

# **Echocardiography in the human fetus**

**Echocardiografie in de humane foetus**

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR  
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM  
OP GEZAG VAN DE RECTOR MAGNIFICUS  
PROF. DR. C.J. RIJNVOS  
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.  
DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP  
WOENSDAG 20 SEPTEMBER 1989 OM 15.45 UUR

DOOR

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GEBOREN TE LONDEN, ENGELAND

1989

PASMANS OFFSETDRUKKERIJ B.V., 's-GRAVENHAGE

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*"We owe respect to the living, to the dead  
we owe only truth".*

Voltaire, 1694-1775

*In memory of my mother*

ISBN 90-7011654-5

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## Chapter 1

# Introduction

### 1.1 Introduction

The death rate amongst infants with congenital heart disease has dropped from 25% to <10% over the last twenty years. This is mainly the result of major developments in diagnostic procedures and new methods of treatment in the postnatal period. A further reduction in the morbidity rate may result from early diagnosis using intrauterine echocardiography. During the last ten years technological advances in ultrasound have made it possible to perform non-invasive studies of the human fetal heart. The prenatal detection of congenital heart disease may be important for the following reasons:

- obstetric management may be adjusted regarding timing, mode and location of the delivery (in the vicinity of a paediatric cardiology unit)
- pregnancy termination may be considered in cases with severe cardiac anomalies considered to be inoperable or associated with a very high morbidity and mortality, or when chromosomal abnormalities are present.
- Karyotyping may be performed since cardiac anomalies may be associated with chromosomal defects
- essential information may be obtained for genetic counseling
- reassurance can be given to parents when normal cardiac structure has been demonstrated.

### 1.2 Objectives

The objectives of this study were as follows.

The first objective was to assess and review current non-invasive methods of studying normal and abnormal human fetal cardiac morphology and function. A discussion of the four currently used ultrasonic techniques to define fetal cardiac anatomy and physiology can be found in chapter 2.

The second objective consisted of the analysis of results obtained following examination of a group of patients deemed at increased risk of producing a child with congenital heart disease. The data from a group of 1577 pregnant women are presented in chapter 3.

Patients with certain complications of pregnancy are also considered to be at risk of carrying a child with congenital heart disease, either alone or in

combination with other structural or chromosomal aberrations. The third objective, therefore, was to analyse 440 patients collected in this category. The data can be found in chapter 4.

The fourth objective was to establish and, therefore, understand possible pitfalls and errors when assessing fetal cardiac anatomy ultrasonically. To this end an ultrasonic-pathologic correlation was made wherever possible. The appropriate correlations in 12 cases are presented in chapter 5.

Fetal cardiac arrhythmia may be entirely benign or life threatening. It is imperative to correctly define the type of arrhythmia and its possible association with congenital heart disease before a realistic prognosis can be given or before considering therapeutic options. The objective of chapter 6 was to describe methods of recording and definition of fetal cardiac arrhythmia and to assess the outcome in this group.

## Chapter 2

## Introduction to ultrasound studies of normal and abnormal fetal cardiac anatomy and function

*"The heart and circulation are of paramount importance for the survival of all mammalian life, far more important than the type of the extremities, the shape of the head, or even the intelligence of the animal."*

Helen B. Taussig. Am.J.Cardiol 50:555, 1982

### Introductory remarks

In the human embryo the cardiovascular system is the first functioning system, with blood beginning to circulate by the end of the third week.

Development of the heart is first seen at 32 or 33 postmenstrual days, when splanchnic mesenchymal cells ventral to the pericardial coelom aggregate to form a pair of elongated strands called cardiogenic cords (Moore, 1977). By day 36 a single heart tube has formed with contractions of the heart tube also occurring at this time.

The general external postnatal appearance of the heart is seen as the heart tube grows and bends to the right with development and partition of the heart into four chambers being completed between the fourth and seventh weeks (Anderson and Ashley, 1974; Moore, 1977; Klinkenbijn, 1988). Differentiation of the primitive aortic arches into the basic postnatal arrangement of aortic and pulmonary circulations is completed between the sixth and eighth weeks.

Thus the critical period of heart development occurs between day 32 and day 62 and deviation from this normal pattern at any moment during this period may result in several cardiac defects. Defects of the cardiac septa are relatively common as a result of the complexity of partitioning.

### *Development of the conducting system.*

Initially the sinoatrial node is found within the right wall of the sinus venosus; it becomes incorporated, with the sinus venosus, into the wall of the right atrium and is to be found at the entrance of the superior vena cava into the right atrium.

The atrioventricular node and bundle of His are formed by cells from the left wall of the sinus venosus and the atrioventricular canal, and are situated just anterior to the opening of the coronary sinus in the base of the interatrial septum.

The sinoatrial and atrioventricular nodes are normally the only pathway from the atria to the ventricles with histological differentiation of these specialised

tissues continuing up to and after birth (Patten, 1968; Anderson and Taylor, 1972).

Following the development of high resolution ultrasound techniques in the early 1980s, interest has been focused on the possibility of utilising these improved techniques to define both the normal and abnormal morphology and physiology in the human fetal heart.

Currently four ultrasound techniques are employed in the definition of fetal cardiac structure and function:

- a. real-time cross-sectional ultrasound
- b. real-time directed M-mode techniques
- c. pulsed Doppler ultrasound
- d. colour coded Doppler flow mapping techniques.

A description of the normal ultrasonic appearance of the fetal heart will be provided in Chapter 2.1. An introduction to the first two techniques (a and b) will be presented in Chapter 2.2 and 2.3. Part of the same patient material is referred to in both Chapter 2.2 and 2.3. In Chapter 2.4 and 2.5 the Doppler techniques (c and d) will be discussed.

### *References*

- Anderson RH, Taylor IM. Development of atrioventricular specialised tissue in human heart. *Brit.Heart J*, 34:1205, 1972.
- Anderson RH, Ashley GT. Growth and development of the cardiovascular system: (a) anatomical development. In: JA Davis and J Dobbing (Eds). *Scientific Foundations of Paediatrics*, Philadelphia, WB Sanders & Co, 1974, pp 165-198.
- Klinkenbijn J, Wenink ACG. Morphology of sections through the fetal heart. *International Journal of Cardiology*, 20: 87-98, 1988.
- Moore KL: In: *The Developing Human, Clinically oriented Embryology*. WB Sanders, 1977, pp 259.
- Patten BM. *Human Embryology*. 3rd Ed. New York, McGraw-Hill Book Co, 1968.

## 2.1. Ultrasonic recognition of fetal cardiac morphology

In this section a more detailed ultrasonographic description of those cardiac cross-sections most important in the search for cardiac structural defects will be presented. The following cross-sections are included:

- 2.1.1. the four chamber view
- 2.1.2. left heart connections
- 2.1.3. right heart connections
- 2.1.4. outflow tracts.

### 2.1.1 *The four chamber view*

Approximately 70 - 80% of congenital heart abnormalities can be excluded from a normal four chamber view (Allan et al, 1986; Copel et al, 1987). It is the easiest view to obtain and recognise and is achieved by a direct transverse plane across the fetal thorax. It is the easiest plane to use in routine scanning as it lies between that for measuring the biparietal diameter and that for measuring the abdominal circumference. The fetal stomach and the apex of the heart should be visualised on the left side of the fetus. The fetal position is not important as the position of the spine is always used for orientation. The "rule of thumb" for orientation is given in Figure 1.

- On ultrasound the four chamber view is presented as follows (Figs.2a-2b):
- the heart fills approximately 1 /3 of the fetal thorax
  - the right and left atria are approximately equal in size
  - the right and left ventricular cavities are more or less equal in size at the level of the valves
  - the right ventricle is closest to the sternum, the left atrium closest to the spine (fig.2a)
  - mitral and tricuspid valves open with each cardiac cycle
  - ventricular walls and interventricular septum are more or less equal in thickness
  - the tricuspid valve inserts more apically than the mitral valve
  - the right ventricular apex has a "triangular" shape due to increased trabeculations and the moderator band
  - the foramen ovale flap is seen with movement into the left atrium
  - the pulmonary veins insert into the left atrium - seen on either side of the spinal crest
  - the ventricular septum appears intact.

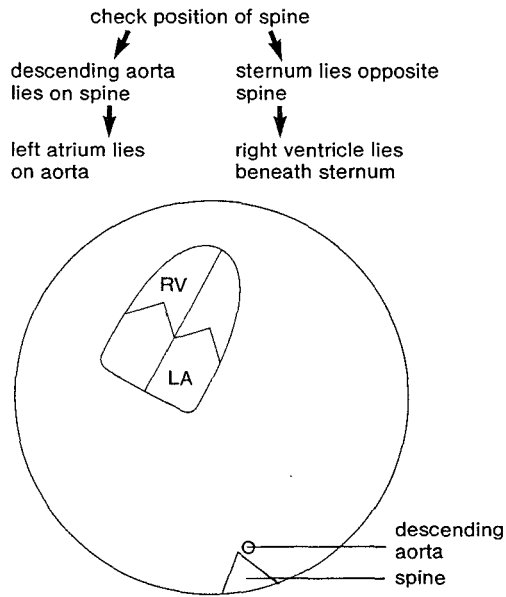


Fig.1. Diagram to show orientation for obtaining a 4-chamber view.

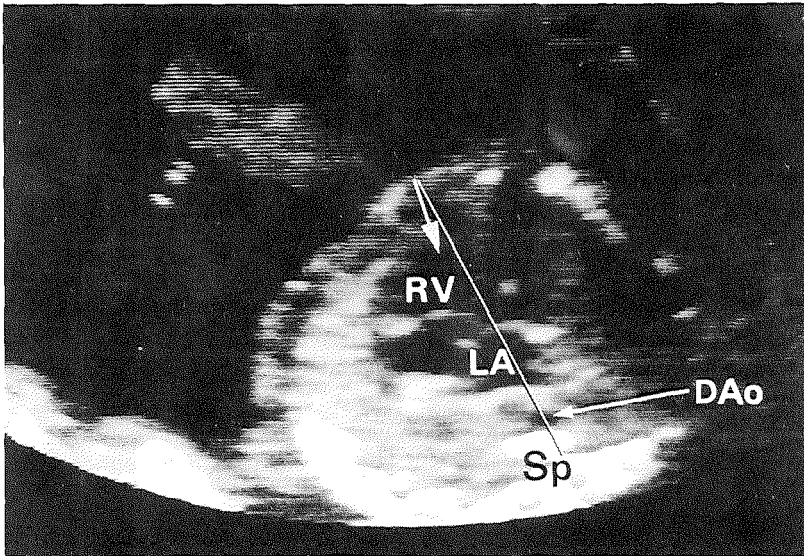


Fig.2a. Fetal 4-chamber view. If an imaginary line is drawn from the spine (sp) to the sternum, the first structure under the sternum will be the right ventricle (RV). The structure closest to the descending aorta (DAo) will be the left atrium (LA).

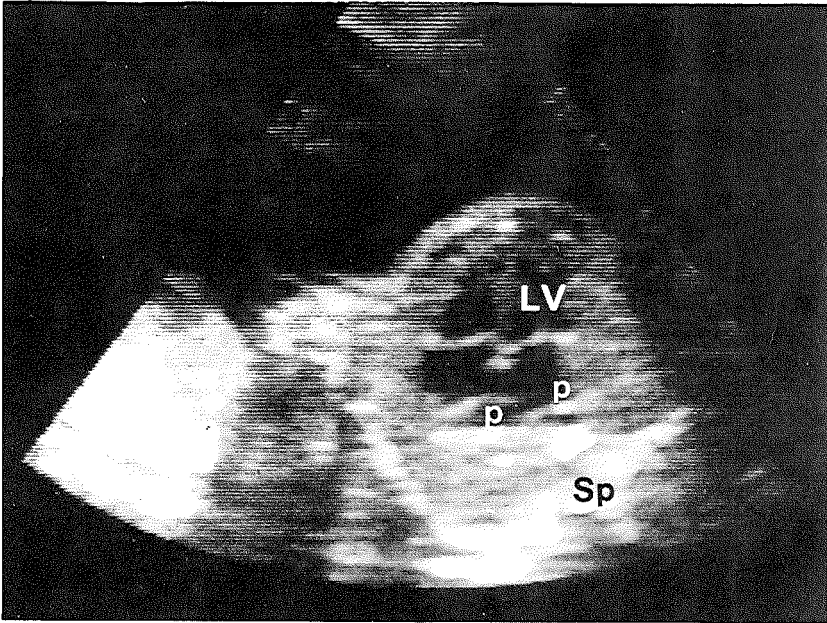


Fig.2b. Fetal 4-chamber view. LV=left ventricle, p=pulmonary vein.

### 2.1.2 *Left heart connections.*

From the four chamber position (orientation unimportant, spine as landmark), cranial angulation of the transducer produces the "five chamber view" or the four chamber aortic root view (Figs. 3a - 3c):

- turning the transducer lengthwise will produce a left ventricular long axis view.
- continuity between (a) the anterior wall of the aorta and interventricular septum, (b) posterior wall of the aorta and anterior mitral valve leaflet should be identified.
- still turning the transducer longitudinally shows the aortic arch with innominate, carotid and subclavian arteries to the head and neck.
- the ascending aorta lies to the right of the main pulmonary artery and angles out to the right.

### 2.1.3 *Right heart connections*

The pulmonary artery is closer to the chest wall and runs straight towards the spine (Fig.4a). Orientating the transducer along the length of the right ventricular outflow tract shows the pulmonary valve. Scanning the base of the

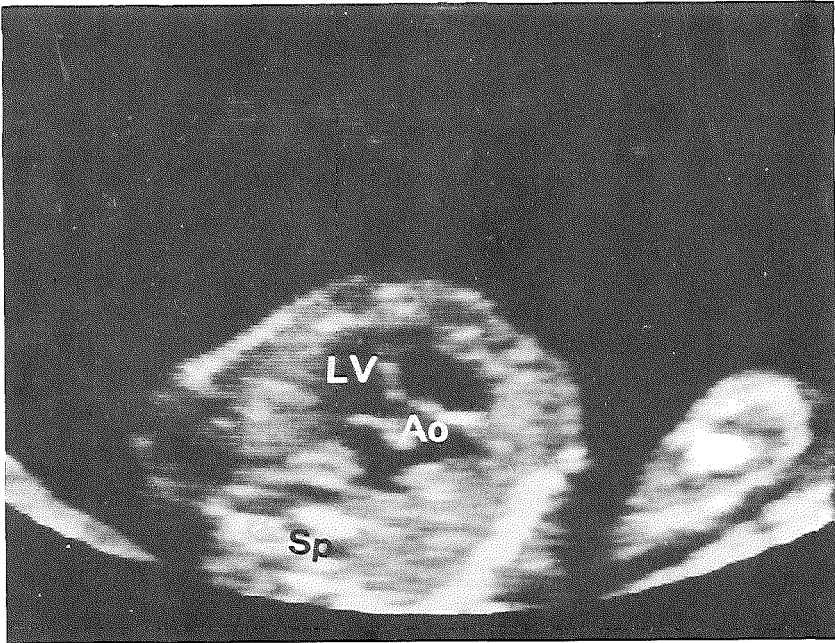


Fig.3a. Fetal "5"-chamber view. Ao=aortic root.

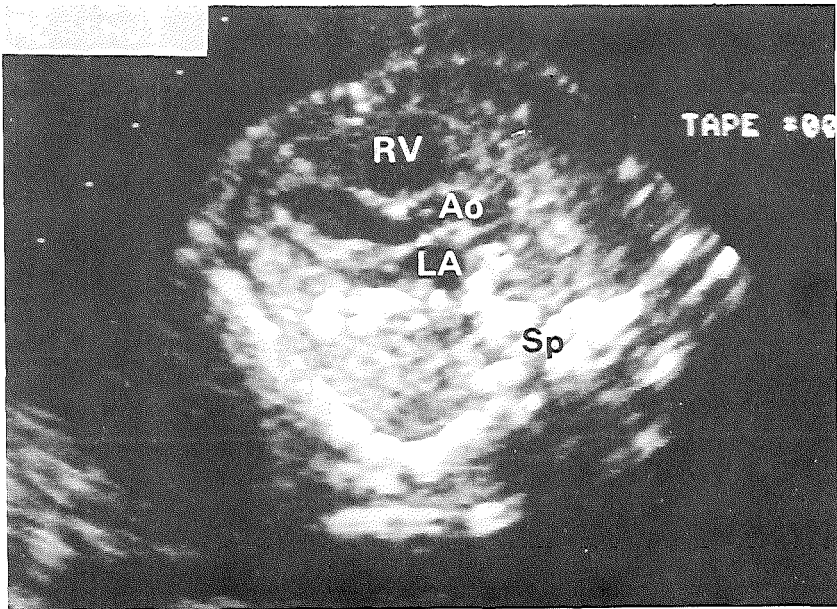


Fig.3b. Fetal left ventricular long axis view. LA=left atrium.



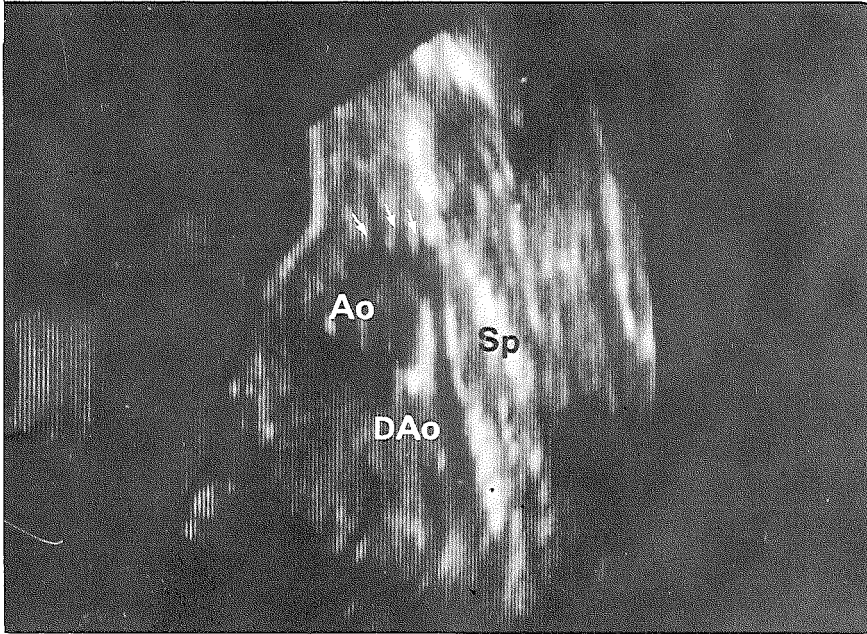


Fig.3c. Fetal aortic arch view. The head and neck vessels are seen vertically from this position (arrows). DAo=descending aorta.

heart lengthwise brings the inferior and superior vena caval connections into view (Fig.4b). Further angulation in a horizontal direction visualises the main pulmonary artery, right and left pulmonary arteries and /or the ductus arteriosus (Fig.5a-5c). A parasternal short axis view shows both ventricles, the right rather elongated and the left seen as a circle, "sitting" on the diaphragm (Fig.6).

#### 2.1.4 *Outflow tracts*

The pulmonary valve is anterior and cranial to the aortic valve. The pulmonary artery is connected to the anterior (right) ventricle and gives rise to the right and left pulmonary arteries and the ductus arteriosus (Figs.4a, 5a - 5c). The origins of the pulmonary artery and aorta are at 90° to each other.

The aorta arises from the posterior (left) ventricle, is in the centre of the chest and continues into the aortic arch. The arch gives rise to the innominate, carotid and subclavian arteries (Figs.3a - 3c).

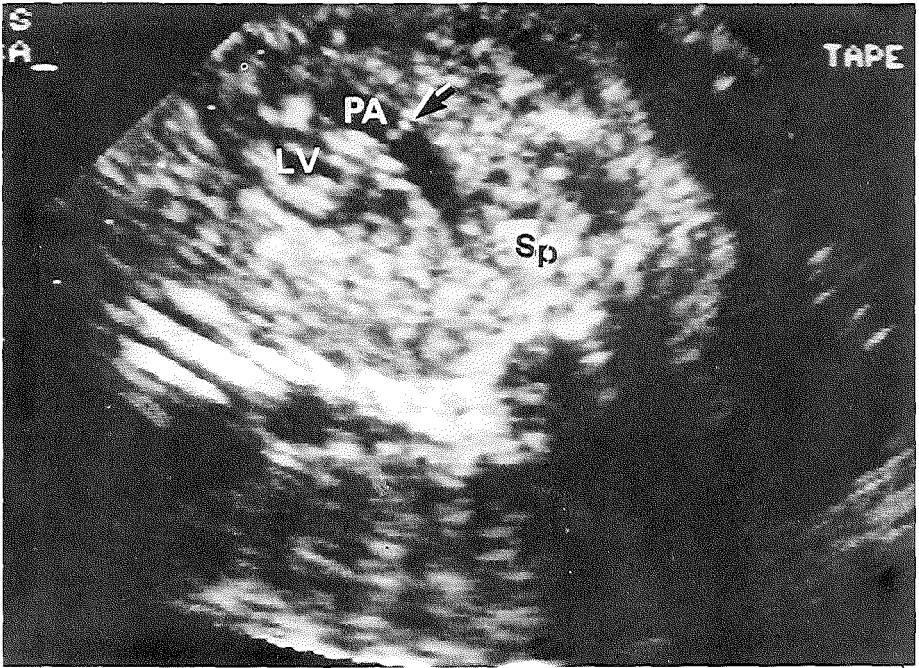


Fig.4a. Fetal right ventricular outflow tract. PA=pulmonary artery. Arrow indicates closed pulmonary valve.

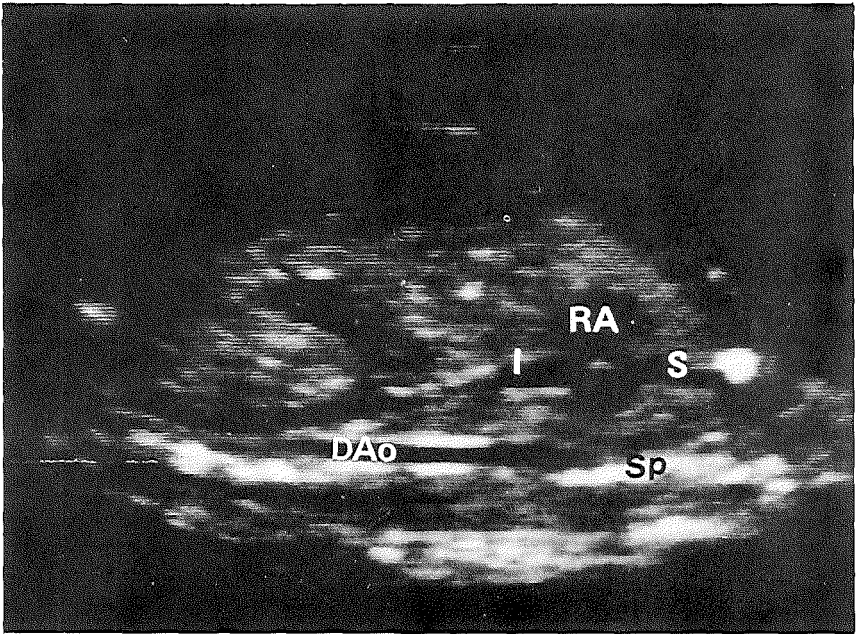


Fig.4b. Fetal inferior (I) and superior (S) vena caval connections to the right atrium (RA).

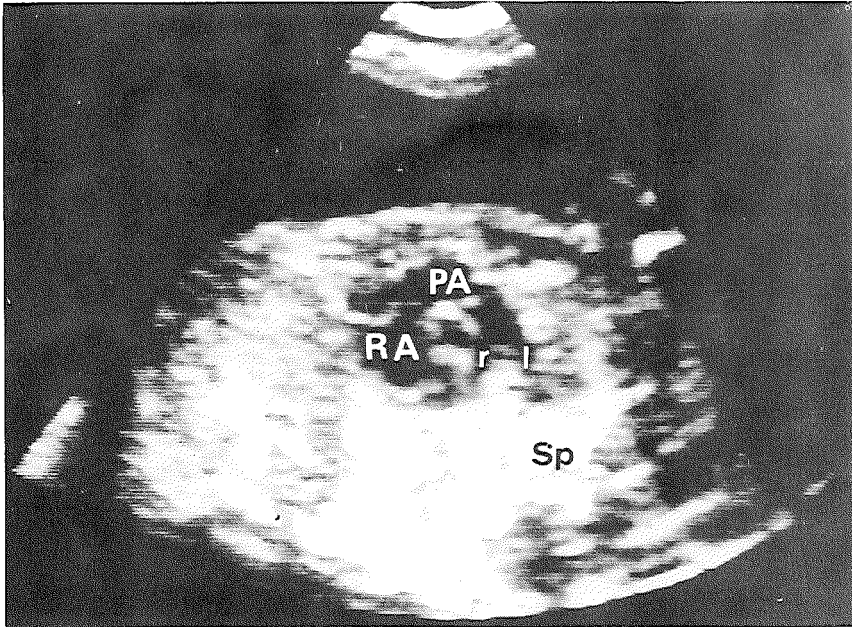


Fig.5a. Fetal parasternal short axis pulmonary artery view with right (r) and left (l) pulmonary arteries.

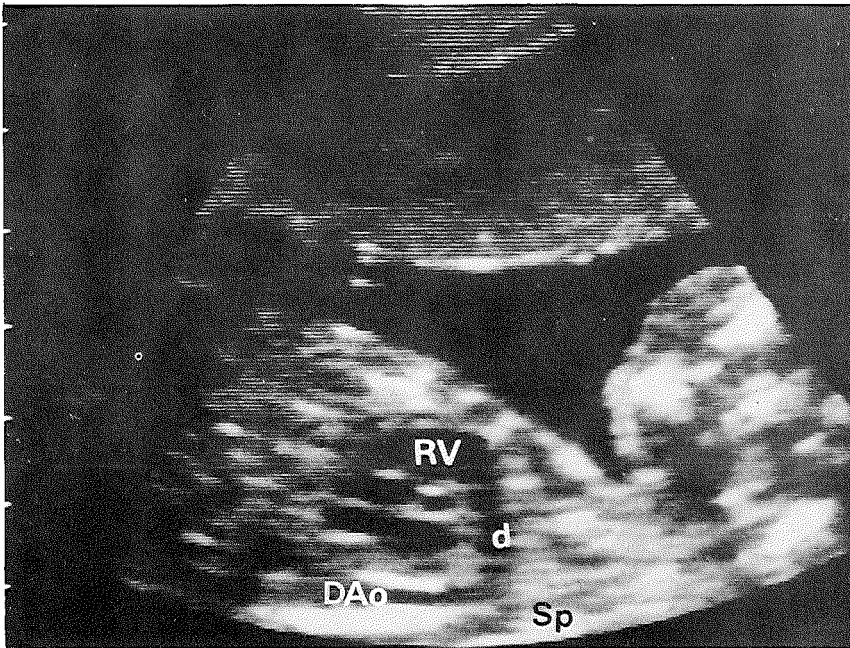


Fig.5b. Fetal ductus arteriosus (d) connecting the RV and the descending aorta.

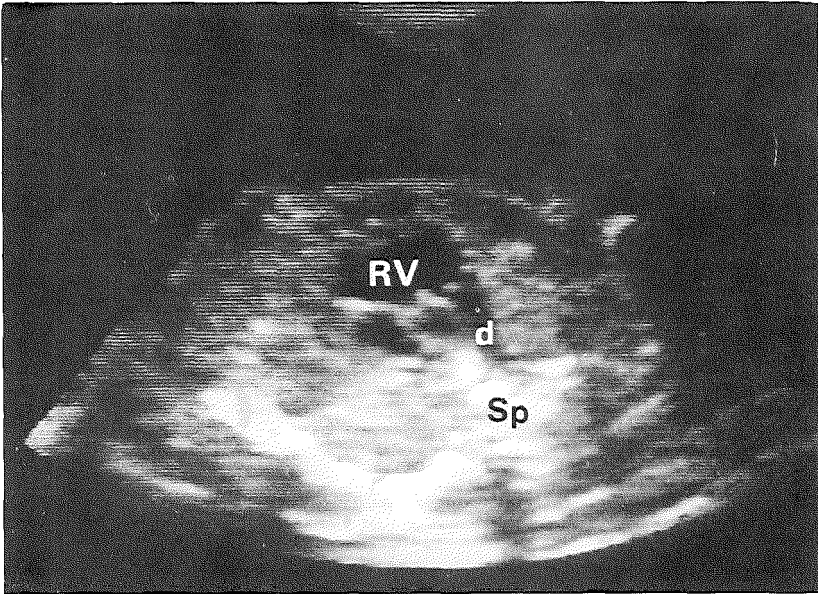


Fig.5c. Fetal ductus arteriosus (d).

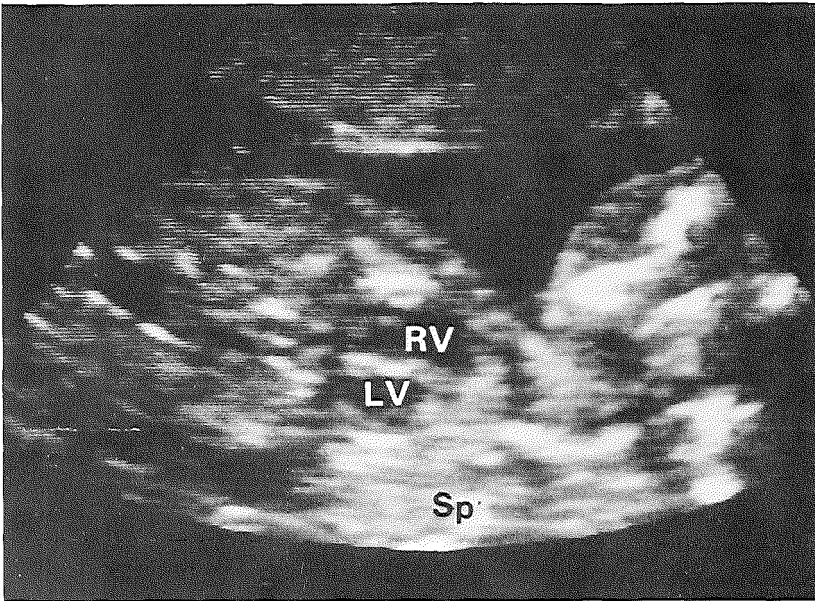


Fig.6. Fetal parasternal short axis view.

### *Summary*

The morphologic characteristics and connections of the fetal heart should be sequentially identified. Using both transverse and longitudinal planes the **venous-atrial junctions** are identified by visualising the venae cavae to the right atrium and pulmonary veins to the left atrium.

To visualise the **atrio-ventricular junction** the transverse plane should be used to identify the four chamber view.

The ventriculo-arterial connections are identified using transverse and longitudinal planes to visualise the pulmonary artery and branches to the right, and aorta and branches, to the left.

### *References*

Allan LD, Crawford DC, Chita SK, Tynan MJ. Prenatal screening for congenital heart Disease. *Br Med J* 292, 1717-1719 (1986)

Copel JA, Pilu G, Green J, Hobbins JC, Kleinman CS. Fetal echocardiographic screening for congenital heart disease: The importance of the four-chamber view. *Am J Obstet* 157, 648-655 (1987).

## 2.2 Fetal Cardiac Structure and Function as Studied by Ultrasound. A Review

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Published in Clinical Cardiology, Vol 7: 239-253 (1984)

### *Summary*

Present combined two-dimensional real-time and M-mode echocardiograph systems allow detailed analysis of fetal cardiac structure and function. Standard scanning planes for systematic investigation of various cardiac structures are described. There is a curvilinear increase in left ventricular volume (Q<sub>lv</sub>), stroke volume (Q<sub>lvs</sub>), and output (Q<sub>lv</sub>) during the last trimester of pregnancy with a mean Q<sub>lv</sub> value at term of  $126 \pm 11$  ml/kg/min. Scanning for cardiac defects should preferably be done between 18 and 24 weeks of gestation. In a total of 444 patients referred to our ultrasound unit for ultrasonic analysis of fetal cardiac structure, a total of 13 cardiac defects were diagnosed. The incidence of structural cardiac defects present among those with fetal dysrhythmia was 15%.

**Key words:** fetal heart, diagnostic ultrasound, cardiac defects, fetal blood flow, pulsed-wave Doppler.

### *Introduction*

Examination of the fetal heart by pulsed ultrasound was first described by Robinson et al. (1968) who reported on fetal cardiac imaging and identification of the interventricular septum. It was not until the introduction of real-time scanners that information on cardiac anatomy in relation to the various stages of the cardiac cycle could be obtained. This paper will discuss the use of two-dimensional (2-D) real-time and M-mode echocardiographic techniques in the analysis of normal and abnormal fetal cardiac structure and function.

### *Fetal Cardiac Structure*

Using two-dimensional real-time ultrasound, the motion of the fetal heart can be observed at around 6 weeks of gestation, although structural analysis is not possible until approximately 16 weeks of gestation. The heart is still rather small at this stage, so complete examination may be difficult. The heart is most easily imaged between 18 and 24 weeks of gestation. During the late third trimester the fetal spine is often in an anterior position and with increased shadowing caused by the ribs, visualization of all structures may not be achieved.

The heart of the fetus can be viewed in planes unobtainable postnatally because the fetal lungs are fluid filled and present no obstruction to the ultrasound beam.

The position of the heart is also different from that of the neonate due to the relatively large size of the liver, causing the apex of the heart to be more horizontal and the right ventricle to be more anterior to the left ventricle. A number of transverse and longitudinal planes are employed although the examination is really a continuous sweep, allowing each scanning view to follow on to another, thereby demonstrating normal cardiac anatomy.

The position of the fetal spine is first sought as a reference and fetal position is noted. In the transverse axis at the level of the fetal chest the four-chamber view (Fig.1) is the easiest to recognize. The right ventricle is closest to the chest wall and anterior to the left ventricle and its coarser trabeculations and the moderator band are landmarks. The tricuspid valve is seen to insert more apically than the mitral valve. Pulmonary venous connections to the left atrium can also be identified from this view as well as the flap of the foramen ovale as it moves within the left atrium. Cranial angulation of the transducer shows the aortic root leaving the left ventricle, and by moving the transducer to the sternomanubrial junction the aorta can be seen wedged between the right and left atria to give the aortic wedge plane (Allan et al., 1980).

Finally, by tilting the transducer toward the right shoulder the left ventricular long-axis plane (Fig 2) is achieved. The right ventricle is seen anteriorly and the origin of the aortic root from the left ventricle. The anterior wall of the aorta is seen to be continuous with the interventricular septum and the posterior wall with the anterior leaflet of the mitral valve.

In the longitudinal axis the tricuspid-pulmonary plane will identify the right atrium with its connection to the inferior and superior vena cavae, the tricuspid valve connected to the right ventricle, and the pulmonary valve which is anterior and cranial to the aortic root. The ductus plane obtained by oblique sagittal angulation reveals the pulmonary trunk sweeping posteriorly and, via the ductus arteriosus, connecting with the descending aorta (Fig. 3). The aortic root is seen as a circle in this view. Further sagittal angulation shows the aortic arch, with vessels to the head and neck (Fig. 4) which can be traced to the descending aorta. Scanning to the left of the sternum reveals the left ventricle seen in short axis, with the right ventricular outflow tract and pulmonary valve arching over in an anterior position (Fig. 5).

### *Comments*

Achievement of the above-mentioned scanning planes allows the diagnosis of normal atrioventricular and arterial connections. Failure to identify the structures normally seen in these views is suspicious for abnormality. A normal four-chamber scan excludes hypoplasia of the right or left ventricle, absence of an atrioventricular connection, and various atrioventricular defects. Aortic and pulmonary atresia or truncus arteriosus can be excluded by visualization

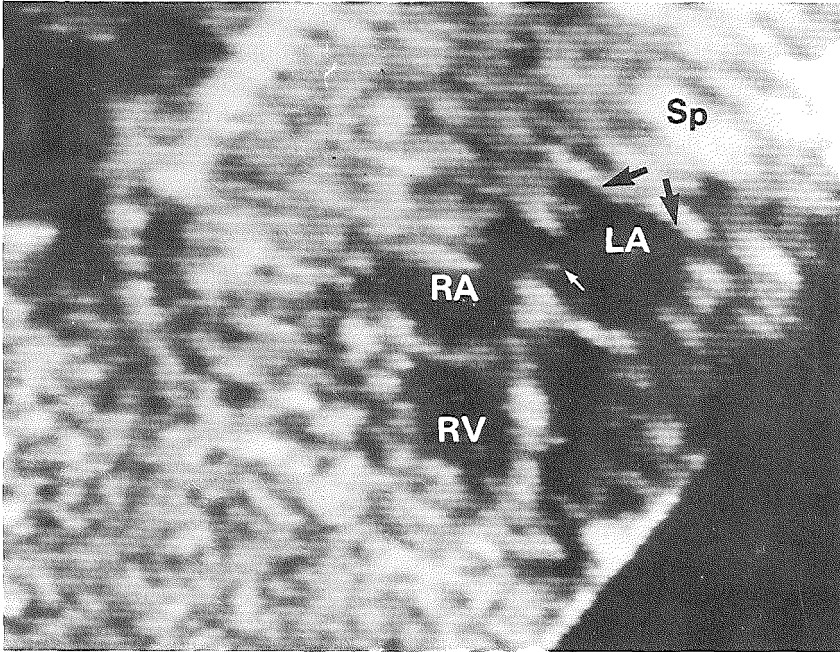


Fig.1. Normal four-chamber view. SP=fetal spine, RA=right atrium, LA=left atrium, RV=right ventricle, small arrow=part of foramen ovale mechanism, large arrows=pulmonary veins.

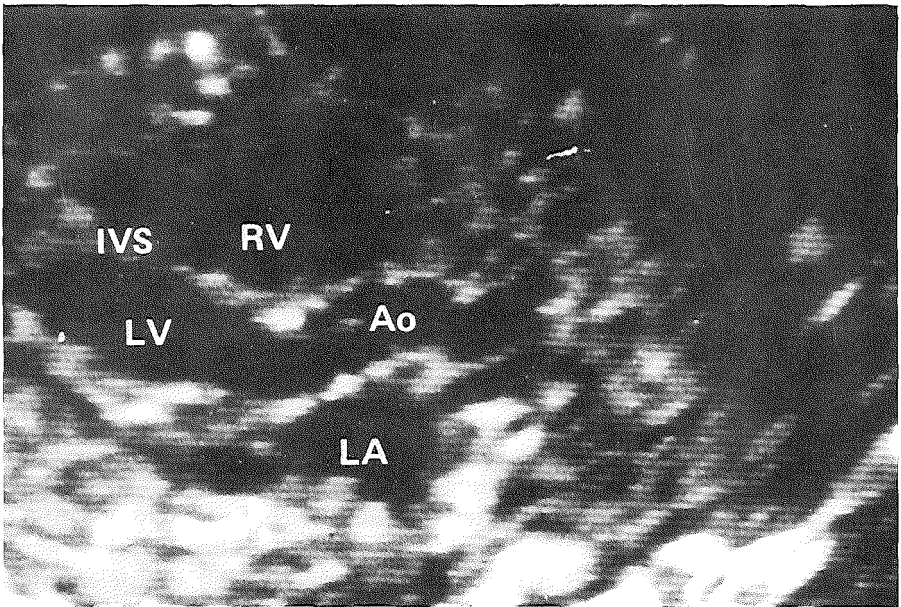


Fig.2. Normal left ventricle long-axis view. RV=right ventricle, LV=left ventricle, IVS=interventricular septum, Ao=aortic root, LA=left atrium.



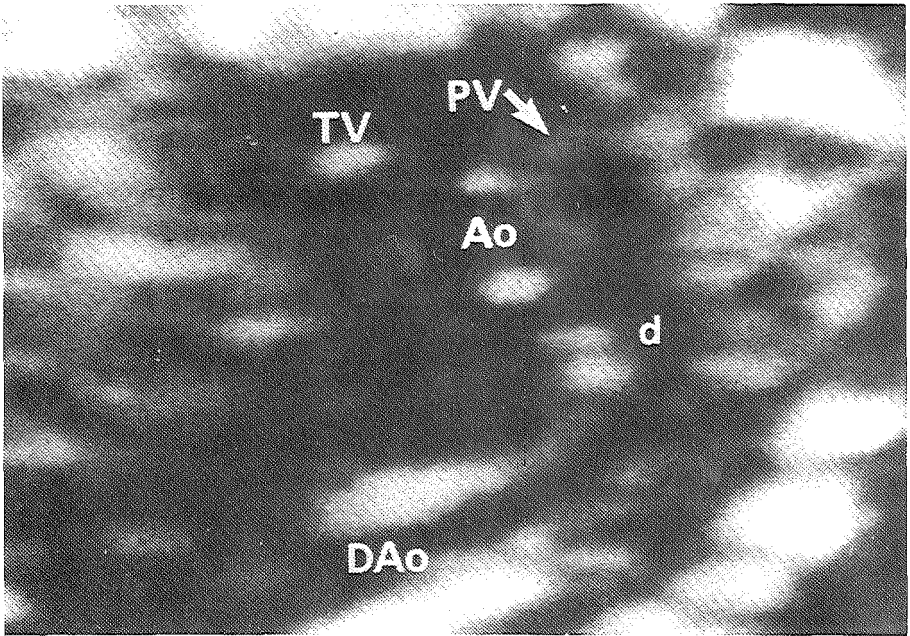


Fig.3. Normal ductus view. TV=tricuspid valve, PV=pulmonary valve, Ao=aortic root, d=ductus arteriosus, DAo=descending aorta.

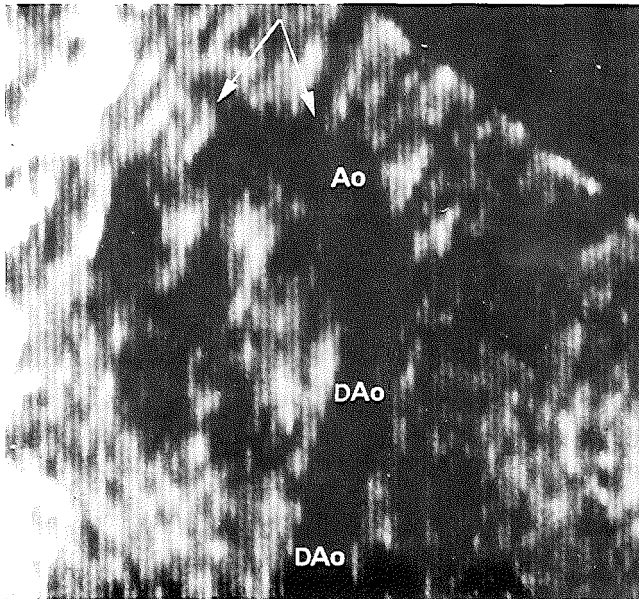


Fig.4. Normal aortic arch view. In this still-frame the spine is to the right. Ao=aortic arch, DAo=descending aorta, arrows=arteries to head and neck.

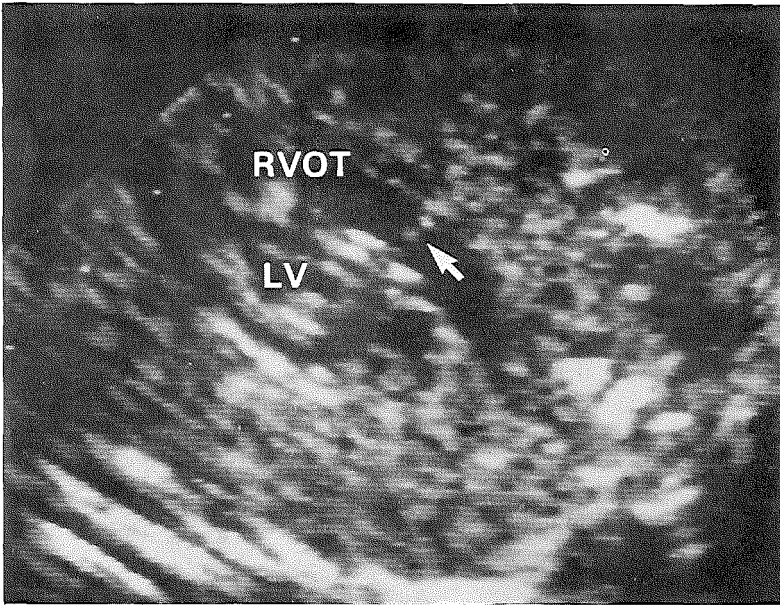


Fig.5. Normal short-axis left ventricular view. LV=left ventricle, RVOT=right ventricular outflow tract. Arrow indicates closed pulmonary valve in this frame.

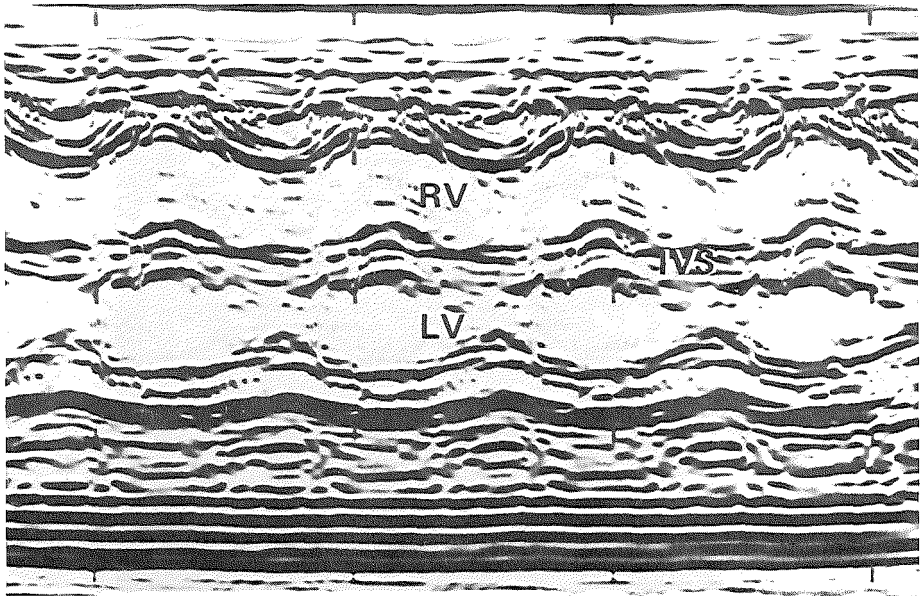


Fig.6. M-mode recording through the fetal right ventricle (RV) and left ventricle (LV), IVS=interventricular septum.

of normal aortic root, pulmonary trunk, and ductus views. The aortic arch view may exclude hypoplasia of the aortic isthmus although coarctation of the aorta may be missed if the ductus is situated in front of the aorta.

It is possible to establish normal cardiac anatomy in the fetus, thereby excluding major congenital cardiac malformations. Mild degrees of stenosis or obstruction to ventricular outflow tracts, or small atrial or ventricular septal defects may be missed due to the inherent limitations of this technique.

### *Fetal Cardiac Geometry and Function*

With the introduction of the real-time ultrasound scanners with high-image quality and the introduction of time-motion (M-mode) recording systems, it also became possible to study the various geometric and functional aspects of the human fetal heart. Most reports in literature on fetal cardiac geometry and function are based on the results from M-mode studies (Allan et al., 1982; Baars et al., 1977; Hobbins et al., 1978; Sahn et al., 1980; Wladimiroff and McGhie, 1981a; Wladimiroff et al., 1979, 1982). The examination procedure which was followed in our own studies has been described in detail elsewhere (Wladimiroff and McGhie, 1981a, b). In short, a cross section through the left and right ventricle, at right angles through the interventricular septum at or just below the level of the mitral and tricuspid valve leaflets is obtained (Fig. 6), depicting the left and right ventricle (LV and RV), the interventricular septum (IVS), the left ventricular posterior wall, and the right ventricular anterior wall. From each M-mode recording 10 consecutive cardiac cycles are included in the measurements of the left and the right ventricular transverse diameter and thickness of the interventricular septum (IVS) in millimeters in the end-diastolic (ED) and end-systolic (ES) phase of the cardiac cycle. The transverse diameter is measured from the endocardial surface of the right ventricular anterior wall and left ventricular posterior wall, respectively. The ED phase of the cardiac cycle is determined by the largest, the ES phase by the smallest measurement of this particular diameter.

### *Left and Right Ventricular Transverse Diameter*

Figures 7 and 8 demonstrate the data distribution of the transverse diameter of the left ventricle in end-diastolic (ED) and end-systolic (ES) phase of the cardiac cycle against gestational age and the linear regression line in 193 normal pregnancies between 28 and 40 weeks of gestation (Vosters, 1983). There is a linear increase in the transverse diameter of the left ventricle both in the ED ( $p < 0.001$ ) and ES phase ( $p < 0.001$ ) of the cardiac cycle. Figures 9 and 10 show the transverse diameter of the right ventricle in ED and ES phase of the cardiac cycle.

Here also, a linear increase in the transverse diameter can be observed (ED and ES;  $p < 0.001$ ). The ratio between the right and the left ventricular transverse

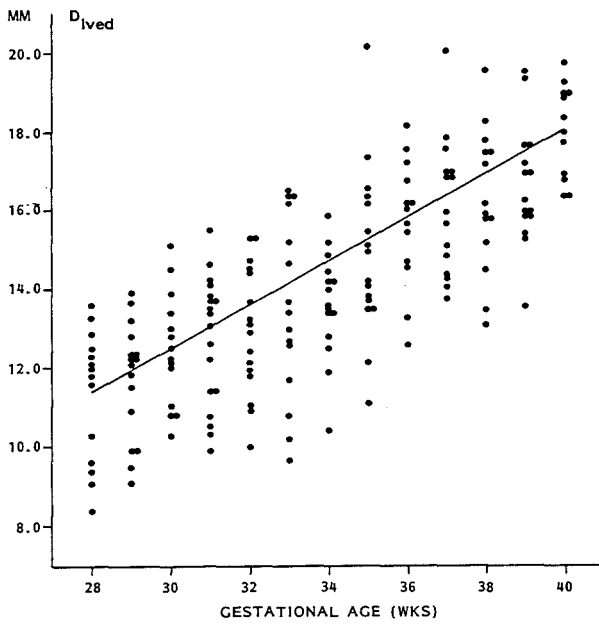


Fig.7. Normal values and linear regression line for the left ventricular diameter (ED) in the antenatal study (D<sub>lved</sub>).

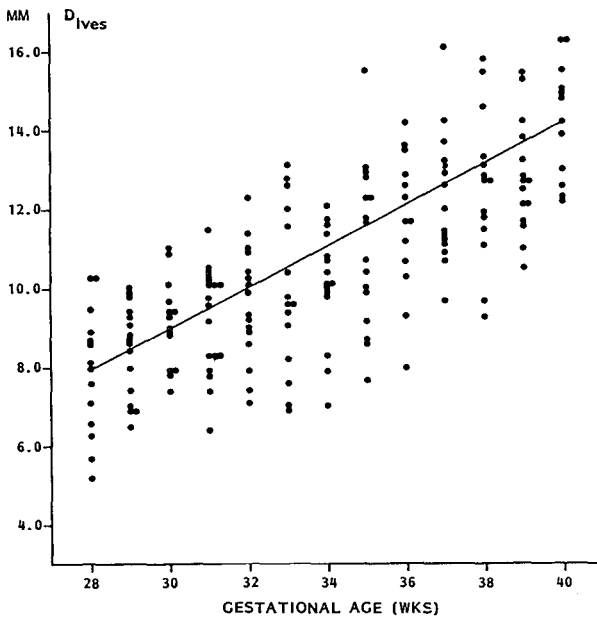


Fig.8. Normal values and linear regression line for the left ventricular diameter (ES) in the antenatal study (D<sub>lves</sub>) (Vosters, 1983).

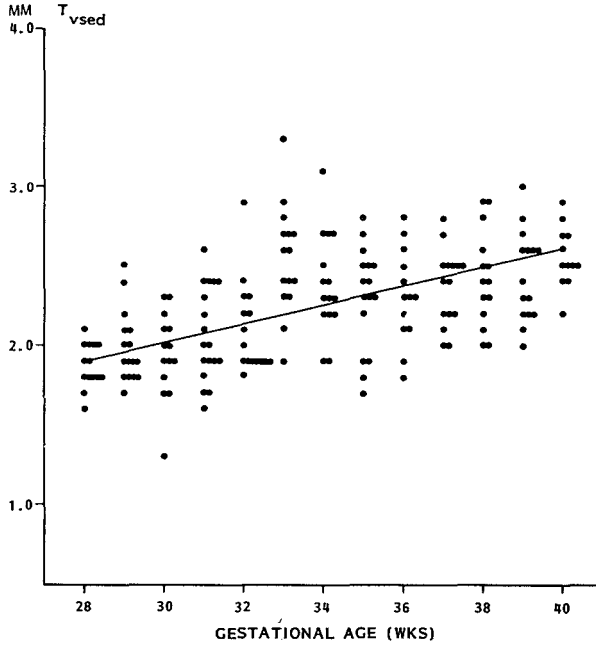


Fig.9. Normal values and linear regression line for the right ventricular diameter (ED) in the antenatal study (Drved) (Vosters, 1983).

