DOPPLER VELOCITY ASSESSMENT OF VENOUS RETURN IN THE HUMAN FETUS

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Evaluatie van de veneuze return in de humane foetus met behulp van Doppler bloedsnelheidsmetingen

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"Some who do not know, and especially those who have experience, are more practical than others who know".

Aristoteles

Aan mijn ouders

Contents

Chapter 1
INTRODUCTION AND DEFINITION OF OBJECTIVES

1.1 Introductory remarks

Studies in the human fetus are limited by the methods available for investigation. Pressure and volume flow measurements in the fetal cardiovascular system require invasive techniques that are not performed at present. However, information on fetal circulatory performance may be helpful in the evaluation of pathologic conditions. With the introduction of Doppler ultrasound non-invasive examination of the fetal vessels became possible. In the last decade cardiovascular research in the human fetus has focused on the study of arterial, cardiac and umbilical blood flows. Four factors mainly determine cardiac performance: (i) afterload (ii) cardiac contraction force (iii) heart rate (iv) preload.

Examination of the factor afterload in the fetal circulation has been characterized by Doppler studies of the fetal descending aorta and umbilical artery in the second half of pregnancy (Marsal et al. 1984; Trudinger et al. 1985;Tonge 1987).

The second factor, cardiac contraction force, is even more difficult to study in the fetus. Efforts have been made by a number of investigators (Maulik et al. 1985; Kenny et al. 1986; Reed et al. 1986; Allan et al. 1987), who all tried to quantify cardiac stroke volume and force by means of Doppler velocimetry at the level of the atrioventricular valves and in the outflow tracts. However, it was pointed out that the reproducibility of these data is disappointingly low and large within and between variation was documented (Beeby et al. 1991).

The third factor is the fetal heart rate, which is relatively easy to obtain. Studies have shown that as a result of the Frank-Starling mechanism fetal heart rate changes within the normal heart rate range do not seem to considerably influence fetal cardiac output (Kenny et al. 1987; van der Mooren et al. 1991).

Finally, little is known about the factor preload and the hemodynamics of the fetal venous vasculature, although it has become clear from animal experimental work

(Rudolph and Heymann 1967; Rudolph 1983) that venous return is an important factor in cardiac functioning. With the presence of three shunts (foramen ovale, ductus arteriosus and ductus venosus) and the placenta as a third circulation venous blood flow and pressures in the normally developing fetus are significantly different from the physiologic situation in adults.

In this thesis data are presented on Doppler venous cardiac inflow, in particular from the umbilical vein, ductus venosus and inferior vena cava in (i) the late first and early second trimester fetus and (ii) the late second and third trimester fetus. The inclusion of early pregnancy flow studies was based on the significant changes occurring at placental level around 13 to 14 weeks of gestation with emphasis on the process of trophoblast invasion, resulting in low resistance placental vascular dynamics (Pijnenburg et al. 1980; Jauniaux et al. 1991). The transvaginal approach now allows fetal flow velocity waveform recording as early as 9 to 10 weeks.

Late pregnancy studies were mainly performed to establish the effect of fetal variables such as breathing movements, behavioural states and cardiac arrhythmias on fetal venous cardiac inflow.

Obviously, proper interpretation of venous inflow velocity parameters is only feasible when related to other parameters of cardiovascular performance, such as afterload and heart rate.

1.2 Definition of objectives

The first objective was to review the available literature on fetal venous return and to assess the various methods of investigating human fetal venous hemodynamics (Chapter 2).

The second objective was to collect data on the nature and reproducibility of fetal flow velocity waveforms in late first and early second trimester pregnancies. To appreciate venous inflow velocities in relation to total cardiovascular dynamics, attention was also focused on waveform patterns at cardiac and arterial level (Chapter 3).

The third objective of the study was (i) to ascertain the exact anatomical relationship between vessels responsible for fetal venous return in late second and third trimester pregnancies; (ii) to establish reproducibility and normal values during this period of pregnancy (Chapter 4).

The fourth and last objective was to determine the influence of fetal internal variables such as breathing movements, behavioural states and cardiac arrhythmias on venous flow velocity waveforms in late pregnancy (Chapter 5).

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Chapter 2
THE FETAL CIRCULATION WITH EMPHASIS ON VENOUS RETURN

2.1 Introductory remarks

Knowledge of the fetal circulation has been acquired over the centuries with remarkable slowness. Most investigations were performed either on bought, stolen or exhumed corpses or on animals. Invasive studies on the human fetus are limited. Introduction of non-invasive methods like ultrasonography and Doppler measurements has enormously accelerated and increased our insights into the normal and abnormal fetal circulation. This chapter will describe the acquisition of knowledge on fetal hemodynamics, in particular the embryological, anatomical and physiological aspects of fetal venous vasculature and blood flow with emphasis on venous return. Finally, the Doppler techniques available for obtaining this information will be discussed.

2.2 Historical background

The understanding of the normal circulation in adults was developed during the Egyptian and Greek period, in which famous physicians like Aristotle and Herophilus tried to explain the function of the vascular system. The uniqueness of the fetal circulation and its anatomical structures was first recognized by Galen (130-200 AD) who probably studied the anatomy of the cardiovascular system in animal preparations. Nevertheless Galen gives the first description of the foramen ovale and a vessel that could only be the ductus arteriosus in *De usu partium*, a part of his immense opus (200 books) (Harris 1973). Although he accurately observed the postnatal obliteration of these structures, Galen also fitted them into his wrong perception of 'lifegiving pneuma as the source of vitality". Moreover, he

assumed that blood passes directly from the right to the left ventricle through a porous interventricular septum. This was disputed by the Arabic physician Ibn al-Naphis (± 1210 - 1288), who discovered the lung circulation (Shampo and Kyle 1987).

The many anatomical drawings and sketches from Leonardo da Vinci (1452 - 1519) were only published more than 400 years after his death, but they feature among other interesting anatomical structures the ductus arteriosus/ligamentum arteriosum (Franklin 1941a). In 1561 Gabriele Falloppio (1523 - 1562) published his book *Observationes anatomicae*, in which the ductus arteriosus is mentioned for the first time since Galen. In this book the word "placenta" (Latin for cake) is given to the organ that had, until that period, been called in Italian and vulgar Latin "secundinas" (what comes second). His teacher was the famous Flemish anatomist Andreas Vesalius (1514 - 1564), who wrote in 1543 his famous work *De humani corporis fabrica libri septem*, often referred to as "the Fabrica". In it is an accurate description of the junctions of the portal and hepatic venous branches, but no mention of the third fetal shunt, the ductus venosus. This vessel was first recognized by Vesalius in 1561 in a critical response to Falloppio's work, which was only published three years later (1564) as *Anatomicarum Gabrielis Falloppii Observationum Examen*. The year 1564 saw also two other important contributions for fetal circulation research: *De humano fetu libellus* from Giulio Cesare Arantius (1534 - 1589) and a note from Leonardo Botallus (± 1530 - 1600). Arantius used another term for Falloppio's "placenta", namely "uteri iecur" (uterine liver) regarding the placenta as à vascular centre from which blood passed to the fetal organs for their nutrition. Description of the ductus venosus, which carries Arantius' name, was only published in the third, enlarged edition of his book in 1579, 18 years after Vesalius' contribution (Franklin 1941b).

A similar misattribution occured with the ductus arteriosus and foramen ovale. In a short work, published as an appendix to another manuscript, Botallus described a persistent foramen ovale in a calf, a structure already extensively described by Galen, Vesalius and Arantius (Franklin 1941a). Through a number of coincidences he ended up being credited with having discovered both the foramen ovale

(trou de Botal in the French literature) and the ductus arteriosus (ductus Botallii in the Basel Nomenclature). Hieronymus Fabrizius ab Aquapendente (1533 - 1619) published in 1600 in his book *De formatu fetu* for the first time precise illustrations of the fetal shunts and the cardiovascular system (Mani 1967).
In conclusion, one should call the ductus venosus "ductus Vesalii" and the ductus arteriosus "ductus Galeni"(Franklin 1941a; Mani 1967).
It should be emphasized that none of the above-mentioned anatomists or physicians appreciated the true physiology of the fetal circulation and the differences from the adult situation. This older era of circulatory speculation ended with the publication in 1628 of William Harvey's *Exercitatio anatomica de mot cordis et sanguinis in animalibus*. He perceived that the fetal ductus arteriosus does not bring blood from the aorta to the lungs "for their nourishment" as had been postulated previously, but that the right ventricle pumps blood through the ductus to the aorta, bypassing the lungs, which were "motionless and useless".
After him a number of investigators (Haller , Sabatier, Wolff, Bichat and Kilian) refined Harvey's perceptions of the fetal circulation to a detailed concept of venous blood returning from the placenta and its distribution at cardiac level (Franklin 1941a). Finally, Barclay and colleagues were able to demonstrate for the first time in 1939, using cineangiography with X-ray techniques, the hemodynamics of the (lamb) fetal circulation (Barclay et al. 1939). Whereas the functional role of the foramen ovale and ductus arteriosus had been well established, the prenatal role of the ductus venosus was still unclear. Similar to the observations in fetal lamb, it has been proposed by Edelstone and Rudolph that the ductus venosus acts as a passive shunt of well-oxygenated umbilical venous blood to maintain a stable oxygen delivery to the vital fetal organs (brain and heart) (Edelstone and Rudolph 1979).

The historic development of Doppler ultrasound is much shorter. Christian Johann Doppler (1842) described shifts in red light from binary stars (Dopplersterne), which was called after him the Doppler effect. It was the great contribution of the Dutch physicist Buys Ballot (1845), which lead to the appli-

cation of the Doppler effect to sound. He used a moving trainwagon with an orchestra and documented the changes in their music tones by observers along the railway. Technology needed more than a century to develop systems that could use these observations. Satomura (1956 and 1959) first realised that red blood cells can reflect ultrasound waves, thus changing the frequency in accordance with the Doppler effect. Following the application of these findings in adult cardiology, the fetal circulation was studied by a combination of two-dimensional ultrasound and Doppler systems (FitzGerald and Drumm 1977; Gill and Kossoff 1979; Eik-Nes et al. 1980).

2.3 Embryology and Anatomy

In the embryonic period the liver rudiment can be distinguished as early as the third week of gestation (Barry 1963). Blood from the yolk sac is transported through the hepatic sinusoids via the vitelline (or omphalomesenteric) vessels into the sinus venosus, whereas blood from the chorionic villi bypasses the liver to empty into the sinus via the right and left umbilical veins (Edelstone 1980; Chacko and Reynolds 1953). During the fifth week of gestation the right umbilical vein and the proximal portion of the left umbilical vein degenerate. The rest of the left umbilical vein forms anastomoses with the hepatic sinusoids to create a new channel, which is called the ductus venosus (Moore 1977; Gilbert 1989). Flow through these early anastomoses is considered to play an important role in the organogenesis of the venous structures and segmentation in the human liver (Lassau and Bastian 1983). The ductus venosus is localised in the fetal liver, approximately between the right and left lobe (Fig.1). Its course is from caudal to cranial, from ventral to dorsal and sometimes slightly oblique to the left or right side. Its origin is at the ventral side of the umbilical sinus, thus resembling macroscopically a continuation of the intra-abdominal part of the umbilical vein (Huisman et al. 1992a). Its end has been reported to be variable, most often in the terminal portion of the inferior vena cava (Balique et al. 1984).

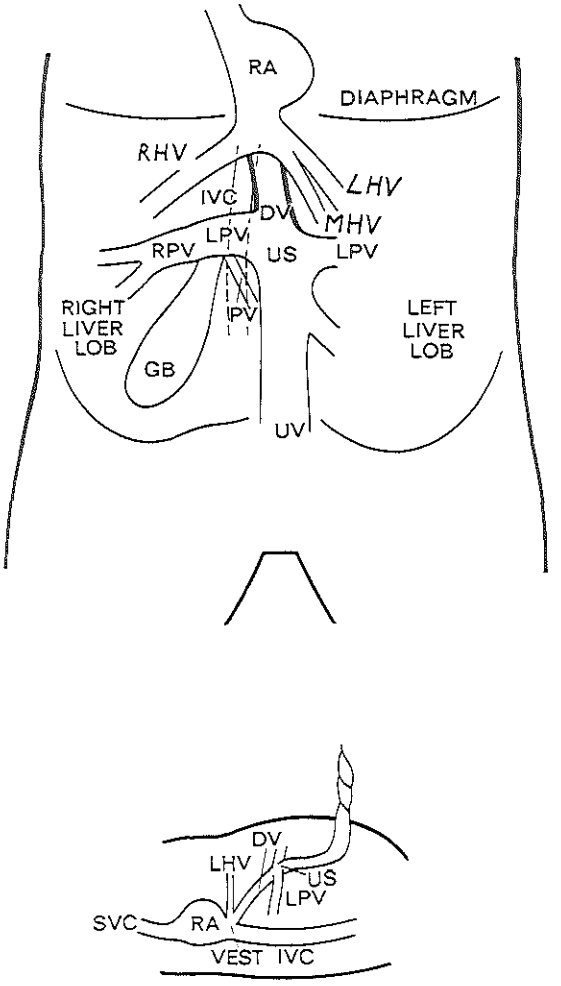

Figure 1: Schematic illustration of anatomical relationships of the venous vasculature in the fetal liver. Anterior view (upper panel) and sagittal view (lower panel).

RA = right atrium
US = umbilical sinus
GB = gallbladder
RPV = right portal vein
MHV = middle hepatic vein
LHV = left hepatic vein
VEST = vestibulum
SVC = superior vena cava
UV = umbilical vein
PV = portal vein
LPV = left portal vein
RHV = right hepatic vein
DV = ductus venosus
IVC = inferior vena cava

The fate of the sinus venosus is insignificant as compared with its embryologic role: it is incorporated in the dorsal heart wall. The proximal portion of the right vitelline vein persists as a hepatocardiac connection, forming the part of the inferior vena cava which extends from the liver to the heart (Gilbert 1989). This termination of the inferior vena cava at the level of the diaphragm is complex; hepatic veins together with the ductus venosus conjoin approximately just below the entrance into the right atrium (Figure 1). Recently, it was reported that the dilatation of the terminal part of the inferior vena cava is, in fact, a funnel-like cavity or vestibulum which contains the orifices of the three hepatic veins, the inferior vena cava, a phrenic vein and the ductus venosus (Huisman et al. 1992a). The vestibulum continues through the diaphragm where it connects the right atrium as the thoracic part of the inferior vena cava. From the position of the foramen ovale flap (mobile septum primum) and the crista dividens (rigid septum secundum) in the right atrium two functional blood flow pathways can be discerned (Amoroso et al. 1942; Kiserud et al. 1992b): a left ductus venosus-foramen ovale pathway that delivers blood directly to the foramen ovale circumventing the right atrium, and a right inferior vena cava-right atrium pathway that delivers blood into the right atrium through the right portion of the proximal inferior vena cava. The left and medial hepatic veins enter the left ductus venosus-foramen ovale pathway, while the right hepatic vein enters the right inferior vena cava-right atrium pathway (Kiserud et al. 1992b).

An anatomical variant with the ductus venosus terminating into the left hepatic vein has been documented (Balique et al. 1984), as well as anomalous pulmonary vein connections (Duff et al. 1977; Rammos et al. 1990). A congenital arteriovenous fistula between the left internal mammary artery and the ductus venosus has also been reported (Stanford et al. 1970). Finally, congenital absence of this shunt is possible and can cause neonatal portal hypertension (Paltauf 1888; MacMahon 1960; Blanc 1960; Leonidas and Fellows 1976).

In human term fetuses and newborn the ductus venosus is approximately 2 cm long and its length is a linear function of gestational age (Chacko and Reynolds 1953; Meyer and Lind 1966). It forms the connection between the umbilical sinus

and the inferior vena cava; its diameter is a little smaller than that of the inferior vena cava, but about one half of its origin, the umbilical sinus. At this point the ductus venosus displays its smallest diameter and has been the subject to many investigations with respect to the existence of a muscular sphincter (Barron 1942; Chacko and Reynolds 1953; Meyer and Lind 1966). A thickening at the level of the umbilical-portal sinus conjunction has been described, consisting of oblique, circular and longitudinal smooth muscle fibers together with elastic tissue. The scarcity of muscle fibers has lead to the conclusion, that this conjunction does not represent a functional sphincter but it rather plays a role in the postnatal closure (Meyer and Lind 1965 and 1966; Salzer 1970; Ferraz de Carvalho and Rodrigues 1975).

2.4 Preload physiology

It is remarkable to notice that most published reports have been concentrating on the physiology of the left heart and arterial vascular system. This is also reflected in the data available on fetal cardiology and on venous return.

One of the pioneers in the field of venous return in adults is Arthur C. Guyton (1989), who was the first to determine cardiac output by equating venous return curves with cardiac response curves. It was pointed out that the heart could only perform properly under conditions of normal venous return. Many situations which result in cardiac compromise have their origin in an abnormal preload.

Under normal conditions cardiac output is mainly controlled by the following variables:

(i) right atrial pressure, which exerts a backward force on the veins to impede blood flow into the right atrium;

(ii) the mean systemic filling pressure, which forces systemic blood flow towards the heart and is related to blood volume;

(iii) muscular movement, which together with the presence of venous valves is part of the force which enables the return of blood from the extremities. Whether this factor plays an important role in fetal venous return, is unknown.

