Sharland G.K., Lockhart S.M., Heward A.J. and Allan L.D. Prognosis in fetal diaphragmatic hernia. *Am J Obstet Gynecol* 1992; **166**: 9-13

Shimokawa H, Hara K, Malda H, Mujamoto S, Koyanagi T, Nakano H. Intrauterine treatment of idiopathic hydrops fetalis. *J Perinat Med* 1988; **16**: 133-138

Sideris I.G. and Nicolaides K.H. Amniotic fluid pressure during pregnancy. *Fet Diag Ther* 1990; **5**: 104-108

Soothill P. Intrauterine blood transfusion for non-immune hydrops fetalis due to parvovirus B19 infection. *Lancet* 1990; **336**: 121-122

St.John Sutton M.G., Raichler J.S., Reichek N. and Huff D.S. Quantitative assessment of right and left ventricular growth in the human fetal heart: pathoanatomic study. *Circulation* 1984; **70**: 935-941.

Tabor A., Philip J., Marsen M., Bang J., Obel F.B. and Morgaard-Pedersen B. Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. *Lancet* 1986; **i**: 1287-

93.

Tabor B.L. and Maier J.A. Polyhydramnios and elevated intra uterine pressure during amnioinfusion. *Am J Obstet Gynecol* 1987; **156**: 130-131

Thomas I.T. and Smith D.W. Oligohydramnios cause of the non-renal features of Potter's syndrome including pulmonary hypoplasia. *J Pediat* 1974; **84**: 811-814.

Versmold H.T., Kitterman J.A., Phibbs R.H., Gregory G.A. and Tooley W.H. Aortic blood pressure in the first 12 hours of life in infants with birth weights of 610 to 4,220 grams. *Pediatrics* 1981; **67**: 607-613

Veille J-C. and Sivakoff M. Fetal echocardiographic signs of congenital endocardial fibroelastosis. *Obstet Gynecol* 1988; **72**: 219-222

Weiner C.P., Heilskov J., Pelzer G., Grant S., Wenstrom K. and Williamson R.A. Normal values for human umbilical venous and amniotic pressures and their alteration by fetal disease. *Am J Obstet Gynecol* 1989[a]; **161**: 714-717

Weiner C.P., Pelzer G.D., Heilskov J., Wenstrom K.D. and Williamson R.A. The effect of intravascular transfusion on umbilical venous pressure in anaemic fetuses with and without hydrops. *Am J Obstet Gynecol* 1989[b]; **161**: 1498-

1501

Westin B., Nyberg R. and Enhörning G. A technique for the perfusion of the previable human fetus. *Acta Pæd* 1958; **47**: 339-349.

Whittle M. Cordocentesis. *Br J Obstet Gynaecol* 1989; **96**: 262-264

Wilde P. Acquired heart disease. In: *Doppler echocardiography: An illustrated clinical guide*. Churchill Livingstone, Edinburgh. 1989: 49-97

Wren C., Sullivan I., Bull C. and Deanfield J. Percutaneous balloon dilatation of aortic valve stenosis in neonates and infants. *Br Heart J* 1987; **58**: 608-612

APPENDIX I: Forms for termination of pregnancy:

IN CONFIDENCE

ABORTION NOTIFICATION

Please leave blank

ABORTION ACT 1967
FORM OF NOTIFICATION (England and Wales)

This form is to be COMPLETED BY THE PRACTITIONER TERMINATING THE PREGNANCY and sent in a sealed envelope within SEVEN DAYS of the termination to:-

The Chief Medical Officer
Department of Health
Richmond House
79 Whitehall
LONDON
SW1A 2NS

OR

The Chief Medical Officer
Welsh Office
Cathays Park
CARDIFF
CF1 3NQ

in respect of the termination of the pregnancy in Wales

PLEASE USE BLOCK CAPITALS AND NUMERALS FOR DATES THROUGHOUT

---

1. PRACTITIONER TERMINATING THE PREGNANCY

NAME I, ...

PERMANENT ADDRESS of .....