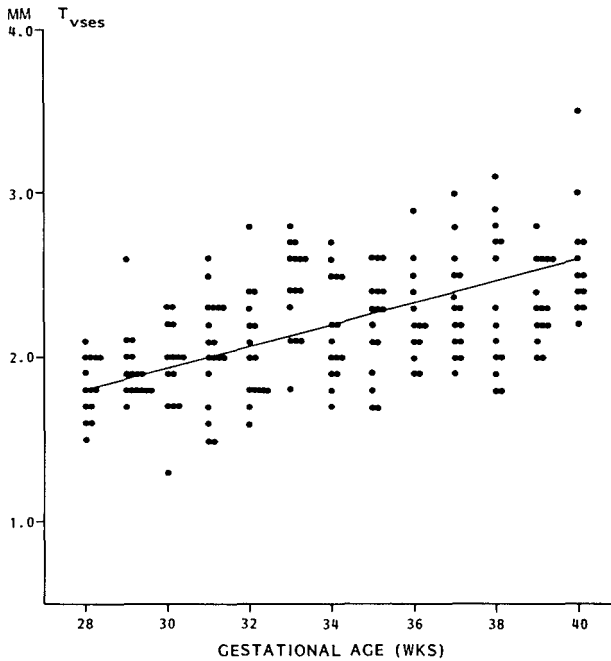


Fig.10. Normal values and linear regression line for the right ventricular diameter (ES) in the antenatal study (Drves) (Vosters, 1983).

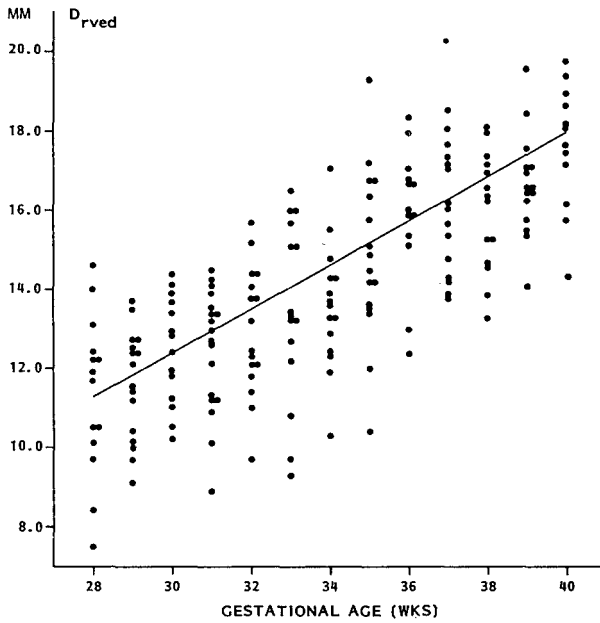


Fig.11. Normal values and the linear regression line for the interventricular septal thickness (ED) in the antenatal study (Tvsed) (Vosters, 1983).

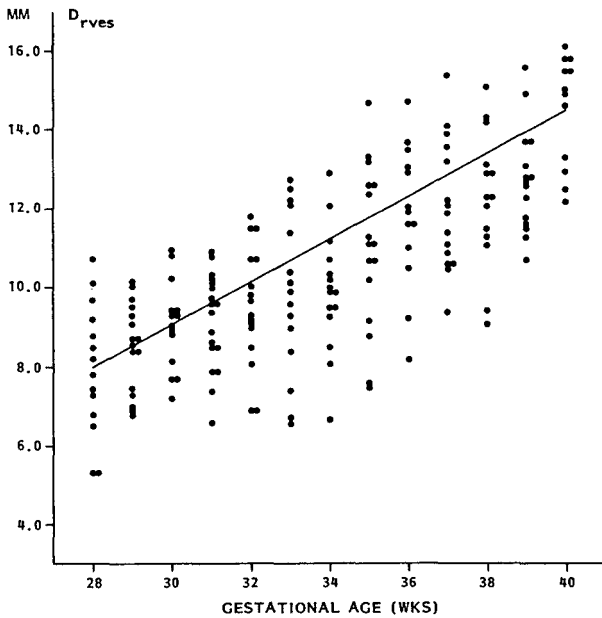


Fig.12. Normal values and the linear regression line for the interventricular septal thickness (ES) in the antenatal study (Tvses) (Vosters, 1983).

diameter at corresponding moments in the cardiac cycle showed no significant change between 28 and 40 weeks of gestation. For the entire antenatal study period the mean right-to-left ventricular ratio was  $1.0 \pm 0.04$  both during ED and ES. The change in the interventricular septal thickness depicts a linear increase, both in ED and ES (Figs. 11 and 12;  $p < 0.001$ ).

### *Comments*

Only a limited number of reports is available on cardiac ventricular geometry in the human fetus. Published data were either obtained from a compound-B scanner, a two dimensional real-time system, or from time-motion (T-M) recordings. Comparison of the results derived from these three different methods is difficult, particularly since the compound-B scanning technique must be considered less accurate with regard to the delineation of the endocardial lining of both ventricles and the definition of the end-diastolic and end-systolic phase of the cardiac cycle. The low success rate in the studies by Garrett and Robinson (1970) and Winsberg (1972) is understandable in light of the less developed equipment available at the time. However, even with present real-time equipment, an antenatal success rate of only 72% (Sahn et al., 1980) and 78% (Vosters, 1983) had to be accepted. Whereas Winsberg (1972), Allan et al. (1982), and ourselves (Vosters, 1983; Wladimiroff et al, 1979) have carried out measurements from the long-axis view of the fetal heart at the level of the mitral valve leaflets, Sahn et al. (1980), as well as Garrett and Robinson (1970) studied left and right ventricular geometry from 4-chamber views. It is not surprising that with differences in equipment, scanning planes, and periods of pregnancy during which the measurements were made, the results have been variable.

The left-to-right ventricular relationship has been studied extensively. It seems that the two ventricles are of equal thickness in midgestation, but that there is a slight right ventricular preponderance at term (Hort, 1955, 1966; Emery and MacDonald, 1960; Recavarren and Arias-Stella, 1964). Emery and Mithal (1961) reported a mean weight of the left ventricle at birth of  $5.7 \pm 1.1$  g (1 SD) and of the right ventricle  $6.3 \pm 1.4$  g (1 SD). Keen (1955) and Hort (1966) used only the free walls of the ventricles. Keen concluded that both ventricles were of approximate equality at term, whereas Hort found the left ventricle to be smaller. The difference was ascribed to a difference in the plane of section. Hort also concluded that at birth the external surface of the right ventricular wall was larger than the left. From our data on interventricular septal thickness it appears that during the antenatal period there is no significant difference in septal thickness between end-diastolic and end-systolic phase of the cardiac cycle. The increase in septal thickness from 28 to 40 weeks of gestation was 33% (ED) and 32% (ES), respectively. Comparable data on septal thickness are only available from two other studies. In one study carried out in the human fetus (Allan et al, 1982), slightly higher septal thickness values were found. The number

of observations between 28 and 40 weeks was, however, much smaller ( $n=42$ ) than that in our study. In another study in fetal dogs (Williams et al, 1978) near term values of  $2.08 \pm 0.27$  mm (1 SD) at aortic level and  $2.83 \pm 0.40$  mm (1 SD) at midventricular wall level were found. This implies that septal thickness varies considerably with respect to the level at which the measurement is carried out. Antenatal information on septal development was also obtained from weight studies in the human fetus, in which the septum was either kept separate (Keen, 1955) or allotted between the left and right ventricle in proportion to their respective weight (Herrmann and Wilson, 1922; Lewis, 1914; Muller, 1883). Anatomical studies (Fulton et al., 1952; Keen, 1955) have shown that the septum in its increase follows the free wall of the left ventricle closely and is not influenced by the behavior of the right ventricular free wall. Hislop and Reid (1972) also found that the septum grew with the left ventricle rather than with the right, supporting the findings of the two previous investigators. However, this does not mean that the septum, by its contraction, does not assist the right and left ventricle. From these studies it also appeared that the increase in interventricular septal weight during the third trimester of pregnancy is approximately 200-250%. At term the weight of the septum averaged about 18% of the total ventricular weight.

### *Left Ventricular Volume*

Wladimiroff and McGhie (1981a) developed a method for estimating left ventricular volume from two-dimensional images. The largest longitudinal and transverse diameter of the left ventricle were measured during ED and ES by means of a computer-linked light pen system. Based on the assumption that the anteroposterior axis of the left ventricle, which could not be measured, is equal to the transverse axis and the shape of the left ventricle is approaching a prolate ellipsoid, an estimation of left ventricular volume ( $Q_{lv}$ ) can be made. The results showed that in the third trimester of pregnancy, the longitudinal-to-transverse axis ratio of the left ventricle is  $1.75 \pm 0.1$  (1 SD) during the ED phase and  $1.90 \pm 0.1$  (1 SD) during the ES phase of the cardiac cycle. From the above, it was decided to multiply the transverse diameter on the fetal left ventricle measured from M-mode recordings by 1.75 during ED and by 1.90 during ES in order to obtain an estimate of the longitudinal axis of the left ventricle. There is a curvilinear increase in left ventricular volume ( $Q_{lv}$ ), both during the end-diastolic ( $Q_{lved}$ ; Fig.13) and end-systolic phase ( $Q_{lves}$ ; Fig. 14) of the cardiac cycle. The  $Q_{lved}$  rose from 1.5 ml and  $Q_{lves}$  from 0.7 ml at 28 weeks to 5.6 ml and 2.8 ml, respectively, at 40 weeks of gestation ( $p < 0.001$ ).

### *Comments*

Assessment of volume was restricted to the left ventricle, since no information



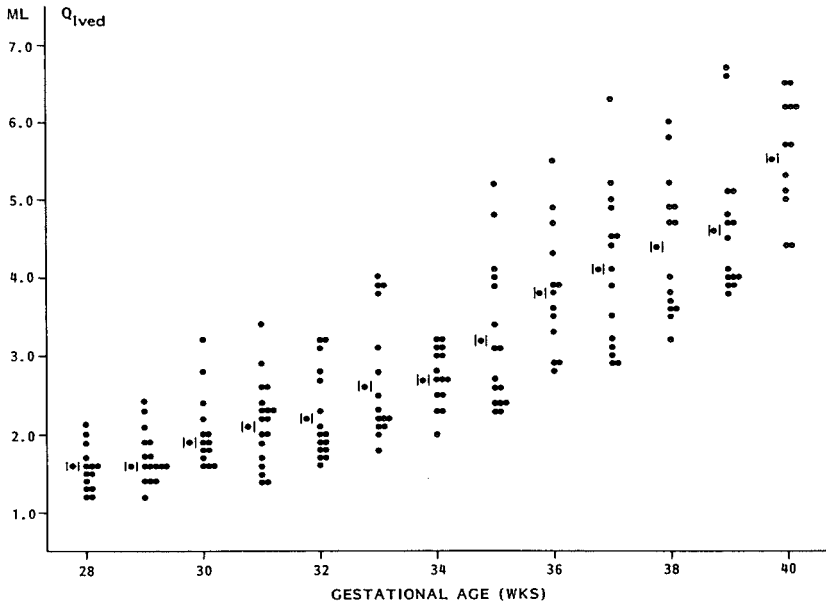


Fig.13. Normal values (.=mean) for left ventricular volume (ED) in the antenatal study ( $Q_{1ved}$ ) (Vosters, 1983).

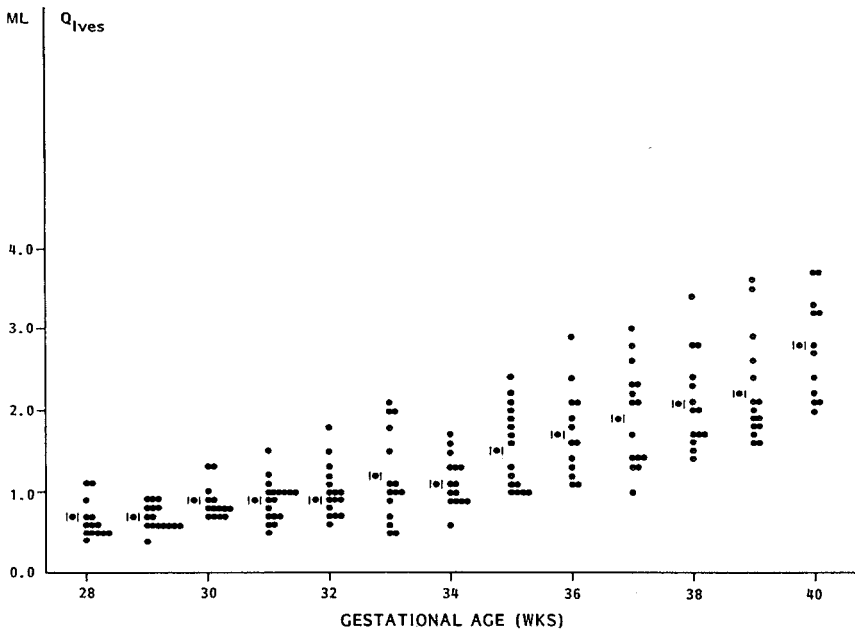


Fig.14. Normal values (.=mean) for left ventricular volume (ES) in the antenatal study ( $Q_{1ves}$ ) (Vosters, 1983).

could be obtained on the longitudinal axis of the right ventricle on the same long-axis plane. For the calculation of left ventricular volume during the end-diastolic and end-systolic phase of the cardiac cycle, assumptions were made for the shape of the left ventricle as well as for the relationship between the transverse and anteroposterior diameter of the ventricle. The theoretical basis for the prolate ellipsoid shape of the left ventricle was originally derived from angiographic studies in the adult (Davila and Sanmarco, 1966; Dodge et al., 1960; Hermann and Bartle, 1968). Later studies of our own based on human fetal autopsy specimens support this approach. It is clear that, based on the previous assumptions, the values for left ventricular volume presented here should only be considered to be an approximation rather than a true representation of that ventricular volume. Verification of our data was not possible due to the absence of comparative studies in the literature.

### *Left Ventricular Stroke Volume (Qlvs) and Output (Q'lv)*

The difference between left ventricular volume in the end-diastolic (Qlved) and end-systolic (Qlves) phases of the cardiac cycle represents left ventricular stroke volume (Qlvs). Likewise left ventricular volume (Qlv), Qlvs demonstrated a curvilinear increase during the last trimester of pregnancy (Fig. 15). The mean Qlvs value for each week of pregnancy was therefore presented. Mean Qlvs rose from 0.9 ml at 28 weeks to 2.8 ml at 40 weeks of gestation ( $p < 0.001$ ). Left ventricular output (Q'lv) was calculated from the product of stroke volume and heart rate. Mean Q'lv increased in a curvilinear fashion from 125 ml/min at 28 weeks to 391 ml/min at 40 weeks of gestation ( $p < 0.001$ ; Fig. 16). In 19 patients fetal Q'lv measurements were carried out within 7 days of delivery, allowing calculation of fetal Q'lv per kg body weight. A mean volume of  $126 \pm 11$  ml/kg/min was found.

### *Comments*

In our own study both fetal Qlves and Q'lv showed a threefold increase during the third trimester of pregnancy. In Fig. 17 both mean Q'lv values and 50-percentile fetal weight values for male infants of primigravida (Tables of Kloosterman, 1970) have been plotted against gestational age. From this figure it can be seen that Q'lv parallels fetal weight with advancing gestation. Similar observations were made in the fetal lamb between 60 and 147 days of gestation (Rudolph and Heymann, 1970). Considerable data are available on the actual ventricular output per kg fetal body weight from fetal lamb studies. Comparison of these data and our own is difficult because of the different techniques used. Initially, measurements were carried out under acute circumstances in the fetal lamb exteriorized from the uterus with umbilical-placental blood flow maintained (Assali et al., 1965; Dawes et al., 1954; Mahon et al., 1966; Rudolph et al.,

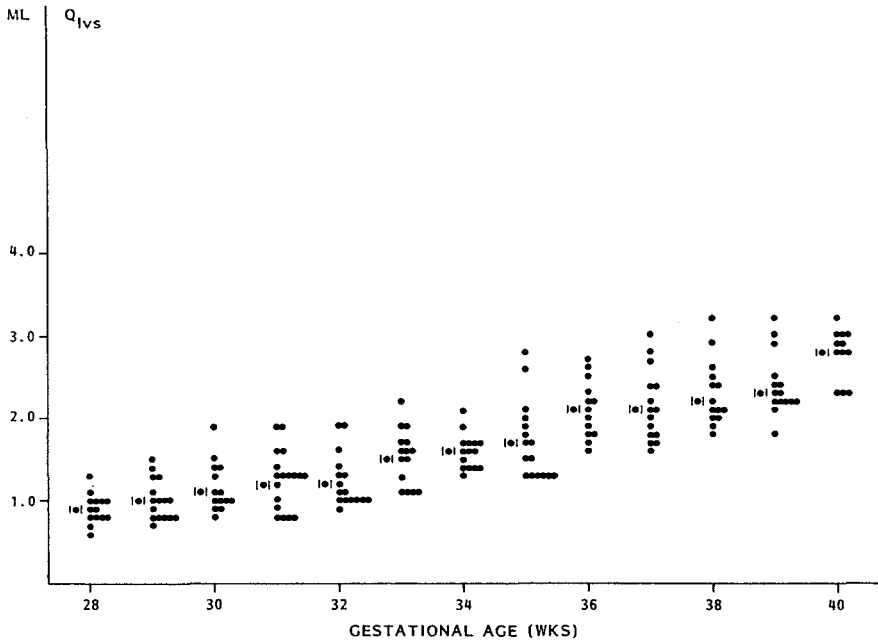


Fig.15. Normal values (.=mean) for the left ventricular stroke volume ( $Q_{lvs}$ ) in the antenatal study (Vosters, 1983).

1967). Combined ventricular output measurements have been done by either the Fick method, indicator dilution curves, or electromagnetic flow transducers. It is obvious that exteriorization of the fetus from its intrauterine environment will result in a progressive fall in umbilical blood flow. Chronically instrumented fetal lambs which were kept in utero offered data which could be considered nearer the physiological situation (Anderson et al., 1981; Rudolph and Heymann, 1977). Only two ultrasonic studies on fetal ventricular output have been reported in the literature (Winsberg, 1972; Wladimiroff and McGhie, 1981a). Obviously ultrasound, being a noninvasive technique, provides only indirect information on cardiac function. On the other hand, because of its noninvasiveness it is the only technique allowing assessment of cardiac function in the human fetus under entirely physiological circumstances.

Left ventricular output in the fetal lamb varies between 97 (Assali et al., 1975) and 250 ml/kg/min (Kirkpatrick et al., 1973). The ultrasonically determined  $Q'_{lv}$  values range between 109 (Winsberg, 1972) and 126 ml/kg/min (Vosters, 1983). Right ventricular output also showed a large variation from 138 (Assali et al., 1965) to 327 ml/kg/min (Fixler et al., 1973). This high value reported by Fixler and co-workers may be the result of a decreased right-to-left shunt due to a rise in left atrial pressure. This may be determined by

the geometric influence of the flow probes on the left side of the heart. In a number of fetal lamb studies, only combined ventricular output values were presented. Combined ventricular output was calculated as being as low as 235 ml/kg/min (Assali et al., 1965) and as high as 1080 ml/kg/min (Rudolph et al., 1967). Another striking detail in these fetal ventricular output studies is the difference of opinion on the contribution of each ventricle to the total output. Right-to-left ventricular output relationship varied from equal (50-50%; Mahon et al., 1966) to left ventricular preponderance (45-55%; Dawes et al., 1954), or right ventricular preponderance (60-40% by Anderson et al., 1981 and 67-33% by Rudolph et al., 1974). Based on these relationships and a mean  $Q'lv$  value of 126 ml/kg/min in our study, total ventricular output may be as low as 229 ml/kg/min and as high as 382 ml/kg/min. An estimation of the right-to-left ventricular relationship in humans will not be known until similar studies on right ventricular cardiac output by ultrasound have been carried out. However, from blood flow studies in the fetal descending aorta by others and ourselves, there seems to be some indication that there is some degree of right ventricular preponderance in the human fetus (Tonge et al., 1983).

#### *Left and Right Ventricular Preejection Period*

Another means of expressing cardiac function is measurement of the preejection period (PEP), which is determined by the myocardial contractility and the loading conditions of the heart, that is the end-diastolic ventricular pressure and end-diastolic aortic pressure. In the human fetus the PEP is calculated as the interval between the Q wave in the maternal abdominal lead fetal ECG and the opening of the aortic valve as recorded by Doppler ultrasound (Evers et al., 1982; Murata et al., 1978). The PEP demonstrates a significant positive relationship with gestational age (Evers et al., 1982; Murata et al., 1978; Wolfson et al., 1977). Evers et al. (1982) noted that the increase in PEP duration was nearly identical to the rate of increase in QRS duration with gestational age. This suggests the prolongation of the time required for electrical activation to be responsible for the lengthening of the PEP. These authors also found that the PEP in fetuses who showed spontaneous or late decelerations on the day of measurement were at or below the 10th percentile of the controls. Both prolonged (Murata et al., 1978) and shortened (Organ et al., 1974) PEP values have been found during periods of fetal distress. According to Evers et al. (1982) this discrepancy can be explained by the fact that under conditions of impending or early fetal distress the PEP initially becomes prolonged, but with further deterioration of the fetal condition a shortening of the PEP occurs. The true predictive value of the PEP as an early antepartum indicator of developing fetal distress has not been established yet.

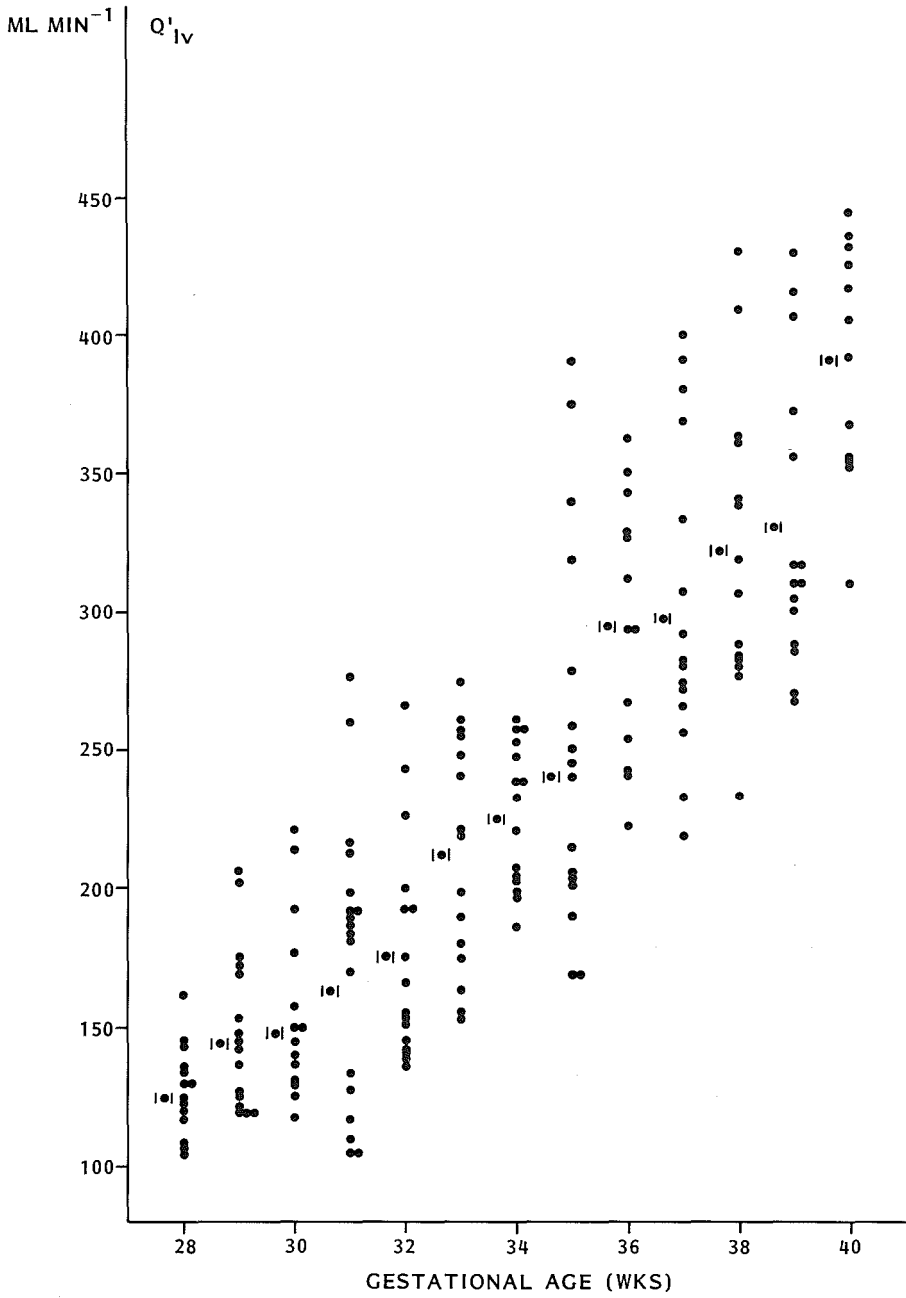


Fig.16. Normal values (.=mean) for the left ventricular output ( $Q'_{lv}$ ) in the antenatal study (Vosters, 1983).

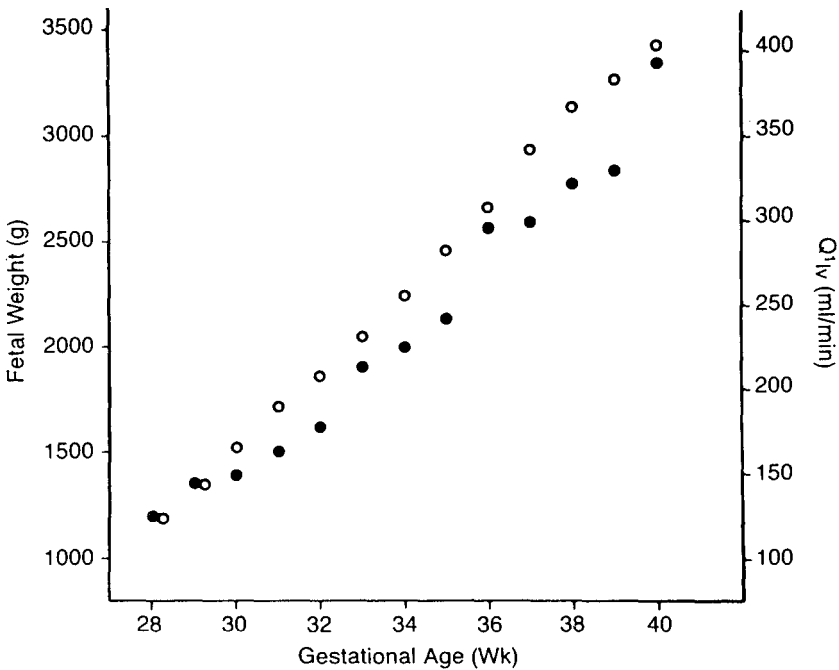


Fig.17. Relationship between (●) birth weight (50th percentile values for male infants of primigravida according to Tables of Kloosterman, 1970) and (○) left ventricular output (Q'lv) (mean values) (Vosters, 1983).

### *Prenatal Diagnosis of Cardiac Structural Abnormalities and Dysrhythmias*

Increasing attention has been paid to the prenatal diagnosis of fetal congenital heart disease and cardiac dysrhythmias by means of two-dimensional real-time ultrasound (Allan et al., 1981; Filkins et al., 1981; McCallum et al., 1981; Stewart et al., 1983a, b) and M-mode recordings (Kleinman et al., 1980; Stewart et al., 1983b; Wladimiroff et al., 1981). The indications in our ultrasonic unit for structural analysis of the fetal heart are listed in Table I. As has been stated previously, evaluation of the fetal heart is preferably done between 16 and 24 weeks of gestation since then the heart is large enough for two-dimensional examinations and there is a comparatively large amniotic fluid compartment, which serves as an excellent transmission medium for the ultrasound beam, resulting in optimal images of the various fetal soft tissue structures (e.g., the heart). Between January 1, 1982 and October 31, 1983 a total of 444 patients was referred to our department for ultrasonic analysis of fetal cardiac structure. The total number of examinations was 880, which means that nearly each patient underwent 2 examinations. Of these patients, 70% were referred to our unit because of an increased risk of fetal cardiac structural abnormality; the remaining

Table I Indications for fetal structural cardiac examinations by ultrasound.

## Hereditary predisposition

## Fetal

Severe growth retardation

Dysrhythmia

Polyhydramnios

Ascites

## Maternal

Age above 40 years

Diabetes

Exposure to cardiac teratogens

Exposure to rubella or other viruses in early gestation

Connective tissue disorder

30% were referred because of an abnormal ultrasonic observation in the present pregnancy such as fetal ascites, severe growth retardation, polyhydramnios, dysrhythmia, or presence of other structural abnormalities such as omphalocele. The antenatal detection of structural cardiac abnormalities is becoming of major importance, since often the structural abnormality will be amenable to surgery. Antenatally, this may lead to both adjustment of obstetric measurement and mode of delivery. The neonatologist and pediatric cardiologist should be informed in order to assure a smooth and efficient transfer of the affected fetus from the delivery room to the pediatric cardiology unit. In some cases, however, the abnormality is not compatible with life. This may result in the parents opting for termination of pregnancy or avoidance of any obstetric intervention depending on the pregnancy duration.

Table II demonstrates the 13 correctly diagnosed cardiac structural abnormalities; Figures 18 and 19 depict 2-D real-time images of patients 4 and 13. There were 3 false positive and 3 false negative findings (Table III). We examined 40 patients with fetal cardiac dysrhythmias. In this group the ultrasonic examination included not only an overall assessment of fetal size and structure, placental location, and amount of amniotic fluid, but also a search for cardiac structural defects and possible signs of cardiac compromise, such as pericardial effusion, increase in right heart size, and ascites. The type of fetal dysrhythmia was analyzed by means of M-mode recordings of atrial and ventricular rate and rhythm and supra-abdominal fetal electrocardiogram (Figs. 20 and 21). Finally, the effect of fetal cardiac dysrhythmia on blood flow was assessed by means of pulsed Doppler measurements of blood flow in the fetal descending aorta. Table IV depicts the types of dysrhythmia and the incidence (15%) of structural cardiac defects in this particular group. Three types of dysrhythmias were observed: ectopic beats (n=25), tachycardia (above 180 beats/min, n=6), and bradycardia (below 100 beats/min, n=9). The ectopics were usually supraventricular and disappeared before or shortly after birth. In one case ventricular extrasystoles were seen. In two cases associated cardiac structural abnormality was diagnosed. Bradycardia was diagnosed as complete atrioventricular (A-V) block in 6 cases,

Table II *Structural abnormalities detected*

	Gestational age (wks)
1. Univentricular AV connection (single LV), concordant arterial connections with subpulmonary stenosis, atrial isomerism, CCHB	20
2. Ectopia cordis, DORV, VSD + hypoplastic LV	22
3. ASD (Holt-Oram syndrome)	23
4. Complete atrioventricular septal defect	27
5. Incomplete atrioventricular septal defect	27
6. VSD + omphalocele (trisomy 18)	28
7. Complete AVSD, atrial isomerism, CCHB, tetralogy of Fallot	29
8. Double outlet right ventricle (trisomy 13)	30
9. Univentricular heart + coarctation	30
10. Coarctation aorta + abnormal tricuspid valve	33
11. Tetralogy of Fallot, VSD, primum septum not identified, dysplasia of AV valves (trisomy 18)	34
12. VSD (trisomy 18)	35
13. Obstruction at foramen ovale level	36

Table III False positive and false negative findings

False positive	1x TGA (positional) 1x Ventricular inversion (positional) 1x 2° Atrial septal defect (positional)
False negative	1x Trabecular ventricular septal defect 1x Perimembranous ventricular septal defect 1x Coarctation aorta

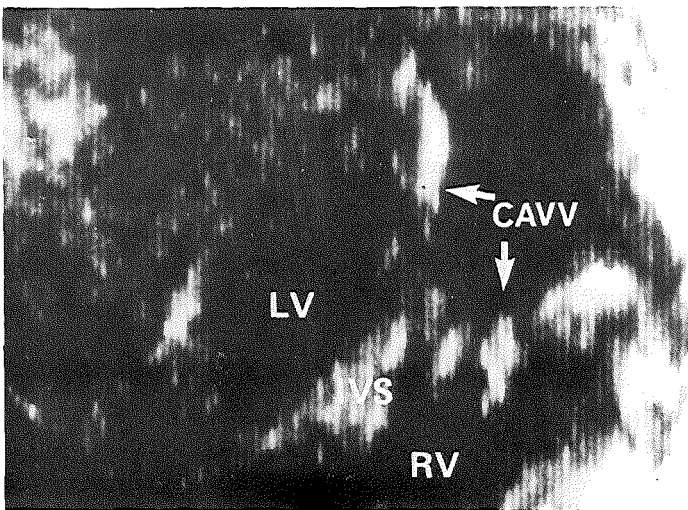


Fig.18. Four-chamber view in a fetus with complete atrioventricular septal defect. LV=left ventricle, RV=right ventricle, IVS=interventricular septum, CAVV=common atrioventricular valve.



Table IV Dysrhythmia and cardiac structural defects

Type of dysrhythmia	No of patients	Cardiac structural defect
Ectopic beats	25	2
AV block	6	2
Tachydysrhythmias	6	—
Bradycardia	3	2
Total	40	6 (15%)

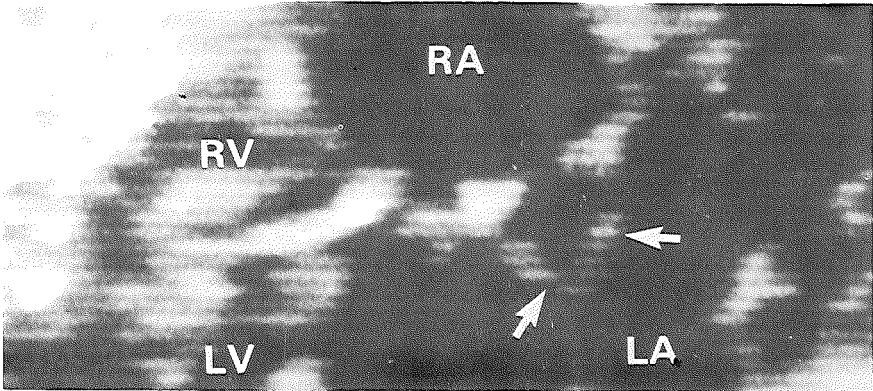


Fig.19. Four-chamber type view with foreshortening of the right and left ventricles (RV and LV) to bring the right and left atria (RA and LA) more clearly into view. Arrows indicate obstructive structure at level of foramen ovale. In real-time images the RA and RV were dilated and there was paradox motion of the interventricular septum.

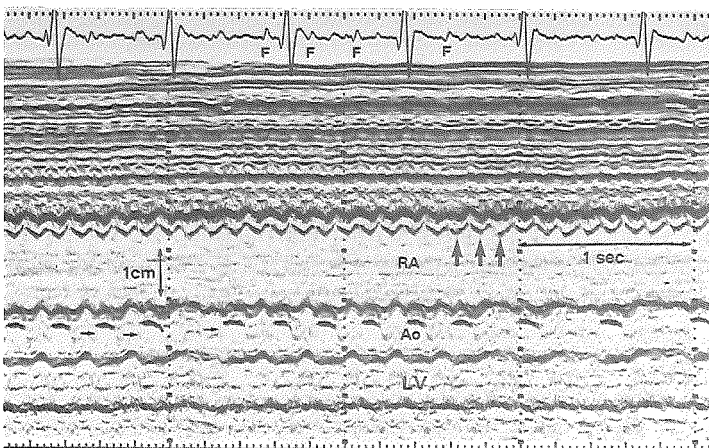


Fig.20. M-mode recording showing atrial flutter at 480 beats/min with variable conduction. F=fetal QRS complex, RA=right atrium, Ao=aortic root, LV=left ventricular-left atrial junction. Heavy arrows indicate rapid regular contractions of the right atrial wall; small arrows indicate opening of the aortic valve.

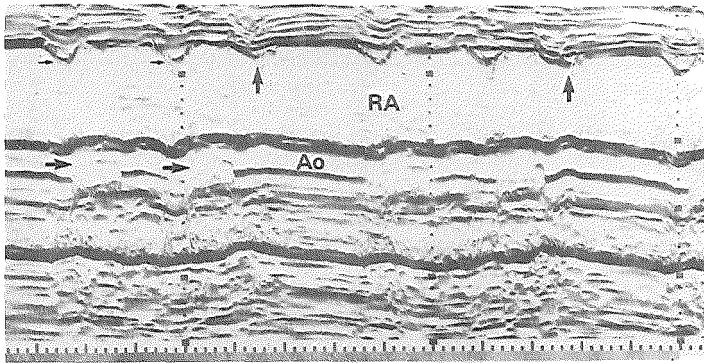


Fig.21. M-mode recording showing probable supraventricular ectopics. RA=right atrium, Ao=aortic root. Arrows indicate a premature movement of the right atrial wall which does not appear to be followed by opening of the aortic valve (small arrows).

second degree A-V block in one case, probable mild sinus bradycardia in one case. In the remaining patient the cause was unclear. Bradycardia was associated with a structural cardiac abnormality in 4 out of 9 patients. Tachycardia was established as paroxysmal supraventricular tachycardia with spontaneous resolution in the 32nd week of pregnancy in one case, atrial flutter with variable A-V conduction in 5 cases. Cardioversion of the tachy-dysrhythmia by means of maternal administration of 0.75 mg digitalis per day was unsuccessful in three cases.

### *Comments*

The majority of the cardiac defects in Table II were diagnosed fairly late in pregnancy (i.e., late 2nd and 3rd trimester). The reason for this is that nearly all patients were referred for abnormal obstetric findings secondary to the cardiac defects such as polyhydramnios and fetal growth retardation. These problems usually develop late in pregnancy.

Another important observation is the high number of chromosomal abnormalities (30%), in particular, trisomy-13 and 18 in conjunction with structural cardiac defects. Since these particular fetuses also displayed severe growth retardation, it is advised to perform amniocentesis for karyotyping in all cases which display both growth retardation and a cardiac defect.

In total, three cardiac defects were missed (i.e., coarctation aorta once and a ventricular septal defect twice). Particularly the first abnormality will remain difficult to diagnose since the classic location of the coarctation is behind the ductus arteriosus, which during fetal life is wide open thus hiding any defect behind it. The three false-positive observations were due to (1) abnormal position

of the fetal heart as a result of fetal ascites and hydrothorax, severe scoliosis, and omphalocele; (2) a variant of a normal atrial septum.

Since the fetal electrocardiogram monitors ventricular depolarization, but usually not atrial depolarization, the use of combined 2-D real-time and M-mode echocardiography should now be considered the most useful means for diagnosing abnormalities of cardiac rhythm and function. Our data indicate that a diagnosis of fetal dysrhythmia should always be followed up by careful structural analysis of the fetal heart.

Whereas there have been a number of reports of successful fetal cardioversion by administration of various medications via the mother, with digitalis being the most commonly used (Dumesic et al., 1982; Harrigan et al., 1981; Kerenyi et al., 1980), we failed to cardiovert three cases of tachydysrhythmia.

The main reason for this failure is most likely the relatively low doses of digoxin administered to the mother under the given circumstances. Higher dosages are probably needed in order to reach therapeutic levels in the fetus.

The clinical use of ventricular function studies described earlier in this paper has been until now limited. New developments may be expected through combining cardiac structural and functional studies with blood flow studies in the fetal descending aorta. Documentation of such a fetal cardiovascular profile will undoubtedly further deepen our insight into cardiac physiology and pathophysiology of the unborn infant.

## References

- Allan LD, Tynan MJ, Campbell S, Wilkinson JL, Anderson RH: Echocardiographic and anatomical correlates in the fetus. *Br Heart J* 44, 444-452 (1980).
- Allan LD, Tynan MJ, Campbell S, Anderson RH: Normal fetal cardiac anatomy; a basis for the echocardiographic detection of abnormalities. *Prenatal Diagn* 1, 131 (1981).
- Allan LD, Joseph MC, Boyd EGCA, Campbell S, Tynan MJ: M-mode echocardiography in the developing human fetus. *Br Heart J* 47, 573-583 (1982).
- Anderson DF, Bissonnette JM, Faber JJ, Thornburg KL: Central shunt flows and pressures in the mature fetal lamb. *Am J Physiol* 241, 60 (1981).
- Assali NS, Morris JA, Beck R: Cardiovascular haemodynamics in the fetal lamb before and after lung expansion. *Am J Physiol* 208, 122 (1965).
- Baars AM, Merkus JMWM: Fetal echocardiography: A new approach to the study of the dynamics of the fetal heart and its component parts. *Eur J Obstet Gynaecol Reprod Biol* 7, 91-95 (1977).
- Davila JC, Sanmarco ME: An analysis of the fit of mathematical models applicable to the measurement of the left ventricular volume. *Am J Cardiol* 18, 31 (1966).
- Dawes GS, Mott JC, Widdicombe JG: The foetal circulation in the lamb. *J Physiol* 126, 563 (1954).
- Dodge HT, Sandler H, Baller DW, Lord JD: The use of biplane angiography for the measurement of left ventricular volume in man. *Am Heart J* 60, 762 (1960).
- Dumesic DA, Silverman NH, Tobias S, Golbus MS: Transplacental cardioversion of fetal supra-ventricular tachycardia with procainamide. *N Engl J Med* 307, 1128 (1982).
- Emery JL, MacDonald MS: The weight of ventricles in the later weeks of intra-uterine life. *Br Heart J* 22, 563 (1960).
- Emery JL, Mithal A: Weights of cardiac ventricles at and after birth. *Br Heart J* 23, 313 (1961).

- Evers JLH, Van Dis P, Jongsma HW, Martin CB Jr, De Haan J, Crevels JA, Arts THM, Dieleman J: Systolic time intervals of the fetal cardiac cycle. In Proceedings of the 1st International Symposium on Fetal Echocardiology, Strasbourg (Eds. Milupa diététique), 1982, p. 181.
- Filkins KA, Brown TF, Levine RO: Real-time ultrasonic evaluation of the fetal heart. *Int J Gynaecol Obstet* 19, 35 (1981).
- Fixler DE, Stage L, Rudolph AM: Evaluation of a Doppler catheter probe to measure cardiac output. *J Surg Res* 15, 243 (1973).
- Fulton RM, Hutchinson EC, Jones AM: Ventricular weight in cardiac hypertrophy. *Br Heart J* 14, 413 (1952).
- Garrett WJ, Robinson DE: Fetal heart size measured in vivo by ultrasound. *Pediatrics* 46, 25-27 (1970).
- Harrigan JT, Kangos JJ, Sikka A, Spisso KR, Natarajan N, Rosenfeld D, Leiman S, Korn D: Successful treatment of fetal congestive heart failure secondary to tachycardia. *N Engl J Med* 304, 1527 (1981).
- Herrmann GR, Wilson FN: Ventricular hypertrophy. A comparison of electrocardiographic and postmortem observations. *Heart* 9, 91 (1982).
- Herrmann HJ, Bartle SH: Acute mitral regurgitation in man. Hemodynamic evidence and observations indicating an early role for the pericardium. *Circulation* 36, 839 (1968).
- Hislop A, Reid L: Weight of the left and right ventricle of the heart during fetal life. *J Clin Pathol* 25, 534 (1972).
- Hobbins JC, Kleinman C, Creighton D: Fetal echocardiography: Indirect evaluation of in utero fetal flow patterns. In Proceedings of Society for Gynecologic Investigation. 25th Annual Meeting, Atlanta, Georgia, 1978, p. 48.
- Hort W: Morphologische Untersuchungen am Herzen vor, während und nach der postnatalen Kreislaufumschaltung. *Virchows Arch-Pathol Anat* 326, 458 (1955).
- Hort W: The normal heart of the fetus and its metamorphosis in the transition period. In *The Heart and Circulation in the Newborn and Infant* (D.E. Cassels ed.), Grune and Stratton, New York, 1966, p. 210.
- Keen EN: The post natal development of human cardiac ventricles. *J Anat* 89, 484 (1955).
- Kerenyi TD, Gleicher N, Meller J, Brown E, Steinfeld L, Chitkara U, Raucher H: Transplacental cardioversion of intrauterine supraventricular tachycardia with digitalis. *Lancet* 2, 393 (1980).
- Kirkpatrick SE, Covell JW, Friedman WF: A new technique for the continuous assessment of fetal and neonatal cardiac performance. *Am J Obstet Gynecol* 116, 963 (1973).
- Kleinman CS, Hobbins JC, Jaffe CC, Lynch DC, Talner NS: Echocardiographic studies of the human fetus. In Proceedings Symposium on Development Biology of the Society for Pediatric Research. New York, 1978.
- Kloosterman GJ: On intrauterine growth. *Int J Gynaecol Obstet* 8, 895 (1970).
- Lewis T: Observation on ventricular hypertrophy with especial reference to preponderance of one or other chamber. *Heart* 5, 367 (1914).
- McCallum WD: Fetal cardiac anatomy and vascular dynamics. *Clin Obstet Gynecol* 24, 837-849 (1981).
- Mahon WA, Goodwin JW, Paul WM: Measurement of individual ventricular outputs in the fetal lamb by an indicator dilution technique. *Circ Res* 19, 191 (1966).
- Müller W: Die Massenverhältnisse des menschlichen Herzens. Leopold Voss, Hamburg und Leipzig, 1883.
- Murata Y, Martin ChB, Ikenoue T, Lu PS: Antepartum evaluation of the pre-ejection period of the fetal cardiac cycle. *Am J Obstet Gynecol* 132, 278 (1978).
- Organ LW, Berstein A, Smith KC, Rone IH: The pre-ejection period of the fetal heart: Patterns of change during labor. *Am J Obstet and Gynecol* 120, 49 (1974).
- Recavarren S, Arias-Stella J: Growth and development of the ventricular myocardium from birth to adult life. *Br Heart J* 26, 187 (1964).
- Robinson DE, Garrett WJ, Kossoff G: Fetal anatomy displayed by ultrasound. *Invest Radiol* 3, 442 (1968).

- Rudolph AM, Heymann MA: The circulation of the fetus in utero. Methods for studying distribution of blood flow, cardiac output and organ flow. *Circ Res* 21, 163 (1967).
- Rudolph AM, Heymann MA: Circulatory changes during growth in the fetal lamb. *Circ Res* 26, 289 (1970).
- Rudolph AM, Heymann MA, Lewis AB: Physiology and pharmacology of the pulmonary circulation in the fetus and newborn. In *Lung Biology in Health and Disease. The Development of the Lung*. W.A. Hodson, ed. Marcel Dekker, New York, 1977, p.497.
- Sahn DJ, Lange LW, Allen HD, Goldberg SJ, Anderson C, Giles H, Haber K: Quantitative real-time cross-sectional echocardiography in the developing normal human fetus and newborn. *Circulation* 62, 588-597 (1980).
- Stewart PA, Wladimiroff JW, Essed CE: Prenatal ultrasound diagnosis of congenital heart disease associated with intrauterine growth retardation. A report of 2 cases, *Prenatal Diagn* 3, 279 (1983a).
- Stewart PA, Tonge HM, Wladimiroff JW: Arrhythmia and structural abnormalities of the fetal heart. *Br Heart J* 50, 550-554 (1983b).
- Tonge HM, Struyk PC, Custers P, Wladimiroff JW: Vascular dynamics in the descending aorta of the human fetus in normal late pregnancy. *Early Human Dev* 9, 21 (1983).
- Vosters RPL: Fetal and early neonatal cardiac ventricular geometry and function. An echographic study. Thesis, Erasmus University, Rotterdam (1983).
- Winsberg F: Echocardiography of the fetal and newborn heart. *Invest Radiol* 7, 152-158 (1972).
- Wladimiroff JW, Vosters RPL, Vletter W: Ultrasonic measurement of fetal and neonatal ventricular dimensions. *Contrib Gynec Obstet* 6, 109 (1979).
- Wladimiroff JW, McGhie J: Ultrasonic assessment of cardiovascular geometry and function in the human fetus. *Br J Obstet Gynaecol* 88, 870-875 (1981a).
- Wladimiroff JW, McGhie JS: M-mode ultrasonic assessment of fetal cardiovascular dynamics. *Br J Obstet Gynaecol* 88, 1241-1245 (1981b).
- Wladimiroff JW, McGhie JS, Hovestreydt-Snijder RP, Tasseron EWK: M-mode and pulsed Doppler ultrasound assessment of severe fetal bradycardia. A case report. *Br J Obstet Gynaecol* 88, 1246 (1981).
- Wladimiroff JW, Vosters RPL, McGhie JS: Normal cardiac ventricular geometry and function during the last trimester of pregnancy and early neonatal period. *Br J Obstet Gynaecol* 89, 839-844 (1982).
- Wolfson RN, Zador IE, Pillay SK, Timor Tritsch JE: Antenatal investigation of human fetal systolic time intervals. *Am J Obstet Gynecol* 129, 203 (1977).

### 2.3 The role of diagnostic ultrasound in the study of fetal cardiac abnormalities

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Published in *Ultrasound in Medicine and Biology*, Vol 10: 457-463 (1984)

#### *Abstract*

Between January 1982 and April 1983, a total of 315 patients was scanned for fetal Congenital Heart Disease (CHD). In 70% of these patients, there was an increased risk for CHD in their offspring, in the remaining 30% abnormal findings were made by ultrasound in the present pregnancy. Nine cardiac defects were correctly diagnosed. There were three false positive and three false negative findings. The presence of fetal dysrhythmia, Intra-Uterine Growth Retardation (IUGR), ascites or polyhydramnios warrants a structural analysis of the fetal heart. Prenatal scanning for CHD should preferably be carried out in centres which can guarantee a high degree of scanning experience, up-to-date scanning equipment and close cooperation with a well-established neonatal and pediatric cardiology unit.

**Key words:** Congenital heart disease, Prenatal diagnosis, 2-D real-time ultrasound, Dysrhythmia, Intrauterine growth retardation.

#### *Introduction*

Fetal heart activity has been documented by means of a monoaural stethoscope as early as 1818 by Mayor and in 1821 by Lejumeau de Kergaradec. It was only twenty five years ago that the first heart rate recordings from fetal scalp electrodes were obtained. It was only with the introduction of more superior real-time equipment in the mid-seventies that geometric and later functional data on the fetal heart became available. Several centres in the United States, Canada, Australia and Europe are now developing the expertise for early detection of Congenital Heart Disease (CHD). In the United States CHD accounts for some 8 per 1000 or 30,000 infants per year (McCallum, 1981). The main purpose of prenatal diagnosis of CHD will be adjustment of obstetric management both during pregnancy and labour and immediate postnatal care by the neonatologist and pediatric cardiologist to assure early treatment.

Presently the three ultrasound techniques which play a crucial role in the assessment of fetal cardiac structure and function are 2-D real-time, M-mode and pulsed Doppler ultrasound. In this communication we will discuss our own experience in prenatal diagnosis and management of fetal cardiac abnormalities.

### *Material and methods*

Between January 1982 and April 1983 a total of 315 patients was referred to our Ultrasound Unit for a fetal heart scan. The examinations were performed using a two-dimensional phased array real-time system (Hewlett Packard, 77020A), or a mechanical sector scanner (Diasonics, Cardio Vue 100), both with real-time directed M-mode recording facilities. Measurement of mean blood flow velocity at the lower thoracic level of the fetal descending aorta was performed by means of a combined linear-array real-time scanner (Organon Teknika) and pulsed Doppler system (PEDOF) as described by Eik-Nes et al (1980) and recording of the pulsatile vessel diameter using a dual time distance recorder according to Sindberg-Eriksen et al. (1981). Seventy percent of these patients (Group I) were seen by us because of increased risk for a structural cardiac defect in their offspring. The remaining 30% (Group II) was referred because of abnormal ultrasonic findings in the present pregnancy which warranted a detailed cardiac scan.

Structural examination of the fetal heart is preferably done between 17 and 26 weeks of gestation since the heart is then large enough for 2-D real-time examination and there is a comparatively large amniotic fluid compartment, serving as an excellent transmission medium for the ultrasound beam. In group I the vast majority of referrals (95%) took place between 17 and 25 weeks, only a very small number of patients was sent to us at a later stage. In group II pregnancy duration at the time of referral varied between 20 and 36 weeks. A total of 680 scans was performed in 315 patients, e.g. two scans per patient.

Optimal fetal cardiac scans are usually obtained when the fetal spine is situated posteriorly or laterally. Visualization of the heart may be restricted when the spine is anterior (shadowing), during excessive fetal movements, maternal obesity and oligohydramnios. Standard cardiac scans are short axis, long axis and 4-chamber views. Tomographic views in the short axis are parallel to the minor axis of the heart. These views are displayed as though the observer were looking from the abdomen towards the head.

Tomographic views in the long axis plane are parallel to the major axis of the heart and perpendicular to the dorsal and ventral surfaces of the chest. These planes of section are displayed as though the observer were looking from the left side of the patient.