(iv) negative intrathoracic pressure during inspiration, which also acts with the venous valves to aid return of blood to the thorax (Scher 1989). Breathing movements have been recognized in fetuses as early as 11 weeks of gestation, but an explanation for their occurrence has yet to be provided. It is clear, however, that fetal breathing movements increase blood flow velocities at the level of the venous entrance into the right atrium, probably as a result of both a reduction in vessel diameter and increased inflow of blood (Huisman et al. 1993);

(v) peripheral resistance or afterload, which is important in determining venous return on its way to the right atrium. This last factor is completely different in the neonate and adult when compared with the fetal situation, since in the latter the placental circulation is situated between the arterial and venous vascular system.

Not only the different sites of oxygenation imply different hemodynamics, but also different venous blood pressures have significant implications regarding the physiology of venous return. For instance, in fetal sheep the umbilical venous pressure is 15 mm Hg (Dawes 1984), whereas the human fetal umbilical venous pressure is reported to be only 5 mm Hg (Weiner et al. 1989). Umbilical venous pressures have been measured through cordocentesis and would allow calculation of central venous pressure based on umbilical venous pressure recording and Doppler velocimetry in the umbilical vein, ductus venosus (Kiserud et al. 1992a) or inferior vena cava. The knowledge of central venous pressure would shed new light on fetal hemodynamics.

The function of veins mainly depend on their specific physical properties. Since veins have a large cross-sectional area, blood flow experiences low resistance resulting in a relatively small pressure drop from venous capillaries to the right heart as compared with the reduction of blood pressure from the aorta towards the arterial capillaries (Scher 1989). Another important factor is the venous compliance. Increases in volume and pressure impose very little stretch on its thin-walled, elastic vessel structure. Because of its cross-section , compliance and length, the veins can contain a large proportion (60 % to 80 % in adults) of the circulating blood volume. Their capacity and compliance are optimally utilized in the role of a variable blood reservoir that receives or releases blood volume

with only small changes in pressure.

Whereas the functional role of the foramen ovale and ductus arteriosus shunt has been reasonably well-established, the role of the ductus venosus is less clear. The foramen ovale and ductus arteriosus act to bypass the ineffective pulmonary circulation ensuring quick delivery of well-oxygenated blood to the fetal brain and heart (van Eyck 1990). It has been suggested that the ductus venosus serves as a bypass of the hepatic microcirculation for well-oxygenated umbilical venous blood (Peltonen and Hirvonen 1965; Rudolph 1983). From anatomical and angiographic data it was postulated that using its sphincter the ductus venosus could actively regulate umbilical venous blood pressure (Chacko and Reynolds 1953; Reynolds and Mackie 1962). A change in vessel diameter would tend to keep umbilical and portal venous pressures equal while reacting to physiological fluctuations (Edelstone 1980). Edelstone et al. (1978) demonstrated that these pressures are approximately equal in sheep, but can reach large differences in the healthy term fetus in the process of diminishing umbilical perfusion. It is likely that the ductus venosus flow is affected by both umbilical and portal venous pressure (Brinkman et al. 1970; Edelstone et al. 1980a), also because congenital absence of this vessel can lead to substantial portal hypertension and ascites (Paltauf 1888; MacMahon 1960; Blanc 1960; Leonidas and Fellows 1976). In this respect the report by Amoroso et al. (1955) surprisingly suggested that prolonged ductus venosus occlusion in fetal lamb did not alter carotid arterial O_2 saturation nor systemic arterial blood pressure. Therefore, they speculated that the ductus venosus may be of no importance in the mature fetal lamb. The anatomical relationship of the distal end of the inferior vena cava, ductus venosus and foramen ovale, however, implies that similar to the observations in fetal lamb, well-oxygenated umbilical venous blood in the human fetus seems to follow a preferential pathway through the ductus venosus towards the foramen ovale and left heart (Edelstone and Rudolph 1979; Kiserud et al. 1992b).

2.5 Animal experiments

Since the first cineangiographic studies in newborn lambs by Barclay and co-workers (1939) this method has been used by other investigators to study the neonatal circulation (Peltonen and Hirvonen 1964 and 1965). These studies showed that highly variable portions of umbilical venous blood flow entered the ductus venosus during fetal life. It was also demonstrated that ductus venosus blood flow is pulsatile (Lind and Wegelius 1954; Peltonen and Hirvonen 1965). Barclay et al. suggested that the umbilical vein supplied the left and central portions of the liver, while the portal vein supplied the right liver lobe (Barclay et al. 1944). Lind presumed a similar mechanism of blood flow distribution in the human fetus (Lind and Wegelius 1954). Information from these exteriorized sheep fetuses or human fetuses after caesarean section, however, may not represent the actual situation in-utero. Umbilical blood flow will be decreased and thus will effect ductus venosus shunting. A more reliable method is the radio-active-labelled microsphere technique, which enables accurate measurements in chronically-catheterised animal fetuses in-utero (Rudolph and Heymann 1967). Calculation of the ductus venosus shunt fraction has been performed in the fetal lamb. A considerable variation in shunt fraction ranging from 34 to 91 % was demonstrated. In another fetal lamb study it was demonstrated that 9 % of the portal venous blood flow passed through the ductus venosus together with an average umbilical venous portion of 53 % (Edelstone et al. 1978). This portion was not correlated with the umbilical venous blood flow nor was it correlated with gestational age.

Although Barron demonstrated the presence of nerve fibres innervating the smooth muscle cells around the ductus venosus in fetal sheep (Barron 1942 and 1944), a mechanism involving innervated muscle fibres remains considerably controversial in the human fetus. Meyer and Lind (1966) found little smooth muscle and neural fibres in the ductus venosus vessel wall, while Chacko and Reynolds (1953) observed a muscular sphincter with nerve fibres entering its adventitial layer. Pearson and Sauter (1968, 1969 and 1971) also identified nerve

fibres originating from the anterior and posterior vagal trunks and terminating in a slight muscular thickening at the origin of the ductus venosus. Vagal stimulation in exteriorized fetal lambs was reported to result in no changes in the ductus venosus by one group (Edelstone et al. 1980b), but to lead to vasodilatation of the ductus with simultaneous contraction of other intrahepatic vasculature according to others(Arstila 1965). Finally, Ehinger et al. (1968) reported a distinct accumulation of alpha-adrenergic nerves at the junction of the umbilical sinus and the ductus venosus in the human fetus, while Coceani et al. (1984) observed the same in the fetal lamb. Administration of phentolamine (an alpha-adrenergic antagonist), however, did not change either umbilical venous or ductus venosus blood flow (Edelstone et al. 1980b). Only a minimal increase in umbilical venous flow was observed after administration of atropine, a cholinergic antagonist, but no effect was seen on ductus venosus flow. It seems likely, therefore, that the autonomic nervous system wields little influence on the regulation of ductus venosus blood flow (Edelstone 1980).

The influence of various vasoactive substances on the ductus venosus blood flow have been studied in-vitro and in-vivo in animal experiments. Peltonen and Arstila et al. (1964 and 1965) demonstrated in some lambs a dilating effect of epinephrine, norepinephrine and acetylcholine on the ductus venosus, but their findings should be considered with scepticism due to many methodological inaccuracies. It was pointed out that in vitro administration of these agents produced contraction of the ductus venosus and umbilical sinus (Ehinger et al. 1968). This controversy was explained by the observation that these vasoactive substances also had a considerable impact on the liver and systemic circulation (Edelstone 1980). McCuskey (1966) showed that epinephrine and norepinephrine administration to fetal rabbits resulted in hepatic circulatory vasoconstriction, although acetylcholine caused hepatic vasodilatation. Already in 1956, Dawes reported that injections of epinephrine and norepinephrine into fetal lambs produced an increase in umbilical blood flow proportional to a rise in blood pressure. This was confirmed by others (Zink and van Petten 1980). Examination of blood flow distribution at the level of the portal vein demonstrated that acetylcholine,

norepinephrine and epinephrine reduced liver blood flow and subsequently increased ductus venosus flow in the fetal lamb (Edelstone 1980). Animal studies also demonstrate that alpha-adrenergic venoconstriction has a relatively minor effect on mobilization of blood and on cardiac output. Responses that have been ascribed to venomotor changes may be due to the actions of vasoactive drugs or reflexes on arteriolar rather than on venous vessels (Benett et al. 1984; Scher 1989). A few reports have appeared on the effect of prostaglandins (or eicosanoids) and their inhibitors on the vessel wall of the ductus venosus in fetal lamb. Firstly, it was reported that the cyclooxygenase inhibitor indomethacin contracted both the fetal and neonatal ductus venosus in vitro (Adeagbo et al. 1982; Sideris et al. 1982). Prostaglandin E_2 and I_2, both products of the cyclo-oxygenase reaction, relaxed the ductus venosus, thus suggesting a prostaglandin-mediated relaxing mechanism (Adeagbo et al. 1982; Coceani and Olley 1988). Conversely, a prostaglandin endoperoxide analog and PGF_{2a} were contractile. Later, the PGH_2 relaxing and thromboxane TXA_2 constricting action was described, supporting the influence of prostaglandin on patency and closure of the ductus venosus in fetal lambs (Coceani et al. 1983; Adeagbo et al. 1985).

Moreover, PGE_1 and PGE_2 were reported to reopen the ductus venosus in the newborn lamb (Sideris et al. 1982; Morin 1987) and to induce vasoconstriction in the placental bed (Novy et al. 1974). Finally, Adeagbo, Coceani et al. (1988 and 1990) discovered that the lamb ductus venosus sphincter, like the ductus arteriosus, relies on an intramural cytochrome P-450 mechanism to develop its contractile tone. It should be emphasized that all experiments reflect the situation in fetal and neonatal sheep, which in our opinion is not completely similar to the human situation. There is only one report of PGE_1 application in a human neonate with total anomalous pulmonary venous connection to the portal system, in which the use of a prostaglandin seemed to have induced improved shunting through the ductus venosus (Bullaboy et al. 1984). Moreover, the dosage of prostaglandins which was administered to the neonatal lamb was ten times the dose used to open the ductus arteriosus in newborn infants with congenital heart disease (Morin 1987). Therefore, it seems likely that there is an effect of prosta-

glandins on the ductus venosus tone, but not to an extent that it causes alterations in blood flow.

The effect of several experimental manipulations to simulate various distressing perinatal conditions probably bears more clinical relevance. Reduction in umbilical venous return by reduction in fetal blood volume or compression of the umbilical cord and induction of fetal hypoxemia have been investigated. A decrease in umbilical blood flow by 25 - 50 %, as a result of partial clamping of the fetal descending aorta did not alter hepatic arterial or portal venous blood flow to liver or ductus venosus (Edelstone et al. 1980a). In exteriorized fetal lambs it was shown that occlusion of the ductus venosus for five minutes did not change arterial O_2 saturation or systemic arterial blood pressure (Amoroso et al. 1955). Fetal hypoxemia induced by administration of a low oxygen gas mixture to the maternal sheep, resulted in a considerable increase in vascular resistance across the umbilical sinus and ductus venosus in association with a 24 % decrease in umbilical venous blood flow (Brinkman et al. 1970). It was speculated that this decrease lead to reduction in the umbilical to ductus venosus fraction. In contrast, Behrman and coworkers (1970) reported that in fetal monkeys the ductus venosus portion increased from 53 % to 90 % when umbilical vein blood flow was reduced by 41 %. Edelstone et al. (1980a) attempted to identify the alterations in the different hepatic branches under the same experimental conditions. They demonstrated that induction of fetal hypoxemia had no effect on the blood flow fractions towards the liver or ductus venosus. However, a 50 % reduction in umbilical blood flow by partial cord compression increased the portion of umbilical venous blood shunted through the ductus venosus from 44 to 72 % (Itskovitz et al. 1987). At the same time preferential ductus venosus flow through the foramen ovale was also enhanced (29 to 47 %). With 75 % reduced umbilical venous flow, there was a progressive fall in fetal oxygen consumption, but also a significant increase in oxygen extraction (Itskovitz et al. 1983).

Altogether, it was suggested that cord compression modified the distribution of venous return and cardiac output with the purpose of maintaining optimal oxygen delivery to the vital organs.

Re-establishment of ductus venosus patency would be interesting in the light of treatment of severe portal hypertension in adults. Asuncion and Silva (1971 and 1979) demonstrated in adult cadavers that dilatation of the obliterated vascular structure is possible, but the absence of endothelial lining and the difficulty associated with an anterior approach of the liver prevents the use of the ductus venosus in surgical treatments. However, Balique and coworkers (1984) challenged this view and reported a successful grafting of a patent ductus venosus in a rabbit. In their opinion, it may be possible to use this technique in man once the problems of long term resistance and patency have been solved.

2.6 Doppler techniques; transabdominal versus transvaginal Doppler ultrasound

Particularly during the late first and early second trimester of pregnancy marked developmental changes occur both at fetal and placental level which should have an impact on fetal cardiovascular performance. Fetal heart rate changes from 170-180 bpm to 140-150 bpm with appearance of beat to beat variation most likely resulting from parasympathetic nerve development (Wladimiroff and Seelen 1972). At the same time there is a remarkable differentiation in fetal movement patterns (de Vries et al. 1982). Furthermore, around 14 weeks a continuous intervillous flow pattern has been observed (Jauniaux et al. 1991). This is associated with an abrupt increase of the mean uterine blood flow velocity, which possibly corresponds to the complete dislocation of the trophoblast plugs allowing uninhibited blood supply to the intervillous space (Jauniaux et al. 1992).

Transvaginal images under matched conditions are in general superior in quality to transabdominal sonograms. The dominant factor for this difference is the amount of overlying tissues. Transvaginal sonography in early pregnancy will allow higher emission frequencies, more strongly focused beams and a closer approach of the fetus than the transabdominal approach resulting in better image resolution (Schats 1991; Kossoff et al. 1991). Following a more detailed visualiza-

tion of fetal cardiac or extra-cardiac vessel structures Doppler waveform recording became possible as early as the late first trimester of pregnancy (Schaaps and Soyeur 1989; Wladimiroff et al. 1991). Colour Doppler or velocity imaging will be helpful in locating fetal arterial and maternal vessels, but less so in establishing fetal intra-cardiac and venous blood flow in early pregnancy (Kurjak et al. 1990; Huisman and Wladimiroff 1992).

When applying ultrasound and Doppler techniques energy levels should be taken into account (Miller 1991). The most often used standard to describe the intensity from a certain system is the Spatial Peak Temporal Average Intensity (I_{SPTA}). Energy output levels from the transvaginal Doppler transducer are clearly situated in the lower regions for acoustic output of Japanese and American diagnostic ultrasound equipment (Ide 1989). This is determined by the fact that the fetus is closer to the transducer with the transvaginal approach than with the abdominal approach and needs to reflect less energy to be detected. Studies have demonstrated that the energy exposure on the surface of the fetus (I_{SPTA}: 1.2 - 1.9 mW/cm^2) is well within the Food and Drug Administration (FDA) guidelines of 94 mW/cm^2. (Hussain et al. 1992). Moreover, the physical and psychomotor development of children exposed to transvaginal ultrasonography did not differ from that of non-exposed infants (Gershoni-Baruch et al. 1991).

The acceptance of the transvaginal method by patients in early pregnancy is excellent (Schats 1991; Huisman unpublished data). The preference of transvaginal to transabdominal ultrasound was mainly due to the fact that a full bladder was not necessary using the first approach. Next to the discomfort experienced from pressure of the abdominal transducer on a tense bladder, this method also means that the patients have to drink about one liter of fluid one hour before the abdominal scan is performed (Schats 1991). This disruption of the daily routine together with the possibility of quick diagnosis (without waiting for a full bladder) makes transvaginal sonography the method of choice in ultrasound assessment in early pregnancy.

Whereas under 13-14 weeks of gestation the superiority of the transvaginal approach is unchallenged, the growing fetus will render this technique increa-

singly difficult beyond that stage of pregnancy (table 1). Beyond 14 weeks fetal flow velocity waveforms will nearly always be obtained by means of transabdominal Doppler ultrasound.

Transvaginal fetal echocardiography has shown to be effective in the visualization of normal early fetal cardiac anatomy and, therefore, suggested to have a significant potential for the diagnosis of gross fetal cardiac anomalies during the late first and early second trimester of pregnancy (Dolkart and Reimers 1991; Johnson et al. 1992). Present transvaginal Doppler techniques allow detailed information on fetal waveform characteristics and velocities as early as 8-9 weeks of gestation (Huisman et al. 1992b).

Table 1 : The success rate of transvaginal and transabdominal Doppler ultrasound in obtaining fetal flow velocity waveforms relative to gestational age.

	gestational age (weeks)						
	10	11	12	13	14	15	16
transvaginal scan (%)	100	100	100	60	20	0	0
transabdominal scan (%)	0	0	0	40	80	100	100

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Chapter 3
DOPPLER ASSESSMENT OF VENOUS RETURN RELATIVE TO CARDIAC PERFORMANCE AND AFTERLOAD IN EARLY PREGNANCY

3.1 Introductory remarks

Very little is known about fetal hemodynamics during the early stages of pregnancy. As has already been pointed out, venous return is closely associated with other aspects of cardiovascular physiology. Examinations of Doppler flow velocity waveforms are subject to fetal movements. Moreover, in early pregnancy vessel dimensions are small when compared with later gestation. All this will have an effect on the reproducibility of waveform recordings. This chapter will therefore start with a subchapter (3.2) on the reproducibility of Doppler flow velocity measurements in early pregnancy.

The next two subchapters will deal with cardiac performance (3.3) and afterload (3.4) in late first and early second trimester fetuses. Finally, in subchapter 3.5 preload in this early stage of pregnancy will be evaluated by Doppler studies in the inferior vena cava and ductus venosus.