.....

hereby give notice that I terminated the pregnancy of the woman named overleaf, and to the best of my knowledge the particulars on this form are correct. **I further certify that I joined/did not join† in giving Certificate A having seen/not seen† and examined/not examined† her before doing so.**

Signature ..... **Date** .....

---

2. CERTIFICATION In all non-emergency cases state particulars of practitioners who joined in giving Certificate A.

	1. To be completed in **all** cases.	2. Do **not** complete if the operating practitioner joined in giving Certificate A.
NAME	.....	.....
PERMANENT ADDRESS	.....	.....
	.....	.....

(tick appropriate box)

Did the practitioner named at 1 certify that he saw/and examined the pregnant woman before giving the certificate? ☐ **YES** ☐ **NO**

Did the practitioner named at 2 certify that he saw/and examined the pregnant woman before giving the certificate? ☐ **YES** ☐ **NO**

DO NOT COMPLETE IF SECTION 20 BELOW APPLIES

Please leave these boxes blank

3. NAME AND ADDRESS OF PLACE OF TERMINATION .....

.....

☐☐☐☐☐

Was the patient a NHS case terminated in an approved place under an agency agreement? **(tick appropriate box)** ☐ **YES** ☐ **NO** ☐

---

† **delete as appropriate**

Form HSA4 (Revised 1991)

4. WOMAN'S FULL NAME AND PERMANENT ADDRESS (INCLUDING COUNTRY IF RESIDENT OUTSIDE ENGLAND AND WALES)

Surname .....

Forename(s) .....

Address .....

..... **Postcode** [| | | | | | | |]

PRESENT ADDRESS IN ENGLAND AND WALES

.....

.....

..... **Postcode** [| | | | | | | |]

Please leave these boxes blank

[ ]

[| | | | | | | |]

[ ]

5. DATE OF BIRTH .....DAY .....MONTH .....YEAR [| | | | | |]

6. MARITAL STATUS **(tick appropriate box)**

1 [ ] Single 3 [ ] Widowed 5 [ ] Separated

2 [ ] Married 4 [ ] Divorced NK [ ] Not Known

[ ]

7. PARITY

Number of woman's previous:- (Enter number - If NIL enter 0)

a. (i) Livebirths ..... [ ]

(ii) Stillbirths ..... [ ]

(iii) Spontaneous miscarriages ..... [ ]

b. Legal terminations ..... [ ]

8*. ADMISSION Date of admission to place of termination .....DAY .....MONTH .....YEAR [| | | | | |]

9*. TERMINATION Date of termination .....DAY .....MONTH .....YEAR [| | | | | |]

10*. DISCHARGE Date of discharge from place of termination .....DAY .....MONTH .....YEAR [| | | | | |]

11*. DAY CASE **(tick appropriate box)**

Was this a planned day case? [ ] **YES** [ ] **NO** [ ]

*** If the method of treatment used to terminate the pregnancy was Antiprogesterone with Prostaglandin without any supplementary surgical termination do not complete sections 8-11 but INSTEAD complete section 20**

Please leave these boxes blank

12. GESTATION 1. Specify number of weeks by completing a or b as appropriate

a. Pregnancy has NOT exceeded its 24th week

Gestation estimated at.....weeks

b. Pregnancy HAS exceeded its 24th week (ensure that section 14 is also completed)

Gestation estimated at .....weeks

2. Methods of estimation **(tick appropriate box(es))**

☐ LMP ☐ Ultrasound ☐ Other - specify:-.....

13. GROUNDS The certified ground(s) for terminating the pregnancy stated on CERTIFICATE A were:-

(tick appropriate box(es))

☐ **A** that the continuance of the pregnancy would involve risk to the life of the pregnant woman greater than if the pregnancy were terminated. — **A** State main medical condition(s):-

☐ **B** that the termination is necessary to prevent grave permanent injury to the physical or mental health of the pregnant woman. — **B** State main medical condition(s):-

☐ **C** that the pregnancy has NOT exceeded its 24th week and that the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman. — **C** State main medical condition(s):-

☐ **D** that the pregnancy has NOT exceeded its 24th week and that the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of any existing child(ren) of the family of the pregnant woman. — **D** State number of children:-

☐ **E** that there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped:- STATE

EITHER (i) (a) Diagnosis.....

