DOPPLER ECHOCARDIOGRAPHY IN THE HUMAN FETUS

normal flow velocities and the effect of fetal variables

DOPPLER ECHOCARDIOGRAFIE IN DE HUMANE FOETUS

normale bloedstroomsnelheden en de invloed van foetale variabelen

met samenvatting in het Nederlands

DOPPLER SONOKARDIOGRAPHIE IN DEM HUMANEN FOETUS

normale Flußgeschwindigkeiten und der Einfluß foetaler Variablen

mit Zusammenfassung auf deutsch

1992
BOEK EN OFFSETDRUKKERIJ LETRU
HELMOND
tel. 04920-37797

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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 18 MAART 1992 OM 15.45 UUR

DOOR
KARIN VAN DER MOOREN
GEBOREN TE HEERLEN

PROMOTIECOMMISSIE:

Promotor: Prof.Jhr.Dr. J.W. Wladimiroff

Overige leden: Prof.Dr. K. Maršál
Prof.Dr. H.P. van Geijn
Prof.Dr. P.E. Treffers

'A journey of a thousand miles
starts from beneath one's feet'

Lao Tse

Aan mijn ouders

CONTENTS

Chapter 1

INTRODUCTION AND DEFINITION OF OBJECTIVES

2D-real time echocardiography has now been used for over a decade with particular emphasis on the assessment of fetal cardiac anatomy (Lange et al., 1980). Detailed fetal cardiac imaging is possible as from 16 weeks' gestation onwards allowing the early detection of severe cardiac malformations (Stewart, 1989). More recently, transvaginal transducers have become available, allowing fetal cardiac examinations to be carried-out as early as 11 weeks' gestation (Wladimiroff et al., 1991).

Fetal Doppler echocardiography was first introduced in the mid eighties (Maulik et al., 1985) to provide information on fetal cardiac function during the second half of pregnancy. The introduction of colour coded Doppler was a further step towards a more detailed evaluation of cardiac anatomy and function; its significance is currently being determined (Chiba et al., 1990). Doppler echocardiographic studies have been carried-out in both normal fetuses and in fetuses with structural cardiac anomalies and arrhythmias (Huhta et al., 1985, Reed et al., 1986a, 1987a). Also, a method has become available to study blood flow velocity waveforms in the fetal ductus arteriosus (Huhta et al., 1987). This is of clinical importance, since it has been recognised that certain drugs given to the mother, may constrict the fetal ductus arteriosus and thus compromise the fetal circulation (Arcilla et al., 1969). Constriction of the ductus arteriosus causes peak systolic and diastolic velocities to rise (Moise et al., 1988). Fetal right ventricular output is divided between the ductus arteriosus and the fetal lungs, the greater majority of blood by-passing the lungs. It may be hypothesised that conditions affecting the pulmonary vascular bed, like pulmonary hypoplasia, could influence blood flow velocity waveforms in the ductus arteriosus.

For the interpretation of fetal cardiac and ductus arteriosus blood flow velocity waveforms, knowledge of normal waveform parameters is essential. Furthermore, internal variables affecting blood flow velocity waveforms have to be recognised and their effect on cardiac haemodynamics has to be established. Relevant intrinsic fetal variables that have been identified so far, are fetal heart rate changes including fetal arrhythmias, fetal breathing movements (Maršál et al., 1984) and lately fetal behavioural states (van Eyck, 1987). Until now, scant information is available regarding the effect of these variables on fetal cardiac haemodynamics.

The objectives of this thesis were as follows.

1. To establish the intra-observer variability in the assessment of fetal atrio-ventricular flow velocity parameters in the second half of pregnancy. The results are discussed in chapter 3.2.
2. To assess the distribution of flow velocity waveform parameters at fetal atrioventricular and outflow tract level during the second half of normal pregnancy and to determine whether these parameters are fetal heart rate dependent in the normal fetal heart rate range. Data are presented in chapter 4.1.
3. To determine whether flow velocity waveform parameters at fetal atrio-ventricular and outflow tract level are changed by fetal breathing movements and, if so, whether this change is gestational-age dependent.
   To investigate whether time-averaged velocity at fetal atrioventricular and outflow tract level during fetal breathing movements is different from that observed during fetal apnoea. This is discussed in chapter 4.2.
4. To establish the distribution of flow velocity waveform parameters from the fetal ductus arteriosus during the second half of normal gestation and to determine whether there is fetal heart rate dependency for these parameters in the normal fetal heart rate range. Results are presented in chapter 5.1.
5. To determine whether flow velocity waveforms in the ductus arteriosus change during fetal breathing movements. If so, to establish (i) whether this change is gestational age-dependent and (ii) whether the presence of normal breathing related ductal blood flow velocity changes is indicative of absent pulmonary hypoplasia in cases of prolonged severe oligohydramnios following premature rupture of membranes. Data are presented in chapter 5.2.
6. To investigate the relationship between fetal ductal blood flow velocity waveforms and fetal behavioural states. Data are presented in chapter 5.3.
7. To determine the nature of flow velocity waveforms at atrioventricular and outflow tract level during blocked and conducted supraventricular extrasystoles when compared with waveforms obtained from normal sinus beats; to assess the relation between these waveform changes and the preceding beat-to-beat interval. This is discussed in chapter 6.

Chapter 2

VARIABLES INFLUENCING FETAL BLOOD FLOW VELOCITY WAVEFORMS: A LITERATURE SURVEY

Fetal blood flow velocity waveforms are influenced by a number of intrinsic variables, notably fetal behavioural states, breathing movements and heart rate changes.

This chapter provides a literature survey on these variables; in the sub-chapter on heart rate changes emphasis has been put on rhythm disturbances. Also in this thesis, the role of fetal breathing movements in fetal lung development will be addressed. A separate sub-chapter on fetal lung development has therefore been included.

2.1 DEVELOPMENT OF FETAL BEHAVIOUR

2.1.1 DEVELOPMENT OF STATE VARIABLES THROUGHOUT PREGNANCY

In the evaluation of human fetal behavioural aspects, Nijhuis (1982) noted the importance of the following three state parameters: fetal body movements, fetal eye movements and fetal heart rate pattern. These parameters each show a characteristic development during gestation.

First half of gestation

Fetal body movements can be observed from 7.5 weeks of gestation onwards (De Vries et al., 1982a). Sixteen different fetal motor patterns have been described by the age of 15 weeks, the rate of occurrence varying considerably for the different movements (De Vries et al., 1982a, 1982b). Most of the patterns can be observed throughout gestation as well as after birth (De Vries et al., 1982a, Prechtl et al., 1985). Fetal motility shows a periodicity from early on (De Vries et al., 1982a). Whereas at 8 weeks fetal activity still follows an irregular pattern, grouping of activities or bursts can be seen during the weeks thereafter. After 14 weeks, these bursts are followed by longer episodes of fluctuating activity, separated by pauses of up to 14 minutes. Periodicity is again different for the several motor patterns (De Vries et al., 1982b). The incidence of general movements for instance increases

rapidly from 2% at 8 weeks to 12.5% at 10 weeks and remains fairly constant thereafter. Total fetal activity at 13 weeks' gestation varies from 13% to 34% (De Vries et al., 1987). Fetal breathing movements show a similar pattern, which is discussed elsewhere in this section. No diurnal variation is present for any of the motor patterns (De Vries et al., 1987).

Fetal eye movements have been recognised from about 16 weeks of gestation onwards. Low-frequency eye movements can be encountered in early pregnancy, which remain constant in incidence and appearance throughout gestation (Birnholz, 1981).

Fetal heart rate shows an initial rise from 120 to 180 bpm (beats per minute) between 6 and 10 weeks (Robinson and Shaw-Dunn, 1973), followed by a decrease from 11-13 weeks onwards (Wladimiroff and Seelen, 1973, Sorokin et al., 1982) to about 140 bpm at 19 weeks (Allan et al., 1983). Beat to beat variation is minimal up to 14-15 weeks (Wladimiroff and Seelen, 1973). Diurnal variation in heart rate, if present, cannot be reliably established during this phase due to technical difficulties in obtaining good-quality long-term fetal heart rate recordings (Swartjes et al., 1990).

Second half of gestation

Fetal body movements do not undergo obvious changes in appearance or incidence during this phase of development (De Vries et al., 1987). Already at 20 weeks a significant diurnal variation can be observed in fetal motility, with the lowest incidence values in the morning and the highest during the evening (De Vries et al., 1987). Also, increasingly rest-activity cycles can be seen (Visser et al., 1981).

Fetal eye movements of the low-frequency type do not change in incidence until 38 weeks (Birnholz, 1981) when a decrease becomes apparent (Horimoto et al., 1990). Rapid eye movements lasting approximately 1 second develop during the second trimester (Birnholz, 1981), with a tendency to clustering from about 24 weeks of gestation onwards (Inoue et al., 1986). Occasionally, nystagmoid eye movements can be seen (Birnholz, 1981, Roodenburg et al., 1991). The cumulative incidence of slow and rapid eye movements increases from 29% between 33 and 36 weeks to 47% between 37 and 41 weeks (Horimoto et al., 1990). In another study only a slight increase in the total number of fetal eye movements was observed (Roodenburg et al., 1991).

Fetal heart rate gradually declines to a mean heart rate of 130 bpm at term (Sorokin et al., 1982, Allan et al., 1983). Developmental changes in heart rate variability can also be observed throughout the second half of

pregnancy. Heart rate decelerations predominate between 20 and 30 weeks of gestation. They are associated with body movements in approximately 60% of cases (Sorokin et al., 1982). The frequency of accelerations and acceleration-decelerations increases with advancing gestational age, the frequency of decelerations diminishes, while the association between heart rate variability and movements becomes stronger (Sorokin et al., 1982).

Related to the rest-activity cycles in fetal motility, recurrent episodes of low and high heart rate variation can be seen from 27 weeks of gestation onwards (Visser et al., 1981). Already at 20-22 weeks, high-variation episodes correlate positively with an increased number of general movements (De Vries et al., 1987). The proportion of time spent in high FHR (fetal heart rate) variation increases to 55% at 34 weeks whereas the time spent in low FHR variation remains constant at about 28% (Dawes et al., 1982). At term, the duration of a rest-activity cycle is about 80 minutes; at earlier gestation this appears to be shorter (Visser et al., 1987).

Diurnal rhythms can be observed for both fetal heart rate and its variation. According to De Vries et al. (1987), at 20-22 weeks' gestation fetal heart rate is lowest between 2400 and 0600 hours and heart rate variation is lowest between 0600 and 1100 hours. In fetuses near term, fetal heart rate is lowest between 0200 and 0600 hours and highest between 0900 and 1000 hours (Patrick et al., 1982). According to the same authors, a significant positive relationship exists between the mean daily heart rate and the mean hourly heart rate of individual fetuses and their mothers. The mechanism responsible for this correlation between maternal and fetal circadian rhythms has not been elucidated yet, but could be maternal body temperature, or the release of catecholamines or other hormones. It seems likely that fetal heart rate is at least partially controlled by the maternal cardiovascular, endocrine or metabolic environment (Patrick et al., 1982).

2.1.2 DEVELOPMENT OF COINCIDENCE OF STATE VARIABLES

Coincidence of state variables is some form of coordination between the cyclic patterns of heart rate, eye and body movements not yet corresponding to the definition of true behavioural states. As has been pointed out earlier, already in the first half of gestation clustering of fetal body movements can be seen which cannot be explained by chance (De Vries et al., 1982a, Swartjes et al., 1990). Since it is technically difficult to obtain reliable long-term records of fetal eye movements or fetal heart rate this early in pregnancy, data regarding incidence patterns of these parameters before 20 weeks'

gestation are not available (Swartjes et al., 1990). From 25 weeks of gestation onwards, fetal eye and body movements and heart rate patterns have been studied by several authors (Visser et al., 1987, Dogtrop et al., 1990, Swartjes et al., 1990). At this time, differentiation of fetal heart rate in patterns A, B, C and D according to Nijhuis (1982) is technically possible, and presence or absence of eye movements can be established (Dogtrop et al., 1990, Swartjes et al., 1990). Between 25 and 30 weeks of gestation, a linkage has been demonstrated between fetal eye movements and fetal heart rate patterns and between fetal body movements and heart rate patterns, but not between fetal eye and body movements (Dogtrop et al., 1990). There is a preference for eye or body movements to occur simultaneously with fetal heart rate pattern B, although the linkage is then still far from complete. This is in agreement with a study by Visser et al (1987), who investigated state variables at 30-32 weeks' gestation. They also report a higher incidence of fetal eye and body movements during heart rate pattern B when compared with heart rate pattern A. Similarly, at a gestational age of 32 weeks a higher percentage of coincidence of 1F to 4F than can be expected by chance, has been found (Swartjes et al., 1990).

2.1.3 FETAL BEHAVIOURAL STATES

According to Prechtl et al. (1985), who studied full-term and preterm low-risk neonates, behavioural states are temporary stable conditions of neural and autonomic functions known as sleep and wakefulness. Fetal behavioural states have first been described by Nijhuis et al. in 1982. In the human fetus, behavioural states are present when the following criteria are met: a) particular conditions of the state variables recur in specific, fixed combinations; b) these combinations are temporarily stable; c) there are clear state transitions which do not last longer than 2-3 minutes (Nijhuis, 1982). In particular, this phenomenon of alignment between the variables at the transitions has been found to develop at around 36-38 weeks' gestational age in the preterm neonate (Prechtl, 1985). Other studies have confirmed the development of fetal behavioural states at 36-38 weeks' gestation in fetuses from multiparae (Rizzo et al., 1988) and nulliparae (Van Vliet et al., 1985b, Van Woerden et al., 1989), states appearing at a somewhat later gestational age in the fetuses of nulliparae. Fetuses from multiparous women spend more time in state 1F when compared with nulliparous pregnancies, whereas the other percentages of state do not differ (Van Woerden et al., 1989). Swartjes et al. (1990) demonstrated that at 38 weeks' gestation coincidence of 1F to 4F had increa-

sed to 80% and true behavioural states were found in half of the recordings; they did not differentiate between multiparous and nulliparous gravidae. Furthermore, they observed that for transitions from 1F to 2F, FHR changed as first or second parameter, while for transitions from 2F to 1F it changed relatively late. For eye and body movements there did not appear to be a preferred sequence. It is therefore suggested that motility and heart rate are regulated separately by the fetal central nervous system.

2.2 FETAL BREATHING MOVEMENTS; FETAL PULMONARY DEVELOPMENT

2.2.1 FETAL BREATHING MOVEMENTS

Approximately 100 years ago, Ahlfeld (1905) was the first to hypothesise the existence of human fetal breathing movements following observation and palpation of the human maternal abdominal wall. It took, however, many years before this theory was generally accepted and proven. Direct information regarding the existence of fetal breathing movements was obtained in experiments on exteriorised lamb fetuses (Dawes et al., 1972). With the development of sonographic equipment, the presence of fetal breathing has also been established in the human species and this phenomenon is still being investigated in many centres (Dawes, 1974, Maršál, 1977, Natale, 1980, Roberts et al., 1980, Trudinger et al., 1980, Nijhuis et al., 1983, Harper et al., 1987).

The evaluation of human fetal breathing movements usually takes place by counting and describing these movements from real time images, although some authors use a tracking device or time distance recorder in an attempt to more accurately quantitate breathing movements (Maršál, 1978, Adamson et al., 1983). Adamson et al. (1983) have found a good correlation between incidence records made by an observer and the data obtained by a tracking device. The use of an electronic movement detector may give rise to false fetal breathing movement signals, so that its application may be prone to pitfalls (Maršál, 1977). Observation by real-time ultrasound seems so far a reliable approach in the establishment of fetal breathing movements. Doppler ultrasound has been used for this purpose as well; Mantell (1980) has recorded thoracic excursions together with fetal heart rate by means of two Doppler fetal heart detectors as well as abdominal excursions together with umbilical vein flow. In this way he was able to observe changes in umbilical

vein flow during fetal breathing.

A fetal breathing movement is usually defined as a downward movement of the diaphragm with concomittant inward movement of the chest wall and outward movement of the abdominal wall (Maršál, 1977, 1978, Patrick et al., 1978, Harper et al., 1987). Fetal breathing is predominantly diaphragmatic. The chest wall plays a rather passive role (Maršál, 1977, Liggins, 1984), although studies in fetal lamb suggest some involvement of the thoracic musculature (Wigglesworth et al., 1979). In the same species, Boddy and Dawes (1975) discern rapid, irregular movements corresponding to the above-mentioned definition, which are present during the great majority of fetal breathing time; a second type is described as very slow gasping of the fetus at a rate of 1-4 breaths per minute and which was seen only about 5% of the time. In the human fetus, Luther et al. (1984) describe deep and shallow fetal breathing: the first type is associated with both chest and abdominal wall movements, the latter type is only associated with movements of the thoracic wall. Maršál (1977) recognises three types of human fetal breathing movements. Usually, smooth movements can be seen corresponding to the above-mentioned definition. Sometimes a prolonged inspiratory phase is noted. Rarely, an interruption appears in the course of inspiration. In the human fetus, gasping is supposed to be associated with fetal distress, hypoxaemia and acidaemia (Boddy and Dawes, 1975, Assali (ed), 1968).

The human fetus displays continuous breathing when the interval between breaths is less than 6 seconds (Harper et al., 1987, Maršál, 1978, Roberts et al., 1979, Patrick et al., 1980a). Few authors apply other criteria with respect to the definition of continuous breathing (Van Vliet et al., 1985a). Data regarding breathing rate during continuous breathing in the human fetus vary from 40 to 70 breaths per minute (Dawes, 1974, Junge et al., 1980, Moessinger et al., 1987, Natale et al., 1988), as had already been noted by Ahlfeld (1905). Apnoeic intervals varying from 65 minutes at 30 weeks to 120 minutes at 38 weeks can be seen in the normally developing fetus (Patrick et al., 1980b).

Fetal breathing activity is episodic in nature with a circadian biological rhythm (Patrick et al., 1978, Roberts et al., 1979). Rest-activity cycles of 1-1.5 hours can be observed in human fetuses over 24 weeks' gestation (Junge and Walter, 1980, Natale et al., 1985). It has been suggested that in fetuses well before term these cycles may be shorter (Visser et al., 1987). Fetal breathing is generally considered as an indicator of fetal well-being (Boddy et al., 1974, Platt et al., 1978) and probably plays a role in preparing the fetus for extra-uterine life (Maršál, 1977, Harper et al., 1987).

Until now, several maternal and fetal factors have been identified that may influence the presence and maybe also the pattern of fetal breathing movements. Among these are gestational age, time of day, maternal food intake and maternal plasma glucose level, maternal end-tidal carbon dioxide level, fetal behavioural state or fetal electrocortical activity, fetal distress, in particular during fetal growth retardation or infection, maternal use of nicotin, drugs or alcohol, and labour. Some of these factors are probably interrelated. Whether fetal breathing can be influenced by external factors like palpation of the maternal abdomen is controversial (Maršál, 1977).

Gestational age

Human fetal breathing movements can be seen from about 10 weeks of gestation onwards (De Vries et al., 1982a). Their incidence increases from 2% at 10 weeks (De Vries et al., 1982b) to 30-40% at 30 weeks and remains fairly constant thereafter (Patrick et al., 1980a, Roberts et al., 1980, Connors et al., 1989). Some authors however could not demonstrate such a correlation (Harper et al., 1987). Early in gestation fetal breathing is usually irregular and sporadic (Natale et al., 1988), from about 28 weeks of gestation onwards it becomes more regular and episodic (Trudinger et al., 1980, Natale et al., 1988). Some authors report a decline in breathing rate with advancing gestational age from 70 per minute at 25-29 weeks to 50 per minute at 38-39 weeks (Patrick et al., 1980, Moessinger et al., 1987), although others report a constant breathing rate throughout the last trimester (Roberts et al., 1979). Trudinger et al. (1980) describe a change in breathing pattern with advancing gestational age. At 20-24 weeks, rapid isolated bursts of 4 to 10 breaths are noted. By 28 to 30 weeks, the episodes of breathing seem to become longer. From 30 to 34 weeks, breathing movements are characterised by a few 'inspiratory' efforts followed by an expiratory recoil. Breathing time is then longer and breathing rate still irregular. After 36 weeks, this pattern of breathing disappears and breathing becomes slower with regular 'in' and 'out' breaths. They therefore state that the type of fetal breathing present is an indication for the degree of fetal maturity.

Diurnal variation

The incidence of fetal breathing movements is subject to diurnal periodicity. The first data regarding this issue stem from fetal lamb laboratory studies, at mid-gestation until term. A minimum in fetal breathing incidence during the early hours of the morning, gradually rising to a maximum shortly after dusk has been reported (Boddy and Dawes, 1975). In the human fetus at 20-22

weeks, the highest fetal breathing incidence has also been observed during afternoon and evening with a peak incidence up to 13% (De Vries et al, 1987). Later in gestation, the diurnal variation shows a different pattern. In fetuses beyond 30 weeks of gestation fetal breathing movements diminish over the day and reach a minimum incidence of about 10% between 1900 and 2400 hours; they increase between 0400 and 0700 hours while the mother is asleep to a maximum incidence of 45% (Patrick et al, 1980a). Before 30 weeks a similar pattern is seen, but incidence maxima up to 20% are then reached between 2400 and 0800 hours (Natale et al., 1988). One third trimester study, however, reports peak breathing incidences between 1900 and 2200 hours (Roberts et al., 1979).

Maternal food intake and plasma glucose level

Many authors agree that the incidence of fetal breathing movements increases following maternal meals or oral or intravenous glucose administration to the mother (Natale et al., 1980, Luther et al., 1984, Meis et al., 1985, Harper et al., 1987). In the fetal lamb, continuous intravenous glucose administration sufficient to produce significantly higher than physiological fetal glucose concentrations was followed by an increase in fetal breathing movements after a lag time of up to 2 hours (Natale et al., 1980). The nature of fetal breathing did not change. Conversely, during fetal hypoglycaemia following maternal fasting in sheep, fetal breathing movements were reduced or had ceased.

In the human fetus beyond 30 weeks, the incidence of fetal breathing movements increases significantly during the second and third hour following maternal meals (Trudinger et al., 1980, Meis et al., 1985, Natale et al., 1985). Maternal plasma glucose levels increase prior to the increase in fetal breathing movements. At this stage of pregnancy, oral administration of 50 g of glucose to the mother is followed by an increase in the percentage of time spent breathing from 20% to 60%, one hour after maternal peak glucose levels have been reached (Natale et al., 1980). Fetal breathing activity remains elevated during the second and third hour following glucose administration without a change in fetal breathing rate. When the mother is given an intravenous bolus of 25 g of glucose, peak glucose levels are reached within 10 minutes and a peak fetal breathing incidence of 58% is observed 45 minutes later. The degree of fetal breathing stimulation by a 800 kcal maternal meal, by oral glucose administration of 50 g or by intravenous glucose injection of 25 g appears to be very similar (Natale et al., 1980): there is a lag time of about 1 hour between the peak in maternal plasma glucose concentration and the peak in fetal breathing; the increase in fetal breathing activity occurs when mater-

nal plasma glucose levels are falling again. In none of these study designs a change in fetal breathing rate has been established.

Studies on fetal breathing between 24 and 28 weeks of gestation show that following maternal meals only a slight increase of fetal breathing movements can be observed (Natale et al., 1988). Similar observations were made in another study, in which the effect of maternal glucose administration on fetal breathing movements at 24 and 36 weeks was assessed (Meis et al., 1985). In this study, fetal breathing increases after glucose infusion at 36 weeks of gestation, but does not at 24 weeks. Trudinger et al. (1980) describe comparable fetal breathing reactions in a group of fetuses at 20-40 weeks' gestation and add that stimulation of fetal breathing by maternal oral glucose administration does not alter fetal breathing patterns. They report a post-stimulation breathing incidence of 45-72% in fetuses after 30 weeks' gestation. Harper et al. (1987) studied fetuses from 19 to 39 weeks of gestation and found a linear relationship between gestational age and percent time spent breathing after intravenous glucose administration. They suggest that an increase in fetal breathing following glucose administration can already be seen during the early second half of gestation. Their data, however, suggest hardly any breathing response from 20 to 25 weeks' gestation, percentages being in the range of 0-5%. This corresponds to fasting values during this period of gestation (Connors et al., 1989). De Vries et al. (1987) also state that an increase in fetal breathing 60-120 minutes following maternal meals can already be seen as early as 20-22 weeks of gestation. However, they used the period of 120-180 minutes following maternal meals as a reference, which does not necessarily represent the baseline incidence of fetal breathing. An increase of deep breathing as opposed to shallow breathing following oral administration of 75 g of glucose has been observed in fetuses beyond 30 weeks of gestation (Luther et al., 1984). In the same study, a slight increase in fetal breathing rate from 37 to 42 breaths per minute following maternal glucose ingestion, as well as an increase in breathing episode length from 17 to 30 seconds have been described.

From these studies it may be inferred that fetal breathing can be stimulated by means of glucose administration to the mother, and that this response can be measured sonographically from about 25 weeks of gestation onwards. The exact mechanism through which glucose stimulates fetal breathing movements is not known. The time delay between peak maternal plasma glucose levels and peak fetal breathing incidence suggests that some metabolite of glucose may be involved. The most likely mediator in this breathing response seems carbon dioxide, a product of aerobic oxidation of glucose.

Maternal end-tidal carbon dioxide level

The fetal lamb shows increased breathing activity following maternal hypercapnia (Dawes, 1974) and following cerebral ventricular perfusion with bicarbonate (HCO3-) (Hohimer et al., 1983).

Connors studied pregnant women near term and found a relationship between the percentage of time of fetal breathing movements and maternal end-tidal pCO2 (Connors et al., 1988). Conversely, there is a decrease in fetal breathing with maternal hyperventilation. The same authors describe a developmental change in the fetal response to maternal carbon dioxide, which increases from 24 to 30 weeks of gestation with only a limited change thereafter (Connors et al., 1989). During the entire study period, the minimum CO2-level necessary for fetal response appears to remain constant. This observation suggests some form of fetal cerebral maturation of responsiveness to CO2.

Fetal breathing movements have been studied in relation to maternal static and dynamic activity, maternal hyperventilation and maternal hyperoxygenation (Maršál, 1977). An increased incidence of these movements has been found immediately after maternal exercise, whereas movements decrease following hyperventilation and hyperoxygenation. These results are partly in agreement with the hypothesis of a CO2-mediated fetal breathing response, since maternal activity temporarily increases maternal plasma CO2-levels, and maternal pCO2 changes are reflected closely in the fetal pCO2 (Maršál, 1977). It must be kept in mind, however, that maternal exercise might also stimulate fetal breathing incidence by hormonal alterations, for instance increased catecholamine levels (Boddy and Dawes, 1975). The decrease in fetal breathing movements following hyperoxygenation is less clear, since there seems to be no consistent relationship between maternal and fetal oxygen tension (Maršál, 1977). Moreover, it has been demonstrated in fetal lamb studies that hyperoxygenation is not associated with changes in fetal breathing incidence (Boddy and Dawes, 1975).

It seems likely that carbon dioxide is a major mediator in the fetal breathing response to maternal glucose intake. This is in fact not surprising since carbon dioxide also regulates postnatal breathing by acting upon peripheral and central chemoreceptors (Philipson, 1981). It has been shown from studies in fetal lamb that the central (Hohimer et al., 1983) and peripheral (Murai et al., 1985) chemoreceptors are also operative and effective during prenatal life. Postnatally, afferent neuronal input from these chemoreceptors to the respiratory center may result both from a tonic level of carbon dioxide and from phasic changes in carbon dioxide superimposed on the steady state

level resulting from respiration (Philipson, 1981). In the fetal circulation, continuous removal of CO2 via the placenta may diminish these phasic changes (Connors et al., 1988). Other factors influencing fetal breathing may now determine whether the tonic CO2-level present is sufficient to allow an episode of fetal breathing to occur.

Fetal electrocortical activity and fetal behavioural state

Human fetal breathing movements occur more often during fetal low-voltage, high frequency electrocortical activity with rapid eye movements before 36 weeks of gestation, and during fetal behavioural state 2 thereafter (Van Vliet et al., 1985a). These observations are in agreement with animal laboratory data (Maloney et al., 1980). Furthermore, fetal breathing displays a fairly regular character during FBS 1 compared with a more irregular pattern during FBS 2 (Nijhuis et al., 1983). These authors even state that regular fetal breathing is a concomittant of FBS 1. Junge et al. (1980) report a decreased breathing rate during FBS 1 when compared with FBS 2 (50/min and 60/min, respectively). This association seems to be independent from factors like glucose or CO2-level, since both substances have no apparent influence on human fetal behavioural state or state parameters (heart rate variability, gross body movements and rapid eye movements)(Connors et al., 1988). It should, however, be kept in mind that hypercapnia in maternal sheep has been shown to cause an increase in low-voltage electrocortical activity in the fetal lamb (Boddy et al., 1974). Furthermore, administration of glucose to the human neonate leads to an increase in REM-sleep (Trudinger et al., 1980). It is therefore possible that the ultrasonographic methods available do not permit the detection of rapid changes of fetal behavioural state or state-related parameters over short time intervals.

Fetal distress

In fetal distress, especially in the presence of fetal growth retardation or infection, human fetal breathing movements are reduced or even absent (Maršál, 1977, Mantell, 1980). A significant relationship has been found between the presence or absence of fetal breathing movements prior to delivery, and Apgar score, birth weight and mode of delivery (Platt et al., 1978). The exact mechanism through which fetal distress causes diminishment of fetal breathing movements remains unclear. Hypoxaemia and hypoglycaemia have been suggested as possible causes in cases of fetal growth retardation. Both conditions lead to cessation of fetal breathing in the fetal lamb (Boddy et al., 1974). It has been shown that in cases of growth retardation in

the human fetus changes in fetal heart rate pattern, for instance repetitive decelerations, are associated with moderate to severe fetal hypoxaemia, acidaemia, or both. A fetal pO2 in the lower normal range as is found in many growth-retarded fetuses, however, is generally associated with a reactive fetal heart rate pattern (Visser et al., 1990).

Another factor that may compromise fetal well-being is early rupture of membranes with subsequent oligohydramnios. This condition may result in pulmonary hypoplasia, depending in part on the time of onset and duration of the oligohydramnios (Nimrod et al., 1988, Shenker et al., 1991). Fetal breathing has been extensively studied under these circumstances, because interference with fetal breathing movements may be one of the major factors responsible for the development of pulmonary hypoplasia (Wigglesworth et al., 1982, Dorman et al., 1984a, Liggins, 1984). Roberts et al. (1991) found a decrease in fetal breathing movements during the first two weeks following rupture of membranes, with a return to a normal fetal breathing incidence thereafter. Fetal pulmonary hypoplasia may arise if this period of two weeks coincides with a vulnerable period in fetal lung development.

This subject is discussed in more detail in the section on fetal lung development.

Maternal use of drugs, nicotin and alcohol

Maternal intake of drugs like hypnotics and sedatives, and of alcohol and nicotin may cause a decrease in fetal breathing movements (Gennser et al., 1975, Maršál, 1977, Natale, 1980). This suggests that some form of central regulation is involved in fetal breathing. Prostaglandin synthetase inhibitors like indomethacin on the other hand, result in a marked increase in fetal breathing incidence in the fetal lamb irrespective of fetal electrocortical activity (Kitterman et al., 1979, Hohimer et al., 1985). Therefore, one or more components of the prostaglandin system may also play a role in the control of fetal breathing movements.

Labour

According to some authors, fetal breathing movements may be reduced at the onset of labour (Richardson et al, 1979). Others, however, state that this happens only when fetal condition is compromised (Boddy and Dawes, 1975), and suggest that a normal fetal breathing incidence during labour is a reliable indicator of fetal well-being.

In conclusion, the presence or absence of fetal breathing movements seems to be basically determined by fetal electrocortical activity and diurnal periodicity. Rest-activity cycles have been recognised in the fetus in the second half of pregnancy. 'Activity', or low voltage electrocortical activity associated with rapid eye movements (REM-sleep), facilitates fetal breathing, while 'rest' or non-REM-sleep inhibits fetal breathing. Diurnal variations are superimposed on these rest-activity cycles.