3.2 Doppler flow velocity waveforms in late first and early second trimester fetuses; reproducibility of waveform recordings

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INTRODUCTION

Transvaginal and transabdominal Doppler ultrasonography is a non-invasive method of studying early human fetal cardiac and extracardiac hemodynamics. Flow velocity waveforms obtained from different vascular sites are influenced by various factors, such as preload, afterload (including arterial pressure and vascular resistance), heart rate and the intrinsic contractile properties of both cardiac ventricles. It was suggested that a relatively low vascular resistance is present at cerebral level compared to umbilical artery level in the late first trimester fetus (Wladimiroff et al. 1991 and 1992). With the increasing use of Doppler techniques to assess early fetal hemodynamics it is necessary to define the reproducibility of flow velocity waveform data in early pregnancy, especially, since cardiovascular changes during this period could have a marked influence on consistency of flow velocity measurements (Wladimiroff et al. 1991).
The aim of the present study was to assess the reproducibility of Doppler flow measurements in early pregnancy with respect to within patient and between patient variance.

MATERIAL AND METHODS

Study patients

A total of 54 women with a normal singleton pregnancy consented to participate in the study. The study protocol was approved by the Hospital Ethics Committee. Gestational age varied between 11 and 16 weeks and was determined from the last menstrual period and confirmed by ultrasonic measurement of the crown-rump length or biparietal diameter. Patients were selected in three subgroups, namely 11 to 12 weeks, 13 to 14 weeks and 15 to 16 weeks of gestation to guarantee a homogeneous distribution of study subjects and to assess possible differences between these groups. Each woman was included in this cross-sectional study only once.

Recording technique

A combined real-time and pulsed Doppler system (Hitachi EUB - 450, Hitachi Medical Corporation, Tokyo) was used with a carrier frequency of 3.5 MHz (Doppler mode and transabdominal real-time) and 6.5 MHz (transvaginal real-time). The system operates at power outputs of <100 mW/cm^2 spatial peak temporal average in both imaging and Doppler modes by manufacturer's specifications. The high-pass filter was set at 100 Hz.

Depending on fetal size and position a transvaginal or transabdominal approach was chosen. Doppler studies were performed by one examiner (PAS), whereas the data analysis was carried out by an independent investigator (TWAH). Nine fetal vascular sites were examined: the umbilical artery and vein, descending aorta, inferior vena cava, ductus venosus, mitral and tricuspid valve, pulmonary artery and ascending aorta. The total examination period was limited to 30 minutes. Recordings were performed with the women in semi-recumbent position and during fetal apnea. Depending on fetal position and accessibility of vascular structures, Doppler measurements were obtained at two to five different sites on three to five different occasions at five minute time intervals. Each recording consisted of three to five technically acceptable waveforms. Doppler sample

volume length was 0.1 to 0.3 cm. The angle between the Doppler cursor and the assumed direction of blood flow was always kept below 30 degrees. Both sample volume length and angle insonation were kept the same at each vascular site for each patient.

Flow velocity waveforms in the umbilical artery were obtained from a free-floating loop of the umbilical cord. Umbilical vein Doppler measurements were taken from the intra-abdominal part close to the cord insertion. Flow velocity waveforms at atrioventricular valve level were documented from the four chamber view, whilst recordings from the ascending aorta were obtained from the five chamber view (Groenenberg et al. 1991; van der Mooren et al. 1992). The pulmonary artery waveform was obtained from the echocardiographic short-axis view (Groenenberg et al. 1991). Flow velocity waveforms from the lower thoracic part of the fetal descending aorta were recorded from a sagittal cross-section through the fetal trunk that displayed a major section of the fetal spine. Flow velocity waveforms from the inferior vena cava were obtained in a sagittal view, which included the fetal right atrium and right ventricle (Reed et al. 1990). The sample volume was positioned over the inferior vena cava immediately proximal to the right atrium with special regard to the assumed direction of blood flow. Finally, the ductus venosus waveform recording was documented from a transverse cross-sectional scanning plane of the fetal abdomen by placing the sample volume immediately above the umbilical sinus (Huisman et al. 1992).

Data analysis

During each recording at least three consecutive, optimal flow velocity waveforms were documented on hard copies. A microcomputer (Olivetti M24; Olivetti B.V., Leiden, the Netherlands) linked to a graphics tablet was used for analysis of the Doppler recordings. For all recorded waveforms the time-averaged velocity was calculated. For the umbilical artery and descending aorta the pulsatility index was determined (Gosling & King 1975). Waveforms obtained in the descending aorta, inferior vena cava, ductus venosus, pulmonary artery and ascending aorta were also analysed for the peak systolic velocity. In the latter two vessels also the

acceleration time was calculated. The peak systolic / diastolic ratio was determined in the inferior vena cava and ductus venosus, while the percentage reverse flow was only present and determined in the inferior vena cava. Finally at atrioventricular level the E-wave and A-wave peak velocities and their ratios were calculated for both mitral and tricuspid valve.

Statistical analysis

Total variance was partitioned in a between patient and a within patient component, assuming a random effects model. The coefficient of variation in waveform recording was defined as the between patient component or within patient component as a percentage of the mean value. To test the homogeneity of variances in the subgroups, Cochran's C test was applied (maximum variance / sum (variances)).

RESULTS

Relevant data are presented in tables 1 and 2.

In this early pregnancy period success rates of Doppler recording varied for different vessels. Umbilical artery flow velocity waveforms were obtained in all 22 women studied, resulting in 88 recordings, while Doppler measurements in the pulmonary artery only succeeded in 16 out of 25 women studied with 61 recordings as a result.

Since the test for homogeneity of variances demonstrated no significant differences in standard deviations between and within the subgroups 11 to 12, 13 to 14 and 15 to 16 weeks of gestation, all data from the 54 participating women were combined. Mean values for the different parameters at each vascular site are shown together with the between patient and within patient standard deviation, calculated by taking the square root of the respective variance components.

Flow velocity waveform recording in early pregnancy was characterized for almost all studied parameters by within patient coefficients of variation in the

range 2.2 - 5.7 %. Percentage reverse flow showed a slightly higher coefficient of variation compared with the other parameters (8.8 %). Only the acceleration time as a parameter demonstrated significantly higher values: 24.5 % and 18.6 % for the pulmonary artery and ascending aorta, respectively.

DISCUSSION

Although Doppler studies are frequently used to describe fetal haemodynamics, it is surprising to notice that very few studies have been performed on the reliability of the measurements. Kenny et al.(1986) and Al-Ghazali et al.(1989) reported a good reproducibility both for cross-sectional diameter measurements and Doppler velocities at fetal outflow tract level in advanced pregnancy, whereas Beeby et al.(1991) documented poor reliability for diameter and Doppler measurements at atrioventricular valve level.

To our knowledge this is a first study on early pregnancy Doppler measurements with a description of waveform reproducibility. Our data suggest that fetal flow velocity waveforms in early pregnancy are well reproducible in the individual patient. As expected, most parameters demonstrated much larger variabilities for between patient values than for within patient values. Poor reproducibility was established for the acceleration time. At cardiovascular level these data are similar to our observations in late pregnancy, demonstrating reproducible flow velocity waveforms at both atrioventricular and outflow tract levels (Groenenberg et al. 1991; van der Mooren et al. 1992). An explanation for the relatively lower reproducibility of the acceleration time could be found in the poorly tracable steep ascending limb of the waveform by hand. Moreover, several reports have appeared about the effect of sampling site on acceleration time measurements (Panidis et al. 1986; Shaffer et al. 1990). In this study these limitations lead to high between patient as well as high within patient variance components.

Relatively low varience components between - and within patients were documented for the peak velocity ratios both at atrioventricular level (E/A ratio) and at

Table 1: Reproducibility data of Doppler velocity waveform recording at umbilical and extracardiac level in 11 to 16 week-old normal fetuses.

vessel	no. of women studied	successful recordings/ waveforms	flow velocity parameter	mean value	between pat. SD (coefficient of variation)	within pat. SD (coefficient of variation)
UV	17	53 / 159	TAV	8.6	1.7 (19.8 %)	0.3 (3.5 %)
UA	22	88 / 271	TAV	11.9	5.4 (45.4 %)	0.6 (5.0 %)
			PI	2.1	0.6 (28.6 %)	0.08 (3.8 %)
DA	21	83 / 252	TAV	16.6	6.4 (38.6 %)	0.7 (4.2 %)
			PI	2.3	0.5 (21.7 %)	0.1 (4.3 %)
			PSV	38.1	9.5 (24.9 %)	0.9 (2.4 %)
IVC	17	65 / 199	TAV	12.3	3.9 (31.7 %)	0.7 (5.7 %)
			PSV	23.5	7.0 (29.8 %)	0.7 (3.0 %)
			S/D ratio	1.7	0.2 (11.8 %)	0.09 (5.3 %)
			% rev. fl.	19.4	5.6 (28.9 %)	1.7 (8.8 %)
DV	18	69 / 222	TAV	28.5	7.2 (25.3 %)	1.0 (3.5 %)
			PSV	37.2	8.3 (22.3 %)	1.0 (2.7 %)
			S/D ratio	1.2	0.06 (5.0 %)	0.03 (2.5 %)

Table 2: Reproducibility data of Doppler velocity waveform recording at atrioventricular and outflow tract level in 11 to 16 week-old normal fetuses.

vessel	no. of women studied	successful recordings / waveforms	flow velocity parameter	mean value	between pat. SD (coefficient of variation)	within pat. SD (coefficient of variation)
MV	21	86 / 269	TAV	8.9	1.6 (18.0 %)	0.5 (5.6 %)
			E-wave	20.4	3.3 (16.2 %)	1.0 (4.9 %)
			A-wave	37.1	3.7 (10.0 %)	0.9 (2.4 %)
			E/A ratio	0.6	0.05 (8.3 %)	0.02 (3.3 %)
TV	23	94 / 286	TAV	9.6	1.6 (16.7 %)	0.5 (5.2 %)
			E-wave	23.0	3.7 (16.1 %)	1.0 (4.3 %)
			A-wave	40.9	4.6 (11.2 %)	0.9 (2.2 %)
			E/A ratio	0.6	0.05 (8.3 %)	0.02 (3.3 %)
PA	16	61 / 185	TAV	11.9	2.7 (22.7 %)	0.6 (5.0 %)
			PSV	34.4	7.2 (20.9 %)	1.1 (3.2 %)
			accel. time	29.4	12.3 (41.8 %)	7.2 (24.5 %)
AA	17	71 / 217	TAV	13.6	2.2 (16.2 %)	0.7 (5.1 %)
			PSV	42.1	6.2 (14.7 %)	1.3 (3.1 %)
			accel. time	36.1	9.4 (26.0 %)	6.7 (18.6 %)

TAV = time-averaged velocity; PSV = peak systolic velocity; PI = pulsatility index; S/D = peak systolic / diastolic velocity; SD = standard deviation; % rev.fl. = percentage reverse flow; E = early filling phase; A = atrial contraction phase; accel. time = acceleration time;
UV = umbilical vein; UA = umbilical artery; DA = descending aorta; IVC = inferior vena cava; DV = ductus venosus; MV = mitral valve; TV = tricuspid valve; PA = pulmonary artery; AA = ascending aorta

the level of the ductus venosus and inferior vena cava (peak S/D ratio). In terms of relative differences, these parameters show very constant values. Moreover, their mean value is, in fact, a combination of two measurements with their own variabilities.

The same applies for the percentage reverse flow, which is calculated from a combination of three separate measurements, i.e. integrals of systolic and early diastolic forward flow and late diastolic retrograde flow. Our results demonstrate that in early pregnancy a higher variance exists for percentage reverse flow compared with other parameters, as reflected by a within patient coefficient of variation of 8.8 %. An increase of percentage reverse flow has recently been described as an important parameter in the evaluation of fetal growth retardation (Reed et al. 1990; Rizzo et al. 1992). Since the within patient variance is rather high, repeated measurements might improve the reliability of the parameter and, therefore, increase the clinical applicability.

In conclusion, flow velocity waveforms obtained in late first and early second trimester fetuses display an good reproducibility. All parameters demonstrate, in our judgement, acceptable coefficients of variation for within patient variance, except for the acceleration time which turned out to be poorly reproducible.

SUMMARY

The objective of this study was to assess the reproducibility of Doppler flow measurements at the umbilical vein and artery, descending and ascending aorta, mitral and tricuspid valve, pulmonary artery, inferior vena cava and ductus venosus in early pregnancy.

In a cross-sectional study Doppler measurements were obtained in a total of 54 women at 11 to 16 weeks of gestation, at two to five different vascular sites, on three to five different occasions, at five minutes time intervals. The total variance in the various flow velocity parameters were partitioned in a between patient and within patient component by analysis of variance and from these calculations coefficients of variation in waveform recording were calculated.

Flow velocity waveform recording was characterized by coefficients of variation in the range between 2.2 and 5.7 % except for the acceleration time (18.6 - 24.5 %) and percentage reverse flow (8.8 %).

In conclusion, our data suggest that fetal flow velocity waveforms in early pregnancy demonstrate good reproducibility in the individual patient, while all parameters depict larger variabilities for between patient values. Acceleration time turned out to be poorly reproducible. If a single flow velocity measurement is used for the future evaluation of clinical conditions in early pregnancy, one has to consider that normal values will display a rather wide range.

3.3 Evaluation of fetal cardiac performance by cardiac Doppler flow velocity recording in early pregnancy

3.3.1 Fetal cardiac flow velocities in the late first trimester of pregnancy; a transvaginal Doppler study

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INTRODUCTION

Transabdominal Doppler ultrasound studies in women during the second half of pregnancy have shown that normal pregnancy is characterized by low fetal and placental vascular resistance levels (Griffin et al. 1984; Trudinger et al. 1987; Reuver et al. 1987).

The introduction of transvaginal sonography has opened the possibility of studying the fetus in the first trimester of pregnancy in more detail (Timor-Tritch et al. 1988). Insight into fetal cardiac performance in the late first trimester of pregnancy would be of interest because vagal function develops during this period resulting in a lowering of baseline fetal heart rate and the appearance of beat to beat variation (Wladimiroff and Seelen 1972). Moreover, absence of end-diastolic flow velocities has been demonstrated in the umbilical artery between 8 and 13 weeks of gestation, reflecting a relatively high placental vascular resistance during this early stage of pregnancy (den Ouden et al. 1990).

The objective of the present study was twofold:
(i) to determine the success rate in obtaining technically acceptable fetal flow velocity waveforms at atrioventricular (AV) valve and outflow tract levels in the late first trimester of pregnancy (ii) to assess fetal cardiac performance during this early stage of gestation.

MATERIAL AND METHODS

Study patients

Thirty women with a normal singleton pregnancy were randomly selected to participate in the study. Maternal age ranged between 23 and 38 years (median 27). Gestational age ranged between 11 and 13 weeks (median 12). The study protocol was approved by the Hospital Ethics Committee in June 1989.
All pregnant women consented to participate in the study.

Recording technique

A combined transvaginal real-time and pulsed Doppler system (Hitachi E.U.B. 450 Medical Corporation, Tokyo, Japan) with a carrier frequency of 6.5 MHz (real-time) and 3.5 MHz (Doppler) was used. The system operates at power outputs of less than 100 mW/cm^2 spatial peak temporal average (SPTA) in both imaging and Doppler modes by manufacturer's specifications. Each woman was included in the study only once. Doppler studies were performed by one examiner (J.W.W.). Flow velocity waveforms at the fetal AV valve level were obtained from the four chamber view. Flow velocity waveforms from the fetal ascending aorta were recorded from the five chamber view and fetal pulmonary artery flow velocity waveforms were obtained from the echocardiographic short axis view. Doppler sample volumes were placed immediately distal to the AV and semilunar valves. The angle between the Doppler cursor and the assumed direction of flow was always $\leq$ 20. Sample volume length was 0.1-0.3 cm. Peak velocities (cm/s) and time-averaged velocities (cm/s) were determined at both the AV valve and

outflow tract level.

Heart rate (beats/min) was calculated from peak velocity time intervals in the ascending aorta. All Doppler studies were performed with the women in the semi-recumbent position and during fetal apnea because fetal breathing movements modulate blood flow velocity waveforms (Marsal et al. 1984).

The total examination time was limited to 15 minutes in each instance.

Data and statistical analysis

All flow velocity waveforms were recorded on hard copies. A microcomputer (Olivetti M 24, Olivetti BV, Leiden, The Netherlands) linked to a graphics tablet was used for analysis of the Doppler recordings. An average of three consecutive flow velocity waveforms with the highest velocity and of similar appearance was used to establish each value. The paired t-test was applied to compare flow velocity waveforms from the ascending aorta and pulmonary artery. Data are presented as mean values ± 1 SD.