(b) Method(s) of diagnosis (tick appropriate box(es))

☐ Amniocentesis ☐ Ultrasound ☐ Chorionic Villus Sampling ☐ Other - specify .....

OR (ii) Condition in pregnant woman causing suspected condition in fetus. Complete 1 and 2

1. Condition in woman - specify:-.....

.....

2. Suspected condition in fetus - specify:-.....

.....

EMERGENCY ONLY Termination was immediately necessary, as stated on CERTIFICATE B:-

☐ **F** to save the life of the pregnant woman — **F or G** - state main medical condition(s):-

OR

☐ **G** to prevent grave permanent injury to the physical or mental health of the pregnant woman

14. OVER 24 WEEKS GESTATION If the pregnancy was terminated after it had exceeded its 24th week please give below a full statement of the medical condition of the pregnant woman/fetus.

15. SELECTIVE TERMINATION Was this a selective termination? **(tick appropriate box)** ☐ **YES** ☐ **NO**

State:- (i) original number of fetuses .....

(ii) number of fetuses reduced to .....

All other relevant sections of the form should also be completed

Please leave these boxes blank

16. METHOD **(tick appropriate boxes)**

Cervical preparation? ☐ **YES** ☐ **NO**

.....

Surgical termination:-

☐ Vacuum aspiration

☐ Dilatation and Evacuation

☐ Hysterotomy

☐ Hysterectomy

☐ Other surgical - specify:-

.....

*Medical termination:-

☐ Prostaglandin only

☐ Prostaglandins with:- **(tick appropriate boxes)**

☐ Oxytocin

☐ Antiprogesterone (if used see also section 20 below)

☐ Other medical agents-specify:-

.....

* Do not enter an evacuation of retained products of conception as a further method of termination.

17. COMPLICATIONS* **(tick appropriate box(es))**

☐ None ☐ Haemorrhage ☐ Uterine Perforation ☐ Sepsis

☐ Other - specify:- .....

*Do not enter an evacuation of retained products of conception as a complication.

18. STERILISATION **(tick appropriate box)**

Was a sterilisation operation performed? ☐ **YES** ☐ **NO**

19. DEATH OF WOMAN

In the case of death, specify:-

(i) Date .....DAY .....MONTH .....YEAR

(ii) Cause .....

20. ANTIPROGESTERONE WITH PROSTAGLANDIN Do not complete this section unless the method used was Antiprogesterone with Prostaglandin

(i) Date of treatment with Antiprogesterone .....DAY .....MONTH .....YEAR

Name .....

Address of place of treatment .....

(ii) Date of treatment with Prostaglandin .....DAY .....MONTH .....YEAR

Name .....

Address of place of treatment .....

(iii) Date termination confirmed .....DAY .....MONTH .....YEAR

(iv) Was the patient a NHS case treated under an agency agreement? **(tick appropriate box)** ☐ **YES** ☐ **NO**

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APPENDIX II: Umbilical venous pressure before and after sampling:

No:	Gestn:	Pressure before:	Pressure after:
2	20	7	7
13	30	2	2
15	19+5	3	2
20	19+3	6	6
45	21+2	9	9
49	24	8	7
53	25+3	5	5
58	20	3	3
100	22+6	6	6
105	29+3	4	4

APPENDIX III: Follow up forms:

UNITED MEDICAL AND DENTAL SCHOOLS
OF
GUY'S AND ST. THOMAS'S HOSPITALS
(UNIVERSITY OF LONDON)

FETAL MEDICINE UNIT
15th FLOOR GUY'S TOWER
LONDON BRIDGE SE1 9RT

DIRECTOR: Mr. D.J. MAXWELL
MRCOG MRACOG

DIRECT LINE 071-955 4835

DIVISION OF OBSTETRICS AND GYNAECOLOGY
GUY'S HOSPITAL
2nd FLOOR NEW GUY'S HOUSE (OFFICE)
LONDON SE1 9RT

DIRECT LINE 071-955 4387

Fetal Medicine No:

Date:

Dear

In order to complete our records, and ensure that we continue to provide a good service to our patients, we ask everybody who has a scan to fill in the details below and return this form to us. This is best done after the baby's six week check.