Tomographic views in the 4-chamber plane are along the major axis of the heart and parallel to the dorsal and ventral surfaces of the chest. The planes of section are displayed as though the observer were looking down upon the heart.

### *Results*

Table 1 presents the referrals of at-risk patients (Group I), whereas Table 2 gives the referrals of patients with abnormal ultrasound findings in their present

Table 1. Risk factors for fetal congenital heart disease (CHD) and number of cases studied

Reasons for referral in Group I	Number of cases
CHD - parent	45
CHD - previous child	99
Juvenile diabetes.	30
Epilepsy (maternal)	25
Maternal heroin usage	18
Advanced maternal age > 40 years	11
<b>Total</b>	<b>228</b>

Table 2. Fetal pathology necessitating a search for CHD

Reasons for referral in Group II	Number of cases
Dysrhythmia (fetal)	38
Polyhydramnios	10
Fetal ascites	5
IUGR	12
Miscellaneous (fetal infection, omphalocele)	22
<b>Total</b>	<b>87</b>

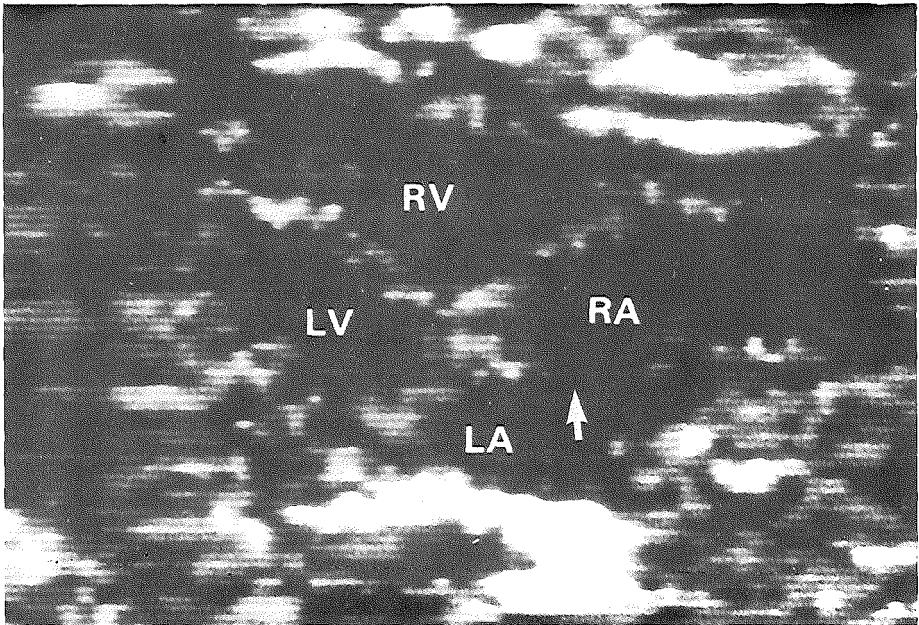


Fig.1. Four-chamber view of fetal heart with suspected 2° ASD (see arrow) at 29 weeks.



Table 3. Scanning results in 315 patients in which a structural analysis of the fetal heart was carried-out

TGA=transposition of great arteries; ASD=atrial septal defect; VSD=ventricular septal defect

Total patients	315
Total ultrasound examinations	680
True positive	9
False positive	
1 x TGA	3
1 x ventricular inversion (positional)	
1 x 2° ASD	
True negative	276
False negative	
1 x trabecular VSD	3
1 x perimembranous VSD	
1 x coarctation aorta	
Not yet delivered	24

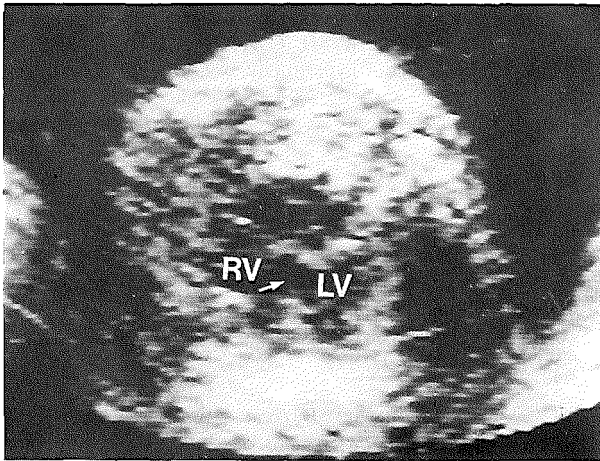


Fig.2. Four-chamber view of fetal heart (case 8, Table 4) at 35 weeks depicting a ventricular septal defect (see arrow).

pregnancy (Group II). Group I mainly comprises patients with CHD in one of the parents (n=45), CHD in a previous child (n=99) and juvenile diabetes (n=30). Group II is mainly determined by patients with fetal dysrhythmia (n=38) and fetal pathology such as infections and omphalocele (miscellaneous; n=22). From Table 3 it can be seen that 9 structural cardiac defects were correctly diagnosed. In three cases a false positive diagnosis, and in three cases a false negative diagnosis was made. The three false positive were all determined by malpositioning of the heart due to other abnormalities such as omphalocele or hydrothorax. In one patient, examination of 4-chamber view of the fetal heart convincingly showed a 2° Atrial Septal Defect (ASD) (fig. 1). The infant died

Table 4. Prenatal findings and fetal outcome in 9 patients with correctly diagnosed fetal CHD.

Case	Gestational age (wks)	Prenatal findings	Fetal outcome
1	21	gross ascites, hydrothorax, isomeric atria, absent right AV connection, great arterial connections not clearly identified, CCHB	pregnancy terminated at 21 weeks. Ascites, hydrothorax, left atrial isomerism, univentricular AV connection (single LV), concordant arterial connections, subpulmonary stenosis, asplenia, rocker bottom feet.
2	22	ectopia cordis, DORV, VSD + hypoplastic LV	pregnancy termination at 22 weeks. Cardiac pathology confirmed.
3	28 <sup>+</sup>	IUGR, irregular bradycardia, complete AVSD	term vaginal delivery. Complete AVSD + wandering pacemaker. To date alive and well.
4	29	polyhydramnios, ascites, PE, isomeric atria, complete AVSD, TDF, gross ventricular hypertrophy, CCHB	stillborn at 31 weeks. Ascites, left atrial isomerism univentricular left AV connection with straddling AV valve, TDF right aortic arch with aberrant left subclavian artery, asplenia.
5	31	severe IUGR, DORV	stillborn at 34 weeks. Cardiac pathology confirmed.
6	33	maternal heroin usage, coarctation aorta + abn. tricuspid valve	infant died following cardiac surgery. Cardiac pathology confirmed.
7	34	severe IUGR, univentricular heart and coarctation aorta, SVE	stillborn at 34 weeks. Cardiac pathology confirmed.
8	35	IUGR, polyhydramnios, VSD, great vessels not visualized, 2° AV block	Caesarean Section at 38 weeks. 2° AV block, † 12 hrs post partum, TOF, trisomy 18.
9	36	obstructive foramen ovale, gross right heart dilatation, SVE	term vaginal delivery, SVE post partum. At age 6/12: normal heart size and rhythm.

IUGR = intra uterine growth retardation; SVE = supraventricular ectopics; CCHB = complete congenital heart block; AV = atrioventricular; LV = left ventricle; AVSD = atrioventricular septal defect; PE = pericardial effusion; TOF = tetralogy of Fallot; DORV = double outlet right ventricle; VSD = ventricular septal defect.

a few days later as a result of severe growth retardation and cystic kidneys. Although autopsy revealed a large primum septum, it was not considered a true structural defect. Table 4 demonstrates the prenatal findings and clinical outcome in the nine correctly diagnosed cardiac defects. Figures 2 and 3 represent ultrasonic images of the structural cardiac defects in cases 3 and 8 from Table 4.

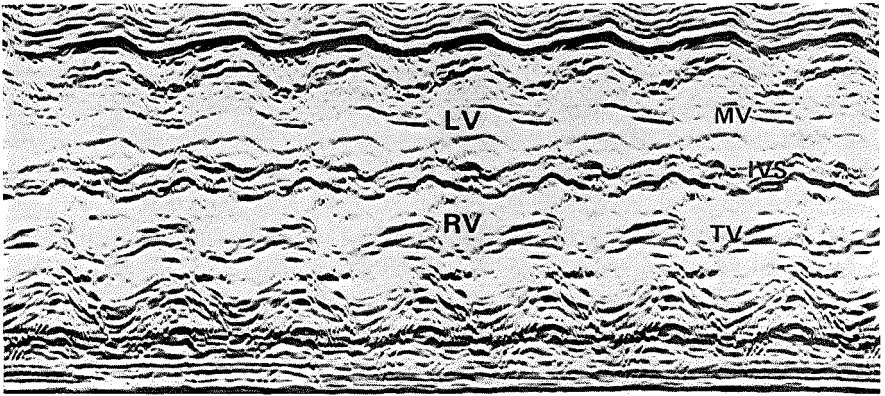


Fig.3. Normal M-mode recording at 34 weeks of the left (LV) and right cardiac ventricle (RV) at right angle to the intra-ventricular septum (IVS) at the level of mitral (MV) and tricuspid valve (TV) leaflets.

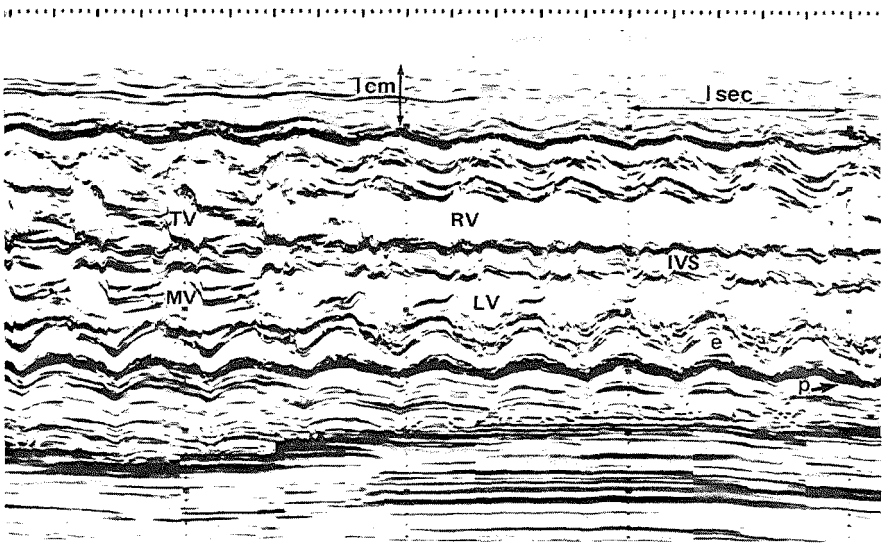


Fig.4. M-mode recording at 31 weeks at the same level of the cardiac ventricles as described in Fig.3. e=pericardial effusion; p=pericardium.

### Discussion

Information relating to the fetal heart structure has been obtained in the past using B-mode (Garrett et al., 1979; Egeblad et al., 1975) and M-mode techniques

(Winsberg, 1972; Baars en Merkus, 1977) but these methods provided limited information. Recent advances in real-time 2-D equipment permit the identification of fetal cardiac anatomy in greater detail (Allan et al., 1980, 1981; Sahn et al., 1980; Lange et al., 1980; Wladimiroff and McGhie, 1981a, b; Silverman et al., 1982; Wladimiroff et al., 1982; Nisand et al., 1982). Combined use of 2-D real-time and M-mode echocardiography may provide useful additional information on cardiac geometry and function in case of fetal structural heart disease (Allan et al., 1982). It should be stressed, however, that at the present stage, only moderate to gross cardiac defects can be diagnosed. Figures 4 and 5 represent M-mode recordings in normal pregnancy (Fig. 4) and in a case of unexplained pericardial effusion. Serial monitoring of effusion area on M-mode recordings will point out possible minor changes in pericardial fluid collection (De Vore et al., 1982). In an earlier study we found a cardiac structural defect in about 20% of cardiac dysrhythmias (Stewart et al., 1983). Particularly here, M-mode analysis of atrial and ventricular rate and rhythm will identify the type of dysrhythmia.

When the presence of a cardiac structural defect has been established, one should always look for possible signs of cardiac compromise, such as pericardial effusion, increase in right heart size and ascites. Lately pulsed Doppler systems have been introduced for the measurement of blood flow in the descending aorta (Eik-Nes et al., 1980, 1984; Marsal et al., 1984) and umbilical vein (Gill and Kossoff, 1979; Gill et al., 1984). These systems have been shown to be helpful in the assessment of fetal cardiac function during fetal dysrhythmia and developing fetal cardiac compromise (Wladimiroff et al., 1983b). Cardiac forward failure will result in a reduction in aortic blood flow.

In Table 4 we demonstrated that in the presence of severe congenital cardiac defects, pregnancy was either terminated (cases 1 and 2) or obstetric treatment abandoned (cases 4, 5 and 7) depending on the gestational age. When the cardiac defect is amenable to postnatal medical and surgical treatment, obstetric management should be directed towards a safe delivery of a mature infant. Sometimes intrauterine treatment has to be considered, particularly in case of supraventricular tachycardia which may lead to cardiac insufficiency. Up until now maternal administration of digitalis has not been very successful in these instances. The question as to whether vaginal delivery of caesarean section should be the best approach, will depend on the severity of the cardiac lesion, the presence of associated cardiac dysrhythmia and possible signs of cardiac compromise.

Finally, it should have become clear from this paper that despite the enormous improvements in diagnostic ultrasound equipment, prenatal scanning for fetal cardiac structural defects may still result in false positive and false negative findings. It should also have become clear that this kind of work should be pursued in centres which can guarantee a high degree of scanning experience, up-to-date scanning equipment and close cooperation with a well-established neonatal and pediatric cardiology unit.

## References

- Allan LD, Tynan MJ, Campbell S, Wilkinson JL and Anderson RH (1980) Echocardiographic and anatomical correlates in the fetus. *Br Heart J* 44, 444-452.
- Allan LD, Tynan MJ, Campbell S and Anderson RH (1981). Identification of congenital cardiac malformations by echocardiography in midtrimester fetus. *Br Heart J* 46, 358-362.
- Allan LD, Joseph MC, Boyd EGCA, Campbell S and Tynan MJ (1982) M-mode echocardiography in the developing human fetus. *Br Heart J* 47, 573-583.
- Baars AM and Merkus JMWM (1977) Fetal echocardiography: a new approach to the study of the dynamics of the fetal heart and its component parts. *Eur J Obstet Gynaecol Reprod Biol* 7, 91-95.
- Eik-Nes SH, Brubakk AO and Ulstein M (1980). Measurement of human fetal blood flow. *Br Med J* 280, 283-285.
- Eik-Nes SH, Marsal K and Kristofferson K (1984). Methodology and basic problems related to blood flow studies in the human fetus. *Ultrasound in Med & Biol* in press.
- Egeblad H, Bang J and Northened A (1975). Ultrasonic identification and examination of fetal heart structures. *J Clin Ultrasound* 3, 95-103.
- Garrett WJ and Robinson DE (1970). Fetal heart size measured in vivo by ultrasound. *Pediatrics* 46, 25-27.
- Gill RW and Kossoff G (1970). Pulsed Doppler combined with B-mode imaging for blood flow measurement. *Contribution to Gynecology and Obstetrics* 6, 139-141.
- Gill RW, Warren PS, Kossoff G and Garrett WJ (1984). Umbilical venous flow in normal and complicated pregnancy. *Ultrasound in Med & Biol* in press.
- Lejumeau De Kergaradec JA (1821). Memoire sur l'auscultation appliquee à l'etude de la grossesse. *Communication Acad Med* 26XI 1821, Paris, Méquignon, Harves, 1822, 1-37.
- Lange LW, Sahn DJ, Allan LD, Goldberg SJ, Anderson C and Giles H (1980). Qualitative real-time cross-sectional echocardiographic imaging of the human fetus during the second half of the pregnancy. *Circulation* 62(4), 799-806.
- Marsal K, Eik-Nes SH, Lindblad A and Lingman G (1984). Blood flow in the fetal descending aorta; intrinsic factors affecting fetal blood flow, fetal breathing and cardiac arrhythmia. *Ultrasound in Med & Biol* in press.
- Mayor FI (1818). *Bibliothèque Universelle de Genève*.
- McCallum WD (1981). Fetal cardiac anatomy and vascular dynamics. In *Clinical Obstetrics and Gynaecology* pp 837-849. (Edited by R.M. Pitrin and J.R. Scott). Harper and Row Publishers.
- Nisand I, De Geeter B, Rassier F, Spierlman A and Dellenbach P (1982). Intervalles de temps systoliques chez le foetus humain. In *Proc. 1st Symp Int d'Echocardiologie Foetale* (Edited by A. Chevalier), pp 187-196, Strasbourg.
- Sahn DJ, Lange LW, Allen HD, Goldberg SJ, Anderson C, Giles H and Haber K (1980). Quantitative real-time cross-sectional echocardiography in the developing normal human fetus and newborn. *Circulation* 62, 3, 588-597.
- Silverman NH, Snider AR, Golbus NS and Stanger P (1982). Perspectives on fetal echocardiography. In *Proc 1st Symp International d'Echocardiologie Foetale* (Edited by A. Chevalier) pp 95-109, Strasbourg.
- Stewart PA, Tonge HM and Wladimiroff JW (1983). Arrhythmia and structural abnormalities of the fetal heart. *Br Heart J* 50, 550-554.
- De Vore GR, Donnerstein RL, Kleinman CS, Platt LD and Hobbins JC (1982). Fetal echocardiography-II. The diagnosis and significance of a pericardial effusion in the fetus using real-time-directed M-mode ultrasound. *Am J Obstet Gynecol* 144, 693-780.
- Winsberg F (1972). Echocardiography of the fetal and newborn heart. *Invest Radiol* 7, 152-158.
- Wladimiroff JW and McGhie JS (1981a). M-mode ultrasonic assessment of fetal cardiovascular dynamics. *Br J Obstet Gynaecol* 88, 1241-1245.
- Wladimiroff JW and McGhie JS (1981b). Ultrasonic assessment of cardiovascular geometry and function in the human fetus. *Br J Obstet Gynaecol* 88, 870-875.

- Wladimiroff JW, Vosters R and McGhie JS (1982). Normal cardiac ventricular geometry and function during the last trimester of pregnancy and early neonatal period. *Br J Obstet Gynaecol* 89, 839-844.
- Wladimiroff JW, Molenaar JC, Niermeyer MF, Stewart PA and van Eyck J (1983a). Prenatal diagnosis and management of omphalocele. *Europ J Gynaec Reprod Biol* 16, in press.
- Wladimiroff JW, Struyk P, Stewart PA, Custers P and De Villeneuve VH (1983b) Fetal cardiovascular dynamics during cardiac dysrhythmia. Case report. *Br J Obstet Gynaecol* 90, 573-577.

## 2.4 Doppler fetal echocardiography

Fetal cardiac blood flow differs from that seen postnatally. In the fetus simultaneous ejection of blood from the right and left ventricles results in flow into the systemic circulation. Blood from the venae cavae flows either into the left atrium through the foramen ovale, then into the descending aorta, or through the tricuspid valve, into the pulmonary artery, with most of the flow continuing through the ductus arteriosus into the descending aorta.

Pulsed Doppler fetal echocardiography has been demonstrated to be a useful technique in the assessment of fetal cardiovascular dynamics (Maulik et al, 1984; Maulik et al, 1985; Huhta et al, 1985; Meijboom 1985; Reed et al, 1986; Tonge 1987, De Smedt et al, 1987; Allan et al, 1987; Shenker et al, 1988) in both normal and abnormal fetal hearts.

In conjunction with real-time two-dimensional imaging Doppler echocardiography can be used to measure flow velocity at the level of all the cardiac valves.

It should, however, be realised that the pulse repetition frequency (PRF) is determined by the depth of the structure being interrogated and that peak maximum velocities can only be accurately measured at an angle as close to 0° as possible from the transducer.

It has been shown (Reed et al, 1986) that when considering the atrioventricular valves, early diastolic filling velocities (the "E" wave) were consistently lower than the velocities measured in late diastole (the "A" wave). The A wave coincides with atrial contraction. This pattern differs from that in childhood and adulthood when early diastolic velocities are dominant. This finding in the fetus may reflect the decreased diastolic compliance of the fetal heart and possibly explains the importance of atrial systole for normal cardiac function in the fetus.

Flow velocities across the tricuspid valve were also demonstrated to be higher than these across the mitral valve, which suggests right heart dominance, consistent with studies in fetal animals (Rudolph and Heymann, 1971).

Concerning velocities measured across the arterial valves, higher velocities were generally measured across the aortic valve, despite increased preload volume to the right ventricle compared with the left. This possibly reflects a better mechanical performance of the left ventricle or a difference in afterload prenatally.

The detection of abnormal fetal flow velocities e.g. increased, absent, regurgitant or disturbed velocities may provide valuable haemodynamic information following detection of structural or functional abnormalities. (Figs. 1 and 2).

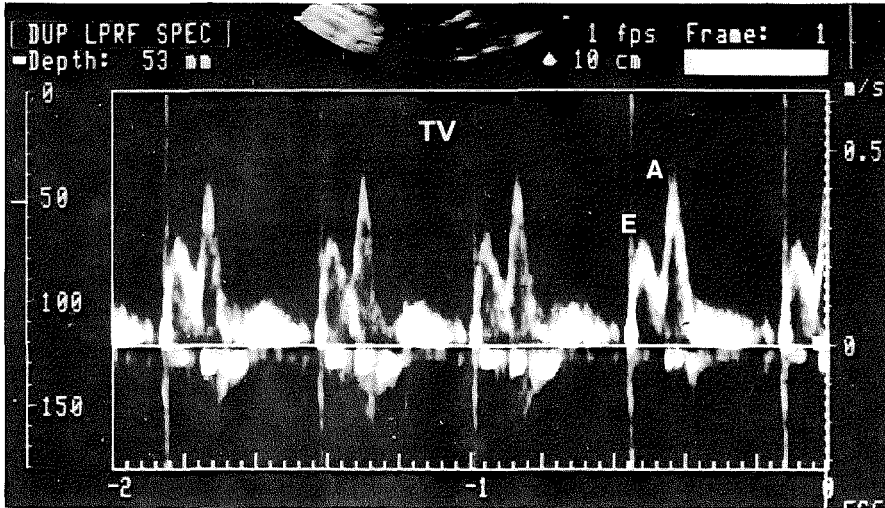


Fig.1. Normal fetal Doppler profile recorded at the level of the tricuspid valve. Normal forward flow is displayed above the zero line. E=early diastolic filling; A=late diastolic filling.

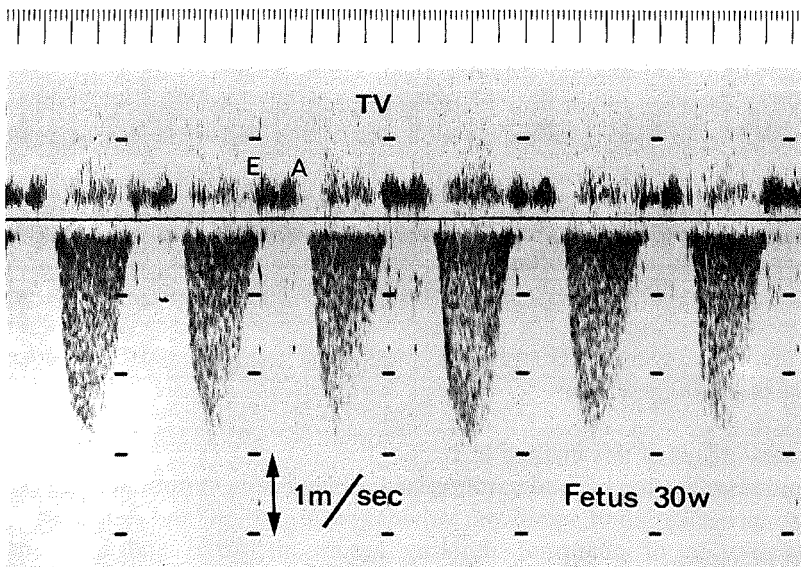


Fig.2. Doppler profile recorded at the level of the tricuspid valve in a fetus with Ebstein's anomaly. Note reduced forward flow (see also Fig.1) and severe regurgitation in systole (displayed below the zero line).

## References

- Allan LD, Chita SK, Al-Ghazali W, Crawford DC, Tynan M. Doppler echocardiographic evaluation of the normal human fetal heart. *Br.Heart J.*1987;57:528-533.
- De Smedt MCH, Visser GHA, Meijboom EJ. Fetal cardiac output estimated by Doppler echocardiography during mid- and late gestation. *Am.J.Cardiol.*1987;60:338-342.
- Huhta JC, Strasburger JF, Carpenter RJ, Reiter A, Abinader E. Pulsed Doppler fetal echocardiography. *J.Clin.Ultrasound* 1985;13:247-254.
- Maulik D, Nanda NC, Saini VD. Fetal Doppler echocardiography: Methods and Characterization of normal and abnormal haemodynamics. *Am.J.Cardiol.*1984;53:572-578.
- Maulik D, Nanda NC, Moodley S, Saini VD, Thiede HA. Application of Doppler echocardiography in the assessment of fetal cardiac disease. *Am.J.Obstet.Gynecol.*1985;151:951-956.
- Meijboom EJ. Quantification of cardiac blood flow by Doppler technique. Thesis, Erasmus University, Rotterdam, 1985.
- Reed KL, Meijboom EJ, Sahn DJ, Scagnelli SA, Valdes-Cruz LM, Shenker L. Cardiac Doppler flow velocities in human fetuses. *Circulation* 1986;73:41-46.
- Rudolph AM, Heymann MA. Fetal and neonatal circulation and respiration. *Annu.Rev.Physiol.*1971;38:87-95.
- Shenker L, Reed KL, Marx GR, Donnerstein RL, Allen HD, Anderson CF. Fetal cardiac Doppler flow studies in prenatal diagnosis of heart disease. *Am.J.Obstet.Gynecol.*1988; 158: 1267-1273.
- Tonge HM. A Doppler ultrasound study of human fetal vascular dynamics. Thesis, Erasmus University, Rotterdam, 1987.

## 2.5 Colour-coded Doppler flow mapping

The most recent advance has been the introduction of colour-coded Doppler flow mapping techniques whereby the Doppler shift is displayed in colour during the real-time examination (Maulik et al, 1986; Kurjak et al, 1987; Devore et al, 1987). Doppler colour flow mapping displays the Doppler shift in three ways:

- 1) red colour indicates a Doppler shift towards the transducer;
- 2) blue colour indicates a Doppler shift away from the transducer;
- 3) mosaic colour (red /orange or blue /green) indicates multiple Doppler shifts suggestive of turbulent flow.

The power output (SPTA, spatial-peak temporal average) required for fetal real-time colour coded Doppler flow mapping is considered to be acceptable at less than 100 mW /cm<sup>2</sup>

The advantages of this method are:

- rapid visualisation of fetal cardiovascular blood flow in normal hearts;
- easy identification of significant valvular regurgitation (and stenoses);
- visualisation of abnormal shunting across interatrial and interventricular structures;
- adjunctive information to be obtained in complex lesions;
- the possibility to study extracardiac blood flow directions and profiles.



A study was performed to assess the value of colour Doppler flow mapping techniques in fetal congenital heart disease. The study comprised 180 normal and 16 abnormal fetal hearts (Table 1).

Table 1. Anomalies examined with colour Doppler

hypoplastic left heart syndrome	x 2
Ebstein anomaly	x 2
complete atrioventricular septal defect	x 2
ventricular septal defect	x 4
tetralogy of Fallot	x 1
cardiomyopathy	x 2
complex heart disease	x 1
fetal hydrops	x 2

Currently colour-coded Doppler flow mapping offers most benefit for fetal cardiovascular examination and is a valuable adjunct to the other ultrasound techniques already described.

Ultrasound examination time may be reduced, especially for haemodynamic evaluation, as interfacing the colour-coded information allows more rapid identification of the areas to be interrogated, especially when abnormal flow patterns are expected.

Expected technological advances will further improve the usefulness of this technique as enhanced processing of information will allow evaluation of smaller structures more accurately than is presently feasible.

### *References*

- Centers for Disease Control Temporal trends in the incidence of malformation in the United States, selected years, 1970-71, 1982-83. *MMWR*, 1985;34:1ss-3ss.
- Devore GR, Hovenstein J, Siassi B, Platt LD. Doppler color flow mapping: A new technique for the diagnosis of congenital heart disease. *Am.J.Obstet.Gynecol.*1987;156:1054-1064.
- Kurjak A, Breyer B, Jurkovic D, Alfirevic Z, Miljan M. Colour flow mapping in obstetrics. *J.Perinat.Med.*1987; 15:271-281.
- Maulik D, Nanda NC, Hsiung MC. Doppler color flow mapping of the fetal heart. *Angiology* 1986;37:628-632.
- The safety of ultrasound in clinical diagnostic examinations. In: *Ultrasound in Medicine. Recommendations on the subject of ultrasound.* Health Council of the Netherlands: 13; 33-49, 1986.

## Chapter 3

**Fetal echocardiography in a high risk population**

*"The conception of the common cardiac malformations as primeval hearts is probably applicable to many, if not all, spontaneously occurring malformations, abnormalities and syndromes and, possibly to genetic diseases, enzyme deficiency and even "inborn errors" of metabolism. They are all part of the random selection, mutations, and recombinations of DNA that give nature its great diversity".*

Helen B.Taussig, Am.J.Cardiol. 50:557, 1982.

***Introductory remarks***

The estimated incidence of congenital heart disease (CHD) is in the order of 4 - 8 per 1000 live births (Ferencz et al, 1985). CHD represents a heterogeneous group of disorders caused by Mendelian disorders, chromosomal abnormalities, teratogenic exposure and a large group considered to be multi-factorial in origin (Nora 1968; Nora and Nora 1978; Sanchez 1978; Whittemore et al, 1982; Nora and Nora, 1984; Rose et al, 1985; McKusick, 1986; Boughman et al, 1987; Clark, 1987; Nora and Nora, 1988).

If the CHD is the only malformation in a child, the inheritance is usually multifactorial, and risks of recurrence are based upon empirical observations preferentially from the population under study. Recently it has been shown that the risk of recurrence for various types of CHD, where maternal CHD is present, is higher than where paternal CHD is present. (Rose et al., 1985; Nora and Nora, 1987). This might imply either intrauterine factors or the action of mitochondrial genes (which are maternally derived) in the expression of the liability for a congenital heart defect.

The type of CHD in the index case may differ from the type in other affected relatives with certain correlation between specific defects (Dennis and Warren, 1981; Emmanuel et al., 1983).

If a cardiac defect is caused by a monogenic disorder (inherited as autosomal, or X-linked, dominant or recessive) then the recurrence risk is usually higher. Moreover, the recurrence risk and the variability of a heart defect has to be established separately.

Patients with a known increased risk for having a child with CHD should be offered fetal echocardiography in each pregnancy.

The nature of these risk groups is provided in Table 1. The patients were studied over a 6 year period from 1.1.1982 to 1.1.1988.

In Chapters 3.1 - 3.4, four articles provide information concerning fetal CHD in four of the sub-groups, namely, familial predisposition, maternal diabetes mellitus, maternal exposure to anti-convulsants and maternal morphomimetic abuse.

The patients in this study group were referred nationally. For this reason it was not feasible to perform echocardiography in every neonate. However, all neonates were examined at least once at the age of 6 weeks.

The false negative diagnoses were derived when CHD was diagnosed at any time after birth, and even CHD diagnosed years after birth has been included.

The category of false positive was designed to include prenatally suspected CHD not confirmed postnatally. However there were no false positive diagnoses. The category "incidence CHD" was derived from the total number of diagnosed anomalies whether detected pre- or postnatally.

As described in Chapter 2 the optimal period for fetal echocardiography is between 16 and 24 weeks of gestation. In the high risk population 95% of the fetuses were examined in this period. The remainder were scanned after 24 weeks of gestation because of late first attendance at an antenatal clinic. Maternal obesity frequently hampered the investigation, especially in the patients seen before 20 weeks of gestation, necessitating repeat visits.

In the entire group of 1577 patients there were 18 correctly predicted structural anomalies (Table 2). In 11 cases CHD was diagnosed by ultrasound postnatally despite normal prenatal findings (Table 3). In a further 5 cases anomalies not diagnosable by ultrasound even postnatally were discovered by other techniques (Table 4). These 5 cases were further excluded from the calculations of sensitivity and specificity (Table 5).

When considering the recurrence of CHD in the group with previous children with CHD the incidence of 1.5% is not as high as one would expect from the literature. This is possibly explained by the relatively low number of pregnancies (673) screened.

The fact that a higher number of anomalies were not detected by prenatal ultrasound than were detected in this group is related to the types of defects not diagnosed (see Table 3). Such anomalies may also be difficult to diagnose with ultrasound postnatally. A search for specific anomalies may be prompted only after clinical signs and symptoms. Sometimes even the clinical signs preceding diagnosis may appear later in childhood. This was the case in a child with secundum atrial septal defect which was only diagnosed at age 4 years. Obviously, similar cases will continue to be undetected in fetal life.

In the group maternal and paternal CHD the findings in this study are at variance with the observations reported by Rose et al., (1985) and Nora and Nora (1987) of a higher recurrence rate of CHD when the mother is affected. No increased recurrence (see Table 1) was observed in this series when inheritance was considered multifactorial.

In this series 3 of the 4 detected fetal anomalies in the maternal group were caused by monogenic disorders (Holt-Oram Syndrome, Asymmetric septal hypertrophy and Di George Syndrome). The fourth detected anomaly (incomplete atrioventricular septal defect) occurred as a part of a familial cluster with grandpaternal, maternal and 2 siblings with a concordant anomaly.

Table 1. Fetal echocardiography - High risk population  
 Indications for fetal structural cardiac examinations by ultrasound in the high risk population (1982-1988)

	No	False Neg.	False Pos.	True Pos.	Incidence CHD	Mortality
previous child CHD	673	6	-	4	10 (1.5%)	2 (20%)
maternal CHD	156	1	-	4	5 (3.2%)	2 (40%)
paternal CHD	54	1	-	-	1 (1.8%)	1 (100%)
other relative CHD	84	-	-	1	1 (1.2%)	-
maternal juvenile diabetes	178	-	-	4	4 (2.2%)	2 (50%)
maternal anti-convulsants	213	2	-	1	3 (1.4%)	-
maternal age >40 yrs	36	-	-	-	-	-
maternal morphometric	106	1	-	4	5 (4.7%)	2 (40%)
abuse misc (exp.poss.chem. teratogens, maternal SLE etc	73	-	-	-	-	-
	1577	11 (0.7%)	-	18 (1.1%)	29 (1.8%)	8 (28%)

Table 2. Correctly predicted anomalies in 1577 high risk pregnancies

Type of defect	N
Ventricular septal defect	7
Incomplete atrioventricular septal defect	1
Tetralogy of Fallot 3 Tricuspid dysplasia and coarctation	1
Large right heart (pulmonary stenosis)	1
Double outlet right ventricle	1
Atrial septal aneurysm	1
Ectopia cordis	1
Holt-Oram syndrome	1
Asymmetric septal hypertrophy	1
	18

Table 3. Postnatal cardiac defects in 1577 high-risk pregnancies with normal prenatal findings

Type of defect	N
Membranous ventricular septal defect	3
Muscular ventricular septal defect	2
Secundum atrial septal defect	2
Coarctation	1
Supravalvar aortic stenosis	2
Tetralogy of Fallot	1
	11

Table 4. Postnatal cardiac defects in 1577 high-risk pregnancies undetectable by ultrasound only

Absent right pulmonary artery	1
Small muscular ventricular septal defect (3 already closed spontaneously)	4

The anomaly (ventricular septal defect) not detected prenatally was concordant with the maternal defect. However this defect was only diagnosed at 3 years of age.

In the paternal CHD group no recurrences were detected prenatally. The defect not diagnosed prenatally (supravalvar aortic stenosis) was concordant but more severe than in the father.

More patients need to be screened to test these observations further as the numbers in this series are small.

The prenatal diagnosis of congenital heart disease will allow appropriate counselling for the parents, concerning further obstetric management, expected prognosis, and surgical possibilities.

Parents should however, be informed of the risk of a false negative finding. The false negative cases usually represented defects (VSD, ASD, coarctation)

which may also be difficult to diagnose postnatally if only ultrasound techniques are used. The non-prediction of the case of tetralogy of Fallot may possibly be explained by other reported cases (Allan et al., 1984, Todros et al., 1988) as well as our own experience (see Chapter 3.2) demonstrating dramatic changes in the morphologic appearance of some anomalies in the course of pregnancy. The natural history of congenital heart disease in the fetal period is still largely unknown and needs further elucidation.

Table 5. Sensitivity and specificity of cardiac scanning in the high risk population.

	CHD present	CHD absent	
CHD suspected	true positive 18 (a)	false positive 0 (b)	a + b = 18
CHD not suspected	false negative 11 (c)	true negative 1548 (d)	c + d = 1559
	a + c = 29	b + d = 1548	totaal 1577

Using the method of Grant (1984) the following values were found  
*Sensitivity* identifies the fetuses who have CHD

$$\frac{a}{a+c} = \frac{18}{18+11} \times 100\% = 62\%$$

*Specificity* identifies the fetuses without CHD

$$\frac{d}{b+d} = \frac{1548}{0+1548} \times 100\% = 100\%$$

*Positive predictive value* shows the likelihood of correct prediction of CHD

$$\frac{a}{a+c} = \frac{18}{18} \times 100\% = 100\%$$

*Negative predictive value* identifies the number of fetuses correctly predicted not to have CHD

$$\frac{d}{c+d} = \frac{1548}{1559} \times 100\% = 99\%$$

The relatively low sensitivity has already been explained and results from the nature of the defects missed.

However, overall, fetal echocardiography is clearly a reliable technique, in experienced hands, in excluding major congenital heart disease in fetuses at increased risk.

### *References*

- Allan CD, Crawford DC, Tynan M: Evolution of coarctation of the aorta in intrauterine life. *Br Heart J* 1984; 52: 471-473.
- Boughman JA, Berg KA, Astemborski JA, Clark EB, McCarter RJ, Rubin JD, Ferencz C: Familial risks of congenital heart defect assessed in a population - based epidemiologic study. *Am J Med Genet* 1987; 26: 839-849.
- Clark EB: Mechanisms in the pathogenesis of congenital cardiac malformations. In: *Genetics of cardiovascular disease 1987*, 3-13. Eds: MEM Pierpont, JH Moller, Martinus Nijhoff Publ.
- Dennis NR, Warren J: Risk to the offspring of patients with some common congenital heart defects. *J Med Genet* 1981; 18: 8-16.
- Emmanuel R, Somerville J, Patel RG, Withers R: Evidence of congenital heart disease in the offspring of parents with atrioventricular defects. *Br Heart J* 1983; 49: 144-147.
- Ferencz C, Rubin JD, McCarter RJ, Brenner JI, Neill CA, Perry LW, Hepner SI, Downing JW: Congenital heart disease. Prevalence at live birth. *Am J Epidemiol* 1985; 121: 31-36.
- Grant A, Principles for clinical evaluation of methods of perinatal monitoring. *J Perinat Med* 1984; 12: 227-231.
- McCusick VA: Mendelian inheritance in man: Catalogs of autosomal dominant, autosomal recessive and X-linked phenotypes; 1986, 7th ed Baltimore: The Johns Hopkins Press.
- Nora JJ: Multifactorial inheritance hypothesis for the etiology of congenital heart disease: The genetic-environmental interaction. *Circulation* 1968; 18: 604-617.
- Nora JJ and Nora AH: The evolution of specific genetic and environmental counseling in congenital heart diseases. *Circulation* 1978; 57: 205-213.
- Nora JJ and Nora AH: The genetic contribution to congenital heart diseases. 1984 In Nora JJ, Takao A (eds) "Congenital Heart Disease: Causes and Processes". Mt. Kisco, NY; Futura pp 3-13.
- Nora JJ, Nora AH: Maternal transmission of congenital heart disease: New recurrences risk figures and the questions of cytoplasmic inheritance and vulnerability to teratogens. *Am J Cardiol* 1987; 59: 459-463.
- Nora JJ, Nora AH: Update on counseling the family with a first-degree relative with a congenital heart defect. *Am J Med Genet* 1988; 29: 137-142.
- Rose V, Gold RJM, Lindsay G, Allen M: The risk of recurrence of four types of congenital heart defects in the children of affected parents. *J Am Coll Cardiol* 1985; 6: 376-382.
- Sanchez - Cascos A: The recurrence risk in congenital heart disease. *Eur J Cardiol* 1978; 7: 197-210.
- Todros T, Presbitero P, Gaglioti P, Demarie D: Pulmonary stenosis with intact ventricular septum: documentation of development of the lesion echocardiographically during fetal life. *Int J Cardiol* 1988; 19: 355-360.
- Whittemore R, Hobbins JC, Engle MA: Pregnancy and its outcome in women with and without surgical treatment of congenital heart disease. *Am J Cardiol* 1982; 50: 641-650.

### 3.1 Prenatal ultrasonic diagnosis of familial asymmetric septal hypertrophy

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Published in *Prenatal Diagnosis*, Vol 6: 249-256 (1986)

#### *Summary*

Hypertrophic cardiomyopathy usually manifests clinically in the second or third decade of life. Two dimensional echocardiography is a reliable indicator of the presence of the disease. This technique is of use in the screening of fetuses at risk for familial cardiomyopathy. This report describes the prenatal echographic detection of hypertrophic cardiomyopathy in the fetus of a mother with hypertrophic cardiomyopathy localized to the apical region of the left ventricle.

*Key words* Fetal echocardiography, Familial cardiomyopathy

#### *Introduction*

Hypertrophic cardiomyopathy (including asymmetric septal hypertrophy) is a primary disease of cardiac muscle, which does not usually manifest clinically (Epstein et al., 1974) until the second or third decade of life and which may be a frequent cause of morbidity and mortality in adults (Frank and Braunwald, 1968). There may be a marked variation in the distribution of the hypertrophy as shown by two-dimensional echocardiography (Maron et al., 1981 a, b). There is a substantial evidence that in the absence of other cardiac or systemic disease which may cause cardiomyopathy many cases of asymmetric septal hypertrophy are due to a genetic defect that is transmitted as an autosomal dominant trait with high penetrance (Nasser et al., 1967; Clark et al., 1973; Epstein et al., 1974; Larter et al., 1976; Van Dorp et al., 1976; Emanuel et al., 1983).

It is characterized by disproportionate thickening of the ventricular septum with respect to the left ventricular free wall (Epstein et al., 1974). Left ventricular obstruction may occur but is not present in the majority of patients with asymmetric septal hypertrophy.

Hypertrophic cardiomyopathy does occur in infancy (Shand et al., 1971; Barr et al., 1973; Maron et al., 1982; Fiddler et al., 1978) but may be difficult to



diagnose clinically as it may often mimic other congenital malformations (Maron et al., 1982). Thickening of the ventricular septum may also be found in infants of diabetic mothers (Gutgesell et al., 1979) but despite the clinical and pathological similarities with the hypertrophic cardiomyopathy in older children and adults, its transient and non-familial nature suggest that it is a separate disease.

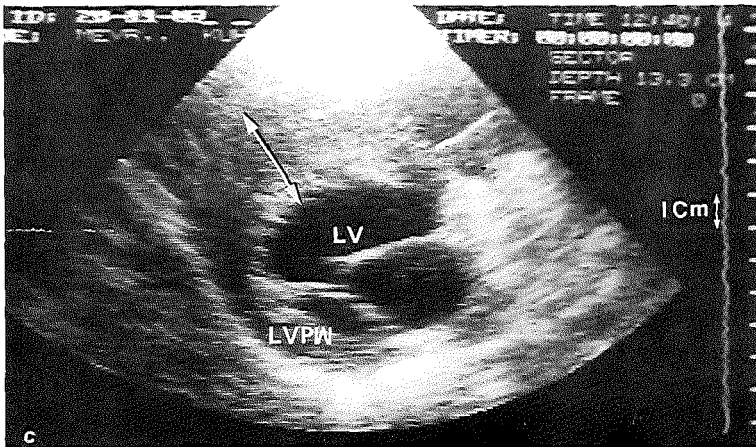
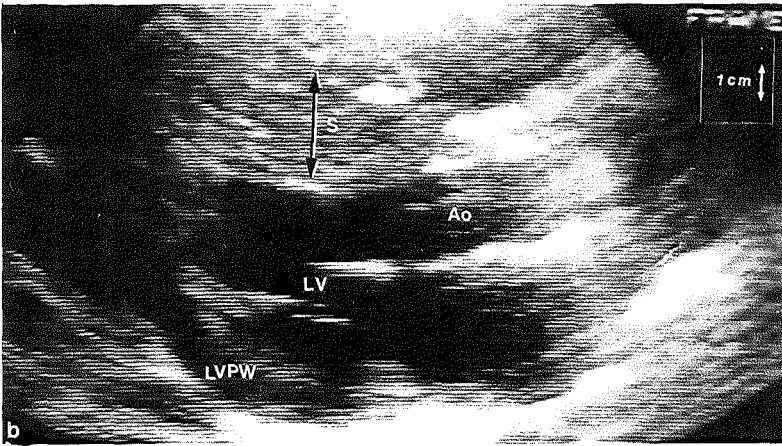
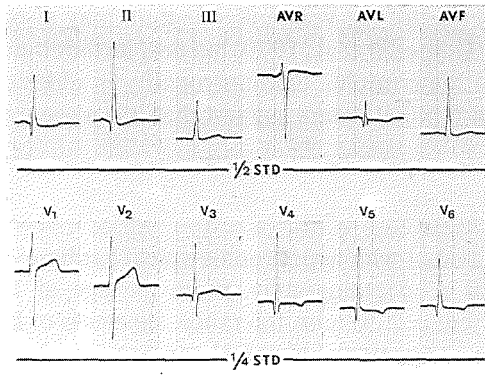
### *Case report*

A 25-year-old gravida I with hypertrophic apical cardiomyopathy was referred to this unit for fetal echocardiography. From the age of 12 years the patient had complained of reduced exercise tolerance, shortness of breath and tiredness. At the age of 16 years hypertrophic apical cardiomyopathy was diagnosed. She was re-evaluated at age 22 years at which time she was classified as New York Heart Association functional class II. The electrocardiogram showed left ventricular hypertrophy with 'strain' pattern and deep Q waves in V4-V6 (Figure 1a). Myocardial biopsy revealed hypertrophic changes and myocardial cellular disarray. Cardiac catheterization showed normal pressure values. Left ventricular angiography revealed clear narrowing of the apical section during systole. Echocardiography showed generalized hypertrophy with disproportionate thickening of the apical area (figure 1b, c). The ratio of the interventricular septum / left ventricular posterior wall was greater than 1.3. Early in pregnancy the clinical and echocardiographic findings of the patient were unchanged. There was no evidence of diabetes during the pregnancy.

Echocardiography of the fetus (Hewlett Packard 77020A or Dasonics Cardio Vue 100) was first performed at 19 weeks of gestation. Two-dimensional and M-mode evaluation revealed normal cardiac structure and measurements (Figure 2a, b). A repeat examination at 21 weeks showed no change. However, at the next visit at 27 weeks of gestation both two-dimensional and M-mode echocardiography showed generalized hypertrophy with a markedly thickened interventricular septum (Figure 3a, b). Repeat scans at 32 and 36 weeks of gestation suggested no obvious changes.

A female infant weighing 3710 g was delivered by forceps at term. The Apgar score was 9 at 1 min and 10 at 5 min.

The immediate neonatal period passed without complications and mother and baby were discharged on the 7th day. In the following 15 months no medical problems occurred and psychomotor development was uneventful. Physical examination at birth and in the following 15 months revealed a minimal ejection murmur, located at the fourth level intercostal space. No other abnormalities were found. Electrocardiograms, recorded at birth and repeated at 6 weeks, 3 months, 7 months and 15 months of age showed sinus rhythm with biventricular hypertrophy and ST-T abnormalities and deep Q waves in V4-V6 (Figure 4a). Chest X-ray: heart size enlarged; cardio-thoracic ratio: 0.58.



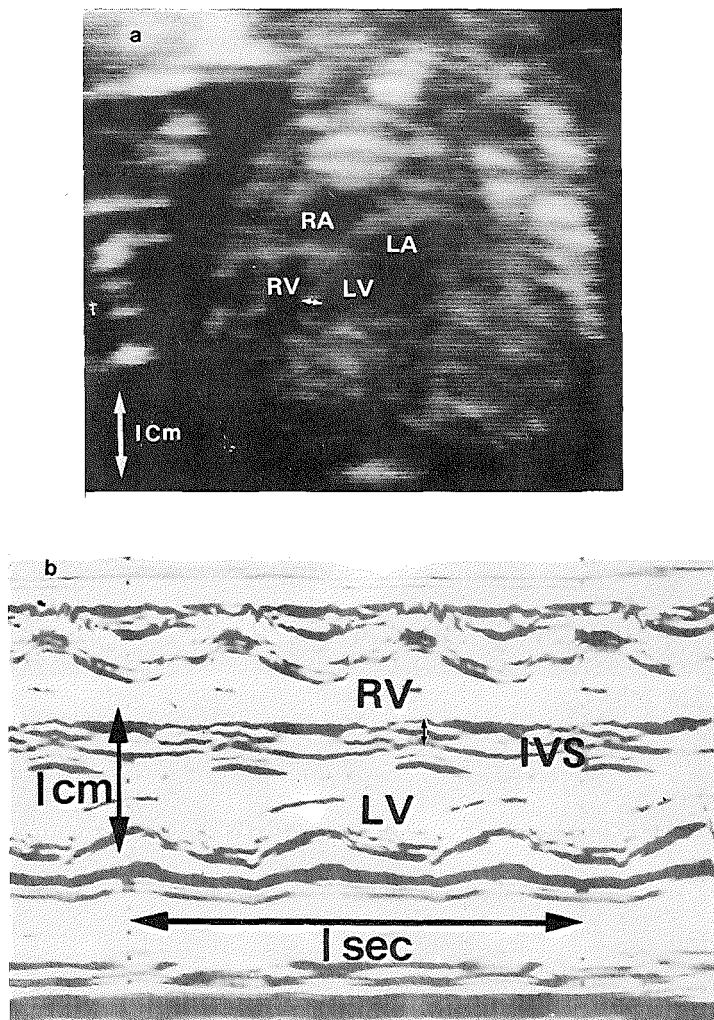


Fig.2(a). Four-chamber view of fetal heart at 19 weeks gestation. RA=right atrium, RV=right ventricle, LA=left atrium, LV=left ventricle, Sp=fetal spine, S=interventricular septum, arrows mark borders of septum. (b)Fetal M-mode recording at 19 weeks gestation. RV=right ventricle, LV=left ventricle, IVS=interventricular septum.

Fig.1(a). Maternal electrocardiogram showing left hypertrophy and 'strain' pattern with abnormal Q waves in V4-V6. (b)Maternal parasternal long axis view echocardiogram. LV=left ventricle, LVPW=left ventricular posterior wall, Ao=aorta, S=interventricular septum, arrows mark borders of septum. (c)Maternal short axis view echocardiogram. LV, LVPW and S as for Figure 1b.

NB. Both mother and child were difficult ultrasonic subjects but in real-time images the borders of the septum were clear in both patients.