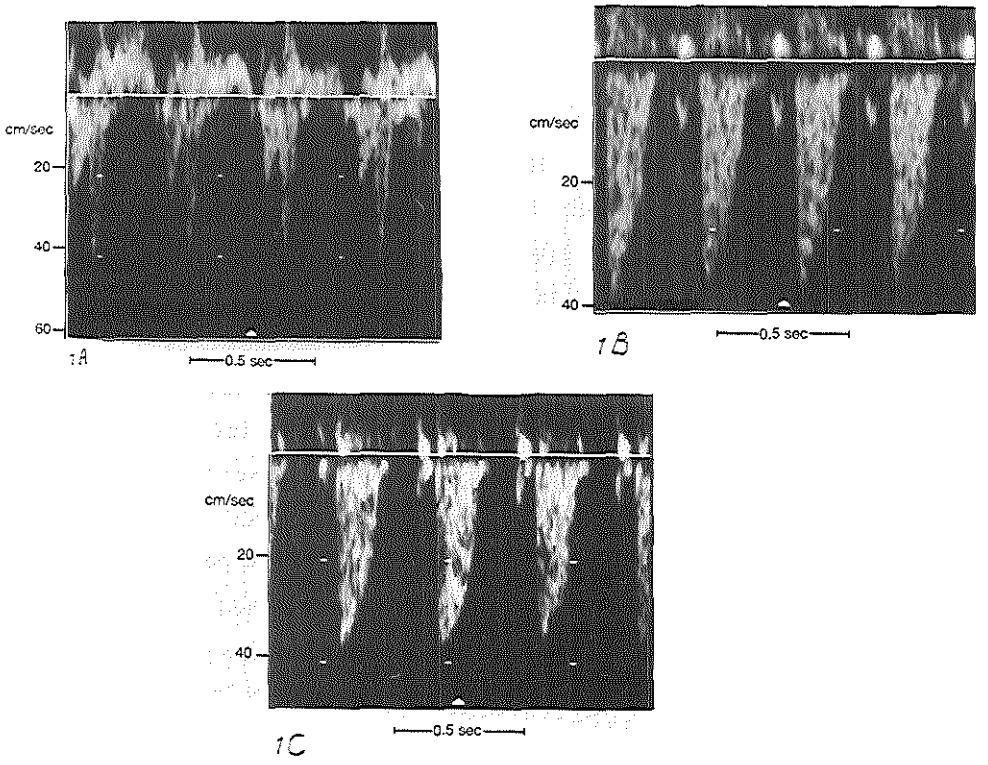

Figure 1: Flow velocity waveforms at AV valve level (Figure 1a), from the ascending aorta (Figure 1b) and from the pulmonary artery (Figure 1c) in late first trimester normal fetuses.

RESULTS

Among the 30 fetuses, acceptable flow velocity waveforms were obtained at the AV valve level in 19 (63%), from the ascending aorta in 15 (50%) and from the pulmonary artery in 17 (56%) (Figure 1). Successful recording of both transmitral and transtricuspid flow velocity waveforms was achieved in six fetuses only; there were no significant differences in the peak and time-averaged velocities between the two valve levels. In the other 13 fetuses, there was no assurance as to the origin of the flow velocity waveforms at the AV valve level. We, therefore, selected for each of the 19 fetuses the flow velocity waveforms with the highest velocity for further analysis. Early diastolic filling velocities (E-wave) and late diastolic velocities coinciding with atrial contraction (A-wave), as well as outflow tract velocities are presented in table 1.

A-wave peak velocities were nearly twice as high as E-wave peak velocities. Comparison between aortic and pulmonary artery flow velocity waveforms was feasible in 15 fetuses; no statistically significant difference in peak and time-averaged velocity between the two vessels was found. Fetal heart rate ranged between 146 and 188 beats/min (mean 169 $\pm$ 5). No statistically significant correlation existed between cardiac flow velocities and heart rate.

DISCUSSION

The purpose of this study was to define fetal cardiac flow velocity waveforms in the late first trimester of pregnancy. There are several reasons to believe that fetal Doppler studies recorded with transvaginal ultrasound equipment in this period are safe. All measurements were carried out after the completion of embryonic structural development. The output levels for the transvaginal Doppler transducer are clearly situated in the lower regions for acoustic output of Japanese and American ultrasonic diagnostic equipment (Ide 1989). This placement is

Table 1: Peak and time-averaged velocities (mean ± 1 SD) at AV and outflow tract level in normal fetuses during the late first trimester of pregnancy.

	AV valve level				
	E-wave	A-wave	E/A ratio	ascending aorta	pulmonary artery
peak velocity (cm/s)	20.5 ± 3.2	38.6 ± 4.7	0.53 ± 0.05	32.1 ± 5.4	29.6 ± 5.1
time-averaged velocity (cm/s)		8.9 ± 1.4		11.2 ± 2.2	10.8 ± 2.1

determined by the fact that the fetus is closer to the transducer with the transvaginal approach than with the transabdominal approach and needs to reflect less energy to be detected. Therefore, the fetus may be exposed to lower output levels with the transvaginal approach. However, as in any sonographic examination, the total examination time should be kept as short as possible. In the present study this period was 15 minutes.

Fetal flow velocity waveform recordings were successful in $\geq$ 50 % of the women examined. Fetal motor activity, especially of the trunk, was the main cause of failure to obtain acceptable waveforms. This was particularly true for transmitral and transtricuspid flow velocity waveforms. Because mitral and tricuspid valve structures are situated close to each other on a four chamber cross-sectional view, distinction between trans mitral and transtricuspid flow velocity waveforms was facilitated by the presence of a fluid-filled stomach serving as a landmark for establishing the left side of the heart.

The clear A-wave (late diastolic filling) dominance at the AV valve level reflects the relative stiffness of the cardiac ventricles in early gestation. The peak systolic and time-averaged flow velocities at both the AV valve level and the outflow tract level are lower than those observed in second and third trimesters of pregnancy (Reed et al. 1986; Allan et al. 1987).

Flow velocities at the cardiac level are subject to preload, contractile function,

afterload and heart rate. With respect to afterload, during the late first trimester of pregnancy, umbilical artery flow velocity waveforms are characterized by absent end-diastolic flow (den Ouden et al. 1990), reflecting a relatively high umbilical-placental resistance compared with that of later pregnancy. From fetal lamb studies, it appears that cardiac function is particularly sensitive to change in afterload which is determined by blood pressure and vascular resistance (Gilbert 1982). Because no data are available on fetal blood pressure and venous and arterial volume flow in the late first trimester, it is unknown how umbilical - placental resistance affects cardiac flow velocity waveforms at this stage of pregnancy.

Fetal heart rates in the late first trimester of pregnancy are higher than those observed (120 to 165 beats/min) in second and third trimester pregnancies, a finding that is determined by parasympathetic immaturity (Wladimiroff and Seelen 1972). Fetal heart rate independence has been established for peak flow velocities in the fetal ductus arteriosus in the heart rate range of 100 and 180 beats/min (van der Mooren et al. 1989). A similar finding was obtained at the AV valve and outflow tract level in the present study, with heart rates of 145 to 190 beats/min. It is therefore unlikely that heart rate is responsible for the observed difference in fetal cardiac flow velocities between the late first trimester and later stages of pregnancy.

Flow velocities in the ascending aorta are higher than those documented in the pulmonary artery. However, this difference is not statistically significant.

Differences have been established in late pregnancy that were attributed to the relatively lower afterload to the left ventricle as a result of low cerebral vascular resistance (Groenenberg et al. 1989). If afterload plays a role, it is of interest to note that late first trimester studies of the fetal internal carotid and middle cerebral arteries suggest cerebral vascular resistance in this period is virtually similar to that observed in late gestation (Wladimiroff et al. 1992).

It can be concluded that despite the limitations of noninvasive Doppler techniques, transvaginal Doppler echocardiography can be used to study early human fetal cardiac function.

SUMMARY

In 30 normal women with a singleton pregnancy, transvaginal Doppler ultrasound was used to record flow velocity at the fetal atrioventricular (AV) valve and outflow tract levels (ascending aorta, pulmonary artery) at 11 to 13 weeks of gestation. Technically acceptable flow velocity waveforms were recorded at the AV valve level in 19 fetuses and in the ascending aorta and pulmonary artery in 15 and 17 fetuses, respectively. Successful documentation of both transmitral and trans tricuspid flow velocity waveforms was achieved in six fetuses only.
Peak velocities during atrial contraction (A-wave) were nearly twice as high as those during early diastolic filling (E-wave) reflecting low ventricular compliance. Peak and time-averaged flow velocities in the outflow tract were lower than those observed in second and third trimester pregnancies with mean values of 32.1 ± 5.4 (± SD) and 11.2 ± 2.2 cm/s, respectively in the ascending aorta and 29.6 ± 5.1 and 10.8 ± 2.1 cm/s in the pulmonary artery.

3.4 Evaluation of fetal afterload by arterial Doppler flow velocity recording in early pregnancy

3.4.1 Fetal and umbilical flow velocity waveforms between 10 - 16 weeks' gestation: a preliminary study

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INTRODUCTION

The introduction of transvaginal pulsed Doppler systems has allowed the possibility of studying fetal flow velocity waveforms as early as 10 weeks' gestation. Preliminary data have shown that in the late first trimester of pregnancy, end-diastolic velocities in the fetal descending aorta and umbilical artery are nearly always absent, suggesting a high fetal placental vascular resistance (Wladimiroff et al. 1992). At the same time, end-diastolic velocities have been observed in fetal intracerebral arteries, suggesting a relatively low vascular resistance at the cerebral level (Wladimiroff et al. 1992). Previous Doppler studies have detected end-diastolic flow velocities in the fetal descending aorta and umbilical artery as early as 16 - 18 weeks (Trudinger et al. 1985; van Vugt et al. 1987a and 1987b). Measurable changes in end-diastolic flow velocities may be expected in these vessels in the early second trimester of pregnancy. That the fetal heart rate (FHR) between 10 - 15 weeks' gestation is subject to a marked reduction may be due in part to maturation of the parasympathetic system (Wladimiroff and Seelen 1972). Therefore, any changes in the flow velocity waveform should be related to the FHR.

The objective of the present study was to establish the pulsatility of the normal flow velocity waveforms from the umbilical artery, fetal descending aorta and fetal intra-cerebral arteries between 10 - 16 weeks' gestation and the relationship of these waveforms to the FHR.

MATERIAL AND METHODS

We studied 77 normal singleton pregnancies. Maternal age varied between 21 - 35 years (median 26), and gestational age ranged between 10 - 16 weeks (median 12). All pregnancies were uneventful. Each woman was included in the study only once. The study protocol was approved by the Hospital Ethics Committee, and all women consented to participate in the study.

Ultrasound Doppler studies were performed with a Hitachi EUB 450 (Hitachi Medical Corp., Tokyo, Japan). We used a combined transvaginal real-time and pulsed Doppler system with a carrier frequency of 6.5 Mhz (real-time) and 3.5 MHz (Doppler), or a combined transabdominal real-time and pulsed Doppler system with a carrier frequency of 3.5 MHz (real-time and Doppler), depending on fetal size and position relative to the ultrasound probe. Both systems operate at a power output of less than 100 mW/cm^2 spatial peak temporal average in the imaging and Doppler modes.

Pregnancy duration was estimated from the last menstrual period and confirmed by ultrasound measurements of the crown-rump length (10-12 weeks) or bi-parietal diameter (12-16 weeks). Doppler studies were performed by one examiner (JWW).The maximal flow velocity waveform in the umbilical artery was obtained from a free-floating loop of the umbilical cord (Figure 1). Maximal flow velocity waveforms from the lower thoracic part of the fetal descending aorta were recorded from a sagittal cross-section through the fetal trunk, displaying a major section of the fetal spine. Maximal flow velocity waveforms at the fetal cerebral level were imaged on a transverse cross-section through the lower part of the fetal cerebrum, showing a heart-shaped cross-section of the brain stem

with the anterior lobes representing the pedunculi cerebri (Wladimiroff et al. 1986). Anterior to this heart-shaped structure and on either side of the midline, one can see an oblique cross-section of the internal carotid artery as it divides into its middle and anterior cerebral branches. It was usually not possible to differentiate between the internal carotid, anterior and middle cerebral arteries. For all recordings, the high-pass filter was set at 100 Hz. The Doppler sample volume length was 0.1-0.3 cm.

We performed all Doppler studies with the women in the semirecumbent position and during fetal apnea. The total examination time was limited to 15 minutes in each instance. All flow velocity waveforms were recorded on hard copies. A microcomputer (Olivetti M24; Olivetti B.V., Leiden, the Netherlands) linked to a graphics tablet was used for analysis of the Doppler recordings. In each recording, waveform analysis consisted of calculation of the pulsatility index (PI), which is derived by dividing the difference between peak systolic and end-diastolic velocity by the averaged velocity over the entire cardiac cycle (Gosling and King 1975). At all three recording levels, we used an average of three consecutive flow velocity waveforms with the highest velocity and similar appearance to establish each value.

The Spearman correlation test was used to compare flow velocity waveform indices with gestational age. Partial correlation coefficients were computed after controlling for gestational age to assess the relationship between each of the flow velocity waveform indices and the FHR (Kleinbaum and Kupper 1978).

RESULTS

Transvaginal scanning was carried out in all 36 women at 10-12 weeks, in five of 11 at 13 weeks, and in three of 21 at 14 weeks' gestation. Trandabdominal scanning was performed in the remaining six women at 13 weeks, in 18 of 21 at 14 weeks, and in all nine at 15-16 weeks.

Technically acceptable waveforms were obtained in the umbilical artery in 61

women (79 %), in the fetal descending aorta in 50 women (65 %) and at the intracerebral level in 26 women (34 %). Recording failures were not confined to a particular gestational age. Fetal heart rate was calculated in all 77 women.

At 10-12 weeks' gestation, end-diastolic flow velocity waveforms were always absent in the fetal descending aorta and umbilical artery, but were present in 15 (58%) of the 26 intracerebral artery waveform recordings. End-diastolic flow velocity waveforms in the fetal descending aorta and umbilical artery first appeared at 13 weeks and were always present from 15 weeks of gestation. A statistically significant negative correlation with gestational age was established for the PI from the umbilical artery (r_s = -0.78; p < .001), fetal descending aorta (r_s = -0.79; p < .001), and fetal intracerebral arteries (r_s = -0.56; p < .005) and for the FHR (r_s = -0.72; p < .001). The correlation between the different waveform indices and FHR, controlled for gestational age, was not statistically significant.

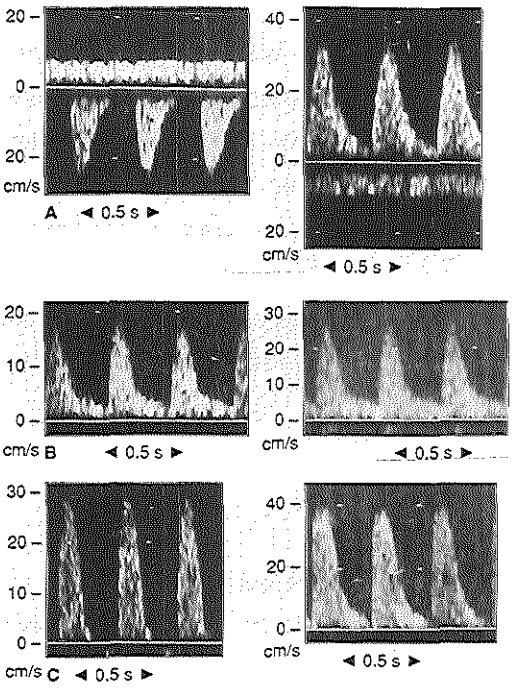

Figure 1: Maximal flow velocity waveforms in the umbilical artery (left panels), fetal descending aorta (middle panels) and at the intracerebral arterial level (right panels) at 11 weeks (a) and 16 weeks (b).

DISCUSSION

These preliminary data show that transvaginal flow velocity waveform recording was successful up to approximately 14 weeks' gestation. After that time, transvaginal recording became increasingly difficult because of increasing fetal size; those parts of the fetus situated further away from the transducer became inaccessible to sonographic imaging. At 15-16 weeks, therefore, waveform recording was always carried out using the transabdominal approach. Difficulty in visualizing the intracerebral vessels and frequent abrupt movements of the fetal head were responsible for the relatively low success rate in obtaining technically acceptable waveform recordings at the cerebral level.

The presence of end-diastolic flow velocities in the intracerebral arteries in 15 of 26 fetuses at 10-12 weeks' gestation suggests a relatively low cerebral vascular resistance compared with that at the fetal trunk and umbilical placental level. Four of nine fetuses displaying absent end-diastolic flow in the intracerebral arteries were studied at 10-11 weeks' gestation. End-diastolic velocities in the fetal descending aorta and umbilical artery were always absent at 10-12 weeks' gestation; their appearance after 12 weeks' gestation, resulting in a drop in PI, suggests a reduction in fetal placental vascular resistance. Of interest at this point is the secondary trophoblast invasion of the spiral arteries during the early second trimester of pregnancy, resulting in low-resistance uteroplacental vessels (Brosens et al. 1967; de Wolf et al. 1973). This ensures optimal placental perfusion, which is necessary to accommodate the increased blood flow to the developing fetus. Simultaneous uterine artery and fetal umbilical flow velocity waveform recording may elucidate the exact temporal relationship between these hemodynamic changes. The significant drop in FHR in this study confirms earlier reports on the maturation of the parasympathetic nervous system during the late first and early second trimesters of pregnancy (Wladimiroff and Seelen 1972). The lack of correlation between FHR and PI in the different vessels suggests heart rate independency of the flow velocity waveforms between 10-16 weeks' gestation.

Finally, the documentation of normal waveforms in the fetal intracerebral arteries, descending aorta and umbilical artery will allow studies on peripheral hemodynamics in complicated pregnancies.

SUMMARY

Maximal flow velocity waveform recording was attempted in the umbilical artery, fetal descending aorta and at the fetal intracerebral level using a cross-sectional study design in 77 normal singleton pregnancies between 10-16 weeks'gestation. At 10-12 weeks, end-diastolic flow velocities were always absent in the fetal descending aorta and umbilical artery, but were present in 58 % of the intracerebral artery waveforms. The pulsatility index at all three levels decreased significantly with advancing gestational age , suggesting a reduction in fetal and umbilical placental vascular resistance during the late first and early second trimesters of normal pregnancy. Waveform changes were not related to fetal heart rate.