Carbon dioxide, which is the end-product of oxidative glucose metabolism, may modify this pattern by acting upon fetal peripheral and central chemoreceptors. So, increased maternal glucose levels may produce an episode of fetal breathing even during 'rest', whereas low plasma glucose levels may lead to apnoea during active sleep. Since maternal plasma carbon dioxide tension increases during slow-wave, non-REM sleep (Natale et al., 1988), this may account for the increase in fetal breathing incidence at night and early morning. Maturation of fetal carbon dioxide receptors throughout gestation may lead to an increasing overall breathing incidence, as well as an increasing response to maternal glucose intake with advancing gestational age. It has been suggested that breathing patterns may maturate as well, although data regarding this issue are scarce.

In stages of prolonged fetal distress, fetal breathing may become too 'expensive' in terms of fetal energy consumption, thus causing diminished incidence or even absence of fetal breathing. Hypoxaemia or acidaemia might mediate this response. Whether the diminished fetal breathing incidence during labour is also due to a degree of hypoxaemia, is not clear. It is likely, however, that still unknown humoral factors are involved in breathing regulation as well, since for instance prostaglandin synthetase inhibitors cause a profound stimulation of fetal breathing. It has been shown that administration of indomethacin to third trimester fetal lambs increases fetal breathing. Prostaglandins have been shown to influence lung fluid and surfactant production in the fetal sheep, and may be involved in fetal breathing regulation as well.

2.2.2 FETAL PULMONARY DEVELOPMENT

Fetal lung growth and maturation

Fetal lung development consists of pulmonary growth and pulmonary maturation, processes that normally take place simultaneously. In literature, there is some confusion in defining these two processes. For the discussion of fetal lung development the following definitions were adopted: Lung growth is due to an increase in cell number. Lung maturation can be divided in i. histological maturation, which is a process of cellular differentiation, and in ii. biochemical maturation, with a concomittant increase in surfactant production in the course of pregnancy.

The human fetal lung grows at a slower rate than the fetal body, so that lung/body weight ratio decreases with advancing gestational age (Cassin et al., 1964, Wigglesworth et al., 1981b). Fetal lung growth can among others be evaluated post-mortally by determining absolute weight (wet or dry), lung weight relative to fetal body weight, concentration of DNA/g of lung tissue, protein content and radial alveolar count (Askenazi et al., 1979, Wigglesworth et al., 1981a, 1981b, Cooney et al., 1982). For the evaluation of lung development most authors use at least two of these parameters. If lung growth is compromised, pulmonary hypoplasia may result. Pulmonary hypoplasia can be unilateral or bilateral, depending on the underlying cause. Rarely, this condition is primary (Friedberg et al., 1974, Swischuk et al., 1979), but usually a form of encroachment upon the fetal lung(s) is present. Pulmonary hypoplasia is a serious condition with a high neonatal mortality (Thibeault et al., 1985, Shenker et al., 1991). In case of survival there is often severe immediate-onset respiratory distress needing high-pressure ventilation (Thibeault et al., 1985), accompanied by haemodynamic complications such as persistent fetal circulation (Friedberg et al., 1974, Swischuk et al., 1979).

In pulmonary hypoplasia absolute and relative weight of the hypoplastic lung are reduced, as well as total DNA/g of lung tissue, total protein content and radial alveolar count. Variability in these parameters can be considerable, because various stages of the condition can be present at birth (Wigglesworth et al., 1981a, 1981b).

Histological changes associated with pulmonary hypoplasia will be discussed later on.

Cellular lung maturation (Emery (ed), 1969, Maloney et al., 1980, Perelman et al., 1980, Pitkin et al., 1986) begins with the embryonic phase. An outgrowth from the ventral wall of the primitive foregut appears when the embryo is about three weeks old. Branching of both main stem bronchi occurs

at 7 weeks of embryonic age. When the embryo is about 8 weeks old (10 weeks gestational age), the embryonic phase blends into the pseudoglandular phase. The lungs now histologically look like a piece of glandular tissue, consisting of a loose mass of connecting tissue with an actively proliferating central lobular mass. Primitive bronchi ramify through these mesenchymal tissues, and some capillaries, arterioles and arteries can be seen. At the 16th week of gestation, all the pre-acinar future conducting airways are formed (Assali (ed), 1968, Maloney et al., 1980). Some time later, at about 18 weeks of gestation, the first signs of the canalicular phase are noted: the relative amount of connective tissue diminishes and the lungs become more vascular. The capillaries are not yet in close contact with the epithelial cells. Pulmonary arteries and arterioles show a compact layer of medial smooth muscle cells; throughout gestation the arteries and arterioles are more muscular than in the adult (O'Neal et al., 1957, Hislop et al., 1972). By 23-26 weeks of gestation, the saccular phase begins, during which the respiratory exchange surface rapidly increases; there is thinning of the epithelium, and subepithelial orientation of the capillary network is noted with the formation of blood-air barriers. Alveoli can already be observed at 28 weeks' gestation, and the alveolar phase of development is clearly present at 36 weeks. New alveolar units are then formed throughout prenatal and neonatal life and until the latter half of the first decade (Maloney et al., 1980).

Pulmonary vascular development parallels airway development (Hislop et al., 1972); data regarding this issue have mostly been obtained in fetal lamb studies. The number of small muscular pulmonary arteries increases with advancing gestational age, thus increasing the total cross-sectional area of the pulmonary vascular bed (Levin et al., 1976). During the same period of gestation, pulmonary vascular resistance decreases. Pulmonary blood flow increases out of proportion to the increase in fetal weight during advancing gestational age (Rudolph and Heymann, 1974), and during the latter half of gestation pulmonary blood flow is relatively high (Cassin et al., 1964). Rudolph and Heymann (1974) describe transient physiological changes in pulmonary vascular resistance in the fetal lamb, with an increase in pulmonary blood flow when pulmonary vascular resistance falls. The major site of pulmonary vascular resistance is in the small muscular arteries and veins (Tod et al., 1991). In fetal lambs it has been shown that this resistance decreases rapidly following expansion of the lungs with N2 or O2 well before term.

Surfactant production, a manifestation of biochemical lung maturation, increases rapidly during the last six weeks of human pregnancy (Nakamura et al., 1988). Detailed discussion of surfactant production and regulation is

beyond the scope of this thesis.

Other aspects of fetal lung development

The fetal lung produces fluid from an early stage (Kitterman, 1984). This subject has been studied mainly in the animal fetus. For adequate development and maturation of the lung both secretion of lung fluid and its retention within the airways are probably necessary (Wigglesworth et al., 1979, 1981, 1982). However, the exact mechanism through which this happens is still unclear. Lung fluid is formed by active transport across pulmonary epithelium into the tracheo-bronchial lumen, where it establishes a positive pressure within the lung (Adzick et al., 1984, Liggins, 1984). Tracheal outflow is retarded by a laryngeal mechanism during apnoea, giving rise to an elevated pressure within the trachea and probably resulting in increased pulmonary distension (Adzick et al., 1984, Harding et al., 1984, Liggins, 1984). When the lung fluid leaves the trachea it is either swallowed or else flows into the amniotic space where it constitutes up to one third of amniotic fluid volume (Adzick et al., 1984).

There is evidence that humoral factors influence lung fluid production. This issue has been studied in detail in fetal sheep (Kitterman, 1984). Lung liquid flow begins to diminish two days prior to delivery and eventually stops probably due to the increase in circulating catecholamines. Most of the fluid is then removed, probably through the pulmonary circulation. Other substances, for instance prostaglandin E2 and arginine vasopressin, appear to be able to influence lung fluid production as well, but it has not been clarified yet whether they play a role in the intact fetus.

The production rate of lung fluid is not influenced by normal pressure changes within the fetal thorax as in fetal breathing movements (Kitterman, 1984). Fetal breathing movements however appear to be involved in the maintenance of pulmonary expansion necessary for adequate pulmonary development (Wigglesworth et al., 1982, Adzick et al., 1984, Kitterman, 1984, Liggins, 1984).

2.2.3 FACTORS INFLUENCING FETAL LUNG GROWTH

Several animal laboratory experiments suggest that hormones have little influence on fetal lung growth when lung weight relative to body weight is considered (Kitterman, 1984). A number of physical conditions have however been identified that play an important role in fetal lung growth, and to some extent in maturation. These will be discussed below.

Intrathoracic space

All abnormalities which result in a smaller than normal intrathoracic cavity can interfere with fetal lung growth and be responsible for the development of fetal pulmonary hypoplasia both in animals and in man (Kitterman, 1984, Liggins, 1984). Among the conditions known in this respect are fetal hydrops, congenital diaphragmatic hernia and skeletal anomalies deforming the thoracic cage (Wigglesworth et al., 1981a). Also rare conditions like amyoplasia of the diaphragm have been identified as a cause of pulmonary hypoplasia. Paralysis of the diaphragm may, apart from limiting intrathoracic space, interfere with fetal breathing movements and this may have an additional negative effect on fetal lung growth (Wigglesworth et al., 1979, Kitterman, 1984, Liggins, 1984), as will be discussed later.

Intrauterine space

An adequate amount of amniotic fluid seems to be important for fetal lung growth (Kitterman, 1984). Of the conditions that cause oligohydramnios, bilateral renal agenesis, obstructive lesions of the urinary tract and early rupture of membranes are the most important (Shenker et al., 1991). In the human fetus, oligohydramnios is usually defined as the absence of amniotic fluid pools of more than 2 cm depth (Nimrod et al., 1988).

The way in which oligohydramnios inhibits lung growth is not yet fully understood. Possible explanations are compression of the fetal chest and abdomen resulting in decreased space for lung growth, restriction of fetal breathing movements and diminishment of the volume of fluid within the fetal lung (Talfryn Thomas, 1974, Kitterman, 1984). According to fetal rabbit experiments, inhibition of fetal breathing is not the predominant cause of pulmonary hypoplasia in these cases (Adzick et al., 1984). This is among others confirmed by human ultrasonographic studies in cases of bilateral renal agenesis, where fetal breathing movements of increased incidence are observed, but neonatal outcome is uniformly poor due to severe pulmonary hypoplasia (Moessinger et al., 1987). Third trimester fetal lamb experiments suggest that oligohydramnios increases spinal flexion, leading to compression of abdomen and lungs, thus causing loss of fetal lung liquid (Harding et al., 1990). In this study, a possible additional role of diminished fetal breathing incidence was not considered.

Bilateral renal agenesis and urinary outflow tract obstruction usually lead to severe oligohydramnios in an early stage of pregnancy. There is invariably concomittant severe pulmonary hypoplasia, and often compression deformities are seen (Potter's facies, limb deformities). Postmortally, in these fetuses very

low lung/body weight ratios are found. Because of the severity of the pulmonary hypoplasia in these cases, it has been suggested that in the normal fetus a still unknown humoral factor, excreted in the fetal urine, may play an important additional role in normal fetal lung growth. Other authors however question this possibility, since the direction of flow of lung is usually outward and it is therefore unlikely that little if any amniotic fluid enters the lung (Talfryn Thomas et al., 1974, Wigglesworth et al., 1981a). Furthermore, in cases of tracheal or laryngeal agenesis, in which no amniotic fluid can reach the lung, near-normal lung development (Talfryn Thomas et al., 1974, Wigglesworth et al., 1982) or even pulmonary hyperplasia has been described (Watson et al., 1990).

Premature rupture of membranes is also a notorious cause of pulmonary hypoplasia, and sometimes compression deformities are seen as well (Talfryn Thomas et al., 1974, Thibeault et al., 1985). However, oligohydramnios due to prolonged amniotic leakage does not invariably lead to pulmonary hypoplasia (Vintzileos et al., 1989). In general, both in the animal and the human fetus the likelihood of developing pulmonary hypoplasia increases with the earlier onset of ruptured membranes and with prolonged oligohydramnios (Nimrod et al., 1984, 1988, Shenker et al., 1991). In both animal and human fetuses, the effect was most pronounced when oligohydramnios began during the canalicular stage of lung development (Wigglesworth et al., 1981b, Nimrod et al., 1984, Moessinger et al., 1986). It is, however, not possible to identify with certainty fetuses that will develop pulmonary hypoplasia on the basis of such data. Cases have been described, in which pregnancy was complicated by oligohydramnios of several weeks' duration, but eventually resulted in the birth of a healthy neonate (Moessinger et al., 1987). Alternatively, pulmonary hypoplasia can result from premature rupture of membranes associated with severe oligohydramnios of as short as 6 days' duration (Thibeault et al., 1985). Also, partial pulmonary hypoplasia with transient respiratory symptoms has been described (Perlman et al., 1976, McIntosh, 1988).

When pulmonary hypoplasia is due to oligohydramnios, there is often a delay in cellular maturation (Wigglesworth et al., 1981a). Histologically, the defect in pulmonary hypoplasia appears to be a deficiency of late fetal development. Bronchi and bronchioli are usually adequately developed. There is however gross retardation in the development of lung parenchyma. In some instances alveoli fail to develop and the entire lung is comprised of primitive tubular structures similar to those found in the pseudoglandular or canalicular phase of gestation. The lung is collapsed and seems to have contained little fluid (Wigglesworth et al., 1981a). The histological appearance of lungs in

pulmonary hypoplasia can vary significantly from one patient to another, depending on the time of onset, duration and nature of the inhibiting factor(s). Due to the delay in cellular maturation the distensiblity of the lung is usually reduced also (Kitterman, 1984).

Abnormalities in the pulmonary vascular bed have been described as well: the total size of the pulmonary vascular bed is reduced (Wigglesworth et al., 1981a) and there are less pulmonary vessels per unit of lung tissue (Levin et al., 1978). Also, an increase in pulmonary arterial smooth muscle is reported, maybe as a result of a normal amount of blood passing through a reduced pulmonary vascular bed (Naeye et al., 1976). The last three findings may account for the fixed high pulmonary vascular resistance that is usually found in neonates with pulmonary hypoplasia.

It is still controversial whether pulmonary hypoplasia is accompanied by a delay in biochemical maturation. Some authors report decreased surfactant levels in hypoplastic lungs comparable to levels found in hyaline membrane disease (Wigglesworth et al., 1981a, Nakamura et al., 1988), whereas others measured adequate values, depending in part on the underlying cause of the pulmonary hypoplasia (Kitterman, 1984). One study even reports accelerated biochemical maturation in the presence of prolonged rupture of membranes (Richardson et al., 1974). However, in this publication no data were presented regarding the severity of the oligohydramnios. It is suggested by Wigglesworth et al. (1981a) that fetal lung growth may be impaired by any influence which reduces thoracic volume, but that maturation arrest is due specifically to loss of the ability of the lung to retain lung liquid. This may explain the immature aspect and low surfactant content of lungs in pulmonary hypoplasia following oligohydramnios, when compared with the usually mature aspect of hypoplastic lungs in diaphragmatic hernia.

By means of ultrasound, attempts have been made to differentiate between human fetuses developing pulmonary hypoplasia and normal fetuses. Among these methods are measurement of thoracic circumference (Nimrod et al., 1986), thoracic-abdominal circumference ratio (Johnson et al., 1987), fetal lung length (Roberts et al., 1990), chest area, chest area minus heart area, chest area/heart area ratio, and chest area minus heart area divided by chest area ratio (Vintzileos et al., 1989). These parameters are useful but late indicators of the presence of pulmonary hypoplasia. Recently it has been suggested that the presence of fetal breathing movements is indicative of normal fetal lung development, and that their absence is a reliable parameter of pulmonary hypoplasia (Blott et al., 1987, 1988). This has however been refuted by others (Fox et al., 1985, Moessinger et al., 1987).

Normal balance of volume and pressure in the lung

As has been mentioned before, fetal lung fluid generates a positive pressure within the lung of the fetal lamb (Adzick et al., 1984, Liggins, 1984). When fetal breathing movements are absent, the pressure in the fetal lamb trachea is even higher, which may be important in regulating the volume of fluid within the lungs. So there is evidence that lung fluid serves as an internal stent for the lung, distending potential airways and stimulating growth and differentiation (Wigglesworth and Desai, 1979, Adzick et al., 1984). Oligohydramnios may increase lung fluid loss by compression of the lungs, thus leading to pulmonary hypoplasia. It has indeed been shown that in oligohydramnios following drainage of amniotic fluid, loss of lung fluid occurs leading to severe pulmonary hypoplasia in the fetal sheep (Harding et al., 1990). Lung fluid production was not affected by the oligohydramnios according to this study.

During breathing movements in the fetal lamb a considerable negative pressure is created on inspiration (Kitterman, 1984), and the volume of fluid within the potential airways and airspaces increases about 20% (Murai et al., 1984). Thus, amplitude of pressure changes as well as tidal volume changes during fetal breathing movements may influence fetal lung development. It seems that integration of fetal breathing movements and fluid secretion by the lungs is necessary for lung growth and differentiation (Wigglesworth et al., 1979).

Fetal breathing movements

Fetal breathing movements of normal incidence and intensity are important for normal lung development (Wigglesworth et al., 1979, Kitterman, 1984). This issue has been discussed earlier.

2.3 FETAL HEART RATE CHANGES AND FETAL ARRHYTHMIAS

Normal variations in heart rate in the second trimester human fetus include episodes of bradycardia of 70-100 bpm lasting a couple of seconds, as well as short episodes of acceleration with heart rates of 160-180 bpm. These episodes increase in frequency as pregnancy advances (Allan et al., 1983). Occasional supraventricular or ventricular extrasystoles are also considered to be part of the normal variation. In the near term fetus, longer periods of bradycardia may be a normal component of fetal heart rate variation. Overnight, fetal heart rates of 95-100 bpm may be observed for as long as 10-20 minutes, and

mean hourly measurements between 2000 and 0800 hours are reported to be less than 120 bpm in 12% of time in these fetuses. This may be even more pronounced if maternal daily heart rate, which partly appears to determine the fetal heart rate 'set-point', is low. Since in near-term fetuses mean daily amplitude of fetal heart rate accelerations is inversely related to mean daily fetal heart rate, individual differences in heart rate as well as heart rate variation may be considerable (Patrick et al., 1982).

When an abnormal fetal heart rate or rhythm is considered, the aforementioned normal fetal heart rate variation, related to gestational age, has to be taken into account. In mid-trimester fetuses, a sustained (several minutes) bradycardia of less than 100 bpm, a sustained tachycardia of more than 180-200 bpm, or more than one in ten irregular beats warrant further analysis since an arrhythmia may then be present (Allan et al., 1983).

The definitive diagnosis of the type of arrythmia present, can best be made by means of M-mode echocardiography (Allan et al., 1983, Silverman et al., 1985, Steinfeld et al., 1986, Reed et al., 1987a, Stewart, 1989). Atrial and ventricular wall motion can thus be recorded simultaneously, allowing a reconstruction of the fetal electrocardiogram. Additionally, simultaneous recordings of atrial wall and atrioventricular or semilunar valve movement can be performed. In early gestation this may provide technical difficulties; pulsed Doppler velocimetry may then be useful in establishing a diagnosis (Chan et al., 1990).

Approximately 2% of pregnancies exhibit a fetal cardiac arrhythmia. For a detailed discussion of all types of fetal arrhythmias the reader is referred to Stewart's thesis (1989). Here, only supraventricular extrasystoles will be considered.

Extrasystoles of atrial and ventricular origin have been described in up to 10% of normal fetuses (Allan et al., 1983) and about 1% of healthy neonates (Southall et al., 1980), the atrial type being the most frequent (Lingman et al., 1986a). Usually, supraventricular extrasystoles are benign and disappear spontaneously in the course of pregnancy or shortly after birth. However, an increased incidence in fetal distress and complications of pregnancy was noted in fetuses exhibiting extrasystoles (Lingman et al., 1986a). Associated structural cardiac abnormalities have also been described (Stewart et al., 1983). Moreover, in a minority of these fetuses supraventricular tachycardia may develop later in pregnancy (Stewart, 1989). Therefore, a careful structural cardiac analysis as well as regular monitoring of heart rhythm seems to be indicated when atrial ectopics are diagnosed.

Supraventricular extrasystoles may be conducted or blocked, depending

on whether the premature atrial pulse is conducted to the ventricles, giving rise to a premature beat, or not. In both cases the arrhythmia usually presents as an irregular heart rhythm. When extrasystoles occur every two or three beats, this is referred to as bigeminy or trigeminy. If blocked ectopics occur every second beat, ventricular rhythm is halved and a bradycardia ensues (Redman, 1958, Harrigan et al., 1977, Webster et al., 1977, Shenker et al., 1979, Crawford et al., 1985, Todros et al., 1990). This condition has to be differentiated from other causes of bradycardia, such as sinus bradycardia, for instance following maternal abdominal wall compression (Hon et al., 1962, Shenker, 1979, Steinfeld et al., 1986), fetal distress or atrioventricular block (Webster et al., 1977, Shenker, 1979, Minagawa et al., 1987, Machado et al., 1988, Todros et al., 1990).

Chapter 3

REPRODUCIBILITY OF CARDIAC FLOW VELOCITY WAVEFORM RECORDINGS

3.1 INTRODUCTION

Reproducibility studies are necessary to appreciate changes in flow velocity waveforms under pathophysiological circumstances. In this thesis, flow velocity waveform recording was carried-out at fetal atrioventricular and outflow tract level. The reproducibility of flow velocity waveform recordings at fetal cardiac outflow tract and ductus arteriosus level was recently established on the same equipment as used in the present study (Groenenberg et al., 1991). Subchapter 3.2. will therefore deal with the reproducibility of waveforms collected at atrioventricular level.

3.2 REPRODUCIBILITY OF FETAL CARDIAC FLOW VELOCITY WAVEFORMS AT ATRIOVENTRICULAR LEVEL

K. van der Mooren*, J.W. Wladimiroff* and W.G.J. Hop**
*Department of Obstetrics and Gynaecology, **Department of Biostatistics, Erasmus University, Rotterdam, The Netherlands
(submitted)

INTRODUCTION

Fetal Doppler echocardiography is increasingly being used in the evaluation of fetal heart function both in normal and abnormal circumstances. Although it has generally been recognised that Doppler flow measurements may give rise to errors in velocity calculations, few reports have so far been published concerning the reproducibility of fetal intracardiac Doppler measurements. Analysis of flow velocity integral measurements in the fetal cardiac outflow tracts showed a low interobserver variability in one study (Kenny et al., 1986). Another study regarding the reproducibility of ultrasonic measurement of fetal cardiac haemodynamics (Beeby et al., 1991) showed a high interobserver variability for both cross-sectional valve area and Doppler flow

velocity measurements, as well as a high intraobserver variability for cross-sectional valve area measurements. Intra-observer variability for Doppler flow velocity measurements was moderate. A study regarding the intraobserver variability of fetal outflow tract and ductus arteriosus flow velocity recordings was recently performed in our Department (Groenenberg et al., 1991). The parameters studied were peak systolic velocity, time-averaged velocity, acceleration time, acceleration velocity and area-under-curve. The coefficients of variation within patients between recordings were ≤7% for peak systolic velocity, time-averaged velocity and area-under-curve at all three sites. The coefficients of variation within patients between analyses were ≤3% for each of these parameters. Acceleration time showed a moderate reproducibility in both outflow tracts whereas the variation between tests was larger for the ductus arteriosus. Acceleration velocity showed a poor reproducibility at all sites.

In the present study, the intraobserver variability between tests within patients and between analyses within tests was established for flow velocity waveform recordings at fetal mitral and tricuspid valve level.

MATERIAL AND METHODS

A total of 25 women consented to participate in the study. Normal pregnancy was defined by a normal fetal biparietal diameter and birthweight between the 5th and 95th percentile according to Kloosterman's tables, corrected for maternal parity and fetal sex (Kloosterman, 1970). The pregnancy duration was determined from the last menstrual period and confirmed by ultrasonic measurements of the biparietal diameter between 14 and 18 weeks of gestation. The median maternal age was 29 yr (range 20-37 yr), the median parity was 1 (range 0-6).

A combined mechanical sector scanner and pulsed Doppler system (Diasonics CV 400, Milpitas, CA) with a carrier frequency of 3.5 and 3.0 MHz was used for blood flow velocity measurements at the mitral and tricuspid valve. The sector scanner operates at power outputs less than 100 mW/cm^2 spatial peak/temporal average in both imaging and Doppler modes by manufacturers' specifications. Two dimensional imaging was used to ensure the correct position of the pulsed Doppler gate both before and after each Doppler tracing was obtained. Maximum flow velocity waveforms from the mitral and tricuspid valve were recorded from the four chamber view. The Doppler sample volume was placed immediately distal to the valve leaflets. The Doppler sample volume length ranged between 0.1 and 0.4 cm. Doppler tracings were accepted when the angle between the Doppler cursor and the

assumed direction of flow was 10 degrees or less. Doppler studies were performed by one examiner (K.v.d.M). All blood flow velocity waveforms were obtained during fetal apnoea with the patient in a semirecumbent position, and stored on videotape. For both valves, peak-E wave, peak-A wave and time-averaged velocities as well as period time were studied. From hardcopies the analysis of four consecutive waveforms was carried out using a microcomputer (Olivetti M240, Scaramagno, Italy) linked to a graphics tablet. Resolution of the graphics tablet was 0.05 mm. The analysing programme uses 400 datapoints to describe the four waveforms on one hardcopy. Resolution of the analysing programme was 0.325 mm for the x-axis and 0.5 mm of the y-axis of one hardcopy. Flow velocity waveform analysis consisted of tracing the outer border of the densest part of the Doppler spectrum envelope of each waveform with a cursor and defining the onset, both maxima and the end of the waveform. Peak-E and peak-A wave velocities were defined by the top of the densest part of the Doppler spectrum envelope. Time-averaged velocity was calculated by dividing the sum of velocities over one period time by the number of datapoints.

Reproducibility study.

In each patient Doppler recordings were performed twice at both valves, with a time delay between the recordings of approximately 15 minutes. Of each recording two hardcopies were made. These hardcopies did not reveal the identity or gestational age of the patient, nor the date or time of recording. After collecting the hardcopies, they were shuffled in a random order and all analysed in one session. Both Doppler recording and waveform analysis was performed by one investigator (K.v.d.M.). Statistical analysis consisted of Nested analysis of variance to separate the total variation in components due to differences between patients, differences between repeated tests within patients and differences between analyses of hardcopies. The level of statistical significance was set at 0.05.

RESULTS

Poor quality flow velocity waveforms were obtained in two patients in one or both recordings at both valves. To exclude any possible difference in outcomes between tests arising from discrepant fetal heart rates, analyses were only performed if fetal heart rates at the two tests differed less than 5 bpm. This was based on earlier data suggesting fetal heart rate dependency of flow velocity parameters obtained at atrioventricular level. This criterium led to the exclusion of another two patients, leaving 21 women for further analysis. The

success rate in recording flow velocity waveforms was identical for both valves, probably because both are obtained from the four chamber view without changing transducer position. Table 3.1 gives standard deviations corresponding to the three sources of variation for each vessel.

Table 3.1. Standard deviations (coefficients of variation between parameters) derived from analyses of variance. SDp corresponds to differences between patients, SDt corresponds to differences between repeated tests within patients and SDa corresponds to differences between analyses of hardcopies.

mitral valve

	peak-E wave velocity (cm/s)	peak-A wave velocity (cm/s)	time-averaged velocity (cm/s)
SDp*	5.6 (16%)	3.3 (7%)	2.2 (13%)
SDt*	1.0 (3%)	1.1 (2%)	0.4 (2%)
SDa*	0.4 (1%)	0.5 (1%)	0.4 (2%)

tricuspid valve

	peak-E wave velocity (cm/s)	peak-A wave velocity (cm/s)	time-averaged velocity (cm/s)
SDp*	7.2 (19%)	5.9 (12%)	2.9 (15%)
SDt*	1.5 (4%)	1.3 (3%)	0.6 (3%)
SDa*	0.5 (1%)	0.6 (1%)	0.5 (2%)

* The SDp and SDt components were significantly ($p<0.001$) greater than zero in all instances

For none of the parameters did the standard deviations corresponding to the two consecutive tests significantly correlate with gestational age. This is shown for peak-E wave velocity at mitral level in Figure 3.1. The regression lines between the differences in period time between tests and the standard deviations between tests were also calculated for both valves in all patients; no significant relationship could be found. In Figure 3.2 this is shown graphically for peak-E wave velocity at mitral level.

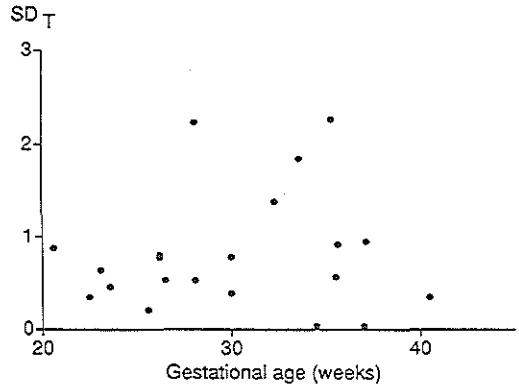

Figure 3.1. Standard deviations of both testoutcomes of peak-E wave velocity at mitral level versus gestational age (weeks) of 21 patients. Each datapoint is obtained by averaging the outcomes of two separate hardcopy readings (r=0.10, p=0.7).

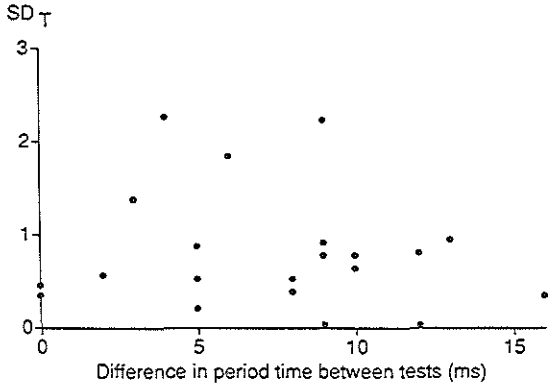

Figure 3.2. Standard deviations of both testoutcomes of peak-E wave velocity at mitral level versus the difference in period time (ms) between both readings of 21 patients. Each datapoint is obtained by averaging the outcomes of two separate hardcopy readings (r=-0.11, p=0.62).

DISCUSSION

The present results show that analyses from hardcopies can be performed with a high reproducibility for peak-E, peak-A and time-averaged velocities at atrioventricular level, the coefficient of variation being 2% or less. Also the variation between repeated tests at an interval of 15 minutes is small for these parameters (≤4%). Since the E/A-ratio is obtained by dividing peak-E by peak-A wave velocities, this parameter was not separately analysed. No considerable differences in period time between both tests were present, and it was shown by means of regression statistics that these minor variations in fetal heart rate were not responsible for the small variation between tests. Variability of the parameters appeared to be gestational age independent in this study.

So far, little information has been published regarding the intra-observer variability of fetal cardiac Doppler flow velocity measurements. Kenny et al. (1986) found an acceptable inter-observer variability for flow velocity integral and cross-sectional valve area measurements. Beeby et al. (1991) studied both inter and intraobserver variability of cross-sectional valve area and Doppler flow velocity measurements. They concluded that the inter-observer variability was unacceptably high for both measurements, whereas the reproducibility of cross-sectional measurements within observers was also poor. The intra-observer variability for cardiac Doppler flow velocity measurements was however better and improved further with increasing experience of the investigator. It should be noted that in this study Doppler interrogation angles of up to 30 degrees were accepted. Since this may lead to flow velocity measurement errors of up to 10%, this may have accounted for part of the reported variability. Furthermore, differences in fetal heart rate between observers and between measurements were sometimes large. It was shown by us (this thesis, chapter 4.1) that atrioventricular flow velocity parameters are fetal heart rate dependent within the normal fetal heart rate range. Therefore, as far as atrioventricular flow velocity measurements are concerned, differences in fetal heart rate between measurements may have contributed to the variability in their study.

In our study, the intra-observer variability for atrioventricular Doppler flow velocity parameters was very low. This may in part be explained by the fact that care was taken to keep the Doppler interrogation angle within 10 degrees. Furthermore, virtually no differences in period time existed between measurements.