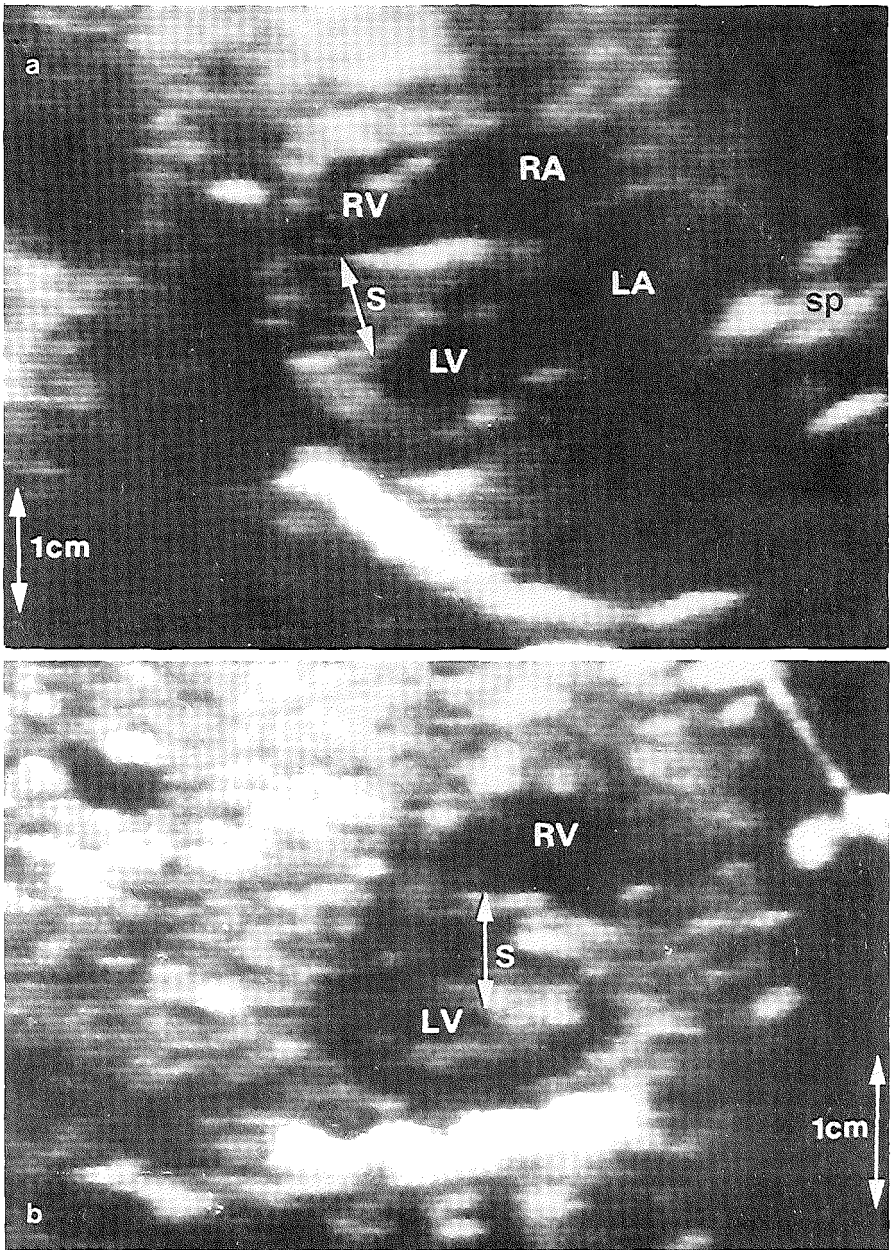


Fig.3(a). Four-chamber view in fetal heart at 27 weeks gestation. RA=right atrium, RV=right ventricle, LA=left atrium, LV=left ventricle, Sp=fetal spine, S=interventricular septum, arrows mark borders of septum. (b)Short axis view of fetal heart at 27 weeks gestation. RV, LV, S and arrows as for Figure 3a.

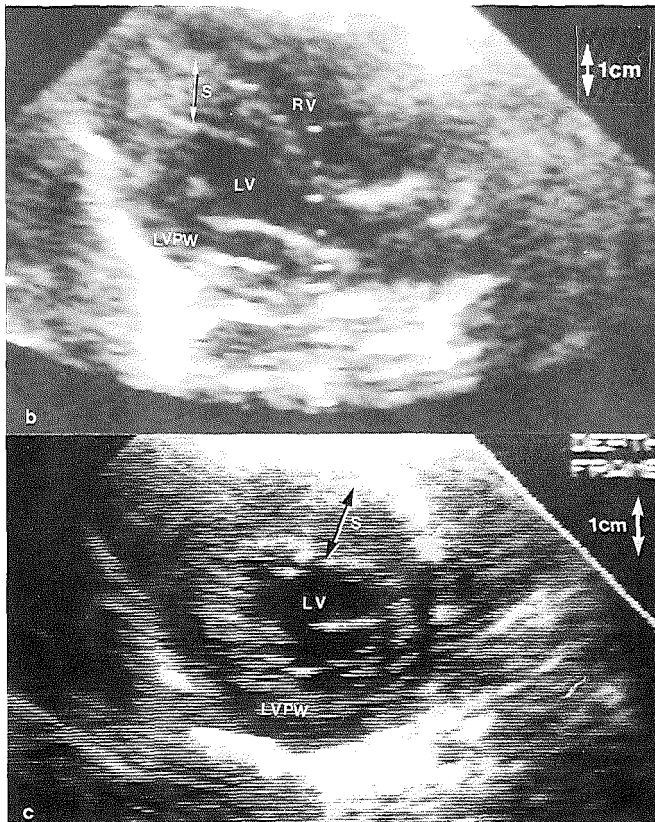
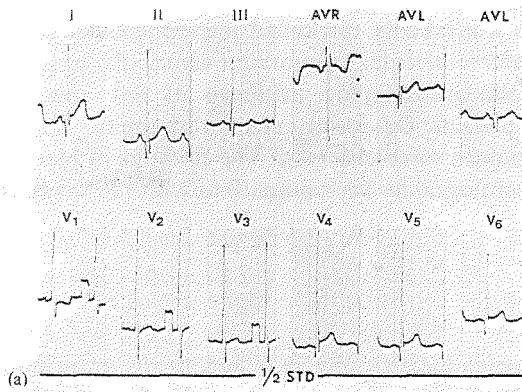


Fig.4(a). Postnatal electrocardiogram at age 7 months showing biventricular hypertrophy with ST-T abnormalities and deep Q waves in V4-V6. (b)Postnatal parasternal long axis view at age 7 months. RV=right ventricle, LV=left ventricle, LVPW=left ventricular posterior wall, S=interventricular septum, arrows indicate borders of septum. (c)Postnatal short axis view at age 7 months. LV, LVPW, S and arrows as for Figure 4b.

Echocardiography performed at birth and thereafter revealed a generalized hypertrophy with a markedly thickened interventricular septum (Figure 4b, c). The ratio of the interventricular septum /left ventricular posterior wall was greater than 1.3. No echocardiographic evidence of left ventricular outflow tract obstruction was present. On serial echocardiographic studies in the following 15 months no changes were observed. The findings of electrocardiogram, chest X-ray and echocardiography are compatible with the diagnosis of hypertrophic cardiomyopathy.

### *Discussion*

Asymmetric septal hypertrophy is a genetically transmitted disease with a high degree of penetrance which may be difficult to detect clinically, in early life. It has been shown to mimic many other forms of congenital heart disease. Maron et al. (1982) studied 20 infants with hypertrophic cardiomyopathy, 14 of whom had been initially diagnosed with a congenital cardiac malformation other than hypertrophic cardiomyopathy. His group also stated that ventricular septal thickening was substantial both in patients studied before and after the age of 6 months indicating that the condition may be present early in life and is probably congenital. The findings in our case with severe thickening of the interventricular septum at 27 weeks of gestation support this view. It is of interest to note that the two-dimensional images at 19 and 21 weeks of gestation were unremarkable and that the M-mode echocardiographic measurements (St. John Sutton et al., 1984; Allan et al., 1982) were normal.

In the neonatal period and during the first 15 months of life the infant was asymptomatic and heart disease would not have been suspected if prenatal echocardiography had not been performed.

To the best of our knowledge this is the first report of the prenatal diagnosis of this disease. We feel that it would be of great interest to do a prospective longitudinal echocardiographic study of all fetuses at risk for genetically transmitted hypertrophic cardiomyopathy to try to gain further insight into the early pathogenesis and manifestation of this disease.

### *Acknowledgements*

We are grateful to the Dutch Prevention Fund (Project number 28-926) for funding this work.

### *References*

- Allan LD, Joseph MC, Boyd EGCA, Campbell S, Tynan M. (1982). M-mode echocardiography in the developing human fetus. *Br Heart J* 47, 573-583.

- Barr PA, Celermajer JM, Bowdler JC, Cartmill TB. (1973). Idiopathic hypertrophic obstructive cardiomyopathy causing severe right ventricular outflow tract obstruction in infancy. *Br Heart J* 35, 1109-1115.
- Clark CE, Henry WL, Epstein SE. (1973). Familial prevalence and genetic transmission of idiopathic hypertrophic subaortic stenosis. *New Engl J Med*, 289, 709-714.
- Emanuel R, Marcomichelakis J, Withers R, O'Brien K. (1983). Asymmetric septal hypertrophy and hypertrophic cardiomyopathy. *Br Heart J* 49, 309-316.
- Epstein SE, Henry WL, Clark CE et al. (1974). Asymmetric septal hypertrophy. *Ann Intern Med* 81, 650-680.
- Fiddler GI, Tajik AJ, Weidmann WH, McGoon DC, Ritter DG, Guilani ER. (1978). Idiopathic hypertrophic subaortic stenosis in the young. *Am J Cardiol* 42, 793-799.
- Frank S, Braunwald E. (1968). Idiopathic hypertrophic subaortic stenosis with clinical analysis of 126 patients with emphasis on the natural history. *Circulation* 37, 759-788.
- Gutgesell HP, Speer ME, Rosenberg WC. (1979). Characterisation of the cardiomyopathy in infants of diabetic mothers. *Circulation* 61, 441-450.
- Larter WE, Allen HD, Sahn DJ, Goldberg SJ. (1976). The asymmetrically hypertrophied septum. Further differentiation of its causes. *Circulation* 53, 19-27.
- Maron BJ, Edwards JE, Henry WL, Clark CE, Bingle GJ, Epstein SE. (1974). Asymmetric septal hypertrophy (ASH) in infancy. *Circulation* 50, 809-820.
- Maron BJ, Gottdiener JS, Bonow RO, Epstein SE. (1981a). Hypertrophic cardiomyopathy with unusual locations of left ventricular hypertrophy undetectable by M-mode echocardiography: identification by wide-angle two-dimensional echocardiography. *Circulation* 63, 409-418.
- Maron BJ, Gottdiener JS, Epstein SE. (1981b). Patterns and significance of the distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a wide-angle two-dimensional echocardiography study of 125 patients. *Am J Cardiol* 48, 418-428.
- Maron BJ, Tajik AJ, Ruttenberg HD et al. (1982). Hypertrophic cardiomyopathy in infants: clinical features and neonatal history. *Circulation* 65, 7-17.
- Nasser WK, Williams JF, Mishkin ME et al. (1967). Familial myocardial disease with and without obstruction to left ventricular outflow. Clinical, hemodynamic and angiographic findings. *Circulation* 35, 638-652.
- Shand DG, Sell CG, Oates JA. (1971). Hypertrophic obstructive cardiomyopathy in an infant. propranolol therapy for three years. *New Engl J Med* 285, 843-844.
- St.John Sutton MG, Gewitz MH, Shah B et al. (1984). Quantitative assessment of growth and function of the cardiac chambers in the normal human fetus: a prospective longitudinal echocardiographic study. *Circulation* 69, 645-654.
- Van Dorp WG, ten Cate FJ, Vletter WB, Dohmen H, Roelandt J. (1976). Familial prevalence of asymmetric septal hypertrophy. *Eur J Cardiol* 4/3, 349-357.

### 3.2 Early prenatal detection of double outlet right ventricle by echocardiography

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Published in British Heart Journal, Vol 54:340-342 (1985)

#### *Summary*

A double outlet right ventricle with subpulmonary ventricular septal defect and right sided hypoplastic aorta was diagnosed in a 22 week fetus of a mother with diabetes mellitus. Elective termination of pregnancy was carried out and the echocardiographic findings were confirmed. Early prenatal detection of congenital heart disease may allow elective termination of pregnancy when the fetus has severe defects.

The first description of double outlet right ventricle was provided in 1793 by Abernethy,<sup>1</sup> which was subsequently given the term "double outlet right ventricle" by Witham in 1957.<sup>2</sup> Double outlet right ventricle is a rare condition forming  $\leq 1\%$  of all congenital heart defects, and the term refers to a group of complex and heterogenous malformations that have in common only the origin of both great vessels from the right ventricle. Other cardiac malformations are always present, and frequently multiple abnormalities coexist. These may include one or more ventricular septal defects, systemic or pulmonary or left ventricular outflow obstruction, and major atrioventricular valve abnormalities.

Double outlet right ventricle may occur with any atrial situs, several different atrioventricular connections, and many other variations. Situs solitus and atrioventricular concordance are, however, the most common findings.

Cross sectional echocardiography has proved useful in the diagnosis of double outlet right ventricle. A segmental sequential approach that reliably identifies both ventricles and great vessels is mandatory. Many of the associated cardiac lesions are of paramount clinical importance and are recognisable by echocardiography. These features of diagnosis are critical in prenatal diagnosis as echocardiography is the only tool available, and further advice and obstetric management must be based on these findings.

We report the detection of double outlet right ventricle with subpulmonary ventricular septal defect and a right sided hypoplastic aorta in a 22 week old fetus of a mother with diabetes mellitus class C, type I (White classification).<sup>3</sup>

#### *Case report*

A 21 year old gravida I with diabetes mellitus type C, who had been diabetic since the age of 13 years, underwent amniocentesis at 16 weeks gestation, which



showed a normal female karyotype. She was referred to this unit for prenatal echocardiography in view of the known association of cardiac structural abnormalities in the offspring of diabetic patients. Ultrasonic examination of the fetus was carried out at 22 weeks' gestation with a Dasonics Cardio Vue 100 mechanical sector scanner with 5 MHz transducer. Fetal size was appropriate for gestational age. Scanning of the fetal heart showed atrioventricular concordance and a large subpulmonary ventricular septal defect. Both great vessels were connected to the right ventricle with a side by side position with the aorta, which appeared hypoplastic, to the right of the pulmonary artery (Fig. 1a). The pulmonary artery was seen to be continuous with the mitral valve. No other structural anomalies were observed in the fetus.

### *Necropsy findings*

The parents were informed of the findings and requested termination of the pregnancy, which was performed at 23 weeks' gestation. A female fetus weighing 400 gr was delivered. Postmortem examination of the heart confirmed the antenatal echocardiographic findings. There was a large subpulmonary perimembranous ventricular septal defect and a slit-like muscular ventricular septal defect in the inlet septum. Both great vessels were connected to the right ventricle with the aorta to the right of the pulmonary artery (Fig. 1b). There was subaortic stenosis and slight underdevelopment of the descending aorta. Tubular hypoplasia of the aortic arch was found between the left subclavian and left common carotid arteries. The pulmonary valve was in fibrous continuity with the mitral valve. No other structural anomalies were present in the fetus.

### *Discussion*

Diabetes mellitus is known to be associated with an increased risk of fetal abnormalities,<sup>4,5</sup> including skeletal, central nervous system, genitourinary, gastrointestinal, and cardiac anomalies. Cardiovascular anomalies may occur in approximately 5% of these infants.<sup>6,7</sup>

Amniocentesis, which in this unit is performed routinely in juvenile diabetics for alpha fetoprotein estimation and karyotyping, had been performed at 16 weeks' gestation and showed a normal concentration of alpha fetoprotein and normal female karyotype. Had this not been the policy karyotyping would have been performed after detection of the cardiac abnormalities to exclude chromosomal abnormality. The prognosis in patients with double outlet right ventricle depends on the severity of associated lesions, and the haemodynamic disturbances may be extremely variable. Clinical presentation is influenced by the presence or absence of pulmonary stenosis, the position of the ventricular septal defect in relation to the great arteries, and other associated major defects - for example, left ventricular outflow obstruction, mitral valve abnormalities, and aortic arch abnormalities such as coarctation, hypoplasia, or even complete interruption.

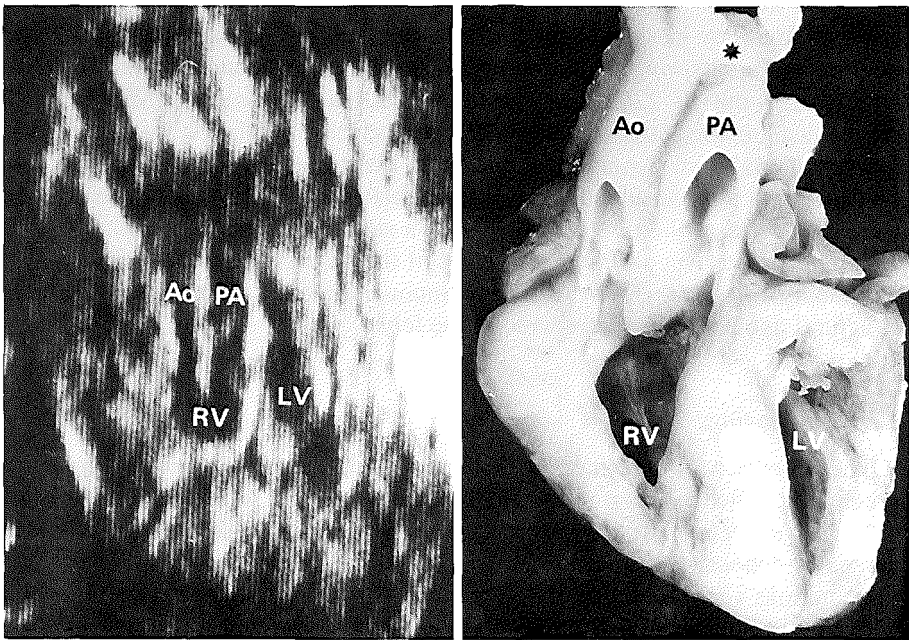


Fig.1(a). Longitudinal cross sectional echocardiogram in the fetus showing both great vessels connected to the right ventricle (RV). In real-time images the aorta (Ao) was traced to the head and neck vessels and looked hypoplastic; the pulmonary artery (PA) was also traced to its bifurcation. The ventricular septal defect was not visualised in this plane. (b)Morphological appearance of the fetal heart cut in a section equivalent to the echocardiogram in (a). The outflow tract into the aorta is narrow and the ascending aorta slightly underdeveloped. There is tubular hypoplasia (\*) between the left subclavian and left common carotid arteries. Lv, left ventricle.

Patients with the abnormalities described in the fetus in this report tend to present early in life and, clinically, may resemble patients with complete transposition and ventricular septal defect since the haemodynamic effects are similar. Franks and Lincoln studied 46 patients from the Brompton Hospital who underwent surgical correction of double outlet right ventricle between April 1973 and April 1981.<sup>8</sup> The patients were subdivided into groups according to the position of the ventricular septal defect, five had additional abnormalities. The overall mortality in this group was 80%. Palliation alone carried a mortality of 36%, and in the patients without significant pulmonary stenosis was not always possible. In patients with subpulmonary defects systemic saturation is usually low and pulmonary banding may reduce this still further to unacceptable levels.

The detection of serious fetal cardiac abnormalities allows the option for termination of pregnancy<sup>9 10</sup> if they are diagnosed early enough in gestation, and the parents in our case requested this option after being told of the poor prognosis.

Ideally, scanning of fetuses at risk for structural cardiac defects should be performed between 17 and 24 weeks' gestation. During this period of pregnancy the heart is large enough for adequate visualisation, and there is enough amniotic fluid surrounding the fetus to provide a good ultrasonic window. In the present case optimal imaging of the fetal heart was possible only at 22 weeks' gestation because of maternal obesity.

When congenital heart disease is diagnosed later in pregnancy or when the defect is considered amenable to surgery, or if the parents choose that the pregnancy should continue, steps can be taken to ensure optimal timing of delivery and immediate postnatal care in the paediatric cardiology unit.

We thank Dr C E Essed (Erasmus University, Rotterdam) for performing the necropsy and the Dutch Prevention Fund for funding this work.

### *References*

- <sup>1</sup> Abernethy J. Surgical and physiological essays. London: James Evans, 1793: 163.
- <sup>2</sup> Witham AC. Double outlet right ventricle. *Am Heart J* 1957; 53: 928-39.
- <sup>3</sup> White P. Diabetes mellitus in pregnancy. *Clinics in Perinatology* 1974; 1: 331-47.
- <sup>4</sup> Day RE, Insley J. Maternal diabetes mellitus and congenital malformation. *Arch Dis Child* 1976; 51: 935-38.
- <sup>5</sup> Gabbe SG. Congenital malformations in infants of diabetic mothers. *Obstet Gynecol Surv* 1977; 32: 125-32.
- <sup>6</sup> Rowland TW, Hubbell JP Jr, Nadas AS. Congenital heart disease in infants of diabetic mothers. *J Pediatr* 1973; 83: 815-20.
- <sup>7</sup> Nora JJ, Nora AH. Congenital heart disease: environmental factors. In: Nora JJ, Nora AH, eds. *Genetics and counseling in cardiovascular diseases*. Springfield, Illinois: Charles C Thomas, 1978: 147-54.
- <sup>8</sup> Franks R, Lincoln C. Surgical management of the double outlet right ventricle. In: Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, eds. *Paediatric cardiology Volume 5*. London: Churchill Livingstone, 1983: 441-50.
- <sup>9</sup> Silverman NH, Enderlein MA, Golbus MS. Ultrasonic recognition of aortic valve atresia in utero. *Am J Cardiol* 1984; 53: 391-2.
- <sup>10</sup> Stewart PA, Tonge HM, Wladimiroff JW. Arrhythmia and structural abnormalities of the fetal heart. *Br Heart J* 1983; 50: 550-54.

### 3.3 Antenatal real-time ultrasound diagnosis of a congenital cardiac malformation

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Published in European Journal of Obstetrics and Gynecology and Reproductive Biology, Vol 14: 233-237 (1983)

A case is presented of the antenatal diagnosis of a congenital cardiac abnormality in the fetus of a narcotic dependent mother, diagnosed by two-dimensional echocardiography.

Infants born to narcotic dependent mothers require intensive management for their withdrawal symptoms, which may include respiratory and feeding difficulties. Possible cardiac abnormalities may not be considered as a cause for these symptoms until more overt signs appear.

The clinical course of infants with coarctation of the aorta, which occurs in 1/1600 live births, is related to the type and degree of coarctation and to the presence, or absence, of other cardiac lesions. Antenatal knowledge of a cardiac malformation should allow the planning of suitable modes of delivery and prompt treatment even before the onset of obvious clinical signs.

**Keywords:** antenatal ultrasonic diagnosis; cardiac abnormality; maternal narcotic dependence

#### *Case report*

An 18-yr-old gravida I, addicted to heroin and maintained on 40 mg methadone daily, was admitted to hospital at 32 wk of gestation for assessment of clinical and ultrasound evidence of fetal growth retardation. Real-time echocardiography, using a Toshiba SAL 20A, revealed a grossly dilated right ventricle, right atrium and pulmonary artery and thickened, abnormal-looking tricuspid valve (Fig. 1a). The great arterial connections were normal. The ascending aorta was not seen in its entirety, but the pulmonary artery and valve were seen in apparent continuity with the descending aorta (probably due to the ductus arteriosus). The ratio of the pulmonary artery to the aortic root diameter was approximately 2:1. The fetal heart rate was 140 beats per minute, which is within normal limits. There was a normal beat-to-beat variation. There were no signs of cardiac failure, e.g. enlarged fetal liver or fetal ascites. A female infant was delivered by forceps at term, with a weight of 2.9 kg. A repeat echocardiogram 3 h post-partum was consistent with the antenatal ultrasound examination. The infant had no

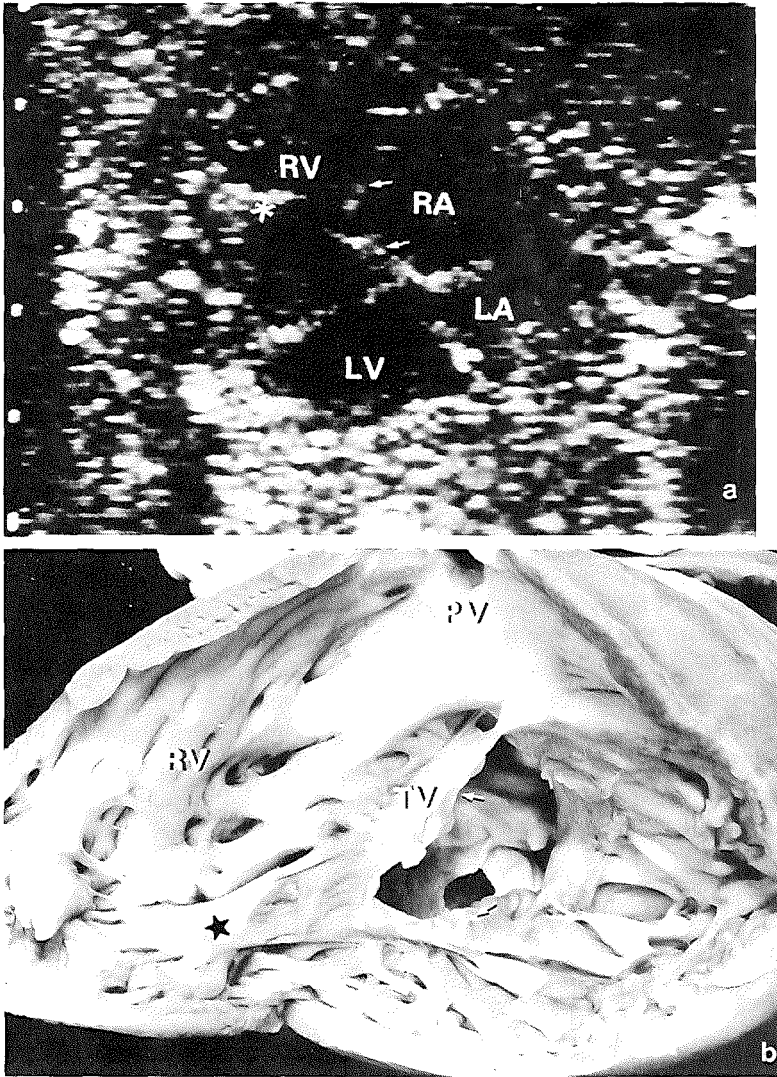


Fig.1a. Four-chamber view showing grossly dilated right atrium, right ventricle and tricuspid valve (TV) annulus. In real-time images the TV appeared thickened and the anterior TV leaflet had an abnormal motion pattern. \*=The papillary muscle of the TV; LV=left ventricle.

Fig.1b. Anatomic specimen showing the right side of the heart. The right ventricle (RV), pulmonary valve annulus and tricuspid valve (TV) annulus were dilated. The TV leaflets were highly dysplastic. Note that the anterior papillary muscle was fused with the anterior wall of the RV (\*).

problems directly post partum, but at the age of 24 h, due to increased respiratory rate and poor feeding, she was transferred to the pediatric cardiology unit for further assessment. On examination the infant was found to have a systolic pressure difference of 10 mm Hg between the right arm and leg. The lower half of the body was cyanotic. The electrocardiogram showed sinus rhythm, an axis of  $+135^\circ$  and evidence of reduced left ventricular activity and right atrial and ventricular hypertrophy in the precordial leads. The chest X-ray showed a cardiothoracic ratio of 0.55, a prominent right atrium and normal lung vascularity. Echocardiography confirmed the previous findings and showed a narrowed segment of aorta.

Cardiac catheterisation and angiocardiography showed a preductal coarctation of the aorta with a hypoplastic isthmus, a persistent left-sided ductus arteriosus (Fig.2), secondary pulmonary hypertension and an anatomically patent foramen ovale.

At the age of 3 days the infant underwent surgical correction of the coarctation, whereby the subclavian artery was used to bypass the hypoplastic segment, because subclavian flap aortoplasty repair was not possible. The ductus arteriosus was closed. Four days post-operatively the infant developed an A-V block which was treated with an increased dosage of isoprenaline, but during the fifth post-operative night a bradycardia developed, followed by asystole and attempts at resuscitation were unsuccessful.

At autopsy, the right ventricle, right atrium, pulmonary artery and ductus arteriosus were grossly abnormal (Fig.1b). The anterior leaflet was hypoplastic and thickened, while the anterior papillary muscle was a rudimentary rim which was fused with the anterior wall of the right ventricle (Fig.1b; asterisk). The chordae were short and attached directly to the right ventricular wall. All leaflets showed thickened, nodular areas in their rims. The tricuspid valve was probably incompetent. Apart from the cardiac abnormalities the infant was normal.

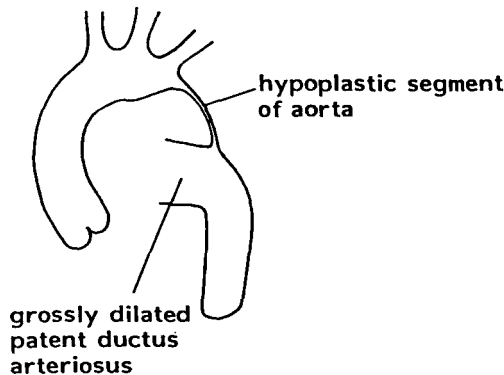


Fig.2. Drawing to show degree and site of hypoplasia of the aorta.

## Discussion

Ultrasonic evaluation of the fetal heart facilitates the diagnosis of major structural and rhythm abnormalities in utero. Qualitative information obtained by real-time cross-sectional techniques (Lange et al., 1980) showed that demonstration of normal fetal cardiac anatomy was fairly easy. Success rates for visualising the four-chamber, short axis great artery, ascending and descending aorta plus arch, and inferior/superior vena cavae views were 96, 95, 87 and 76%, respectively.

A study (Kleinman et al., 1980) using two-dimensional and M-mode echocardiography described the possibilities of using a combination of these methods to diagnose fetal congenital heart disease and cardiac dysrhythmias.

A description of fetal cardiac anatomy and vascular dynamics (McCallum, 1981) pointed out that advances in Doppler ultrasound instruments provide new techniques for studying fetal blood flow. Further development of these techniques may provide important new information of fetal well-being.

Filkins et al. (1981) described a case in which an increased cardiothoracic ratio was found antenatally. After delivery the infant was found to have complex congenital heart disease and trisomy 18. Although precise abnormalities were not diagnosed prior to delivery, cardiac malformation was suspected on the basis of cardiomegaly.

The indications for fetal echocardiography in our unit are listed in Table I. Maternal exposure to cardiac teratogens including anticonvulsants, lithium chloride, alcohol, narcotics, folic acid antagonists, oral contraceptives and dextro amphetamines should prompt evaluation of the fetal heart. Fetuses exposed in early gestation to viruses including rubella, coxsackie B, herpes or cytomegalic virus should also be evaluated.

Antenatally, in the case reported here, the reason for the dilatation of the right side of the heart was thought possibly to result from a coarctation of the aorta because the enlarged pulmonary valve was not thought to be stenotic, although the coarctation was not visualised on the antenatal echocardiogram. The incompetence of the tricuspid valve probably increased the effects of the coarctation, resulting in such gross dilatation of the right side of the heart.

Table I. Indications for fetal echocardiographic examinations

Hereditary predisposition	
Fetal	Maternal
Growth retardation	Age above 40 yr
Arrhythmia	Diabetes
Polyhydramnios	Exposure to cardiac teratogens
Ascites	Exposure to rubella or other viruses in early gestation
	Connective tissue disorders

The relatively small size of the left heart was not thought to be due to hypoplasia of the left ventricle, as the left ventricular apex reached the same level as the right ventricular apex. In a previous report of antenatal echocardiographic diagnosis of hypoplastic aortic arch (Allan et al., 1981) the diagnosis was suspected on the basis of failure to visualise the aortic arch. In this case part of the aortic arch was visualised, including head and neck arteries, but it would appear the coarctation was obscured by the dilated ductus arteriosus which lay directly in front of the coarctation. This allowed visualisation of the pulmonary artery, in apparent continuity with the descending aorta, in the echocardiographic planes available in this fetus. The dilated ductus arteriosus could also explain the absence of cardiac failure during the antenatal period. An increased incidence of congenital abnormalities related to narcotic abuse has been described in a group of 830 infants born to drug-dependent mothers (Ostrea and Chavez, 1979). These abnormalities included cardiac defects.

It would appear that ultrasound examination, especially including cardiac examination, is a useful adjunct in the management of pregnancies of drug-dependent mothers because of increased risk and the fact that early symptoms in the neonate may be related to the narcotic abstinence syndrome and not initially to a possible congenital cardiac malformation.

### *Acknowledgements*

We wish to thank Professors V.H. de Villeneuve and E.Bos and Dr.C.E.Essed for clinical, surgical and pathological findings.

### *References*

- Allan LD, Tynan M, Campbell S and Anderson RH (1981): Identification of congenital cardiac malformations by echocardiography in midtrimester fetus. *Br Heart J*, 46, 358-362.
- Filkins KA, Brown TF and Levine RO (1981): Real-time ultrasonic evaluation of the fetal heart. *Int J Gynaec Obstet*, 19, 35-39.
- Kleinman CS, Hobbins JC, Jaffe CC, Lynch DC and Talner NS (1980): Echocardiographic studies of the human fetus: prenatal diagnosis of congenital heart disease and cardiac dysrhythmias. *Pediatrics*, 65, 1059-1067.
- Lange LW, Sahn DJ, Allen HD, Goldberg SJ, Anderson C and Giles H (1980): Qualitative real-time cross-sectional echocardiographic imaging of the human fetus during the second half of pregnancy. *Circulation*, 62, 799-806.
- McCallum WD (1981): Fetal cardiac anatomy and vascular dynamics. *Clin Obstet Gynecol* 24, 3, 837-849.
- Ostrea EM Jr, Chavez CJ (1979): Perinatal problems (excluding neonatal withdrawal) in maternal drug addiction: a study of 830 cases. *J Pediatr* 94, 292-295.



### 3.4 The role of ultrasound in the early diagnosis of fetal structural defects following maternal anticonvulsant therapy

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Published in: *Ultrasound in Medicine and Biology* Vol 14: 8: 657-660, 1988.

#### *Abstract*

A total of 162 pregnant subjects using anticonvulsant drugs were examined for fetal congenital defects over a period of five years. In 138 of these subjects, alpha-feto-protein (AFP) levels were determined in amniotic fluid at 16 weeks of gestation to rule out spina bifida. In all instances, a fetal anomaly scan was performed between 18 and 20 weeks of gestation. AFP levels were always within the normal range; neonatal examination revealed no spina bifida; however, in seven newborns, a single, or multiple structural defects were established.

Apart from cases of severe hydrocephaly, hypospadias and radius aplasia, the anomalies were too small to be detected by present-day ultrasound equipment. Couples should be informed of the limitations of ultrasound in the early detection of structural defects previously associated with the use of anticonvulsant drugs.

**Keywords:** ultrasound, anticonvulsant drugs, fetal structural defects.

#### *Introduction*

Present real-time ultrasound equipment allows the diagnosis of a considerable number of fetal structural anomalies as early as 16 weeks of gestation. This is particularly important when there is an increased risk of an affected infant as is the case following the use of anticonvulsive agents. Under these circumstances, the risk of fetal spina bifida is increased 1.5 to 2 - fold, (Meinardi et al, 1983). Also, other structural anomalies e.g., cleft palate, cardiac and skeletal defects have been associated with anticonvulsant agents. In the Netherlands, pregnant subjects using these agents are offered amniocentesis for AFP determination at 16 weeks of gestation, to exclude spina bifida. Some of the other abnormalities, however, may only be diagnosed by ultrasound.

In this communication, the results of a prospective study on the role of ultrasound in the early diagnosis of fetal structural defects, associated with maternal use of anticonvulsant drugs will be presented.

### *Patients and Methods*

Between January 1982 and April 1987, a total of 162 pregnancies (164 fetuses), associated with the use of anticonvulsant drugs, were studied. In 138 of these pregnancies AFP determination in amniotic fluid was carried-out at 16 weeks of gestation to exclude spina bifida. In all instances, an ultrasound examination of fetal anatomy was performed between 18 and 20 weeks, using a 2-dimensional mechanical sector scanner (Diasonics CardioVue 100; transducer carrier frequency: 5MHz) to rule out other structural defects. Following delivery, a careful search for congenital defects was made by the neonatologist. In case of pregnancy termination as a result of a lethal structural defect, a post-mortem examination was carried-out. A follow-up study concerning growth and development in infancy and childhood is programmed and will be the subject of future publication.

### *Drug regime*

The following anticonvulsant agents were used, separately or in combination:

- **barbiturates**  
phenobarbital: increased risk of cardiac anomalies, cleft lip and palate, mental retardation, dysmorphic features (Janz, 1982),
- **benzodiazepines**  
diazepam: usually in combination with other anticonvulsant drugs; possibly a slight increased risk of cleft lip (Janz, 1982),
- **hydantoin derivatives**  
phenytoin: increased risk of cardiac anomalies, cleft lip and palate, skeletal abnormalities, mental retardation, dysmorphic features (Janz, 1982),
- **other anticonvulsant drugs**  
*carbamazepine*: increased risk of spina bifida and/or encephalocele (0.5%), (Nakane et al, 1980; Hiilesmaa et al, 1981; Lindhout, 1985; Robert et al, 1986). In combination with valproic acid and phenobarbital or with phenytoin, possibly an increased risk of various other structural defects.  
*valproic acid*: increased risk of spina bifida (1-2%), cardiac anomalies, cleft lip and palate and skeletal defects (Robert and Guibaud, 1982; Lindhout, 1985).

When more than one agent was used, it was nearly always a combination of carbamazepine and valproic acid, or carbamazepine and phenobarbital.

### *Results*

In all 138 subjects who underwent amniocentesis, a normal AFP level in amniotic fluid was established. Neonatal examination revealed no spina bifida. In seven infants, one or several structural anomalies of a different nature were observed.

Table 1 presents the antenatal and postnatal diagnoses of structural defects by

Table 1. A prospective study of the role of ultrasound in 162 pregnant subjects using anticonvulsant drugs

Anticonvulsant drug	number of pregnancies	patient number	antenatal findings	postnatal findings
<b>A. Monotherapy</b>				
carbamazepine	45	1	severe hydrocephaly	TOP; hydrocephaly, bilateral cleft lip and palate, hypospadias
		2	transient hydrocephaly	no abnormalities
		3	--	small muscular VSD
valproic acid	33	4	--	two cord vessels
		5	--	bulging forehead, low ear implant
phenytoin	27	6	hydospadia	hypospadias, cleft palate
		7	--	hydantoin syndrome
phenobarbital	17	8	left radius aplasia	left radius aplasia, left blepharophimosis, asymmetric face
diazepam	2		--	--
<b>B. Combined therapy</b>				
usually: carbamazepine + valproic acid or carbamazepine + phenobarbital	38	9	small transient VSD	no abnormalities

TOP = Termination of pregnancy

VSD = Ventricular septal defect

ultrasound relative to the type of anticonvulsant agent used. The following structural anomalies were recognized by ultrasound before birth:

- hypospadias (phenytoin); after birth, there also appeared to be a cleft palate (patient 6),
- left radius aplasia (phenobarbital); after birth, there also appeared to be a blepharophimosis on the left side and asymmetrical face (patient 8),
- severe hydrocephaly, which was characterized by a raised ventricle /hemisphere ratio according to van Egmond et al (1985). Pregnancy was terminated at 19 weeks of gestation. The anomaly was confirmed by autopsy. After delivery, there also appeared to be a bilateral cleft lip and palate and hypospadias (carbamazepine, patient 1).

In the remaining four newborns, one or several structural defects were not detected before birth:

- the hydantoin syndrome (phenytoin) characterized by slight growth retardation,

- microcephaly, a flat nasal bridge, hypertelorism and hypoplasia of the distal phalanges (patient 7),
- two vessels in umbilical cord (one artery and one vein; valproic acid) (patient 4),
  - bulging forehead and low ear implant (valproic acid) (patient 5),
  - small muscular ventricular septal defect without haemodynamic consequences (carbamazepine) (patient 3).

Twice a transient anomaly was documented by ultrasound:

- ventriculomegaly at 18 weeks of gestation, which had disappeared three weeks later (carbamazepine). Postnatal development was normal (patient 2),
- membranous ventricular septal defect at 20 and 24 weeks of gestation (combination of carbamazepine and phenobarbital), which could not be traced after birth (patient 9).

### *Discussion*

In the present study, the most frequently prescribed anticonvulsant drug was carbamazepine (27.5%), followed by valproic acid (18.9%) and a combination of several agents (20.7%).

When discarding the case of two umbilical vessels, the incidence of structural defects was 3.6%. This incidence was not related to a specific drug. Antenatal ultrasound was successful in detecting serious structural anomalies, such as hydrocephaly, hypospadias and radius aplasia. However, a number of less serious defects were missed. A number of these postnatally established anomalies, such as low implantation of the ears, flat nasal bridge, bulging forehead, abnormal distal phalanges, cleft palate with normal lip development and small ventricular septal defects, are still extremely difficult to establish with present-day equipment. Some of these prenatally undetected defects are significant, in that, at a latter stage, mental development may become retarded. (Hill et al., 1982). This should be pointed out when counselling women using anticonvulsive drugs.

In the presence of a serious structural defect, such as spina bifida, pregnancy termination is usually considered. Although ultrasound has been claimed to be as reliable, or even superior, to AFP determination in amniotic fluid in the early diagnosis of spina bifida, it will very much depend on the expertise of the ultrasonographer as to which policy will be adopted. In The Netherlands, women at risk of spina bifida, will generally be offered amniocentesis at 16 weeks of gestation. No amniocentesis was performed in 24 women, either because of absence of the normally accepted indications for the procedure or because of advanced gestational age. Twice, hydrocephaly was diagnosed in association with the use of carbamazepine. In one case, the parents opted for termination of the pregnancy because of the severity of the ventriculomegaly. After delivery, there also appeared to be a bilateral cleft lip and palate and hypospadias. In the other case, there was only slight transient ventriculomegaly, which underlines

the importance of serial scans following such an observation and the need of follow-up studies.

The prenatal diagnosis of two cases of hydrocephaly in the present study is of interest in the light of an earlier observation of four cases of encephalocele, associated with the use of the same drug, carbamazepine (Rosa, personal communication). In this cohort of 164 exposed fetuses, two showed the combination of hypospadias with another midline fusion defect: one with cleft palate and one with bilateral cleft lip and palate and hydrocephaly. We compared this with data from the Eurocat Registry which monitors a population of births in the North-Eastern region of the Netherlands during the years 1981 - 1986 (Eurocat Registry 1987). This Registry notifies all hypospadias with the exception of glandular hypospadias as a single malformation. In this Registry, a combination of anomalies was found in two cases: one hypospadias with cleft palate and hypertelorism, and one hypospadias with unilateral cleft lip and palate and other anomalies diagnosed as camptomelic dysplasia (M.C.Cornel, personal communications). The denominators for these two Registry cases are 50.379 live and still births with 53 hypospadias, 22 cleft palates, 31 cleft lips and 46 cleft lips and palate (totals of single and multiple anomalies) (Eurocat Registry 1987). Therefore, the double occurrence of the combination of hypospadias with facial defects in our small cohort suggests a specific association of these midline fusion defects with treated maternal epilepsy. A similar association was observed in a study reporting ten valproate exposed spina bifida cases of which two showed hypospadias in addition to the closure defect of the neural tube (Lindhout and Schmidt, 1984). The intrauterine closure of a ventricular septal defect has been reported by others (Allan, personal communication) and ourselves (Stewart et al, 1986). Documentation of transient abnormalities during the antenatal period, may contribute to a better understanding of the teratogenic risks of certain anticonvulsant drugs and deepen insight into the pathogenesis and natural course of fetal abnormalities relative to the use of teratogenic drugs. It can be concluded, that ultrasound has a role to play in the early detection of fetal anomalies related to the use of anticonvulsant drugs. However, the above-mentioned limitations should be pointed out to those women who seek counselling because of the use of these drugs.

## References

1. Egmond-Linden A.van, Wladimiroff J.W., Niermeijer M.F., Stewart P.A. (1986). Fetal hydrocephaly: diagnosis, prognosis and management. *Ultrasound Med.Biol.* 12, 939-944.
2. Eurocat Registry. (1987). Eurocat Groningen, Drenthe, Human Genetics Institute, Groningen, The Netherlands.
3. Hiilesmaa A.K., Teramo K., Granstrom M.L., Bardy A.H. (1981). Fetal head growth retardation associated with maternal anti-epileptic drugs. *Lancet* ii, 165-167.
4. Hill R.M., Verniand W.M., Rettig G.M., Tennyson L.M., Craig J.P. (1982). Relationship between anti-epileptic drug exposure of the infant and developmental potential. In: *Epilepsy, Pregnancy*

- and the Child (edited by Janz D., Dam M., Richens A., Bossi L., Helge H., Schmidt D), pp 409-417, Raven Press, New York.
5. Janz D. (1982). On major malformations and minor anomalies in the offspring of parents with epilepsy: Review of literature. In: *Epilepsy, Pregnancy and the Child* (edited by Janz D., Dam M., Richens A., Bossi L., Helge H., Schmidt D.), pp 211-232, Raven Press, New York.
  6. Lindhout D., Schmidt D. (1984). Spina bifida and in-utero exposure to valproate. *Lancet* 2, 396.
  7. Lindhout D. (1985). Teratogenesis in maternal epilepsy: new aspects of prevention. Free University, Amsterdam, (Academic Thesis), pp 61-77.
  8. Meinardi H. (1983). The relationship between the use of anticonvulsant drugs in pregnancy and fetal structural defects. *Dutch Med.J.* 27, 2012-2016.
  9. Nakane Y., Okuma T., Takahashi R., Sato Y., Wada T. et al (1980). Multi-institutional study on teratogenicity and fetal toxicity of anti-epileptic drugs. A report of a collaborative study group in Japan. *Epilepsia* 21, 663-680.
  10. Robert E., Guibaud P. (1982). Maternal valproic acid and congenital neural tube defects. *Lancet* ii, 937.
  11. Robert E., Lofkvist E., Manguier F., Robert J.M. (1986). Evaluation of drug therapy and teratogenic risk in Rhone-Alpes district population of pregnant epileptic women. *Eur. Neurol.* 24, 436-443.
  12. Stewart P.A., Wladimiroff J.W., Niermeijer M.F., Witsenburg M., Elzenga N.J., Spritzer R. (1986). Prenatal ultrasound diagnosis of congenital heart defects. *Dutch Med.J.* 130, 2040-2045.

## Chapter 4

## Fetal echocardiography in patients with complications in the present pregnancy

### *Introductory remarks*

Certain complications of pregnancy may be associated with fetal CHD, either alone, or in combination with structural anomalies of other organ systems and / or chromosomal abnormalities.

Chapter 4.1 lists the indications for fetal echocardiography in patients with 2nd and 3rd trimester pregnancy complications.

For the purposes of calculating the abnormality rates the entire group has been included. For more detailed information concerning the fetuses referred with an arrhythmia see Chapter 6.

The patients were studied over a six year period from 01.01.82 - 01.01.88.

In Chapter 4.2 two articles document the fetal pathology diagnosed in combination with chromosomal abnormalities.

Chapter 4.3 describes the relationship between fetal CHD and intrauterine growth retardation.

The article in Chapter 4.4 addresses the diagnosis of two cases with complex abnormalities of situs combined with CHD, not previously described.

### 4.1 Indications for fetal echocardiography

Patients with pregnancy complications are at a high risk of having associated congenital heart disease (CHD) (between 11% and 41%, see Table 1), especially when referred with polyhydramnios, suspected pathology of other fetal organ systems (see chapter 4.2), and omphalocele (Wladimiroff et al., 1983)

Patients were scanned between 16 and 41 weeks of gestation - usually in the late second, or third trimester. Most late referrals were due to the late occurrence in pregnancy of abnormal obstetric findings. In the Netherlands routine ultrasound scanning in every pregnancy is not standard practice. Routine screening may have detected a number of severe anomalies before the onset of obstetric complications. Earlier diagnosis would enable intervention when lethal defects are found.

In the majority of the referred cases (>95%) in whom CHD was diagnosed in our unit, the cardiac anomaly was not suspected by the referring unit despite the frequently correct suspicion of other organ system anomalies.

In the entire group of 440 patients there were 79 correctly predicted cardiac

Table 1. Fetal echocardiographic findings from 440 cases of 2nd and 3rd trimester complicated pregnancies

Presenting indication	No	False neg.	False pos.	True pos.	Incidence CHD	Mortality
Extrasystoles (+ 12 NSR)	139	1	-	6		
Bradycardia	22	-	-	12		
Tachycardia	28	-	-	4		Discussed further in Chapter 6
Polyhydramnios	53	1	1	10	11 (20%)	9 ( 81%)
Fetal ascites	37	-	1	5	5 (13.5%)	4 ( 80%)
IUGR	51	1	1	5	6 (11%)	5 ( 83%)
Suspected Fetal Pathology	75	-	-	31	31 (41%)	27 ( 87%)
Omphalocele	19	-	1	6	6 (31.5%)	6 (100%)
Miscellaneous (inf.etc.)	16	-	-	-		
	440	3 (0.7%)	4 (0.9%)	79 (18%)		

False negative, false positive and true positive findings refer only to CHD. Precise definition of other organ system anomalies is outside the scope of this thesis.



anomalies (Table 1). In three cases CHD was diagnosed postnatally, either by ultrasound or at postmortem (Table 2), despite normal prenatal ultrasound findings. False negative findings were defined when despite normal prenatal ultrasound findings CHD was detected after birth, either clinically or at post mortem. The diagnoses which were missed were similar to those also not recognised in the high risk group (Chapter 3).

False positive diagnoses were defined when no CHD was detected postnatally, either clinically or at postmortem, despite convincing ultrasound findings prenatally. In four cases a false positive diagnosis of CHD was made (Table 3) - in each case resulting from either an anatomic or positional variant. The false positive diagnosis of transposition of the great arteries (TGA) was made early on in the study, and was made in the absence of complete identification of the entire trajectory of each vessel. The side-by-side parallel position of the great vessels (a marker postnatally) was in fact caused by distortion of the position of the heart due to enormous serous effusions.

The overall mortality (91%) in the group of fetuses displaying CHD and other anomalies predicts a very poor prognosis even when not associated with an abnormal karyogram (38% of the cases) - see Chapter 4.2. This may partly be explained by the severity of the CHD, but was also related to the frequently devastating combinations of anomalies (see Appendix)

The sensitivity and specificity calculated from this group (Table 4) indicate a great reliability in the detection of CHD in patients with other fetal or obstetric pathology.

Table 2. False negative findings in 440 complicated pregnancies

Membranous VSD	(associated with duodenal atresia and trisomy 21)
2° ASD	(associated with supraventricular extrasystoles)
TOF	(associated with oligohydramnios and IUGR)

Table 3. False positive findings in 440 complicated pregnancies

		n=
2° ASD	) anatomic variant	1
VSD + overriding aorta		1
Ventr. inversion	) positional(ascites,omphalocele)	1
TGA		1

Table 4. Assessment of fetal echocardiography for the detection of heart defects in 440 complicated pregnancies.

	CHD present	CHD absent	
CHD suspected	(a) true positive 79	(b) false positive 4	a + b = 83
CHD not suspected	(c) false negative 3	(d) true negative 354	c + d = 357
	a + c = 82	b + d = 358	totaal 440

*Sensitivity* identifies the fetuses who have CHD

$$\frac{a}{a+c} = \frac{79}{82} \times 100\% = 96\%$$

*Specificity* identifies the fetuses without CHD

$$\frac{d}{b+d} = \frac{354}{358} \times 100\% = 99\%$$

*Positive predictive value* shows the likelihood of correct prediction of CHD

$$\frac{a}{a+b} = \frac{79}{83} \times 100\% = 95\%$$

*Negative predictive value* identifies the number of fetuses correctly predicted not to have CHD

$$\frac{d}{c+d} = \frac{354}{357} \times 100\% = 99\%$$

## References

Wladimiroff JW, Molenaar JC, Niermeyer MF, Stewart PA, Van Eyck J: Prenatal diagnosis and management of omphalocele. *European Journal of Obstetrics, Gynecology and Reproductive Biology* 16: 19-23, 1983.

## 4.2 Fetal cardiac pathology as a result of chromosomal abnormalities

An abnormal karyotype was determined in 29 of 75 fetuses (38%) who also had CHD combined with other anomalies (see Appendix). Table 1 lists the frequency of abnormal karyotype.

Tables 2-5 give a more detailed description of the types of cardiac anomalies associated with these chromosomal abnormalities. This is followed by two articles (Chapters 4.2.1 and 4.2.2) dealing with chromosome related cardiac and extracardiac anomalies.

Table 1. Chromosomal abnormalities in complicated pregnancies with CHD

Trisomy 18	(n=12)
Trisomy 13	(n= 7)
Trisomy 21	(n= 5)
47 XYY	(n= 1)
46 xi (xq)	(n= 1)
45 XO	(n= 1)
46 X, der, (Y)	(n= 1)
46 XX, del(22)(q11.1q 12.1)	(n= 1)

Table 2. Types of CHD in pregnancies complicated by Trisomy 21

Trisomy 21 (n=5)	- TOF
	- CAVSD
	- DORV
	- VSD + duodenal atresia
	- CAVSD + duodenal atresia

Table 3. Types of CHD in pregnancies complicated by Trisomy 18

Trisomy 18 (n=12)	- VSD
2x	- VSD + MCA
	- AVSD + MCA
	- DORV + MCA
	- TOF + MCA
	- HLHS + MCA
	- Complex CHD
	- VSD + omphalocele
2x	- DORV + omphalocele
	- CAVSD + encephalocele

Table 4. Types of CHD in pregnancies complicated by Trisomy 13

Trisomy 13 (N=7)	- DORV
	- VSD
	- Complex CHD + MCA
	- VSD + MCA
	- DORV + MCA
	- TOF + MCA
	- DORV + omphalocele

Table 5. Types of CHD in pregnancies complicated by miscellaneous chromosomal abnormalities

47 XYY	(n=1)	- Complex CHD
46 xi (xq)	(n=1)	- CAVSD + MCA
45 XO	(n=1)	- HLHS + cystic hygroma
46 X, der, (Y)	(n=1)	- Ebstein + PS
46XX, del(22)(q11.1q12.1)	(n=1)	- TOF

TOF = Tetralogy of Fallot, CAVSD = Complete atrioventricular septal defect, DORV = Double outlet right ventricle, VSD = Ventricular septal defect, MCA = Multiple congenital anomalies, HLHS = Hypoplastic left heart syndrome, PS = Pulmonary stenosis.