Date of birth: Sex of baby:

Any problems during the pregnancy:

Any problems found after birth:

Please return this form to:

Jo Motteram,
Midwife,
Fetal Medicine Unit,
15th Floor, Guy's Tower,
Guy's Hospital,
St. Thomas' Street,
London SE1 9RT.

Yours sincerely,

UNITED MEDICAL AND DENTAL SCHOOLS
OF
GUY'S AND ST. THOMAS'S HOSPITALS
(UNIVERSITY OF LONDON)

FETAL MEDICINE UNIT
15th FLOOR GUY'S TOWER
LONDON BRIDGE SE1 9RT

DIRECTOR: Mr. D.J. MAXWELL
MRCOG MRACOG

DIRECT LINE 071-955 4835

DIVISION OF OBSTETRICS AND GYNAECOLOGY
GUY'S HOSPITAL
2nd FLOOR NEW GUY'S HOUSE (OFFICE)
LONDON SE1 9RT

DIRECT LINE 071-955 4387

Fetal Medicine No:

Date:

Dear Dr,

Your patient

Name:

Hospital No:

was scanned here today. We would be most grateful if the following details could be provided after delivery, and the form returned to us.

Date of delivery: Sex of baby:

Birthweight:

Any problems during pregnancy:

Any problems found after delivery:

Please send this form to:

Jo Motteram,
Midwife,
Fetal Medicine Unit,
15th Floor, Guy's Tower,
Guy's Hospital,
St. Thomas' Street,
London SE1 9RT

Yours sincerely,

APPENDIX IV: Amniotic pressure with normal liquor volume:

No:	Gestn:	Pressure:	No:	Gestn:	Pressure:
1	25	8	77	20+4	6
2	20	11	78	15	10
3	28	4	79	16+2	4
4	35	16	80	16+5	4
5	27	12	81	16+6	6
8	20	7	82	16+2	6
9	21	8	83	17+3	5
10	32	15	84	16	4
11	20+4	4	85	16+6	12
12	33+5	4	86	16+2	4
14	20	18	87	16+3	3
17	15+6	6	88	17+2	6
20	19+3	10	89	16+1	4
21	20+2	7	90	25+3	8
22	19+2	6	92	19	14
23	36	11	93	21+4	14
24	19+3	10	94	18+1	12
25	21	6	95	20	12
26	16	12	96	30	13
27	18+6	3	97	31	4
28	31+4	6	98	19+5	14
30	21	11	101	21+5	8
31	33+5	4	102	24+2	8
35	34+1	5	103	19	10
36	32+5	7	104	15+5	5
37	29	2	105	29+3	6
38	22+5	14	106	17+2	4
39	16+3	13	107	16+3	6
40	17+3	11	108	16+1	5
41	17+2	6	109	32	10
43	28	9	110	19+3	9
44	14	8	111	21+4	8
45	21+2	10	112	15+4	11
48	22+4	20	113	18+1	6
50	19+5	10	114	17	6
51	20+3	8	115	16	6
52	23	5	116	20+4	9
54	16+3	6	117	19	9
55	29	5	119	23	4
56	30+1	11	120	33	23
58	20	9	121	16+2	11
60	25	12	122	16+4	5
62	17	6	123	16+2	3
63	17	11	124	16+3	5
64	24+5	6	125	16+1	8
67	16+3	4	126	14+5	5
68	16	9	127	16+5	6
69	17	2	128	23	8
70	16+6	4	129	14+5	11
71	16+2	5	130	22	22
72	16+3	5	131	16+2	7
74	18	7	132	16+4	9
76	29+4	8	133	16+5	3

Appendix IV continued:

No:	Gestn:	Pressure:	No:	Gestn:	Pressure:
134	15+1	8	185	22	4
135	19+4	7	186	17	10
136	22+1	10	187	24	6
137	18+4	10	188	17	8
138	32+5	4	189	19	13
139	22	4	190	24+5	9
140	33+1	5	191	19	8
141	23	12	192	19	10
143	22+3	6	194	16+2	13
144	19+6	10	195	27+6	12
145	15+2	4	196	29+3	3
146	17	4	197	20	11
147	18	3	198	19+5	5
148	22	5	199	35+2	9
149	23+5	10	200	18+6	5
150	23+3	8	201	22	10
151	18+6	13	202	19+5	8
152	18+4	8	203	33+5	8
153	17	8	204	18+6	7
154	18	11	205	22	5
155	25	7	207	25+4	7
156	14	10	208	22+3	9
157	22	12	210	19+4	45
158	17	5	211	27	8
159	16+2	5	212	36+4	11
160	15+6	6	213	14	2
161	15+6	6	214	20+3	5
162	15	6	216	33+1	9
163	16+3	6	217	18	6
164	26+3	5	218	16+5	10
165	19	7	219	19+6	7
166	22	7	220	18	11
167	18	13	221	16	12
168	20+2	8	222	27+5	7
169	16+1	7	223	18+3	8
170	17+3	5	224	37+5	8
171	14+6	4	225	22+6	10
172	20	5	226	18+6	3
173	15+2	6	228	18+4	13
174	15+2	13	230	22+3	6
175	15	11	231	21	3
176	15	5	232	30	20
177	19	4	233	22	6
179	18	8	234	31+4	6
180	17+3	4	235	19+5	3
181	17+1	6	236	21	6
182	16+2	2	237	19	5
183	16+5	5	238	17+1	8
184	32+1	7			

APPENDIX V: Amniotic pressure in polyhydramnios.

No:	Gestn:	Pressure:	No:	Gestn:	Pressure:
29	31	42	73	33	10
33	23	18	91	31	14
42	32	9	99	29	32
47	35	18	178	31+1	10
57	20+3	6	193	31+5	15
59	24	16	209	35+6	13
65	33+3	13	227	25+6	38

APPENDIX VI: Amniotic pressure in oligohydramnios.

Intact Membranes:			Ruptured Membranes:		
No:	**Gestn:**	**Pressure:**	**No:**	**Gestn:**	**Pressure:**
6	22+4	1	15	19+5	24
18	25	1	16	20+6	12
19	16+6	8	46	27+3	6
32	18	14	53	25+3	2
34	22	6			
61	36+4	2			
66	38+2	9			
75	19+3	6			
118	25+2	8			
142	22+5	4			
206	18	10			
215	28	9			

APPENDIX VII: Umbilical venous pressure in normal fetus.

No:	Gestn:	Pressure:	No:	Gestn:	Pressure:
2	20	7	135	19+4	2
5	21	3	136	22+1	3
13	30	2	137	18+4	7
14	20	2	142	22+5	11
15	19+5	3	148	22	5
16	20+6	4	149	23+5	2
20	19+3	6	155	25	1
45	21+2	9	164	26+3	3
49	24	8	199	35+2	6
50	19+5	1	207	25+4	6
53	25+3	5	208	22+3	3
58	20	3	216	33+1	6
100	22+6	6	222	27+5	2
105	29+3	4	224	37+5	5
109	32	8	233	22	2
111	21+4	2	236	21	3
116	20+4	9	239	33+5	4
118	25+2	3	240	24	3

APPENDIX VIII: Umbilical venous pressure in abnormal fetus.

Cardiac abnormality			Nonimmune hydrops		
No:	**Gestn:**	**Pressure:**	**No:**	**Gestn:**	**Pressure:**
7	32	3	28	31+4	12
10	32	10	42	32	10
56	30+1	8	47	35	10
75	19+3	2	55	29	11
76	29+4	6	57	20+3	12
93	21+4	4	65	33+3	14
97	31	5	73	33	16
184	32+1	4	91	31	10
196	29+3	4	96	30	7
230	22+3	3	99	29	5
241	37+5	7	119	23	5
243	32+3	11	143	22+3	5
			227	25+6	10
			242	30	10

Diaphragmatic hernia

No:	**Gestn:**	**Pressure:**
11	20+4	2
12	33+5	8
225	22+6	4

APPENDIX IX: Umbilical arterial pressure.