In conclusion, measurement of fetal cardiac Doppler flow velocities seems a reliable procedure in the hands of an experienced investigator, provided that possible sources of variability are recognised and controlled as

far as possible. Cross-sectional valvular measurements, however, probably have a poor reproducibility because the resolution of the current sonographic equipment is close to valvular diameters. Also, it is assumed in volume flow calculations that the fetal cardiac valves are circular, which is not necessarily so. Further, an error in diameter measurement will be squared in volume flow measurement, thus augmenting the inaccuracies even more. This implies, that at this moment fetal cardiac volume flow measurement should be considered unreliable.

Chapter 4

FETAL INTRACARDIAC DOPPLER FLOW MEASUREMENTS

4.1 NORMAL FETAL INTRACARDIAC DOPPLER FLOW VELOCITY WAVEFORMS

4.1.1 INTRODUCTION

Flow velocity waveform recording at atrioventricular and outflow tract level can now be carried-out as early as 11 weeks of gestation using transvaginal transducers (Wladimiroff et al., 1991) and as early as 14 weeks using the transabdominal approach (Wladimiroff et al., personal communication). Some authors have attempted to calculate fetal cardiac volume blood flow by including valve area measurements (Allan et al., 1987, De Smedt et al., 1987, Reed et al., 1987b). Fetal cardiac volume flow measurement is however prone to errors, partly because the small valvular diameters give rise to relatively large errors in area calculation (Eik-Nes et al., 1984), and partly because it is assumed that fetal cardiac valves are circular (Reed et al., 1986a, Allan et al., 1987). In one study a high inter- and intra-observer variability for cardiac volume flow measurements have been established, which was mainly due to errors in area measurement (Beeby et al., 1991).

In this thesis fetal cardiac haemodynamics was studied semi-quantitatively by analysing flow velocity waveforms only. At outflow tract level, peak systolic velocity, time-averaged velocity and acceleration time can be calculated. Peak systolic velocity is related to stroke volume (Hatle and Angelsen, 1981), time-averaged velocity may thus in some way reflect volume flow. Acceleration time has been shown to be related to mean arterial pressure (Machado et al., 1987) and hence to ventricular afterload (Sonnenblick and Downing, 1963).

At atrioventricular level, peak-E wave velocity, peak-A wave velocity, time-averaged velocity and E/A-ratio can be studied. Peak-E wave velocity reflects rapid ventricular filling, whereas peak-A wave velocity represents atrial contraction. The E/A-ratio is used as a measure of ventricular compliance (Reed et al., 1986b). Under normal fetal heart rate conditions, peak-A wave velocity is usually higher than peak-E wave velocity, resulting in E/A-

ratios lower than 1 (Reed et al., 1986b). This suggests a reduced ventricular compliance when compared with the adult, as had already been shown in fetal and adult animal studies (Romero et al., 1972). E/A-ratios increase with advancing gestational age to values above 1 after birth, reflecting increasing ventricular compliance (Reed et al., 1986b). In the human adult, aging is associated with a decrease in E/A-ratio (Labovitz and Pearson, 1987) indicating decreasing ventricular compliance. In isolated cat papillary muscle experiments, it has been shown that ventricular relaxation is not a mere passive recoil of the myocardium, but an active process that is determined by the entire cardiac loading pattern (Gillebert et al., 1989). Postnatal human cardiac Doppler studies also describe ventricular relaxation as an active process (Labovitz and Pearson, 1987) and show that heart rate, ventricular systolic function and diastolic load influence time course and rate of lengthening of cardiac muscle (Bahler et al., 1983). The E/A-ratio therefore probably depends in part on ventricular preload as well, as has been suggested in other postnatal human Doppler flow studies (Channer et al., 1986, Choong et al., 1987). Furthermore, E/A-ratio may to some extent be determined by ventricular afterload and contractile state. To our knowledge, no quantitated data on fetal ventricular relaxation and factors influencing it, have been reported.

A prenatal right ventricular dominance has been established in many species including man (Rudolph and Heymann, 1974, Kenny et al., 1986, Reed et al., 1987b). In the ovine fetus it was shown that right ventricular geometry is different from that of the left ventricle, resulting in a higher right ventricular systolic wall stress (Wright Pinson et al., 1987). This might explain a greater right ventricular sensitivity to arterial pressure. On the basis of these data it can be hypothesised that right and left ventricular systolic and diastolic function may differ in the fetus. In the lamb fetus different right and left ventricular responses to changes in preload and afterload have been observed when stroke volume is considered (Reller et al., 1987).

The next study discusses flow velocity waveforms at the four fetal cardiac valves in relation to fetal heart rate and describes gestational age-related changes of the aforementioned parameters between 18 and 38 weeks of pregnancy. Ductus arteriosus flow velocity waveforms in relation to intrinsic variables during the second half of pregnancy are considered in chapter 5.

4.1.2 FETAL ATRIOVENTRICULAR AND OUTFLOW TRACT FLOW VELOCITY WAVEFORMS DURING THE NORMAL SECOND HALF OF PREGNANCY

K. van der Mooren*, L.G. Barendregt** and J.W. Wladimiroff*
*Department of Obstetrics and Gynaecology, **Department of Biostatistics, Erasmus University, Rotterdam, The Netherlands
Published in Am. J. Obstet. Gynecol. 1991, 165, 668-674.

INTRODUCTION

Transabdominal Doppler techniques can be used to determine flow velocities at the level of the human fetal heart from about 16 weeks of gestation onwards (Reed et al., 1986a, Allan et al., 1987). This allows semi-quantitative information about fetal cardiac function to be obtained in a non-invasive way. Both cross-sectional and serial measurements of cardiac flow velocities have been performed by several centres at different gestational ages (Kenny et al., 1986, Reed et al., 1986b, 1987b, Hata et al., 1987). However, to our knowledge a detailed analysis of waveforms collected from all four fetal cardiac valves has never been carried-out in a longitudinal setting. Moreover, few data have been published concerning the influence of variables such as fetal heart rate on fetal cardiac flow velocity waveforms.

The objective of the present study was twofold:

1. To establish the distribution of: a.peak systolic velocity, acceleration time and time-averaged velocity in the fetal cardiac outflow tract (ascending aorta and pulmonary artery); b.time-averaged velocity, peak-E wave velocity, peak-A wave velocity and E/A-ratio at atrioventricular level (mitral valve and tricuspid valve) between 18 and 38 weeks of pregnancy;
2. To determine whether there is fetal heart rate dependency for one or more of the aforementioned parameters within the physiological fetal heart rate range (i.e. 110-160 bpm), and if so, to establish the relationship between fetal period time (the reciprocal of heart rate) and the parameter concerned.

MATERIAL AND METHODS

A total of 40 women with normal singleton pregnancies consented to participate in the study. The study protocol was approved by the Hospital Ethics Committee. Fetal cardiac Doppler examinations were carried out at 3 to 4 weeks intervals between 18 and 38 weeks of gestation. The first examination was performed between 18 and 22 weeks of gestation.

Normal pregnancy was defined by a normal fetal biparietal diameter and birthweight between the 5th and 95th percentile according to Kloosterman's tables, corrected for maternal parity and fetal sex (Kloosterman, 1970). The pregnancy duration was determined from the last menstrual period and confirmed by ultrasonic measurements of the biparietal diameter between 14 and 18 weeks of gestation. The median maternal age was 29 yr (range 18-41 yr), the median parity was 1 (range 0-6).

A combined mechanical sector scanner and pulsed Doppler system (Diasonics CV 400, Milpitas, CA) with a carrier frequency of 3.5 and 3.0 MHz was used for blood flow velocity measurements in the ascending aorta, pulmonary artery, and at the mitral and tricuspid valve. The sector scanner operates at power outputs less than 100 mW/cm^2 spatial peak/temporal average in both imaging and Doppler modes by manufacturers' specifications. Two dimensional imaging was used to ensure the correct position of the pulsed Doppler gate both before and after each Doppler tracing was obtained. Maximum flow velocity waveforms from the ascending aorta were recorded from the "five chamber view" (Figure 4.1). Maximum flow velocity waveforms from the pulmonary artery were collected from the conventional short axis view (Figure 4.2). Maximum flow velocity waveforms from the mitral and tricuspid valve were recorded from the four chamber view (Figure 4.3).

At all sites, the Doppler sample volume was placed immediately distal to the valve leaflets. The Doppler sample volume length ranged between 0.1 and 0.4 cm. Doppler tracings were accepted when the angle between the Doppler cursor and the assumed direction of flow was 10 degrees or less. Doppler studies were performed by one examiner (K.v.d.M). All blood flow velocity waveforms were obtained during fetal apnoea and stored on videotape. From hardcopies the analysis of four consecutive waveforms was carried-out using a microcomputer (Olivetti M240, Scaramagno, Italy) linked to a graphics tablet. The following parameters were calculated:

- in the two outflow-tract vessels: peak systolic velocity (cm/s), acceleration time (ms) and time-averaged velocity (cm/s); also the ratios of these parameters at both sites were calculated, as well as the period time (ms).
- at atrioventricular level: time-averaged velocity (cm/s), peak velocities of E- and A-wave (cm/s), E/A-ratio and period time (ms); also, the ratio of tricuspid to mitral time-averaged velocity was included.

Peak velocities were measured from the zero-line to the highest point of the Doppler velocity peak. Acceleration time was measured as the time between the onset of ejection and the peak of velocity (Machado et al., 1987). Time-

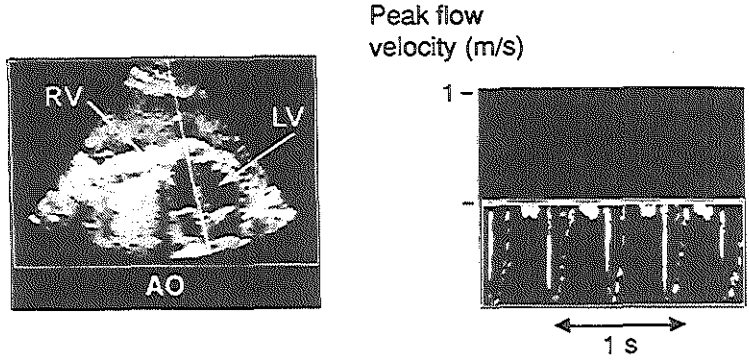

Figure 4.1. Two-dimensional five chamber view of the fetal heart with Doppler flow velocity waveform tracing from the ascending aorta (AO) at 36 weeks of gestation. LV= left ventricle; RV= right ventricle.

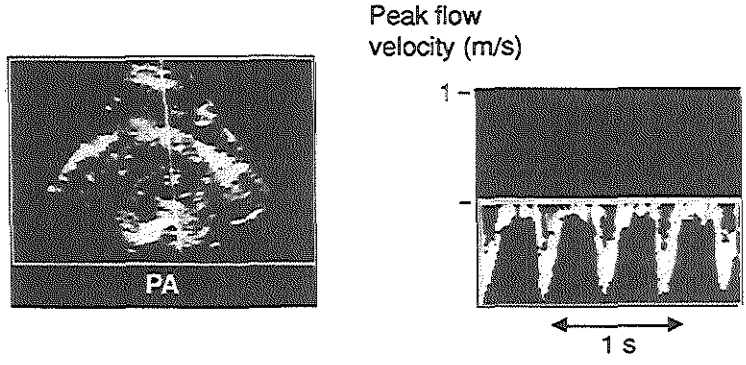

Figure 4.2. Two-dimensional short axis view of the fetal heart with Doppler flow velocity waveform tracing from the pulmonary artery (PA) at 36 weeks of gestation.

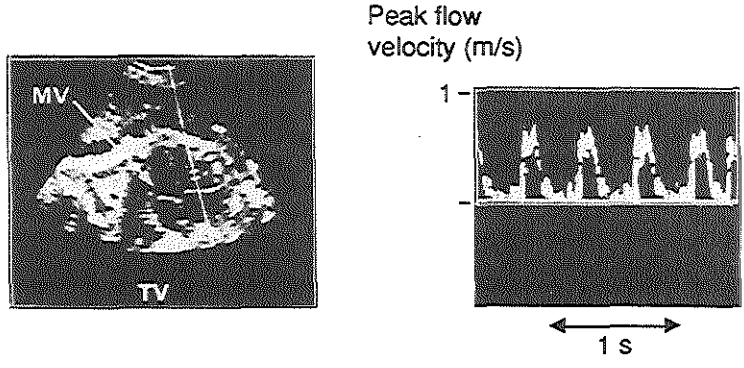

Figure 4.3. Two-dimensional four chamber view of the fetal heart with Doppler flow velocity waveform tracing at tricuspid valve level (TV) at 36 weeks of gestation. MV= mitral valve.

averaged velocity was calculated as area-under-curve divided by period time.

All Doppler studies were performed two hours following breakfast or lunch with the patient in a semi-recumbent position. The duration of one investigation never exceeded 30 minutes. Statistical analysis included assessment of the relationship between all parameters studied and gestational age by repeated measurements analysis of variance, for which the BMDP programme 5V (BMDP statistical software manual, vol.11, 1988, University Press of California) was used. P-values were determined by means of the sign-test. The relationship between each parameter and fetal heart rate was studied as follows. For every patient, the available data were interpolated in a linear fashion to a gestational age of 30 weeks to rule out the influence of gestational age on the parameters. The reason for selecting 30 weeks was determined by the range of gestational ages (18-38 weeks) studied. For each adjusted parameter and period time the correlation coefficient was then calculated, and the corresponding p-value established. Left-to-right differences of the means per fetus were assessed using the paired t-test. The lower level of statistical significance was set at 0.05.

RESULTS

The success rate for obtaining good-quality flow velocity waveforms was 99% for the ascending aorta, 97% for the pulmonary artery, 99% for the mitral valve and 97% for the tricuspid valve. In 4% of the mitral valve measurements and 18% of the tricuspid valve measurements it was not possible to separate E- and A-wave. This was more common with high-normal fetal heart rates. In these cases analysis of the waveform only included time-averaged and peak-A wave velocities. In each patient it was possible to obtain at least four serial recordings at all cardiac levels during the study period. On average, five investigations were performed in each pregnancy. Serial recordings of one particular valve or vessel were never longer than six weeks apart. In total, 233 studies were performed at a mean gestational age of 28.7 weeks (SD 5.8 weeks).

The relationship between any of the flow velocity waveform parameters and gestational age was approximately linear for each patient. It also appeared, that the regression lines, by which the relation between parameter and gestational age for each of the patients could be described, differed significantly from patient to patient with respect to both the intercept and the slope. Therefore, the following statistical model was adopted as the basis for the calculation of approximate 95%-prediction-bounds for each of the parameters, when the gestational age is known:

y= a + b(x - 30) + e, with y= the parameter concerned; x= gestational age (weeks); a= the intercept of the regression line; b= the slope of the regression line; e= an error term.

Thus, for each of the parameters a regression line was constructed with its 2.5% and 97.5% confidence limits. The values for a, b and e for each flow velocity waveform parameter, as well as the p-values of the slopes are listed in Table 4.1.

Period time in this study ranged from 361 to 535 ms, corresponding to a fetal heart rate of 166 to 112 bpm, respectively. Average period time showed a significant increase with advancing gestational age, the regression equation being y= 380.2 + 1.33x ($p<0.0001$), with y= average period time (ms) and x= gestational age (weeks).

In those fetuses in which it was not possible to separate E- and A- wave at mitral level, the average period time (± 1SD) was 393 ± 20 ms, compared to an average period time of 425 ± 16 ms in fetuses with distinct mitral E- and A-waves. At tricuspid level these figures were 400 ± 22 and 423 ± 18 ms, respectively.

All parameters studied showed a significant increase with advancing gestational age. Peak systolic and time-averaged velocity as well as acceleration time showed higher values in the aorta compared with the pulmonary artery in most fetuses. The ratio for pulmonary to aortic peak systolic velocity did not change during the second half of pregnancy, with a mean ratio of 0.8 ± 0.0003 (1SD). The ratio for pulmonary to aortic time-averaged velocity, however, increased with advancing gestational age ($p=0.0005$), as did the ratio for pulmonary to aortic acceleration time ($p=0.0001$). Time-averaged velocity, peak-A wave and peak-E wave velocities were higher at tricuspid than at mitral level ($p<0.0001$). E/A-ratio was higher at mitral than at tricuspid level ($p<0.03$). The ratio for tricuspid to mitral time-averaged velocity did not change with advancing gestational age, the mean ratio being 1.097 ± 0.001 (1SD). These results are also summarised in Table 4.1. In Table 4.2 mean absolute differences (± 1SD) between all right and left heart parameters are presented with their corresponding level of significance.

At outflow tract level, no correlation could be demonstrated for any of the parameters and period time. The correlation coefficients at atrioventricular level with their respective p-values are presented in Table 4.3; negative correlations were found for time-averaged velocity and peak-A wave velocity at both sites. A positive correlation existed between period time and peak-E wave velocity as well as E/A-ratio.

Table 4.1. Absolute values and standard errors of the parameters determining the regression lines for all flow velocity parameters with gestational age according to the general formula: y=a+b(x-30)+e.

	a	b	Sa	Sb	Error	p-value
PA PSV (cm/s)	60.1	1.18	6.9	0.06	10.4	<0.0001
PA TAV (cm/s)	21.7	0.53	1.0	0.02	2.4	<0.0001
PA ACT (ms)	51.7	1.96	25.9	0.25	19.8	<0.0001
AO PSV (cm/s)	74.8	1.35	13.9	0.08	21.8	<0.0001
AO TAV (cm/s)	24.1	0.46	2.3	0.01	3.9	<0.0001
AO ACT (ms)	60.6	1.37	12.4	0.10	19.6	<0.0001
MV TAV (cm/s)	17.4	0.30	0.8	0.01	1.3	<0.0001
MV PEV (cm/s)	34.4	0.76	5.5	0.08	11.9	<0.0001
MV PAV (cm/s)	47.4	0.17	5.3	0.06	12.9	0.0008
MV EAR	0.73	0.01	0.001	0.00001	0.005	<0.0001
TV TAV (cm/s)	19.0	0.33	1.05	0.006	1.7	<0.0001
TV PEV (cm/s)	39.6	0.85	4.5	0.09	10.6	<0.0001
TV PAV (cm/s)	54.0	0.31	3.8	0.06	12.6	<0.0001
TV EAR	0.74	0.013	0.0006	<0.00001	0.002	<0.0001
PA PSV / AO PSV	0.80	0.001	0.0003	0.00002	0.03	1.0
PA TAV / AO TAV	0.91	0.006	0.001	0.00005	0.007	0.0005
PA ACT / AO ACT	0.85	0.014	0.003	0.00003	0.009	<0.0001
TV TAV / MV TAV	1.1	-0.000	0.001	0.000006	0.009	0.9

Abbreviations: PSV=peak systolic velocity; TAV=time-averaged velocity; ACT=acceleration time; PEV=peak-E wave velocity; PAV=peak-A wave velocity; EAR=E/A-ratio; PA=pulmonary artery; AO=ascending aorta; MV=mitral valve; TV=tricuspid valve; Sa=standard error of the intercept; Sb=standard error of the slope; x=gestational age.

Table 4.2: Mean left to right differences for the parameters studied, with their respective levels of significance; the figures are based upon the mean paired differences per fetus (paired t-test).

	ascending aorta	pulmonary artery	difference (absolute)	standard deviation of differences	p-value
mean peak systolic velocity (cm/s)	73.0	58.4	14.6	3.3	<0.001
mean time-averaged velocity (cm/s)	23.4	21.0	2.4	1.4	<0.001
mean acceleration time (ms)	58.5	48.5	10.0	4.3	<0.001

	mitral valve	tricuspid valve	difference (absolute)	standard deviation of differences	p-value
mean time averaged velocity (cm/s)	16.9	18.5	-1.6	0.9	<0.001
mean peak-E wave velocity (cm/s)	33.2	37.2	-4.0	0.4	<0.001
mean peak-A wave velocity (cm/s)	47.0	53.6	-6.6	2.3	<0.001
mean E/A-ratio	0.71	0.69	0.02	0.007	<0.03

Table 4.3: Correlation coefficients and p-levels for the relationship between period time and atrioventricular flow velocity parameters interpolated in a linear fashion to a gestational age of 30 weeks.

mitral valve

	r	p-value
time-averaged velocity (cm/s)	-0.34	0.03
peak-E wave velocity (cm/s)	0.71	<0.001
peak-A wave velocity (cm/s)	-0.32	0.05
E/A-ratio (-)	0.67	<0.001

tricuspid valve

	r	p-value
time-averaged velocity (cm/s)	-0.42	0.007
peak-E wave velocity (cm/s)	0.55	<0.001
peak-A wave velocity (cm/s)	-0.48	0.002
E/A-ratio (-)	0.59	<0.001

DISCUSSION

In the human fetal heart, both right and left ventricle eject in parallel into the systemic circulation: the right ventricle into the ductus arteriosus and descending aorta, the left ventricle into the ascending aorta (Rudolph and Heymann, 1974). Therefore, right and left ventricular output are not necessarily equal. In fact, many fetal echocardiographic studies are indicative of a distinctive right-heart dominance in the human fetus (Reed et al., 1986a, Allan et al., 1987), although this is disputed by some (St. John Sutton et al., 1984).

In this prospective longitudinal study an increase with advancing gestational age was found for all flow parameters concerned. The distribution of the parameters increased towards term, which is in agreement with the increasing variance of biometrical parameters with advancing gestational age. Fetal heart rate showed a significant decline towards term, as has been reported earlier (Kenny et al., 1986).

Cardiac performance is influenced by heart rate, preload, afterload and intrinsic properties of both ventricles. From lamb studies it appears that cardiac function is particularly sensitive to changes in afterload (Gilbert, 1982), which is determined by blood pressure and vascular resistance. The gestational age-related rise in normal peak systolic flow velocity and time-averaged velocity at semilunar level may be accounted for by increased volume flow through the semilunar valves, raised contractility or reduced afterload. Age-related reduction in afterload may occur in the human fetus as

a result of the physiological decrease in placentar vascular resistance as expressed by increased end-diastolic flow velocities in the umbilical artery during the second half of gestation (Trudinger, 1987). Peak systolic velocity correlates to some extent with time-averaged velocity. Since volume flow is equal to mean velocity multiplied by area, the observed increase in peak systolic and time-averaged velocity may also reflect increased left and right ventricular stroke volume and output. The non-invasive nature of human fetal Doppler studies does not allow differentiation between these explanations.

Calculation of volume flow was not attempted, due to the considerable error related to vessel and valve area measurements (Eik-Nes et al., 1984). Therefore, we cannot provide data concerning the presumed right ventricular dominance in the human fetus. The linear increase in peak systolic velocity in both arteries with advancing gestational age is in agreement with other studies, as are the absolute values (Kenny et al., 1986, Reed et al., 1986a, Allan et al., 1987, Hata et al., 1987). Also, time-averaged velocity showed a linear increase with advancing gestational age. These data are in agreement with those presented by Kenny et al. (1986), but at variance with other reports in which at semilunar level no relationship between peak systolic (Allan et al., 1987) and time-averaged velocity (Reed et al., 1986b, Allan et al., 1987) and pregnancy duration could be established. The only explanation for these discrepant findings could be the fact that in the present study only flow velocity waveforms obtained at an interrogation angle of 10 degrees or less were collected. This is in contrast to the other reports in which interrogation angles up to 30 degrees were accepted.

The higher peak systolic and time-averaged velocities in the ascending aorta compared with the pulmonary artery observed in normal pregnancy may be due to the difference in semilunar valve area between the two vessels (Allan et al., 1987). Alternatively, relatively low fetal cerebral vascular resistance with subsequently lower left ventricular afterload may be responsible for the documented difference (Van den Wijngaard et al., 1988). Of interest is that the acceleration time in the pulmonary artery was shorter than in the aorta, which is in agreement with a previous study by Machado et al. (1987). Doppler echocardiographic studies on pulmonary hypertension in adults have demonstrated a close negative correlation between acceleration time and mean arterial pressure in the pulmonary artery as measured by cardiac catheterisation (Kitabatake et al., 1983, Serwer et al., 1986). If a similar correlation is assumed in the normally developing fetus, the difference in acceleration time between the two outflow tract vessels would be in support of a different afterload in the two circuits.

In contrast to Machado et al. (1987) we found an increase in acceleration time with advancing gestational age for both vessels. This is not surprising, since the afterload to both ventricles is mainly determined by placental vascular resistance which is characterized by a fall during the second half of pregnancy (Trudinger, 1987). Moreover, both cerebral vascular resistance (Van den Wijngaard, 1988), which is partly responsible for left ventricular afterload, and pulmonary vascular resistance (Levin et al., 1976) are subject to a reduction during the third trimester of pregnancy. This may explain the ratio increase with advancing gestational age for both pulmonary to aortic time-averaged velocity and acceleration time.

No correlation could be found between period time and any of the outflow tract parameters. This is in agreement with other observations, which show that only in case of abnormally high or low fetal heart rates does the effect of the Frank-Starling mechanism become apparent (Tonge et al., 1986, Reed et al., 1987a).

Time-averaged velocity at tricuspid and mitral level increased with advancing gestational age with higher tricuspid velocities in nearly all fetuses, reflecting a rising ventricular output and/or decreasing afterload and/or improving myocardial contractility during the second half of pregnancy. Whereas similar results with slightly lower absolute values were reported by Reed et al. (1986b) and De Smedt et al. (1987), no such increase was established by Allan et al. (1987). Peak-E wave and peak-A wave velocities as well as E/A-ratios displayed a rise at both mitral and tricuspid level, with absolute values of peak-A and peak-E wave velocities being higher at tricuspid valve level. E/A-ratios were higher at mitral valve level. The increase in peak-E wave velocity and E/A-ratio suggests a shift of blood flow from late towards early diastole as a result of increased ventricular compliance with advancing gestational age. Similar observations have been done by others (Kenny et al., 1986, Reed et al., 1986b). Improvement in atrial contractility may be the cause for the rising peak-A wave velocities. The higher E/A-ratios at mitral level may reflect a relatively lower left ventricular afterload, higher myocardial compliance (Reed et al., 1986b), or both.

Our findings are partly at variance with those reported by others. Reed et al. (1986b) observed an increase of tricuspid peak-E wave velocity and a decrease of mitral peak-A wave velocity with advancing gestational age, while tricuspid peak-A wave velocity and mitral peak-E wave velocity did not show a significant change. Also, the absolute values were lower than observed in the present study. Hata et al. (1987) reported an increase of both mitral and tricuspid peak-A wave velocity during second and third trimester, but did not

study peak-E wave velocities. At first sight these discrepancies seem quite impressive. The possible influence of the use of angle-correction has been mentioned earlier. Moreover, none of the fore-mentioned authors has taken into account the influence of period time on atrioventricular waveforms, which could at least in part explain the observed differences. In the present study, a negative correlation between peak-A wave velocity and time-averaged velocity and period time was established within the normal heart rate range at both atrioventricular valve levels. A positive correlation with period time for peak-E wave velocities and E/A-ratios was found. This indicates, that at lower fetal heart rates blood volume shifts from late to early diastole, resulting in waveforms resembling those documented in older fetuses with more compliant ventricles. Preload changes may also account for this (Choong et al., 1987).

The negative correlation between atrioventricular time-averaged velocity and period time may be explained by changing valve area as has been suggested by Kenny et al. (1987). This could be due to changes in ventricular filling. In conclusion, our results show that the normal second half of pregnancy is characterized by increasing flow velocities at both atrioventricular and outflow tract level, suggesting rising ventricular stroke volume and output and reduction in ventricular afterload. Flow velocity and acceleration time in the ascending aorta suggests a relatively lower afterload to the left ventricle. Transmitral and transtricuspid flow velocities are heart rate dependent.

4.2 FETAL BREATHING AND FETAL CARDIAC HAEMODYNAMICS

4.2.1 INTRODUCTION

Flow studies during breathing have been performed before and after birth, both in animals and in man.

Adult animal experiments

During inspiration a decrease in left ventricular stroke volume and an increase in right ventricular stroke volume and pulmonary blood flow have been found, whereas during expiration the opposite was observed (Brecher and Hubay, 1955). During inspiration, venous return through both superior and inferior vena cava increases due to the fall in pressure around the right heart; with the onset of expiration the return of blood flow is reduced (Brecher and Hubay, 1955, Summer et al., 1979). Thus, changes in venous return account for the

varying right ventricular stroke volume during the respiratory cycle. The findings at left ventricular outflow tract level are more difficult to explain. It has been suggested that a phase lag is responsible for the apparent opposite effect on the left ventricle: during inspiration right ventricular output increases, and after a certain delay this affects left ventricular output. Others hypothesise that during inspiration the capacitance of the pulmonary vessels is increased, thereby reducing the filling of the left ventricle. It may also be possible that the enlarging right ventricle during inspiration compresses the left ventricle, thus decreasing its filling (Summer et al., 1979). These explanations are based on the assumption that the decrease in left ventricular output is due to a decrease in filling. It has also been suggested that left ventricular ejection during inspiration could be impeded by the fall in pressure around the heart relative to the pressure in the aorta, thus increasing left ventricular afterload (Summer et al., 1979).

Fetal animal experiments

During fetal breathing movements relatively large negative intrathoracic pressures are generated (Kitterman, 1984). The volume of fluid within the potential airways then increases by about 20% (Murai et al., 1984); Liggins (1984) demonstrated mathematically how downward movement of the diaphragm with inward movement of the chest can produce an increase in lung volume during inspiration. Furthermore, ventilation of third trimester fetal lamb lungs without oxygenation well before term causes a decrease of pulmonary vascular resistance at the level of the small pulmonary vessels (Tod et al., 1991), thus lowering right ventricular afterload.

Postnatal human blood flow studies

During respiration it was shown that the fall in left ventricular stroke volume during inspiration was mainly caused by a reduction in left ventricular filling (Zoghbi et al., 1990) due to transient inspiratory pooling of blood in the pulmonary veins, while aortic systolic blood pressure changed but little (Ruskin et al., 1973); no convincing evidence for the 'phase lag' theory was found. Pulsed Doppler echocardiography shows that during inspiration early diastolic velocities at mitral level are reduced, while atrial contraction velocity remains unchanged (Dabestani et al., 1988). Others report decreased Doppler velocities of both early and late left ventricular filling on inspiration, with increased velocities at tricuspid level (Zoghbi et al., 1990).

Human fetal Doppler flow studies

Human fetal haemodynamics change during fetal breathing movements. Mantell (1980) observed fetal breathing movements with Doppler ultrasound techniques and noted a slowing of umbilical venous blood flow velocity during fetal 'inspiration'. Trudinger (1987) describes a decrease of peak-systolic and end-diastolic umbilical artery velocities on inspiration and an increase of both during expiration. He attributes this to opening of the pulmonary vascular bed on inspiration with subsequent pooling of blood in the pulmonary circulation; during expiration this blood is sqeezed out of the lungs. Maršál et al. (1984) report similar fluctuations during fetal respiration in the umbilical vein. They also describe an overal increase in volume blood flow in both the fetal descending aorta and the umbilical vein during fetal breathing when compared with fetal apnoea. This suggests some major alterations in the distribution of blood flow during the fetal breathing state.

We will now report on the effect of fetal breathing movements on fetal intracardiac Doppler flow velocity waveforms in normal third trimester pregnancies. The relationship between flow velocity waveforms in the ductus arteriosus and fetal breathing movements will be discussed in chapter 5.

4.2.2 THE EFFECT OF FETAL BREATHING MOVEMENTS ON FETAL CARDIAC HAEMODYNAMICS

K. van der Mooren*, Th. Stijnen** and J.W. Wladimiroff*

*Department of Obstetrics and Gynaecology, **Department of Biostatistics, Erasmus University, Rotterdam, The Netherlands

To be published in Ultrasound Med. & Biol. 1991

INTRODUCTION

Human fetal breathing movements have been observed on ultrasound examination from approximately 10 weeks of gestation onwards (de Vries et al., 1982a). Some authors state that the prevalence of fetal breathing movements increases with advancing gestational age until a maximum at a gestational age of 32 weeks is reached (Natale et al., 1988). In third trimester fetuses, episodes of continuous fetal breathing movements of more than 10 breaths may be present (Trudinger at al., 1980). Fetal breathing activity has shown to have a profound effect on fetal haemodynamics. In the lamb fetus, when measured electro-magnetically, aortic flow was found to increase by 20%

above the "non-breathing" level (Walker, 1984). In the human fetus, the mean velocity over time increases during high amplitude breathing movements, both in the umbilical vein and in the descending aorta (Maršál et al., 1984). Recently, it was demonstrated that breathing-dependent modulations in fetal ductal blood flow velocity increase exponentially with advancing gestational age (van Eyck et al., 1990).