3.4.2 Intracerebral, aortic and umbilical artery flow velocity waveforms in the late first trimester fetus

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INTRODUCTION

Third trimester pregnancies are characterized by forward end-diastolic flow velocities in umbilical and fetal arterial vessels reflecting the presence of a low resistance feto-placental unit(Trudinger et al. 1985). Following the introduction of a Doppler method for recording flow velocity waveforms in the human fetal internal carotid artery in third trimester pregnancies, direct evidence for the presence of reduced cerebral vascular resistance in cases of intrauterine growth retardation (IUGR) due to placental insufficiency was provided (Wladimiroff et al. 1986; Arduini et al. 1987; Groenenberg et al. 1989).

Transvaginal sonography allows more detailed visualisation of fetal structural development in early pregnancy (Timor-Tritsch et al. 1988) and as a result is a potential tool for Doppler recording of blood flow in first trimester fetal vessels such as the common and internal carotid artery, descending aorta, the cardiac outflow tract and umbilical artery. A preliminary study on umbilical artery flow velocity waveforms using trans-abdominal continuous wave Doppler ultrasound has demonstrated high pulsatility as a result of absent end- diastolic flow velocities reflecting high umbilical-placental vascular resistance (den Ouden et al. 1990). Because early pregnancy is particularly characterized by rapid growth of the fetal head, it is unknown whether a relatively low vascular resistance is present at the cerebral level.

The objective of this study was twofold: (i) to determine the success rate in obtaining technically acceptable flow velocity waveforms in the fetal intracerebral circulation, descending aorta and umbilical artery in late first trimester pregnancies (ii) to relate intracerebral artery flow velocity waveforms to those obtained from the descending aorta and umbilical artery to establish possible preferential blood flow to the fetal cerebrum at this early stage of gestation.

MATERIAL AND METHODS

Thirty normal singleton pregnancies were included in the study. Maternal age varied between 23 and 38 years (median 27 years). Gestational age ranged between 11 and 13 weeks (median 12 weeks). All pregnant women consented to participate in the study. The study protocol was approved by the Hospital Ethics Committee. A combined transvaginal real-time and pulsed Doppler system (Hitachi E.U.B. 450 Medical Corporation, Tokyo, Japan) with a carrier frequency of 3.5 and 6.5 MHz was used. The system operates at power outputs of < 100 mW/cm^2 spatial peak-temporal average in both imaging and Doppler modes by manufacturer's specifications. Each woman was included in the study once. Doppler studies were performed by one examiner (JWW). Maximum flow velocity waveforms were collected from the fetal intracerebral circulation, descending aorta and umbilical artery. Intracerebral artery flow velocity waveforms were documented on a transverse cross-section through the lower part of the fetal cerebrum; this shows a heart-shaped cross-section of the brain stem with the anterior lobes representing the cerebral peduncles (Wladimiroff et al. 1986). No distinction could be made between internal carotid, middle or anterior cerebral artery waveforms. Flow velocity waveforms from the lower thoracic part of the fetal descending aorta were recorded from a sagittal cross-section through the fetal trunk, displaying a major section of the fetal spine (Eik-Nes et al. 1980). The flow velocity waveform in the umbilical artery was obtained from a free-floating

loop of the umbilical cord (McCallum et al. 1978). Sample volume length was 0.1 to 0.3 cm. The pulsatility of the waveforms was expressed by the pulsatility index (PI), which is derived by dividing the difference between peak systolic and end-diastolic velocity by the mean flow velocity over the entire cardiac cycle (Gosling and King 1975). Heart rate (beats per minute) was calculated from peak velocity time intervals in the descending aorta. All Doppler studies were performed with the woman in the semi-recumbent position and during fetal apnea because fetal breathing movements modulate blood flow velocity waveforms (Marsal et al. 1984). The total examination time was limited to 15 minutes in each instance.
All flow velocity waveforms were recorded on hard copies. A microcomputer (Olivetti M 24, Olivetti BV, Leiden, the Netherlands) linked to a graphics tablet was used for analysis of Doppler recordings. An average of three consecutive flow velocity waveforms of similar appearance and with the highest velocity was used to establish each value. Data are presented as mean ± 1 SD.

RESULTS

Technically acceptable flow velocity waveforms were obtained from intracerebral arteries in 21 (70%), from the descending aorta in 15 (50%) and from the umbilical artery in all of the 30 fetuses studied. Although flow velocity waveforms in the descending aorta and umbilical artery display absent end-diastolic flow, flow velocity waveforms in the intracerebral arteries are characterized by forward flow throughout the cardiac cycle (Figure 1, page 60). The PI in the fetal descending aorta was 2.5 ± 0.2, in the umbilical artery 2.6 ± 0.3 and in the intracerebral artery 2.0 ± 0.2. Fetal heart rate ranged between 146 and 188 beats/min with a mean value of 170 ± 6 beats/min. No statistically significant correlation existed between flow velocity in all three vessels and the heart rate.

DISCUSSION

The objective of this study was to establish the nature of intracerebral, aortic and umbilical flow velocity waveforms in late first trimester pregnancies. Flow velocity waveform recording was successful in more than half of the women examined. Fetal motor activity, particularly of the trunk, was the main cause of failure to obtain acceptable waveforms. Exact identification of the intracerebral vessels under investigation was not possible, although positioning of the sample volume anterior to the cerebral peduncles should limit the origin of the waveforms to the internal carotid, middle and anterior cerebral artery. Intracerebral forward end-diastolic flow, as opposed to absent end-diastolic flow in the descending aorta and umbilical artery, reflects comparatively lower vascular resistances in the fetal cerebrum. This is supported by the observation that the mean intracerebral PI value in this study is only marginally higher than that established in late second trimester pregnancies (van den Wijgaard et al. 1989). In contrast, a similar comparison for the mean PI in the descending aorta and umbilical artery revealed that late first trimester pregnancies are associated with considerably higher values, i.e. by factor 1.4 for the descending aorta and by factor 2.0 for the umbilical artery.

Our late first trimester fetal heart rates are higher than those observed in second and third trimester pregnancies; this is due to parasympathetic immaturity (Wladimiroff and Seelen 1972). Heart rate dependency was established in normal third trimester pregnancies for all three fetal vessels(van Eyck et al. 1987). The rather narrow heart rate distribution may explain the absence of heart rate dependency of fetal flow velocity waveforms in the present study.

It can be concluded that the transvaginal Doppler technique can be used to study the early human fetal circulation. The intracerebral velocity waveforms suggest a relatively low vascular resistance at fetal cerebral level in early gestation.

SUMMARY

Our objectives were to determine the success rate in obtaining flow velocity waveforms in the first trimester fetal circulation and to establish possible preferential flow to the fetal cerebrum at this early stage of gestation.
Flow velocity waveforms were recorded in the umbilical artery, fetal descending aorta and fetal intracerebral arteries in 30 normal pregnancies between 11 and 13 weeks of gestation. Technically acceptable flow velocity waveforms were obtained from the descending aorta in 15 fetuses, from the intracerebral circulation in 17 fetuses and from the umbilical artery in all 30 fetuses. Absent end-diastolic flow velocities in the descending aorta and umbilical artery were associated with forward flow throughout the cardiac cycle in intracerebral arteries. This suggests a relatively low vascular resistance at cerebral level in the late first trimester normal fetus.

3.5 Evaluation of fetal preload by venous Doppler flow velocity recording in early pregnancy

3.5.1 Normal fetal Doppler inferior vena cava, transtricuspid and umbilical artery flow velocity waveforms between 11 and 16 weeks' gestation

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INTRODUCTION

Flow velocities in the inferior vena cava have been studied both in the adult (Appleton et al. 1987) and in the fetus (Reed et al. 1990). During the second half of normal pregnancy transabdominal Doppler ultrasonography has shown that waveforms from the fetal inferior vena cava are characterized by a two-component forward flow pattern reflecting ventricular systole and early diastole (passive atrial filling) and a one-component reverse flow pattern reflecting atrial contraction (Reed et al. 1990). At the same time, flow velocity waveforms from the fetal internal carotid artery, descending aorta and umbilical artery depict a low vascular resistance at the fetal cerebral trunk and umbilical-placental level (Wladimiroff et al. 1986; Griffin et al. 1984; Schulman 1987). In the growth-retarded fetus, raised umbilical-placental vascular resistance (Wladimiroff et al. 1986; Griffin et al. 1984; Schulman 1987) and increased reverse flow in the inferior vena cava (Reed et al. 1990) was established.

Transvaginal scanning greatly enhances the ultrasonographic image quality of the

developing fetus. Recent studies with transvaginal Doppler ultrasonography at the cardiac (Wladimiroff et al. 1991) and extracardiac artery level (Wladimiroff et al. 1992) in normal late-first-trimester fetuses demonstrated flow velocity waveforms that clearly differ from those seen during the late second and third trimesters of pregnancy. In the umbilical artery end-diastolic velocities were nearly always absent. At the atrioventricular level peak E-wave velocities, representing early diastolic filling, were only 45 % to 50 % of peak A-wave velocities, representing atrial contraction. Because cardiac performance is also determined by preload, it was hypothesized that late-first-trimester fetuses would show inferior vena cava flow velocity waveforms that were different from those observed later in pregnancy.

The objective of the current study was to determine the flow velocity waveform patterns in the fetal inferior vena cava and to relate these waveforms to transtricuspid and umbilical artery waveforms and fetal heart rate (FHR) during late-first trimester and early second trimester pregnancies.

MATERIAL AND METHODS

A total of 40 normal singleton pregnancies at 11 to 16 weeks of gestation (median 14 weeks) was studied. The protocol for the Doppler studies was approved by the Hospital Ethics Review Board. All pregnant women consented to participate in the study. Maternal age ranged between 18 and 37 years (median 28 years).

Ultrasonographic Doppler studies were performed by means of a Hitachi EUB 450 (Hitachi Medical Corporation, Tokyo, Japan). A combined transvaginal real-time and pulsed Doppler system with a carrier frequency of 6.5 MHz (real-time) and 3.5 MHz (Doppler) or a combined transabdominal real-time and pulsed Doppler system with a carrier frequency of 3.5 MHz (real-time and Doppler) was used depending on fetal size and position relative to the ultrasonographic probe. Both systems operate at a power output of < 100 mW/cm^2 spatial peak temporal average (SPTA) in imaging and Doppler modes.

The pregnancy duration was determined from the last menstrual period and confirmed by ultrasound measurements of the crown-rump length (11 to 12 weeks) or the biparietal diameter (13 to 16 weeks). Each women was included in the study once. Doppler studies were performed by one examiner (JWW). Flow velocity waveforms from the inferior vena cava were obtained in a saggital view which included the fetal right atrium, right ventricle and ascending aorta (Reed et al. 1990). The sample volume was positioned over the inferior vena cava immediately proximal to the right atrium. Transtricuspid flow velocity waveforms were recorded from the two-dimensional image in the four-chamber view (Reed et al. 1986). The sample volume was placed immediately distal to the tricuspid valve. At both recording levels the angle between the Doppler cursor and the assumed direction of flow was always $\leq$ 30 degrees and the sample volume length 0.1 to 0.3 cm. The flow velocity waveform in the umbilical artery was obtained from a free-floating loop of the umbilical cord (McCallum et al. 1978). For all recordings the high pass filter was set at 100 Hz.

All Doppler studies were performed with the women in semi-recumbent position and during fetal apnea. The total examination time was limited to 15 minutes in each instance. All flow velocity waveforms were recorded on hard copies. A microcomputer (Olivetti M24, Olivetti B.V., Leiden, The Netherlands) linked to a graphics tablet was used for analysis of the Doppler recordings. Waveform analysis in the inferior vena cava consisted of calculation of: (i) the ratio between the time-velocity integral during systole and the time-velocity integral during early diastole and (ii) the time-velocity integral during reverse flow (atrial contraction) which is expressed as a percentage of total forward flow during systole and early diastole (passive atrial filling) (Reed et al.1990). Peak velocities at E wave (passive atrial filling) and A wave (atrial contraction) as well as E/A ratios were calculated from transtricuspid flow velocity waveforms. Waveform analysis in the umbilical artery consisted of calculation of the Pulsatility Index (Gosling and King 1975) which is derived by dividing the difference between peak systolic and end-diastolic velocity by the averaged velocity over the entire cardiac cycle. At all three recording levels, an average of three consecutive flow velocity waveforms

with the highest velocity and similar appearance was used to establish each value.

Linear regression analysis was used to compare flow velocity waveform parameters with gestational age. Partial correlation coefficients after controlling for gestational age were computed in order to assess the relationships between the different flow velocity waveform parameters and between each of these parameters and fetal heart rate (Kleinbaum and Kupper 1978). Partial correlation coefficients were used to avoid two parameters becoming artificially correlated when both are correlated with gestational age.

RESULTS

Transvaginal scanning was carried out in all women at 11 to 12 weeks, in 50 % of women at 13 weeks and 20 % of women at 14 weeks of gestation. Transabdominal scanning was performed in the remaining 50 % of women at 13 weeks, in 80 % of women at 14 weeks and in all women at 15 to 16 weeks of gestation. Technically acceptable waveforms were obtained from the fetal inferior vena cava in all 40 women, at umbilical artery level in 35 women (87.5%) and at tricuspid valve level in 31 women (77.5%). Recording failures were not confined to a particular gestational age. Figure 1 represents flow velocity waveforms from all three recording levels at 11 and 16 weeks of gestation, respectively. A statistically significant negative correlation with gestational age was established for the ratio of time-velocity integrals of flow from the inferior vena cava during systole to time-velocity integrals of flow during early diastole ($r=-0.74$; $p<0.0001$), the percentage of reverse flow in the inferior vena cava ($r=-0.80$; $p<0.0001$), the Pulsatility Index from the umbilical artery ($r=-0.74$; $p<0.0001$) and fetal heart rate ($r=-0.66$; $p<0.0001$). FHR varied between 170 and 180 beats/min at 11 weeks and between 140 and 150 beats/min at 16 weeks of gestation. End-diastolic flow velocities in the umbilical artery were absent in all cases at 11 to 12 weeks and in 54% of cases at 13 to 14 weeks. They were present in all cases at 15 to 16

weeks of gestation. A statistically significant positive correlation with gestational age was found for peak E-wave velocities ($r=+0.83$; $p<0.0001$), peak A-wave velocities ($r=+0.73$; $p<0.0001$) and E/A ratios ($r=+0.73$; $p<0.0001$) from trans-tricuspid waveforms. No correlation existed between the different waveform parameters and between each of these waveform parameters and heart rate, when controlling for gestational age.

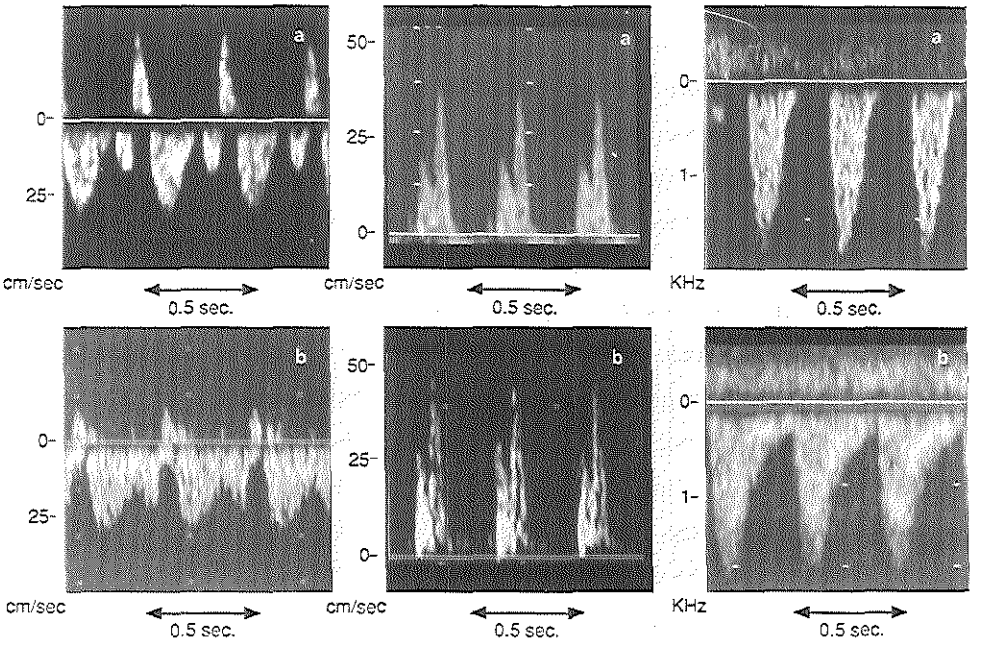

Figure 1: Doppler flow velocity waveform tracings from the inferior vena cava (IVC), tricuspid valve (TV) and umbilical artery (UA) at 11 weeks (upper panel;a) and 16 weeks of gestation (lower panel;b).

DISCUSSION

Combined two-dimensional real-time and pulsed Doppler ultrasonography has been used to establish flow data in human fetuses under physiologic and pathophysiologic circumstances. To our knowledge the current study is a first effort to document changes in flow velocity waveform characteristics at fetal inferior vena cava and tricuspid valve level in late first and early second trimester pregnancies.Transvaginal waveform recording became increasingly less successful after 12 weeks of gestation. This was mainly due to increasing fetal size resulting in large parts of the fetus becoming inacessible to ultrasonographic imaging. For this reason, transabdominal waveform recording was carried out in all cases after 14 weeks of gestation. Similar to those in late gestation, flow velocity waveforms from the fetal inferior vena cava in early pregnancy depict a two-component forward and one-component reverse flow pattern. Technically acceptable waveforms in this vessel were obtained in all instances, whereas this was not the case for waveform recordings at the other two scanning levels. This difference in recording rate was determined by the fact that the prime objective was to obtain acceptable waveform from the fetal inferior vena cava. Because of the predetermined maximum study period of 15 minutes, this often resulted in less time being available for documentation of waveforms originating from the tricuspid valve level or umbilical artery.