#### 4.2.1 Prenatal Diagnosis and Management of Congenital Heart Defect: Significance of Associated Fetal Anomalies and Prenatal Chromosome Studies.

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Published in American Journal of Medical Genetics, Vol 21:285-290 (1985)

A fetal cardiac defect was found prenatally by ultrasound in 13 of 230 women (5.6%) with a suspected fetal anomaly. Pregnancy duration varied between 17 and 39 weeks (mean 28 weeks). The reasons for referral of the 13 patients were: suspected fetal structural defect (n=4), oligo- or polyhydramnios (n=2), severe fetal growth retardation (n=1), fetal cardiac arrhythmia (n=1), or a combination thereof (n=5). Abnormal chromosomes were found in 5 out of 13 fetuses (38%)-ie, four through prenatal and one through postnatal analysis.

The present study demonstrates that fetal cardiac structural anomalies often are diagnosed in combination with ultrasonically established associated abnormality. Cytogenetic analysis of amniotic cells greatly improves diagnosis and obstetric management, especially when the cardiac defect per se is considered

amenable to surgical treatment and other major structural defects have been ruled out.

**Key words:** congenital heart disease, real-time ultrasound, prenatal chromosome studies.

### *Introduction*

It has been estimated that 0.5% of all live-born infants have a chromosome abnormality. Although the overall incidence of heart defects among patients with chromosome aberrations is 30%, involvement of the heart may range from a few to nearly 100% in specific syndromes, with 90% and above in trisomy 13 and 18 and 40-50% in trisomy 21 (Nora and Nora, 1978). Since heart anomalies occur in about 1% of the population in general, the contribution of chromosome abnormalities to the total number of cases with structural heart defects can be considered appreciable (Polani, 1968).

Present real-time ultrasound techniques enable observation of fetal structure and function as early as 12-16 weeks of gestation. Detailed study of the fetal heart has resulted in an increasing rate of prenatal diagnosis of cardiac defects (Kleinman et al, 1980; Allan et al, 1980; Stewart et al., 1983).

This paper presents data concerning fetal cardiac defects and the importance of prenatal chromosome analysis in pregnancies in which a cardiac defect has been identified.

### *Patients and methods*

Between January 1982 and January 1984, 230 patients were referred to our ultrasound unit for fetal structural assessment. Reasons for referral were unexplained abnormal structural findings by ultrasound (renal, skeletal, gastrointestinal, neural tube etc.), oligo- or polyhydramnios, severe growth retardation, fetal cardiac arrhythmia. Pregnancy duration varied between 7 and 39 weeks (mean 28 weeks). Detailed ultrasound examination included (1) two-dimensional real-time assessment (Diasonics Cardio-View 100 mechanical sector scanner) of fetal size and structure, placental localization, and amount of amniotic fluid, and (2) time motion analysis (Hewlett Packard 77020 A Ultrasound Imaging System) of atrial and ventricular rate in case of cardiac arrhythmia. When a prenatal diagnosis of fetal cardiac structural abnormality was made, amniocentesis for cytogenetic study of amniotic cells was advised.

### *Results*

A fetal cardiac defect was diagnosed in 13 of 230 cases (5.6%). In 12 of these patients, it was diagnosed prenatally, in one only after delivery. The reason

for referral was: suspected fetal noncardiac structural defect (n=4), oligo- or polyhydramnios (n=2), severe fetal growth retardation (n=1), fetal cardiac arrhythmia (n=1), or a combination thereof (n=5). Gestational age at the time of the ultrasound examination ranged from 20 to 36 weeks, maternal parity from 1 to 3, and maternal age from 22 to 33 years. There was no previous history of congenital heart defect in sibs, parents, or other relatives.

Tables I and II give the prenatal findings of ultrasound, amniocentesis, and fetal outcome. In all 13 patients there were additional abnormal findings, such as polyhydramnios (n=7), moderate to severe growth retardation (n=8), other major structural defects (n=5), fetal cardiac arrhythmia (n=6), or signs of cardiac compromise (right heart dilatation, ascites; n=3). Amniocentesis for chromosome study was carried out in 7 of 13 cases (54%).

In two cases no amniocentesis was carried out for medical reasons: oligohydramnios (Patient 2) and a cardiac defect incompatible with life (Patient 8). In one patient (No.12), fetal death occurred before planned amniocentesis. In the remaining three cases (Nos. 5, 11, and 13), other centers failed to perform amniocentesis before referral to us, when it was too late to do an amniocentesis. In case 3 a fetal cardiac defect (VSD) was only established after birth; however, prenatal chromosome study was carried out because of ultrasonically diagnosed fetal duodenal atresia, which is often associated with trisomy 21.

Fetal chromosome abnormalities (trisomy 18 and 21) were found in 5 of 13 patients (38%)-four prenatally and one postnatally. The stillborn child from case 2 had congenital malformations compatible with a diagnosis of trisomy 13-ie, microcephaly, microphthalmia, cleft palate, micrognathia, midline abdominal wall defect, and polydactyly. Chromosome studies on this child failed, but the father had a balanced translocation between chromosome 13 and 14. Even if a paternal balanced 13-14 translocation only gives a low risk for a trisomy 13 in the offspring (Boué and Gallano, 1984), this diagnosis in the stillborn child in case 2 is the most likely and more probable than a diagnosis of a syndrome malformation complex such as the Meckel syndrome.

In the four patients with a prenatally diagnosed chromosome abnormality, pregnancy termination was carried out in three (Nos. 1, 3, and 4), and spontaneous term delivery of a live infant occurred in one case, who died soon after birth (No. 6). Patient 2 elected to continue her pregnancy despite severe fetal abnormality. Intrauterine death occurred at 34 weeks. In Patient 5, with a postnatally established trisomy 18, cesarean section was performed at 39 weeks because of severe fetal growth retardation.

In the group of seven patients with normal chromosomes at pre- or postnatal study, pregnancy was terminated in three (Nos. 7-9) because of the severity of the cardiac defects or associated structural abnormalities. Intrauterine death occurred in two (Nos. 11 and 12), and spontaneous delivery took place in the remaining two cases (Nos. 10 and 13).

Table 1. Pre- and postnatal findings in six pregnancies with fetal cardiac defect and chromosome abnormality\*

Case	Gestational age (wks)	Prenatal findings	Amniocentesis	Outcome
1	27	Omphalocele; VSD; FGR	+ Trisomy 18 (47, XX, +18)	Termination of pregnancy at 29 wks; omphalocele; VSD; SFD
2	31	DORV; oligohydramnios; FGR	-	Stillborn at 34 wks; DORV; SFD; suspected trisomy 13 (father carrier t(13;14))
3	31	Polyhydramnios; duodenal atresia; increased risk for Down syndrome	+ Trisomy 21 (47, XX, +21) Down syndrome	Termination of pregnancy at 33 wks; duodenal atresia; VSD
4	34	Polyhydramnios; hemimelia of upper limbs; VSD; FGR	+ Trisomy 18 (47, XY, +18)	Termination of pregnancy at 36 wks; phocomelia upper limbs; VSD; SFD
5	35	Polyhydramnios; second-degree AV-block; VSD; great vessels not visualized; FGR	-	Cesarean section at 39 weeks; second-degree AV-block; SFD; died 12 h after birth; TOF; trisomy 18 (47, XY, +18)
6	36	Polyhydramnios; tetralogy of Fallot; VSD; dysplasia of AV valves; FGR	+ Trisomy 18 (47, XX, +18)	Term vaginal delivery; TOF; dysplasia of AV valves; SFD; died 30 min after birth

\*VSD = ventricular septal defect; TOF = tetralogy of Fallot; DORV = double outlet right ventricle; AVSD = atrioventricular septal defect; FGR = fetal growth retardation; SFD = small for dates.

Table II. Pre- and postnatal findings in seven pregnancies with fetal cardiac defect and normal chromosomes\*

Case	Gestational age (wks)	Prenatal findings	Amniocentesis	Outcome
7	20	Polyhydramnios; ascites; hydrothorax; CHD; isomeric atria; absent right AV connection; great arterial connections not identified stenosis; asplenia;	+ 46, XX	Termination of pregnancy at 21 wks; ascites; hydrothorax; left atrial isomerism; univentricular AV connection (single LV); concordant arterial connections; subpulmonary rocker-bottom feet (Ivemark syndrome)
8	22	Encephalocele; amelia right arm; gastroschisis; ectopia cordis; DORV; VSD; hypoplastic LV; FGR	—	Termination of pregnancy at 22 wks; encephalocele; amelia right arm; gastroschisis; DORV; VSD; hypoplastic LV; SFD; 46, XY
9	27	Polyhydramnios; holoprosencephaly; cystic kidneys; incomplete AVSD (Meckel syndrome)	+ 46, XY	Termination of pregnancy at 28 wks; holoprosencephaly; cystic kidneys; polydactyly; incomplete AVSD
10	28	Complete AVSD; irregular bradycardia; FGR	+ 46, XX	Term vaginal delivery; complete AVSD and wandering pacemaker; SFD; alive and well
11	29	Polyhydramnios; ascites; complete AVSD; atrial isomerism; tetralogy of Fallot; CHB	—	Stillborn at 31 wks; ascites; complete ACSD; atrial isomerism; tetralogy of Fallot; CHB; asplenia (Ivemark syndrome); 46, XX
12	34	Univentricular heart, with coarctation aorta; FGR; ectopics	—	Stillborn at 34 wks; univentricular heart with coarctation of aorta; SFDD; 46 XY
13	36	Obstruction at foramen ovale level; SV ectopics; right ventricular overload	—	Term vaginal delivery; obstruction at foramen ovale level; 46, XY; alive and well

\*VSD = ventricular septal defect; CHB = congenital heart block; DORV = double outlet right ventricle; AVSD = atrioventricular septal defect; SV = supraventricular ectopics; FGR = fetal growth retardation; SFD = small for dates; LV = left ventricle.



## *Discussion*

The low failure rate in the prenatal diagnosis of congenital heart disease in the present study demonstrates the possibilities of detecting structural cardiac defects during pregnancy, using real-time equipment, together with scanning expertise in a specialized center.

All 13 pregnancies with fetal cardiac defects were referred because of associated gestational problems. The high incidence (40% in this study) of fetal chromosome abnormalities clearly emphasizes the necessity to perform amniocentesis for chromosome studies in all pregnancies in which a fetal cardiac defect has been demonstrated, since this will influence both counseling of the parents and management of pregnancy and delivery.

As demonstrated in case 1 an omphalocele-which in itself is usually treatable by operation-is often associated with more serious defects, such as heart abnormalities and chromosome aberrations (Mayer et al., 1980; Wladimiroff et al., 1983). In case 5 cesarean section could have been avoided if a prenatal chromosome study had been carried out, whereas in case 6 the result of the chromosome study became available only 1 day before delivery. Consequently, neonatal management was conservative and the infant died 30 min postpartum.

If the heart defect is the only established malformation and fetal chromosomes are normal, the prognosis will depend largely on the nature of the heart abnormality. This is demonstrated in cases 7-9, 11, and 12, in which the severity of the heart defect and /or associated structural abnormalities resulted in termination or in stillbirth, whereas the nature of the cardiac defect in cases 10 and 13 was such that pregnancy was allowed to continue.

The present study demonstrates that fetal structural heart abnormalities are often diagnosed in combination with ultrasonically established associated anomalies. Cytogenetic analysis of amniotic cells greatly improves the diagnosis and obstetric management, especially when the cardiac defect per se is considered amenable to surgical treatment and other major structural defects have been ruled out. Future improvements of the resolution of echographic imaging techniques may allow an earlier prenatal diagnosis of congenital heart defect as from week 16 of pregnancy (Wladimiroff et al., 1984).

## *Acknowledgements*

We thank Mrs. Veldhuizen for typing out the manuscript. Part of this work was supported by the Dutch Prevention Fund, Projectn° 29-296.

## *References*

- Allan LD, Tynan MJ, Campbell S, Wilkinson JW, Anderson RH (1980): Echocardiographic and anatomical correlates in the fetus. *Br Heart J* 44: 444-451.
- Boué A, Gallano P (1984): A collaborative study of the segregation of inherited chromosome structural rearrangements in 1356 prenatal diagnoses. *Prenat Diagn* 4:45-67.

- Kleinman CS, Hobbins JC, Jaffe CC, Lynch DC, Talner NS (1980): Echocardiographic studies of the human fetus: Prenatal diagnosis of congenital heart disease and cardiac dysrhythmias. *Pediatrics* 65: 1059-1067.
- Mayer T, Black R, Matlak ME, Johnson DG (1980): Gastroschisis and omphalocele, an eight year review. *Ann Surg* 20:783-787.
- Nora JJ, Nora AH (1978): Congenital heart disease:Chormosomal anomalies. In Nora JJ, Nora AH (eds): "Genetics and Counseling in Cardiovascular Diseases." Springfield, IL: Charles C Thomas, p 9-44.
- Polani PE (1968): Chromosomal abnormalities and congenital heart disease. *Guy's Hosp Rep* 117: 323-329.
- Stewart PA, Tonge HM, Wladimiroff JW (1983): Arrhythmia and structural abnormalities of the fetal heart. *Br Heart J* 50: 550-554.
- Wladimiroff JW, Molenaar JC, Niermeijer MF, Stewart PA, Van Eyck J (1983): Prenatal diagnosis and management of omphalocele. *Eur J Obstet Gynaecol Reprod Biol* 16: 19-23.
- Wladimiroff JW, Stewart PA, Vosters RPL (1984): Fetal cardiac structure and function as studied by ultrasound. *Clin Cardiol* 7: 239-255.

#### 4.2.2 Cardiac and extra-cardiac anomalies as indicators for trisomy 13 and 18; A prenatal ultrasound study

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In Press: *Prenatal Diagnosis* 9; 1989

##### *Summary*

The purpose of the present study was to establish sonographic markers for prenatal diagnosis of trisomy 13 and 18. Retrospective analysis of sonographic morphology was therefore carried-out in seven fetuses with trisomy 13 and 16 fetuses with trisomy 18. Gestational age ranged between 17 and 39 weeks (median: 28 weeks). Polyhydramnios and symmetrical growth retardation was present in 14 of 23 fetuses. A cardiac anomaly was diagnosed in all 23 fetuses, the majority representing a ventricular septal defect (n=8) and double outlet right ventricle (n=8). Extra-cardiac anomalies were characterized by a high incidence of limb deformities (polydactyly, clenched hands, club feet; n=15) and omphalocele (n=7).

We conclude that the combined appearance of cardiac and extra-cardiac anomalies should prompt fetal karyotyping. Cardiac anomalies in combination with fetal limb deformities and omphalocele are suspicious for trisomy 13 and 18.

**Key words:** fetal cardiac anomaly; fetal extra-cardiac anomaly; fetal karyotyping; polyhydramnios.

## *Introduction*

Congenital heart defects represent a heterogeneous group of disorders caused by chromosome abnormalities, mendelian disorders, teratogenic exposures, and unknown etiologic mechanisms. Both from referral centres with large series of fetal cardiac anomalies (Wladimiroff et al, 1985; Copel et al, 1988; Benacerraf et al, 1988; Crawford et al, 1988) and from population-based studies of these anomalies (Berg et al, 1988) there is evidence of a considerably higher percentage of associated chromosomal abnormalities (30-45%) than has been estimated from postnatal data (5-10%) (Campbell, 1965; Hook, 1982). This discrepancy between pre and postnatal findings may relate to the high fetal wastage in the presence of a chromosomal anomaly.

Prenatal identification of a chromosomal abnormality associated with fetal congenital heart disease may not only avoid unnecessary surgical intervention, but will also provide genetic information should fetal demise occur before delivery. Particularly in the presence of trisomy 13 and 18, fetal outcome is extremely poor with mean survival of 130 and 40 days (Redheendran et al, 1981; Carter et al, 1985).

Sonographic description of fetal morphology has become increasingly detailed, resulting in a number of reports which highlight the nature of fetal structural anomalies relative to trisomies, monosomies, sex chromosome anomalies and triploidies (Wladimiroff et al, 1988; Copel et al, 1988; Benacerraf et al, 1988). This communication deals with sonographic findings of cardiac and extra-cardiac structural pathology in fetuses with trisomy 13 and 18 in a level 3 referral centre over a period of five years.

## *Material and Methods*

A total of seven fetuses with trisomy 13 and 16 fetuses with trisomy 18 was retrospectively analysed. Reasons for referral to our Ultrasound Unit were: a small-for-dates uterus ( $n = 3$ ), a large-for-dates uterus ( $n = 11$ ) or unexplained abnormal structural findings by ultrasound ( $n = 9$ ). Gestational age at the time of the ultrasound examination ranged from 17 to 39 weeks (median 28 wks), maternal parity from 1 to 4 (median 3) and maternal age from 19 to 40 years (median 36 years). There was no previous history of congenital defects in sibs, parents or other relatives.

Detailed ultrasound examination included: (i) two-dimensional real-time assessment (Diasonics Cardio-Vue 100, mechanical sector scanner) of fetal size and structure, placental localization and amount of amniotic fluid and (ii) time motion analysis (Hewlett Packard 77020 A Ultrasound Imaging System) of atrial and ventricular rate in case of cardiac arrhythmia. Fetal size was determined by measurement of head and upper-abdominal circumference (Campbell, 1976). Oligohydramnios was diagnosed when the largest amniotic fluid pocket was 1 cm or less (Manning et al, 1980), polyhydramnios was present when the largest

amniotic fluid pocket was 8 cm or more (Manning et al, 1980). When a fetal structural anomaly was established, karyotyping was performed in amniotic fluid (amniocentesis;  $n = 17$ ), fetal cord blood (Daffos et al, 1985) (cordocentesis;  $n = 3$ ) or chorionic villi (Pijpers et al, 1988) (transabdominal placental biopsy;  $n = 3$ ). All ultrasound studies were carried out before knowledge of the cytogenetic diagnosis. Necropsy was available from all 23 infants.

### *Results*

Abnormal sonographic findings were made in all 23 fetuses. All seven fetuses with trisomy 13 displayed single or multiple cardiac defects (Table 1), the majority representing double outlet right ventricle and hypoplastic left ventricle. There was one incomplete diagnosis (patient 3). Extra-cardiac structural pathology in these seven fetuses consisted of abnormalities of hands and feet, including polydactyly and club feet (five fetuses) and symmetrical intrauterine growth retardation (IUGR) (four fetuses). Three fetuses presented with an omphalocele, two with bilateral hydronephrosis, two with facial anomalies (hypotelorism, facial cleft) and one with holoprosencephaly. Twice there was a two-vessel cord and twice there was polyhydramnios.

Single or multiple cardiac anomalies were also documented in all 16 fetuses with trisomy 18 (Table 2), the majority presenting with a ventricular septal defect, double outlet right ventricle or complete atrio-ventricular septal defect. There was one incomplete diagnosis (patient 6) and one misclassification (patient 10) due to an anatomic variant. Extra-cardiac structural pathology in trisomy 18 mainly consisted of abnormal hands and feet (polydactyly, clenched hands, club feet; ten fetuses), symmetrical IUGR (11 fetuses) and polyhydramnios (ten fetuses). Four fetuses displayed an omphalocele. Single observations of a fetal anomaly included duodenal atresia, bilateral hydronephrosis, encephalocele, spina bifida, cystic hygroma, diaphragmatic hernia and facial cleft.

Three out of 23 fetuses were scanned between 16 and 20 weeks, three between 21 and 25 weeks, ten between 26 and 30 weeks, six between 31 and 35 weeks and one between 36 and 40 weeks of gestation. Before 25 weeks referral was solely determined by sonographic findings of fetal structural anomalies (omphalocele, spina bifida, encephalocele, hydronephrosis); after 25 weeks other pathology like polyhydramnios and symmetrical IUGR became apparent and was the main reason for referral to our Ultrasound Unit.

### *Discussion*

The incidence of trisomy 13 is in the order of one in 5000 births. Most common anomalies include congenital heart disease, omphalocele, renal pathology, polydactyly, holoprosencephaly and symmetrical growth retardation (Patau et al, 1960; Rowe et al, 1978; Johnson et al, 1982). The incidence of trisomy 18

Table I. Gestational age at referral, prenatal diagnosis of fetal heart disease and postpartum pathology in seven cases of trisomy 13.

Case no.	Gestational age (wks)	Prenatal diagnosis	Pathology
1	33+	VSD	VSD,
2	33+	VSD	VSD
3	27+	CAVSD, hypoplastic LV overriding aorta? (heart severely displaced)	hypoplastic LV TGA, pulmonary atresia
4	25	hypoplastic LV, DORV	hypoplastic LV, DORV
5	30	hypoplastic LV, DORV	hypoplastic LV, DORV
6	30+	hypoplastic LV, DORV	hypoplastic LV, concordant great vessels
7	21	TOF	VSD, overriding aorta, aorto-pulmonary window

VSD = ventricular septal defect, TGA= transposition great arteries, CAVSD = complete atrio-ventricular septal defect, DORV = double outlet right ventricle, LV = left ventricle, TOF = tetralogy of Fallot

Table II. Gestational age at referral, prenatal diagnosis of fetal heart disease and post partum pathology in 16 cases of trisomy 18.

Case no.	Gestational age (wks)	Prenatal diagnosis	Pathology
1	20	VSD	VSD
2	20+	VSD	VSD
3	28	VSD	VSD, hypoplastic aortic arch
4	27	VSD, large right heart	VSD, large right heart
5	27	VSD, 2° ASD, overriding aorta	VSD, 2° ASD overriding aorta
6	35	VSD, 2:1 AVB, great vessels not seen	TOF, 2:1 AVB
7	17	CAVSD	CAVSD
8	34	CAVSD	CAVSD
9	30	CAVSD, DORV	CAVSD, DORV
10	34	CAVSD, TOF	deficient muscular septum, dysplastic AV valves, absent papillary muscles, TOF
11	37	CAVSD, overriding aorta	CAVSD, overriding aorta
12	29	TOF	TOF
13	25	DORV	DORV
14	27	DORV	DORV
15	29	DORV	DORV
16	32	DORV	DORV

VSD = ventricular septal defect, CAVSD = complete atrioventricular septal defect, 2° ASD = secundum atrial septal defect, DORV = double outlet right ventricle, AVB = atrioventricular block, AV = atrioventricular, TOF = tetralogy of Fallot.

is about one in 3000 births. Anomalies most commonly seen in this chromosomal disorder are congenital heart disease, renal anomalies, diaphragmatic hernia, clenched hands with tendency for overlapping index finger over third, fifth finger over fourth, rocker bottom or clubfeet, omphalocele, polyhydramnios and symmetrical growth retardation (Edwards et al, 1960; Rowe et al, 1978; Johnson et al, 1982).

Our results show that a considerable number of features representing trisomy 13 and 18 can be diagnosed by prenatal ultrasonography. A discrepancy exists regarding the incidence and type of cardiac anomaly between our fetal study and postnatal data (Greenwood et al, 1975). Especially for trisomy 13, the incidence of cardiac anomalies in the present study (100%) is higher than reported from postnatal observations (80%). As in newborns, a high incidence of ventricular septal defect was documented (eight of 23 fetuses). However, there was also a high incidence of double outlet right ventricle (eight of 23 fetuses) with hypoplastic left heart in four of seven fetuses with trisomy 13 and complete atrio-ventricular septal defect in four of 16 fetuses with trisomy 18. This discrepancy may be explained by the high rate of intrauterine deaths with subsequent fetal maceration rendering post partum necropsy impossible. We do not share the view that a large proportion of cardiac anomalies related to trisomy 13 and 18 will be less optimally identified by prenatal ultrasound, particularly in the second trimester of pregnancy (Benacerraf et al, 1988). In experienced hands the accuracy of prenatal sonography for detecting fetal cardiac anomalies is considerable, with sensitivity and specificity rates of at least 80 and 99% (Crawford et al, 1988; Stewart and Wladimiroff, 1989).

The high incidence of limb deformities (15 of 23 fetuses) and omphalocele (7 of 23 fetuses) is specific enough to prompt prenatal karyotyping, since these fetuses are at risk for trisomy 13 and 18. Omphalocele was nearly always associated with ventricular septal defects as has been described before (Crawford et al, 1985). It has been pointed out by others (Copel et al, 1988; Benacerraf et al, 1988; Crawford et al, 1988) and ourselves that the presence of combined cardiac and extra-cardiac structural anomalies is highly suspicious for a chromosomal abnormality. Prenatal karyotyping is mandatory in these cases to determine further obstetric care and offer complete parental counselling.

A frequent finding in the present study was the combined appearance of symmetrical IUGR and polyhydramnios (14 of 23 fetuses). Since IUGR due to impaired placental perfusion is usually asymmetrical and associated with oligohydramnios, the combination of symmetrical IUGR and polyhydramnios should raise suspicion regarding the presence of fetal structural and/or chromosomal anomalies. IUGR and polyhydramnios were only diagnosed after 25 weeks of gestation, following the clinical finding of a large-for-dates uterus. Whereas there is no information available on the mechanism causing polyhydramnios under these circumstances, its late appearance is of practical significance in that it may impose limitations on obstetric management, in particular pregnancy termination if a lethal trisomy is established. Of additional concern is that five

of our patients were 36 years or older and therefore under existing regulations in The Netherlands should have been offered fetal karyotyping during the late first trimester or early second trimester of pregnancy by means of chorionic villus sampling or amniocentesis. Since especially in the first half of the second trimester there are no clinical warning signs of a lethal fetal trisomy, a routine fetal anomaly scan at that time will be the only means of detecting these affected fetuses earlier in gestation. Subsequent transabdominal placental biopsy or cordocentesis will permit rapid karyotyping and in case of a positive result, provide an acceptable argument for pregnancy termination.

We conclude that in the presence of polyhydramnios and symmetrical IUGR a detailed search for fetal structural anomalies is warranted. Combined appearance of cardiac and extra-cardiac anomalies should prompt fetal karyotyping. Cardiac anomalies in combination with fetal limb deformities (polydactyly, clenched hands, club feet) and omphalocele are suspicious for trisomy 13 and 18.

### *Acknowledgement*

We are grateful to the "Rotterdam Clinical Genetics Foundation" for their financial support.

### *References*

1. Benacerraf, B.R., Miller, W.A., Frigoletto, Jr F.D.(1988). Sonographic detection of fetuses with trisomies 13 and 18: Accuracy and limitations. *Am.J.Obstet.Gynecol.*158, 404-409.
2. Berg, K.A., Clark, E.B., Astemborski, J.A., Boughman, J.A. (1988). Prenatal detection of cardiovascular malformations by echocardiography: An indication for cytogenetic evaluation. *Am.J.Obstet.Gynecol.*159, 477-481.
3. Campbell, M. (1965). Causes of malformations of the heart. *Br.Med.J.*2, 895-899.
4. Campbell, S. (1976). Fetal growth. In: Beard, R.W., Nathanielz, W.B.(Eds). *Fetal Physiology and Medicine*. London: Saunders Co.Ltd. 271-278.
5. Carter, P.E., Pearn, J.H., Bell, J., Martin, N., Anderson, N.G. (1985). Survival in trisomy 18: life tables for use in genetic counseling and clinical pediatrics. *Clin.Genet.*27, 59-61.
6. Copel, J.A., Cullen, M., Green, J.J., Mahoney, M.J., Hobbins J.C., Kleinman, C.S. (1988). The frequency of aneuploidy in prenatally diagnosed congenital heart disease: An indication for fetal karyotyping. *Am.J.Obstet.Gynecol.*158, 409-413.
7. Crawford, D.C., Chapman, M.G., Allan, L.D. (1985). The use of echocardiography in the investigation of anterior abdominal wall defects in the fetus. *Br.J.Obstet.Gynaecol.* 92, 1034-1036.
8. Crawford, D., Chita,S.K., Allan, L.D. (1988). Prenatal detection of congenital heart disease: Factors affecting obstetric management and survival. *Am.J.Obstet.Gynecol.*159, 352-356.
9. Daffos, F., Capella-Pavlovsky, M., Forestier, F. (1985). Fetal blood sampling during pregnancy with the use of a needle guided by ultrasound: a study of 606 consecutive cases. *Am.J.Obstet.Gynecol.*153, 655-660. 10.Edwards, J.H., Harnden, D.G., Cameron, A.H., Preese, H.L., Laite, M.B., Donalson, J.T. (1960). A new trisomic syndrome. *Lancet* 1, 787-790.
11. Greenwood, R.D., Rosenthal, A., Parisi, L., Fyler, D.C., Nadas, A.S. (1975). Extracardiac abnormalities in infants with congenital heart disease. *Pediatrics* 55, 485-492.
12. Hook, E.B. (1982). Contribution of chromosome abnormalities to human morbidity and mortality. *Cytogenet.Cell.Genet.* 33, 101-106.

13. Johnson, T.R., Corson, V.L., Payne, P.A., Stetten, G. (1982). Late prenatal diagnosis of fetal trisomy associated with severe intrauterine growth retardation. *Johns Hopkins Med.J.* 151, 242-245.
14. Manning, F.A., Platt, L.D., Sipos, L. (1980). Antepartum fetal evaluation: development of a fetal biophysical profile. *Am.J.Obstet.Gynecol.*136, 787-791.
15. Patau, K., Smith, D.W., Therman, E., Inhorn, S.L., Wagner, H.P. (1960). Multiple congenital anomaly caused by an extra chromosome. *Lancet* 1, 790-793.
16. Pijpers, L., Jahoda, M.G.J., Reuss, A., Wladimiroff, J.W., Sachs, E.S. (1988). Transabdominal chorionic villus biopsy in 2nd and 3rd trimester pregnancies to determine fetal karyotype. *Brit.Med.J.*297, 822-823.
17. Redheendran, R., Neu, R.L., Bannerman, R.M. (1981). Long survival in trisomy 13 syndrome: 21 cases including prolonged survival in two patients, 11 and 19 years old. *Am. J.Med.Genet.*8, 167-172.
18. Rowe, R.D., Uchida, I.A., Char, F. (1978). Heart disease associated with chromosomal abnormalities. In: Keith, J.D., Rowe, R.D., Vlad, P., (Eds). *Heart disease in Infancy and Childhood*. New York: MacMillan Publishing Company Inc, 897-925.
19. Stewart, P.A., Wladimiroff, J.W., Reuss A, Pijpers L (1989). Echocardiography in the early diagnosis of cardiac malformations. In: Cosmi, E.V., DiRenzo, G,C, (Eds). *Proceedings of the 11th Meeting of the European Society of Perinatology*. Amsterdam: Elseviers Publishers pp 665-669.
20. Wladimiroff, J.W., Stewart, P.A., Sachs, E.S., Niermeijer, M.F. (1985). Prenatal diagnosis and management of congenital heart defect: Significance of associated fetal anomalies and prenatal chromosome studies. *Am.J.Med.Genet.*21, 285-290.

### 4.3 Prenatal ultrasound diagnosis of congenital heart disease associated with intrauterine growth retardation

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Published in *Prenatal Diagnosis*, Vol 3: 279-285 (1983)

#### *Summary*

Two fetuses with extreme growth retardation (IUGR) of 31 and 34 weeks gestation were studied using a combination of two-dimensional echocardiography (2DE), pulse wave Doppler (PWD) and differential measurement of the instantaneous vessel diameter techniques. The first fetus was diagnosed as having univentricular heart or possible double outlet right ventricle (DORV). Descending aorta blood flow was reduced as was indexing for weight.

The second fetus was diagnosed as having univentricular heart with periodic bigeminal and trigeminal rhythm. Descending aorta blood flow was measured on two occasions and was reduced both times. Indexing for weight was within



normal limits the first time and showed gross reduction on the second occasion prior to fetal demise. Fetal death occurred in both cases at 34 weeks gestation. Cardiovascular evaluation in fetuses with IUGR is useful as the detection of severe congenital cardiac abnormalities may substantially alter the management of these pregnancies, in particular caesarean section may be avoided when the prognosis for the fetus is considered hopeless.

**Key words** Prenatal ultrasound, Congenital heart disease, Intrauterine growth retardation.

### *Introduction*

Ultrasound techniques are widely used in general obstetric practice to measure fetal growth and maturity. Information relating to the fetal heart has been obtained in the past using B-mode (Garrett and Robinson, 1970; Egeblad et al., 1975) and M-mode techniques (Winsburg 1972; Baars and Merkus, 1977) but these methods provide limited information. However, recent advances in real-time 2DE equipment permits the identification of fetal cardiac anatomy in greater detail (Allan et al., 1980, 1981; Sahn et al., 1980; Lange et al., 1980; Wladimiroff and McGhie 1981a,b; Wladimiroff et al., 1982). In addition use of PWD techniques (Eik-Nes et al., 1980a,b; Wladimiroff, 1981) provides the means for transcutaneous measurement of blood flow in the fetal aorta, which together with differential measurement of the instantaneous vessel diameter (Sindberg-Erikson et al., 1981) enables assessment of fetal cardiovascular dynamics.

We have previously successfully applied a combination of these techniques in the evaluation of fetal cardiac dysrhythmias (Wladimiroff et al., 1981c; Wladimiroff et al., 1983). In the present paper the value of 2DE and PWD techniques to assess cardiac structure and aortic blood flow in two fetuses with extreme IUGR is discussed. M-mode echocardiographic study in these two cases may have provided useful information concerning cardiac output and more precise measurements of structural anatomy, but was not available in either case.

### *Case 1*

A 34 year-old gravida III was referred at 31 weeks gestation with extreme IUGR. Real-time ultrasound using a Toshiba SAL20A showed severe oligohydramnios and a non-hydropic fetus with an abdominal circumference of 20.5 cm consistent with 25 weeks (Campbell, 1976). It was not possible to measure the head circumference due to the position. The fetal heart showed both great arteries connected to a single ventricle (Figure 1). Two atria were identified but the left sided atrium and atrioventricular (AV) valve were grossly hypoplastic. Both atria appeared to empty into the single ventricle. A diagnosis of double

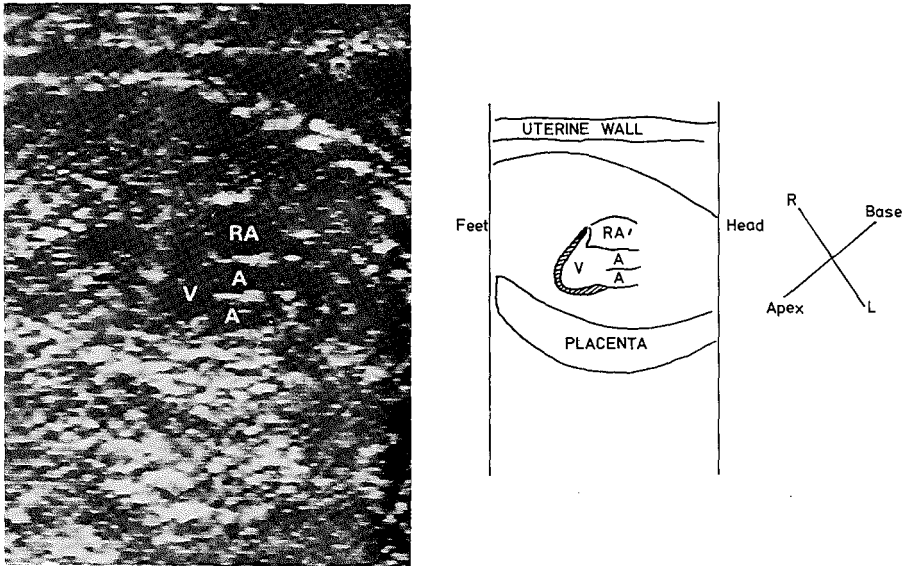


Fig.1. Left, still frame from two-dimensional echocardiogram of case 1. Right: diagram representing frame on left. RA=right atrium, V=ventricle, A=great artery.

inlet univentricular heart or DORV was made. Averaged mean blood flow in the fetal descending aorta was reduced (Table 1) but the flow indexed for body weight was within the lower limits of normal according to the data presented by Eik-Nes et al., (1982) and our own data in Table 1. No other abnormalities

Table 1. Results of blood flow measurements in fetal descending aorta. Mean  $\pm$  SD

	Mean blood flow velocity in fetal descending aorta (cm/sec)	Maximum % change in aortic wall diameter	Mean blood flow in descending aorta	
			ml/min	ml/min/kg
Case 1	44.5 $\pm$ 2.1 52.0 $\pm$ 2.1	9.0 $\pm$ 1.0	215	196
Case 2				
1st recording (am)	53.0 $\pm$ 1.6	9.1 $\pm$ 1.0	225	225
2nd recording (pm)	24.8 $\pm$ 2.4	3.3 $\pm$ 0.7	129	129
Normal values (Tonge et al., unpublished data) (30-34 weeks gestation; N=10)	70.1 $\pm$ 7.9	14.6 $\pm$ 3.9	390.2 $\pm$ 94.0	236.1 $\pm$ 42.0

were detected by ultrasound but adequate visualization was impossible due to the lack of amniotic fluid. The patient came from another hospital and after discussion with her gynaecologist it was decided to wait for the natural outcome of this pregnancy and not to perform a caesarean section in view of the severity of the cardiac disease. Fetal death occurred at 34 weeks gestation and a female fetus weighing 1100 grams was delivered (<2.3 per cent according to Tables of Kloosterman (1970), correction being made for maternal parity and fetal sex) with multiple congenital abnormalities consistent with possible trisomy 13. Chromosomal analysis was unsuccessful.

Autopsy of the heart revealed normal atrial situs and concordant atrioventricular connections. The left atrium and mitral valve were extremely small. The left ventricular cavity was grossly hypertrophied with a minute cavity. There was a membranous ventricular septal defect. There was an overriding aorta and narrowing of the right ventricular outflow tract. This was functionally a DORV with the anatomic features of Tetralogy of Fallot (Figure 2). The placenta showed no gross abnormalities.

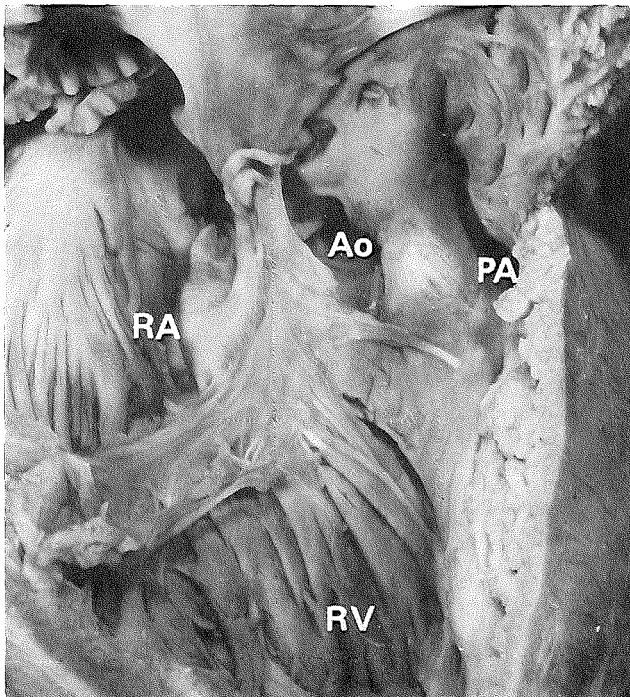


Fig.2. Photograph of specimen from case 1. RA=right atrium, RV=right ventricle, Ao=aorta, PA=pulmonary artery.

### Case 2

A 24 year-old gravida I was transferred from another hospital at 34 weeks gestation for possible caesarean section, with extreme IUGR and episodes of fetal arrhythmia. Real-time ultrasound using a Toshiba SAL20A showed a non-hydrotic fetus with a head circumference of 25.3 cm consistent with 27 weeks gestation (Campbell, 1976). There was a normal amount of amniotic fluid. Echocardiography demonstrated both great arteries with a side-by-side appearance connected to a single ventricle. One atrium with vena caval connections and one large AV valve were identified (Figure 3). A very small echo-free area was seen, posterior to the AV valve. The aortic arch was not visualized. Periodic episodes of bigeminal and trigeminal rhythm were noted but precise definition could not be established due to lack of M-mode recording facilities.

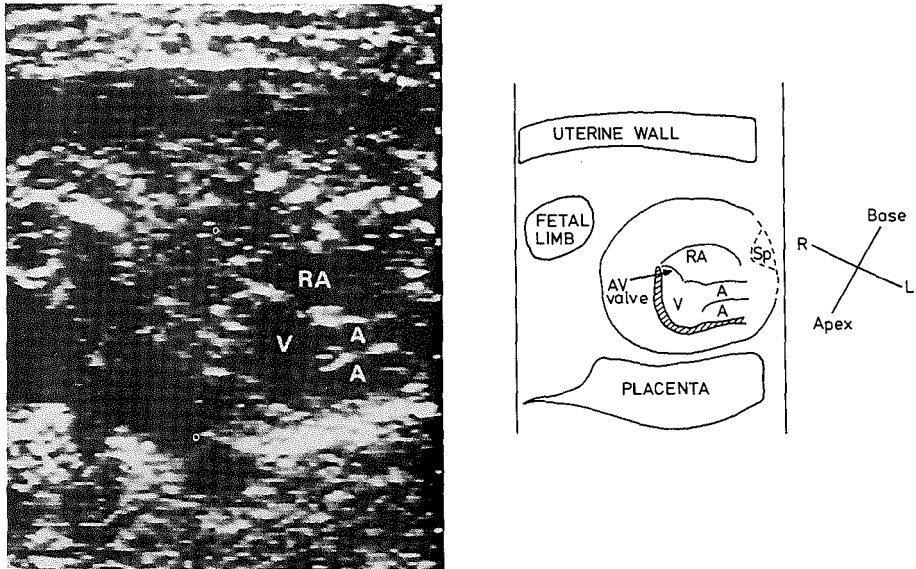


Fig.3. Left, still frame from two-dimensional echocardiogram of case 2. Right: diagram representing frame on the left. RA=right atrium, V=ventricle, A=great artery, AV=atrioventricular valve, Sp=fetal spine.

Measurement of averaged mean blood flow in the fetal descending aorta was performed on two occasions during regular heart rate (Table 1) with an interval of a few hours between study-and indexing for body weight was within the normal limits on the first occasion and severely reduced on the second. Fetal demise occurred soon after the second examination at 34 weeks gestation. A male fetus weighing 1000 grams was delivered (<2.3 per cent according to

Tables of Kloosterman (1970), correction being made for maternal parity and fetal sex).

Autopsy of the heart revealed a univentricular heart of right ventricular trabecular type without evidence of left ventricular tissue (Figure 4). The left atrium was extremely hypoplastic with no AV connection and probably related to the echo-free area seen antenatally. The great arteries were normally related but malpositioned resulting in a side-by-side appearance. The aortic isthmus was hypoplastic. There were no other congenital abnormalities. The placenta showed no gross abnormalities.

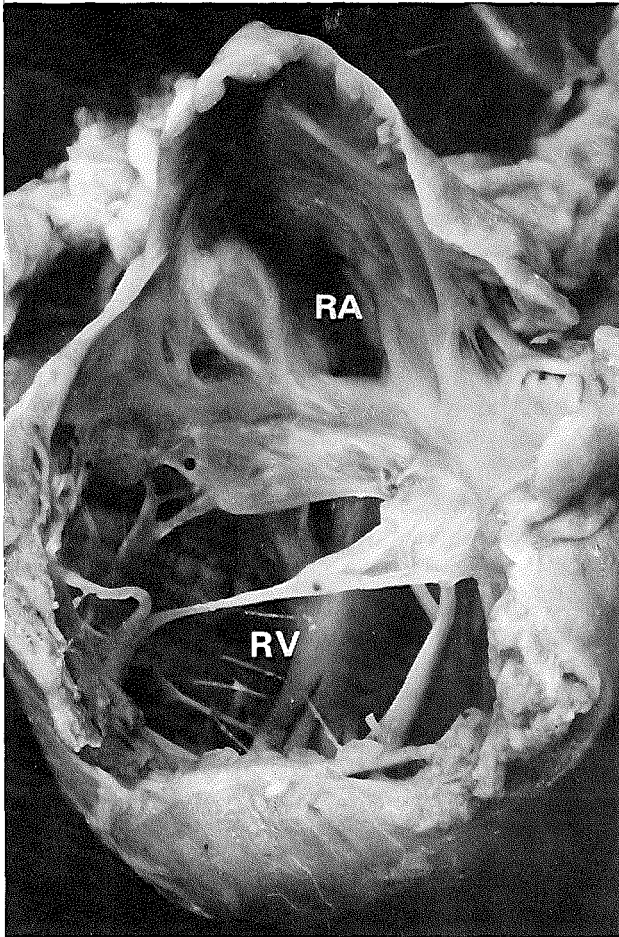


Fig.4. Photograph of specimen from case 2. RA=right atrium, RV=right ventricle.

## *Discussion*

The incidence of IUGR computed by Galbraith et al., (1979) was 6.7 per cent of 8000 births, defined as births below the 10 percentile weight-gestational age growth curve suggested by Gruenwald (1963). This figure was further broken down to 1.9 per cent associated with congenital anomalies and 4.9 per cent with non-anomalous IUGR. Chromosomal abnormalities occur in approximately 3.5 per cent of all pregnancies. After abortions have taken their toll this is reduced to 0.5 per cent of livebirths. Congenital heart disease (CHD) is present in about 30 per cent of these with the incidence ranging from a few to nearly 100 per cent. The incidence is between 90 and 100 per cent in trisomies 13 and 18, 40 to 50 per cent in trisomy 21, partial short arm deletion of chromosome no.4 (4p-), partial long arm deletion of no. 18 (18q-) dropping to around 20 per cent in partial short arm deletion of no. 5 (5p-) and 45 X Turner's syndrome (Rowe et al., 1978). Babies with chromosomal abnormalities often have low birth weights for gestational age. Isolated CHD is not generally considered to be strongly associated with IUGR (Feldt et al., 1969). A report by Kleinman et al., (1980) described the prenatal detection of CHD in two cases of IUGR. In our own small series of severe IUGR (11 fetuses) 2 have had CHD.

The possibility of chromosomal and/or multiple congenital defects was considered in both our cases, particularly in case 1, because of the oligohydramnios. After delivery, this fetus exhibited signs compatible with trisomy 13 although chromosomal analysis was unsuccessful.

It is common policy that extreme IUGR is treated by caesarean section with the aim of reducing infant mortality and morbidity. In case 2 this was the reason to transfer the patient to our hospital as the IUGR was considered most likely to result from placental insufficiency. The diagnosis of severe congenital heart disease with compromised cardiovascular status prompted discussion as to the prognosis and further management of this fetus, which, in any case, died within a few hours of admission shortly after the second investigation.

After discussion between the referring gynaecologist and the parents in case 1 a conservative policy had been adopted with the decision not to interfere surgically with this pregnancy, which ended in intrauterine death at 34 weeks gestation.

The results of the cardiovascular dynamic studies in the fetus in case 1 demonstrated reduced mean blood flow in the descending aorta as well as low indexed flow for body weight. The results obtained from case 2 indicate that on the first occasion indexing for body weight was within range of normal although the mean blood flow was reduced. On the second occasion gross reduction had occurred in both parameters and fetal demise occurred shortly afterwards. Perhaps some fetal hearts with severe abnormalities are able to compensate for a period and provide flow appropriate for weight to a point where mechanical or electrical failure of the heart occurs. However, the reasons why some fetuses with similar abnormalities achieve term deliveries and others die in utero remains unclear.

We conclude that ultrasonic evaluation of the fetal cardiovascular system is

mandatory in cases of severe IUGR, as the diagnosis of serious cardiac malformation may substantially alter plans for further management of these fetuses, particularly as caesarean section may be avoided when the prognosis for the fetus is considered hopeless.

### *Acknowledgements*

We would like to thank Dr.J.J.Bol of St.Ignatius Hospital, Breda, for referring case 1 and Dr.R.Schats for the artwork.

### *References*

- Allan LD, Tynan MJ, Campbell S, Wilkinson JW, Anderson RH (1980). Echocardiographic and anatomical correlates in the fetus. *Br Heart J*; 44; 444-451.
- Allan LD, Tynan M, Campbell S, Anderson RH (1981). Normal fetal cardiac anatomy - a basis for the echocardiographic detection of abnormalities. *Prenat diag*; 1; 131-139.
- Baars AM, Merkus JMW (1977). Fetal echocardiography: a new approach to the study of the fetal heart and its component parts. *Eur J Obstet Gyn Reprod Biol*; 72; 91-100.
- Campbell S (1976). Fetal growth. In: Beard RW, Nathanielsz PW (Eds.). *Fetal Physiology and Medicine*, London, WB Saunders, 271-301.
- Egeblad H, Bang J, Northeved A (1975). Ultrasonic identification and examination of fetal heart structures. *J Clin Ultrasound*; 3; 95-105.
- Eik-Nes SH, Brubakk AO, Ulstein M (1980a). Measurement of human fetal blood flow. *Br Med J*; 280; 283-285.
- Eik-Nes SH, Marsal K, Person PH, Ulstein MK (1980b). Ultrasonic measurement of blood flow in human fetal aorta and umbilical vein. In: Dawes GS (Ed.). *Proceedings of 7th Conference on Fetal Breathing and other Measurements*, Oxford, 1-8.
- Eik-Nes SH, Marsal K, Brubakk AO, Kristofferson K, Ulstein M (1982). Ultrasonic measurement of human fetal blood flow. *J Biomed Eng* 4; 28-36.
- Feldt RH, Strickler GB, Weidman WH (1969). Growth of children with congenital heart disease. *Am J Dis Child* 117; 573-579.
- Galbraith RS, Karchman EJ, Piercy WN, Low JA (1979). The clinical prediction of intrauterine growth retardation. *Am J Obstet Gynecol* 133; 281-286.
- Garrett WJ, Robinson DE (1970). Fetal heart size measured in vivo by ultrasound. *Pediatr* 46; 25-27.
- Gruenewald P (1963). Chronic fetal distress and placental insufficiency. *Biol Neonate* 5; 215-265.
- Kleinman CS, Hobbins JC, Jaffe CC, Lynch DC, Talner NS (1980). Echocardiographic studies of the human fetus: prenatal diagnosis of congenital heart disease and cardiac dysrhythmias. *Pediatr* 65; 1059-1067.
- Kloosterman GJ (1970). On intrauterine growth. *Int J Gynaecol Obstet* 8; 895-901.
- Lange LW, Sahn DJ, Allen HD, Goldberg SJ, Anderson C., Giles H (1980). Qualitative real-time cross-sectional echocardiographic imaging of the human fetus during the second half of pregnancy. *Circulation* 62; (4), 799-806.
- Rowe RD, Uchida IA, Char F (1978). Heart disease associated with chromosomal abnormalities. In: Keith JD, Rowe RD, Vlad P (Eds.). *Heart Disease in Infancy and Childhood*, 3rd edn, New York, Macmillan, 897-925.
- Sahn DJ, Lange LW, Allen HD, Goldberg SJ, Anderson C, Giles H, Haber K (1980). Quantitative real-time cross-sectional echocardiography in the developing normal human fetus and newborn. *Circulation* 62; (3), 588-597.

- Sindberg-Erikson P, Gennser G, Linstrom G (1981). Characteristics of pulse waves in the fetal aorta descendens. In: Kurjak A, Kratochwil A (Eds.). *Recent Advances in Ultrasound Diagnosis 3* Amsterdam: Excerpta Medica: 234-240.
- Winsberg F (1972). Echocardiography of the fetal and newborn heart. *Invest Radiol*, 3; 152-158.
- Wladimiroff JW (1981). The present state of art in the study of human fetal cardiovascular performance. In: Kurjak A (Ed.). *Progress on Medical Ultrasound, Vol 2*, Amsterdam: Excerpta Medica; 43-57.
- Wladimiroff JW, McGhie JS (1981a). Ultrasonic assessment of cardiovascular geometry and function in the human fetus. *Br J Obstet Gynaecol*, 88; 870-875.
- Wladimiroff JW, McGhie JS (1981b). M-mode ultrasonic assessment of fetal cardiovascular dynamics. *Br J Obstet Gynaecol*, 88; 1241-1245.
- Wladimiroff JW, McGhie JS, Hovestreydt-Snijder RP, Tasseron EWK (1981c). M-mode and pulsed Doppler ultrasound assessment of severe fetal bradycardia. A case report. *Br J Obstet Gynaecol*, 88; 1246-1248.
- Wladimiroff JW, Vosters R, McGhie JS (1982). Normal cardiac ventricular geometry and function during the last trimester of pregnancy and early neonatal period. *Br J Obstet Gynaecol*, 89; 839-844.
- Wladimiroff JW, Struijk PC, Stewart PA, Custers P, de Villeneuve VH (1983). Fetal cardiovascular dynamics during cardiac dysrhythmia. A case report. *Br J Obstet Gynaecol*, 90; 573-577.

#### 4.4 Left Atrial Isomerism Associated With Asplenia: Prenatal Echocardiographic Detection of Complex Congenital Cardiac Malformations

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Published in *Journal American College of Cardiology*, Vol 4: 1015-1020 (1984)

Complex congenital heart disease with suspected isomerism of the atria was diagnosed in two fetuses of 20 and 29 weeks' gestation using two-dimensional and M-mode scanning techniques. The first pregnancy was terminated at 21 weeks' gestation and stillbirth occurred at 31 week' gestation in the second pregnancy. At postmortem examination, a thoracoabdominal discordancy was found; the spleen was absent and the arrangement of the abdominal vessels was as anticipated for asplenia, but the thoracic situs revealed a bilateral right-sided arrangement with left isomerism of the atria. The heart, otherwise, showed complex abnormalities as anticipated for asplenia.