In the present study the following questions were addressed: i) are blood flow velocity waveforms at atrioventricular and outflow tract level modulated by fetal breathing movements; if so, is this modulation gestational age-dependent; ii) is time-averaged velocity during fetal breathing movements different from that observed during apnoea.

MATERIAL AND METHODS

A total of 24 women with normal singleton pregnancies consented to participate in the study. Twelve women were studied in the presence of fetal breathing movements, the remaining 12 women were examined during fetal apnoea. Both groups were matched for maternal and gestational age and maternal parity. Median maternal age was 28 yr (range 22-34 yr), median gestational age was 30 weeks (range 27-40 weeks), median maternal parity was 1 (range 0-3). The gestational age was calculated from a reliable menstrual history and early sonographic measurement of fetal crown-rump length or biparietal diameter. Fetal birth weight was between the 10th and 90th percentile for gestational age according to Kloosterman's Tables (1970) corrected for maternal parity and fetal sex. All participants were non-smokers and no medications were prescribed. All studies were performed two hours after breakfast or lunch, with the participants in the semirecumbent position. Fetal biometry, echocardiography and intracardiac blood flow velocity measurements were carried out using a combined two-dimensional real-time and pulsed Doppler system (Diasonics CV 400, Milpitas, CA) with a carrier frequency of 3.5 MHz (spatial peak, temporal average intensity of less than 100 mW per cm^2 for pulsed Doppler). Doppler studies were performed by one examiner (K.v.d.M).

Maximum Doppler flow velocity waveforms at mitral and tricuspid valve level were obtained from the 4-chamber view. At outflow tract level, maximum flow velocity waveforms in the fetal ascending aorta were recorded from the 5-chamber view and in the pulmonary artery from the conventional echocardiographic short axis view. Doppler sample volumes were placed immediately distal to each of the four valves and were kept as small as possible relative to the dimensions of the fetal heart with a maximum length

of 0.4 cm. The angle between the Doppler cursor and assumed flow direction was always kept below 10 degrees. Flow velocities were maximised by fine transducer angulations in the azimuthal plane. To ensure the presence of fetal breathing activity throughout a Doppler flow velocity recording, fetal breathing movements still had to be present after completion of the recording. The presence of fetal breathing movements was established from rhythmic inward and outward excursions of the thoracic cage and downward and upward movements of the diaphragm visualised on 2-dimensional real-time images. Fetal apnoea was defined as the absence of fetal breathing movements for 6 s or more. All blood flow velocity waveforms obtained during periods of apnoea and breathing activity were stored on videotape. From hard copies analysis of five consecutive waveforms was carried-out using a microcomputer (Olivetti M240, Scaramagno, Italy) for calculation of the following parameters (mean ± 1SD) during the inspiratory and expiratory phase of the breathing cycle and during apnoea:

- at atrioventricular level: time-averaged velocity (cm/s), peak E-wave velocity (cm/s) and peak A-wave velocity (cm/s);
- at outflow tract level: period time (ms), acceleration time (ms) and time-averaged velocity (cm/s).

Percentage modulation by breathing activity was calculated for each of the flow velocity parameters according to the formula:
(F inspiratory phase - F expiratory phase) / F expiratory phase x 100%, in which F represents the particular flow velocity parameter involved.

Regression analysis was carried-out to determine differences in time-averaged flow velocity between the inspiratory and expiratory phase of the breathing cycle relative to gestational age. Differences in averaged flow velocity between periods of breathing and apnoea were established using the t-test for paired comparisons with the lower level of statistical significance set at 0.05.

RESULTS

The mean period time was 426 ± 19 ms (range 392-461 ms) during breathing activity and 427 ± 27 ms (range 389-447 ms) during apnoea. Data on flow velocity waveform parameters during fetal breathing and apnoea as well as the percentage modulation during breathing are presented in Tables 4.4 and 4.5.

Table 4.4. Mean ± 1 SD of time-averaged velocity (cm/s), peak-E wave velocity (cm/s) and peak-A wave velocity (cm/s) during the inspiratory and expiratory phase of fetal breathing movements (including modulation) and during apnoea at mitral valve and tricuspid valve level.

mitral valve level

	insp. phase	exp. phase	change abs.	%	breathing	apnoea
time-averaged velocity (cm/s)	20.8±2.2	18.2±1.8	2.6±0.7	10-18	19.5±2.1	18.6±1.6
peak-E wave velocity (cm/s)	45.8±5.9	34.3±4.1	11.5±3.5	20-63	40.1±4.8	38.4±4.2
peak-A wave velocity (cm/s)	50.4±4.7	47.1±3.9	3.3±2.8	-5-+8	48.8±4.9	47.8±3.6

tricuspid valve level

	insp. phase	exp. phase	change abs.	%	breathing	apnoea
time-averaged velocity (cm/s)	22.6±2.5	17.0±1.7	5.6±1.8	17-54	19.8±1.9	20.1±2.0
peak-E wave velocity (cm/s)	51.3±6.3	38.4±4.5	12.9±3.0	23-42	44.9±5.3	43.9±4.8
peak-A wave velocity (cm/s)	61.0±6.5	47.5±4.0	13.5±3.5	19-37	54.3±5.4	54.4±3.6

A visual display of flow velocity modulation in the ascending aorta during fetal breathing is is presented in Figure 4.4. The correlation coefficient (r) for the degree of breathing-related modulation in time-averaged velocity relative to gestational age was 0.55 (p=0.06) and 0.46 (p=0.13) at mitral and tricuspid valve level, and 0.70 (p=0.01) and 0.88 (p=0.0002) at ascending aorta and pulmonary artery level, respectively. Time-averaged velocity at mitral valve and ascending aorta level was significantly higher during breathing than during apnoea, mean differences being 0.85 ± 0.71 cm/s (p = 0.002) and 0.94 ± 0.44 cm/s (p = 0.001), respectively. No such difference was observed at tricuspid valve and pulmonary artery level with time-averaged velocity differences of 0.33 ± 1.12 cm/s (p = 0.3) and 0.09 ± 1.15 cm/s (p = 0.8).

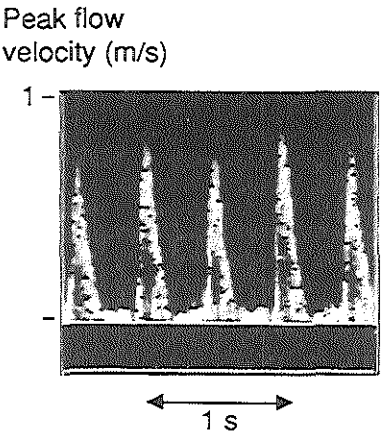

Figure 4.4. Visual display of flow velocity modulation at the level of the ascending aorta during fetal breathing movements.

Table 4.5. Mean ± 1 SD of acceleration time (ms) and time-averaged velocity (cm/s) during the inspiratory and expiratory phase of fetal breathing movements (including modulation) and during apnoea in the ascending aorta and pulmonary artery.

ascending aorta level

	insp. phase	exp. phase	change abs.	%	breathing	apnoea
acceleration time (ms)	58.5±4.0	58.0±4.5	0.5±2.1	-3-+5	58.3±4.2	57.6±6.3
time-averaged velocity (cm/s)	27.2±1.6	23.5±0.9	3.7±1.0	8-20	25.4±1.2	24.4±1.2

pulmonary artery level

	insp. phase	exp. phase	change abs.	%	breathing	apnoea
acceleration time (ms)	49.1±6.4	48.8±4.9	0.3±3.1	-7-+13	49.0±5.5	50.4±6.2
time-averaged velocity (cm/s)	24.0±2.0	19.6±1.3	4.0±1.5	12-31	21.8±1.5	21.9±1.4

DISCUSSION

To our knowledge this is the first quantitated study on breathing-related cardiac flow velocity changes in the human fetus. Period times during fetal breathing activity and apnoea reflected normal fetal heart rates between 130 and 155 bpm. Time-averaged flow velocities were clearly modulated by fetal breathing movements at all four cardiac valve levels. Percentage modulation of time-averaged velocity varied between 10% and 54% at atrioventricular level and between 8% and 31% in the cardiac outflow tract. We suggest that these breathing related velocity changes are determined by changes in venous return as a result of fluctuations in intrathoracic pressure during fetal breathing activity. Breathing-related modulation of time-averaged velocity increased with advancing gestational age at outflow tract level and to a lesser extent at atrioventricular level. A similar observation was done in the ductus arteriosus (Van Eyck et al., 1990) and may in part be explained by the reduction in down-stream impedance at umbilical placental level during the third trimester of pregnancy.

Acceleration time at outflow tract level demonstrated very little modulation by breathing movements. Acceleration time is mainly determined by arterial afterload which is less subject to fluctuations by breathing activity than the venous preload.

When considering the E- and A-wave of the atrioventricular valves separately, it appears that whereas the E-wave representing the passive atrial filling phase is modulated at both sides of the heart, for the A- wave this is only so for the tricuspid valve. At mitral valve level virtually no change in atrial contraction occurs during fetal breathing activity. This observation is difficult to explain since we have no direct access to variables which may affect atrial contraction, in particular afterload. Intrinsic ventricular differences may also account for this.

Of interest is that the time-averaged flow velocity at the level of the mitral valve and ascending aorta was significantly higher during fetal breathing movements than during apnoea. Volume flow equals time-averaged flow velocity multiplied by vessel area. Although valve areas are unknown in the present study, it is unlikely that they change considerably as a result of breathing activity. If this is so, then the raised time-averaged flow velocities on the left side of the heart suggest increased left ventricular output in the presence of fetal breathing movements, probably through increased shunting of blood through the foramen ovale during fetal breathing activity (Van Eyck et al., 1991). Since increased left ventricular output would benefit cerebal blood supply, one may speculate on the role of fetal breathing movements in

maintaining blood supply to the vital organs.

Both postnatal animal experiments (Summer et al., 1979) and postnatal human intracardiac Doppler flow studies (Dabestani et al., 1988) have unanimously demonstrated that during inspiration stroke volume at tricuspid valve and pulmonary artery level increases, whereas stroke volume at mitral valve and ascending aorta level decreases. Conversely, during expiration right heart stroke volume decreases, whereas left heart stroke volume increases. Obviously, the intrauterine and postnatal situation can not be compared due to the intrauterine non-functioning of the lungs and the presence of right-to-left shunting at foramen ovale and ductus arteriosus level. These data show, however, that breathing may cause impressive changes in cardiac haemodynamics.

Finally, from the present study it has become clear that in order to assure a steady state situation during fetal cardiac flow velocity waveform recordings, these should be collected during fetal apnoea.

4.3 CONCLUSIONS

The increase of peak systolic velocity, time-averaged velocity and acceleration time at outflow tract level with advancing gestational age suggests increasing stroke volume, increasing cardiac output and decreasing afterload. The afterload of both ventricles differs, probably due to the influence of fetal cerebrum and lungs on left and right ventricular afterload. Outflow tract flow velocity parameters are fetal heart rate independent within the normal fetal heart rate range, which is in agreement with other studies.

The E/A-ratio may be considered as a parameter of ventricular diastolic function. It increases with advancing gestational age, reflecting increasing myocardial compliance, changing ventricular afterload, or both. The E/A-ratio at mitral level is higher than at tricuspid level, suggesting a different afterload to the ventricles, different compliance of the ventricles due to differences in ventricular geometry, or both. E/A-ratio is fetal heart rate dependent at both heart sides, suggesting some influence of heart rate on fetal ventricular relaxation, although preload changes may also account for this. Atrioventricular time-averaged velocity is negatively correlated with period time, which may be due to an increase in valve area with increasing stroke volume.

Fetal inspiration and expiration cause momentary changes in stroke volume at the four cardiac valve levels. Since we did not record flow velocity waveforms together with fetal thoracic and abdominal excursions, we cannot

reliably determine whether the observed flow velocity waveform changes actually took place during fetal inspiration or expiration. These flow velocity fluctuations probably occur as a result of changes in intra-thoracic pressure and hence ventricular preload. E/A-ratios at mitral and tricuspid valve level are affected differently, suggesting differences in ventricular compliance or a difference in preload distribution. As has been discussed earlier, a different geometry of the ventricles may be responsible for differences in ventricular compliance. Differences in left and right ventricular preload may also play a role; during inspiration, an increase in venous return to the right atrium may be expected as a result of decreased intra-thoracic pressure. Since inferior vena cava return exceeds superior vena cava return and inferior vena cava blood flow is positively correlated with foramen ovale blood flow (Anderson et al., 1981), this would preferentially affect the left heart.

In our study, overall volume blood flow in the left heart during fetal breathing movements appeared to increase when compared with fetal apnoea, while blood flow through the right heart remained the same. This suggests that combined cardiac output increases during fetal breathing; the Frank-Starling mechanism may compensate for these preload changes. It suggests also, that the fetal breathing state is accompanied by a redistribution of blood flow in favour of the left heart and thus of the fetal cerebrum (and upper limbs). This hypothesis is supported by a study on foramen ovale blood flow velocity waveforms during fetal breathing, showing an increase of right-to-left blood flow on fetal inspiration mainly during early diastole (van Eyck et al., 1990). A study of vena cava inferior flow during fetal breathing might provide further evidence of this theory. It is interesting to speculate that fetal breathing, apart from preparing the fetus for extra-uterine life, may be of haemodynamic importance during intra-uterine life.

Chapter 5

DOPPLER STUDIES IN THE FETAL DUCTUS ARTERIOSUS

5.1 NORMAL DOPPLER FLOW VELOCITY WAVEFORMS IN THE FETAL DUCTUS ARTERIOSUS

5.1.1 INTRODUCTION

The ductus arteriosus is a blood vessel which connects the main pulmonary trunk with the descending aorta. Together with the foramen ovale, it serves as a right to left shunt at cardiac level. Patency of the ductus arteriosus is of vital importance for the fetus, since constriction of this vessel, which occasionally occurs spontaneously or following administration of indomethacin to the mother (Arcilla et al., 1969), is associated with fetal circulatory failure. Ductal patency is maintained in utero by a complex regulatory mechanism, that has not been fully elucidated yet. However, in animal laboratory studies valuable information regarding this issue has been obtained. Since sonographic and especially Doppler echocardiographic methods have recently become available, semi-quantitave information on ductus arteriosus haemodynamics is now being collected in the human fetus as well.

Physiological considerations

According to fetal lamb studies (Heymann and Rudolph, 1975), the diameters of the ascending aorta, the descending aorta and the ductus arteriosus are about equal, whereas the pulmonary trunk is slightly larger. The relative sizes of these vessels reflect the proportions of cardiac output carried by them. The preload of the right ventricle is formed by the superior vena cava return, coronary sinus return and about 60% of the inferior vena cava return. The rest of inferior vena cava blood flow is directed from right to left atrium through the foramen ovale, which together with pulmonary venous return determines the preload of the left ventricle. The fetal cardiac ventricles function in parallel, and cardiac output can thus be regarded as the combined output of the two ventricles. The right ventricle ejects about two thirds of the combined ventricular output, and 90% of this portion (corresponding to 60% of the combined ventricular output) is diverted from the lungs through the ductus

arteriosus into the descending aorta. Approximately 7% of the combined ventricular output flows through the lungs. The left ventricle ejects one third of the combined ventricular output, from which 20% flows to head and upper limbs, 10% to the descending aorta and 3% to the coronary circulation (Heymann and Rudolph, 1975, Anderson et al., 1981). The right ventricle therefore provides the majority of blood flow to the lower body and the placenta. So, the ductus arteriosus reduces work load on the fetal heart by diverting more than half of the combined ventricular output away from the lungs and shunting lesser oxygenated blood directly towards the place of gas exchange. Maintenance of ductal patency seems therefore essential for the fetal circulation.

In a correlative echocardiographic and morphometric study Angelini et al. (1988) have shown that in the human fetus from 10 to 33 weeks' gestation the size of the great vessels around the fetal heart differs from that measured in the lamb fetus. In the human fetus, pulmonary trunk and arteries are relatively larger, whereas the ductus arteriosus is smaller. This may indicate that in the human fetal cardiovasular system blood flow distribution may be different from that in the lamb fetus, with larger pulmonary artery flow and lung perfusion, and relatively less blood flow through the ductus arteriosus.

Maintenance of ductal patency in utero

The ductus arteriosus is maximally dilated in utero due to the predominant presence of dilating substances which at birth are withdrawn from the circulation, thus allowing the ductus arteriosus to constrict (Friedman et al., 1983).

There is strong evidence that relaxing prostaglandins are involved in the maintenance of ductal patency (Starling and Elliot, 1974, Coceani et al., 1975, 1978, Heymann and Rudolph, 1976, Friedman et al., 1983, Sideris et al., 1983, Clyman, 1987, Olley and Coceani, 1987). First, cyclo-oxygenase inhibitors are able to cause constriction of the animal and human ductus arteriosus (Heymann and Rudolph, 1976, Friedman et al., 1983, Moise et al., 1988, Eronen et al., 1991); second, some prostaglandins are able to re-open the constricted ductus arteriosus (Sideris et al., 1983), and third, prostaglandin synthetic enzymes are present in the ductus arteriosus wall (Starling and Elliot, 1974, Clyman, 1980a). The strongest vasodilator in this respect is PGE2 (Starling and Elliot, 1974, Heymann and Rudolph, 1976, Coceani et al., 1978, Friedman et al., 1983, Sideris et al., 1983), which is among others produced in the adventitia of this vessel and probably diffuses into the media, causing relaxation (Olley and Coceani, 1987). However, recent studies suggest that also extra-ductal sources of PGE2 may may be important in regulating ductal

patency, since PGE2 has been shown to be present in the fetal circulation in high concentrations (Starling and Elliot, 1974, Clyman, 1980a).

Another vasodilator produced in the ductal wall is PGE1, although it is less potent than PGE2. Some studies describe a gestational-age-dependency of ductal response to relaxing prostaglandins, the effect being greater in the immature than in the mature ductus arteriosus (Clyman et al., 1980b). In agreement with this observation is the finding by Clyman et al. (1980b) that prostaglandin synthetase inhibitors appear to have a greater contractile effect on the immature than on the mature lamb ductus arteriosus. Moise et al. (1988) however could not observe any gestational age dependency in the response to indomethacin in the human fetus, whereas Eronen et al. (1991) state that indomethacin-induced vasoconstriction of the human ductus arteriosus increases with advancing gestational age.

Recently, also prostaglandins with a contractile ductal influence have been identified, like PGF2a (Starling and Elliot, 1974). PGF2a is also produced in the ductal wall. It has no effect on the ductus arteriosus in a low-oxygen environment, but produces vasoconstriction in a high-oxygen environment as occurs at birth. This has led to the hypothesis that ductal regulation takes place through the combined action from both dilating and contractile prostaglandins, the former predominating before birth and the latter being formed under the influence of increasing fetal plasma oxygen tensions after birth (Olley and Coceani, 1987). However, the exact nature of this constrictory agent has still to be found. Also, the mechanism through which PGE2 establishes ductal patency has not been elucidated yet. c-AMP may play a role, since it is present in the smooth muscle of many species and has a strong vasodilatory effect; also, PGE2 is associated with increased c-AMP levels in a low-oxygen environment (Starling and Elliot, 1974, Heymann and Rudolph, 1976). Adenosine is another candidate for the maintenance of ductal patency, since it is a potent vasodilator which is present in the fetal circulation in adequate amounts (Mentzer et al., 1985). In the high oxygen environment after birth, PGF2a is supposed to increase c-GMP levels which may be responsible for ductal constriction (Starling and Elliot, 1974).

Some authors believe that for the regulation of ductal patency the autonomous innervation of the ductus is important (Boreus et al., 1969, Aronson et al., 1970, McMurphy and Boreus, 1971). It has indeed been shown that sympathetic nerve fibres are present in the muscular layer of the ductus arteriosus in animal and human fetuses from about half of gestation onwards (Allan, 1955, Boreus et al., 1969, Aronson et al., 1970); data concerning cholinergic receptor function in the fetal ductal media are contra-

dictory (Allan, 1955, Boreus et al., 1969, Aronson et al., 1970, Noel and Cassin, 1976). However, the data regarding innervation of the fetal ductus arteriosus are conflicting or show at least a great variability (Aronson et al., 1969, McMurphy and Boreus, 1971). It is therefore still difficult to evaluate whether neurohumoral factors play a significant role in the regulation of ductal patency and blood flow.

Cyclo-oxygenase inhibitors, especially indomethacin, are increasingly used in obstetric care for various reasons, like prevention of premature labour (Dudley and Hardie, 1985, Niebyl and Witter, 1986, Huhta et al., 1987, Eronen et al., 1991). In human pregnancy, cases of fetal circulatory failure have been described following administration of cyclo-oxygenase inhibitors to the mother (Arcilla et al., 1969), which has been confirmed in animal laboratory studies (Heymann and Rudolph, 1976). The most important common macroscopic finding was constriction of the ductus arteriosus associated with fetal heart failure. The limited lateral resolution of current 2D-real time ultrasonic equipment prohibits exact measurement of the diameter of the ductus arteriosus in utero (Huhta et al., 1987). Recently, a method for recording blood flow velocities in the human fetal ductus arteriosus has become available and normal peak systolic and peak diastolic velocities were established cross-sectionally during the second half of pregnancy (Huhta et al., 1987). It has been shown that ductal constriction following administration of indomethacin to the mother, can be reliably assessed by Doppler echocardiography since it produces increased peak systolic and peak diastolic ductal velocities in this vessel (Huhta et al., 1987, Eronen et al., 1991). Secondary effects, like tricuspid regurgitation, can also be appreciated in this way (Moise et al., 1988, Eronen et al., 1991).

For a proper understanding and interpretation of fetal Doppler flow velocity waveforms, normal values corrected for intrinsic variables such as fetal breathing movements, fetal behavioural states and fetal heart rate have to be established. This will be dealt with in the following subchapters.

5.1.2 FLOW VELOCITY WAVEFORMS IN THE HUMAN FETAL DUCTUS ARTERIOSUS DURING THE NORMAL SECOND HALF OF PREGNANCY

K. van der Mooren*, L.G. Barendregt** and J.W. Wladimiroff*
*Department of Obstetrics and Gynaecology, **Department of Biostatistics, Erasmus University, Rotterdam, The Netherlands
Published in Ped. Res. 1991, 30, 487-490

INTRODUCTION

The ductus arteriosus is a large vessel that connects the pulmonary trunk with the descending aorta during fetal life. Thus it acts as a right-to-left shunt at cardiac level, diverting a considerable amount of the combined ventricular output away from the lungs. In this way the total work load on the fetal ventricles is reduced, inasmuch as a large pulmonary blood flow would represent wasted circulation (Heymann and Rudolph, 1975).

Doppler echocardiographic techniques are increasingly being used to study the human fetal heart (Huhta et al., 1985). Also a technique for recording blood flow velocity waveforms in the human fetal ductus arteriosus became available (Huhta et al., 1987). For a proper interpretation of Doppler data, the influence of variables such as fetal behavioural states, fetal breathing movements and fetal heart rate should be taken into account. Recently it was demonstrated that ductus arteriosus peak systolic velocity is fetal behavioural state dependent, being reduced significantly during active sleep as compared with quiet sleep (this thesis, chapter 5.3). Ductal peak systolic and peak diastolic velocities appeared to be fetal heart rate-independent in this group. It was also demonstrated that ductal peak flow velocity is modulated by fetal breathing movements (this thesis, chapter 5.2). There is a significant reduction in ductal peak systolic flow velocity during inspiration as compared with expiration, and this difference in peak systolic flow velocity increases exponentially with advancing gestational age, reflecting the developing pulmonary vascular bed.

To our knowledge, a detailed analysis of normal fetal ductal waveforms has never been carried-out in a longitudinal setting.

The objective of the present study was twofold:

1. To establish the distribution of peak systolic, peak diastolic and time-averaged velocities as well as acceleration time in the fetal ductus arteriosus between 18 and 38 weeks of pregnancy;

2. To determine whether there is fetal heart rate dependency for one or more of the aforementioned parameters within the physiological fetal heart rate range (i.e. 110-160 bpm), and if so, to establish the relationship between fetal period time (the reciprocal of heart rate) and the parameter concerned.

MATERIAL AND METHODS

A total of 40 women with normal singleton pregnancies consented to participate in the study. The study protocol was approved by the Hospital Ethics Committee. Fetal ductal Doppler examinations were carried out at 3 to 4 weeks' intervals between 18 and 38 weeks of gestation. The first examination was performed between 18 and 22 weeks of gestation.

Normal pregnancy was defined by a normal fetal biparietal diameter and birthweight between the 5th and 95th percentile according to Kloosterman's tables, corrected for maternal parity and fetal sex (1970). The pregnancy duration was determined from the last menstrual period and confirmed by ultrasonic measurements of the biparietal diameter between 14 and 18 weeks of gestation. The median maternal age was 29 yr (range 18-41 yr), the median parity was 1 (range 0-6).

A combined mechanical sector scanner and continuous Doppler system (Diasonics CV 400, Milpitas, CA) with a carrier frequency of 3.5 MHz was used for blood flow velocity measurements in the ductus arteriosus. The sector scanner operates at power outputs less than 100 mW/cm^2 spatial peak/temporal average in both imaging and Doppler modes by manufacturers' specifications. Two dimensional imaging was used to ensure the correct position of the Doppler interrogation beam both before and after each Doppler tracing was obtained. Maximum flow velocity waveforms from the ductus arteriosus were collected from the conventional short axis view. The aortic arch was differentiated from the ductus arteriosus by identification of the aortic arch vessels. The Doppler beam was positioned at the junction of ductus arteriosus with aorta descendens (Huhta et al., 1987), and Doppler tracings were accepted when the angle between the Doppler beam and the assumed direction of flow was 10 degrees or less. Doppler studies were performed by one examiner (K.v.d.M). All blood flow velocity waveforms were obtained during fetal apnoea and stored on videotape. From hardcopies the analysis of four consecutive waveforms was carried out using a microcomputer (Olivetti M240, Scaramagno, Italy) linked to a graphics tablet. The following parameters were calculated: peak systolic velocity (cm/s), acceleration time (ms), time-averaged velocity (cm/s), peak diastolic velocity (cm/s)

and period time (ms).

Peak velocities were measured from the zero-line to the highest point of the Doppler velocity peak. Acceleration time was measured as the time between the onset of ejection and the peak of velocity. Time-averaged velocity was calculated as area-under-curve divided by period time. Peak diastolic velocities were measured from the zero-line to the maximum of the Doppler flow velocity waveform during the late diastolic phase of the cardiac cycle.

All Doppler studies were performed two hours following breakfast or lunch with the patient in a semi-recumbent position. The duration of one investigation never exceeded 30 minutes.

Statistical analysis included assessment of the relationship between the parameters studied and gestational age by repeated measurements analysis of variance, for which the BMDP programme 5V (BMDP statistical software manual, vol.11, 1988, University Press of California) was used. P-values were determined by means of the sign-test. The relationship between each parameter and fetal heart rate was studied as follows. For every patient, the available data were interpolated in a linear fashion to a gestational age of 30 weeks to rule out the influence of gestational age on the parameters. For each adjusted parameter and period time the correlation coefficient was then calculated, and the corresponding p-value established. The lower level of statistical significance was set at 0.05.

RESULTS

The success rate for obtaining good quality flow velocity waveforms from the ductus arteriosus was 94%. In each patient it was possible to obtain at least four serial recordings during the study period. On average, five investigations were performed in each pregnancy. Serial recordings were never longer than six weeks apart.

The relationship between any of the flow velocity waveform parameters and gestational age was approximately linear for each patient. It also appeared, that the regression lines, by which the relation between parameter and gestational age for each of the patients could be described, differed significantly from patient to patient with respect to both the intercept and the slope. Therefore, the following statistical model was adopted as the basis for the calculation of approximate 95%-prediction-bounds for each of the parameters, when the gestational age is known:

y= a + b(x - 30) + e, with y= the parameter concerned; x= gestational age (weeks); a= the intercept of the regression line; b= the slope of the regression line; e= an error term.

Thus, for each of the parameters a regression line was constructed with its 2.5% and 97.5% confidence limits. The values for a, b and e for each flow velocity parameter, as well as the p-values of the slopes are listed in Table 5.1.

Table 5.1. Absolute values and standard errors of the parameters determining the regression lines for the ductus arteriosus flow velocity parameters with gestational age according to the general formula: y=a+b(x-30)+e.

	a	b	Sa	Sb	error (e)	p-value
PSV (cm/s)	102.9	3.4	79.4	0.8	112.8	*
PDV (cm/s)	11.6	0.6	3.2	0.01	2.8	*
TAV (cm/s)	40.4	1.4	18.4	0.1	22.8	*
ACT (ms)	64.8	1.7	38.8	0.2	72.3	*

*p<0.0001

Abbreviations: PSV=peak systolic velocity; PDV=peak diastolic velocity; TAV=time-averaged velocity; ACT=acceleration time; Sa=standard error of the intercept; Sb=standard error of the slope; x=gestational age (weeks).

There was considerable variability in measurements between fetuses at any particular gestational age. The data distribution for ductal peak systolic and peak diastolic velocity relative to gestational age is presented in Figure 5.1 and 5.2. Period time in this study ranged from 358 to 537 ms, corresponding to a fetal heart rate of 167 to 112 bpm respectively. Average period time showed a significant increase with advancing gestational age, the regression equation being y= 371.1 + 1.53x (p<0.0001), with y= average period time (ms) and x= gestational age (weeks).

The parameters studied showed a significant increase with advancing gestational age, as is shown in Table 5.1. Mean values (± 1SD) at 20 weeks of gestation as compared with 38 weeks of gestation were for peak systolic velocity: 65.6 ± 10.9 vs 126.3 ± 32.1 cm/s; for peak diastolic velocity: 5.4 ± 1.4 vs 15.4 ± 3.4 cm/s; for time-averaged velocity: 24.8 ± 3.9 vs 50.1 ± 14.5 cm/s; for acceleration time: 47.5 ± 8.7 vs 78.4 ± 10.2 ms. No correlation could be demonstrated for any parameter and period time. Ductal acceleration time was significantly higher than pulmonary acceleration time (p<0.001) and ascending aortic acceleration time (p<0.001).

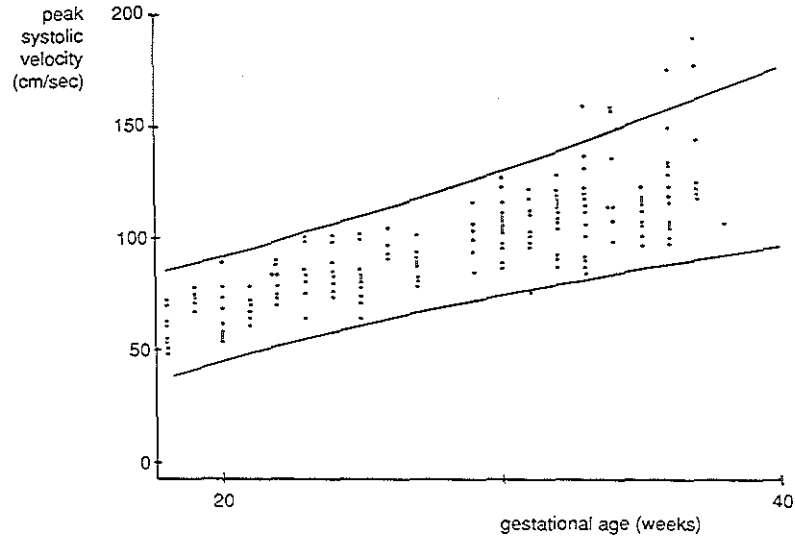

Fig. 5.1. Data distribution with 2.5% and 97.5% confidence limits for fetal ductal peak systolic velocity relative to gestational age.