Peak velocities at both E- and A-waves of transtricuspid waveforms display a marked rise with advancing gestational age, suggesting an increase in early diastolic atrial filling and active atrial contraction. This may be a result of raised cardiac compliance or increased ventricular relaxation rate. However, this cannot be substantiated because of lack of pressure data. At the same time there is a drop in ratios for time-velocity integrals of flow during systole to time-velocity integrals of flow during early diastole and a drop in percentage reverse flow in the fetal inferior vena cava. The lack of any relationship between inferior vena cava flow parameters and flow parameters originating from the other two measuring points, when standardized for gestational age, suggests a multi-

factorial cause of the observed venous waveform changes with advancing gestational age. Ventricular compliance, right-to-left atrial pressure differences and cardiac afterload may play a role in this. Absolute values for percentage reverse flow in the fetal inferior vena cava at 11 to 12 weeks gestation are twice the values found at 16 weeks and four times the values established during late third trimester pregnancies (Huisman et al. 1991). Reed et al.(1990) established that values for percentage reverse flow are the lowest in the heart rate range between 120 and 160 bpm, which are normal rates for late second and third trimester pregnancies. During bradycardia (<120 bpm) and tachycardia (>160 bpm), a rise in percentage reverse flow in the inferior vena cava was noted, suggesting less optimal atrial contraction under these circumstances. In this study, FHR was subject to a marked reduction, which has been attributed mainly to maturation of the parasympathetic system (Wladimiroff and Seelen 1972). The absence of a correlation between heart rate and percentage reverse flow in the inferior vena cava suggests that heart rate is independent of the percentage reverse flow changes observed between 11 and 16 weeks of gestation. At the same time a marked reduction in Pulsatility Index in the umbilical artery was observed. This reduction was mainly determined by the appearance of end-diastolic flow as from 13 to 14 weeks. This may be explained by a drop in umbilical-placental vascular resistance. In favor of this supposition is that this development coincides with a resurgence of endovascular trophoblast migration with a second wave of cells moving into intramyometrial layers of the spiral arteries. This will result in destruction of the medial musculo-elastic tissue in the vessel wall and conversion of the thick-walled muscular spiral arteries into flaccid sac-like uteroplacental vessels (Brosens et al. 1967; de Wolf et al. 1973). In this way, the placenta establishes its own low-pressure high conductance vascular systems which are necessary to accommodate the increased blood flow to the developing fetus. It has also been demonstrated that this intravascular invasion by extravillous trophoblast is hampered in women who at a later stage develop pre-eclampsia or feature intrauterine growth retardation (Khong et al. 1986; Robertson et al. 1981). If there is a relationship between the aforementioned

normal vascular changes at placental level and the observed changes in fetal blood flow velocity waveforms in late first trimester pregnancies, then it would be of interest to examine fetal flow velocity waveforms in those early pregnancies which are at increased risk of subsequent development of pre-eclampsia or intrauterine growth retardation. Significant flow velocity waveform changes have been observed at umbilical-placental, cardiac and cerebral level under these pathological circumstances in late gestation (Groenenberg et al. 1989). It can be concluded from the current study that late first and early second trimester normal pregnancies are associated with remarkable changes in fetal flow velocity waveforms at both cardiac and extracardiac levels. These changes are independent of the reduction in FHR observed at this stage of early pregnancy. The reduction in inferior vena cava flow reversal may be a result of raised ventricular compliance or increased ventricular relaxation rate.

SUMMARY

Our objectives were to determine flow velocity waveform patterns in the fetal inferior vena cava and to relate these waveforms to transtricuspid and umbilical artery waveforms and fetal heart rate in early gestation. Doppler waveforms were recorded in 40 normal fetuses at 11 to 16 weeks of gestation. Only transvaginal scanning was carried out at 11 to 12 weeks and only transabdominal scanning was employed at 15 to 16 weeks. The ratio of time velocity integrals of flow from the inferior vena cava during systole and early diastole, the percentage of reverse flow in this vessel, the pulsatility index from the umbilical artery and fetal heart rate were negatively correlated with gestational age. Peak E-wave and peak A-wave velocities and E/A ratios from the transtricuspid waveforms were positively correlated with gestational age.

It is concluded that late first and early second trimester pregnancies are associated with remarkable changes in fetal flow velocity waveforms at both the cardiac and the extracardiac level.

3.5.2 Flow velocity waveforms in the ductus venosus, umbilical vein and inferior vena cava in normal human fetuses at 12 - 15 weeks of gestation

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INTRODUCTION

The introduction of transvaginal Doppler ultrasound has allowed flow velocity waveform studies at fetal cardiac and extra-cardiac arterial level as early as 11-12 weeks of gestation (Wladimiroff et al. 1991 and 1992a). Information has recently become available on the nature of flow velocity waveforms from the ductus venosus (Kiserud et al. 1991; Huisman et al. 1992a) and inferior vena cava (Reed et al. 1990; Huisman et al. 1991) in late pregnancy. The ductus venosus is a blood vessel functioning exclusively in the fetal circulation as a shunt between the umbilical vein and inferior vena cava, thus bypassing the hepatic micro-circulation (Rudolph 1983). Well-oxygenated blood from the umbilical vein will course almost directly through the ductus venosus towards the foramen ovale and left heart favoring flow to the fetal cerebrum and trunk.

Data on inferior vena cava flow velocity waveforms collected by transvaginal Doppler ultrasound between 12 and 16 weeks of gestation demonstrate a significantly higher percentage of retrograde flow during atrial contraction than observed in late pregnancy (Huisman et al. 1991; Wladimiroff et al. 1992b). This has been attributed to a relatively low cardiac ventricular compliance in late first and early second trimester pregnancies.

The question arises as to whether this is also reflected in the flow velocity waveform pattern from the ductus venosus and umbilical vein.

Moreover, a marked drop in heart rate as a result of parasympathetic nerve maturation has been demonstrated in late first trimester fetuses (Wladimiroff and Seelen 1972).

The objective of the present study was, therefore, three-fold: (i) to establish the success rate in obtaining technically acceptable flow velocity waveforms in the human fetal ductus venosus, umbilical vein and inferior vena cava in early gestation; (ii) to determine the normal pattern of flow velocity waveforms in these vessels and their interrelationship; (iii) to investigate the relation between these venous waveforms and cardiac cycle length during this early stage of gestation.

METHODS

A total of 45 normal singleton pregnancies was included in the study. Maternal median age was 25 years (range 21 - 34 years) and median gestational age was 13 weeks (range 12 - 15 weeks). All pregnant women consented to participate in the study which was approved by the Hospital Ethics Committee. Each woman was included in the study only once. Doppler recordings were collected with the women in the semi-recumbent position and during fetal apnea since fetal breathing movements modulate venous blood flow velocity waveforms (Marsal et al. 1984).

A combined transvaginal real-time and pulsed Doppler system (Hitachi E.U.B.450 Medical Corporation, Tokyo, Japan) with a carrier frequency of 3.5 MHz (Doppler) and 6.5 MHz (real-time) or a combined transabdominal real-time and pulsed Doppler system with a carrier frequency of 3.5 MHz (real-time and Doppler) was used depending on fetal size and position relative to the ultrasound probe. The system operates at power outputs of less than 100 mW/cm^2 spatial peak-temporal average in both imaging and Doppler modes by manufacturer's specifications. The high pass filter was set at 100 Hz. At all three recording levels the angle between the Doppler beam and the assumed flow direction was always kept below 30°. A sample volume of 0.1-0.2 cm was used for all recordings.

The fetal ductus venosus is localized in the liver, approximately between the right and left liver lobe. Its course is from caudal to cranial, from ventral to dorsal and slightly oblique to the left. It originates from the ventral side of the umbilical sinus and joins the inferior vena cava close to the right atrium.

The sample volume was placed immediately above the umbilical sinus, visualized in a transverse cross-sectional view. The ductus venosus itself was not visible. However, waveforms were accepted as originating from this vessel on the basis of their similarity to ductus venosus waveforms observed in late pregnancy (Huisman et al. 1992a). Flow velocities from the umbilical vein were obtained from a transverse cross-section of the fetal abdomen at the level of the cord insertion. The sample volume was placed over the intra-abdominal part of the umbilical vein 1 - 2 mm from the cord insertion. Flow velocity waveforms from the inferior vena cava were recorded in a sagittal view, which included the fetal right atrium, right ventricle and ascending aorta (Reed et al. 1990). The sample volume was positioned over the inferior vena cava immediately distal to its widening and entrance in the right atrium. This allows Doppler measurements solely from the inferior vena cava without interference by the flows of the conjoining hepatic veins and the ductus venosus (Huisman et al. 1992b).

The total examination time was limited to 15 minutes in each instance.

All flow velocity waveforms were recorded on hard copies. A microcomputer (Olivetti M24, Olivetti BV, Leiden, The Netherlands) linked to a graphics tablet was used for analysis of the Doppler recordings. An average of three consecutive flow velocity waveforms with the highest velocity and of similar appearance was used to establish each value. Waveform analysis in both the ductus venosus and inferior vena cava consisted of: (i) time-averaged velocity; (ii) peak systolic and peak diastolic velocity; (iii) the ratio between these peak velocities.

Time-averaged velocity in inferior vena cava was calculated from its forward components. In the same vessel, reverse flow during late diastole was expressed as a percentage of total time-velocity integral of forward flow (Reed et al. 1990). In the umbilical vein, only time-averaged velocity was calculated.

To investigate reproducibility of flow velocity waveforms, Doppler recordings from

the ductus venosus, umbilical vein and inferior vena cava were collected in 21 other women. In 18 out of these 21 women, recordings were obtained from two vessels; in the remaining three women, recordings were collected from all three vessels. This resulted in a total of 15 recordings from each vessel. In each patient, waveform recordings were obtained on three different measuring occasions with a time interval of approximately 5 minutes. Each recording consisted of three to five waveforms, per vessel. In this way, short term within patient variation and between patient variation could be established for each of the waveform parameters. The reliability (R, %) of fetal waveform recording in one particular patient was defined as the variance component between patients divided by the sum of variance components within patients and between patients (Fleiss 1986).
To determine normal values, maximum fetal flow velocity waveforms were collected in 45 women in a particular sequence, that is from the ductus venosus, the intra-abdominal section of the umbilical vein and inferior vena cava.
The ductus venosus / umbilical vein ratio and the ductus venosus/inferior vena cava ratio were determined for the time-averaged velocities in each fetus.
The within - and between patient variance components were computed by analysis of variance. The ANOVA normality assumptions were checked by graphical methods. The assumption of homogeneity of variances across patients was tested by Bartlett's test. No deviations were found. Linear regression analysis was performed to assess the relationships between the different flow velocity waveform parameters and fetal heart rate. Data are presented as mean ± 1SD.

RESULTS

Between 12 and 15 weeks of gestation, flow velocity waveforms in the umbilical vein are characterized by a continuous forward pattern, in the ductus venosus by a pulsatile systolic and diastolic forward component and in the inferior vena cava by a pulsatile systolic and early diastolic forward component and a late diastolic retrograde component (Figure 1).

The results of the reproducibility study are presented in table 1. Instead of variance components, standard deviations are presented by taking the square root. Reliability of waveform recording in a particular patient ranged between 91 and 99 % for all parameters studied, except for the peak systolic/diastolic ratios in the ductus venosus (79.3 %) and inferior vena cava (80.2 %).

In the group of 45 women studied for establishing normal mean values, technically acceptable waveform recordings were obtained in the ductus venosus in 40 (89%), in the umbilical vein in 37 (82%), and in the inferior vena cava in 20 women (44.5%). There was no obvious difference in failure rate between the transvaginal and transabdominal approach. Recordings in one or more of these venous vessels were collected transvaginally in all 7 women at 12 weeks, in 6 out of 11 women at 13 weeks and in 4 out of 13 women at 14 weeks. Transabdominal recordings were performed in all 9 women at 15 weeks of gestation.

The mean (± SD) value for the time-averaged velocity in the ductus venosus was 28.8 (6.1) cm/s, in the umbilical vein 9.7 (2.9) cm/s and in the inferior vena cava 10.9 (2.5) cm/s. In the latter vessel the mean percentage (SD) of retrograde flow was 23.3 (5.9) %. The mean (± SD) value for the ductus venosus/ umbilical vein ratio was 3.2 (0.8) and for the ductus venosus /inferior vena cava ratio 2.7 (0.6). Peak systolic/diastolic velocity ratio was 1.1 (0.1) for the ductus venosus and 1.6 (0.2) for the inferior vena cava. Mean fetal heart rate (± SD) was 160 (8) b.p.m. No statistically significant correlation could be established between the different venous flow velocities and cardiac cycle length ($r = 0.1 - 0.45$).

DISCUSSION

The purpose of the present study was to determine the nature of the flow velocity waveform in the ductus venosus and its relationship to waveforms in the umbilical vein and inferior vena cava during the late first and early second trimester of pregnancy.

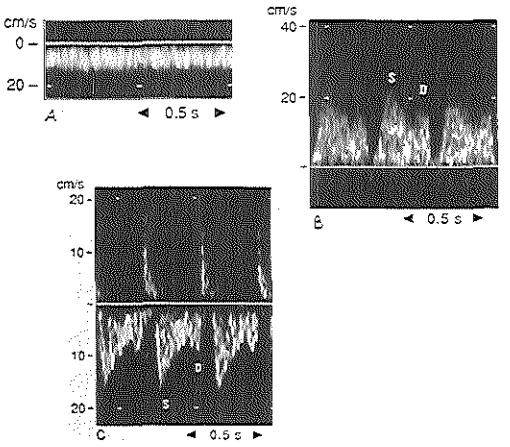

Figure 1: Flow velocity waveforms in the umbilical vein (A), ductus venosus (B) and inferior vena cava (C) in a normal pregnancy of 12 weeks of gestation.
S = systole; D = diastole

Whereas the transvaginal approach is invariably the method of choice for fetal blood flow velocity studies at 12 weeks, this is not so for fetuses beyond this gestational age. The route of examination is largely determined by the size and position of the growing fetus at the time of examination. From 15 weeks onwards, only the transabdominal approach will ensure adequate information on waveform patterns from the fetal circulation.

Except for the peak systolic/diastolic ratio, reproducibility of waveform recording was good as demonstrated by reliability values of higher than 90 %. These relatively high reliability values are a result of a relatively low short-term within patient variance associated with a much larger between patient variance. This suggests that measurements obtained in one particular patient are reproducible, but large differences in mean values can be encountered when studying more patients in the same gestational age group. The relatively lower reliability values for the peak systolic/diastolic ratios are caused by very small variations in the peak systolic and peak diastolic velocities between patients.

The high success rate in obtaining technically acceptable flow velocity waveforms in the ductus venosus while less so in the umbilical vein and the inferior vena cava, was probably mainly determined by the sequence in which the three

venous vessels were studied within the designated time period of 15 minutes. The mean fetal heart rate of 160 b.p.m. established in the present study is higher than that observed in late pregnancy, which may be partly determined by parasympathetic immaturity (Wladimiroff and Seelen 1972). Heart rate independency was established for flow velocity waveforms from all three venous vessels. The narrow heart rate distribution may, however, have played a role in this.

The waveform pattern in the three venous vessels is not essentially different from that seen in late pregnancy (Kiserud et al. 1991; Huisman et al. 1991 and 1992a; Reed et al. 1990). The ductus venosus blood flow velocity waveform demonstrates a specific biphasic pattern with mean values for the time-averaged velocity being 3.2 and 2.7 times higher than that determined in the umbilical vein and inferior vena cava, respectively. A possible explanation is the smaller vessel size of the ductus venosus compared with the other two venous vessels, which would imply that the intraabdominal part of the umbilical vein diameter is even larger than that of the inferior vena cava. Evidence for this has been provided in a study on anatomical relationships in the early human fetal hepatic vasculature (Huisman et al. 1992b).

Of interest is the abrupt change of a non-pulsatile flow pattern in the umbilical vein into a clearly pulsatile flow pattern in the ductus venosus, which is also seen in late pregnancy (Huisman et al. 1992a). During ventricular systole, the right atrium unfolds after its contraction. This will lead to a passive suction in compliant vessels resulting in a pulsatile profile in both the inferior vena cava and ductus venosus. The absence of pulsations in the umbilical vein, although situated further away from the right atrium, is not properly understood. However, umbilical venous pulsations may be observed both in normal first trimester pregnancies up to 9 - 10 weeks (Rizzo et al. 1992) and in the third trimester in cases of intrauterine growth retardation (Indik et al. 1991), probably reflecting a high placental vascular resistance.

No retrograde flow was established in the ductus venosus. This is in spite of the fact that during the late first and early second trimester of pregnancy, the percentage of retrograde flow in the inferior vena cava is approximately five-fold

of that seen near term (Huisman et al. 1991; Wladimiroff et al. 1992b). In addition, the peak systolic / diastolic velocity ratio remains constant throughout pregnancy in the ductus venosus (1.1 ± 0.1) (Huisman et al. 1992a). This together with the absence of retrograde flow permits its differentiation from the flow pattern in the inferior vena cava (peak S/D ratio throughout pregnancy 1.7 ± 0.3) (Huisman et al.1991). The most likely explanation for the presence of only forward flow in the ductus venosus is the single direct connection between the umbilical vein and the fetal venous cardiac inflow ensuring a sufficient supply of well-oxygenated blood to the fetus under continuous pressure. Late diastolic reversal of ductus venosus flow has only been observed in late pregnancy in a case of fetal supraventricular tachycardia and congestive heart failure (Kiserud et al. 1991).