Situs describes the arrangement of organs within the body. Generally, the situs of the abdominal organs, thoracic organs and atria will correspond, but



this is not always the case and it is customary to describe each group separately (1). In situs solitus, the "morphologically right" structures are found on the right, and in situs inversus, the "morphologically right" structures are found on the left side of the body in mirror-image fashion. In some patients, however, neither situs solitus nor situs inversus exists and the organs are then isomeric. In isomerism, paired organs such as lungs and atria have bilateral morphologically right or morphologically left characteristics.

Disturbances in the development of asymmetry of organs and its relation with agenesis of the spleen were extensively documented and recognized as a developmental complex by Ivemark (2) in 1955 and by Putschar and Manion (3) in 1956. Abnormalities of the spleen gained interest among cardiologists when Van Mierop et al. (4,5) emphasized the association between absent spleen and bilateral rightsidedness and when Moller et al. (6) showed the relation between polysplenia and bilateral left-sidedness, because congenital heart disease was almost invariably present in the former and frequently less complex or even absent in the latter.

This report describes two cases of prenatal diagnosis of complex congenital heart disease with suspected atrial isomerism. Postmortem analysis revealed left atrial isomerism in association with asplenia. Van Mierop (7) mentioned experience with one case of "asplenia heart" and "polysplenia abdomen," but to our knowledge, the combination of left atrial isomerism and asplenia has not previously been reported.

## *Case Reports*

### *Case 1*

A healthy 23 year old woman, gravida I, was referred at 20 weeks' gestation with fetal ascites and arrhythmia. Two-dimensional echocardiography (Hewlett-Packard 77020A) revealed a normal-sized fetus with gross ascites and hydrothorax. The heart of the fetus was thought to be situated in the left side of the chest (Fig.1) and there was a large atrium without evidence of septation. A vessel thought to be the inferior vena cava was seen to drain into the left side of the atrium. Pulmonary venous connections were not identified. These findings suggested the presence of atrial isomerism. A single atrioventricular (AV) valve was connected to a large, left-sided hypertrophied ventricle that contracted poorly. A small chamber was visualized to the right of the main chamber and had no AV connection of its own. A thick echogenic area was seen in the region of the common AV valve and was thought to represent an absent right-sided AV-connection. Both great arteries ran parallel to each other and appeared to be connected to the main chamber. Fetal M-mode echocardiography demonstrated complete heart block with an atrial rate of 105 /min and a ventricular rate of 45 /min.

In view of the severity of the fetal cardiac lesions, the severe congestive heart

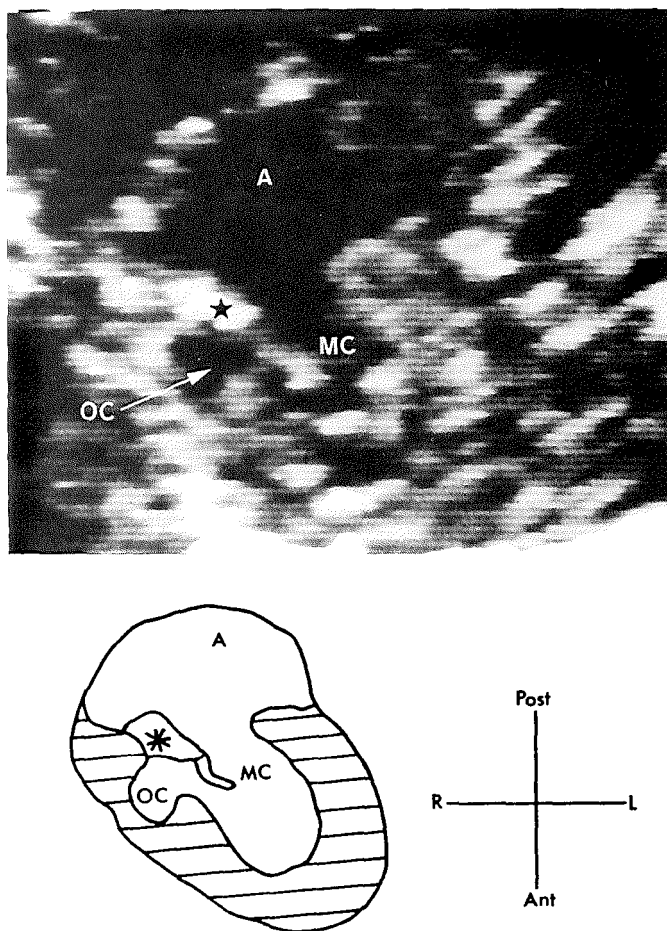


Fig.1. Case 1. Four-chamber view (top) and line diagram (bottom) of the two-dimensional echocardiogram. A=large atrium without evidence of septation.; Ant=anterior; L=left; MC=main chamber; OC=outlet chamber; P=posterior; R=right. \*=thick echogenic area representing an absent atrioventricular connection.

failure and the early gestational age, the parents requested termination of the pregnancy. This occurred at 21 weeks of gestation. A female fetus weighing 650g was delivered with a distended abdomen and edema. There was a "short neck" and rocker bottom feet. No further external abnormalities were noted. Chromosome analysis revealed a normal female karyotype.

*Pathologic findings*

Postmortem examination revealed 100 ml of ascites and bilateral pleural effusions of 9 ml. The spleen was absent. The lungs showed a bilateral bilobed architecture with bilateral hyperarterial bronchi. Contrary to the impression obtained from the echographic studies, the apex of the heart was positioned in the right chest (Fig.2). Inspection showed that the right- and left-sided atrial appendages had the typical characteristics of a morphologic left atrium (Fig.2). The systemic veins were abnormal with the inferior cava vein running to the left and anterior to the abdominal aorta. The vein continued as an azygos vein and drained into a left-sided superior cava vein. There was no right-sided superior cava vein. The hepatic veins drained directly into the left-sided atrium.

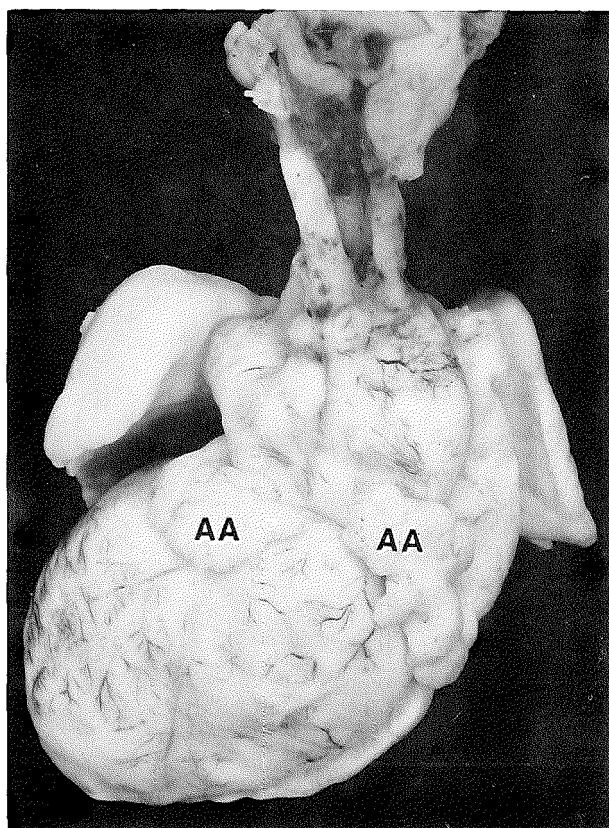


Fig.2. Case 1. Heart-lung specimen obtained at autopsy. The ventricular apex points to the right. The atrial appendages (AA) embrace the arterial pedicle and both show the characteristics of morphologic left atrial appendages.

The heart itself showed a complex malformation. There was left atrial isomerism with an almost common atrium due to a large primum type atrial septal defect. The atrial septum was represented by a tiny shelf; the right and left pulmonary veins drained in the back of the atrium immediately adjacent to this septal vestige. The atria were almost completely separated from the underlying ventricular mass by a deeply wedged groove; the AV junctional side was small and composed of a common AV orifice. Both atria drained into a single ventricle with left ventricular trabecular characteristics (Fig.3). A small outlet chamber was present in the left anterior shoulder of the ventricular mass, showing right ventricular trabecular characteristics. The arterial connections were concordant with the pulmonary trunk in anterior position, arising from the outlet chamber. There

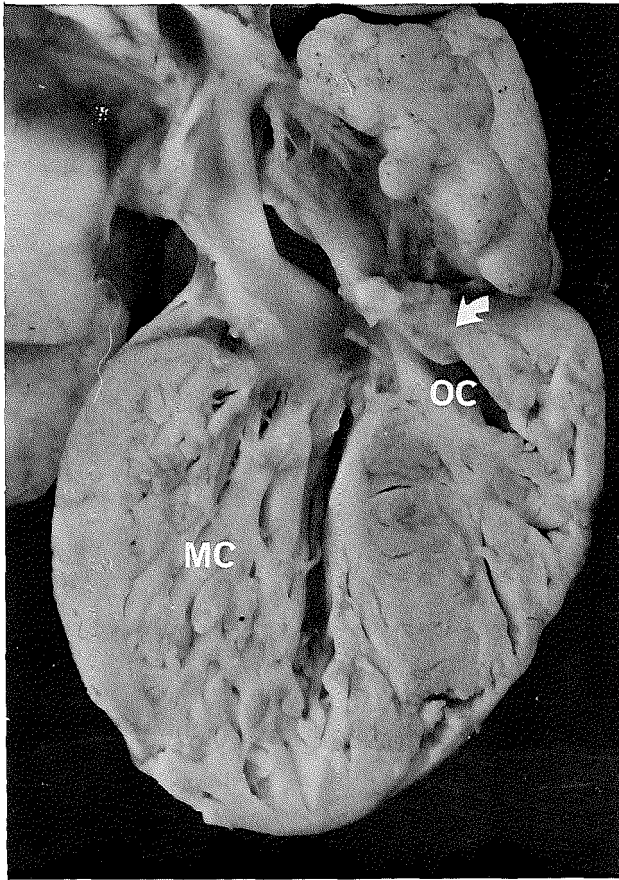


Fig.3. Case 1. Cross section through the heart. There is a common atrioventricular orifice through which both atria drain into a main chamber (MC) with left ventricular trabecular characteristics. The small outlet chamber (OC) is seen on the left.

was subpulmonary stenosis. The aorta was in fibrous continuity with the common AV valve and arose posterior and to the right of the pulmonary trunk. The ductus arteriosus arose in its usual position from the proximal segment of the left pulmonary artery, following the bifurcation, and connected to the base of the brachiocephalic trunk, being the first artery to arise from a left-sided aortic arch. The ductus was narrowed and most likely functionally restrictive.

Hence, a complex cardiac malformation was present characterized by: 1) abnormal systemic and pulmonary venous connections to a "common atrium" with left atrial isomerism, 2) a univentricular AV connection through a common AV valve into a main chamber with left ventricular characteristics and a rudimentary chamber of right ventricular characteristics in the left anterior shoulder of the heart, and 3) concordant arterial connections with inverted normally related great arteries. The heart could thus be classified as a mirror-image Holmes heart.

### *Case 2*

A healthy 32 year old woman, gravida III, was referred at 29 weeks' gestation with fetal ascites. Her previous children are normal. Two-dimensional echocardiography (Diasonics Cardio Vue 100) revealed polyhydramnios and a fetus with gross ascites. There was a small pericardial effusion. A large atrium without evidence of septation was identified and thought possibly to be isomeric. Vena caval and pulmonary venous connections were not identified. One large atrioventricular valve was seen to connect the single atrium to two grossly hypertrophied ventricles (Fig.4). A bridging leaflet of the AV valve was seen to have chordal attachments to the crest of the interventricular septum. The great vessels appeared concordant and the pulmonary artery was of small caliber. The aorta was dilated and appeared to override the ventricular septum. The anatomy of tetralogy of Fallot was suspected. M-mode echocardiography indicated complete heart block with an atrial rate of 100 /min and a ventricular rate of 51 /min.

### *Pathologic findings*

Stillbirth occurred at 31 weeks of gestation and a female fetus weighing 1,500 g was delivered. The abdomen was distended. The left small toe was abnormally implanted. No other external abnormalities were noted. There was asplenia. The heart, which had been received detached from the lungs, demonstrated left atrial isomerism. Vena caval and pulmonary venous drainage sites could not be clearly identified. The atria contained a large primum type septal defect (Fig.5A). Both atria drained through a common AV orifice. The common valve was mainly connected to the left-sided ventricle, with only a minimal part directly emptying into the right-sided ventricle (Fig.5B). The myocardial architecture was sponge-

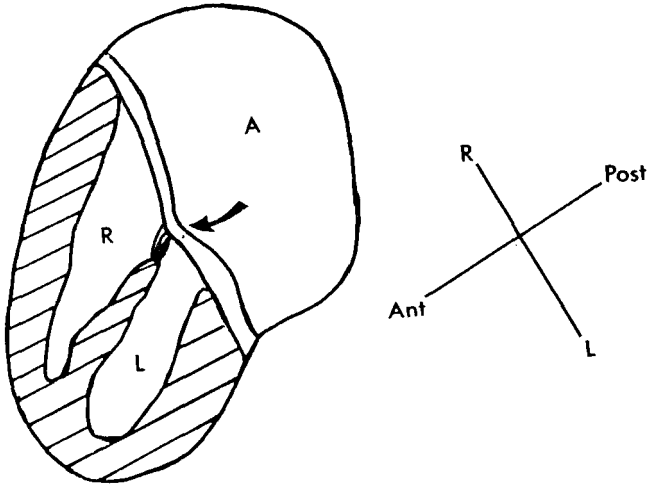
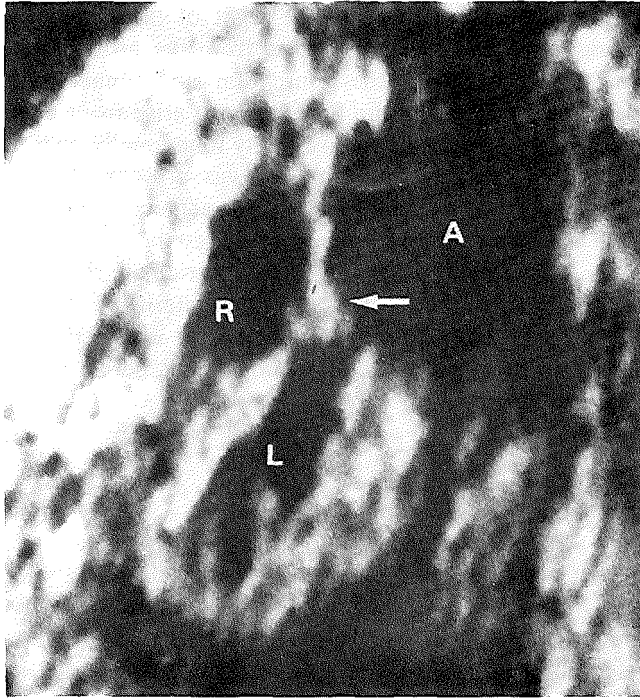


Fig.4. Case 2. Four-chamber view (top) and line diagram (bottom) of the two-dimensional echocardiogram. The arrow indicates a single atrioventricular valve which, on the two-dimensional echocardiogram, was seen to have chordal attachments to the crest of the septum. A=large atrium without evidence of septation; L=left-sided chamber; R=right-sided chamber.

like, which made it difficult to ascertain the nature of the ventricles on the basis of the trabecular characteristics. (Fig.5B). The arterial connections were concordant, with fibrous continuity between the aortic valve and the common AV valve. The pulmonary trunk and ascending aorta showed normal relations. The outflow tract toward the pulmonary trunk showed an anteriorly displaced infundibular septum as in tetralogy of Fallot. There was a right aortic arch with aberrant left subclavian artery with retroesophageal position.

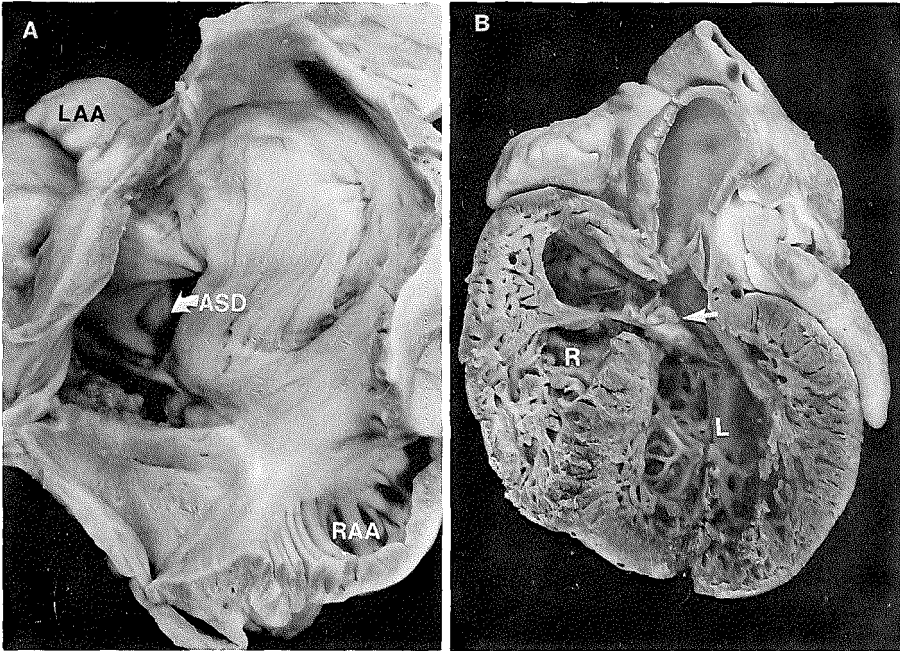


Fig.5. Case 2. Heart specimen. A, The inside of the atria revealing a large primus type atrial septal defect (ASD). The arrangement of the pectinate muscles, characteristic of a left atrial appendage (LAA), can be seen inside the right-sided atrial appendage (RAA).

B, The heart cut in a plane to correspond with the two-dimensional echocardiographic view seen in Figure 4. The myocardium has a spongy appearance. The arrow indicates the atrioventricular valve, which for its greater part empties into the left-sided ventricle (L). R=right-sided ventricle.

### *Discussion*

In recent years, there has been increasing interest in cardiac abnormalities that occur in the setting of symmetry syndromes such as the so-called asplenia and polysplenia syndromes. The number of patients admitted to pediatric cardiac units afflicted with these anomalies is substantial and has been reported (8) as approximating 10% of all admissions.

*Right versus left isomeric syndrome (asplenia versus polysplenia)*

Asplenia or right isomeric syndrome is almost always associated with a complex cardiac malformation (2,3,9-14). The polysplenia or left isomeric syndrome shows a more variable picture with an occasional normal heart at one end of the spectrum and severe and complex malformations at the other (6,15).

The mode of predicting these cardiac abnormalities in the neonate has gradually shifted from attempts to visualize the spleen by injection of radioactive substances to echographic detection of the abdominal vessels (16). In right and left isomerism, the vena cava and aorta are both situated on the same side of the spine. In the right isomeric syndrome, the inferior cava vein is positioned anteriorly. In the left isomeric syndrome, the major vein in the abdomen runs posteriorly. Hence, in neonates, the position of these vessels is often used as an indication of the type of cardiac abnormality to be expected.

*Present cases*

Our present observation of two cases of thoracoabdominal visceral discordancy indicates that exceptions occur, because the abdominal situs showed an absence of the spleen and the arrangement of the abdominal vessels was as anticipated in cases with asplenia, while the thoracic situs revealed a bilateral left-sided arrangement with left isomerism of the atria. Apart from the morphology of the atrial appendages, however, the cardiac malformations in both patients showed the complexity anticipated for asplenia. Thus far, our experience indicates that these cases are unusual, and we have been unable to find any previous reports of this combination of defects. However, other discrepancies in situs have previously been reported in patients with asplenia. Putschar and Manion (3) emphasized that absence of the spleen could occur with and without associated malformations and with various types of abnormalities in situs. A discordant anatomy between bronchi and atria in asplenia has been documented (17) and "asplenia-like" visceral abnormalities have been described (18) with a normal spleen and even in the presence of multiple spleens. Indeed, it is clear that "crossover" cases exist between the classic examples of the asplenia and polysplenia syndromes (19). as previously outlined (4-6). From that point of view, therefore, one should avoid diagnosing one of these syndromes on the basis of a single item, be that the presence or absence of the spleen, the position of the abdominal vessels or the anatomy of bronchi and atrial appendages.

*Prognosis*

Patients with a "classic" asplenia have a poor prognosis and 79 to 94% die before the age of 1 year (5,15), with congestive heart failure and anoxia being major causes of death. The risk of sudden and severe infection is high. The two fetuses in this report showed evidence of severe congestive heart failure



and this was most likely the cause of death in Case 2. Moreover, congestive heart failure would probably have caused the death in Case 1 if the pregnancy had not been terminated at 21 weeks of gestation. It has been a major concern that the echocardiogram in this patient was mistakenly interpreted as showing the heart with the apex in the left side of the chest, while the autopsy unequivocally showed the apex to be on the right. Careful review of the videotapes still showed the heart to be apparently left-sided. We have no satisfactory explanation for this phenomenon other than to suggest that the precise prenatal echographic identification of the position of the heart may be hampered in patients with severe hydrothorax and ascites.

### *Implications*

It remains to be answered whether these findings constitute a new entity or whether the combination of defects reported represents a lethal group of abnormalities that tends to remain undetected because death occurs in utero and postmortem analysis is usually not carried out. Recent advances in ultrasound equipment have shown that detailed analysis of the fetal heart is possible (20-22), and prenatal echographic evaluation of the heart is increasing. In fact, the prenatal diagnosis of severe congenital cardiac abnormalities with the suspicion of atrial isomerism resulted in precise postmortem investigation in our cases. On that basis, we may perhaps postulate that more cases with this particular anatomic arrangement may be identified in the future with the increasing use of prenatal echocardiography.

We are grateful to J.H.Deelen, MD, Onze Lieve Vrouwe Gasthuis, Amsterdam for referring Case 1, R. de Boer, MD, Groot Ziekengasthuis, 's Hertogenbosch for referring Case 2 and Alize Bijl and Marsha Schenker for secretarial assistance.

### *References*

- 1 Becker AE, Anderson RH. Pathology of congenital heart disease. Postgraduate Pathology Series London: Butterworths, 1981:211.
- 2 Ivemark IB. Implication of agenesis of the spleen on the pathogenesis of conotruncus anomalies in childhood: analysis of the heart malformations in splenic agenesis syndrome, with fourteen new cases. *Acta Paediatrica* 1955; 44(suppl 104): 1-110.
- 3 Putschar WG, Manion WC. Congenital absence of the spleen and associated anomalies. *Am J Clin Pathol* 1956; 26: 429-70.
- 4 Van Mierop LHS, Wigglesworth FW. Isomerism of the cardiac atria in the asplenia syndrome. *Lab Invest* 1962; 11: 1303-15.
- 5 Van Mierop LHS, Gessner IH, Schiebler GL. Asplenia and polysplenia syndrome. *Birth Defects: Original Article Series* 1972; 1: 74-82.
- 6 Moller JH, Nakib A, Anderson RC, Edwards JE. Congenital cardiac disease associated with polysplenia. A developmental complex of bilateral "left-sidedness." *Circulation* 1967; 36: 789-99.

- 7 Van Mierop LHS. Discussion on chapter 19. In: Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, eds. *Paediatric Cardiology*, vol 5. Edinburgh: Churchill Livingstone, 1983: 203-4.
- 8 Deanfield JE, Leanage R, Stroobant J, Chrispin AR, Taylor JFN, Macartney FJ. Use of high kilovoltage filtered beam radiographs for detection of bronchial situs in infants and young children. *Br Heart J* 1980; 44: 577-83.
- 9 Polhemus DW, Schafer WB. Congenital absence of the spleen: syndrome with atrioventricularis and situs inversus. *Pediatrics* 1952; 9: 696-708.
- 10 Polhemus DW, Schafer WB. Congenital absence of the spleen. *Pediatrics* 1955; 16: 495-7.
- 11 Schonfeld EA; Frischman B. Syndrome of spleen agenesis, defects of the heart and vessels and situs inversus. *Helvetica Paediatrica Acta* 1958; 13: 636-40.
- 12 Ruttenberg HD, Neufeld HN, Lucas RV Jr, et al. Syndrome of congenital cardiac disease with asplenia: distinction from other forms of congenital heart disease. *Am J Cardiol* 1964; 13: 387-406.
- 13 Landing BH, Lawrence TK, Payne VC Jr, Wells TR. Bronchial anatomy in syndromes with abnormal visceral situs, abnormal spleen and congenital heart disease. *Am J Cardiol* 1971; 28: 456-62.
- 14 Silver W, Steier M, Chandra N. Asplenia syndrome with congenital heart disease and tetralogy of Fallot in siblings. *Am J Cardiol* 1972; 30: 91-4.
- 15 Rose V, Izukawa T, Moës CAF. Syndromes of asplenia and polysplenia. A review of cardiac and non-cardiac malformations in 60 cases with special reference to diagnosis and prognosis. *Br Heart J* 1975; 37: 840-52.
- 16 Huhta JC, Smallhorn JF, Macartney FJ. Two dimensional echocardiographic diagnosis of situs. *Br Heart J* 1982; 48: 97-108.
- 17 Caruso G, Becker AE. How to determine atrial situs? Considerations initiated by 3 cases of absent spleen with a discordant anatomy between bronchi and atria. *Br Heart J* 1979; 41: 559-67.
- 18 Freedom RM. Aortic valve and arch anomalies in the congenital asplenia syndrome. Case report, literature review and re-examination of the embryology of the congenital asplenia syndrome. *Hopkins Med J* 1974; 135: 124-35.
- 19 Van Praagh R, Weinberg PM, Matsuoka R, Van Praagh S. Malpositions of the heart. In: Adams FH, Emmanouilides GC, eds. *Moss Heart Disease in Infants, Children and Adolescents*. 3rd ed. Baltimore: Williams & Wilkins, 1983: 424.
- 20 Lange LW, Sahn DJ, Allen HD, Goldberg SJ, Anderson C, Giles H. Qualitative real-time cross-sectional echocardiographic imaging of the human fetus during the second half of pregnancy. *Circulation* 1980; 62: 799-806.
- 21 Allan LD, Tynan M, Campbell S, Anderson RH. Normal fetal cardiac anatomy - a basis for the echocardiographic detection of abnormalities. *Prenat Diagn* 1981; 1: 131-9.
- 22 Stewart PA, Wladimiroff JW, Essed CE. Prenatal ultrasound diagnosis of congenital heart disease associated with intrauterine growth retardation. *Prenat Diagn* 1983; 3: 279-85.

## Chapter 5

# Ultrasound and pathology correlates

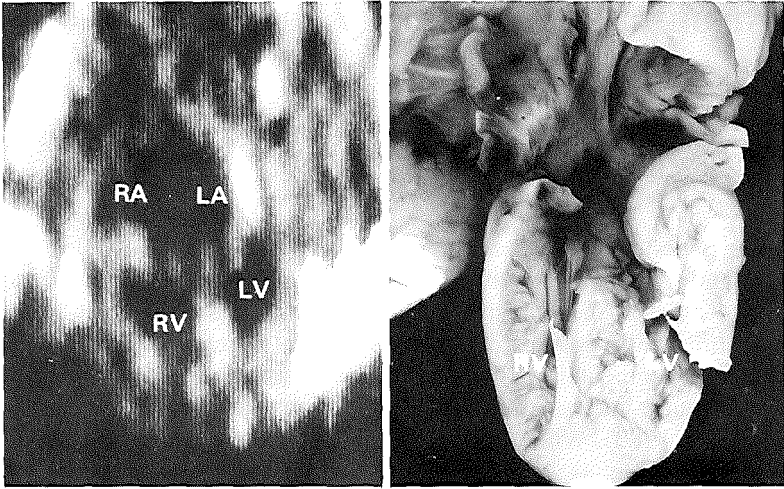
## Introductory remarks

During the study period an attempt was made, where possible to correlate the prenatal ultrasound findings with the postmortem specimens. This is mandatory, to confirm the prenatal diagnosis and to understand how errors (misclassifications, false positive diagnoses etc) in interpretation may have occurred.

Sequential segmental analysis of cardiac morphology was performed during both ultrasound and postmortem examination (Becker and Anderson, 1981; Gussenhoven, 1983). When feasible specimens were opened, and photographed in planes as close as possible to the appropriate ultrasound images to aid comparison. Close correlation may be achieved (case 10) even when the specimen is very small.

Concomitant defects such as aortic arch anomalies, dysplasia of the valve leaflets and outflow tract stenoses may be missed by prenatal ultrasound. In some cases this may be caused by inability to completely visualize all structures, especially later in gestation or when multiple defects are present. Certain types of defect may not be identifiable by ultrasound. In yet other cases (cases 11 and 12) rare anatomic variants may confuse the issue, leading to erroneous interpretation.

Given the above it is obvious that, whenever possible, careful postmortem examination should be performed.



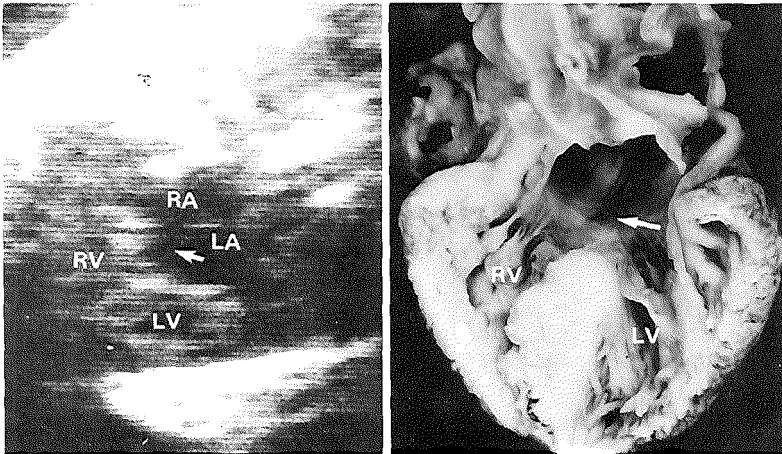
Case 1 - 17 weeks

Ultrasound

- Complete atrioventricular septum defect

Pathology

- Complete atrioventricular septum defect



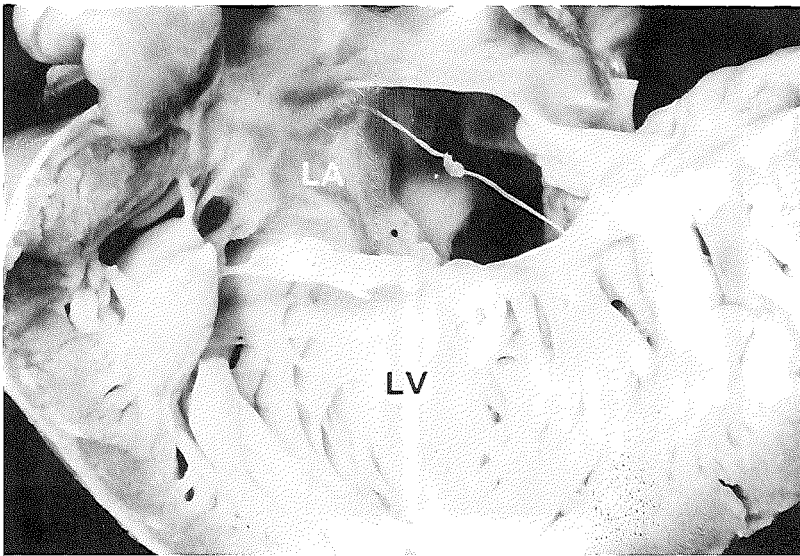
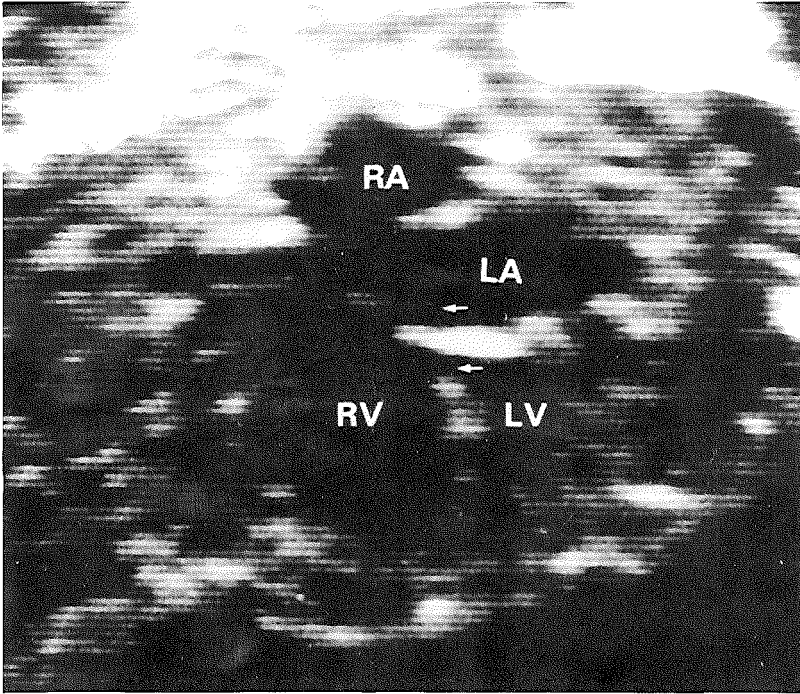
Case 2 - 27 weeks

Ultrasound

- Complete atrioventricular septum defect

Pathology

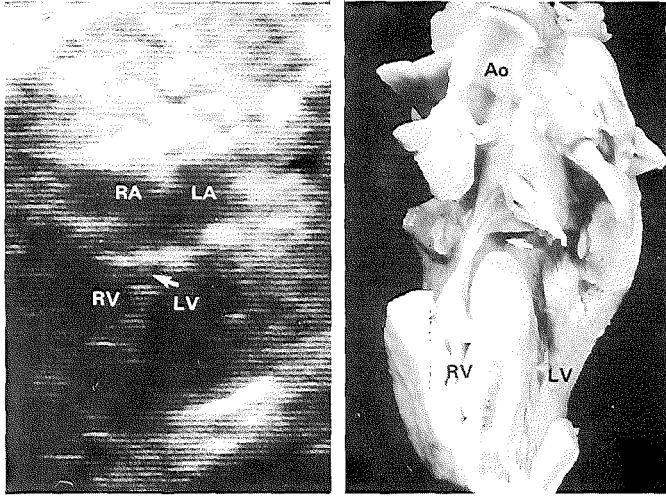
- Complete atrioventricular septum defect  
- Hypoplastic aortic isthmus



Case 3 - 28 weeks

Ultrasound  
- Complete atrioventricular septum defect

Pathology  
- Complete atrioventricular septum defect



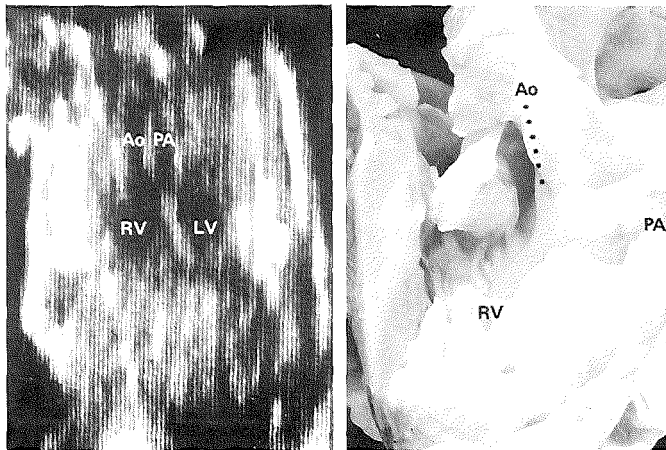
Case 4 - 30 weeks

**Ultrasound**

- Complete atrioventricular septum defect and overriding aorta

**Pathology**

- Complete atrioventricular septum defect, aorta probably normal - appeared displaced due to septal architecture



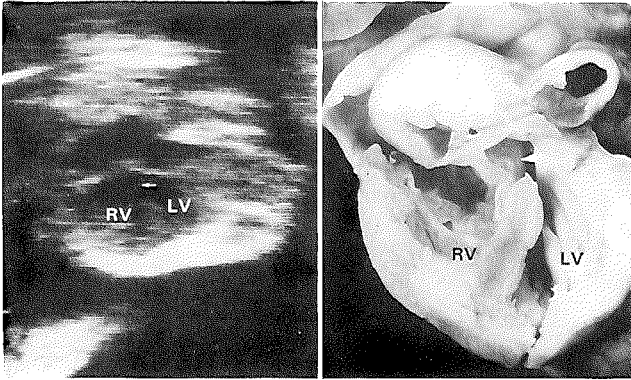
Case 5 - 25 weeks

**Ultrasound**

- Ventricular Septal Defect
- Double outlet right ventricle

**Pathology**

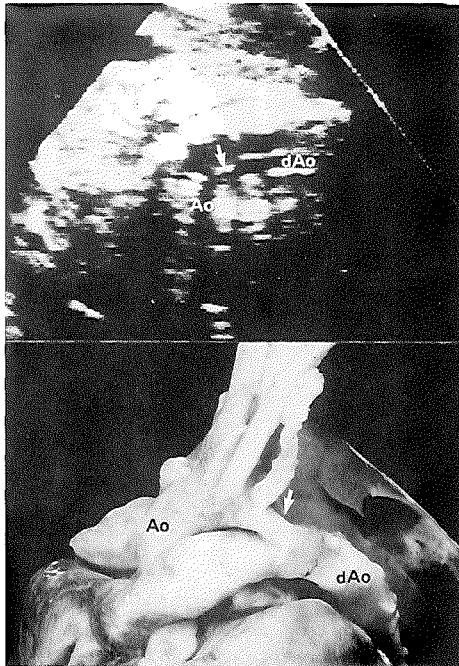
- Ventricular Septal Defect
- Double outlet right ventricle
- Dysplastic tricuspid valve



Case 6 - 32 weeks

Ultrasound  
 - Ventricular Septal Defect  
 - Overriding aorta

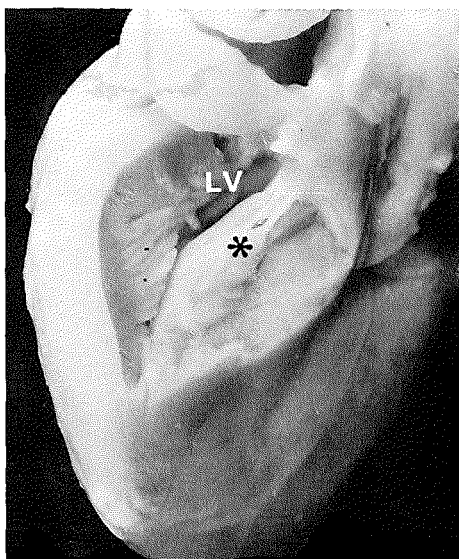
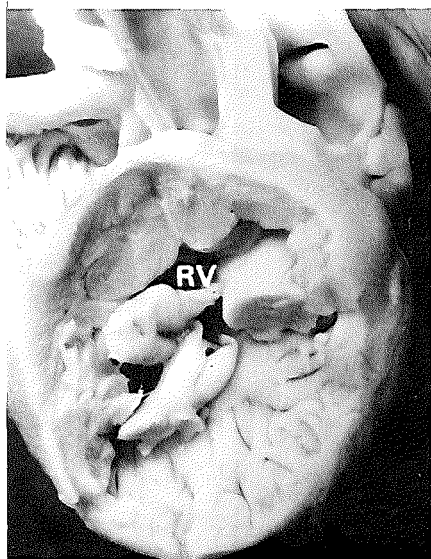
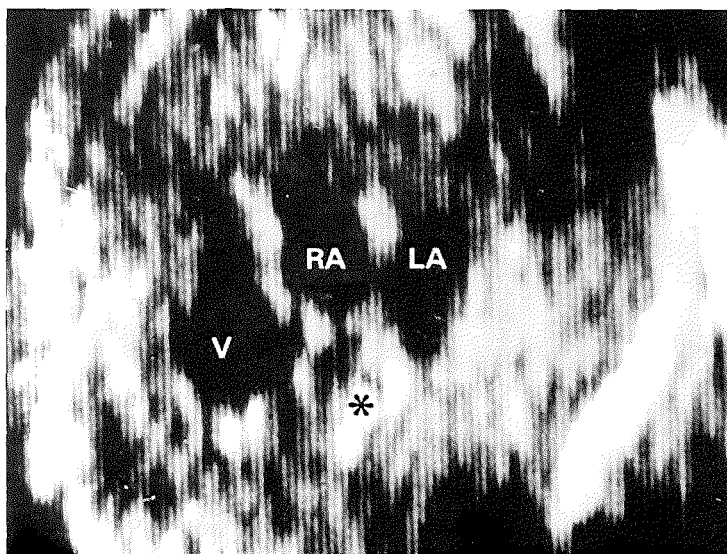
Pathology  
 - Ventricular Septal Defect  
 - Double outlet right ventricle



Case 7 - 28 weeks

Ultrasound  
 - Hypoplastic aortic isthmus

Pathology  
 - Hypoplastic aortic isthmus



## Case 8 - 31 weeks

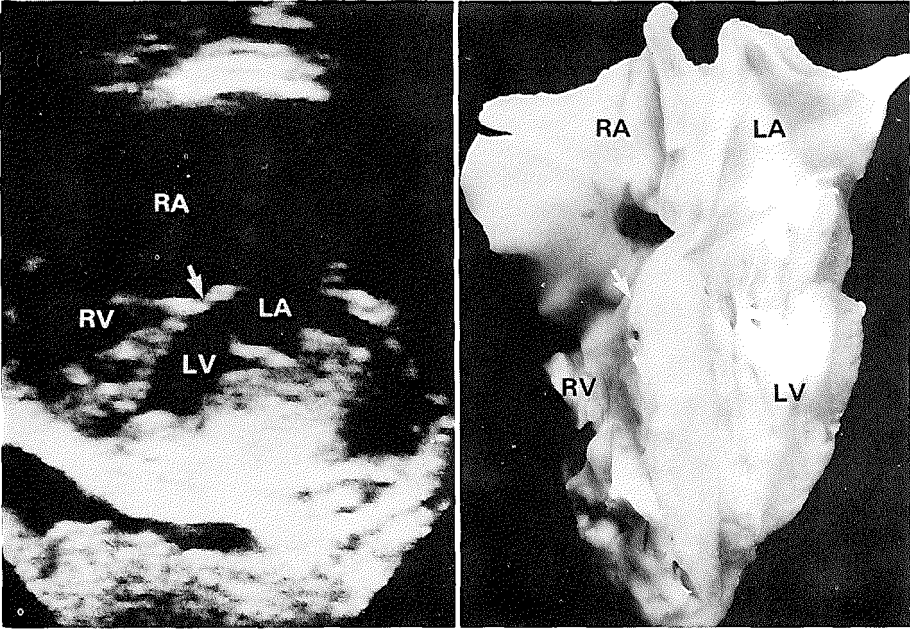
## Ultrasound

- Dextrocardia
- ? absent left sided atrioventricular connection
- ? abnormal papillary muscle in hypoplastic LV
- Double outlet right ventricle

## Pathology

- Dextrocardia
- Hypoplasia left heart
- Parachute mitral valve
- Double outlet right ventricle with pulmonary outflow tract stenosis and preductal coarctation





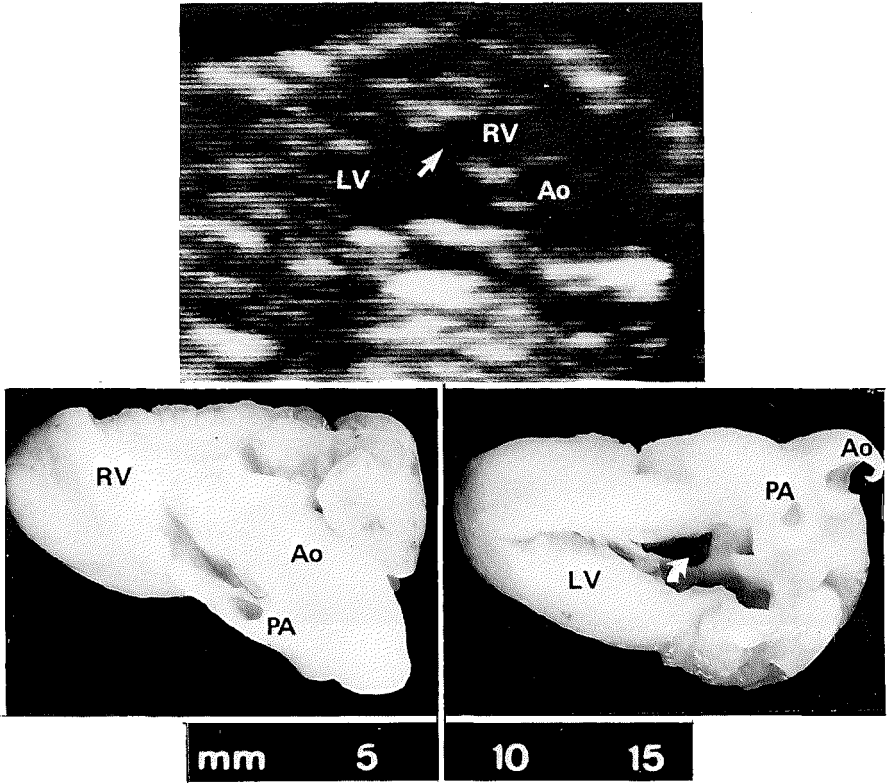
## Case 9 - 35 weeks

## Ultrasound

- Severe RA dilatation
- ? Ebstein anomaly or obstructed foramen ovale (no echographic evidence of valve displacement - arrow indicates septal leaflet insertion)

## Pathology

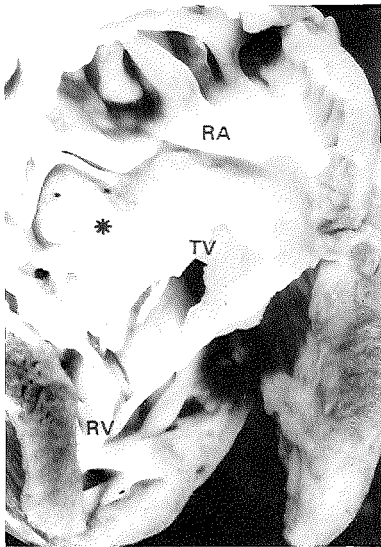
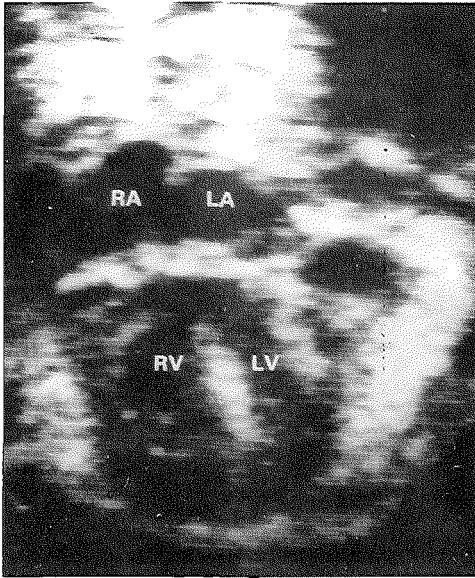
- Severe RA dilatation
- Tricuspid dysplasia with "knobby" tissue.
- No* septal leaflet displacement



Case 10 - 16 weeks

Ultrasound  
- Tetralogy of Fallot

Pathology  
- Tetralogy of Fallot



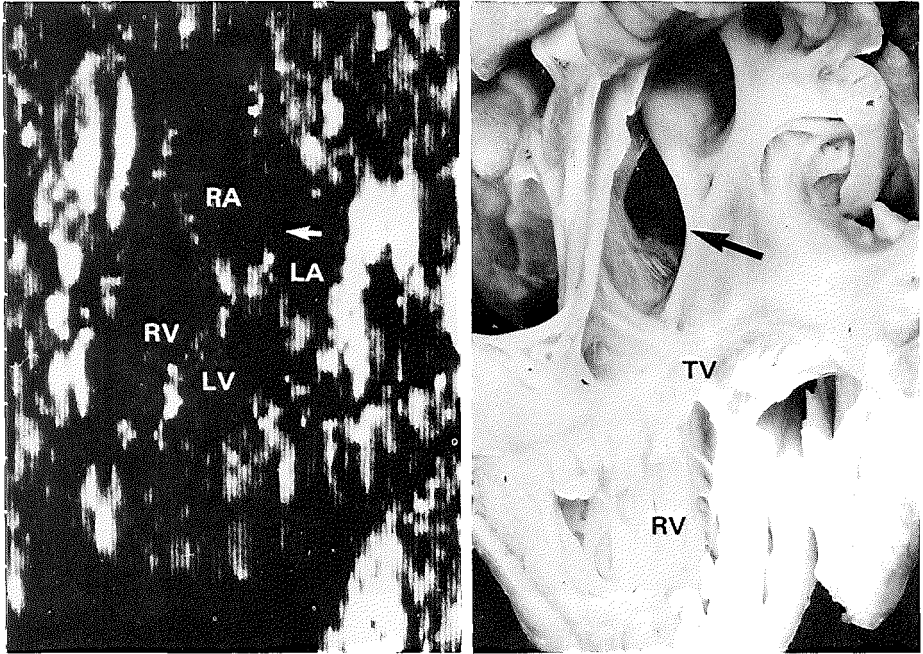
Case 11 - 34 weeks

#### Ultrasound

- Complete atrioventricular septum defect
- Tetralogy of Fallot

#### Pathology

- Deficiency of the muscular atrioventricular septum (replaced by membranous septum\*)
- Dysplastic tricuspid (TV) and mitral valves (MV) with no papillary muscles
- Tetralogy of Fallot



Case 12 - 29 weeks

**Ultrasound**

- Secundum atrial septal defect

**Pathology**

- Anatomic variant, superior and inferior limbus met in central fibrous body

**References**

Becker AE, Anderson RH, 1981: Pathology of Congenital Heart Disease, pp 3-27, Butterworths, London.

Gussenhoven WJ, Becker AE, 1983: Congenital heart disease: Morphologic echocardiographic correlations. Churchill Livingstone, Edinburgh.

## Chapter 6

**Fetal cardiac arrhythmia****Introductory remarks**

Fetal echocardiography is advised when a disturbance in fetal heart rate and / or rhythm has been identified. A definition of fetal cardiac arrhythmia and methods of diagnosis are provided in Chapter 6.1.

Fetuses with arrhythmia were studied over a 6 year period from 01.01.82 to 01.01.88.

In Chapter 6.2 fetal extrasystoles and their outcome are discussed.

In Chapter 6.3 the article describes the findings related to fetal bradyarrhythmia.

In Chapter 6.4 two articles detail the findings related to fetal tachyarrhythmia.

The article in Chapter 6.5 describes the findings related to various fetal atrial arrhythmias and aneurysm /redundancy of the foramen ovale.

**6.1 Fetal cardiac arrhythmia; definition and methods of recording**

In the study group of 189 fetuses referred with an arrhythmia, three types of arrhythmia were observed: ectopic beats, bradyarrhythmia and tachyarrhythmia.

Ectopic beats were defined as a persistent irregularity in fetal heart rate and rhythm, bradyarrhythmia as a persistent rate  $< 100$  beats per minute, and tachyarrhythmia as a persistent rate  $> 180$  beats per minute.

Suspicious of fetal cardiac rhythm disturbances are usually based on findings in routine prenatal care. Postnatally, precise definition of an arrhythmia based on recording of atrial (P wave) and ventricular (QRS complex) systole is possible. However, due to the inability of the transabdominal fetal electrocardiography to detect P wave activity, 2-D directed M-mode echocardiography is the most suitable method for attempting to determine fetal arrhythmias.

The M line is directed through the structures to be examined. Atrial systole is identified by movement of the atrial wall towards the atrial septum or aortic root and ventricular systole inferred from opening of the arterial valve (Fig. 1), or onset of ventricular wall motion towards the septum (Fig. 2). Atrial systole may also be inferred from the "A" wave seen in Fig. 2 in the tricuspid valve.

**6.2 Fetal extrasystoles**

Ectopic beats were usually supraventricular and frequently appeared to be blocked. In 4 of the 139 cases ventricular ectopics were suspected.