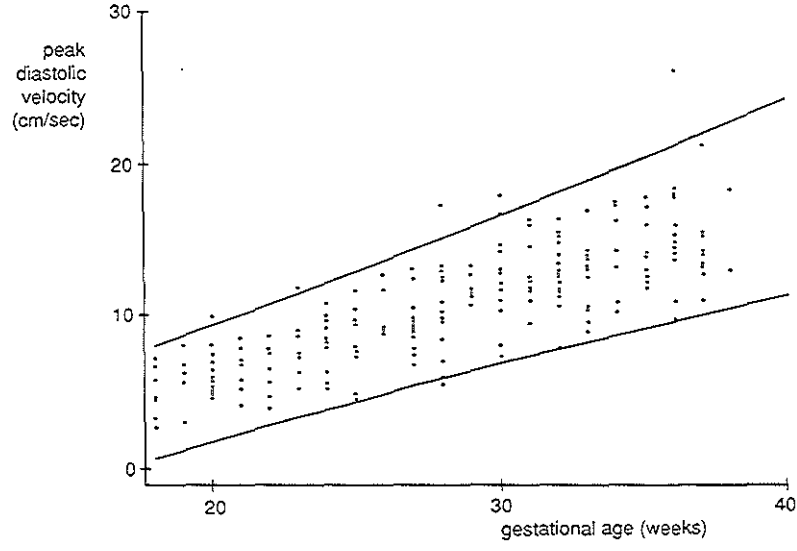

Figure 5.2. Data distribution with 2.5% and 97.5% confidence limits for fetal ductal peak diastolic velocity relative to gestational age.

DISCUSSION

In the human fetal heart, both right and left ventricle eject in parallel into the systemic circulation: the right ventricle into the ductus arteriosus and descending aorta, the left ventricle into the ascending aorta (Rudolph and Heymann, 1974). The ductus arteriosus thus acts as a right-to-left shunt reducing the work load on the fetal heart (Heymann and Rudolph, 1975). As can be concluded from animal laboratory experiments, the dilatation of the ductus arteriosus in utero is maximal (Friedman et al., 1983), and a widely patent ductus arteriosus appears to be essential for normal fetal development (Heymann and Rudolph, 1975).

In the present study, we analysed fetal ductal flow velocity waveforms obtained longitudinally during the second half of pregnancy. An increase with advancing gestational age was found for all flow velocity parameters concerned. The distribution of these parameters increased towards term, which is in agreement with the increasing variance of biometric parameters with advancing gestational age. Fetal heart rate showed a significant decrease towards term. All parameters were fetal heart rate independent. The gestational age related rise in ductal peak systolic and time-averaged velocities is in agreement with the gestational age-related rise in semilunar peak systolic and time-averaged velocities we observed in an earlier study (this thesis, chapter 4.1). It was pointed out that this velocity rise could be explained by increasing ventricular stroke volume and output, as well as by a reduction in ventricular afterload. Right ventricular afterload is determined to a considerable part by placentar vascular resistance, which shows a decrease with advancing gestational age (Trudinger, 1987). Since volume flow is equal to mean velocity times area, the observed increase in peak systolic and time-averaged velocities in the ductus arteriosus may also reflect increased right ventricular stroke volume and output. However, other variables such as the diameter and compliance of the ductus arteriosus and downstream vessels (e.g. descending aorta) may play a role in the composition of the flow velocity waveform pattern in the ductus arteriosus. In a recent study, increased umbilical-placental resistance was associated with reduced peak systolic velocities in the ductus (Groenenberg et al., 1989). The non-invasive nature of human fetal Doppler studies does not allow differentiation between these explanations.

Ductal peak diastolic velocity also increased during the second half of pregnancy. Like the increase of end-diastolic velocities in umbilical artery and descending aorta towards term, this is indicative of decreasing placentar vascular resistance. The observed increase of acceleration time in the ductus arteriosus with advancing gestational age favours this assumption. Also, ductal

acceleration time is higher than that observed in the pulmonary artery and the ascending aorta. Since Doppler echocardiographic studies have shown a close negative correlation between acceleration time and mean arterial pressure (Kitabatake et al., 1983, Serwer et al., 1986), this might indicate that mean arterial pressure in the ductus arteriosus is lower than in the main pulmonary artery, suggesting a decrease in afterload from pulmonary artery to ductus arteriosus. This could imply, that the pulmonary vascular bed to some extent adds to right ventricular afterload. It is not surprising that mean ductal arterial pressure seems to be lower than the mean pressure in the ascending aorta, since the left ventricular outflow tract faces an additional afterload from cerebrum and upper extremities.

The linear increase in peak systolic and peak diastolic velocities in the ductus arteriosus with advancing gestational age is in agreement with the findings of Huhta et al. (1987), who performed a cross-sectional study of peak systolic and peak diastolic velocities in normal fetuses during the second half of gestation. However, our values for normal peak systolic velocities seem to be somewhat higher, and we occasionally observed peak flow velocities of about 200 cm/s in the last four weeks of gestation. To our knowledge, data concerning ductal acceleration time or time-averaged velocity have not been published elsewhere so far.

The regulation of ductal patency has not been clarified in detail until now. The role of arterial O2 was recognized long ago, determining ductal tone by either direct action on the ductus arteriosus (Heymann and Rudolph, 1975) or through influencing the production of certain intermediate substances (Coceani et al., 1975). Prostaglandins are probably the most important intermediate substances, originating both from the ductal wall and from extraductal sources (Clyman, 1980a, Friedman et al., 1983). Prostaglandin synthetase inhibitors are increasingly used in obstetric care, for instance for tocolysis, in which case indomethacin is the drug of choice (Niebyl and Witter, 1986, Moise et al., 1988). In the human fetus, even a short course of indomethacin can have a clear constrictive ductal response characterised by a raised peak systolic and peak diastolic flow velocity (Huhta et al., 1987, Moise et al., 1990). Usually, this effect is reversible and does not seem to cause any harm to the fetus (Moise et al., 1988). Moise et al. (1990) showed that during indomethacin induced ductal constriction umbilical pulsatility index did not change. However, constriction of the ductus arteriosus associated with neonatal circulatory failure has been found in one case following administration of indomethacin to the mother (Arcilla et al., 1969). There is also evidence that in utero exposure of the fetus to prostaglandin synthetase

inhibitors may be one of the causes of persistent pulmonary hypertension of the newborn (Turner and Levin, 1984) secondary to ductal constricton.

It is difficult to obtain reliable measurements of the dimensions of the human fetal ductus arteriosus by fetal echocardiography, because the ductus arteriosus can best be visualized in a short axis view and the lateral resolution of the equipment is relatively poor (Moise et al., 1988). Since animal models have demonstrated that ductal constriction correlates very well with Doppler findings (Huhta et al., 1987), Doppler echocardiography may provide valuable indirect information on subtle changes in the calibre of the ductus arteriosus in utero. In case of even slight ductal constriction, both ductal peak systolic and peak diastolic velocity will rise significantly. Close Doppler echocardiographic monitoring, in particular registration of ductal peak systolic and peak diastolic velocity, is therefore indicated in fetuses exposed to prostaglandin synthetase inhibitors. Other Doppler echocardiographic information, like the presence or absence of tricuspid regurgitation, evidence of fetal hydrops and the amount of amniotic fluid should be looked for (Moise et al., 1988). As for Doppler monitoring, the normal values presented in this article could provide a basis for clinical use. According to our findings, the upper limit of 140 cm/s for ductal peak flow velocity that Huhta et al. (1987) have proposed might be an underestimation. Clinicians agree, that indomethacin should not be used after 34 weeks of gestation (Niebyl and Witter, 1986), by which gestational age ductal peak flow velocities in our study did not exceed 160 cm/s. At this time peak diastolic velocity was maximal 18 cm/s. Both parameters are fetal heart rate independent within the physiological fetal heart rate range, as has been demonstrated for the ascending aorta and pulmonary artery (this thesis, chapter 4.1).

It can be concluded that fetal Doppler echocardiography allows monitoring of flow velocity waveforms in the ductus arteriosus during the second half of pregnancy. Waveform analysis in this vessel suggests a reduction in right ventricular afterload during this period of gestation.

5.2 FETAL DUCTAL FLOW VELOCITY WAVEFORMS AND FETAL BREATHING MOVEMENTS

5.2.1 INTRODUCTION

As has been discussed in chapter 4.2.1., profound haemodynamic changes can be observed at cardiac level between inspiration and expiration in animal and human adult studies as well as in the animal fetus. Furthermore, it has been shown in animal fetal experiments, that fetal pulmonary vascular resistance may drop well before term as a result of fetal thoracic expansion, with a concomittant increase in pulmonary blood flow (Rudolph and Heymann, 1974, Tod et al., 1991). It is likely that during fetal inspiration lung volume increases (Murai et al., 1984). We hypothesise that during fetal inspiration pulmonary vascular resistance falls momentarily with an increase in pulmonary blood flow and a decrease in blood flow in the ductus arteriosus. In fetuses with pulmonary hypoplasia a fixed high pulmonary vascular resistance is found. It might be expected therefore that in fetuses developing pulmonary hypoplasia, there may be a redistribution of blood flow in favour of the ductus arteriosus during fetal inspiration.

The next study reports on the relationship between ductal blood flow velocity waveforms and fetal breathing movements both in normal third trimester fetuses and in fetuses at risk of developing pulmonary hypoplasia.

5.2.2 DUCTUS ARTERIOSUS FLOW VELOCITY MODULATION BY FETAL BREATHING MOVEMENTS AS A MEASURE OF FETAL LUNG DEVELOPMENT

J. van Eyck, K. van der Mooren and J.W. Wladimiroff
Department of Obstetrics and Gynaecology, Erasmus University, Rotterdam, The Netherlands
Published in Am. J. Obstet. Gynecol. 1990, 163, 560-566.

INTRODUCTION

Rupture of membranes resulting in prolonged severe oligohydramnios during the second trimester of pregnancy may result in stillbirth or severe neonatal respiratory failure as a result of pulmonary hypoplasia. However, under these circumstances fetal outcome is not uniformly poor (Nimrod et al., 1984).

There is therefore a need for a test to accurately predict a favourable fetal outcome so that optimal obstetric care can be provided for these particular pregnancies.

In cases of prolonged severe oligohydraminos, contradictory findings have been reported with regard to the association between fetal breathing movements and lung performance after birth. According to Blott et al. (1987) the predictive value of the presence of fetal breathing movements for continuing lung growth is 100%, and the predictive value of the absence of fetal breathing movements for pulmonary hypoplasia is 100%; however, Moessinger et al. (1987) reported that the observation of fetal breathing activity is not helpful in identifying those fetuses with pulmonary hypoplasia at birth.

Ductal blood flow in the fetal lamb is modulated by lung expansion (Assali et al., 1965). This effect results from an opening of the pulmonary vascular bed with subsequent reduced shunting of right ventricular output through the ductus arteriosus. Furthermore, increased pulmonary perfusion has been established with advancing gestational age, reflecting developing pulmonary vasculature (Levin et al., 1976). In pulmonary hypoplasia the development of fifth- and sixth generation vessels is impaired with a resultant reduction in development of the pulmonary vascular bed (Levin, 1978). Moreover, pulmonary vascular resistance is raised and is associated with medial muscular hypertrophy of lung arterioles. It may be speculated that fetal breathing-related modulation of ductal flow will be reduced in this situation.

Recently a pulsed Doppler method was introduced for recording blood flow velocity waveforms in the human fetal ductal arteriosus (Huhta et al., 1987). In this study the following questions were addressed. Does breathing-related modulation of ductal flow occur in the human fetus? If so, is this modulation age dependent and is the presence of breathing-related ductal flow modulation in prolonged severe oligohydramnios caused by ruptured membranes indicative of absent pulmonary hypoplasia?

MATERIAL AND METHODS

All women gave informed consent for the study, which was approved by the Ethics Review Board of the University Hospital. The gestational age was calculated from a reliable menstrual history and ultrasonographic measurement of fetal crown-rump length or biparietal diameter. All women were nonsmokers.

The study population consisted of two groups. The first group represented 55 uncomplicated pregnancies with a mean gestational age of 32.3 weeks (range, 25 to 38 weeks) randomly selected at the outpatient clinic between

August 1988 and March 1989 for a cross-sectional study of normal breathing-related fetal ductal peak systolic flow velocity modulation. Recordings were performed from 25 weeks of gestation because approximately at this stage there is an increase in the total number of pulmonary vessels and vasomotor activity, reflecting the developing pulmonary vasculature during the late canalicular phase of lung development (Pringle, 1986). Fetal breathing activity also becomes more regular (Natale et al., 1988). Each subject was included in the study once. One woman had a twin gestation. Mean maternal age was 28.3 years (range, 18 to 42 years); maternal parity ranged from 0 to 5. No medications were prescribed. On ultrasonographic examination there was a normal amount of amniotic fluid. Measurements of the fetal biparietal diameter, upper abdominal and head circumference, and femur length revealed a normal-sized fetus without gross structural anomalies.

The second group consisted of 32 woman who were admitted during the study period either from our own outpatient clinic or were referred from other centers because of premature rupture of membranes before 28 weeks' gestation. Mean gestational age was 22.9 weeks (range, 16 to 27 weeks). Fetal ductal flow velocity measurements were begun at 25 weeks' gestation. Premature rupture of membranes must have resulted in severe oligohydramnios and had to be present over a period of 3 weeks or more before delivery. Severe oligohydramnios was defined as the absence of an amniotic fluid pool of more than 2 cm, measured in two planes on ultrasound examination. Mean maternal age in this group was 27.9 yr (range, 22 to 35 yr); maternal parity varied from 0 to 4. Fetal biparietal diameter, upper abdominal, and head circumference revealed a normal-sized fetus without gross structural defects. In all woman with premature rupture of membranes, tocolysis was established by intravenous administration of fenoterol. No corticosteroids were prescribed, and only cases with no signs of amnionitis were studied.

Fetal ductal flow velocity measurements were performed with a combined two-dimensional real-time and continuous-wave Doppler system (Diasonics CV 400, Milpitas, CA). A 3.0 MHz transducer was used. The sector scanner operated at power outputs ≤ 100 mW/cm^2 in both imaging and Doppler modes by manufacturer's specifications. All woman were studied while in the semirecumbent position. A longitudinal cross-section of the fetal ductus arteriosus was obtained on a short-axis view of the fetal heart parallel to the fetal spine as first described by Huhta et al. (1987). The aortic arch was distinguished from the ductal arch by visualization of the carotid arteries. The cursor line was placed in the ductus near the junction of the ductus and the descending aorta. The angle of insonation was maintained below 5 degrees.

On the same short-axis view, movements of the fetal thoracic wall and diaphragm reflecting breathing movements can be observed, while the Doppler flow velocity measurements in the ductus arteriosus are performed parallel to the ductal flow direction without changing the position of the transducer.

Fetal breathing activity was defined as periodic inward movements of the fetal chest wall with downward movements of the fetal diaphragm. Continuous fetal breathing was considered present when the interval between two consecutive breathing movements was ≤6 seconds. In the normal developing fetus, the second trimester is characterized by irregular and sporadic breathing movements. With advancing gestational age fetal breathing becomes more regular with a reduction in breathing rate (Natale et al., 1988), whereas the percentage of time spent breathing does not differ significantly under fasting conditions (Dornan et al., 1984, Harper et al., 1987). Fetal breathing activity is stimulated by glucose loading (Patrick et al., 1980). This breathing response increases with advancing gestational age (Natale, 1980). For this reason and to obtain accurate timing of breathing-related Doppler flow measurements, it was decided to stimulate fetal breathing activity by maternal glucose administration at the onset of each study period, after normal carbohydrate metabolism had been established (postprandial capillary glucose level ≤7 mmol/L) and after intrauterine growth retardation had been ruled out. Assuming that the severely growth-retarded fetus is chronically hypoxemic, a sudden surge in glucose might lead to the develoment of metabolic acidosis and result in fetal death (Shelly et al., 1975).

In the group of patients with prolonged severe oligohydramnios, 250 ml of a 10% glucose solution (27.5 gm) was given intravenously over a period of 15 minutes. All patients did already have an intravenous line in place. In cases of severe oligohydramnios the percentage of time spent breathing is not markedly altered (Moessinger et al., 1987), or is even increased (Fox and Moessinger, 1985). In the women with normal pregnancies a single dosis of 50 gm of glucose was administered orally. Peak maternal glucose levels are reached approximately 10 minutes after intravenous glucose loading and approximately 60 minutes after oral glucose loading (Natale, 1980). Both routes result in a comparable rise in maternal plasma glucose concentration; moreover, the incidence and fetal breathing rate are not affected differently after oral or intravenous glucose administration (Natale, 1980). We therefore did not consider it ethically appropriate to use the intravenous route in the normal group. Doppler flow velocity waveform recordings in the fetal ductus arteriosus were started at the time of the expected increase in fetal breathing

activity, 30 minutes after intravenous glucose administration (Natale, 1980) and 2 hours after oral glucose administration (Natale, 1980) to the mother. The time delay between the peak of the maternal capillary glucose level and increase in fetal breathing incidence may be explained by the local excess of carbon dioxide produced by increased oxidation of glucose, stimulating the chemosensitive areas of the brain stem (Hohimer et al., 1983, Connors et al., 1988).

Maximum flow velocity waveforms were obtained over a 15-second period after a period of continuous fetal breathing activity was observed. To ensure the presence of fetal breathing activity throughout the Doppler flow velocity recording, fetal breathing movements had still to be present after completion of the recording. The blood flow velocity waveforms were recorded on videotape and approximately 30 consecutive waveforms were obtained from hard copies of each measurement. With a microcomputer (Olivetti M240, Scaramagno, Italy), the difference in peak systolic velocity between two flow velocity waveforms representing the expiratory and inspiratory phase of the fetal breathing movement was calculated. The mean difference in ductal peak systolic flow velocity modulation was established from the total number of waveform recordings during breathing activity. The diastolic portion of the ductal flow velocity waveform was not evaluated because it bears no direct relationship with shunting of blood from the pulmonary artery through the ductus. All Doppler measurements were performed by one observer (K.v.d.M.). Information on fetal ductal flow velocity recordings was not made available to the clinician responsible for the obstetric management.

The diagnosis of pulmonary hypoplasia was based on a reduced lung/-body weight ratio (Wigglesworth and Desai, 1981b) (ratio $\leq$0.015 for gestational ages $\leq$28 weeks or $\leq$0.012 for gestational ages >28 weeks) established at autopsy or on combined clinical finding of (1) immediate onset of severe respiratory insufficiency after birth requiring high-pressure artificial ventilation; (2) chest radiographs demonstrating small lung volume, with the diaphragm elevated above the seventh rib, downward sloping ribs, and a bell-shaped thoracic cage; (3) clinical respiratory disease that did not conform to the classical model of hyaline membrane disease.

The number of blood flow velocity waveforms studied in the fetal ductus arteriosus in normal pregnancy is expressed as mean $\pm$ 1 SD. A scattergram for mean ductal systolic flow velocity modulation in relation to gestational age was developed for all woman without oligohydramnios. From the data collected in normal pregnancy, the regression line as well as the 1st, 5th,

95th, and 99th percentile lines were estimated from linear regression analysis after logarithmic transformation of ductal blood flow velocity modulation. For the estimation of the regression lines it was assumed that the residual term displays a normal distribution with the mean of zero.

RESULTS

Normal pregnancy.

Poor quality fetal ductal flow velocity signals were obtained in six of 55 normal pregnancies because of excessive fetal body movements, lateral position of the fetal spine, or technical failure of the video equipment. In the remaining 49 pregnancies (50 fetuses), a technically acceptable recording during fetal breathing activity was documented. Oral glucose loading was performed in each instance. Mean maternal capillary glucose level was 6.4 ± 1.3 mmol/L, measured in 1 hour after oral glucose administration. Fetal birth weight was between the 10th and 90th percentile for gestational age (Kloosterman, 1970) corrected for maternal parity and fetal sex. Neonatal lung performance was normal. The mean number of blood flow velocity waveforms studied in the ductus arterious was 18.1 ± 6.8.

Modulation of the ductal flow velocity waveform was characterised by a momentary reduction of peak systolic velocity during the inspiration phase (Figure 5.3). Regression analysis of the ductal blood flow velocity modulation data obtained from the 50 normally developing fetuses (open circles, Figure

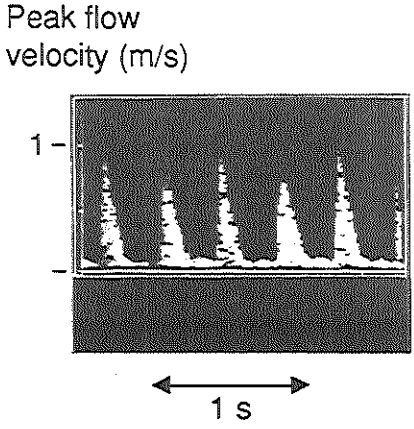

Figure 5.3. Blood flow velocity waveforms obtained from the fetal ductus arteriosus during fetal breathing activity.

5.4) revealed an exponential increase in ductal blood flow velocity modulation with advancing gestational age; the regression equation was ln ΔPV= 0.537 + 0.076 x weeks with R^2 = 0.90, p<0.0001, where ΔPV equals ductal blood flow velocity modulation. The regression equations for the 99th and the 1stpercentile lines were: 0.537 + 0.076 x weeks ± 2.58 x 0.1017, and for the 95th and 5th percentile lines: 0.537 + 0.076 x weeks ± 1.96 x 0.1017, in which 0.1017 equals the estimated standard deviation of the residual term and 2.58 and 1.96 represent the respective two-tailed 1% and 5% points of the standard normal distribution. Figure 5.4 presents the regression line and the estimated four percentile lines after transformation of the variable ln ΔPV back to its normal level by using the antilog.

Prolonged severe oligohydramnios

Of the 32 women who were admitted to our hospital during the study period because of premature rupture of membranes before 28 weeks' gestation, nine were not included in the study because no severe oligohydramnios developed. Six women were removed from the study because amnionitis developed and the women were delivered within 1 week after premature rupture of membranes; three other women were delivered before 25 weeks' gestational age. One woman was removed from the study because of intrauterine growth retardation and preeclampsia necessitating the use of antihypertensive drugs; thus 13 women remained for further analysis. In these 13 women the mean gestational age at the onset of the oligohydramnios was 23.3 ± 4.1 weeks (1 SD) and mean duration of oligohydramnios was 6.8 ± 2.9 weeks (1 SD). The maximum time interval between the last Doppler flow recording and delivery was 7 days. Mean maternal capillary glucose level measured 10 minutes after intravenous glucose administration was 6.2 ± 2.5 mmol/L. Fetal birth weight was between 10th and 90th percentile for gestational age (Kloosterman, 1970), corrected for maternal parity and fetal sex. Fetal heart rate always varied between 120 and 160 beats/min.

Forty-one fetal ductal flow velocity recordings were technically acceptable for further analysis. Prenatal findings and fetal outcome are presented in Tables 5.2, 5.3 and 5.4. The mean number of blood velocity waveforms studied in this group was 16.7 ± 7.6. Seven recordings were obtained in absence of fetal breathing activity. In patient no. 1, absence of fetal breathing activity was documented on three different occasions despite maternal intravenous glucose administration; neonatal lung performance was normal. In patient no. 3. no fetal breathing activity could be documented in three recordings. These recordings were not preceded by intravenous glucose admi-

nistration because glucose metabolism became abnormal after the first Doppler recording. Neonatal lung performance was normal in this case.

Table 5.2. Prenatal findings of group with prolonged severe oligohydramnios resulting in normal neonatal lung performance.

	gestational age			maternal glucose loading (intravenous)	FBM	ΔPV (m/s)
patiënt no.	at onset of oligohydramnios	at Doppler measurement	at delivery			
1	26	27	30	+	-	#
		28		+	-	#
		29		+	-	#
3	27	27	32	+	+	0.13
		29		*	-	#
		30		*	-	#
		31		*	+	0.17
		32		*	-	#
7	24	25	29	+	+	0.12
		26		+	+	0.14
		28		+	+	0.17
		29		+	+	0.13
8	26	29	32	+	+	0.13
		30		+	+	0.16
		31		+	+	0.15
		32		+	+	0.19
9	27	29	35	+	+	0.13
		30		+	-	#
		31		+	+	0.19
		33		+	+	0.20
		34		+	+	0.20
10	22	31	32	+	+	0.19
12	26	27	33	+	+	0.12
		28		+	+	0.12
		29		+	+	0.12
		31		+	+	0.15
		32		+	+	0.18
		33		+	+	0.19
13	16	25	27	+	+	0.10
		27		+	+	0.11

ΔPV Mean ductal peak systolic flow velocity modulation.
* There was no administration of glucose to the mother.
\- No fetal breathing movements could be observed during the measurement.
\# There were no ductal peak flow velocity modulations observed, which is logical since in these cases no fetal breathing movements could be documented.

Table 5.3. Prenatal findings of group with prolonged severe oligohydramnios resulting in pulmonary hypoplasia.

	gestational age			maternal glucose loading (intravenous)	FBM	ΔPV (m/s)
patiënt no.	at onset of oligohydramnios	at doppler measurement	at delivery			
2	25	29	31	+	+	0.08*
		29		+	+	0.04*
		30		+	+	0.08*
4	17	27	30	+	+	0.11*
		28		+	+	0.13*
		29		+	+	0.08*
		30		+	+	0.05*
5	23	28	30	+	+	0.13
		30		+	+	0.12*
6	27	33	34	+	+	0.08*
11	17	26	27	+	+	0.08*

ΔPV Mean ductal peak systolic flow velocity modulation
* Below 1st percentile

Table 5.4. Fetal outcome of group with prolonged severe oligohydramnios.

patient no.	fetal outcome	pulmonary hypoplasia		
		clinical evidence	confirmed at autopsy	lung/body weight ratio
1	Uneventful	-	-	-
2	Died immediately post partum	+	+	0.009
3	Uneventful	-	-	-
4	Died immediately post partum	+	+	0.012
5	Died 4 hr post partum	+	+	0.005
6	2 months of artificial ventilation, bronchopulmonary dysplasia, brain damage	+	-	-
7	Uneventful	-	-	-
8	Uneventful	-	-	-
9	Uneventful	-	-	-
10	Uneventful	-	-	-
11	Died immediately post partum	+	+	0.013
12	Uneventful	-	-	-
13	Uneventful	-	-	-

Despite intravenous glucose administration we were unable to document fetal breathing activity in patient no. 9 in one of five occasions. Thirty-four recordings were obtained during fetal breathing activity (patients 2 - 13). Longitudinal follow-up was feasible in nine of 13 women with oligohydramnios and accounted for 31 ductal blood flow velocity modulation measurements (Figure 5.5). In the remaining three women only one recording was obtained. When the ductal blood flow velocity modulation data nearest to delivery were considered (mean, 3.8 days; range, 0 to 7 days; Figure 5.4, closed circles), five women had ductal blood flow velocity modulation values below the 1st percentile of the reference curve. These reduced values were associated with pulmonary hypoplasia.

For the remaining seven women ductal blood flow velocity modulation values were within the normal range of the reference curve and were associated with normal neonatal lung performance. For the group of women with prolonged severe oligohydramnios that resulted in pulmonary hypoplasia, the mean gestational age on the onset of oligohydramnios was 21.8 ± 4.6 weeks (1 SD) and the mean duration of oligohydramnios was 8.6 ± 2.9 weeks (1 SD). For the group of women with prolonged severe oligohydramnios with normal neonatal lung performance, the mean gestational age at the onset of oligohydramnios was 24.3 ± 3.7 weeks (1 SD) and the mean duration of oligohydramnios was 7.0 ± 2.5 weeks (1 SD). Four of five cases of pulmonary hypoplasia were confirmed at autopsy. In the remaining infant the diagnosis of pulmonary hypoplasia was based on the aforementioned clinical criteria. This infant was treated with 2 months of high-pressure artificial ventilation and now suffers from bronchopulmonary dysplasia and severe brain damage caused by prolonged hypoxia after bilateral pneumothorax. The longitudinal ductal blood flow velocity modulation data (Figure 5.5) revealed that two of three fetuses in which pulmonary hypoplasia eventually developed demonstrated a downward trend in ductal blood flow velocity modulation, resulting in values below the 1st percentile of the reference curve.

DISCUSSION

Our data demonstrate that during normal pregnancy blood flow velocity waveforms obtained from the fetal ductus arteriosus are modulated by fetal breathing movements. During the inspiration phase of the fetal breathing cycle there is a momentary reduction of ductal systolic peak flow velocity. Because of limitations in the lateral resolution of current ultrasonographic equipment, no accurate measurements of ductal diameter could be obtained. Because dilatation of the fetal ductus arteriosus beyond its resting dimension has not

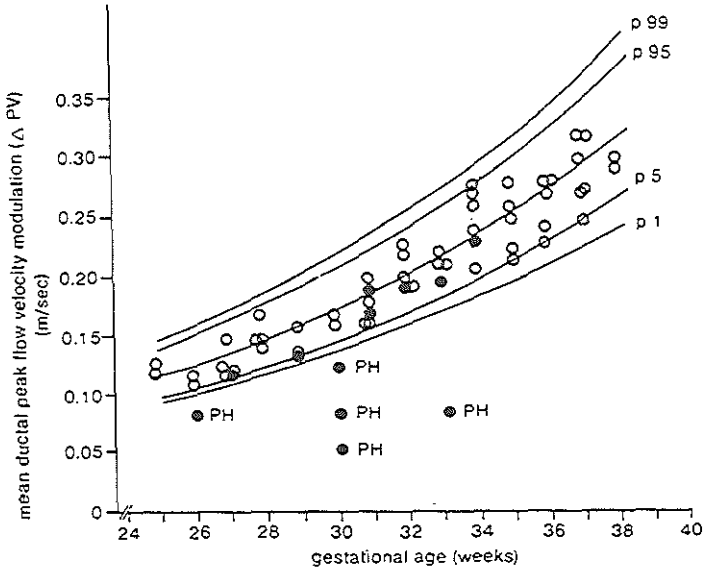

Figure 5.4. Mean breathing-related ductal peak systolic flow velocity modulation (ΔPV) relative to gestational age for a) 49 normal pregnancies (50 fetuses, open circles) with the estimated 1st, 5th, 95th and 99th percentile lines; b) last ΔPV value prior to delivery of 12 cases with prolonged severe oligohydramnios due to ruptured membranes (closed circles; PH= pulmonary hypoplasia).

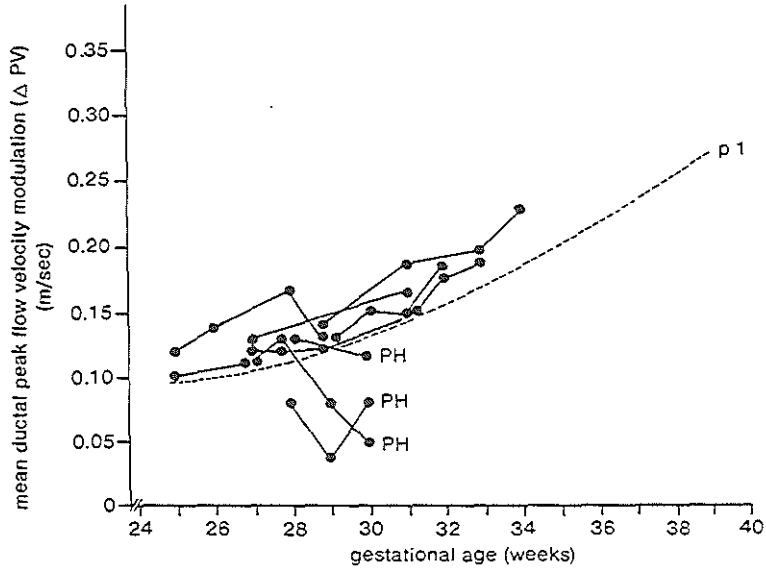

Figure 5.5. The first percentile line of the normal population (dotted line) and the mean breathing-related ductal peak systolic flow velocity modulation (ΔPV) relative to gestational age for 9 cases of prolonged severe oligohydramnios due to ruptured membranes (closed circles) in which serial recordings were obtained (PH= pulmonary hypoplasia).

been observed, and agents have not been identified that are capable of such dilatation, it seems unlikely that the reduction in ductal peak systolic flow velocity during fetal breathing activity is caused by increasing ductal diameter (Friedman et al., 1983). For this reason it is also unlikely that the blood flow velocity changes are caused directly by pressure changes in the fetal chest and abdomen during fetal breathing activity. The observed reduction in ductal peak systolic flow velocity during fetal breathing activity is in agreement with fetal lamb experiments in which it was established that the total pulmonary vascular resistance decreased during lung expansion (Assali et al., 1965). The subsequent increased perfusion of the pulmonary vascular bed was demonstrated by a rise in pulmonary artery flow and decrease in ductal flow, reflecting reduced right to left shunting. Fetal lamb studies have also shown that there is a rise in pulmonary blood flow and reduction in pulmonary vascular resistance with advancing gestational age caused by an increase in the total number of pulmonary vessels and increased vasomotor activity (Levin et al., 1976). In the human fetus this phenomenon begins during the late canalicular phase (±23 through ±26 weeks) and continues during the saccular and alveolar phase of lung development (±26 through ±40 weeks) (Wigglesworth et al., 1981a, Pringle, 1986). This may explain the small modulations in ductal peak systolic flow velocity at 25 weeks and subsequent exponential rise during the third trimester of pregnancy.