No:	**Gestn:**	**Systolic:**	**Mean:**	**Diastolic:**
5	27	9	6	4
29	31	24	20	18
52	23	22	17.5	16
59	24	22	13	8.5
60	25	21	17	14
66	38+2	70	54	50 #
102	24+2	20	17	14
110	19+3	-	8	- *
120	33	45	28	24
140	33+1	50	35	35
195	27+6	19.2	15	14.3
200	18+6	17	14	10 *
231	21	-	8	-

- intrauterine growth retardation, abnormal umbilical artery Doppler blood flow studies

* - normal fetus

APPENDIX X: Left ventricular pressures.

No:	Gestn:	Systolic:	Diastolic:	Pulse:
5	27	36	6	20
6	22+4	20	12	8
35	32+5	72	13	59*
36	34+1	71	9	62*
54	16+3	16	3	13
64	24+5	12	4	8#
100	22+6	36	14	22
141	23	13	6	7~
152	18+4	14	8	6
157	22	30.4	11.5	18.9
185	22	28.6	3.8	24.8
191	19	15.8	3	12.8
194	16+2	21	4.2	16.8
197	20	12	4	8
198	19+5	19	6	13
201	22	26	6	20
202	19+5	32	2	30
203	33+5	75	15	60*
204	18+6	10	4	6
205	22	28	9	19
206	18	6	3	3§
210	19+4	20	3	17
211	27	34.3	5.4	28.9¶
214	20+3	24.5	3	21.5
217	18	24	4	20
221	16	17	1	16
237	19	36.5	16	20.5
238	17+1	18	2	16
244	23	-	-	5
245	28	49	35	14*
246	31+4	48	7	41¤

* - Critical aortic stenosis # - Mitral atresia

~ - Nonimmune hydrops § - Coarctation of aorta

¶ - Ventricular disproportion ¤ - Pulmonary atresia

APPENDIX XI: Right ventricular pressure.

No:	Gestn:	Systolic:	Diastolic:	Pulse:
1	25	40	14	26
5	27	42	10	32
25	21	28	12	16
27	18+6	18	7	9
37	29	40	10	30
41	17+2	12	4	8
54	16+3	16	3	13
62	17	12	4	8
64	24+5	38.7	6.3	32.4#
77	20+4	24.9	1.6	23.3
139	22	14	6	8
141	23	13	6	7~
168	20+2	23	6	17
177	19	22.3	2	20.3
185	22	27.8	3.4	24.4
187	24	31.9	4	27.9†
189	19	18	8	10
191	19	20	4	16
197	20	20.5	2	18
198	19+5	22	5	17
201	22	26	6	20
204	18+6	11	4	7
211	27	36	2.2	23.8¶
245	28	46	12	34*
246	31+4	66	14	52¤

- Mitral atresia, ~ - Nonimmune hydrops, † - VSD, DORV
* - Critical aortic stenosis
¶ - Ventricular disproportion ¤ - pulmonary atresia

APPENDIX XII: Left atrial pressure

No:	Gestn:	Mean Pressure:
21	20+2	1
27	18+6	6
30	21	6
62	17	7
139	22	3
144	19+6	3
157	22	3
168	20+2	4
177	19	4
201	22	2
210	19+4	2
214	20+3	1
219	19+6	2
223	18+3	3

APPENDIX XIII: Right atrial pressure

No:	Gestn:	Mean Pressure:
5	27	4
23	36	5
27	18+6	3
101	21+5	2
144	19+6	3
177	19	3
187	24	2 *
189	19	4
190	24+5	9 #
202	19+5	3
221	16	5

* - DORV, VSD, Pulmonary atresia # - Nonimmune hydrops.