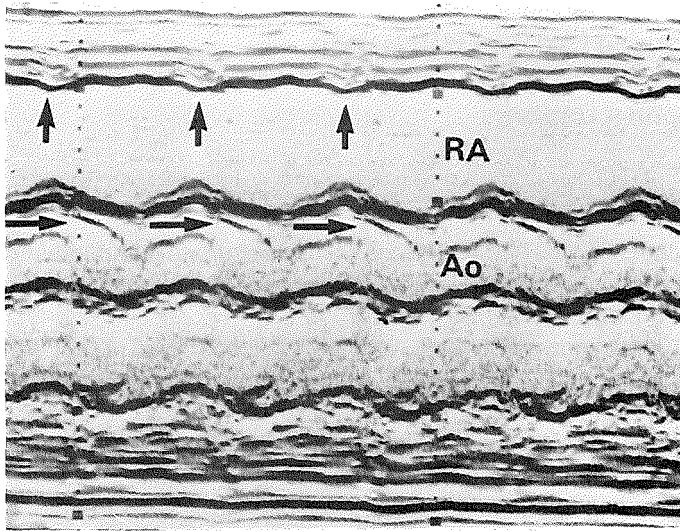


Fig. 1. M-mode echocardiogram recorded through the fetal right atrium (RA) and aortic root (AO). Vertical arrows indicate mechanical atrial systole and the atrial wall is seen to move towards the aortic wall. Horizontal arrows indicate opening of the aortic valve inferring mechanical ventricular systole.

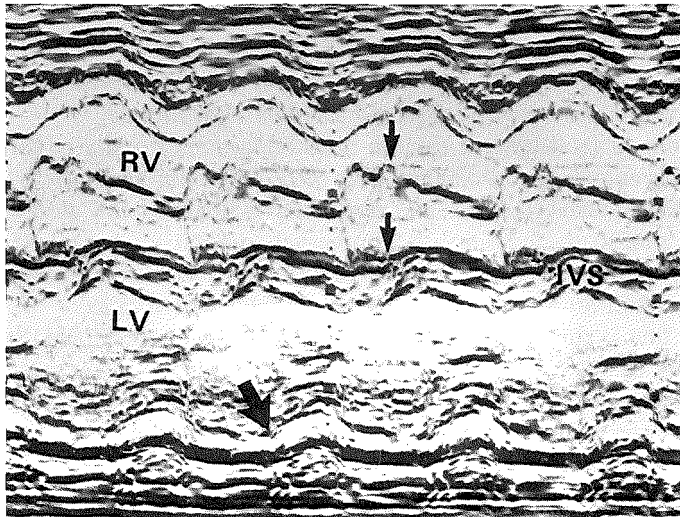


Fig. 2. M-mode echocardiogram recorded through the fetal right (RV) and left ventricles (LV). IVS = interventricular septum. Heavy arrow indicates beginning of mechanical ventricular systole seen by movement of ventricular wall towards the IVS. Smaller arrows show "A" wave indicating mechanical atrial systole.

It is known that premature beats occur in healthy fetuses and neonates (Southall et al., 1980a, 1980b) and that these are associated with a good prognosis. Other investigators (Kleinman et al., 1983, Allan et al., 1983) have made similar statements. However in this series 7 cases (5%) had ectopics associated with structural anomalies (Table); resulting in fetal death in one. It is clear that detailed structural analysis of the heart should be performed in all instances of arrhythmia.

Regular screening of fetuses (weekly) with ectopic beats should be carried out as triggering of a sustained arrhythmia may occur from one of these ectopic beats (Gillette, 1976). This phenomenon occurred in one of the fetuses in this study. Supraventricular ectopics with ½ second bursts of non-conducted atrial flutter were diagnosed at 26 weeks of gestation. At 32 weeks of gestation supraventricular tachycardia was demonstrated with acute hydrops. Caesarean section was performed the same day and a postnatal diagnosis of Wolff-Parkinson-White syndrome was established.

In the vast majority of fetuses with ectopics, obstetric management need not be altered and spontaneous vaginal delivery occurs. The ectopic beats usually disappear during gestation but may be present until a few days after birth. As

Table. Structural cardiac anomalies in 139 cases of fetal extrasystoles (1982-1988)

Case no	Gestational age	Prenatal US	Postnatal US	Mortality
1	31	Aneurysm foramen ovale	Normal structure	
2	36	Aneurysm /obstr.foramen ovale ↑ Right heart	Normal structure ↑ Rt heart	
3	37	Aneurysm /obstr.foramen ovale ↑ Rt heart	Normal structure ↑ Rt heart	
4	31	↑ Right heart. Coarctation / abn TV?	↑ Rt heart, peripheral Pulmonary artery stenosis	
5	32	Thick septum (incomplete exam)	Incomplete atrioventricular septum defect	
6	34	Univentricular heart + coarctation	Univentricular heart + coarctation	Intra uterine death
7	35	Normal structure	Secundum ASD	
Total no of patients		139		
Structural anomaly		7 (5%)		
Mortality		1 (14.3%)		

Fetuses displaying an aneurysm of the foramen ovale (cases 1-3) are further discussed in Chapter 6.5.

an isolated finding they are not associated with any haemodynamic compromise.

Fetuses displaying an aneurysm of the foramen ovale (cases 1-3) are further discussed in Chapter 6.5.

### *References*

Allan LD, Anderson RH, Sullivan ID, Campbell S, Holt DW, Tynan M (1983).  
Evaluation of fetal arrhythmias by echocardiography. *Br Heart J* 50, 240-245.

Gillette PC (1976).

The mechanism of supraventricular tachycardia in children. *Circulation* 54, 133-140.

Kleinman CS, Donnerstein RL, Jaffe CC et al. (1983).

Fetal echocardiography. A tool for evaluation of in utero cardiac dysrhythmias and monitoring of in utero therapy: Analysis of 71 patients. *Am J Cardiol* 51, 237-243.

Southall DP, Johnson AM, Shinebourne EA (1980).

Study of the nature and natural history of disorders of cardiac rhythm and conduction in the apparently healthy infant. In: Godman P. ed. *Paediatric Cardiology, Proceedings of the First World Congress in Paediatric Cardiology*, London, June 1980. Edinburgh: Churchill Livingstone.

Southall DP, Richard J, Hardwick R, Shinebourne EA, Gibbens GLD, Thelwell-Jones H, De Swiet M, Johnston PGB (1980).

Prospective study of fetal heart rate and rhythm patterns. *Arch Dis Child*. 55, 506-511.

### **6.3 Fetal bradyarrhythmia: Diagnosis and outcome**

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Published in *Prenatal Diagnosis*, Vol 8: 53-57 (1988).

Seventeen patients were referred to our ultrasound unit because of fetal bradyarrhythmia (<100 bpm). Duration of pregnancy varied between 21 and 40 weeks. Bradyarrhythmia was diagnosed as atrioventricular block (n=12), mild sinus bradycardia (n=3), and irregular bradycardia (n=2). The association with maternal collagen disease was 29 per cent and with cardiac structural defects 59 per cent. The overall mortality was 41 per cent. There were three abnormal karyotypes (17 per cent) and four cases of cardiac compromise (23 per cent).

Prognosis depends on the nature of the bradyarrhythmia and recognition of



associated pathology such as cardiac structural defects, abnormal karyotype and degree of cardiac compromise.

**Key words:** Fetal bradyarrhythmia, Congenital cardiac defect, Maternal collagen disease

### *Introduction*

Detailed information can now be obtained on normal and abnormal fetal cardiac anatomy as early as 16-18 weeks of gestation using high resolution real-time ultrasound equipment (Sahn et al., 1980; Kleinman et al., 1980; Allan et al., 1981, 1984; Wladimiroff et al., 1984). M-mode echography allows accurate diagnosis of fetal cardiac rate and rhythm (Allan et al., 1983; Stewart et al., 1983; Crawford et al., 1985; Copel and Kleinman, 1986). Both techniques are essential in establishing the correct prognosis and in providing appropriate further obstetric management of cardiac arrhythmias. This report describes the diagnosis, the incidence of associated pathology, obstetric management, and fetal outcome in fetal bradyarrhythmias.

### *Materials and methods*

Between January 1982 and January 1986 a total of 17 patients were referred to our ultrasound unit because of persistent fetal bradyarrhythmia (<100 bpm). Pregnancy duration varied between 21 and 40 weeks. In each patient the following examinations were performed:

- (a) Assessment of cardiac structure, rate, and rhythm using a two-dimensional phased array real-time system (Hewlett-Packard, 77020A) or a mechanical sector scanner (Diasonics, Cardio Vue 100), both with real-time directed M-mode recording facilities. Problems with respect to visualization of the heart may arise when the spine is anterior (shadowing), during excessive fetal movements, maternal obesity, and oligohydramnios. In the present study standard cardiac scans were short axis, long axis, and four chamber views (Wladimiroff et al., 1984; DeVore, 1985).
- (b) A search for possible signs of cardiac compromise such as pericardial effusion, increase in size of the right heart, or ascites.
- (c) A search for associated defects and karyotyping in amniotic fluid when a structure cardiac defect was established.
- (d) Serological studies for maternal collagen disease when no structural defects were found.

After completion of these diagnostic procedures, further management was discussed with the neonatologist and pediatric cardiologist. In the presence of a lethal cardiac or associated defect, termination of pregnancy was offered

depending on gestational age, or abstention from surgical intervention in the pregnancy was advised. In the case of a good prognosis, a careful follow-up was offered with the aim of delivering an infant in optimal condition.

After delivery, all fetuses in this study were examined clinically, ultrasonically (and where necessary underwent other appropriate diagnostic procedures), or at postmortem to enable correlation with the prenatal ultrasonic findings.

### *Results*

Pertinent data are presented in Table 1. Persistent bradyarrhythmia was diagnosed as complete atrioventricular block (n=11), second degree atrioventricular block (n=1), sinus bradycardia (n=3), and irregular bradycardia (n=2). One of the latter two fetuses displayed a complete atrioventricular septal defect (No.5) and a wandering pacemaker was diagnosed postnatally. Ventricular rate in all 17 fetuses varied between 43 and 96 bpm (mean 67.1 bpm).

In five of our patients, bradycardia was associated with maternal collagen disease, in one case maternal symptoms becoming apparent 3 months after delivery. In ten patients (59 per cent), bradycardia was associated with cardiac structural defects. Twice a structural defect was suspected but not correctly defined (Nos. 3 and 6); in one case (No. 3), this was due to excessive maternal weight (104 kg) and advanced gestation (40 weeks). Within the group of cardiac structural abnormalities, there were three abnormal karyotypes (17 per cent) (Nos. 2, 6, and 7), i.e. 47XYY, trisomy 18, and trisomy 21. Cardiac compromise resulting in right heart dilatation, pericardial effusion, or even ascites was observed in four cases (23 per cent) (Nos. 7, 8, 9, and 16).

The overall mortality was 41 per cent and nearly entirely confined to the group of bradyarrhythmias associated with cardiac structural defects. There were two intrauterine deaths at 29 weeks (Nos. 7 and 8) and one neonatal death on day 3 (No. 6). Two pregnancies (Nos. 9 and 10) were terminated on request of the parents at 21 and 26 weeks because of complex cardiac structural abnormalities. In case No. 1, the infant died at 8 months from a complete atrioventricular septal defect, and associated spina bifida. One infant with complete heart block (No. 16) died soon after Caesarean section at 37 weeks due to an absent A-V node (microscopy) in the presence of normal macroscopic anatomy. The ten remaining patients delivered at term either vaginally (n=5) or by Caesarean section (n=5) depending on the referring gynaecologist.

### *Discussion*

Until recently, bradyarrhythmia was frequently considered as sign of fetal distress resulting in emergency Caesarean section. Since the advent of combined two-dimensional real-time and M-mode recording systems, it has become clear that intrauterine cardiac arrhythmias are disorders of the conducting system and

Table 1. Gestational age at the time of diagnosis and pre- and postnatal findings in 17 patients with fetal brady arrhythmia

Patient, type of bradyarrhythmia	Gestational age (weeks) at referral	Mean FHR (bpm)	Prenatal findings	Postnatal findings
1. Sinus bradycardia	36	95	CAVSD (severe maternal obesity)	Died at 8/12, CAVSD + spina bifida
2. Sinus bradycardia	36	60	TOF, trisomy 21	TOF, trisomy 21
3. Sinus bradycardia	40	96	AS(severe maternal obesity)	PS
4. Irregular bradycardia	34	90	No pathology	Infant alive and well-prob recurrence sick sinus syndrome
5. Irregular bradycardia	29	84	CAVSD	CAVSD, wandering pacemaker
6. 2° A-V block	35	60	VSD, trisomy 18	Died postpartum, TOF, trisomy 18
7. 3° A-V block	29	45	Complex CHD, 47XYY, right heart dilatation	IUD, complex CHD, 47XYY
8. 3° A-V block	29	54	Complex CHD + ascites	IUD, complex CHD+asplenia
9. 3° A-V block	21	53	Complex CHD + ascites	TOP, complex CHD+asplenia
10. 3° A-V block	26	62	Complex CHD	TOP, complex CHD
11. 3° A-V block	34	57	Maternal collagen disease	Infant alive and well
12. 3° A-V block	34	69	Maternal collagen disease	Infant alive and well
13. 3° A-V block	33	65	Maternal collagen disease	Infant alive and well
14. 3° A-V block	31	72	Maternal collagen disease	Infant alive and well
15. 3° A-V block	35	62	No pathology	Infant alive and well, maternal collagen disease at 3/12
16. 3° A-V block	33	43	Right heart dilatation	Died on day 1; absent A-V node on microscopy
17. 3° A-V block	36	70	RA tumour	RA tumour

CHD = congenital heart disease; IUD = intrauterine death; CAVSD = complete atrioventricular septal defect; TOP = termination of pregnancy; AS, PS = aortic, pulmonary stenosis; VSD = ventricular septal defect; TOF = tetralogy of Fallot.

are associated with a variety of fetal outcomes. In the present study, the bradyarrhythmias consisted mainly of variable degrees of congenital atrioventricular block. The clinical problems related to bradyarrhythmia are two-fold: (a) the association with maternal collagen disease (5/17=29 per cent), in one case maternal symptoms becoming apparent 3 months after delivery; (b) the association with cardiac structural defects (10/17=59 per cent), which in our study was of a serious nature in the majority of cases.

The present data also demonstrate that the outcome of fetuses with a combination of major cardiac structural abnormality and bradyarrhythmia is poor, whereas in the presence of normal cardiac anatomy the outcome is generally good.

A common cardiac defect in the presence of complete atrioventricular block is atrial isomerism (Crawford et al., 1985). In isomerism, paired organs such as lungs and atria have bilateral morphologically right or morphologically left characteristics. In our series, two of the five patients with complete atrioventricular block and congenital heart disease (patients 8 and 9 in Table 1) were suspected of having atrial isomerism prenatally, and an unusual combination of left atrial isomerism and asplenia was diagnosed at post mortem (Stewart et al., 1984).

The presence of three fetuses with an abnormal karyotype in our material supports an earlier observation in which a close relationship between abnormal karyotype and congenital heart disease was established (Wladimiroff et al., 1985). The limited occurrence of cardiac compromise (23 per cent) in our study confirms Doppler ultrasound data on blood flow in the fetal descending aorta (Tonge et al., 1987), in which it is suggested that at lower heart rates cardiac output is maintained through an increase in stroke volume. The only four cases of fetal cardiac compromise developed at heart rates between 45 and 55 bpm, and might be presumed to have occurred from inadequate ventricular output due to poor filling rather than from poor ventricular output related to heart rate alone.

Vaginal delivery is increasingly being carried out in the presence of bradyarrhythmia without associated pathology. It should be realized, however, that conventional heart rate monitoring is not feasible in the presence of atrioventricular block. Atrial rate monitoring may be employed in the assessment of fetal condition. This should be combined with repeated fetal scalp pH analysis in the presence of adequate cervical dilatation.

It can be concluded that in the presence of a fetal bradyarrhythmia, a correct prognosis can only be made following a proper definition of the exact nature of the bradyarrhythmia as established by echocardiography, the recognition of associated pathology such as cardiac structural defects /abnormal karyotype, and degree of cardiac compromise.

## References

- Allan LD, Tynan M, Campbell S (1981). Normal fetal cardiac anatomy: a basis for the echographic detection of abnormalities. *Prenat Diagn* 1, 131-139.
- Allan LD, Anderson RH, Sullivan ID, Campbell S, Hold DW, Tynan M (1983). Evaluation of fetal arrhythmias by echocardiography. *Br Heart J* 50, 240-245.
- Allan LD, Crawford DC, Anderson RH, Tynan M (1984). Echocardiographic and anatomical correlations in fetal congenital heart disease. *Br Heart J* 52, 542-548.
- Copel JA, Kleinman CS (1986). The impact of fetal echocardiography on perinatal outcome. *Ultrasound Med Biol* 12, 327-335.
- Crawford DL, Chapman M, Allan LD (1985). The assessment of persistent bradycardia in prenatal life. *Br J Obstet Gynaecol* 92, 941-944.
- DeVore GR (1985). The prenatal diagnosis of congenital heart disease. A practical approach for the fetal sonographer. *J Clin Ultrasound* 13, 229-235.
- Kleinman CS, Hobbins JC, Jaffe CC, Lynch DC, Talner NS (1980). Echocardiographic studies of the human fetus: prenatal diagnosis of congenital heart disease and cardiac dysrhythmias. *Pediatrics* 65, 1059-1064.
- Sahn DJ, Lange LW, Allen HD, Goldberg SJ, Anderson C, Giles H, Haber K (1980). Quantitative real-time cross-sectional echocardiography in the developing normal human fetus and newborn. *Circulation* 62, 588-594.
- Stewart PA, Tonge HM, Wladimiroff JW (1983). Arrhythmia and structural abnormalities of the fetal heart. *Br Heart J* 50, 550-554.
- Stewart PA, Becker AE, Wladimiroff JW, Essed CE (1984). Left atrial isomerism associated with asplenia: prenatal echocardiographic detection of complex congenital cardiac malformations. *J Am Coll Cardiol* 4, 1015-1020.
- Tonge HM, Wladimiroff JW, Noordam MJ, Stewart PA (1986). Fetal cardiac arrhythmia and its effect on volume blood flow in the descending aorta of the human fetus. *J Clin Ultrasound* 14, 607-612.
- Wladimiroff JW, Stewart PA, Vosters RPL (1984). Fetal cardiac structure and function as studied by ultrasound. *Clin Cardiol* 7, 239-253.
- Wladimiroff JW, Stewart PA, Sachs ES, Niermeyer MF (1985). Prenatal diagnosis and management of congenital heart defect: significance of associated fetal anomalies and prenatal chromosome studies. *Am J Med Genet* 21, 285-290.

### 6.3.1 *Fetal bradyarrhythmia*

The table updates the information provided in the article "Fetal bradyarrhythmia: diagnosis and outcome". Five new patients were referred in the intervening period for assessment of fetal bradyarrhythmia. Following appropriate diagnostic procedures the further management of the pregnancies followed the principles as described in the article.

Table. Fetal Bradyarrhythmia (1986 - 1988)

Patient, type of bradyarrhythmia	Gestational age (weeks) at referral	Mean FHR (bpm)	Prenatal findings	Postnatal findings
1. 3° A-V block	21	72	Complete atrioventricular septal defect	Complete atrioventricular septal defect, left atrial isomerism, polysplenia, infant alive
2. Irregular bradycardia	37	90	VSD, microcephaly	VSD, ASD, microcephaly, infant alive
3. 3° A-V block	20	65	Maternal collagen disease	Infant alive and well
4. Irregular bradycardia	30	90	Familial sick sinus syndrome	Probable recurrence sick sinus syndrome, infant alive and well
5. 3° A-V block	35	68	Twin pregnancy. One fetus affected. No structural pathology.	Infant alive and well No maternal collagen disease
Total no of patients (1982-1988)	22			
Structural anomaly	12 (54.5%)			
Mortality	8/22 (36%)			

## 6.4 Cardiac Tachyarrhythmia in the Fetus: Diagnosis, Treatment and Prognosis

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Published in *Fetal Therapy*, Vol 2: 7-16, 1987.

**Key words** Fetal tachyarrhythmia, Fetal treatment, Prognosis of fetal tachyarrhythmia

### **Abstract**

Real-time directed M-mode echocardiography permits analysis of atrial and ventricular mechanical systole and allows inference of the type of arrhythmia present. Accurate diagnosis in cases of fetal tachyarrhythmia is of vital importance when therapy is considered, and in planning further management and delivery of an effected infant. Fetal tachyarrhythmia may be life-threatening especially when fetal hydrops is present and aggressive therapy is mandatory in these cases with digoxin being the drug of choice. In our series the incidence (8.3%) of congenital heart disease was as expected, but the incidence (54%) of atrial flutter was surprisingly high. The prognosis was dependent on the presence or absence of fetal hydrops and was not influenced by the type of arrhythmia or gestational age.

### **Introduction**

Increasing attention is being focused on prenatal cardiac examination in high-risk pregnancies, especially in the diagnosis and possible treatment of disturbances in cardiac rate and /or rhythm (1-9). The estimated incidence of tachyarrhythmias is from 1 in 10,000 to 1 in 25,000, but these figures are probably an underestimate since many cases remain asymptomatic and undiagnosed (10, 11). Most tachyarrhythmias are of supraventricular origin, the most common being paroxysmal supraventricular tachycardia (SVT) with heart rates often being above 200-220 beats per minute (bpm) and usually with abrupt onset and termination. Atrial flutter (AF) and fibrillation with rates of 300-480 bpm may also occur. Defects of the conduction system have been established in some infants with prenatal tachyarrhythmias (12). Other possible causes may be cardiomyopathy, cardiac tumor, functional instability of atrial muscle, congenital structural heart disease (5-10%) and cytomegalovirus or Coxsackie B virus infection. Congestive heart failure may develop in 70% of the infants resulting in fetal hydrops (8). Intrauterine treatment of fetal tachyarrhythmias may be defined as transplacental, direct

umbilical venous administration, fetal intramuscular or intraperitoneal administration of antiarrhythmic agents with the aim of normalizing fetal heart rate and rhythm, and abolishing, or preventing fetal cardiac failure. Many agents have been used for this purpose with extremely variable reports of success (8). Accurate differentiation of the type of arrhythmia is important before embarking on any treatment schedule (7).

Possible therapeutic agents are:

- 1 Digoxin is generally considered the drug of choice. Maternal digoxin levels in patients on stable doses are 40-50% lower during the last trimester of pregnancy compared with nonpregnant women. Possible explanations for this phenomenon include increased maternal intravascular volume, delayed gastric emptying, increased glomerular filtration rate and raised fetal metabolism of digoxin. Passive transfer of digoxin across the placenta would explain cord blood digoxin levels being similar to maternal levels at birth. It is known that endogenous digoxin-immunoreactive substances may be detected in the blood from third-trimester pregnant women, human amniotic fluid, umbilical cord blood, and placental homogenates (13). Baseline levels should therefore be established before digoxin therapy is begun. Therapeutic maternal serum levels vary between 0.5 and 2 ng/ml and oral dosage of around 0.25 mg every 8 h is usually necessary to achieve the upper range.
- 2 Verapamil is a calcium antagonist and fetal serum levels have been reported to be 50% of maternal levels. The therapeutic range in maternal serum is 50-100 ng/ml and oral dosage is 80-120 mg every 6-8 h. It has been used in combination with digoxin and adjustment of digoxin dose is likely as serum levels are raised by 30-50%. A combination of verapamil and propranolol should be avoided as both are negative inotropic agents and may unfavorably alter cardiac contractility.
- 3 Propranolol is a beta-adrenergic blocking agent and appears in fetal serum soon after maternal administration and levels are about 20% of those in the mother. Therapeutic maternal serum concentrations vary between 20 and 100 ng/ml; oral maternal dosage is 20-160 mg every 6-8 h. Some reports have suggested that neonatal depressed Apgar scores, bradycardia and hypoglycemia may occur as a result of propranolol (14, 15). It would seem advisable to avoid this drug in initial attempts at fetal cardioversion especially as results with propranolol have been largely disappointing.
- 4 Procainamide crosses the placenta although no data are available on either the mechanism or rate of transfer. The risk of maternal hypotension leading to placental insufficiency and ventricular arrhythmias in previously digitalized patients must be considered before prescribing procainamide (8, 16). Therapeutic maternal serum levels vary between 4 and 14 ng/ml and oral dosage is 6 mg/kg every 4 h.
- 5 Quinidine and digoxin have been used successfully in cases of fetal atrial flutter (17) although we have not yet used this combination of agents ourselves.



Maternal and fetal serum levels are reported to approach a one-to-one level (18). Quinidine is also reported to have oxytocic activity and to be associated with a rare neonatal thrombocytopenia. Fetal eighth nerve damage has been observed after much larger doses than those used clinically. However, the potential for benefit appears to outweigh the risks. Most patients on a stable dose of digoxin show a two- to threefold rise in serum digoxin level when quinidine is added. Oral dosage is 800-1,200 mg daily.

- 6 Amiodarone is a benzofuran derivative and is extremely effective in treating infants and children with tachyarrhythmias refractory to conventional treatment. Insufficient knowledge of fetal-maternal transfer and documented adverse effects of excessive iodine have limited its use in pregnancy (19). However, iodine is known to cross the placenta even against a concentration gradient, to be concentrated in the fetal thyroid gland from as early as 14 weeks and to be associated with neonatal goiter after as little as 12 mg is ingested. Amiodarone 200 mg contains approximately 75 mg iodine within its structure. This agent has an extremely long half-life (4-7 h) and fetal hypothyroidism may result in impaired intellectual performance (20). The risk of such complications for the individual patient is unpredictable and a genetic predisposition has been suggested. The average maintenance oral dosage is 200-400 mg daily.

### *Material and methods*

Between January 1982 and January 1987, 181 cardiac arrhythmias were referred, 31 of which demonstrated normal sinus rhythm at the time of ultrasound examination. Ectopic beats (3 ventricular, 103 supraventricular) were demonstrated in 106 patients, bradyarrhythmia (<100 bpm) in 20 patients and tachyarrhythmia (>180 bpm) in 24. For the purposes of this article only the group with tachyarrhythmias will be discussed, since it is only this group which is subject to prenatal treatment. One fetus referred at 22 weeks of gestation with a tachyarrhythmia of 250 bpm, which had been diagnosed elsewhere at 18 weeks, had died and massive ascites was present. The remainder underwent detailed ultrasonic evaluation to assess fetal size and overall structure (particularly cardiac), placental location, amount of amniotic fluid and signs of cardiac compromise such as pericardial effusion, dilated right heart, ascites and edema. These examinations were performed using a mechanical or phased array sector scanner with either a 3.5 - or 5- mHz transducer (Diasonics Cardio Vue 100 or Hewlett Packard 77020A). M-mode echocardiography was performed to investigate atrial and ventricular mechanical systole.

Atrial systole was identified by movement of the atrial wall towards the atrial septum or aortic or pulmonary trunk. Atrial systole may also be inferred by identifying the 'A' wave of the atrioventricular valve although this pattern may be difficult to interpret in very high heart rates. Ventricular systole was inferred from opening of an arterial valve or onset of ventricular wall motion towards the septum.

In some cases attempts were made to record a transabdominal fetal electrocardiogram (ECG), but due to inability to register atrial depolarization the ECG was not found to be of any diagnostic value. In some cases blood flow measurements were made in the fetal descending thoracic aorta using pulsed Doppler ultrasound.

Twelve fetuses (cases 1-12, gestational age 19-38 weeks) did not receive pharmacological treatment. The remainder (cases 13-24, gestational age 21-38 weeks) were treated with one or more of the following agents: digoxin, verapamil, propranolol, procainamide and amiodarone.

In our laboratory serum digoxin levels between 0.5 and 1.5 ng/ml are considered therapeutic. In the first 10 fetuses treated this range was considered adequate. For the remaining 2 fetuses maternal serum digoxin levels at or above 2 ng/ml were aimed for. The policy was changed as a result of our unpredictable results in the first 10 fetuses and following reports from other centers of successes achieved with higher levels. For our new policy the mothers are admitted and intravenous loading with digoxin is achieved as quickly as possible. Thereafter oral digoxin is continued with a dose large enough to maintain a serum concentration of 2 ng/ml or more. In the last 2 cases maternal blood was also taken to detect the presence of possible digoxin-like substances prior to starting treatment. Of all other agents standard dosages were prescribed. Serum levels of agents other than digoxin and procainamide were not obtained either due to unavailability of assaying techniques or because fetal death had occurred some days prior to delivery.

### *Results*

Twelve fetuses were not treated pharmacologically prior to delivery (Table I). Case 1 had suffered intrauterine death before the 22nd week of gestation. Four fetuses (cases 7-12) were delivered by caesarean section shortly after diagnosis. The remainder were delivered spontaneously at term having been monitored regularly by ultrasound.

Twelve fetuses were treated pharmacologically and the results are presented in Table II. Four previsible fetuses who presented with severe hydrops all died. Cases 13 and 15 both demonstrated AF with 2:1 atrioventricular block. Case 13 died 4 days after presentation to our unit. Following oral digoxin resulting in a maternal serum level of 0.9 ng/ml, i.v. procainamide was given and maternal serum levels of procainamide were thereafter found to be inadequate. Verapamil was given i.v. and fetal death occurred a few hours later. Microscopy of the sinoatrial node revealed no clear abnormalities in this fetus.

In case 15 a high serum digoxin level of 4.5 ng/ml resulted in no maternal toxic consequences. No effect was seen on the fetal heart rate however. Following the addition of verapamil a return to normal sinus rhythm was achieved. However, despite cardioversion the fetus deteriorated and emergency caesarean section was performed at 29 weeks of gestation. Intensive efforts to resuscitate the neonate failed and death resulting from severe hydrops occurred 24 h post partum.

Case 14 presented with chaotic atrial rhythms with severe ascites. Therapeutic maternal serum digoxin levels were achieved without any effect on the fetal heart rate. Following the appropriate intervals i.v. propranolol and oral quinidine were given, also with no effect on the fetal heart rate. However, after the addition of oral verapamil sinus rhythm was noted at 32 weeks of gestation. Despite conversion to normal sinus rhythm there was an increase in fetal hydrops and intrauterine death occurred at 33 weeks and 3 days. At delivery the cord digitalis level was 1.14 ng/ml and postmortem revealed a grossly abnormal posterior mitral valve leaflet (the leaflet consisting mostly of a gelatinous mass) and mild hypoplasia of the left ventricle. Microscopy of the sinoatrial node revealed no clear abnormalities (the echocardiogram had demonstrated apparent normal cardiac anatomy; most likely these abnormalities were not detectable by cross-sectional ultrasound).

Case 16 presented with SVT; again a multidrug regime was attempted, with careful attention being paid to timing, and combinations of the various agents (see above). Therapeutic levels of digoxin were achieved, thereafter verapamil, procainamide and amiodarone were given. One dose of digoxin and Lasix was given intra-abdominally direct to the fetus with no obvious response. Amiodarone was selected as a last resort and cardioversion to a heart rate of 125 bpm was achieved. However, as in case 15, hydrops increased, Doppler blood flow velocity measurements decreased and caesarean section was performed at 31 weeks of gestation. Severe congestive heart failure led to neonatal demise 48 h after delivery. Microscopy of the sinoatrial node revealed no clear abnormalities.

Cases 17-19 presented with paroxysmal SVT (x2) or SVT, none being hydropic at diagnosis. Conversion to sinus rhythm occurred in cases 17 and 18 with adequate maternal serum levels of digoxin. Both infants were delivered spontaneously at term and digoxin therapy was continued postnatally. In case 17, due to technical mishap, cord and amniotic fluid digoxin levels were unsuccessful. The infant displayed ECG evidence of the Wolff-Parkinson-White syndrome at 3 months of age. In case 18 it was noted with interest that amniotic fluid digoxin levels (2.4 ng/ml) were precisely double the value of the cord blood levels. In case 19, despite therapeutic serum levels, fetal cardioversion did not occur and although heart rate was 240 bpm, this was well tolerated until 38 weeks when right heart dilation was noted. Caesarean section was performed following this observation and digoxin therapy continued in infancy. Surprisingly the cord blood digoxin level was subtherapeutic at <0.5 ng/ml.

Cases 20-22 presented with AF. In case 20 mixed atrial rhythms were present with AF predominating. Therapeutic serum levels were achieved and cardioversion occurred at 31 weeks. The infant was delivered spontaneously at term. The cord digoxin level was 0.8 ng/ml. Supraventricular extrasystoles (SVEs) were present at birth and disappeared shortly thereafter. In case 21, 1 period of sinus rhythm was noted when the maternal serum digoxin level was at the lower end of the therapeutic range. Pericardial effusion and right heart dilation were seen at 35 weeks and caesarean section was performed. AF converted

Table I. Fetal tachyarrhythmia in untreated group.

Case No.	Gestational age at diagnosis weeks	Delivery weeks	Diagnosis	Prenatal course	Outcome
1	18	22	HR 250, CHD, HF	IUD	IUD
2	36	term	sinus tachycardia	monitored	AW
3	19	term	PSVT	monitored	AW
4	26	term	PSVT	monitored	AW
5	28	term	PSVT	monitored	AW
6	38	38	SVT, CHF	-	AW,WPW
7	34	35	AF,1:4:1 AVB, CHF	CS	AW
8	36	36	AF, 2:1 AVB, ofo	CS	AW
9	36	36	intermittent AF,CHF,ofa	CS	AW
10	34	34	intermittent AF, HF	CS	AW
11	30	term	intermittent AF	monitored	AW
12	37	term	intermittent	monitored	AW

HR=Heart Rate; CHD=Congenital Heart Disease; HF=Hydrops Fetalis; AW=Alive and Well; PSVT=Paroxysmal Supraventricular Tachycardia; SVT=Supraventricular Tachycardia; CHF=Congestive Heart Failure; AF=Atrial Flutter; AVB=Atrioventricular Block; ofo=obstructive foramen ovale; WPW=Wolff-Parkinson-White syndrome.

Table II. Transplacental treatment of fetal tachyarrhythmia

Case No.	Gestational age at diagnosis weeks	Delivery weeks	Diagnosis	Agent used, route	Control of arrhythmia	Outcome
13	25	26	AF,2:1 AVB, HF	digoxin p.o. procainamide i.v. verapamil i.v.	no	IUD

14	26	33	chaotic atrial rhythms, HF, CHD	digoxin i.v., p.o. propranolol i.v. quinidine p.o. verapamil i.v. Lasix p.o.	yes 32 weeks	IUD
15	27	29	SVT, HF	digoxin p.o. verapamil i.v.	yes	death pp
16	25	31	SVT, HF	digoxin i.v., p.o. verapamil i.v. procainamide i.v. amiodarone p.o. Lasix p.o.	intermittent	death pp
17	21	term	PSVT	digoxin p.o.	yes 24 weeks	AW
18	26	term	PSVT	digoxin p.o.	yes 28 weeks	AW
19	31	term	SVT, CHF	digoxin p.o.	no	AW
20	23	term	PSVT, AF	digoxin p.o.	yes 31 weeks	AW
21	34	35	AF, variable conduction, CHF	digoxin i.v.	intermittent	AW
22	38	38	AF, 2:1 AVB	digoxin i.v.	yes? spontaneous	AW
23	36	37	SVT, AF, CHF	digoxin i.v., p.o.	intermittent	AW
24	23	term	PSVT, transient ascites	digoxin i.v., p.o.	yes 27 weeks	AW

A=Atrial flutter; AVB=atrioventricular block; HF=hydrops fetalis; p.o.=per os; i.v.=intravenous; IUD=intrauterine death; CHD=Congenital Heart Disease; SVT=SupraVentricular Tachycardia; PSVT=Paroxysmal SupraVentricular Tachycardia; CHF=Congestive Heart Failure; AW=Alive and Well; pp=post partum.

abruptly to sinus rhythm 45 min after delivery. At the age of 8 months incomplete right bundle-branch block was noted on the ECG with no other abnormalities being found. Case 22 presented at 38 weeks and as no evidence of cardiac compromise was present it was decided to attempt fetal cardioversion, with the hope that if the heart rate was normalized vaginal delivery would be possible. Spontaneous delivery occurred 48 h later and 1 period of sinus rhythm had been noted with a subtherapeutic maternal serum digoxin level. Immediately post partum sinus rhythm was present and digoxin therapy continued.

In case 23 SVT and bursts of AF were documented. Intermittent fetal sinus rhythm was observed with a maternal serum digoxin level of  $>2$  ng/ml ('baseline' maternal serum level 0.3 ng/ml). Moreover at 37 weeks and 4 days pericardial effusion and right heart dilation occurred. Caesarean section was performed and at birth sinus rhythm was present. There was 1 period of SVT after birth and the poor myocardial contractility noted after birth normalized within a few days. Digoxin and propranolol were necessary to treat the period of SVT and the infant was discharged home on this regime. In case 24, paroxysmal SVT was diagnosed at 23+ weeks. Adequate maternal serum digoxin levels were achieved at 24 weeks ('baseline' maternal serum level  $<0.1$  ng/ml) and sinus rhythm noted for the first time at 27 weeks. Mild ascites developed at 24 weeks but had cleared at 26 weeks. This fetus was delivered vaginally at term and postnatal digoxin therapy continues.

### *Discussion*

The fetuses in this series have not been presented chronologically, as they represent the results over a 5-year period of changing knowledge on this subject. They have been divided into two basic groups, those not receiving pharmacological treatment (50%) and those receiving transplacental therapy (50%). In the untreated group the reason for not treating the fetus was usually advanced gestation and/or signs of cardiac compromise. The fetuses presenting in the second or early part of the third trimester would, under our current policy, be treated, although no clear signs of cardiac failure were documented during pregnancy in these cases.

It is evident, in our series at least, that the presence of moderate to severe fetal hydrops at the time of diagnosis is related to a high mortality rate (80% of the hydropic fetuses, 16% of the total group), especially in the previable group.

Two fetuses had associated structural heart defect (8.3% of total group). Both fetuses died in utero. The fetus (case 1) which had died before referral to this unit had hypoplastic left heart syndrome on autopsy. This defect in combination with a documented heart rate of 250 bpm probably resulted in massive ascites and early fetal death (21). If this fetus had still been alive at the time of our examination, the diagnosis of hypoplastic left heart syndrome would have excluded this fetus from transplacental therapy in view of the uniformly fatal outcome of the structural defect. It is also clear, in the transplacentally treated group

of fetuses with tachyarrhythmias and hydrops fetalis, that despite multiple drug treatment and with a 75% rate of conversion to sinus rhythm fetal or early neonatal death (100%) still resulted. This contrasts sharply with the experience of others (7,9), who described survival in the majority of fetuses with severe hydrops at presentation. No microscopic evidence of sinoatrial node or myocardial disease was present in any of the fetuses who died. In the entire group there was no evidence of intrauterine viral infection. None of the fetuses who died showed any evidence of premature closure of the foramen ovale.

All fetuses in the untreated group survived and are alive and well with ages raging from 18 months to 5 years. Four fetuses in the treated group died (33%), 2 postnatally, 2 in utero probably as a result of severe cardiac failure and myocardial dysfunction. The remaining fetuses have all survived, 4 (cases 17, 18, 20 and 24) having returned to sinus rhythm following treatment. These pregnancies continued normally and spontaneous delivery occurred.

Conversion to sinus rhythm rarely occurred shortly after maternal therapeutic serum levels were achieved. In almost every case we noticed diminution in the periods and length of the tachyarrhythmia (whether it was SVT or AF), then loss of tachyarrhythmia and demonstration of SVEs and finally (sometimes after a few weeks) sinus rhythm. In case 24 mild ascites which appeared at 24 weeks cleared shortly thereafter in the presence of SVEs but after loss of the SVT. This was the only fetus in whom reversal of cardiac failure was achieved. We have only seen 1 fetus (case 20) in whom SVEs were initially diagnosed at 23 weeks and following weekly screening was found at 29 weeks to have AF and paroxysmal SVT, although the group with ectopics is considered at risk for this development (22).

It is unclear why some fetuses respond (or appear to respond) and others develop fullblown hydrops and die in the absence of congenital heart disease or documented infection. It is also unclear why some fetuses, such as case 19 and 4 fetuses in the untreated group (cases 3, 4, 5 and 11), can tolerate high heart rates for long periods and only develop cardiac failure late in gestation or not at all. Of particular concern are fetuses such as cases 14 and 15 who become increasingly hydropic and die despite cardioversion. It is surmised that irreversible myocardial damage may have occurred during the period of tachyarrhythmia. To date no clear answer has emerged. AF is considered rare in fetal life but 7 of the treated fetuses and 6 of the untreated fetuses had AF either alone or in combination with mixed rhythms. Perhaps this can be explained by our policy of using an atrial wall instead of an atrioventricular valve to infer atrial activity. If one directs the M-line across an atrial wall 'flutter' waves are very easy to record even when of short duration. Using the mitral or tricuspid valve movement to indirectly infer atrial contraction has clear pitfalls, especially when the heart is very small and the ventricular rate very high. It is not always possible to see the 'A' waves in these circumstances.

One fetus with prenatal AF developed incomplete right bundle branch block after birth. In our material the incidence of AF, persistent (25%) or intermittent

(29%), was higher than expected (54% overall). The 2 cases of Wolff-Parkinson-White syndrome in our series demonstrated fetal SVT and had no evidence pre- or postnatally of AF.

The advent of fetal blood sampling by umbilical cord puncture may provide further insight into these tachyarrhythmias as it will be feasible to monitor and correct the fetal biochemical and acid base status, and monitor directly fetal serum levels of any drugs used in intrauterine therapy. This technique may, in future, also be used to administer drugs directly to the fetus. Fetal blood flow velocity waveforms may also provide more insight into the cardiovascular status of the fetus with tachyarrhythmia (23) and provide adjunctive information.

As a result of these cases our policy for fetal tachyarrhythmias is currently as follows: if lung maturity is present the fetus will be delivered and treated postnatally. In the previable or premature fetus aggressive action should be undertaken even in the absence of signs of cardiac compromise as it would appear easier to achieve survival if hydrops is not present. All arrhythmias with a heart rate, continuous or intermittent, of over 200 bpm will in future be treated. Maternal loading with digoxin will be intravenous until serum levels are at or above 2 ng/ml are reached. Thereafter, oral digoxin will be continued with a dose necessary to maintain that serum level. The addition of verapamil or other agents will be considered on an individual basis.

### *Conclusions*

Fetal tachyarrhythmia may be life-threatening and in the presence of fetal hydrops has a very poor prognosis especially in the previable fetus. Aggressive therapy is indicated in all cases of tachyarrhythmia with or without hydrops in the hope of preventing irreversible hydrops. Treatment should be given in a team setting with obstetrician, adult and pediatric cardiologist, neonatologist and pharmacologist making treatment decisions.

Careful attention should be paid to possible maternal adverse effects of any drugs used and appropriate monitoring carried out by the adult cardiologist. Therapy should be carried out in a prenatal center experienced in fetal echocardiography and in the vicinity of a pediatric cardiology center for direct postpartum care of an affected fetus. Digoxin is still the drug of choice. If this fails, verapamil may be added. Digoxin combined with propranolol, procainamide or quinidine may be given next, and amiodarone is given as a last resort until more is known about its effect on the fetal thyroid. The incidence of congenital heart disease in our group (8.3%) was as expected. However, the incidence of AF (54%) was surprisingly high.

The prognosis in our series of 24 cases, 12 of which were treated transplacentally, was heavily dependent on the presence or absence of fetal hydrops at diagnosis and not on the type of arrhythmia or gestational age.



### *Acknowledgements*

We would like to thank all colleagues for referring patients to this unit, Prof.A.E.Becker (Academic Medical Center Amsterdam) for fetal histology and Sylvia Noordzij-Landsmeer for preparation of the manuscript.

### *References*

- 1 Kleinman CS, Donnerstein RL, Jaffe CC, et al.: Fetal echocardiography. A tool for evaluation of in utero cardiac dysrhythmias and monitoring of in utero therapy: Analysis of 71 patients. *Am J Cardiol* 1983; 51: 237-243.
- 2 Devore GR, Siassi B, Platt LD: Fetal echocardiography. The diagnosis of cardiac arrhythmias using real-time-directed M-mode ultrasound. *Am J Obstet Gynecol* 1983; 146: 792-799.
- 3 Allan LD, Anderson RH, Sullivan ID, et al.: Evaluation of fetal arrhythmias by echocardiography. *Br Heart J* 1983; 50: 240-245.
- 4 Stewart PA, Tonge HM, Wladimiroff JW: Arrhythmia and structural abnormalities of the fetal heart. *Br Heart J* 1983; 50: 550-554.
- 5 Wladimiroff JW, Struyck P, Stewart PA, et al.: Fetal cardiovascular dynamics during cardiac dysrhythmia: Case report. *Br J Obstet Gynaecol* 1983; 90: 573-577.
- 6 Allan LD, Crawford DC, Anderson RH, et al.: Evaluation and treatment of fetal arrhythmias. *Clin Cardiol* 1983; 7: 467-473.
- 7 Kleinman CS, Copel JA, Weinstein EM, et al.: Treatment of fetal supraventricular tachyarrhythmias. *J Clin Ultrasound* 1985; 13: 265-273.
- 8 Wladimiroff JW, Stewart PA: Treatment of fetal cardiac arrhythmias. *Br J Hosp Med* 1985; 34: 134-140.
- 9 Wiggins JW, Bowes W, Clewell W, et al.: Echocardiographic and intravenous digoxin management of fetal tachyarrhythmias and congestive heart failure. *Am J Dis Child* 1986; 140: 202-204.
- 10 Ramzin MS, Hammacher K, Hinselmann M: Perinatal Medicine. 4th European Congress, Prague (Thieme, Stuttgart 1974).
- 11 Schreiner RL, Hurwitz RA, Rosenfeld CR, et al.: Atrial tachyarrhythmias associated with massive edema in the newborn. *J Perinat Med* 1978; 6: 274-279.
- 12 Ho SY, Mortimer G, Anderson RH, et al.: Conduction system defects in three perinatal patients with arrhythmia. *Br Heart J* 1985; 53: 158-163.
- 13 Graves SW, Valdes R Jr, Brown BA, et al.: Endogenous-immunoreactive substances in human pregnancies. *J Clin Endocrinol Metabol* 1984; 58: 747-751.
- 14 Gladstone GR, Hordof A, Gersony WM: Propanolol administration during pregnancy: Effects on the fetus. *J Pediatr* 1975; 86: 962-964.
- 15 Cottrill CM, McAllister RG Jr, Gettes L, et al.: Propanolol therapy during pregnancy, labor and delivery: evidence for transplacental drug, transfer and impaired neonatal drug disposition. *J Pediatr* 1977; 91: 812-814.
- 16 Zapato-Dias J, Cabrera EC, Mendez R: Experimental and clinical study on effects of procainamide (pronestyl) on heart. *Am Heart J* 1952; 43: 854-870.
- 17 Spinnato JA, Shaver DC, Flinn GS, et al.: Fetal supraventricular tachycardia: in utero therapy with digoxin and quinidine. *Obstet Gynecol* 1984; 64: 730-735.
- 18 Doering W: Quinidine-digoxin interaction: Pharmacokinetics, underlying mechanism and clinical implications. *N Engl J Med* 1979; 301: 400-404. 19 Arnoux P, Seyral P, Llurens M, et al.: Amiodarone and digoxin for refractory fetal tachycardia. *Am J Cardiol* 1987; 59: 166-167.
- 20 Rovet J, Ehrlich R, Sarbara DCS: Intellectual outcome in children with fetal hypothyroidism. *J Pediatr* 1987; 110: 700-704.
- 21 Sahn DJ, Shenker L, Reed KI, et al.: Prenatal ultrasound diagnosis of hypoplastic left heart syndrome in utero associated with hydrops fetalis. *Am Heart J* 1982; 104: 1369-1372.

- 22 Gillette PC: The mechanism of supraventricular tachycardia in children. *Circulation* 1976; 54: 133-140.
- 23 Tonge HM, Wladimiroff JW, Noordam MJ, et al.: Fetal cardiac arrhythmias in their effect on volume blood flow in descending aorta of human fetus. *J Clin Ultrasound* 1986; 14: 607-612.

#### 6.4.1 *Update on fetal tachyarrhythmia*

Between January 1987 and January 1988 four new patients were referred for assessment of fetal tachyarrhythmias (Table). Cases 1 and 2 were treated with transplacental administration of digoxin in the manner previously described. Case 3 was treated postnatally following induced delivery on the day of diagnosis. Case 4 is the subject of the article presented in Chapter 6.4.2.

As stated in Chapter 6.4 the field of fetal tachyarrhythmias and their treatment continues to change rapidly.

Our own variable success in achieving cardioversion was also reflected in the article by Maxwell et al. (1988). Their group treated 22 fetuses with digoxin alone (7 cases) or digoxin and Verapamil (17 cases). The experiences cast doubt on the reliability of placental transfer of digoxin in all cases. Weiner and Thompson (1988) produced evidence that at least in some instances little digoxin administered to the mother actually crosses the placenta. In their case direct intramuscular fetal digitalisation was successful but the necessary frequent ( $\pm$  every 12 hours) number of injections render this technique impractical. However this finding may help explain reported variable results.

Recently the use of other agents such as Flecainide has been considered. Flecainide is known to be safe and effective in various types of paediatric arrhythmias (Wren and Campbell, 1987).

Fetal cardioversion using Flecainide has been reported in one case (Wren and Hunter, 1988). Maxwell et al. subsequently used this treatment in a number of fetuses with "good results" (personal communication, unpublished data).

Our group has also changed the policy of treatment and future cases will be treated initially with digoxin. After loading with digoxin fetal blood serum levels (determined by cordocentesis) will be assessed. If these are inadequate Flecainide will be substituted in an attempt to assess the efficacy of the Flecainide. This policy will throw further light on the placental transfer of digoxin in various fetal circumstances.

Table. Fetal Tachyarrhythmia (1987 - 1988)

Case No.	Gestational age diagnosis - weeks	Delivery weeks	Diagnosis	Prenatal course	Outcome
1	22	term	SVT, CHF	Digoxin p.o., return to NSR, reversal CHF	Alive and well
2	34 <sup>5</sup>	term	AF	Digoxin p.o., no effect development mild CHF induced delivery	Alive and well
3	41	41	PSVT	induced delivery	Alive and well
4	33	34	Ventricular tachycardia or A-V junctional tachycardia, atrial septal aneurysm	Procainamide p.o., no effect development mild CHF, CS	Alive and well

Total no of patients (1982-1988) 28

Structural anomaly 6 (21%)

Mortality 5 (18%)

## *References*

- Maxwell DJ, Crawford DC, Curry PVM, Tynan MJ, Allan LD. Obstetric importance, diagnosis, and management of fetal tachycardias. *British Medical Journal* 297: 107-110, 1988.
- Weiner CP, Thompson MIB. Direct treatment of fetal supraventricular tachycardia after failed transplacental therapy. *American Journal Obstetrics and Gynecology* 158: 570-573, 1988.
- Wren C, Hunter S. Maternal administration of flecainide to terminate and suppress fetal tachycardia. *British Medical Journal* 296: 249, 1988.
- Wren C, Campbell RWF. The response of paediatric arrhythmias to intravenous and oral flecainide. *British Heart Journal* 57: 171-175, 1987.

### *6.4.2 Complete atrioventricular dissociation and His bundle tachycardia in a newborn: problems in prenatal diagnosis and postnatal management*

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A newborn infant with complete atrioventricular dissociation and infranodal tachycardia, detected at 33 weeks gestation by fetal echocardiography, is described. In the perinatal period, infra or juxta-nodal tachycardia was noted, compromising the hemodynamic state of the newborn. A combination of flecainide and propranolol terminated the arrhythmia.

**Key words:** Infant, Hisian tachycardia; Atrioventricular dissociation; Fetal arrhythmia.

## *Introduction*

M-mode echocardiography is a reliable technique in the diagnosis of fetal rhythm disturbances (1,2). Various supra-ventricular tachy-arrhythmias have been described as well as the response to anti-arrhythmic agents (2,3).

In this report we describe the prenatal echocardiographic findings and the postnatal course of a neonate with a tachycardia with narrow QRS complexes and an atrioventricular dissociation.

## *Case report*

Fetal echocardiography was performed in a 30-year-old woman at 33 weeks of gestation following detection of a fetal tachy-arrhythmia. The heart was morphologically normal. Pump failure was manifested by right atrial and

ventricular dilatation and the presence of ascites. M-mode echocardiography (fig.1) revealed complete atrioventricular dissociation with a regular atrial rate of 140 /min and an irregular ventricular rate of 220 min.

A differential diagnosis of ventricular tachycardia or A-V junctional tachycardia with evidence of congestive cardiac failure was made. Transplacental treatment with procainamide was started with doses resulting in a maternal serum procainamide level of 8.5 mg /l (therapeutic range: 4-14 mg /l).

Caesarean section was performed at 34 weeks of gestation. A male infant weighing 2090 g was delivered with Apgar scores of 5 and 9 at 1 and 10 minutes. The concentrations of procainamide in the amniotic fluid and cord blood were 10.7 mg /l and 2.8 mg /l, respectively. After delivery the electrocardiogram showed a complete atrioventricular dissociation with a sinus rate of 150 beats per minute and a ventricular rate of 240 beats per minute with narrow QRS complexes, occasional capture beats and fusion beats.

Three hours after birth, echocardiography showed impaired wall motion without structural abnormalities. Digoxin was administered in a dosage of 10 g/kg intravenously. During the first hours after birth, cardiac failure progressed, necessitating intubation and ventilation.