In the presence of oligohydramnios lung development may be arrested in the canalicular phase (Nimrod et al., 1986), resulting in reduced lung volume and impaired development of the pulmonary vascular bed, which is associated with a fixed high pulmonary resistance (Friedberg and Oechler, 1974, Levin, 1978, Wigglesworth et al., 1981a). This may explain the reduced ductal peak systolic flow velocity modulation observed by us in the fetuses with pulmonary hypoplasia. The predictive value of normal peak systolic flow velocity modulation for continuing lung growth was 100%, as was the predictive value of reduced modulation for pulmonary hypoplasia. Various clinical tests have been suggested with regard to the antepartum diagnosis of developing pulmonary hypoplasia. A close association has been reported between a low fetal thoracic circumference or low thoracic circumference/abdominal circumference ratio and poor neonatal lung performance (Nimrod et al., 1986, 1988, Johnson et al., 1987). Both parameters are useful but late indicators of pulmonary hypoplasia. If it is assumed that breathing-related ductal peak systolic flow velocity modulation and pulmonary vascular resistance are inversely related, then the longitudinal data in our study suggest that serial recording of ductal peak systolic flow velocity modulation during breathing

activity may be helpful in assessing the progression of abnormal lung development. Such assessment would allow a more optimal obstetric management in cases of prolonged severe oligohydramnios as a result of ruptured membranes at a stage of pregnancy when extrauterine survival can be expected. A larger longitudinal study is needed to substantiate this premise.

The secondary rise in breathing-related ductal peak systolic flow velocity modulation in one case (Figure 5.5) may be the result of the administration of 100 mg of indomethacin to the mother shortly before the Doppler flow velocity recording. It has recently been demonstrated that the use of the prostaglandin synthetase inhibitor indomethacin may lead to ductal constriction as determined by a significant rise in ductal peak systolic and peak diastolic velocities. In our case mean peak systolic velocity rose from 1.10 to 1.60 m/s. The subsequent increase in breathing-related ductal peak systolic flow velocity modulation was determined by a more pronounced peak systolic rise during expiration compared with inspiration. Because the constrictive effect of indomethacin may be observed as long as 12 hours after drug administration, studies of ductal flow modulation should be conducted beyond this period (Huhta et al., 1987, Moise et al., 1988). In our study administration of fenoterol was not considered to affect ductal peak systolic flow velocity because the fetal heart rate was within the physiologic range, during which no fetal heart rate dependency of ductal peak systolic flow velocity had been documented (this thesis, chapter 5.1 and 5.3).

Fetal breathing activity itself has been reported to be helpful in the assessment of fetal lung development in cases of prolonged severe oligohydramnios. Fetal breathing movements are important for facilitating lung growth. It has been shown that upper cervical cord injury in rabbit fetuses at 28 to 29 days' gestation results in a reduction in lung weight and total DNA content, and injury before 24 days results in retarded cellular differentiation. These effects were explained by cessation of fetal breathing activity (Wigglesworth and Desai, 1979). Although Blott et al. (1987) suggested that the absence of fetal breathing movements is highly predictive for pulmonary hypoplasia, this finding was challenged by Moessinger et al. (1987) who stated that observation of fetal breathing activity is not helpful in identifying patients with oligohydramnios actually developing fetal pulmonary hypoplasia. Results of our study support the latter statement. We were unable to observe fetal breathing activity on three occasions in one patient (Table 5.2) despite maternal intravenous glucose loading; neonatal lung performance was normal. Conversely, fetal breathing movements were established in five fetuses with pulmonary hypoplasia after birth (Table 5.3).

We conclude that fetal ductal peak systolic flow velocity is modulated by fetal breathing activity in normal late second- and third-trimester pregnancies. This ductal flow modulation exhibits an exponential increase with advancing gestational age, reflecting the developing fetal pulmonary vascular bed. In cases of prolonged severe oligohydramnios caused by ruptured membranes, normal ductal flow modulation is associated with normal neonatal lung performance, whereas pulmonary hypoplasia was established in cases of reduced ductal flow modulation.

5.3 FETAL DUCTAL FLOW VELOCITY WAVEFORMS AND FETAL BEHAVIOURAL STATES

5.3.1 INTRODUCTION

With the introduction of combined real-time and pulsed Doppler ultrasound equipment, a non-invasive method has become available for studying fetal haemodynamics in relation to fetal behavioural states. Van Eyck (1987) established marked behavioural state dependent differences in pulsatility index in fetal thoracic descending aorta and internal carotid artery. Under standardised fetal heart rate conditions there is a statistically significant reduction in pulsatility index in the fetal thoracic descending aorta during behavioural state 2F as compared with behavioural state 1F. This difference is almost entirely determined by changes in end-diastolic blood flow and therefore suggests reduced peripheral vascular resistance during behavioural state 2F, with increased perfusion of fetal skeletal musculature. In the near-term fetus, the individual contributions of state variables to these haemodynamic changes cannot be established, since they only occur in fixed combinations. Before 36 weeks' gestation however, coincidence of state variables is still incomplete and therefore different combinations of two state variables may occur (FHR-pattern A or B, eye or body movements present or absent; FHR-patterns C and D are relatively rare). Van Eyck has also studied fetuses at a gestational age of 27-28 weeks, and reports that the pulsatility index in the fetal thoracic descending aorta is significantly lower during periods of high heart rate variability when compared with episodes of low heart rate variability. This effect was independent of the presence or absence of fetal eye and body movements.

In the fetal internal carotid artery similar observations have been made. Under standardised fetal heart rate conditions, the pulsatility index during

behavioural state 2F is significantly reduced when compared with behavioural state 1F. This decrease suggests a reduced peripheral vascular resistance in the fetal cerebrum during behavioural state 2F.

Finally, in the umbilical artery the pulsatility index is behavioural state independent under standardised fetal heart rate conditions, suggesting that the aforementioned behavioural state related changes in blood flow velocity are of fetal origin.

On the basis of these data we hypothesise that a behavioural state dependent redistribution of blood flow might occur at the level of the cardiac right-to-left shunt(s). The next paper will discuss the effect of fetal behavioural states on fetal ductal flow velocity waveforms.

5.3.2 HUMAN FETAL DUCTAL FLOW VELOCITY WAVEFORMS RELATIVE TO BEHAVIOURAL STATES IN NORMAL TERM PREGNANCY

K. van der Mooren, J. van Eyck and J.W. Wladimiroff
Department of Obstetrics and Gynaecology, Erasmus University, Rotterdam, The Netherlands.
Published in Am. J. Obstet. Gynecol. 1989, 160, 371-374.

INTRODUCTION

The combined use of real-time and pulsed Doppler ultrasonography systems has opened the possibility of studying blood flow velocity waveforms in the human fetus. Intrinsic factors such as fetal breathing movements and cardiac arrhythmia affect fetal blood flow (Maršál et al., 1984, Wladimiroff and Van Bel, 1987). Recently it was demonstrated that in normal pregnancy at 37 to 38 weeks' gestation, blood flow velocity waveforms in the fetal descending aorta and the fetal internal carotid artery (Van Eyck et al., 1987) are affected by fetal behavioural states. In both vessels a significant reduction in the pulsatility index was established during behavioural state 2F (active sleep), compared with behavioural state 1 F (quiet sleep), according to the classification by Nijhuis et al. (1982). It was suggested that these changes reflect a reduced peripheral vascular resistance with the intent to increase perfusion of skeletal musculature and cerebrum to meet increased energy demands during active sleep. The reduced peripheral vascular resistance would subsequently result in a reduced venous return to the right side of the heart. Recently a technique for recording blood flow velocity waveforms in the fetal ductus

arteriosus became available (Huhta et al., 1987). The presence of behavioural state dependency of fetal ductal flow would support the suggestion of behavioural state-dependent fluctuations in venous return to the right side of the heart. The objective of this study was to investigate the relationship between fetal ductal blood flow velocity waveforms and behavioural states in the late phase of normal pregnancy.

MATERIAL AND METHODS

A total of 16 women with normal singleton pregnancies at 37 to 38 weeks' gestation consented to participate in the study. The gestational age was calculated from a reliable menstrual history and early ultrasonographic measurement of fetal crown-rump length or biparietal diameter. Fetal birth weight was between the tenth and the ninetieth percentiles for gestational age, according to Kloosterman's tables corrected for maternal parity and fetal sex (Kloosterman, 1970). All participants were nonsmokers, and no medications were prescribed. All studies were carried out 2 hours after breakfast or lunch with the participants in the semirecumbent position. A twodimensional real-time mechanical sector scanner (Diasonics CV400, Milpitas, CA., carrier frequency 3,5 MHz) was used to obtain a longitudinal cross section of the fetal ductus arteriosus on a short axis view of the fetal heart according to the method described by Huhta et al. (1987). The angle of insonation was always kept ≤ 5 degrees. The waveforms were obtained in behavioural states 1F and 2F, according to the classification by Nijhuis et al. (1982). These behavioural states are defined as follows:

State 1F--quiescence, which can be regularly interrupted by brief gross body movements, which are startles; eye movements are absent; stable heart-rate pattern with a small oscillation band width; isolated accelerations occur but are strictly related to fetal movements.

State 2F--frequent and periodic gross body movements that are mainly stretches and retroflexions and movements of extremities; continuous eye movements; heart-rate pattern with a wider oscillation band width than in state 1F and frequent accelerations during movements.

To establish these behavioural states, the following parameters were simultaneously recorded: (a) fetal heart rate (FHR) obtained from a Doppler ultrasonographic cardiotocograph (Hewlett Packard 8040A, Boblingen, West Germany, carrier frequency 1 MHz); (b) fetal eye movements, which were studied from a transverse view of the fetal face with a two-dimensional real-time linear array scanner (Hitachi EUB-27, Tokyo, carier frequency 3,5 MHz); (c) fetal body movements obtained from a sagittal view of the fetal

trunkwith a two-dimensional real-time mechanical scanner (Diasonics CV400, carrier frequency 3,5 MHz).

The three transducers were placed so that there was minimal interference among the three ultrasonographic modes. Flow velocity recordings were performed only when a clear fetal behavioural state was identified and when this state had been present ≥3 minutes. All recordings were performed during fetal apnoea. The maximum amount of time for the completion of a flow velocity recording after a state determination was 3 minutes. The blood flow velocity waveforms were recorded on videotape over a 15-second period that included on average 30 consecutive cardiac cycles. At least 20 optimal flow velocity waveforms were selected from hard copies of each recording. A microcomputer (Olivetti M240, Scaramagno, Italy) was used to calculate peak flow velocity (cm/s) and acceleration time (ms). It has been shown that FHR should be considered when pulsatility index values are calculated from blood flow velocity waveforms (Mires et al, 1987, Van den Wijngaard et al., 1988). FHR independency was previously demonstrated for the acceleration time in flow velocity waveforms that originated from the fetal descending aorta (Lingman and Maršál, 1986). It was assumed that the same applies for the ductus arteriosus. However, no information is available on the relationship between FHR and aortic peak flow velocity. It was decided to relate the peak flow velocity in the ductus arteriosus to FHR for each fetus and for each fetal behavioural state. All data were divided into groups that represented a FHR range of 5 beats/min. Changes in peak flow velocity and acceleration time in the ductus arteriosus with respect to behavioural states 1F and 2F were tested with the paired Student's t-test. FHR dependency of peak flow velocity in the ductus arteriosus was assessed by analysis of the slopes of the individual regression lines with the Student's t-test.

RESULTS

Poor-quality Doppler ultrasonographic signals were obtained in four participants because of maternal obesity or lateral position of the fetal spine, leaving 12 participants for further analysis. The mean number of blood velocity waveforms studied in the fetal ductus for all participants was 54 ± 28 (1 SD) in behavioural state 1F and 54 ± 25 (1 SD) in behavioural state 2F. FHR in behavioural state 1F ranged between 106 and 160 beats/min. Paired analysis of the data in behavioural states 1F and 2F was performed in the FHR range from 121 to 145 beats/min and resulted in five groups (i.e. 121 to 125, 126 to 130, 131 to 135, 136 to 140, and 141 to 145 beats/min) with a total number of 1095 flow velocity waveforms. No statistical evaluation was attempted in

Table 5.5. Mean paired ductal peak flow velocity difference (peak flow velocity ± 1SD) per fetal heart rate between behavioural state 1F and 2F.

FHR range (beats /min)	number of participants with paired observations	mean peak flow velocity (cm/s)		mean paired difference	SD	statistical significance
		state 1F	state 2F			
121-125	6	122.3	109.9	12.4	6.6	p<0.01
126-130	7	122.0	109.9	13.0	5.5	p<0.001
131-135	10	125.1	110.8	14.3	8.4	p<0.001
136-140	9	128.7	114.9	13.8	8.3	p<0.002
141-145	7	126.1	110.1	16.0	8.2	p<0.01

groups comprising fewer than six participants with paired observations. A statistically significant reduction of peak flow velocity in behavioural state 2F, as compared with behavioural state 1F, was established for all FHR ranges studied (Table 5.5).

A visual display of this reduction is presented in Figure 5.6. The mean paired difference in acceleration time between behavioural states 1F and 2F was -5.17 ± 10.84 (1 SD) ms, which was not statistically significant. The mean slope of regression lines of peak flow velocity in relation to FHR was 0.03 ± 0.16 (1 SD) in behavioural state 1F and -0.02 ± 0.19 (1 SD) in behavioural state 2F.

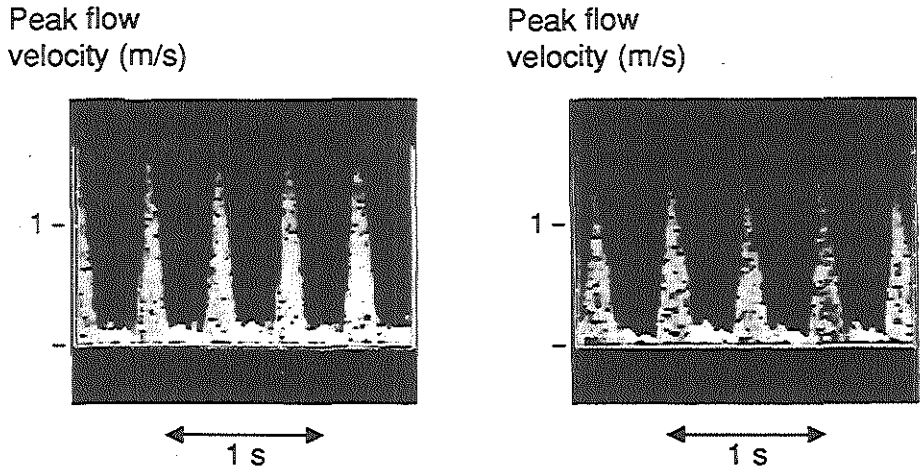

Figure 5.6. Peak flow velocities in the fetal ductus arteriosus in normal late pregnancy (38 weeks) during fetal behavioural states 1F (left) and 2F (right).

DISCUSSION

The succes rate in the obtainment of high-quality Doppler ultrasonographic signals from the fetal ductus arteriosus was 75%, which confirms the feasibility of recording ductal blood flow velocities in the near-term human fetus. Moreover, the ability to obtain flow velocity waveforms with an angle of insonation ≤5 degrees minimises the errors of angle correction in velocity calculations.

Results of this study show a reduction of ductal peak flow velocity in behavioural state 2F, as compared with behavioural state 1F, whereas fetal behavioural state dependency could not be established for the acceleration time. Peak flow velocity and acceleration time determine the acceleration slope of the blood flow velocity waveform, which reflects stroke volume (Hatle and Angelsen, 1981) and myocardial contractility (Alverson and Berman, 1983). The reduction in in ductal peak velocity in behavioural state 2F, in combination with the behavioural state independancy of acceleration time, reflects reduced flow in the fetal ductus arteriosus and suggests a redistribution of left and right ventricular output in favour of the left side of the heart. This would be in agreement with previous studies in which flow velocity waveforms in the fetal descending aorta and the fetal internal carotid artery pointed to a reduced peripheral vascular resistance at fetal trunk and cerebral level during behavioural state 2F (Van Eyck, 1987).

Another possible explanation for the reduced ductal peak flow velocity could be an increase in ductal diameter in behavioural state 2F. Recent studies support the presence of vascoactive factors that influence ductal diameter (Clyman, 1987). Circulating concentrations of adenosine may play a role in the maintenance of ductus arteriosus patency during fetal live (Mentzer et al., 1985). Although prostaglandines have no direct effect on the ductus arteriosus, they are able to reverse the vascoconstrictor action of indomethacin without dilating the ductus beyond its resting dimension (Friedman et al., 1983). Because dilatation of ductus arteriosus beyond its resting dimension has not been observed and no agents that are capable of doing this have been identified, it seems unlikely that the reduction of ductal peak flow velocity in behavioural state 2F is caused by an increase in ductal diameter.

Whereas in studies of fetal bradyarrhythmia and tachyarrhythmia an inverse relationship was demonstrated between aortic peak flow velocity and fetal heart rate (Tonge et al., 1984, Lingman and Maršál, 1986), no data are available with regard to a similar relationship in the normal heart rate range. This study, however, has clearly established fetal heart rate independency of peak flow velocities in the fetal ductus arteriosus. It can be concluded that the

fetal behavioural state should be taken into account in further studies conducted on peak flow velocities in the fetal ductus arteriosus in the late phase of normal pregnancy.

5.4 CONCLUSIONS

Also in the ductus arteriosus, stroke volume and volume blood flow seem to increase with advancing gestation, whilst afterload falls. Ductus arteriosus flow velocity parameters are fetal heart rate independent. During fetal inspiration ductal peak systolic velocity falls while expiratory values remain within the normal range. Acceleration time and peak diastolic velocity do not change during fetal breathing. In the presence of prolonged oligohydramnios, this drop in ductal peak systolic velocity on inspiration was diminished in those fetuses that postnatally showed to have pulmonary hypoplasia. In fetuses that displayed normal ductal peak systolic velocity differences during respiration, pulmonary development proved to be normal. This suggests that in the normal fetus during inspiration pulmonary blood flow increases, resulting in a lower ductal peak systolic velocity. In fetuses with pulmonary hypoplasia, the lungs have a fixed high vascular resistance, so that less blood can enter the pulmonary vascular bed on inspiration.

Van Eyck et al. (1990a) have shown that foramen ovale blood flow increases during fetal inspiration. This suggests additional haemodynamic changes during fetal breathing at the level of the fetal heart. This is discussed further in chapter 4.2.

The fetal vascular Doppler data discussed in chapter 5.3 indicate that a redistribution of blood flow in favour of the left heart takes place during behavioural state 2F when compared with behavioural state 1F. Few other authors have recently investigated human fetal haemodynamics in relation to fetal behaviour. Rizzo et al. (1990) have studied fetal cardiac output in relation to behavioural states at 36-38 weeks' gestation by recording Doppler flow velocity waveforms at atrioventricular level and measuring valve areas. During behavioural state 2F, they report an increase in left ventricular output with a concomittant decrease in right ventricular output while combined cardiac output remains unchanged. They conclude that during state 2F a redistribution of cardiac output in favour of the left side of the heart takes place. This is in agreement with the results from our study on flow velocity waveforms in the ductus arteriosus with respect to behavioural states. Rizzo et al. have found no differences in mitral and tricuspid E/A-ratios between behavi-

oural state 1F and 2F and conclude that a change in preload of both ventricles cannot be responsible for this redistribution. This does not seem a tenable hypothesis, since it has been strongly suggested by Van Eyck et al. (1990b), that the redistribution of blood flow in favour of the left heart during behavioural state 2F is established by an increase of flow velocities through the foramen ovale. This will result in an increased preload of the left ventricle. Furthermore, left ventricular afterload may be expected to be lower during behavioural state 2F when compared with behavioural state 1F. As has been discussed in chapter 4.1.2., the E/A-ratio at fetal atrioventricular level probably does not reflect ventricular preload alone, but the combined effects of preload, afterload, ventricular compliance and heart rate. This may explain the above-mentioned contradictory findings.

Chapter 6

FETAL INTRACARDIAC DOPPLER STUDIES DURING SUPRAVENTRICULAR EXTRASYSTOLES

6.1 INTRODUCTION

Cardiac function can be described in terms of preload, afterload, contractility and heart rate (Sonnenblick et al., 1963, MacGregor et al., 1974, McPherson et al., 1976, Seed and Walker, 1988); preload forms the basis of the Frank-Starling mechanism. Further, it has been shown by invasive animal and human studies that the myocardium of the adult heart has an additional property that serves to maintain cardiac output within normal limits during varying haemodynamic circumstances including arrhythmias, i.e. the force-interval relationship (Freeman et al., 1987, Seed and Walker, 1988).

The Frank-Starling mechanism compensates for changes in end-diastolic volume (roughly equal to preload) as can be seen with varying beat-to-beat intervals. When the beat-to-beat interval increases, end-diastolic volume increases and during the following heart beat the stroke volume will increase to compensate for this. When the beat-to-beat interval falls, to some extent the reverse will take place. There are however limits to this mechanism: when the beat-to-beat interval becomes too large, the myocardial fibres get overstretched so that contraction will be less effective and the mechanism will fail. With too high heart frequencies, diastolic filling time becomes too short, thus giving rise to forward failure. Therefore, an optimum heart rate range exists in which the Frank-Starling mechanism is effective in maintaining cardiac output within physiological limits: the ascending limb of the Frank-Starling curve (Seed and Walker, 1988).

The force-interval relationship adds something extra to this mechanism. It has first been shown in strips of isolated heart muscle that under circumstances of constant pre and afterload, with changing stimulation frequency, the first contraction following a prolonged stimulation interval is augmented. This effect is obviously not due to the Frank-Starling mechanism, but to an intrinsic property of the myocardial muscle tissue; the preceding beat-to-beat interval influences myocardial contractility during a heart beat (Seed and Walker, 1988). The force-interval relationship can be more generally described as a mechanism called 'previous beat contraction history' (Slinker, 1991),

meaning that the preceding beat-to-beat interval influences ventricular performance in each heart beat.

Meanwhile this mechanism has also been identified in the intact animal and in the human heart. The force-interval relationship may express itself in a couple of ways, two of which will be briefly discussed.

Post-stimulation potentiation.

When an isolated animal heart in the laboratory is paced at high heart frequencies under fixed pre and afterload conditions, the first beats after the increase in stimulation frequency show a progressive increase in tension to a new plateau (Freeman et al., 1987). This mechanism is called the Bowditch staircase, after the person who has first described it, and has been identified in the human heart as well (Seed and Walker, 1988). However, it appears that this mechanism plays a rather small role in enhancing cardiac muscle function in vivo.

Post-extrasystolic potentiation.

In the presence of a premature contraction, the premature beat is weak and the beat that follows it is potentiated. Even if the extrasystolic beat is of negligable strength, the following beat will be potentiated as long as depolarisation occurs. Post-extrasystolic potentiation then gradually decays over some beats. As has been explained before, post-extrasystolic potentiation is caused by a length independent mechanism. The time-interval before the extrasystole is inversely related to the strength of the first post-extrasystolic beat. The time interval after the extrasystole is also important, because sufficient time is needed for mechanical restitution of the muscle if the true degree of potentiation is to be expressed (Anderson et al., 1980, Wisenbaugh et al., 1986, Seed and Walker, 1988).

The fetal circulation is entirely different from the adult situation. Among others, ventricular compliance in the fetus is considerably less than postnatally (Romero et al., 1972, McPherson et al., 1976). It is interesting to know whether the fetal ventricular muscle also has the disposal of the Frank-Starling mechanism and the force-interval relationship to maintain cardiac output within certain limits, or that heart rate alone determines cardiac output. Fetal animal laboratory experiments show the presence of both the Frank-Starling mechanism (Kirkpatrick et al., 1976) and the force-interval relationship (Anderson et al., 1980) in the fetal heart (Kirkpatrick et al., 1975). In the normal fetal heart rate range, the fetal heart operates near the upper limit of

the Frank-Starling function curve (Gilbert, 1980, Thornburg and Morton, 1983). The amount of post-extrasystolic potentiation increases with advancing gestational age (Anderson et al., 1984).

In the human fetal heart these mechanisms are difficult to investigate since obviously several relevant haemodynamic factors cannot be controlled or even quantitated. However, fetal Doppler echo-(cardio)graphy provides a noninvasive way to semiquantitatively investigate the fetal cardiovascular system. Tonge et al. (1984, 1986) have made an estimate of fetal volume blood flow at the level of the fetal thoracic descending aorta in normal fetuses and in fetuses exhibiting different kinds of fetal arrhythmias and report that cardiac output is maintained within normal limits over a heart rate range of 50-250 bpm. Within the normal fetal heart rate range, i.e. 120-160 bpm, cardiac output is determined by fetal heart rate. The same has been observed by Wladimiroff et al. (1983) in one fetus demonstrating several forms of arrhythmia within one and the same observation period.

On the basis of these findings it may be concluded that the fetal heart has the possibility to compensate for heart rate changes. From the aforementioned fetal animal laboratory data it is suggestive that both the Frank-Starling mechanism and the force-interval relationship contribute to this. An attempt has been made in the human fetus to differentiate between both mechanisms by measuring Doppler flow velocities across the cardiac valves as well as establishing fractional shortening of both ventricles in fetuses with extrasystoles (Reed et al., 1987a). It was concluded that the Frank-Starling mechanism was operational in the fetal heart since the time-velocity integral of the post-extrasystolic beats is higher than that from normal beats; this observation is in agreement with the aforementioned fetal Doppler studies. Further, it is stated that post-extrasystolic potentiation is present because an increase in fractional shortening was measured in the post-extrasystolic beats when compared with normal beats. However, it has been made plausible by Seed and Walker (1988), that assessment of ventricular function by measurements related to stroke volume, such as fractional shortening, may be biased since such parameters depend in part on pre and afterload which will inevitably vary under these circumstances.

Lingman and Maršál (1987) have also found evidence for the existence of the Frank-Starling mechanism in the human fetal heart by measurement of volume blood flow in the fetal descending aorta. Furthermore, they have determined the rising slope of blood velocity waveforms obtained in this vessel, which is equal to acceleration/mean velocity over the beat. In animal experiments the rising slope has shown to be closely related to ventricular

dP/dt, a parameter for heart muscle contractility (Anderson et al., 1984). In post-extrasystolic beats in the human fetus, the rising slope was increased when compared with normal beats. This indeed suggests that the force-interval relationship exists in the human fetal heart. However, in our experience the acceleration of a flow velocity waveform shows a high intra-observer variability both within patients as within tests (Groenenberg et al., 1991). Therefore it is a parameter that probably has to be regarded with some caution. At this stage, Doppler flow velocity waveform recording does not seem to allow differentiation between the Frank-Starling mechanism and post-extrasystolic potentiation.

Smith et al. (1990) have recently described a case of fetal supraventricular conducted and blocked extrasystoles, which they have analysed by means of electrocardiography during labour. They have measured the pre-ejection period, a measure reflecting the inotropic state of the heart, both in normal beats and in post-extrasystolic beats following conducted and following blocked extrasystoles. They state that any difference in this parameter between post-extrasystolic beats following conducted and following blocked extrasystoles must be due to inotropic potentiation, since in blocked extrasystoles no depolarisation occurs, and hence no inotropic potentiation on the basis of post-extrasystolic potentiation can be present. They have indeed described different patterns of augmentation following these two forms of extrasystoles.

In the next paragraph, Doppler flow velocity data recorded at cardiac level during fetal atrial ectopics will be considered.

6.2 FETAL ATRIOVENTRICULAR AND OUTFLOW TRACT FLOW VELOCITY WAVEFORMS DURING CONDUCTED AND BLOCKED SUPRAVENTRICULAR EXTRASYSTOLES

K. van der Mooren*, J.W. Wladimiroff* and Th. Stijnen**
*Department of Obstetrics and Gynaecology, **Department of Biostatistics, Erasmus University, Rotterdam, The Netherlands
(submitted)

INTRODUCTION

Supraventricular extrasystolic beats, conducted or blocked, are one of the most frequent forms of fetal arrhythmias encountered (Allan et al., 1983, Lingman et al., 1986a). They do not seem to have any negative circulatory effects provided that there are no associated structural anomalies (Lingman et al., 1986a, Stewart, 1989). This association is reported to occur in about 5% of cases (Stewart, 1989). Some authors state, that extrasystoles may be indicative of fetal distress during labour in some instances (Redman, 1958, Lingman et al., 1986a). Premature beats are however found in 1% of healthy neonates (Southall et al., 1980) and in up to 10% of normal fetuses (Allan et al., 1983).

Haemodynamics of the human fetal cardiovascular system can be studied noninvasively and semi-quantitatively by means of Doppler ultrasound techniques. In the human fetus, Doppler echocardiography can be performed from about 11 weeks of gestation onwards (Wladimiroff et al., 1991). To our knowledge, a detailed analysis of the Doppler flow velocity waveforms from outflow tracts and atrioventricular valves has never been performed in a larger series of fetuses with supraventricular extrasystolic beats.

In this study we addressed the following questions:

1) in which way do flow velocity waveforms from outflow tracts and atrioventricular valves change during blocked and during conducted supraventricular extrasystoles when compared with waveforms obtained from normal sinus beats;

2) is there a relation between these waveform changes and the preceding beat-to-beat interval.

MATERIAL AND METHODS

The study group consisted of 17 women, who were referred between November 1988 and May 1989 because of an irregular fetal heart rhythm which was noticed during a routine obstetrical examination. The type of arrhythmia was established by means of M-mode echocardiography (Stewart, 1989). Ten women showed fetal conducted supraventricular extrasystoles (Group 1), whereas five women displayed fetal blocked supraventricular extrasystoles (Group 2). Two women demonstrated both types, and were therefore included in both groups. Group 1 eventually consisted of 12, and Group 2 of seven women. In all instances, extrasystoles occurred at least once in every 10 beats.

All women gave informed consent to participate in the study. The study protocol was approved of by the Hospital Ethics Committee.

The pregnancy duration was determined from the last menstrual period and confirmed by ultrasonic measurements of the biparietal diameter between 14 and 18 weeks of gestation. Before a Doppler study was performed, fetal structural anomalies and signs of fetal cardiac decompensation were excluded by means of a detailed sonographic examination. All pregnancies were uneventful, and birthweights were between the 5th and 95th percentile according to Kloosterman's tables, corrected for maternal parity and fetal sex (Kloosterman, 1970).

The mean maternal age in Group 1 was 28.4 yr (range 23-33 yr), the median parity was 0 (range 0-2), and the mean gestational age was 34.2 weeks (range 27.0-38.3 weeks). The mean maternal age in Group 2 was 26.9 yr (range 23-30 yr), the median parity was 0 (range 0-5) and the mean gestational age was 30.2 weeks (range 25.3 to 36.0 weeks).

Reference charts obtained in a previous study on normal cardiac flow velocity waveforms (this thesis, chapter 4.1) were used for comparison of time-averaged velocity between supraventricular extrasystoles and normal (sinus) beats.