With the use of microspheres, it has been demonstrated in fetal sheep that approximately 50 % of umbilical vein blood volume preferentially streams through the ductus venosus towards the foramen ovale without mixing with less-oxygenated blood from the superior and inferior vena cava (Edelstone and Rudolph 1979). Study in the human fetus does not allow volumetric measurements. However, the differences in blood flow velocities in ductus venosus, inferior vena cava and umbilical vein, as shown by this study, may also indicate a tendency not to mix. High-velocity blood flow from the ductus venosus as part of venous return will mainly be channeled directly to the foramen ovale, while the lower velocity blood stream originating from the superior and inferior vena cava will mainly be directed to the tricuspid valve.

It can be concluded that combined transvaginal and trans-abdominal Doppler ultrasound allows the study of ductus venosus, umbilical vein and inferior vena cava flow velocity waveform patterns in early pregnancy. Fetal heart rate independency was established for all three venous waveform patterns. A pulsatile flow pattern was observed in the ductus venosus and inferior vena cava. The time-averaged flow velocity in the ductus venosus is 2.7 and 3.2 times higher than that in the remaining two venous vessels. The marked difference in flow velocity between the ductus venosus and inferior vena cava may result in a

tendency not to mix and supports the assumption that two channels of venous return exist: inferior vena cava blood flow will be channeled to the tricuspid valve and ductus venosus blood flow will mainly directed towards the foramen ovale.

SUMMARY

The objective was to determine the normal Doppler flow velocity waveform patterns in the human fetal ductus venosus, inferior vena cava and umbilical vein, correlated with fetal heart rate, and to examine their reproducibility and their inter-relationship at 12 to 15 weeks of gestation.

Cross-sectional recordings of 45 normal pregnant women were collected for a data reference range transvaginally and trans-abdominally depending on fetal size and position. Maximum flow velocity waveforms were obtained from the ductus venosus, the intra-abdominal part of the umbilical vein and inferior vena cava. Time-averaged velocities were calculated in all three vessels together with peak systolic, peak diastolic velocity and their ratio in the ductus venosus and inferior vena cava.

Doppler recordings in 21 other patients displayed good reproducibility.

Continuous forward flow in the umbilical vein was associated with pulsatile systolic and diastolic forward flow in the ductus venosus. Retrograde flow was present only in the inferior vena cava. Mean time-averaged velocity (SD) in the ductus venosus was 28.8 (6.1) cm/s, in the umbilical vein 9.7 (2.9) cm/s and in the inferior vena cava 10.9 (2.5) cm/s. No correlation could be established between waveform parameters and fetal heart rate.

Combined transvaginal and transabdominal Doppler ultrasound allows reproducible blood flow velocity recordings at venous level in early pregnancy. Relatively high velocities were observed in the ductus venosus compared with the umbilical vein and inferior vena cava. Differences in flow velocities in the ductus venosus and inferior vena cava suggest that little or no mixing of blood occurs, a situation well-described in sheep.

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Chapter 4
DOPPLER ASSESSMENT OF VENOUS RETURN DURING THE SECOND HALF OF PREGNANCY

4.1 Introductory remarks

An ultrasonic description of the human fetal venous vasculature in the second half of pregnancy has been provided by several investigators(Chinn et al. 1982; Jeanty et al. 1984; Champetier et al. 1989). The ductus venosus can be seen originating from the umbilical sinus (sometimes called the umbilical part of the left portal vein). However, the complexity of the other hepatic vasculature causes difficulty in visualizing the ductus venosus in every instance(Huisman et al. 1992). Before performing a Doppler flow velocity measurement, the exact vascular anatomy of the hepatic region has to be determined. Insight into the relationship between the various components of venous return lead to data on normal flow velocity waveforms from the fetal inferior vena cava and ductus venosus as well as the reproducibility of these Doppler waveform recordings in late second and third trimester pregnancies.

4.2 Anatomy of the venous inflow vasculature

4.2.1 Recognition of a fetal subdiaphragmatic venous vestibulum essential for fetal venous Doppler assessment

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INTRODUCTION

Recently, a sonographic method to obtain Doppler velocity waveforms from the human fetal inferior vena cava by ultrasonic guidance was described (Reed et al. 1990). The proposed site to direct the Doppler beam is situated just proximal to the right atrium. However, visualization of this area by two-dimensional real-time ultrasound demonstrated anatomical relationships, which did not correlate with morphological descriptions in the literature (Chinn et al. 1982; Jeanty et al. 1984; Balique et al. 1984; Moore 1977; Gray 1985; Gilbert 1989). The inferior vena cava is considered to course straight through the diaphragm into the right atrium, while other veins, like the ductus venosus and the hepatic veins, discharge separately into this straight vessel at different locations along its sub-diaphragmatic course through and above the fetal liver (Moore 1977; Gilbert 1989; Gray 1985).

During Doppler studies of the inferior vena cava immediately proximal to the right atrium, often other flow velocity waveforms were encountered, in particular from the left hepatic vein and ductus venosus. Also an unexplained large standard deviation was found while analysing inferior vena cava waveform parameters from this site (Huisman et al. 1991). Two studies suggest a clinical importance of these parameters in cases of arrhythmias and growth retardation (Reed et al. 1990; Chan et al. 1990).

The aim of the present study was to ascertain the exact anatomical relationship between inferior vena cava, ductus venosus and the hepatic veins in the human fetus in the diaphragmatic and subdiaphragmatic area.

MATERIAL AND METHODS

Postmortem specimens of four human fetuses at 18, 26, 28 and 34 weeks of gestation, taken at random, were examined.

The abdominal cavity had been opened in all fetuses during autopsy, while in

three fetuses heart and lungs had been removed immediately superior to the diaphragm to exclude cardiac anomalies. No macroscopically detectable congenital abnormalities were found.

The umbilical vein served as a guide for the exposure of the hepatic vasculature. After the removal of surrounding liver parenchyma, the blood vessels in the hepatic region around and above the intra-abdominal part of the umbilical vein were carefully dissected, so that they could be traced to their origin. Drawings were made of two out of four specimens (Fig.1,2 and 3). Interest was particularly focused on the continuity of the hepatic vasculature. No details are given about the relationship between hepatic vessels and hepatic ligaments and lobulation, since these structures can not be detected with real-time ultrasound.

Next, the anatomical situation at the level of the diaphragm was assessed. An incision was, therefore, made through the diaphragm and the subdiaphragmatic region in all four specimens (Fig.1 and 3).

These preparations demonstrate anatomical details in a three-dimensional way, while ultrasound images from the same area are only a two-dimensional visualization. Nevertheless, sonographic images with enough details were obtained to compare these with the anatomical drawings.

One image (Fig.4) was made from a normal 28 week old fetus in a sagittal scanning plane, in which the umbilical sinus with the arising ductus venosus in the liver served as a landmark. The fetal spine was situated posteriorly. The second ultrasound image is from a normal 36 week old fetus in a transverse to oblique view (Fig.5). In this case, the fetal portal vasculature in the liver was visualized in relation to the inferior vena cava, ductus venosus and the right atrium, while again the umbilical sinus served as the landmark anteriorly in the fetal abdomen.

RESULTS

Anatomical data

The left hepatic lobe is almost as large as the right lobe. The umbilical vein courses posteriorly and slightly cephalically and somewhat to the left of the

midline between the right and left hepatic lobes (Fig.1). No side branches were detected before its termination into the left portal vein. Several small branches, leading to medial and lateral segments of the left hepatic lobe, are present in the umbilical portion of the left portal vein. Two large veins running to the left arise from this portion, which have been identified as the superolateral and the inferolateral branches of the umbilical segment of the left portal vein(Chinn et al. 1982). The gallbladder is situated more laterally to the right. The course of the left portal vein then takes an abrupt right turn, running in front of the ductus cysticus, to form the transverse part of this vessel. At the turn a large vessel arises anteriorly out of this transverse part coursing superoposteriorly, slightly left oblique and more cranial: this is the ductus venosus. It has no side branches and continues in the direction of the diaphragm and right atrium. The transverse part of the left portal vein is continuous with the right portal vein. The right portal vein divides into an anterior and posterior branch. In a posterior view the common portal vein can be visualised behind the umbilical vein (Fig. 2). It connects with the transverse part and runs in the direction of the right portal vein. Also, the inferior vena cava receives posteriorly three small hepatic veins from the right liver lobe.

The anterior view shows that multiple veins arise from the right as well as from the left hepatic lobe. These veins confluence into a left, middle and right hepatic vein (Fig.1). All three vessels course in the direction of the right atrium, which is situated just above the diaphragm. Left and sagittal (or middle) hepatic veins cross anterior to the ductus venosus just below the diaphragm. The exact individual vessel relationship is shown by the dissection, in which the diaphragm has been incised (Fig.1). The various vessel orifices all enter a funnel-like cavity situated just below the diaphragm. This funnel, or even better this vestibulum, therefore receives the abdominal part of the inferior vena cava, the ductus venosus and the orifices of the hepatic veins. In the 18 week specimen as well as in the 34 week specimen there was a separate orifice for a phrenic vein (Fig.1 and 3). The vestibulum continues through the diaphragm where it connects the right atrium as the thoracic part of the inferior vena cava.

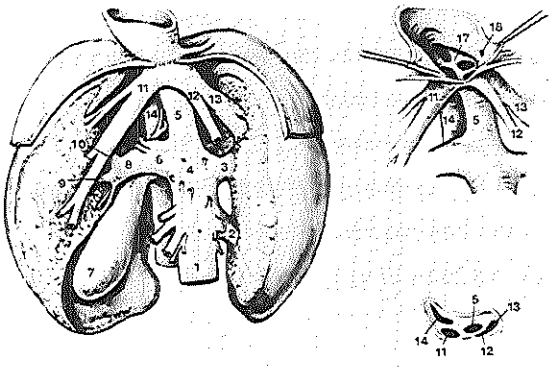

Figure 1: Drawing of a postmortem prepared normal human fetus at 34 weeks of gestation; anterior view of the liver and diaphragm: a) complete preparation b) detail of the subdiaphragmatic area with incision through the diaphragm c) cranial view from b).

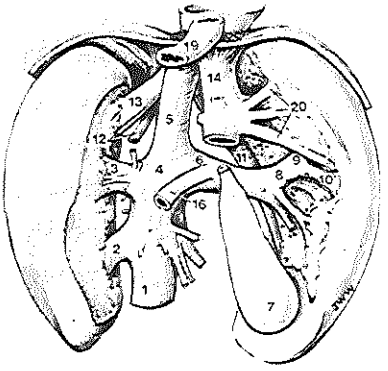

Figure 2: posterior view

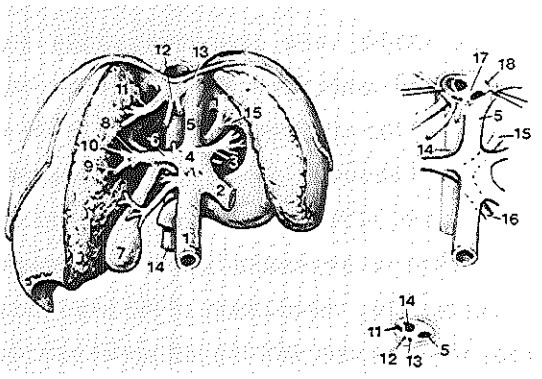

Figure 3: Drawing of a postmortem prepared normal human fetus at 18 weeks of gestation; anterior view of the liver and diaphragm a) complete preparation b) detail of the subdiaphragmatic area with incision through the diaphragm c) cranial view from b).

1. Umbilical vein
2. Inferolateral branch of the left portal vein
3. Superolateral branch of the left portal vein
4. Umbilical part of the left portal vein
5. Ductus venosus
6. Transverse part of the left portal vein
7. Gallbladder
8. Right portal vein
9. Anterior branch of the right portal vein
10. Posterior branch of the right portal vein
11. Right hepatic vein
12. Sagittal hepatic vein
13. Left hepatic vein
14. Inferior vena cava
15. Gastric vein
16. Portal vein
17. Venous vestibulum
18. Phrenic vein
19. Oesophagus
20. Afferent hepatic veins

The anatomical relationship between these venous vessel structures is not essentially different when comparing 18 week and 34 week old fetuses (Fig.1 and 3). One remarkable observation, however, concerns the change in diameter of the hepatic veins relative to the inferior vena cava and ductus venosus with advancing gestational age. In the 18 week old fetus (Fig.3) the diameter of the hepatic veins is only approximately one fifth of that measured at the inferior vena cava and ductus venosus, while this ratio has clearly increased up to approximately one half in the 34 week old fetus (Fig.1).

Sonographic data

The sagittal ultrasound scan from the 28 week fetus indicates that the ductus venosus, the right hepatic vein and the inferior vena cava confluence at the level of the diaphragm before entering the right atrium (Fig.4). The right hepatic vein seems to have approximately the same diameter as the ductus venosus, while the umbilical sinus and inferior vena cava demonstrate slightly wider vessel sizes. Examination of the 36 week fetus shows a similar situation (Fig.5). The ductus venosus arises from the umbilical sinus, which is an important landmark for measurement of the fetal abdomen circumference(Campbell and Wilkin 1975), to join the inferior vena cava. At that site, a clear widening of the venous structure can be detected before its termination in the right atrium. This image also gives a well-defined sonographic visualization of the fetal portal vasculature. The right portal vein, which is continuous with the left portal vein (lp), splits up into an anterior and a posterior branch.

No essential differences can be detected when comparing the drawings of the prepared specimens with the ultrasound images. The limitation of ultrasonic diameter measurements does not allow exact comparison between anatomically obtained vessel sizes and sonographic data.

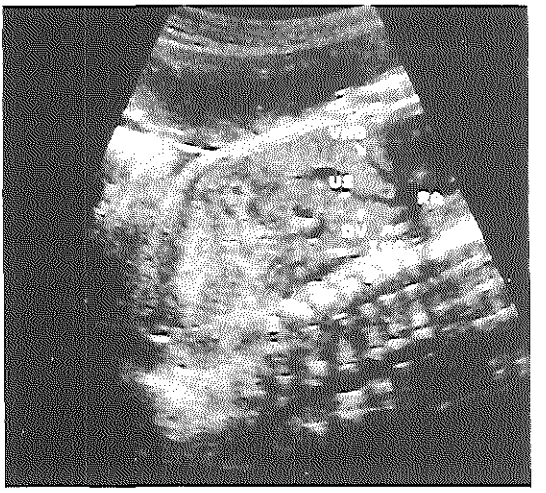

Figure 4: Ultrasonic image from a normal human fetus at 28 weeks of gestation in a sagittal scanning plane. The posteriorly situated fetal spine and the umbilical sinus (US) serve as landmarks. IVC = inferior vena cava; DV = ductus venosus; RA = right atrium; VHD = right hepatic vein

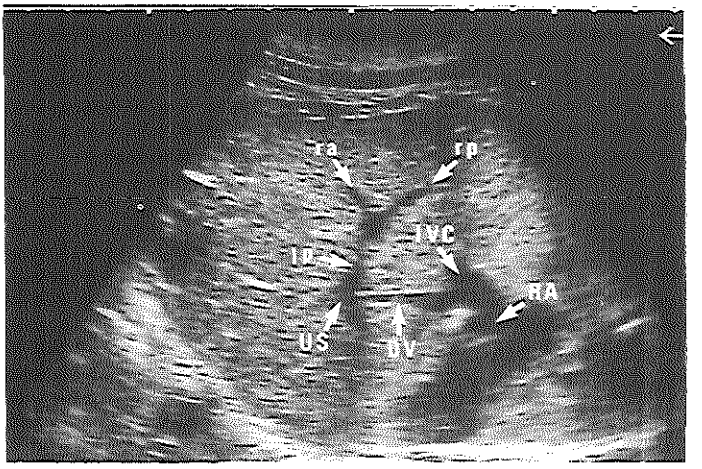

Figure 5: Ultrasonic image from a normal human fetus at 36 weeks of gestation in a transverse to oblique scanning plane. Landmarks are the anteriorly situated umbilical sinus (US) and the left portal vein (lp).

IVC = inferior vena cava; DV = ductus venosus; RA = right atrium; ra = anterior branch right portal vein; rp = posterior branch right portal vein.

DISCUSSION

Study of the venous distribution in the subdiaphragmatic area in dissected specimen showed a different morphology as described in the literature. In intra-uterine life the fetal inferior vena cava does not simply continue from the abdomen to the thorax, but demonstrates a change in structure just below the diaphragm. The abdominal inferior vena cava ends into a funnel-like venous structure, which contains the orifices of the hepatic veins as well as the ductus venosus. This subdiaphragmatic vestibulum is interposed between the abdominal and thoracic part of the inferior vena cava. For reasons of clarity the term subdiaphragmatic vestibulum is used, although part of the venous structure is situated at the level of the diaphragm.