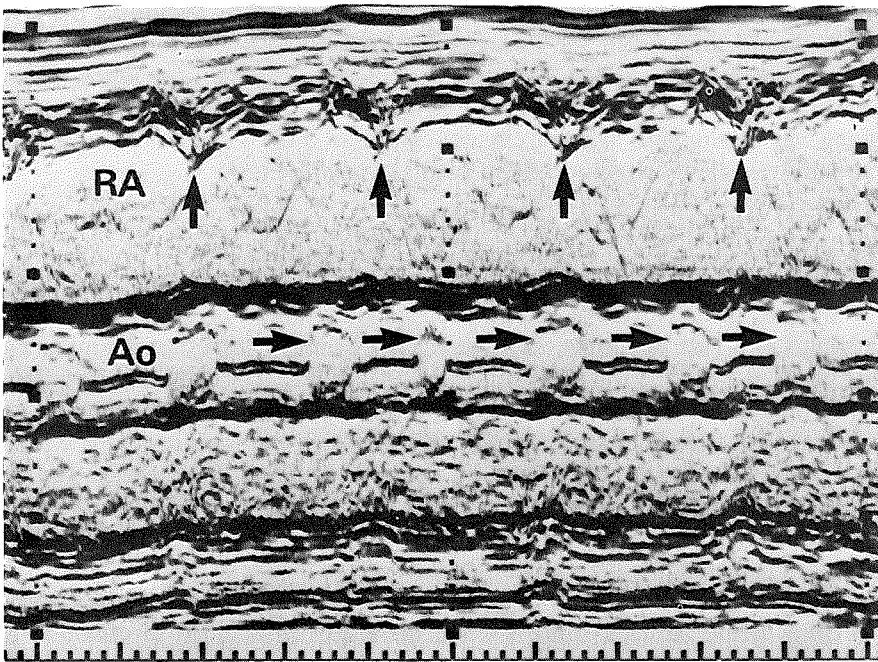


Fig.1. Fetal M-mode recording through right atrium (RA) and aorta (Ao). : atrial contractions; : opening of aortic valve.

Digitalization was completed after 24 hours, without any result. During flecainide infusion in a dose of 2 mg/kg over a 5-minute period sinus rhythm was restored (fig.2).

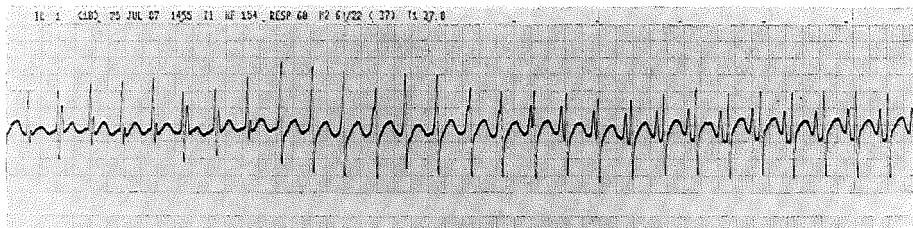


Fig.2. Recording of cardiac rhythm during infusion of flecainide, showing the termination of the arrhythmia.

Twenty-four hours later, cross-sectional echocardiography showed normal wall motion and the infant was weaned from the respirator. Treatment with oral flecainide in a dose of 5 mg 3 times daily was instituted. However, frequent ventricular extrasystoles and non-sustained ventricular tachycardias occurred, which disappeared when the dosage was lowered to 4 mg three times daily and propranolol was added in a dose of 1 mg/kg. The flecainide plasma concentration was 0.45 mg/l. The ventricular arrhythmia disappeared and the infant was discharged, in good clinical condition. Follow-up examination after 5 months revealed a healthy child in normal sinus rhythm.

### *Discussion*

Complete atrioventricular dissociation and low-nodal or Hisian tachycardia in infants is a rare condition. Brechenmacher et al. (4) reported a similar case with fatal outcome and found anatomical evidence for the origin of the arrhythmia in the bundle of His. In its midportion the His bundle was split into several thin and irregularly oriented strands, within which there were many areas of focal degeneration. A re-entrant mechanism utilizing the several separate longitudinally oriented strands is the most likely electrophysiologic basis for the arrhythmia. In our child, the tachycardia in combination with the rise in oxygen consumption after birth induced cardiac failure.

Intravenous administration of flecainide (2 mg/kg), injected slowly over a 5-minute period induced sinus rhythm; therefore we decided to continue this medication orally. However, with a dosage of 5 mg/kg the neonate developed ventricular tachy-arrhythmia. This has been reported to be a side effect of flecainide (5). Addition of propranolol to the maintenance treatment allowed a

reduction of the flecainide dose. This case report demonstrates that administration of intravenous flecainide may restore sinus rhythm in neonates with Hisian tachycardia with complete atrioventricular dissociation.

### *Acknowledgements*

The authors wish to thank Dr.Jura W.Wladimiroff for reviewing the manuscript.

### *References*

- 1 Allan LD, Anderson RH, Sullivan ID, Campbell S, Holt DW, Tynan M. Evaluation of fetal arrhythmias by echocardiography. *Br Heart J* 1983; 50: 240-245.
- 2 Stewart PA, Tonge HM, Wladimiroff JW. Arrhythmia and structural abnormalities of the fetal heart. *Br Heart J* 1983; 50: 550-554.
- 3 Stewart PA, Wladimiroff JW. Cardiac tachyarrhythmia in the fetus: diagnosis, treatment and prognosis. *Fetal Ther* 1987; in press.
- 4 Brechenmacher C, Coumel P, James TN. De subitaneis mortibus. *Circulation* 1976; 52: 377-381.
- 5 Wren C, Campbell RWF, The response of paediatric arrhythmias to intravenous and oral flecainide. *Br Heart J* 1987; 57: 171-175.

## **6.5 Fetal Atrial Arrhythmias Associated with Redundancy/Aneurysm of the Foramen Ovale**

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Published in: *Journal of Clinical Ultrasound*, Vol 16: 643-650 (1988)

### *Abstract*

Fetal arrhythmia was investigated in 148 fetuses. Eight of these fetuses displayed signs of redundancy /obstruction of the foramen ovale, all in combination with various atrial arrhythmias. At presentation four (50%) of these fetuses had mild to moderate congestive cardiac failure and a fifth fetus developed mild cardiac failure four weeks after observation of the aneurysm. All fetuses survived but two fetuses required early delivery because of the cardiac failure. Unnecessary morbidity resulting from the possible development of cardiac failure may be prevented by regular monitoring in these cases.

### *Indexing words*

Prenatal ultrasound, fetal atrial septal aneurysm, fetal arrhythmia.

### *Introduction*

Atrial septal aneurysm may be identified by cross-sectional echocardiography in otherwise apparently normal hearts (1-5) or in association with various cardiac defects (6-10).

In postnatal life atrial septal aneurysms have been associated with, or cited as potential causes of atrial arrhythmias, systemic and pulmonary embolism, atrial septal defects, atrioventricular valve prolapse, systolic clicks and complex abnormalities of the hypoplastic right heart type.

At least 150 cases of atrial septal aneurysm have previously been reported with the largest series being described by Hanley et al (11). The age of the patients ranged from 1 day to 89 years. Atrial septal aneurysm occurred more frequently as an isolated anomaly than in association with other cardiac malformations, although all patients with involvement of the entire atrial septum had complex congenital malformations of the hypoplastic right heart type. Premature obstruction or closure of the foramen ovale has also been described in association with fetal tachyarrhythmias (12), or fetal hydrops (13, 14) although no mention of redundant or aneurysmal formation was made. We present the relevant data concerning the prenatal detection of eight cases of atrial septal aneurysm in association with atrial arrhythmias. None of the fetuses had evidence of other cardiac structural disease.

### *Methods*

Fetal echocardiography was performed in 1273 high-risk patients: 148 (11.6%) were referred for assessment of fetal arrhythmia. The gestational age was between 19 and 41 weeks.

All fetuses with arrhythmia underwent cross-sectional and M-mode investigation using either a Dasonics CardioVue 100 mechanical sector scanner or a Hewlett Packard 77020A phased array scanner, both with M-mode but no Doppler facilities. Colour Doppler flow mapping was performed in one case (Toshiba Sonolayer SSH 65A).

The heart of the fetus may be viewed in planes unobtainable in postnatal life because the fetal lungs are fluid filled and therefore present no obstruction to the ultrasound beam. A number of transverse and longitudinal planes were employed although the examination is really a continuous sweep, allowing each scanning view to follow on to the next, thereby demonstrating normal, or abnormal cardiac anatomy. In the fetuses described in this report the parasternal or subcostal four chamber view, and the subcostal atrial short axis view were the most useful, although the aneurysms were identified from a variety of planes.



In the normal fetus examination by cross-sectional and M-mode echocardiography shows that movement of the foramen ovale has a characteristic biphasic movement into the left atrium through each cardiac cycle.

Movement of the foramen ovale flap towards the atrial septum is related to atrial systole. The foramen ovale then opens and closes more gently during ventricular systole. A sharply defined area of echo dropout is always demonstrable. This pattern of movement has been identified in all other normally structured fetal hearts in our study group (Fig. 1).

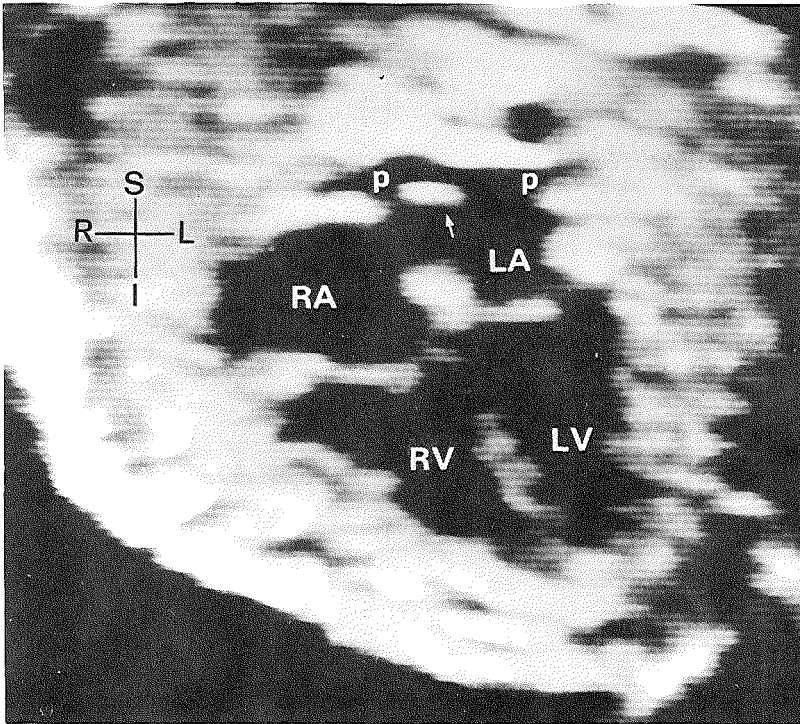


Fig.1. Normal fetal four-chamber view. (RA, right atrium; RV, right ventricle; LA, left atrium, LV, left ventricle; p, pulmonary vein; arrow, normal appearance of foramen ovale flap; S, superior; I, inferior; R, right; L, left).

An aneurysm of the atrial septum was defined as a large, redundant structure at the level of the foramen ovale with abnormal bulging into the left atrium. At maximum excursion into the left atrium the borders of these structures were continuous (as opposed to the normal ultrasonic appearance - see Fig. 1) and occupied between  $1/3$  and  $1/2$  of the left atrial cavity resulting in images similar to that in Figs. 2 and 3.

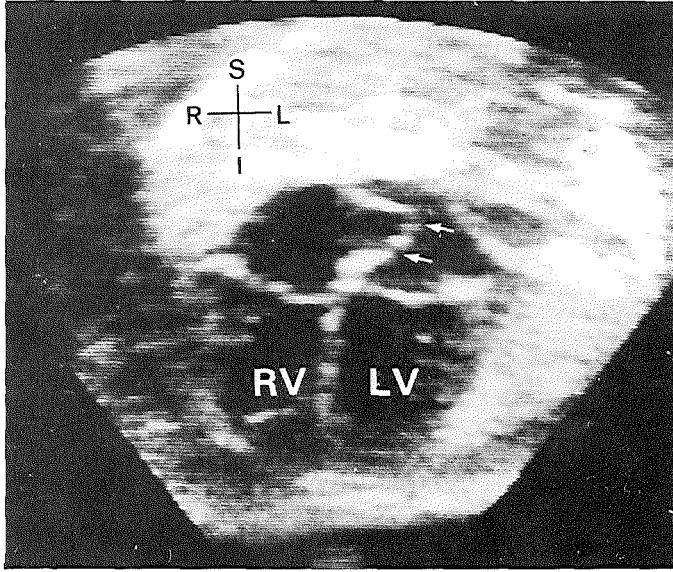


Fig.2. Fetal four-chamber view from case 1 (29 weeks' menstrual age). Arrows indicate aneurysm bulging into left atrium, other labels as in Figure 1.

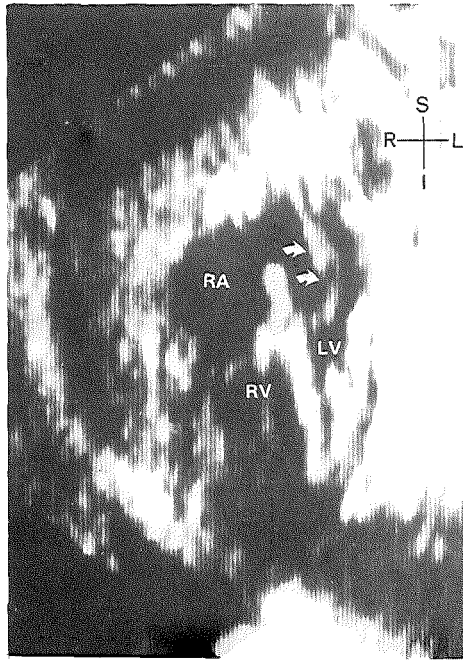


Fig.3. Fetal four-chamber view from case 5 (35 weeks' menstrual age). Labels as in Figure 2. In real-time image the aneurysm prolapsed through the mitral valve and the right heart was dilated.

A careful search was made for cardiac structural defects and possible signs of cardiac compromise, such as pericardial effusion, increase in right heart size and ascites. M-mode analysis of the arrhythmias was achieved by directing the M-line cursor through appropriate fetal cardiac structures to obtain mechanical evidence of atrial and ventricular systole.

The gestational age in the group with findings suggestive of atrial septal aneurysm was between 26 and 38 weeks.

## *Results*

Cases 1-8 are documented in Table I. Cases 1-3 had variable atrial arrhythmias and none developed any signs of cardiac compromise. The periods of paroxysmal supraventricular tachycardia in Case 1 converted to normal sinus rhythm following transplacental digoxin therapy. An oral dose of 0.75 mg digoxin per day was given, and maternal serum digoxin levels were around 1.3 ng/ml. Colour Doppler flow mapping was performed in case 3 and showed clear right to left shunting at the level of the foramen ovale. Postnatal echocardiography revealed normal intracardiac anatomy in all three infants.

Cases 4, 5, 7 and 8 demonstrated supraventricular extrasystoles and Case 6 atrial flutter with 2:1 atrioventricular conduction (ventricular rate 240 beats per minute).

Case 4 developed signs of right heart dilatation at 32 weeks gestation. Vaginal delivery was induced at 36 weeks gestation following a clear increase in the size of the right heart. Echocardiography performed at 11 weeks of age revealed normal intracardiac anatomy and size. In Case 5 the aneurysmal structure was so large that it prolapsed through the mitral valve. At the age of three weeks the heart size had returned to normal and the large atrial septal structure could not be identified. In Case 6 Caesarean section was performed on the day of presentation because of the atrial flutter and early signs of congestive cardiac failure, represented by an enlarged right heart. A large right heart and normal intracardiac anatomy were observed at post natal echocardiography. The neonate was treated postnatally with digoxin. A grossly dilated right heart with paradox septal motion was seen in Case 7 at 37 weeks. At 38 weeks pericardial effusion and ascites were noted. Spontaneous vaginal delivery followed shortly after this examination. Cardiomegaly and ventricular extrasystoles were noted postpartum but at the age of 6 months, the echocardiographic, roentgenographic and electrocardiographic findings had returned to normal.

Right heart enlargement was noted at 37+ weeks in Case 8. This did not increase and spontaneous delivery occurred at 39 weeks. Postnatal cardiological investigation revealed normal sinus rhythm and normal intracardiac anatomy.

Table I. Ultrasound and clinical findings associated with atrial septal aneurysm.

Case No.	Gestational Age	Indication	US findings	Evidence CCF	Prenatal Course	Postnatal Course
1.	26	Arrhythmia	NC, SVE's, PSVT	none	Maternal digoxin therapy. NSR at 29 weeks	digoxin pp, NS
2.	36	Arrhythmia	NC, SVE's, bursts AF	none	Regular monitoring	NS, NSR
3.	38 +	Arrhythmia	NC, SVE's	none	Regular monitoring	NS, NSR
4.	28	Arrhythmia	NC, SVE's	Large right heart at 32 weeks	Regular monitoring	NS, SVE's for 24 hrs
5.	35	Prev. TOF	NC, SVE's	Large right heart	Regular monitoring	NS, cardiomegaly, normal heart size at 3 / 52
6.	36	Arrhythmia	NC, AF 2:1 AVB	Large right heart	CS at 36 weeks	NS, NSR at 45 min, cardiomegaly, digoxin pp
7.	37	Arrhythmia	NC, SVE's	Large right heart	Ascites, pericardial effusion at 38 wks	NS, VE's, cardiomegaly, normal at 6 / 12
8.	37+	Arrhythmia	NC, SVE's	Large right heart	Regular monitoring	NS, cardiomegaly, NSR

AF=atrial flutter; AVB=atrioventricular block; CCF=congestive cardiac failure; CS=Caesarean section; NC=normal connections; NS=normal structure; NSR=normal sinus rhythm; PSVT=paroxysmal supraventricular tachycardia; SVE's=supraventricular extrasystoles; TOF=tetralogy of Fallot; VE's=ventricular extrasystoles

## *Discussion*

Atrial septal aneurysm may be diagnosed by cross-sectional echocardiography and since the first description of this anomaly by Lang and Posselt (15) more than 150 cases have been described either from autopsy studies (16) or more recently from prospective echocardiographic studies during life (11). Hanley et al (11) devised a classification system of fossa ovalis atrial septal aneurysm. This was further subdivided into Types 1A, 1B and 2 which occurred more often as an isolated abnormality, and aneurysm of the entire atrial septum, all of which were associated with complex congenital malformations of the hypoplastic right heart type.

None of the fetuses described in this report had evidence of other congenital heart disease.

As would be expected prenatally all of the aneurysmal structures in the eight affected fetuses were seen to bulge into the left atrium, because of the preferential shunting from right to left atrium through the foramen ovale. None of these structures demonstrated a normal movement pattern on either M-mode (Fig. 4 + 5) or cross-sectional echocardiography.

In normal circumstances the fetal right and left ventricles show more or less a 1 : 1 relationship (17, 18). In Cases 4, 5, 7 and 8 obstruction to flow through the foramen ovale was suspected because of the presence of an enlarged right heart (cases 4, 5 and 8) or an enlarged right heart with mild pericardial effusion and ascites (case 7). In case 4, 5 and 8 this relationship was 1.5 : 1 and in case 7 was 2.5 : 1 with paradox septal motion. Fetal extrasystoles whether of atrial or ventricular origin are generally considered to be benign and of no haemodynamic consequence, even when occurring frequently (19).

In general we would concur with this as in our own series with 83 fetuses with extrasystoles, only the cases described above showed any evidence of cardiac compromise. This was presumably due to obstruction to right-to-left shunting at atrial level and not to the rhythm disturbance itself.

In Case 6 the enlarged right heart may possibly be explained by the presence of a sustained high ventricular rate of 210 beats per minute, but some degree of obstruction to flow at atrial level cannot be completely ruled out as it has been previously suggested (20) that fetal heart rates, below 50 and above 230 beats per minute are associated with cardiac compromise and heart rates within this range are fairly well tolerated. If pulsed Doppler technique had been available accurate information concerning the haemodynamics in these cases may have shed more light on the precise mechanism. Certainly any cases seen in future will be carefully examined by pulsed Doppler and colour coded Doppler flow mapping.

Colour coded Doppler flow mapping techniques were available for case 3. Clear right to left shunting was observed despite the aneurysmal structure. However, we felt this to be inconclusive as the cardiac dimensions were normal so obstruction was not suspected anyway.

Hanley et al (11) described a precise classification system with septal bulging

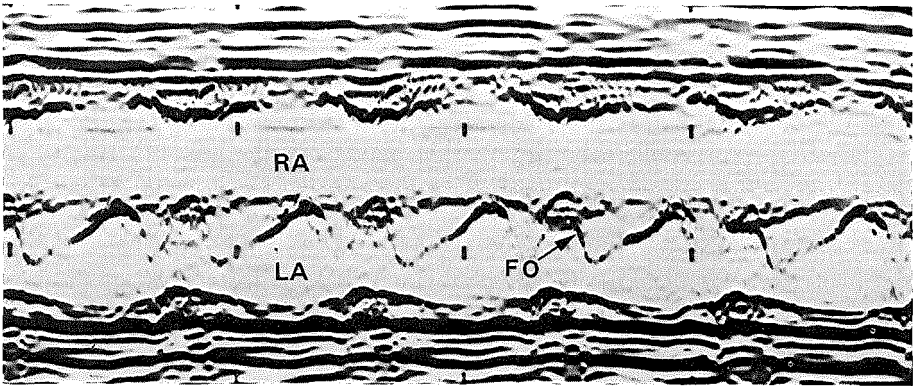


Fig.4. Normal fetal M-mode recorded through the right (RA) and left atria (LA). (Arrow, foramen ovale flap).

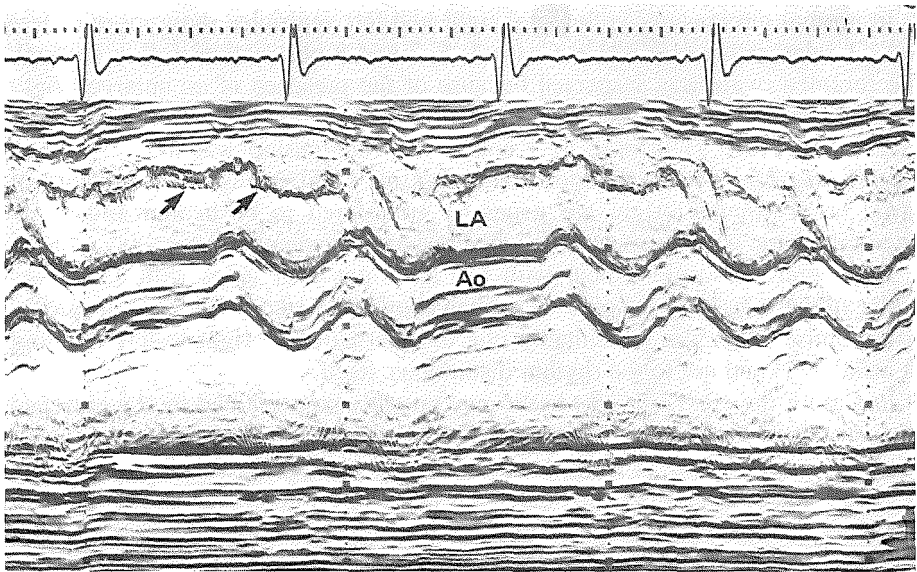


Fig.5. Fetal M-mode recording from case 2. (LA, left atrium; AO, aortic root; arrow, irregular "fixed" foramen ovale flap movement).

not falling within this range being considered as mildly redundant, and therefore excluded. Precise measurement of the fetal aneurysms in our series was not possible due to the inherent difficulties found in fetal echocardiography because of differences in depth and position of the fetal heart in each case. However, all structures were large and fell outside the normal range.

In the early neonatal period, with the earliest echocardiogram being performed on the day of birth and the latest at age 6 months, no echocardiographic or clinical evidence of structural abnormality was noted. Contrast echocardiography was not performed in any of the infants because of the negative clinical and echocardiographic findings. Recently, Belkin et al (21) described the echo contrast findings in 13 patients with echocardiographic features of atrial septal aneurysm.

All 13 patients had echocardiographic evidence of right-to-left shunting, while atrial septal defects were clinically suspected by auscultation and chest radiographs in only three.

Despite the early negative postnatal findings in these eight patients we are rather intrigued that in an ongoing high risk fetal echocardiography programme (therefore every heart very carefully scanned) we have identified these aneurysmal structures only in fetuses displaying an arrhythmia. Over the whole group these aneurysms have been detected in 0.6% of the patients, but in the fetuses referred with a rhythm disturbance 5.4% had an atrial septal aneurysm. It is of interest to note that in the study from Hanley et al (11), 74% of unexplained atrial tachyarrhythmias occurred in patients with a type 2 fossa ovalis aneurysm and was perhaps related to vigorous motion of the aneurysm. Vigorous motion has always been observed in our cases. It has been proposed (11) that atrial septal aneurysm is a congenital malformation and is not acquired secondary to high trans-atrial pressures as has been previously suggested. Perhaps the findings in early life in our series can be explained by these aneurysmal structures becoming plastered against the septal wall as a result of the increase in left atrial pressure after birth producing normal echocardiographic findings at that stage. It remains to be seen whether this kind of prenatal finding will eventually prove to be a marker for other clinically relevant cardiac disease later in life (11) or later ultrasound signs of atrial septal aneurysm.

Another possible explanation may be that this is a form of prematurely obstructed foramen ovale, which may be related to fetal rhythm disturbances (12) or the development of congestive cardiac failure (13, 14). These reports of premature obstruction of the foramen ovale have made no mention of any redundancy or aneurysmal atrial septal structures. However, a recent report by Jouk et al (22) has described a similar anomaly of aneurysm of the foramen ovale related to fetal hydrops but not to arrhythmia. Of the five fetuses in this series with prenatal evidence of cardiac compromise, four had cardiomegaly at birth. The fifth, born in an outlying hospital was not sent for echocardiography until eleven weeks of age so early postnatal information concerning heart size is unavailable.

It remains unclear why some of the aneurysmal structures in our series appear, in the light of available evidence, to be restrictive and others not.

Despite the benign follow up in our eight cases we feel that the unexpected presence of mild to moderate congestive cardiac failure in combination with an aneurysmal, or extremely redundant atrial septum warrants close prenatal attention.

Regular monitoring may prevent unnecessary morbidity due to the possible development of cardiac failure, particularly if the aneurysm is detected early in pregnancy. More haemodynamic information will be necessary in future patients to gain insight into the patho-physiology of this anomaly.

### References

1. Alexander MD, Bloom KR, Hart P, et al: Atrial septal aneurysm: A cause for Midsystolic Click. Report of a Case and Review of the Literature. *Circulation* 63:1186,1981.
2. Ong LS, Nanda NC, Falkoff MD, et al: Interatrial septal aneurysm, systolic click and atrial tachyarrhythmia - A new syndrome? *Ultrasound Med Biol* 8:691, 1982.
3. Vandenbossche JL, Englert M: Effects of respiration on an atrial septal aneurysm of the fossa ovale shown by echographic study. *Am Heart J* 103:922-23, 1982.
4. Hauser AM, Timmis GC, Stewart JR, et al: Aneurysm of the atrial septum as diagnosed by echocardiography: Analysis of 11 patients. *Am J Cardiol* 53:1401-02, 1984.
5. Lazar AV, Pechacek LW, Mihalick MJ, et al: Aneurysm of the interatrial septum occurring as an isolated anomaly. *Cathet Cardiovasc Diagn* 9:167-73, 1983.
6. Vanghese PJ, Simon AL, Rosequist GC, et al: Multiple saccular congenital aneurysms of the atria causing persistent atrial tachyarrhythmias in an infant: report of a case successfully treated by surgery. *Pediatrics* 44:429-33, 1969.
7. Gondi B, Nanda NC: Two-dimensional echocardiographic features of atrial septal aneurysm. *Circulation* 63:452-57, 1981.
8. Iliceto S, Papa A, Sorino M, et al: Combined atrial septal aneurysm and mitral valve prolapse: detection by two-dimensional echocardiography. *Am J Cardiol* 54:1151-53, 1984.
9. Roberts WC: Aneurysm (redundancy) of the atrial septum (fossa ovale membrane) and prolapse (redundancy) of the mitral valve. *Am J Cardiol* 54:1153-54, 1984.
10. Sahn DJ, Allen HD, Anderson R, et al: Echocardiographic diagnosis of atrial septal aneurysm in an infant with hypoplastic right heart syndrome. *Chest* 73:227-30, 1978.
11. Hanley PC, Tajik AJ, Hynes JK, et al: Diagnosis and classification of atrial septal aneurysm by two-dimensional echocardiography: Report of 80 consecutive cases. *J Am Coll Cardiol* 6:1370-82, 1985.
12. Buis-Liem TN, Ottenkamp J, Meerman RH, et al: The Concurrence of fetal supraventricular tachycardia and obstruction of the foramen ovale. *Prenatal Diagnosis* 7:425, 1987.
13. Redel DA, Hansmann M: Fetal obstruction of the foramen ovale detected by two-dimensional Doppler echocardiography in Rijsterborgh H (ed): *Echocardiology*. The Hague: Martinus Nijhoff Publishers, 1981, p425.
14. Pesonen E, Haavisto H, Ammala P, et al: Intrauterine hydrops caused by premature closure of the foramen ovale. *Arch Dis Child*, 58:1015, 1983.
15. Lang FJ, Posselt A: Aneurysmatische Vorwölbung der fossa ovalis in den linker Vorhof. *Wien Med Wochenschr* 84:392-96, 1934.
16. Silver MD, Dorsey JS: Aneurysms of the septum primum in adults. *Arch Pathol Lab Med* 102:62-5, 1978.
17. Allan LD, Joseph MC, Boyd EGCA, Campbell S, Tynan MJ: M-mode echocardiography in the developing human fetus. *Br Heart J* 47:573-583, 1982.
18. Vosters RPL: Fetal and early neonatal cardiac ventricular geometry and function. An echographic study. Thesis. Erasmus University Rotterdam, 1983.
19. Southall DP, Richards J, Hardwick R, et al: Prospective study of fetal heart rate and rhythm patterns. *Arch Dis Child* 55:506-11, 1980.
20. Tonge HM, Stewart PA, Wladimiroff JW: Fetal blood flow measurements during fetal cardiac arrhythmia. *Early Hum Develop* 10:23-4, 1984.
21. Belkin RN, Waugh RA, Kisslo J: Interatrial shunting in atrial septal aneurysm. *Am J Cardiol* 57:310-12, 1986.
22. Jouk PS, Rossignol AM, Denis B, Bost M: Lostium secundum restrictief: un nouveau syndrome malformatif foetal. *Arch Mal Coeur* 4:538-542, 1987.



## Chapter 7

## Conclusions

During the last ten years technological advances in ultrasound have made it possible to perform non-invasive studies of the human fetal heart.

In this thesis the applicability of the various modalities of ultrasound in predicting congenital heart disease in fetuses from various risk groups was studied.

Patients with a known increased risk for fetal congenital heart disease (discussed in chapter 3) must be informed of the risk of a false negative finding. The defects which were not recognised in this study, e.g. atrial septal defect, ventricular septal defect, coarctation of the aorta, are similar to those not always detectable by ultrasound alone postnatally. Recognition of these defects prenatally would not, in any case, have affected the further obstetric management of the patients.

It is clear from the data in Chapter 4 that the diagnosis of congenital heart disease is often made late in pregnancy, for various reasons. So called "routine" screening of the four chamber view in the early second trimester will probably have an impact on the pattern of late referrals. It is entirely realistic to expect that if in "routine" departments an ability to exclude major anomalies of other organ systems is required, a competence to achieve and interpret a normal four chamber view must be demanded.

It would appear from the information gleaned from this project that the spectrum of fetal congenital heart disease is somewhat different to that seen postnatally. This may be, in part, a reflection of the referral patterns with fetuses with major anomalies being more easily recognised and referred to an academic centre. Certainly the combinations of severe anomalies resulting in a very high fetal or early post partum mortality may result in these patients not being included in the neonatal statistics.

The diagnosis of fetal arrhythmia, especially, most often engenders severe anxiety and near panic in many parents. It is important to see these patients as soon as possible as it is usually feasible to reassure them as to the benign nature of the arrhythmia when extrasystoles are present. However, fetal bradyarrhythmia may be life threatening when associated with structural heart disease, and has a poor prognosis. In contrast the prognosis in fetuses with normally structured hearts is good and careful monitoring may detect early signs of cardiac failure allowing delivery of a fetus in good condition. In the latter group exclusion of maternal connective tissue disease is required for counseling purposes. Fetal tachyarrhythmia is also potentially life threatening. Prompt pharmacological treatment may reverse congestive cardiac failure. A viable but compromised fetus may benefit from early delivery and direct neonatal treatment, thereby preventing unnecessary morbidity. Ongoing studies to examine the fetal patho-

physiology under conditions of arrhythmia will doubtless broaden our insight into the cardiovascular mechanisms of compensation in the human fetus.

A major disadvantage in the assessment of fetal congenital heart disease is the fact that ultrasound is the only technique possible. Such adjunctive techniques as electrocardiography, auscultation, angiocardiology etc., imperative in post-natal assessment are obviously impossible. This places a huge burden on the persons performing, interpreting and prognosticating the fetal echocardiogram especially if termination of pregnancy is being considered. This responsibility should not be underestimated.

Another disadvantage is the almost total lack of knowledge of the natural history of fetal congenital heart disease.

Conversely, the ability to confidently exclude major congenital heart disease for parents who have been given a higher than normal risk, however small that increased risk may be, should be considered a vitally important part of their obstetric management.

Hopefully further technical improvements in image quality and processing will result in better images at earlier stages of gestation. In particular improvements in colour-coded Doppler flow mapping techniques may have a marked impact on the non-invasive haemodynamic study of fetuses with congenital heart disease.

Future improvements in transvaginal scanning techniques and equipment may allow exclusion of major defects, including CHD in the late first or early second trimester.

This will prove important especially when obesity is a complicating factor for trans-abdominal scanning.

Earlier diagnosis may also have important psychological and ethical consequences as the so called "age of viability" continues to decrease.

Fetal echocardiography is a reliable tool in experienced hands and will doubtless remain in specialised centres. However an improvement in equipment and expertise overall will most likely result in improved antenatal "cardiac" care for all pregnant patients.

# Summary

## Chapter 1

In the last decade technological advances in ultrasound equipment have opened the door to non-invasive studies of the human fetal heart.

The objective of this study was to evaluate fetal echocardiography in detecting fetal congenital heart disease in pregnancies at increased risk.

Detection of congenital heart disease in intrauterine life may have far reaching consequences for the management of an affected pregnancy. Termination of pregnancy may be offered when lethal defects are found. In non-lethal defects place, mode and time of delivery may be planned for optimal neonatal care.

## Chapter 2

The techniques employed in the ultrasonic recognition of both normal and abnormal fetal cardiac morphology and function are described. The difficulties in excluding all types of congenital heart disease are discussed.

Real-time and M-mode techniques are vital in the analysis of cardiac structure and rhythm.

Doppler techniques may provide haemodynamic information. It can be predicted from preliminary data from the new technique of colour coded Doppler flow mapping that this will become an important adjunct in fetal cardiac diagnosis.

## Chapter 3

A total of 1577 pregnancies considered at higher than normal risk for fetal congenital heart disease were studied to test the validity of fetal echocardiography in excluding major congenital heart disease. Eighteen cases of CHD were detected prenatally (1.1%). There were 11 cases of CHD (0.7%) diagnosed postnatally. These false negatives comprised defects such as ventricular septal defect, atrial septal defect, coarctation of the aorta, and supra-valvar stenoses. These defects are sometimes difficult to diagnose, using only ultrasound, after birth.

The relatively low sensitivity of 63% in the diagnosis of congenital heart disease is explained by the nature of the defects not recognised prenatally.

A complicating factor in early and accurate diagnosis of fetal congenital heart disease is maternal obesity.

Exclusion of major defects has a very strong positive effect on the prospective parents, even when the risks of false negative findings are discussed.

## Chapter 4

Certain complications of pregnancy (e.g. polyhydramnios, intrauterine growth retardation, premature rupture of membranes, premature labour) serve as a warning that fetal anomalies may be present. Congenital heart disease is commonly associated with multiple organ system anomalies and/or karyotype abnormalities.

The data from 440 patients with pathologic pregnancies are analysed in this chapter. CHD was correctly predicted in 79 of the 440 patients (18%). Chromosomal abnormalities were present in 38% of the fetuses with CHD, with or without other structural pathology. There were 3 cases of CHD (0.7%) diagnosed postnatally. These false negative cases were similar to those described in Chapter 3. There were 4 (0.9%) false positive diagnoses all related to positional abnormalities such as distortion of thoracic contents and anatomic variants.

The high mortality (>90%) in fetuses also suffering from congenital heart disease reflects partly the severity of the congenital heart disease but is frequently related to the devastating combinations of abnormalities.

The complications of pregnancy (e.g. polyhydramnios, intrauterine growth retardation, suspected fetal pathology etc.) prompting referral often manifest late in pregnancy.

Chromosomal analysis is best performed prenatally, however late in gestation, obviating the risk of culture failure if intrauterine death occurs.

The documented high sensitivity (96%) and specificity (99%) in the detection of fetal congenital heart disease is largely explained by the severity of congenital heart disease frequently present in these fetuses.

## Chapter 5

A study comparing ultrasonic and pathologic findings is presented.

Careful postmortem analysis is mandatory to confirm diagnoses and to understand how errors in classification may occur.

## Chapter 6

It is only since the advent of real-time directed M-mode recording facilities that fetal arrhythmias can be accurately defined.

A study was performed to document which types of arrhythmia are present in fetal life and their possible association with abnormal morphology. Arrhythmia was investigated in 189 fetuses (43% of all patients referred with complications in pregnancy).

It is shown that fetal extrasystoles (73% of the cases) are fairly common, are infrequently associated with structural defects, in general are completely benign, and usually have no haemodynamic consequences.

Fetal bradyarrhythmia occurs less commonly and if associated with structural

disease (54%), has a poor prognosis. Fetal congenital complete heart block in the presence of normal morphology is strongly associated with maternal connective tissue disease (90%).

Fetal tachyarrhythmia is also relatively uncommon, but may be life threatening in the presence of congestive cardiac failure. Pharmacologic therapy should be attempted in preivable fetuses, with digoxin still the drug of first choice. Mortality may occur (2 cases, 7%) even after conversion to sinus rhythm.

Fetal atrial arrhythmias may be associated with aneurysm of the foramen ovale and fetal congestive cardiac failure.

# Samenvatting

## Hoofdstuk 1

Verdere vooruitgang in echoscopische apparatuur heeft gedurende het laatste decennium de deur geopend voor niet-invasief onderzoek van het hart bij de menselijke foetus. Het doel van het onderzoek, beschreven in dit hoofdstuk, was de evaluatie van foetale echocardiografie met betrekking tot de detectie van aangeboren hartafwijkingen in zwangerschappen met een verhoogd risico voor deze afwijkingen. De detectie van een aangeboren hartafwijking in utero kan verregaande consequenties hebben voor het verdere beleid van de betreffende zwangerschap. Zwangerschapsafbreking kan worden overwogen wanneer een niet met het leven verenigbare afwijking wordt gevonden. In aanwezigheid van een met het leven verenigbaar defect kunnen plaats, wijze en tijdstip van de bevalling worden gepland, opdat men van optimale neonatale zorg verzekerd is.

## Hoofdstuk 2

In dit hoofdstuk worden de verschillende echoscopische technieken ter evaluatie van de normale en abnormale anatomie en functie van het foetale hart beschreven. Ingegaan wordt op de beperkingen van de echoscopische diagnostiek. De gecombineerde real-time en M-mode benadering is essentieel voor analyse van hartstructuur en ritme. Doppler ultrageluid verschaft informatie over de foetale haemodynamiek. Voorlopige gegevens suggereren dat de zogenaamde kleuren Doppler techniek een belangrijke aanwinst gaat vormen in het prenatale hartonderzoek.

## Hoofdstuk 3

In totaal werden 1577 zwangerschappen met een verhoogd risico op aangeboren hartafwijkingen echoscopisch onderzocht. Bij 18 kinderen (1.1%) werd de hartafwijking voor de geboorte en bij 11 kinderen (0.7%) na de geboorte vastgesteld. Fout-negatieve bevindingen betroffen vooral afwijkingen zoals ventrikel septum defect, atrium septum defect en coarctatio aortae. Deze afwijkingen zijn ook na de geboorte, uitsluitend op basis van echoscopisch onderzoek, soms al moeilijk vast te stellen. De relatief lage sensitiviteit van 63% met betrekking tot de prenatale diagnostiek van aangeboren hartafwijkingen binnen de hoge risicogroep is verklaarbaar op basis van de aard van de afwijking, welke prenataal niet wordt herkend. Moederlijke adipositas is een complicerende factor in de

vroege diagnostiek van foetale hartafwijkingen. Uitsluiting van een ernstige hartafwijking heeft een duidelijk positief effect op de a.s. ouders, ook nadat de beperkingen van deze techniek zijn doorgesproken.

#### Hoofdstuk 4

Bepaalde zwangerschapscomplicaties zoals ernstige groeivertraging, hydramnion, vroegtijdig gebroken vliezen en vroegtijdige weeënactiviteit fungeren als een signaal voor de mogelijke aanwezigheid van een foetale structurele afwijking. Binnen deze groep gaan aangeboren hartafwijkingen vaak gepaard met andere orgaanafwijkingen en/of chromosomenafwijkingen. In dit hoofdstuk worden de bevindingen bij 440 pathologische zwangerschappen beschreven. Een aangeboren hartafwijking werd correct vastgesteld in 79 van de 82 pasgeborenen. Een chromosomale afwijking was aanwezig in 38% van deze aangedane pasgeborenen. In 3 gevallen (0.7%) werd de hartafwijking voor het eerst postnataal gediagnostiseerd. De aard van deze hartafwijkingen was overeenkomstig die beschreven in hoofdstuk 3. Er waren 4 (0.9%) fout-positieve bevindingen, allen bepaald door positionele afwijkingen zoals verplaatsing van de intrathoracale organen ten gevolge van een hernia diafragmatica of hydrothorax en anatomische varianten. De hoge intrauteriene sterfte (meer dan 90%) in aanwezigheid van een congenitale hartafwijking, werd deels bepaald door de ernst van de hartafwijking zelf, deels door de combinatie van cardiale en extracardiale afwijkingen. Verwijzing op basis van eerder genoemde zwangerschapspathologie vond in het algemeen wegens late manifestatie relatief laat in de zwangerschap plaats. Wegens de hoge kans op mislukking van de celkweek voor chromosomenonderzoek na intrauterine sterfte, is het aangewezen deze kweek, wanneer geïndiceerd, reeds prenataal te verrichten. De hoge sensitiviteit (96%) en specificiteit (99%) met betrekking tot de detectie van foetale hartafwijkingen binnen de groep van zwangerschaps- pathologie is grotendeels bepaald door de ernst van deze afwijkingen.

#### Hoofdstuk 5

In dit hoofdstuk wordt een vergelijkend onderzoek tussen echoscopische en pathologisch-anatomische bevindingen beschreven. Zorgvuldig pathologisch-anatomisch onderzoek is essentieel voor de beoordeling van de validiteit van prenataal hartonderzoek door middel van echoscopie.

#### Hoofdstuk 6

Dankzij de invoering van gecombineerde real-time en M-mode technieken is het mogelijk geworden de aard van foetale hart-aritmieën nauwkeurig vast te stellen. Onderzoek werd verricht naar de verschillende vormen van foetale

hartaritmie en hun mogelijke associatie met structurele hartafwijkingen. Een foetale ritmestoornis werd vastgesteld in 189 (43%) van de verwezen pathologische zwangerschappen. Foetale extrasystolieën komen relatief vaak voor (73%), echter gaan zelden gepaard met structurele hartafwijkingen en hebben in het algemeen geen haemodynamische consequenties. Foetale bradycardieën komen relatief minder vaak voor, echter zijn in meer dan de helft van de gevallen (54%) geassocieerd met structurele hartafwijkingen en hebben daarom een slechte prognose. Een congenitaal hartblok in aanwezigheid van normale hartstructuren bij de foetus gaat zeer frequent (90%) gepaard met collageenziekte bij de moeder. Foetale tachycardie komt relatief zelden voor, maar kan in aanwezigheid van cardiale decompensatie levensbedreigend zijn. Farmacologische behandeling moet worden overwogen bij die ongeborenen die nog niet de levensvatbare leeftijd hebben bereikt. Ondanks normalisatie van het hartritme, kan alsnog intrauteriene sterfte ten gevolge van een ernstige cardiale decompensatie optreden (2 gevallen, 7%). Foetale hartritme-stoornissen kunnen gepaard gaan met aneurysmata van het foramen ovale.



## Appendix

Tabulation of cardiac anomalies in patients with complications in the current pregnancy: classified according to major presenting symptom

Patients referred with polyhydramnios (n=10)

Gest. age	Karyotype	Prenatal Findings	Postnatal Findings	Mortality
20	Normal	Multiple anomalies, dilated aorta	Multiple anomalies, hypoplastic aortic isthmus	TOP
27	Normal	Meckel syndrome, incomplete atrioventricular septal defect	confirmed	TOP
27	Normal	Hypoplastic aortic arch	confirmed	TOP
27	Trisomy 18	Multiple anomalies, double outlet right ventricle	confirmed	IUD
29	Normal	Dilated aorta, incomplete exam	Tetralogy of Fallot	Alive
29	Normal	Complete atrioventricular septal defect	confirmed	IUD
29	Trisomy 21	Duodenal atresia, ventricular septal defect	confirmed	†PP
32	Trisomy 18	Multiple anomalies, ventricular septal defect	confirmed	†PP
34	Trisomy 18	Complex cardiac anomalies	confirmed	†PP
34	Normal	Thoraco-abdominal conjoined twins, shared heart	monoatrial, triventricular heart	†PP

Patients referred with fetal ascites (n=5)

Gest. age	Karyotype	Prenatal Findings	Postnatal Findings	Mortality
24	45XO	Cystic hygroma, hypoplastic left heart	confirmed	IUD
27	Normal	Ebstein anomaly, congestive cardiac failure	confirmed	IUD
28	Normal	Hypoplastic aorta	confirmed	IUD
35	Normal	Hypoplastic right ventricle	confirmed	IUD
35	Normal	Obstructive foramen ovale	normal heart	Alive

Patients referred with intrauterine growth retardation (n=5)

Gest. age	Karyotype	Prenatal Findings	Postnatal Findings	Mortality
23	Normal	Double outlet right ventricle	confirmed	TOP
26	Trisomy 21	Complete atrioventricular septal defect	confirmed	18/12
30	Trisomy 13	Double outlet right ventricle	confirmed	IUD
31	Normal	Oligohydramnion, enlarged right heart, incomplete exam	Tetralogy of Fallot, cleft palate	†
33	Trisomy 13	Multiple anomalies, ventricular septal defect	confirmed	IUD

Patients referred with suspected pathology: associated with abnormal karyotype (n=11)

Gest. age	Karyotype	Prenatal Findings	Postnatal Findings	Mortality
17	Trisomy 18	Encephalocele, complete atrioventricular septal defect	confirmed	TOP
22	46xi(xq)	Multiple anomalies, complete atrioventricular septal defect	confirmed	TOP
23	Trisomy 18	Multiple anomalies, ventricular septal defect	confirmed	TOP
24	46,X, der (Y)	Ebstein anomaly, pulmonary stenosis	confirmed	Alive
25	Trisomy 13	Multiple anomalies, hypoplastic left ventricle, double outlet right ventricle	confirmed	IUD
27	Trisomy 18	Multiple anomalies, hypoplastic left heart	confirmed	TOP
27	Trisomy 13	Multiple anomalies, complex heart disease	confirmed	IUD
29	Trisomy 18	Multiple anomalies, Tetralogy of Fallot	confirmed	†PP
30	Trisomy 21	Duodenal atresia, complete atrioventricular septal defect	confirmed	†PP
33	Trisomy 18	Multiple anomalies, ventricular septal defect	confirmed	†PP
37	Trisomy 18	Multiple anomalies, complete atrioventricular septal defect	confirmed	†PP

## Patients referred with suspected fetal pathology: associated with multiple anomalies (n=9)

Gest. age	Karyotype	Prenatal Findings	Postnatal Findings	Mortality
19	Normal	Multiple anomalies, partial ectopia cordis	confirmed	†PP
21	Normal	Multiple anomalies, atrioventricular septal defect	confirmed	†PP
21	Normal	Obstructive uropathy, Tetralogy of Fallot	confirmed + anal atresia	Alive
22	Normal	Multiple anomalies, ectopia cordis, double outlet right ventricle	confirmed	TOP
22	Normal	Multiple anomalies, truncus arteriosus	confirmed	TOP
28	Normal	Multiple anomalies, complete atrioventricular septal defect	confirmed	†PP
28	Normal	Multiple anomalies, confirmed coarctation	TOP	
30	Normal	Multiple anomalies, ventricular septal defect	confirmed	†PP
32	Normal	Multiple anomalies, atrial septal defect, ventricular septal defect	confirmed	†PP

## Patients referred with suspected fetal pathology: associated with neural tube defects (n=4)

Gest. age	karyotype	Prenatal Findings	Postnatal Findings	Mortality
16	Normal	Iniiencephaly, Tetralogy of Fallot	confirmed	TOP
31	Normal	Hydranencephaly, meningo-myelocele, dextrocardia, complex heart disease	confirmed	†PP
32	Normal	Hydrocephaly, ectopia cordis, complex heart disease	confirmed	†PP
35	Normal	Encephalocele, complete atrioventricular septal defect	no post mortem	IUD

## Patients referred with suspected fetal pathology: purely cardiac (n=7)

Gest. age	karyotype	Prenatal Findings	Postnatal Findings	Mortality
27	Normal	Cardiomyopathy	endomyocardial fibrosis	IUD
31	Normal	Pericardial effusion	confirmed	Alive
35	Normal	Hypoplastic left heart	confirmed	†PP
35	Normal	Enormous right atrium, ?obstructed foramen ovale, ?Ebstein (no valve displacement)	tricuspid dysplasia, no septal displacement form fruste Ebstein	†PP
35	Normal	Ebstein anomaly	confirmed	Alive
36	Normal	Ebstein anomaly, pulmonary atresia	confirmed	†PP
37	Normal	Ebstein anomaly	idiopathic giant right atrium	Alive

## Patients referred with omphalocele (n=6)

Gest. age	karyotype	Prenatal Findings	Postnatal Findings	Mortality
21	Normal	Multiple anomalies, Tetralogy of Fallot	confirmed	TOP
21	Trisomy 18	Tetralogy of Fallot	confirmed	TOP
24	Trisomy 18	Double outlet right ventricle	confirmed	TOP
27	Trisomy 18	Multiple anomalies, hypo- plastic left heart	confirmed	TOP
28	Trisomy 18	Ventricular septal defect	confirmed + hypoplastic aortic arch	TOP
30	Trisomy 18	Hypoplastic left ventricle	confirmed	†PP

## Acknowledgements

The work presented in this thesis was performed in the Department of Obstetrics and Gynaecology, University Hospital - Dijkzigt, Erasmus Medical School, Rotterdam, The Netherlands, under the auspices of the Foundation of Clinical Genetics Rotterdam.

The continuous support of Professor H.Galjaard is much appreciated.

I am grateful to the Dutch Prevention Fund for financially supporting this study for one year.

Without the invaluable support, advice, and encouragement of Professor Wladimiroff this thesis could not have come to fruition.

I should like to thank Professor J.Hess for his advice during discussions of this thesis.

For their willingness to be members of the committee and for their helpful comments I thank Professor M.F.Niermeijer and Professor G.H.A.Visser.

I would like to thank Jo Van Sabben and Gerda Kroesen for their part in teaching me basic obstetric ultrasound scanning.

Thanks are due to Elma Gussenhoven for her help in the early part of this study in learning to interpret the ultrasound images, and Nienke Essed for her evaluation of the pathologic specimens.

Professor A.E.Becker patiently unravelled the mysteries of cardiac patho-anatomic terminology and provided the superb photographs of the fetal heart specimens.

I thank Annette Reuss for her friendship, for frequently providing a sounding board for me, and for referring many of the patients in this study.

I am grateful to the Audiovisual Department for their photographic expertise.

Meindert Taams spent many hours with me "brainstorming" fetal cardiac ultrasound anatomy and the interpretation of fetal arrhythmias without an ECG.

I wish to thank Paula Vogelaar for the speedy and efficient typing of this manuscript.

I am grateful to all co-authors of the articles and to the patients without whom the articles could not have been written.

Also, I am grateful to all the obstetricians, midwives, and general practitioners who referred patients, often from great distances, and without whom this study could not have been completed.

Last, but not least I wish to thank: The Dr.Catharina Van Tussenbroek Foundation, Diasonics /Sonotron, and The Netherlands Heart Foundation for their generous financial support in meeting printing expenses.

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