A combined mechanical sector scanner and pulsed Doppler system (Diasonics CV 400) with a carrier frequency of 3.5 and 3.0 MHz was used for blood flow velocity measurements in the ascending aorta, pulmonary artery, and at the mitral and tricuspid valve. The sector scanner operates at power outputs less than 100 mW/cm2 spatial peak/temporal average in both imaging and Doppler modes by manufacturers' specifications. Two-dimensional imaging was used to ensure the correct position of the pulsed Doppler gate before and after each Doppler tracing was obtained. Maximum flow velocity waveforms from the ascending aorta were recorded from the "five chamber view". Maximum flow velocity waveforms from the pulmonary

artery were collected from the conventional short axis view. Maximum flow velocity waveforms at mitral and tricuspid valve level were recorded from the four chamber view. At all sites, the Doppler sample volume was placed immediately distal to the valve leaflets. The Doppler sample volume length ranged between 0.1 and 0.4 cm. Doppler tracings were accepted when the angle between the Doppler cursor and the assumed direction of flow was 10 degrees or less, and when after completion of a Doppler recording the Doppler cursor and sample volume still had a good position. Doppler studies were performed by one examiner (K.v.d.M.). All blood flow velocity waveforms were obtained during fetal apnoea and stored on videotape. From hardcopies the analysis of at least 36 consecutive waveforms from each site was carried out using a microcomputer (Olivetti 240) linked to a graphics tablet. The following parameters were calculated:

- in the two outflow tracts:
    1) conducted supraventricular extrasystoles: peak systolic velocity (cm/s) and acceleration time (ms) for sequences consisting of the normal beat immediately preceding the extrasystolic beat, the extrasystolic beat and the post-extrasystolic beat;
    2) blocked supraventricular extrasystoles: peak systolic velocity (cm/s) and acceleration time (ms) for sequences consisting of the normal beat and the post-extrasystolic beat;

  finally, time-averaged velocity from each whole Doppler tracing was calculated;

- at atrioventricular level:
    1) conducted supraventricular extrasystoles: peak-E wave and peak-A wave velocities (cm/s) and E/A-ratios for sequences consisting of the normal beat immediately preceding the extrasystolic beat, the extrasystolic beat and the post-extrasystolic beat; for the extrasystolic beat only peak-A wave velocity was calculated;
    2) blocked supraventricular extrasystoles: peak-E wave and peak-A wave velocities and E/A-ratios for sequences consisting of the normal beat and the post-extrasystolic beat;

  finally, time-averaged velocity from each whole Doppler tracing was calculated.

Sequences were only included if at least three sinus beats preceded a particular extrasystolic beat to exclude possible influence from a previous extrasystole on the normal beat. In 15 fetuses comparisons were made at outflow tract level not only for the post-extrasystolic beat, but also for the sinus beat immediately following this beat and the normal beat. This was done because in animal laboratory experiments a gradual decay of post-extrasystolic potentiation over some beats has been described (Seed and Walker, 1988).

Time-intervals (ms) preceding and following a particular beat were calculated. The former is referred to as filling time, the latter as period time relative to a particular flow velocity waveform. In Figure 6.1 these time intervals are presented in a schematic example of a conducted supraventricular extrasystole at outflow tract level.

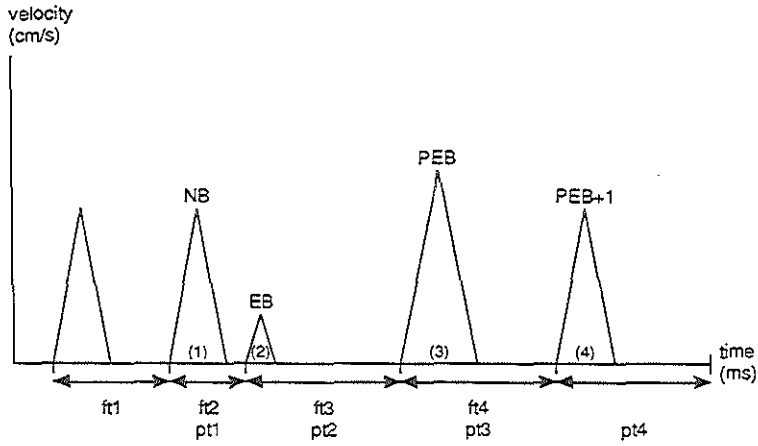

Figure 6.1. Schematic representation of the different time-intervals in a sequence with a conducted supraventricular extrasystole at outflow tract level.

NB= normal beat, the first beat of a sequence; EB= extrasystolic beat, the second beat of a sequence; PEB= post-extrasystolic beat, the third beat of a sequence; PEB+1= the first beat following a PEB, the fourth beat of a sequence; fti= filling time belonging to beat no i; pti= period time belonging to beat no i.

Peak systolic velocities were measured from the zero-line to the highest point of the Doppler velocity peak. Acceleration time was measured as the time between the onset of ejection and the peak of velocity. Time-averaged velocity was calculated as area-under-curve divided by period time.

All Doppler studies were performed two hours following breakfast or lunch with the patient in a semi-recumbent position. The duration of one

examination never exceeded 45 minutes.

Statistical analysis consisted of the following items:

1. For each "sequence" consisting of: normal beat - extrasystolic beat - post-extrasystolic beat, paired analysis by means of the t-test of the above mentioned parameters for extrasystolic versus normal beat and for post-extrasystolic versus normal beat was performed, and the relative differences were calculated in per cent. Also, the sinus beat following the post-extrasystolic beat was compared with the normal beat by means of the paired Student's t-test.

2. At all four measuring sites mean time-averaged velocity during supraventricular extrasystoles was compared with the mean time-averaged velocity established in an earlier study standardised for gestational age (this thesis, chapter 4.1). This was done as follows: for the mean time-averaged velocity obtained in each woman in the present study, the standard deviation score relative to the reference value was calculated. The standard deviation score is the difference of the calculated and the reference mean divided by the standard deviation of the reference population at a particular gestational age. The SDS of a particular patient measures the distance of the value of the patient to the reference mean in standard deviation units. Then a one-sample t-test was used to test whether the mean SDS differed significantly from zero.

3. At outflow tract level the regression lines of filling time with peak systolic velocities for extrasystolic, normal and post-extrasystolic beats, both combined and separately, were established for each woman. Then a one-sample t-test was used to test whether the mean slope of these regression lines significantly differed from zero. Also, the relationship of extrasystolic filling time with peak systolic velocity for the post-extrasystolic beats was established. The level of statistical significance was set at 0.05.

RESULTS

Good quality Doppler registrations were obtained in each instance at all sites. In four women a second recording was necessary due to unfavourable fetal position during the first recording. The time interval between these two recordings never exceeded 30 minutes. The average number (± 1SD) of cycles studied per patient during supraventricular extrasystoles was 29.1 ± 10.2 for the pulmonary artery, 29.5 ± 10.2 for the ascending aorta, 29.3 ± 10.1 for the mitral valve and 26.9 ± 8.1 for the tricuspid valve. In total, 2182 cycles were collected.

Table 6.1. Mean relative differences (in %) of peak systolic velocity (cm/s) and acceleration time (ms) for extrasystolic and post-extrasystolic beats compared with normal beats at all four measuring sites for conducted supraventricular extrasystoles (group 1).

	mean	SD	range	p-value
PA-PSV				
EB	-26.4	12.4	-51 to -14	<0.001
PEB	12.5	2.9	6 to 23	<0.001
PA-ACT				
EB	-36.0	10.3	-53 to -27	<0.001
PEB	22.3	6.4	12 to 30	<0.001
AO-PSV				
EB	-26.4	16.5	-53 to -10	<0.001
PEB	12.0	3.7	8 to 16	<0.001
AO-ACT				
EB	-32.7	8.8	-45 to -20	<0.001
PEB	16.6	4.3	8 to 21	<0.001
MV-E				
PEB	- 1.2	14.4	-26 to 0	0.77
MV-A				
EB	-18.2	28.5	-69 to 20	0.051
PEB	-15.6	10.1	-31 to 0	<0.001
MV-E/A				
PEB	14.9	19.5	0 to 51	0.03
TV-E				
PEB	- 0.01	6.7	- 4.6 to 3.7	0.7
TV-A				
EB	-33.2	21.1	-60 to 0	<0.001
PEB	-20.4	7.3	-31 to -10	<0.001
TV-E/A				
PEB	27.5	19.6	0 to 57	<0.01

PSV=peak systolic velocity; ACT=acceleration time; E=peak-E wave; A=peak-A wave; E/A=E/A ratio; PA=pulmonary artery; AO=ascending aorta; MV=mitral valve; TV=tricuspid valve; EB=extrasystolic beat; PEB=post-extrasystolic beat; SD=standard deviation.

Group 1 (n=12)

- Outflow tract level

All parameters obtained showed significant differences for extrasystolic versus normal beats and for post-extrasystolic versus normal beats (Table 6.1). Particularly, peak systolic velocities in the pulmonary artery and ascending aorta were always higher in post-extrasystolic than in normal beats. Mean extrasystolic filling time (± 1SD) was 331 ± 28 ms, mean post-extrasystolic filling time was 456 ± 54 ms, and mean reference filling time was 435 ± 25 ms. These differences were all statistically significant ($p<0.001$).

- Atrioventricular level

Peak-E wave velocity for post-extrasystolic beats did not differ from peak-E wave velocity for normal beats. Peak-A wave velocity for post-extrasystolic beats was lower than for normal beats. Correspondingly, E/A-ratios at both levels increased during post-extrasystolic beats. Peak-A wave velocity for extrasystoles was lower than for normal beats at tricuspid level, and was not different from normal beats at mitral level (Table 6.1).

Group 2 (n=7)

- Outflow tract level

The parameters obtained showed significant differences for post-extrasystolic versus normal beats in all women (Table 6.2). Peak systolic velocity in the pulmonary artery and ascending aorta was always higher in post-extrasystolic than in normal beats. Mean post-extrasystolic filling time (± 1SD) was 715 ± 42 ms, whereas mean reference filling time was 474 ± 35 ms. This difference was also statistically significant ($p<0.001$).

Table 6.2. Mean relative differences (in %) of peak systolic velocity (cm/s) and acceleration time (ms) for post-extrasystolic beats compared with normal beats at all four measuring sites for blocked supraventricular extrasystoles (group 2).

	mean	SD	range	p-value
PA-PSV PEB	13.9	4.4	10 to 24	<0.001
PA-ACT PEB	31.7	9.7	17 to 36	<0.001
AO-PSV PEB	12.3	4.4	8 to 18	<0.001
AO-ACT PEB	18.8	7.5	0 to 25	<0.001
MV-E PEB	7.0	5.7	-20 to 0	<0.02
MV-A PEB	-15.1	8.3	-25 to 0	<0.005
MV-E/A PEB	13.8	11.1	0 to 30	<0.020
TV-E PEB	- 6.7	12.7	-25 to 11	0.214
TV-A PEB	-29.5	9.3	-42 to -17	<0.001
TV-E/A PE	37.7	27.3	6 to 94	<0.02

PSV=peak systolic velocity; ACT=acceleration time; E=peak-E wave; A=peak-A wave; E/A=E/A ratio; PA=pulmonary artery; AO=ascending aorta; MV=mitral valve; TV=tricuspid valve; PEB=post-extrasystolic beat; SD=standard deviation.

- Atrioventricular level

  At mitral level, peak-E wave velocities for post-extrasystolic beats were lower than peak-E wave velocities for normal beats, whereas at tricuspid level there was no difference. Peak-A wave velocities were lower for post-extrasystolic than for normal beats at both sites. E/A-ratios for post-extrasystolic beats were higher than for normal beats in all cases (Table 6.2).

For both group 1 and 2, none of the documented differences relative to normal beats were related to gestational age.

In 15 fetuses in which at outflow tract level the first sinus beat following a post-extrasystolic beat was compared with the corresponding normal beat, no differences could be established for either peak systolic velocity or acceleration time.

At all four recording sites, the time-averaged velocities recorded during conducted and blocked supraventricular extrasystoles were strikingly lower than time-averaged velocities obtained during sinus rhythm in the controls (Tables 6.3-6.6).

Table 6.3. Mean time-averaged velocity (TAV, cm/s) in conducted supraventricular extrasystoles (group 1) and normal control values (mean±1SD) relative to gestational age (weeks) for pulmonary artery (PA) and ascending aorta (AO) with individual and mean (±1SD) standard deviation score (SDS).

gest. age (weeks)	mean TAV PA	reference TAV PA mean±1SD	SDS	mean TAV AO	reference TAV AO mean±1SD	SDS
27.0	17.1	22.6±1.7	-3.24	22.1	26.6±2.1	-2.14
29.4	17.8	24.4±1.8	-3.67	23.2	27.8±2.4	-1.92
31.5	18.0	25.1±1.9	-3.55	19.4	28.8±2.7	-3.48
33.0	20.8	25.8±2.0	-2.50	19.4	29.4±2.8	-3.57
34.0	25.9	26.3±2.1	-0.19	24.6	29.8±3.0	-1.73
34.2	22.0	26.5±2.1	-2.14	20.4	30.0±3.0	-3.20
35.2	19.7	27.0±2.2	-3.32	21.1	30.4±3.1	-3.00
35.4	20.9	27.2±2.2	-2.86	21.7	30.6±3.1	-2.87
36.0	18.5	27.4±2.3	-3.87	21.1	30.7±3.2	-3.00
37.6	21.4	28.2±2.4	-2.83	22.7	31.5±3.4	-2.59
38.0	18.7	28.4±2.5	-3.88	25.5	31.6±3.4	-1.79
38.3	19.9	28.6±2.5	-3.48	22.7	31.8±3.5	-2.60
			mean SDS: -2.96±1.03*			mean SDS: -2.66±0.64*

* $p<0.001$

The vast majority of the time-averaged velocities is smaller than the lower 2.5% reference limit (i.e. SDS < -1.96). Table 6.7 presents for group 1 at

pulmonary artery and ascending aorta level regression coefficients for peak systolic velocity with filling time as well as the mean regression coefficients for all women. These regression coefficients were highly significant. In the three subgroups consisting of extrasystolic beats, normal beats and post-extrasystolic beats, the regression lines for peak systolic velocity with filling time were not significant.

Table 6.4. Mean time-averaged velocity (TAV, cm/s) in conducted supraventricular extrasystoles (group 1) and normal control values (mean±1SD) relative to gestational age (weeks) for mitral valve (MV) and tricuspid valve (TV) with individual and mean (±1SD) standard deviation score (SDS).

gest. age (weeks)	mean TAV MV	reference TAV MV mean±1SD	SDS	mean TAV TV	reference TAV TV mean±1SD	SDS
27.0	14.1	17.8±1.1	-3.36	15.8	19.7±1.5	-2.60
29.4	16.8	18.6±1.4	-1.29	17.4	20.5±1.6	-1.94
31.5	16.5	19.2±1.5	-1.80	16.1	21.2±1.7	-3.00
33.0	14.4	19.6±1.6	-3.25	15.5	21.7±1.8	-3.44
34.0	16.1	19.9±1.7	-2.24	15.1	22.0±1.8	-3.85
34.2	18.6	20.0±1.7	-0.82	19.0	22.1±1.9	-1.72
35.2	17.3	20.3±1.8	-1.67	15.6	22.4±1.9	-3.58
35.4	16.8	20.4±1.8	-2.00	17.8	22.5±1.9	-2.47
36.0	14.6	20.5±1.9	-3.28	15.7	22.7±2.0	-3.50
37.4	17.8	21.0±2.0	-1.78	16.8	23.2±2.1	-3.05
38.0	17.3	21.1±2.0	-2.00	20.3	23.3±2.1	-1.38
38.3	16.5	21.2±2.1	-2.35	17.4	23.5±2.1	-2.90
			mean SDS: -2.15±0.80*			mean SDS: -2.78±0.78*

* $p<0.001$

Table 6.5. Mean time-averaged velocity (TAV, cm/s) in blocked supraventricular extrasystoles (group 2) and normal control values (mean±1SD) relative to gestational age (weeks) for pulmonary artery (PA) and ascending aorta (AO) with individual and mean (±1SD) standard deviation score (SDS).

gest. age (weeks)	mean TAV PA	reference TAV PA mean±1SD	SDS	mean TAV AO	references TAV AO mean±1SD	SDS
25.3	13.2	21.8±1.7	-5.06	15.7	25.9±2.0	-5.10
27.4	17.6	22.9±1.7	-3.12	16.5	26.9±2.2	-4.75
28.0	17.0	23.1±1.7	-3.59	18.5	27.1±2.3	-3.74
30.2	18.7	24.3±1.9	-2.95	21.9	28.1±2.5	-2.48
30.3	16.4	24.4±1.9	-4.21	17.8	28.2±2.5	-4.16
34.2	17.9	26.5±2.1	-4.10	16.7	30.0±3.0	-4.43
36.0	15.8	27.4±2.3	-5.04	18.3	30.7±3.2	-3.88
			mean SDS: -4.01±0.85*			mean SDS: -4.07±0.85*

*$p<0.001$

There was also no correlation between extrasystolic filling time and peak systolic velocity for post-extrasystolic beats.

Table 6.6. Mean time-averaged velocity (TAV, cm/s) in blocked supraventricular extrasystoles (group 2) and normal control values (mean±1SD) relative to gestational age (weeks) for mitral valve (MV) and tricuspid valve (TV) with individual and mean (±1SD) standard deviation score (SDS).

gest. age (weeks)	mean TAV MV	reference TAV MV mean±1SD	SDS	mean TAV TV	reference TAV TV mean±1SD	SDS
25.3	13.8	17.3±1.3	-2.69	16.7	19.1±1.5	-1.60
27.4	16.4	18.0±1.3	-1.23	17.7	19.9±1.5	-2.80
28.0	13.2	18.1±1.3	-3.77	15.9	20.0±1.6	-2.56
30.2	19.1	18.8±1.5	0.20	18.9	20.8±1.7	-2.29
30.3	15.1	18.8±1.5	-2.47	15.4	20.8±1.7	-3.18
34.2	15.6	20.0±1.7	-2.60	18.8	22.1±1.9	-2.14
36.0	14.4	20.5±1.9	-3.21	16.0	22.7±2.0	-3.35
			mean SDS: -2.25±1.33*			mean SDS: -2.41±0.67+

*p<0.001, +p<0.002

DISCUSSION

Cardiac function is generally described in terms of preload, inotropic state, heart rate and afterload. Preload or diastolic muscle fiber length forms the basis of the Frank-Starling mechanism. However, another important cardiac muscle property, the force-interval relationship, has been identified both in the animal and in the human adult heart (Seed and Walker, 1988). This mechanism becomes apparent in situations where the beat-to-beat interval transiently changes, as in the presence of extrasystolic beats (Wisenbaugh et al., 1986, Seed and Walker, 1988). It was noted, that the extrasystolic contraction occuring prematurely in the cardiac cycle, is weak, and the post-extrasystolic beat, which is delayed, is potentiated. These observations can in part be attributed to haemodynamic mechanisms, because the weak beat occurs after a shorter than usual filling time (lower preload) and meets a higher aortic pressure (higher afterload), whereas the potentiated beat is preceded by a longer than normal time-interval (higher preload) and ejects against a lower aortic pressure (lower afterload). However, several observations show, that this is not the major responsible mechanism; enhanced inotropic state independent of changes in preload and afterload has been found to occur in the first post-extrasystolic beat (Seed and Walker, 1988).

Table 6.7. Slopes for the regression lines from peak systolic velocities (cm/s) for extrasystolic, normal and post-extrasystolic beats with filling time (ms) in pulmonary artery (PA) and ascending aorta (AO) in conducted supraventricular extrasystoles (group 1).

gest. age (weeks)	slope PA	slope AO
27.0	0.25	0.25
29.4	0.13	0.11
31.5	0.14	0.09
33.0	0.16	0.47
34.0	0.34	0.15
34.2	0.16	0.12
35.2	0.33	0.42
35.4	0.19	0.22
36.0	0.15	0.15
37.4	0.12	0.07
38.0	0.11	0.20
38.3	0.17	0.68
	mean slope: 0.19±0.08*	0.24±0.19+

* $p<0.001$, +$p<0.002$

The 19 fetuses studied in this series were all otherwise normal, and supraventricular extrasystoles disappeared either in the course of pregnancy or shortly after birth. In these circumstances supraventricular extrasystolic beats can be considered as a model for the study of fetal cardiac activity in which a disturbance of the regular fetal heart rate gives varying ventricular end-diastolic filling volume and afterload.

At semilunar level statistical analysis was performed for peak systolic velocity and acceleration time. The former reflects stroke volume (Hatle and Angelsen, 1981), the latter is mainly determined by afterload (Machado et al., 1987). Peak systolic velocity for the first post-extrasystolic beat was always higher than for normal beats, probably reflecting the combined effects from post-extrasystolic potentiation, the Frank-Starling mechanism and decreased afterload. Accordingly, peak systolic velocity for extrasystolic beats was always lower than for normal beats. Both animal laboratory experiments and human fetal Doppler studies do indeed suggest that the Frank-Starling mechanism is operative and effective in the fetal heart (Kirkpatrick et al., 1976, Maršál et al., 1984, Reed et al., 1987a). In the normal human fetal heart rate range, changes in cardiac output appear to be mainly determined by heart rate, since in this range the myocardium is functioning at the plateau of the Frank-Starling curve (Gilbert, 1980, Tonge et al., 1986). At lower heart rates, the Frank-Starling mechanism compensates for changes in preload, thus keeping cardiac output constant while ventricular end diastolic filling volumes change. At heart rates higher than 250 bpm and lower than 50 bpm this

mechanism begins to fail (Tonge et al., 1984). In our series it was noted that fetal heart rate following an extrasystole never fell below 80 bpm, so that the functional limit of the Frank-Starling mechanism was not reached.

Furthermore, evidence has been found for the existence of a force-interval relationship in the fetal heart. Studies in the fetal sheep (Kirkpatrick et al., 1975) showed the presence of a positive inotropic effect with increasing contraction frequency (post stimulation potentiation) up to a heart rate of about 270 bpm; at higher heart rates, relaxation of the ventricle became incomplete due to inadequate time for ventricular filling and/or diminished coronary blood flow. Electrocardiographic analysis of a case of human fetal extrasystoles (Smith et al., 1990) demonstrated, that fetal cardiac post-extrasystolic potentiation was indeed taking place, and that this was due in part to inotropic potentiation of the post-extrasystolic beats.

In our study, acceleration time was always increased in post-extrasystolic beats. It has been shown that acceleration time is inversely related to intra-arterial pressure (Machado et al., 1987); therefore, this finding may reflect reduced afterload during a post-extrasystolic beat. Acceleration time for extrasystoles was lower than for normal beats.

At atrioventricular level, peak-E wave velocity remained unchanged during post-extrasystolic beats in all women, while peak-A wave velocity fell and E/A-ratio increased. The increase in E/A-ratio can be explained by a lower afterload during post-extrasystolic beats (this thesis, chapter 4.1). The altered preceding time-interval may also have influenced timing and course of ventricular relaxation (Seed and Walker, 1988). The fall-off of peak-A wave velocity could be related to the prolonged preceding time interval. We found in an earlier study on normal cardiac flow velocity waveforms, that peak-E wave velocity increases with decreasing heart rate, whilst peak-A wave velocity decreases (this thesis, chapter 4.1). Our observation of unchanged peak-E wave velocity during post-extrasystolic beats seems to be in contradiction with these normal findings.

Previously, an inverse relationship has been found to exist between extrasystolic filling time and the amount of potentiation. Also, post-extrasystolic potentiation appears to decay gradually over some beats (Wisenbaugh et al., 1986, Seed and Walker, 1988). However, in this study we found no evidence of decay of post-extrasystolic potentiation following a post-extrasystolic beat, nor were we able to establish a relationship between extrasystolic filling time and peak systolic velocity for the post-extrasystolic beats, or between peak systolic velocities for extrasystolic, normal or post-extrasystolic beats separately with filling time.

These last figures should however be interpreted in combination with another result from this study. There was a marked decrease of time-averaged velocity during supraventricular extrasystoles at all four measuring sites compared with reference values. We suggest, that during a post-extrasystolic beat, due to increased blood volume plus increased pressure at ventricular level, valve areas may become larger. The increased ventricular ejection force probably does not counterbalance this effect. This would result in relatively lower peak systolic and time-averaged velocities during a post-extrasystolic beat, giving rise to an underestimation of fetal blood flow if time-averaged velocity were considered as a measure of flow. Other authors have already suggested the possibility that fetal cardiac valve areas may change (Kenny et al., 1987), and we found evidence for this suggestion in an earlier study on normal blood flow velocity waveforms at fetal cardiac level. Here, a negative correlation of atrioventricular time-averaged velocity with period time was calculated (this thesis, chapter 4.1).

This underestimation of peak systolic velocity in potentiated beats may have confused some of our results. We were not able to establish decay of post-extrasystolic potentiation following a post-extrasystolic beat or an inverse relationship between extrasystolic filling time and peak systolic velocity of the post-extrasystolic beat. It might also explain the constancy of peak-E wave velocity and the decrease of peak-A wave velocity during a post-extrasystolic beat. However, the velocity differences concerned may be such that we could not detect them by Doppler ultrasound, since they may have been smaller than the intra-observer variability established in our Department for these parameters; for peak systolic velocity the coefficients of variation between tests within patients were $\leq 7\%$ at outflow tract level and $\leq 4\%$ at atrioventricular level.

The regression coefficient for peak systolic velocities from extrasystolic, normal and post-extrasystolic beats with filling time was significant for both pulmonary artery and ascending aorta. This also seems to represent the combined effect of haemodynamic factors and post-extrasystolic potentiation at ventricular level. Between peak systolic velocities for extrasystolic, normal and post-extrasystolic beats separately, no relationship could be established with filling time, although this is likely to exist. This discrepancy may also be attributed to either changing valve areas or intra-observer variability.

In conclusion, Doppler examination of the human fetal heart during supraventricular extrasystolic beats indicates that the Frank-Starling mechanism and post-extrasystolic potentiation do exist in the fetal heart, although the relative

contributions from both mechanisms cannot be determined in this way. During supraventricular extrasystoles, the limits of the Frank-Starling mechanism are not reached, supporting the theory that extrasystoles do not have haemodynamic consequences. Further, the suggestion is made, that during an increase in blood volume and/or force of contraction, cardiac valve areas may become larger, thus giving rise to underestimation of fetal blood flow measured by Doppler ultrasound when peak systolic velocity or time-averaged velocity is considered. Therefore, cardiac Doppler data should be interpreted with caution when beat-to-beat intervals rapidly change.

6.3 CONCLUSIONS

As has been stated before, fetal Doppler echocardiography is a semi-quantitative method for obtaining information on systolic and diastolic function of the fetal heart. Supraventricular extrasystoles, nearly always a benign condition, provide a model for studying cardiac systolic and diastolic function with different pre and afterload conditions. The information presented in this and other studies on this subject show that the performance of both ventricles in the human fetus is probably not qualitatively different from the postnatal situation. At outflow tract level, the beat following an extrasystolic beat, was augmented. It is likely that at that moment the momentary preload had increased and the afterload had dropped. This suggests the presence of the Frank-Starling mechanism and the force-interval relationship, although the relative contributions of both mechanisms cannot be separated. At atrioventricular level, following an extrasystole E/A-ratio increased, maybe as a result of the prolonged time interval influencing ventricular relaxation, or as a result of preload and/or afterload changes.

Overall time-averaged velocity during supraventricular extrasystoles dropped markedly probably as a result of increasing valve areas, in spite of increasing myocardial contractile force and stroke volume. So, the figures presented by us may be an underestimation of the true amount of augmentation of post-extrasystolic beats.

Some authors have stated that in blocked atrial extrasystoles post-extrasystolic potentiation does not take place because no depolarisation has occurred. This may well be true, but since Doppler echocardiography does not allow differentiation between the mechanisms contributing to the augmentation of post-extrasystolic beats, no attempts were made in the afore-mentioned study to compare both forms of ectopics. However, we would like to make a

few remarks on this issue here. Post-extrasystolic potentiation is only one way in which the force-interval relationship expresses itself. It may express itself differently in blocked extrasystoles when compared with conducted ectopics. Apart from this, the time-interval preceding the post-extrasystolic beat is much larger in blocked than in conducted ectopics. So, in blocked ectopics preload changes may be larger than in conducted extrasystoles. It may be speculated on the basis of these considerations that quantitative differences may exist in the contributions of both mechanisms to post-extrasystolic augmentation in conducted versus blocked ectopics. However, in both forms the Frank-Starling mechanism and the force-interval relationship are probably important in maintaining cardiac ouput.

Chapter 7

GENERAL CONCLUSIONS

Fetal cardiac flow velocity waveforms can be reliably obtained and analysed in a high percentage of fetuses during the second half of pregnancy. At atrioventricular level, time-averaged velocity, peak-E wave velocity, peak-A wave velocity and E/A-ratio show a good reproducibility both between tests within patients and between analyses within tests. Similar findings were done at outflow tract level (Groenenberg et al., 1991).

At outflow tract level, peak systolic velocity, time-averaged velocity and acceleration time increase with advancing gestation. This probably reflects both circulatory changes, like increasing stroke volume and cardiac output and decreasing afterload, and intrinsic cardiac changes, such as increasing ventricular compliance. The increase in atrioventricular flow velocity parameters with advancing gestation may in part be attributed to improving atrial contraction and cardiac output and increasing ventricular compliance. However, also in the human fetus, E/A-ratio probably represents ventricular diastolic function as a whole. Decreasing afterload may therefore contribute to the atrioventricular waveform changes in the course of pregnancy.

Outflow tract flow velocity parameters are fetal heart rate independent in the normal fetal heart rate range, suggesting that the fetal heart normally operates near the plateau of the Frank-Starling curve. On the other hand, atrioventricular flow velocity parameters except peak-A wave velocity, are positively correlated with period time in the normal fetal heart rate range. This may in part be attributed to preload changes, but may also suggest some influence of heart rate on ventricular diastolic function, as has been observed postnatally.

Fetal breathing causes profound haemodynamic changes throughout the second half of pregnancy. During respiration, peak systolic velocity and time-averaged velocity in the outflow tract vessels fluctuate, while acceleration time remains unchanged. At atrioventricular level, time-averaged velocity likewise fluctuates, as does the E/A-ratio at mitral level. Tricuspid E/A-ratio does not change during respiration. It may be suggested, that during fetal inspiration intrathoracic pressure falls, and venous return to the right atrium increases. Due to opening of the pulmonary vascular bed on inspiration, a pooling of blood in the fetal lungs may occur. These processes would lead to momentary preload changes, causing ventricular stroke volume to fluctuate.

Since it is not likely that these preload changes affect both ventricles similarly, this may account for the observed differences in E/A-ratio pattern between both ventricles during fetal breathing movements. However, geometrical ventricular differences may also play a role. Furthermore, time-averaged velocity on the left side of the heart increases during fetal breathing activity when compared with fetal apnoea, while time-averaged velocity on the right side of the heart is similar for fetal breathing and apnoea. This suggests that during fetal breathing a redistribution of blood takes place in favour of the left side of the heart, and therefore the fetal cerebrum.

In blocked and conducted supraventricular extrasystoles, the beat following the extrasystolic beat is augmented. This is probably due to the combined effects of the time-interval relationship and the Frank-Starling mechanism, although the relative contributions from both mechanisms to this augmentation cannot be distinguished and may differ in these two types of ectopics. E/A-ratios increase following an ectopic beat, which may reflect increasing preload, decreasing afterload, or heart rate-related changes in ventricular diastolic function. Time-averaged velocity during both forms of ectopics is significantly lower than reference values corrected for gestational age. Since ectopics appear to be haemodynamically insignificant, it is proposed, that with major increases in stroke volume and contraction force, valve areas may become larger, so that augmentation of transvalvar velocities is reduced.

In the fetal ductus arteriosus, peak systolic, peak diastolic and time-averaged velocities show a good reproducibility, whereas acceleration time has a slightly larger though acceptable intraobserver variability (Groenenberg et al., 1991). These parameters also increase with advancing gestation, reflecting increasing cardiac output and decreasing ventricular afterload. They are fetal heart rate independent in the normal fetal heart rate range.

During fetal breathing, peak systolic velocity in the ductus arteriosus fluctuates, maximum values being in the normal range, while, probably on inspiration, a drop occurs. It is hypothesised that during inspiration the pulmonary vascular bed opens, allowing more blood to enter the lungs. This would lead to a redistribution of right ventricular output during inspiration. In fetuses at risk of developing pulmonary hypoplasia due to severe oligohydramnios following premature rupture of the membranes, normal peak systolic velocity changes during fetal respiration were associated with normal neonatal lung performance. In cases where these velocity changes were diminished, pulmonary hypoplasia showed to be invariably present after birth. This supports the abovementioned hypothesis, and provides a test which may in case of severe

oligohydramnios identify at an early stage fetuses in which lung development is arrested.

Ductal flow velocity waveforms are also behavioural state-dependent. During behavioural state 2F peak systolic and time-averaged velocity are reduced when compared with behavioural state 1F, while the acceleration time does not change. This suggests a redistribution of blood flow in favour of the left heart in state 2F in order to meet increased metabolic needs of fetal cerebrum and skeletal musculature during this particular behavioural state.

It may be concluded that intrinsic fetal variables have a significant influence on fetal cardiac haemodynamics. They have to be taken into account when interpreting fetal cardiac flow velocity waveforms under pathophysiological conditions. Normal values for intracardiac and ductus arteriosus flow velocity waveform parameters and their relation with intrinsic variables have been presented. They may provide a further basis for the clinical evaluation of the haemodynamically compromised human fetus.

SUMMARY

Chapter 1

The combined use of real-time and pulsed/continuous wave Doppler ultrasound has opened the possibility to study blood flow velocity waveforms at fetal cardiac level and in the ductus arteriosus. This may allow semi-quantitative information on fetal cardiac function. For a correct interpretation of the recorded data, the effect of internal variables has to be established. The following important fetal variables have been recognised: fetal heart rate changes and fetal arrhythmias, fetal behavioural states, and fetal breathing movements.

Objective of the present study was to investigate the relationship between fetal cardiac blood flow velocity waveforms and fetal heart rate changes, including supraventricular extrasystoles; to determine the relationship between fetal cardiac flow velocity waveforms and fetal breathing movements; to investigate the relationship between ductus arteriosus flow velocity waveforms and the above-mentioned fetal variables. Also, gestational-age related changes of flow velocity waveform parameters were considered. The study population consisted of normal fetuses during the second half of pregnancy.

Animal laboratory studies suggest that fetal pulmonary vascular resistance falls during fetal lung expansion. It has been shown in post-mortem fetal studies, that in pulmonary hypoplasia pulmonary vascular resistance is increased. Another objective of this study, therefore, was to investigate whether fetuses developing pulmonary hypoplasia due to prolonged rupture of membranes can be identified by recording ductus arteriosus blood flow velocity waveforms during fetal breathing movements.

Chapter 2

A literature survey is presented on human and animal experimental data regarding maturational aspects of fetal behaviour, fetal breathing movements, fetal pulmonary development, and fetal heart rate changes.

Chapter 3

Data on the reproducibility of fetal atrioventricular blood flow velocity waveforms in the second half of pregnancy have been obtained in 21 normal fetuses. Peak-E wave, peak-A wave and time-averaged velocities were studied

and showed a low intra-observer variability both between tests within patients and between analyses within tests.

Chapter 4

In 40 normal fetuses, intracardiac blood flow velocity waveforms were studied during the second half of pregnancy relative to fetal heart rate and gestational age. The parameters studied at outflow tract level were: peak systolic velocity, time-averaged velocity and acceleration time, reflecting to some extent stroke volume, volume flow and ventricular afterload. At atrioventricular level, peak-E and peak-A wave velocities, E/A-ratio and time-averaged velocity were obtained, representing rapid ventricular filling, atrial contraction, ventricular diastolic function and, to some extent, volume flow. Outflow tract flow velocity waveform parameters appeared to be heart rate independent in the normal fetal heart rate range, suggesting that the fetal heart normally operates near the plateau of the Frank-Starling function curve. Atrioventricular flow velocity parameters on the other hand were fetal heart rate dependent. This may reflect preload changes or heart rate induced changes in diastolic ventricular function. Furthermore, atrioventricular time-averaged velocity was negatively correlated with period time, suggesting increasing valve areas with increasing stroke volume. Outflow tract flow velocity parameters increased with advancing gestational age, suggesting increasing stroke volume and cardiac output and decreasing afterload, respectively. Atrioventricular flow velocity parameters also increased with advancing gestation, suggesting increasing preload and cardiac output, increasing ventricular compliance and decreasing afterload in the course of pregnancy.

Intracardiac flow velocity waveforms in relation to fetal breathing movements were studied cross-sectionally in 12 fetuses during the second half of pregnancy. During fetal breathing movements, time-averaged velocity at the left heart appeared to increase, while time-averaged velocity at the right heart remained unchanged. This suggests a redistribution of blood at cardiac level in favour of the left heart and thus of the fetal cerebrum.

Chapter 5

Recently, Huhta et al. (1987) introduced a continuous wave Doppler method for recording blood flow velocity waveforms in the fetal ductus arteriosus. In this thesis, flow velocity waveforms in the ductus arteriosus were studied longitudinally in 40 normal fetuses and in fetuses at risk of developing pulmonary hypoplasia during the second half of pregnancy. Analysis of ductus

arteriosus flow velocity waveforms consisted of measurement of peak systolic, peak diastolic and time-averaged velocities as well as acceleration time. Peak systolic and time-averaged velocities are probably related to stroke volume and volume flow, while peak diastolic velocity and acceleration time may among others reflect afterload. These parameters were fetal heart rate independent in the normal fetal heart rate range. They increased with advancing gestation, probably reflecting increasing stroke volume and cardiac output, and to some extent decreasing right ventricular afterload.

During fetal breathing movements, peak systolic velocity fluctuated in normal fetuses. In fetuses at risk of developing pulmonary hypoplasia, fluctuation of peak systolic velocity within the normal range was associated with normal lung performance after birth, while a diminished fluctuation was invariably associated with pulmonary hypoplasia. This suggests that on fetal inspiration pulmonary vascular resistance falls, resulting in a momentary redistribution of right ventricular output in favour of the fetal lungs. In fetuses developing pulmonary hypoplasia, the pulmonary vascular resistance is increased, so that less blood can enter the lungs on inspiration. This suggests, that measurement of ductal blood flow velocity waveforms during fetal breathing movements may identify fetuses developing pulmonary hypoplasia at an early stage.

In 16 near-term fetuses, during fetal behavioural state 2, peak systolic velocity in the ductus arteriosus appeared to be lower than during fetal behavioural state 1. This suggests a redistribution of blood flow in favour of the left heart, in order to meet increased metabolic demands at the level of the fetal cerebrum and skeletal musculature during this particular behavioural state.

Chapter 6

Fetal intracardiac flow velocity waveforms were studied cross-sectionally in 19 fetuses demonstrating conducted or blocked supraventricular extrasystolic beats in the second half of pregnancy. These extrasystoles are part of the normal fetal heart rate variation and appear to be haemodynamically insignificant. Supraventricular ectopics provide a model for the study of fetal cardiac function during rapidly changing preload and afterload conditions.

In both types of ectopics, peak systolic and time-averaged velocity of the post-extrasystolic beat was increased, reflecting increased stroke volume. This may be due to the effects of both the force-interval relationship and the Frank-Starling mechanism, although the relative contributions of these mechanisms cannot be distinguished by means of Doppler measurements. The

contributions of both mechanisms to the augmentation of post-extrasystolic beats could also be different in both forms of ectopics. However, no attempts were made to compare the two study groups because quantification of relevant haemodynamical parameters is not possible using this method. Acceleration time of post-extrasystolic beats was increased, reflecting decreased afterload during the post-extrasystolic beats.

Time-averaged velocity during supraventricular ectopics was significantly lower than during normal sinus rhythm. Since ectopics appear to be haemodynamically insignificant, it is suggested that valvular areas increase during post-extrasystolic beats, due to increased myocardial contractility and stroke volume.

SAMENVATTING

Hoofdstuk 1

Met behulp van real-time en pulsed/continuous wave Doppler echografie is het mogelijk om vanaf een zwangerschapsduur van 16 weken bloedstroomsnelheidsprofielen te meten in het hart en de ductus arteriosus van de humane foetus. Op die manier kan de functie van het foetale hart semi-quantitatief worden bestudeerd. Voor een goede interpretatie van de gemeten bloedstroomsnelheidsprofielen moet de invloed van zogenaamde intrinsieke variabelen worden vastgesteld. Tot nu toe zijn de volgende belangrijke foetale variabelen geidentificeerd: variaties in foetale hartfrequentie inclusief foetale aritmieën, foetale gedragstoestanden, en foetale ademhalingsbewegingen.

Het doel van dit onderzoek was: i. het verband te bestuderen tussen foetale cardiale bloedstroomsnelheidsprofielen en foetale variaties in hartfrequentie, waar onder supraventriculaire extrasystoles; ii. het verband vast te stellen tussen foetale cardiale bloedstroomsnelheidsprofielen en foetale ademhalingsbewegingen; iii. het verband te bestuderen tussen bloedstroomsnelheidsprofielen in de ductus arteriosus en genoemde intrinsieke variabelen. Ook zijn veranderingen van deze bloedstroomsnelheidsprofielen in de loop van de zwangerschap onderzocht. De onderzoekspopulatie bestond uit foetussen in de tweede helft van een ongecompliceerde graviditeit.

Dierexperimenteel onderzoek suggereert, dat de foetale longvaatweerstand afneemt tijdens foetale longexpansie. In post-mortem foetaal onderzoek is aangetoond dat in gevallen van longhypoplasie de longvaatweerstand is verhoogd. Een ander onderzoeksdoel van dit proefschrift was daarom om te onderzoeken of foetussen, die longhypoplasie ontwikkelen als gevolg van prematuur gebroken vliezen met ernstig oligohydramnion, vroegtijdig kunnen worden geïdentificeerd door bloedstroomsnelheidsmetingen te verrichten in de ductus arteriosus tijdens foetale ademhalingsbewegingen.

Hoofdstuk 2

De gegevens van een literatuuronderzoek betreffende de ontwikkeling van foetaal gedrag, foetale ademhalingsbewegingen en variaties in foetale hartfrequentie zijn hier gepresenteerd. Zowel dierexperimentele als humane onderzoeken worden besproken.

Hoofdstuk 3

De reproduceerbaarheid van foetale atrioventriculaire bloedstroom-snelheidsprofielen is onderzocht in een populatie van 21 normale foetus in de tweede helft van de zwangerschap. Piek-E snelheid, piek-A snelheid en gemiddelde snelheid werden bestudeerd; voor deze parameters werd een lage intra-observer variabiliteit vastgesteld zowel tussen metingen binnen patienten als tussen analyses binnen metingen.

Hoofdstuk 4

In 40 normale foetussen zijn intracardiale bloedstroomsnelheidsprofielen longitudinaal onderzocht, en de relatie hiervan met de foetale hartfrequentie en zwangerschapsduur is vastgesteld. De bestudeerde parameters op 'outflow tract' niveau waren: piek systolische snelheid, gemiddelde snelheid en acceleratietijd. Deze parameters geven tot op zekere hoogte informatie over respectievelijk slagvolume, cardiac output en afterload. Op atrioventriculair niveau zijn piek-E en piek-A snelheden, gemiddelde snelheid en E/A-ratio gemeten. Deze parameters geven informatie over de 'rapid filling phase', atrium contractie, cardiac output en de diastolische ventrikelfunctie. De 'outflow tract' parameters bleken in het normale hartfrequentiegebied onafhankelijk te zijn van de hartfrequentie, wat erop wijst dat het foetale hart normaliter dichtbij het plateau van de Frank-Starling curve functioneert. De atrioventriculaire parameters waren wel afhankelijk van de foetale hartfrequentie. Dit kan veranderingen in preload weergeven, of duiden op een invloed van de hartfrequentie op de diastolische functie van de foetale ventrikels. Verder was de gemiddelde snelheid op atrioventriculair niveau negatief gecorreleerd met de period time. Dit kan betekenen, dat deze klepoppervlakken toenemen met toenemend slagvolume. De 'outflow tract' bloedstroomsnelheidsparameters namen toe met de zwangerschapsduur, wat respectievelijk kan passen bij toenemende slagvolumina en cardiac output en afnemende afterload. Ook de atrioventriculaire bloedstroomsnelheidsparameters namen toe met de zwangerschapsduur, wat suggereert dat in de loop van de zwangerschap de preload, de cardiac output en de ventriculaire compliance toenemen, terwijl de afterload afneemt.

Cardiale bloedstroomsnelheidsprofielen zijn transversaal onderzocht tijdens foetale ademhalingsbewegingen bij 12 foetussen in de tweede helft van de zwangerschap. Tijdens foetaal ademen was de gemiddelde snelheid in de linker harthelft hoger dan tijdens apnoe, terwijl de gemiddelde snelheid tijdens foetaal ademen in de rechter harthelft niet veranderde. Dit suggereert dat er tijdens foetale ademhalingsbewegingen een redistributie van bloed optreedt op

cardiaal niveau ten gunste van de linker harthelft en dus van, onder andere, de foetale hersenen.

Hoofdstuk 5

Onlangs hebben Huhta et al. (1987) een methode geintroduceerd om bloedstroomsnelheidsprofielen te meten in de foetale ductus arteriosus. In dit proefschrift zijn dergelijke bloedstroomsnelheidsprofielen longitudinaal gemeten in een groep van 40 foetussen vanaf een zwangerschapsduur van 18 weken. Ook werd een groep foetussen longitudinaal bestudeerd die een verhoogd risico had op het optreden van longhypoplasie als gevolg van een ernstig oligohydramnion bij prematuur gebroken vliezen. Analyse van deze bloedstroomsnelheidsprofielen bestond uit het berekenen van piek systolische, piek diastolische en gemiddelde snelheid, en acceleratietijd. Piek systolische en gemiddelde snelheid zijn tot op zekere hoogte gerelateerd aan respectievelijk slagvolume en cardiac output, en piek diastolische snelheid en acceleratietijd aan de afterload. Deze parameters waren alle onafhankelijk van de foetale hartfrequentie. Ze namen toe met de zwangerschapsduur, wat waarschijnlijk een toename in slagvolume en cardiac output weergeeft, alsmede een afname van de afterload van de rechter ventrikel.

Tijdens foetale ademhalingsbewegingen fluctueerden de piek systolische snelheid in de ductus arteriosus in normale foetussen. In foetussen met een verhoogd risico op het optreden van longhypoplasie bij een ernstig oligohydramnion was een normale fluctuatie van deze piek systolische snelheid tijdens foetaal ademen geassocieerd met een normale neonatale longfunctie. Een verminderde fluctuatie echter was steeds gerelateerd aan de aanwezigheid van longhypoplasie. Dit suggereert, dat tijdens foetale inspiratie de longvaatweerstand normaliter daalt, wat leidt tot een tijdelijke redistributie van de output van de rechter ventrikel ten gunste van de foetale longen. In foetussen die longhypoplasie ontwikkelen, is de longvaatweerstand verhoogd, zodat minder bloed de longvaten kan perfunderen. Dit zou inhouden, dat het meten van bloedstroomsnelheidsprofielen in de foetale ductus arteriosus tijdens foetale ademhaling in een vroeg stadium die foetussen zou kunnen identificeren die een longhypoplasie gaan ontwikkelen als gevolg van een ernstig oligohydramnion bij prematuur gebroken vliezen.

In 16 foetussen met een zwangerschapsduur van 37-38 weken bleek de piek systolische snelheid tijdens de foetale gedragstoestand 2F significant lager te zijn dan tijdens gedragstoestand 1F. Dit duidt op een redistributie van bloed ten gunste van de linker harthelft tijdens deze gedragstoestand, waarschijnlijk om te kunnen voldoen aan toegenomen metabole eisen van foetale

hersenen en skeletmusculatuur tijdens gedragstoestand 2F.

Hoofdstuk 6

Foetale intracardiale bloedstroomsnelheidsprofielen werden transversaal bestudeerd in 19 foetussen met voortgeleide en/of niet-voortgeleide supraventriculaire extrasystoles gedurende de tweede helft van de zwangerschap. Deze extrasystoles vormen een deel van de normale foetale variatie in hartfrequentie en hebben voor zover nu bekend haemodynamisch geen consequenties. Deze extrasystoles kunnen zodoende een model vormen voor het bestuderen van de foetale hartwerking tijdens snel wisselende preload en afterload condities.

In beide vormen van extrasystoles namen de piek systolische en gemiddelde snelheid van de post-extrasystolische hartslag toe, wijzend op een toegenomen slagvolume. Dit kan het gevolg zijn van zowel de 'force-interval relationship' als het Frank-Starling mechanisme; de relatieve bijdragen van beide mechanismen aan deze vergroting van het slagvolume kunnen met de huidige Doppler methoden niet worden vastgesteld. Ook kan het zo zijn dat de relatieve bijdragen van beide mechanismen bij de twee genoemde typen extrasystoles verschillend zijn. In deze studie is niet geprobeerd om beide vormen van extrasystoles met elkaar te vergelijken, omdat het niet mogelijk is de relevante haemodynamische factoren ten dezen te quantificeren. De acceleratietijd van post-extrasystolische hartslagen was eveneens toegenomen, wat kan passen bij een verminderde afterload na een extrasystole als gevolg van de langere pauze.

De gemiddelde snelheid tijdens supraventriculaire extrasystoles was significant lager dan referentiewaarden gemeten tijdens normaal sinusritme. Omdat extrasystoles haemodynamisch gezien onschuldig lijken te zijn, zou dit erop kunnen duiden dat klepoppervlakken tijdens post-extrasystolische hartslagen toenemen als gevolg van toegenomen slagvolume en ventriculaire contractiliteit.

ZUSAMMENFASSUNG

1. Kapitel

Mit Hilfe der kombinierten Sektor- und gepulsten Dopplersonographie können ab einer Schwangerschaftsdauer von 16 Wochen Flußmessungen durchgeführt werden im Herz und Duktus Arteriosus des humanen Foetus. Auf diese Weise kann die foetale Herzfunktion semi-quantitativ erfaßt werden. Für eine korrekte Interpretation der gemessenen Doppler Flußgeschwindigkeitsprofile muß aber zuerst der Einfluß sogenannter foetaler Variablen festgestellt werden. Bis heute sind folgende wichtige foetale Variablen identifiziert worden: Variation der foetalen Herzfrequenz einschließlich foetaler Herzrhythmusstörungen, foetale Verhaltenszustände, und foetale Atmung.

Die vorliegende Doktorarbeit beinhaltet folgende Zielsetzungen: den Zusammenhang zu erörtern zwischen: foetalen kardialen Flußgeschwindigkeitsprofilen und Variationen in der foetalen Herzfrequenz einschließlich der foetalen Extrasystolen; foetalen kardialen Flußgeschwindigkeitsprofilen und foetaler Atmung; Flußgeschwindigkeitsprofilen im Duktus Arteriosus und genannten foetalen Variablen. Auch sind Änderungen dieser Flußmessungen im Laufe der Schwangerschaft erfaßt worden. Untersucht wurden Foeten in der zweiten Hälfte einer unkomplizierten Schwangerschaft.

Tierexperimentelle Studien weisen darauf hin, daß der foetale Lungengefäßwiderstand während foetaler Lungenexpansion abnimmt. In postmortalen foetalen Untersuchungen wurde festgestellt, daß in Fällen einer foetalen Lungenhypoplasie der Lungengefäßwiderstand erhöht ist. Ein anderes Untersuchungsziel dieser Arbeit war deshalb, festzustellen, ob Foeten, die Lungenhypoplasie entwickeln infolge eines praematuren Fruchtwasserabgangs mit Oligohydramnion, frühzeitig identifiziert werden können mittels Flußmessungen im Duktus Arteriosus während foetaler Atmung.

2. Kapitel

Die Ergebnisse einer Literaturstudie bezüglich der Entwicklung foetaler Verhaltenszustände, foetaler Atmung und Variationen foetaler Herzfrequenzen werden hier präsentiert. Sowohl animale als auch humane Studien werden diskutiert.

3. Kapitel

Die Reproduzierbarkeit foetaler atrioventrikulärer Flußmessungen wurde in einer Gruppe von 21 normalen Foeten in der zweiten Schwangerschaftshälfte untersucht. E und A Geschwindigkeiten sowie Durchschnittsgeschwindigkeit wurden in diese Studie einbezogen; für diese Parameter wurde eine sehr niedrige Intra-Observer Variabilität festgestellt, sowohl zwischen Messungen innerhalb Patienten als auch zwischen Analysen innerhalb Messungen.

4. Kapitel

In 40 normalen Foeten ab 18 Wochen wurden intrakardiale Flußgeschwindigkeitsprofile seriell gemessen, und der Zusammenhang mit foetaler Herzfrequenz und Schwangerschaftsdauer wurde erörtert. Die Outflow Tract Flußgeschwindigkeitskurven wurden folgendermaßen analysiert: systolische Höchstgeschwindigkeit, Durchschnittsgeschwindigkeit und Beschleunigungszeit. Diese Parameter informieren gewissermaßen über Schlagvolumen, Cardiac Output und Nachlast. Auf atrioventrikulärer Ebene wurden E- und A-Höchstgeschwindigkeiten, Durchschnittsgeschwindigkeit und E/A-ratio untersucht. Diese Parameter sind korreliert mit Rapid Filling Phase, Vorkammerkontraktion, Cardiac Output und diastolische Kammerfunktion. Die Outflow Tract Parameter waren im normalen foetalen Herzfrequenzbereich unabhängig von der foetalen Herzfrequenz, was darauf deutet, daß das foetale Herz normalerweise nahe des Plateaus der Frank-Starlingkurve funktioniert. Die atrioventrikulären Parameter jedoch waren auch im normalen foetalen Herzfrequenzbereich von der foetalen Herzfrequenz abhängig. Dies kann auf Änderungen in Vorlast oder auf einen gewissen Einluß der foetalen Herzfrequenz auf die diastolische Kammerfunktion hinweisen. Die atrioventrikuläre Durchschnittsgeschwindigkeit war außerdem positiv mit der foetalen Herzfrequenz korreliert. Dies kann bedeuten, daß die atrioventrikulären Klappenflächen mit zunehmendem Schlagvolumen zunehmen. Outflow Tract Flußkurvenparameter nahmen zu mit der Schwangerschaftsdauer, was zu einer Zunahme im Schlagvolumen bzw. abnehmender Nachlast passen könnte. Auch die atrioventrikulären Flußkurvenparameter nahmen zu mit der Schwangerschaftsdauer; dies suggeriert, daß im Laufe der Schwangerschaft Vorlast, Cardiac Output und Compliance zunehmen, während die Nachlast abnimmt.

Intrakardiale Flußgeschwindigkeitsprofile wurden außerdem transversal untersucht während foetaler Atmung bei 12 Foeten in der zweiten Schwangerschaftshälfte. Während foetaler Atmung war die Durchschnittsgeschwindigkeit in der linken Herzhälfte höher als während Nicht-Atmung, während die Durchschnittsgeschwindigkeit in der rechten Herzhälfte sich nicht änderte.

Dies suggeriert, daß während foetaler Atmung eine Redistribution von Blut auftritt auf kardialer Ebene zugunsten der linken Herzhälfte und damit unter anderem zugunsten des foetalen Gehirns.

5. Kapitel

Neuerdings haben Huhta et al. (1987) eine Methode eingeführt, um Flußmessungen im foetalen Duktus Arteriosus durchzuführen. In dieser Arbeit sind solche Flußgeschwindigkeitsprofile seriell gemessen in einer Gruppe von 40 Foeten ab 18 Wochen. Auch wurden 13 Foeten seriell studiert, die ein erhöhtes Risiko hatten für die Entwicklung von Lungenhypoplasie wegen Oligohydramnion nach praematurem Fruchtwasserabgang. Die Analyse dieser Flußgeschwindigkeitsprofile umfaßte die Berechnung der systolischen und diastolischen Höchstgeschwindigkeit, der Durchschnittsgeschwindigkeit und der Beschleunigungszeit. Systolische und Durchschnittsgeschwindigkeit informieren gewissermaßen über Schlagvolumen und Cardiac Output, während diastolische Höchstgeschwindigkeit und Beschleunigungszeit über die Nachlast Auskunft geben. Diese Parameter waren alle unabhängig von der foetalen Herzfrequenz. Sie nahmen zu mit der Schwangerschaftsdauer, was wahrscheinlich eine Zunahme des Schlagvolumens und des Cardiac Output reflektiert sowie eine Abnahme der Nachlast der rechten Herzkammer.

Während foetaler Atmung fluktuierte die systolische Höchstgeschwindigkeit im Duktus Arteriosus in normalen Foeten. In Foeten mit erhöhtem Risiko für die Entwicklung einer Lungenhypoplasie war eine normale Fluktuation der systolischen Höchstgeschwindigkeit während foetaler Atmung immer assoziiert mit normaler neonataler Lungenfunktion. Eine zu niedrige Fluktuation hingegen wurde ausschließlich wahrgenommen in Foeten, die nach der Geburt Lungenhypoplasie aufwiesen. Dies weist darauf hin, daß während foetaler Einatmung der Lungengefäßwiderstand normalerweise abnimmt, was zu einer vorübergehenden Redistribution des Output des rechten Herzkammers zugunsten der foetalen Lungen führt. In Foeten, die Lungenhypoplasie entwickeln, ist der Lungengefäßwiderstand erhöht, so daß weniger Blut in die Lungengefäße gelangen kann. Dies würde bedeuten, daß das Messen der Flußgeschwindigkeitsprofile im foetalen Duktus Arteriosus während foetaler Atmung frühzeitig Foeten identifizieren könnte, die eine Lungenhypoplasie entwickeln.

In 16 Foeten von 37-38 Wochen war die systolische Höchstgeschwindigkeit während des foetalen Verhaltenszustandes 2F niedriger als während des Zustandes 1F. Dies weist hin auf eine Redistribution von Blut zugunsten der linken Herzhälfte während des Verhaltenszustandes 2F, wahrscheinlich um

den metabolen Forderungen des foetalen Gehirns und der foetalen Skelettmuskulatur während dieses Zustandes gerecht zu werden.

6. Kapitel

Foetale intrakardiale Flußgeschwindigkeitskurven wurden transversal studiert in einer Gruppe von 19 Foeten mit conducted oder non-conducted supraventrikulären Extrasystolen in der zweiten Schwangerschaftshälfte. Diese Extrasystolen bilden einen Teil der normalen foetalen Variation in Herzfrequenz und haben -soweit jetzt bekannt- keinen nachteiligen Einfluß auf die foetale Haemodynamik. Diese Extrasystolen können demnach ein Modell darstellen, das die Studie der foetalen Herzfunktion während wechselnder Vor- und Nachlast-Zustände ermöglicht.

In beiden Arten der Extrasystolen hatten systolische und Durchschnittsgeschwindigkeit des post-extrasystolischen Herzschlags zugenommen, was auf ein erhöhtes Schlagvolumen hindeutet. Sowohl das Frank-Starling Prinzip als auch post-extrasystolische Potenzierung können hierfür verantwortlich sein. Die relative Bedeutung dieser Mechanismen kann aber mit der vorhandenen Doppler Methodik nicht näher untersucht werden. Die relativen Beiträge dieser Mechanismen könnten für beide Formen der Extrasystolen außerdem unterschiedlich sein. In dieser Studie wurde nicht versucht, die beiden Typen der Extrasystolen miteinander zu vergleichen, weil es ja nicht möglich ist, die relevanten haemodynamischen Faktoren zu quantifizieren. Die Beschleunigungszeit der post-extrasystolischen Herzschläge hatte ebenso zugenommen, was deutet auf eine niedrigere Nachlast nach einer Extrasystole wegen der längeren Pause.

Die Durchschnittsgeschwindigkeit während supraventrikulärer Extrasystolen war niedriger als Referenzwerte, die während eines normalen Sinusrhythmus gemessen wurden. Weil Extrasystolen -haemodynamisch gesehen- harmlos zu sein scheinen, könnte dies darauf hinweisen, daß Herzklappenflächen während post-extrasystolischer Herzschläge zunehmen wegen Zunahme des Schlagvolumens sowie verstärkter Kammerkontraktilität.

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DANKWOORD/ACKNOWLEDGEMENT

Het onderzoek dat in dit proefschrift is beschreven werd verricht op de afdeling Verloskunde/Gynaecologie van het Dijkzigt Ziekenhuis-Erasmus Universiteit, Rotterdam.

In de eerste plaats wil ik Professor Wladimiroff bedanken voor zijn steun en adviezen tijdens het opzetten en uitvoeren van de verschillende studies en tijdens de 'schrijffase', toen ik elders werkzaam was. Vooral ook in die laatste periode was zijn stimulerende begeleiding voor mij erg belangrijk.

I am very grateful to Professor K. Maršál for his willingness to be a member of the committee and for coming all the way from Sweden for this session.

Ook Professor H.P. van Geijn en Professor P.E. Treffers dank ik voor hun bereidheid om zitting te nemen in de promotiecommissie.

Jim van Eyck ben ik bijzonder dankbaar voor twee jaar van goede en prettige samenwerking in het kader van de studies betreffende de ductus arteriosus, evenals voor het kritisch doorlezen van het manuscript. Jim, ik heb je leren kennen als een creatieve onderzoeker, een harde werker, maar vooral ook als een fijne collega met een onverwoestbaar goed humeur. Bedankt!

Patricia Stewart heeft heel wat uren besteed om mij de kneepjes van de foetale Doppler echocardiografie bij te brengen; daarna was zij altijd bereid om mee te denken als dat nodig was. Ik ben haar daarvoor zeer erkentelijk en wil in het bijzonder haar bijdragen aan de totstandkoming van Hoofdstuk 6 noemen.

Leo Barendregt, Wim Hop en Theo Stijnen hebben de statistische bewerking van het leeuwedeel van de data voor hun rekening genomen. Hiervoor, en voor onze regelmatige discussies over de gevonden resultaten dank ik hen hartelijk.

Piet Struyck wil ik bedanken voor het schrijven van het analyse-programma voor de Dopplersignalen, en voor zijn hulp bij het werken met SPSS.

Winnie Ruizendaal en Sylvia Breur dank ik voor hun secretariële bijdragen aan de totstandkoming van de in dit proefschrift opgenomen artikelen.

Een speciaal woord van dank is ook op zijn plaats aan alle zwangere vrouwen die hebben deelgenomen aan mijn onderzoek. Hun gemotiveerdheid en belangstelling gaven kleur aan mijn onderzoek en zorgden voor een persoonlijke noot.

De Audiovisuele Dienst ben ik erkentelijk voor de vakkundige vervaardiging van het fotomateriaal en de figuren.

Het verschijnen van dit proefschrift werd mede mogelijk gemaakt door steun van de Nederlandse Hartstichting, het Fonds Catharina van Tussenbroek, Diasonics BV, Nycomed BV en Schering Nederland BV.

Tenslotte een woord van dank aan Professor J. Valk, Professor T.H.M. Falke en de stafleden van de afdeling Radiodiagnostiek van het Academisch Ziekenhuis der Vrije Universiteit, die mij in de laatste fase de ruimte gaven om mijn proefschrift af te ronden. In het bijzonder dank ik in dit verband echter mijn huidige collega's artsen-assistent, die in deze tijd een deel van mijn werk op de afdeling overnamen.

CURRICULUM VITAE

1959	Born in Heerlen
1966-1972	Public school in Hoensbroek and Sittard
1972-1978	Serviam Scholengemeenschap in Sittard, Gymnasium-ß
1978-1979	University of Leuven, Belgium, Medical School
1979-1985	University of Utrecht, Medical School
1985-1986	Youth Health Care physician, DGGD, Ede
1986-1987	Residency Paediatrics, St. Elisabeth's Gasthuis, Arnhem
1987-1989	Research assistent, Academic Hospital Dijkzigt, Erasmus University Rotterdam, Department of Obstetrics and Gynaecology (Prof.Dr. J.W. Wladimiroff, Prof.Dr. A.C. Drogendijk, Prof.Dr. H.C.S. Wallenburg)
1989-	Residency Radiology, Academic Hospital of the Free University, Amsterdam (Prof.Dr. J. Valk, Prof.Dr. T.H.M. Falke)