For the developmental background it is important to know that an extensive remodeling of the venous vasculature takes place in the human embryonic period. This is nicely depicted in upclimbing developmental stages by Gilbert (1989). In the fourth week of gestation the primitive venous system consists of three sets of symmetrically paired veins: the vitelline, the umbilical and the pre and postcardinal veins. The vitelline veins return blood from the yolk sac and the gut and form the connection with developing hepatic sinusoids and the heart as the hepatocardiac channels. These will form in a process, in which part of the venous system disappears while other parts anastomose, the portal vein plus side branches. By the sixth week the supra-hepatic portion of the inferior vena cava consists of a persisting portion of the right hepatocardiac channel. This hepatocardiac channel comes closest to the vestibulum described here, but in the literature it is already seen as the inferior vena cava (Gilbert 1989).

In embryonic life the sinus venosus, situated in the thorax, receives blood from all three sets of paired veins, but during the fifth week of gestation it is incorporated into the dorsal part of the right atrium, while the veins are remodelled into the inferior and superior vena cava, ductus venosus and the portal system by radical transformations (Moore 1977; Gilbert 1989). In the adult the remnants of the sinus venosus are present in the right atrium as the sinus venarum and coronary

sinus. In textbooks it is presumed that the abdominal inferior vena cava, once constructed by anastomosis of parts from the right sacrocardinal, subcardinal and vitelline veins, becomes the main vessel which directs blood to the right atrium(Moore 1977; Gray 1985; Gilbert 1989). In our opinion it remains an afferent vessel just like the ductus venosus and the hepatic veins,confluencing into a subdiaphragmatic vestibulum, which forms the final connection with the right atrium as the thoracic inferior vena cava. Only when the ductus venosus and the umbilical vein blood supply are interrupted after delivery can the inferior vena cava become the straight main blood vessel, returning deoxygenated blood from the lower body to the right heart. Until now the anatomy of the venous vestibulum as such has not been appreciated or recognized. It is rather described, at that level, as a dilatation of the terminal part of the inferior vena cava or as a variation in entrance of the various veins into inferior vena cava or into the hepatic veins (Richter 1976; Gray 1985). In an elegant ultrasonic evaluation it is demonstrated that various veins enter the inferior vena cava just below the diaphragm, but the exact anatomical morphology is not shown (Jeanty et al. 1984).

With development of gestation there is a marked increase in the dimensions of the hepatic venous return into this vestibulum. It is presumed that the hepatic erythropoiesis is mainly responsible for changes in fetal liver size (Murao et al.1989). Whether our observation that hepatic afferent veins seem to increase relatively in vessel size during advancing gestation can be explained by this development in fetal haemopoiesis remains unclear.

It is remarkable that in both the 18 week and 34 week-old fetus a separate orifice for a phrenic vein could be distinguished in the vestibulum. We could not differentiate, consulting an anatomical textbook (Gray 1985), if it concerns the superior or inferior phrenic vein, although this information has little clinical relevance.

For the clinical evaluation, however, it is important that the presence of the observed vestibulum implies that the data obtained prenatally by Doppler assessment at the inlet of the right atrium provide information on changes in general venous return rather than information on inferior vena cava blood flow alone.

Moreover, a considerable variability in flow recording could result from the influence of blood flow from the various vessels, propelling into the vestibulum. It was proposed in fetal sheep that blood streams with negligible mixing via the venae cavae and ductus venosus into the right atrium (Reuss et al. 1981). One can imagine that small changes in scanning plane (such as may be the case during fetal, maternal or examiner movements) may cause variation in blood flow measurements at the site of this vestibulum. This has been observed in a previous study (Huisman et al.1991).

In conclusion, it is suggested that information on blood flow velocities in the hepatic and subdiaphragmatic area should be obtained more distally in the separate vessels and not at the venous entrance into the right atrium. The possible clinical importance of inferior vena cava flow velocity waveforms should be reconsidered in the light of these new anatomical insights.

SUMMARY

Ultrasonic visualization of the human fetal subdiaphragmatic area demonstrated anatomical relationships, different from descriptions in the literature. Four human fetal postmortem specimens at 18, 26, 28 and 34 weeks of gestation were examined to ascertain morphologic details of intra and perihepatic vasculature. Drawings of these dissected preparations were compared with ultrasonic images from the same region. With both methods the presence of a venous vestibulum immediately proximate to the diaphragm could be demonstrated. The abdominal inferior vena cava ends in a funnel-like structure, which also contains the orifices of the hepatic veins, the ductus venosus and a phrenic vein. A considerable variability in Doppler flow recording could result from blood propelling out of these various vessels into the vestibulum. It is, therefore, suggested that information on blood flow velocities in venous hepatic vessels should be obtained more distally in the separate vessels and not at the entrance into the right atrium.

4.3 Venous Doppler flow velocity waveforms during the second half of pregnancy; reproducibility of waveform recording

4.3.1 Reproducibility of fetal inferior vena cava and ductus venosus waveform recording

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INTRODUCTION

In large cross-sectional studies Doppler measurements accurately reflect the variability in flow velocity waveform parameters between patients. Lately, a number of reports have appeared on fetal venous inflow as studied by Doppler ultrasound (Reed et al. 1990; Huisman et al. 1991 and 1992a; Kiserud et al. 1991). These will be discussed in chapter 4.4. In view of the complex vascular anatomy of this part of the fetal cardiovascular system, there is a need for validation of Doppler flow velocity measurements at fetal venous inflow level.
The objective of the present study was to describe the within patient variance and between observer variance in Doppler recording and analysis of inferior vena cava and ductus venosus flow velocity waveforms in normal term pregnancies.

MATERIAL AND METHODS

A total of 24 women gave informed consent to participate in this study. The inferior vena cava and ductus venosus were studied separately. Reproducibility of Doppler waveform recording was investigated in the inferior vena cava in 14 fetuses, and in the ductus venosus in ten fetuses (Huisman et al. 1993a). In both vessels, pulsed wave Doppler recordings were obtained with a combined curved-linear two-dimensional real-time and pulsed Doppler system (Hitachi EUB 450, Hitachi Medical Corporation, Tokyo, Japan). The Doppler and real-time carrier frequency was 3.5 MHz and the high-pass filter was set at 100 Hz. The spatial peak temporal average power output was less than 100 mW/cm^2 in both imaging and Doppler modes according to manufacturers' specifications.

Two-dimensional ultrasonographic examination excluded fetal anomalies. Doppler waveforms were obtained with the women in semirecumbent position and during fetal apnea, since fetal breathing movements modulate blood flow in the venous vessels studied (Marsal et al. 1984; Kiserud et al. 1992; Huisman et al. 1993b). Since fetal behavioral state 2F (active sleep period) is the most prevelant state (Nijhuis et al. 1982) and behavioral state dependent flow velocity waveform changes have been documented at fetal venous inflow level in term pregnancies (Huisman et al. 1993a; also see chapter 5.3), all Doppler recordings were collected in state 2F.

Inferior vena cava

In the inferior vena cava flow velocity waveforms were obtained at two different locations: in its most proximal part, at the entrance into the right atrium and in a more distal part, under the venous vestibulum (Huisman et al. 1992b). These sites were visualized in a sagittal scanning plane, which includes the right atrium, right ventricle and ascending aorta. The interrogation angle was always $\leq 30°$ and the sample volume was 4 to 5 mm. In each of the 14 fetuses three recordings from both the proximal and distal part of the inferior vena cava were made at time intervals of approximately 10 minutes by one examiner (TWAH). Each

measurement included several seconds of waveform recording resulting in three to five waveforms per hardcopy. These hardcopies did not reveal the identity of the patient, nor the date or time moment of the recording. They were coded with numbers, shuffled in a random order and all analysed in one session. Waveform analysis was performed by an independent examiner (IPvS).

Ductus venosus

In the ductus venosus flow velocity waveforms were obtained at its origin immediately above the umbilical sinus in a transverse to oblique scanning level. The interrogation angle was always $\leq 30°$ and the sample volume 4 to 5 mm. In each of the 10 fetuses three recordings of ductus venosus flow velocity were made at time intervals of approximately 10 minutes by one examiner (TWAH). Each measurement included several seconds of waveform recording resulting in three to five waveforms per hardcopy. These hard copies did not reveal the identity of the patient, nor the date or time moment of the recording. They were coded with numbers, shuffled in a random order and all analysed in one session. Waveform analysis was performed by two separate observers (TWAH and ChB) on different occasions without knowing each other's results.

Data analysis

From every Doppler recording hardcopies were produced using the memory function of the system. Data analysis was performed by tracing the waveforms on the hardcopies, using a graphics tablet and a microcomputer (Olivetti M24).

The inferior vena cava flow velocity waveform consists of a systolic (S) and diastolic (D) forward component, often combined with a late diastolic retrograde component (reverse flow). Time-averaged velocity (cm/s) and peak velocity (cm/s) during both systole (S) and diastole (D) were calculated together with the ratio for the peak velocities (peak S/D ratio). The percentage reverse flow was computed from the integral of the late diastolic retrograde component as percentage of the integral of the total forward component (Reed et al. 1990).

The ductus venosus flow velocity waveform consists of a systolic (S) and

diastolic (D) forward component. Time-averaged velocity (cm/s) and peak velocity (cm/s) during both systole (S) and diastole (D) were calculated together with the ratio for the peak velocities (peak S/D ratio).

Statistical analysis

Statistical analysis was done for each parameter separately using a two-factor analysis of variance assuming a random effects model, from which total variance was partitioned in the variance components due to differences between patients, within patients and between observers. The variance components are expressed by their square root representing the standard deviation. The coefficient of variation in the measurement of a parameter was defined as the within patient, between patient or between observer component as percentage of the mean value. Another method to describe the reproducibility is calculation of the reliability for Doppler recording. Reliability of a certain measurement for a waveform parameter was defined as the between patient variance component as percentage of the sum of the between patient variance and within patient variance component(Fleiss 1989). The student's t-test was used to analyse a possible statistical difference in inferior vena cava Doppler recording for each parameter between measurement from the proximal part and the distal part in 10 out of 14 fetuses.

RESULTS

Reproducibility data from the two venous vessels are presented in table 1 and 2. At the proximal part of the inferior vena cava, within patient coefficient of variation in the Doppler recordings, representing forward flow, ranged between 13.5 to 16.5 %. For the retrograde component this was 25.5 %. At the distal part of the inferior vena cava these coefficients varied between 7.4 % and 13.4 %. A late diastolic retrograde flow component could be documented in only two fetuses.

A statistically significant difference ($p < 0.001$) was demonstrated for all flow velocity waveform parameters between the proximal and distal part of the inferior vena cava with the lower values at the distal level.

Within patient coefficient of variation in ductus venosus recordings was lower than 10 %. For all ductus venosus waveform parameters the between observer coefficient of variation in waveform analysis was approximately 1.5 %.

Table 1: Reproducibility of inferior vena cava velocity waveform recording in 14 normal fetuses

waveform parameter	position	mean value	within patientSD (coefficient of variation)	between patientSD (coefficient of variation)	reliability
TAV (cm/s)	proximal	29.6	4.9 (16.5 %)	3.9 (13.1 %)	38.3 %
	distal	12.3	1.2 (9.3 %)	1.9 (15.7 %)	73.9 %
peak syst. velocity (cm/s)	proximal	54.0	8.4 (15.6 %)	4.9 (9.1 %)	25.1 %
	distal	21.5	1.6 (7.4 %)	4.1 (19.0 %)	86.7 %
peak diast. velocity (cm/s)	proximal	28.5	4.5 (15.8 %)	5.5 (19.2 %)	59.7 %
	distal	13.9	1.9 (13.4 %)	1.5 (11.0 %)	40.0 %
peak S/D ratio	proximal	1.96	0.26 (13.5 %)	0.33 (17.0 %)	61.5 %
	distal	1.58	0.15 (9.5 %)	0.30 (19.4 %)	80.6 %
% reverse flow	proximal	10.6	2.7 (25.5 %)	3.1 (29.2 %)	56.3 %

Table 2: Reproducibility of ductus venosus flow velocity waveform recording in 10 normal fetuses.

waveform parameter	mean value	within patient SD (coefficient of variation)	between patient SD (coefficient of variation)	between observer analysis SD (coef of variation)	reliability
TAV (cm/s)	47.0	4.1 (8.7%)	6.4 (13.6 %)	0.64 (1.4 %)	70.5 %
peak syst. vel.(cm/s)	60.0	5.4 (9.0%)	8.1 (13.5 %)	0.89 (1.5 %)	69.6 %
peak diast. vel.(cm/s)	54.2	5.5 (9.8%)	8.3 (15.3%)	0.93 (1.7 %)	69.5 %
peak S/D ratio	1.15	0.05 (4.3%)	0.03 (2.6%)	0.003 (0.3 %)	23.1 %

TAV = time-averaged velocity; SD = standard deviation; S/D = systolic / diastolic

DISCUSSION

Within patient coefficients of variation in inferior vena cava waveform recording were markedly higher for the proximal part as compared with the distal part. This is also reflected by lower reliability values as a measure of the relative proportion between within patient and between patient variance components. Similar results were reported by Rizzo et al. (1992), who evaluated recording variation at three different sites in the inferior vena cava. They suggest that the portion of the inferior vena cava situated between the entrance of the renal vein and the ductus venosus is the site of choice to record velocity waveforms. However our experience is that, despite the relatively lower reproducibility in the more proximal part, this particular vascular site remains the most informative place to assess fetal hemodynamics, since together with the inflow from the ductus venosus and hepatic veins at the level of the venous vestibulum, Doppler measurements at the entrance of the right atrium will represent total venous return. Changes in flow velocities at the proximal part of the inferior vena cava should, therefore, be interpreted only when these changes exceed the changes caused by within patient variability.

The present study demonstrates an acceptable within patient reproducibility for waveforms originating from the ductus venosus. Between patient waveform assessment, however, shows a relatively larger variability as has already been established as early as 12 to 15 weeks of gestation (Huisman et al. 1993c). This is demonstrated by the high reliability values which express the proportional influence of between patient against within patient variance. As was also pointed out by Kiserud et al. (1992), wide limits of agreement for the ductus venosus waveform parameters imply that liberal ranges for normal measurements should be accepted and that an abnormal velocity value should be interpreted with caution.

Differences in ductus venosus waveform analysis between two observers turned out to be negligible compared to the variability within patients. The relatively low reliability value for the peak systolic/ diastolic ratio is determined by the very

small differences in variance for both the between patient and within patient component. Moreover, the ratio itself is composed of two separate measurements with their own variabilities. The small coefficient of variation confirms the constancy of this particular parameter throughout pregnancy, which had been demonstrated in another study (Huisman et al. 1992a).

It can be concluded that an acceptable within patient reproducibility for venous waveform recordings can be obtained. Venous Doppler waveforms are also the subject of variation, either by variable measurement methods such as sample placement or angle insonation, or by the biological variations in fetal hemodynamics. Therefore, venous Doppler recording results should be interpreted with caution.

4.4 Normal flow velocity waveforms from fetal venous inflow during the second half of pregnancy

4.4.1 Flow velocity waveforms in the fetal inferior vena cava during the second half of normal pregnancy

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INTRODUCTION

Recently, a method to obtain inferior vena cava blood flow velocity waveforms in the human fetus has been described by Reed et al. (1990). They demonstrated that fetal vena cava flow velocity waveform patterns are altered in the presence of intra-uterine growth retardation and cardiac rhythm disturbances. Our interest in inferior vena cava flow was determined by the significant changes occurring in flow velocity waveforms at both cardiac and extra-cardiac arterial level relative to fetal behavioral states (van Eyck et al 1987; van der Mooren et al 1989; van Eyck et al 1990). Normal values are needed, before embarking on inferior vena cava flow velocity waveform recording relative to fetal cyclic rest and activity states.

The objective of the present study was to establish the relationship between the various components of the fetal inferior vena cava flow velocity waveform and gestational age during the second half of normal pregnancy.

SUBJECTS AND METHODS

A total of 60 women gave informed consent to participate in the study. The study protocol was approved by the Hospital Ethics Committee. There were three gestational age groups: 19-22 weeks (n=16); 27-30 weeks (n=22) and 36-39 weeks (n=22). Gestational age was calculated from a reliable menstrual history and from an early ultrasonic measurement of fetal crown-rump length or biparietal diameter. Fetal growth was normal as documented by longitudinal fundal height measurements and confirmed by ultrasonic measurements of fetal upper-abdominal circumference. Birthweights were situated between the 10th and 90th percentile according to Kloosterman's tables corrected for maternal parity and fetal sex (Kloosterman 1970). Pulsed wave Doppler ultrasound recordings in the fetal inferior vena cava were obtained by means of a combined curved-linear array two-dimensional real-time and pulsed Doppler system. The Toshiba SSA-270A manufactured by Toshiba Corporation, Medical Systems Division, Tokyo, Japan (Doppler carrier frequency, 3.75 MHz) was used for the gestational age period 19-22 weeks (P.A.S.). The Hitachi EUB-450, manufactured by Hitachi Medical Corporation, Tokyo, Japan (Doppler carrier frequency, 3.5 MHz) was used for the gestational age period of 27-30 weeks and 36-39 weeks (T.W.A.H.). Intermachine variation was calculated from five patients examined with both systems within a period of 30 minutes. From each patient at least six cycles with each Doppler system were investigated. In both systems the spatial peak temporal average power output was less than 100 mW/cm^2 in both imaging and Doppler modes according to manufacturers' specifications.

Two-dimensional ultrasound examinations were performed to confirm normal fetal cardiac anatomy. The fetal inferior vena cava was localised in a sagittal view directly under the fetal spine, to the right of and parallel with the descending aorta. Only those waveform recordings were accepted in which the interrogation angle between the Doppler beam and assumed direction of blood flow was less than 30^0. The sample volume (2-4 mm), which covered the entire vessel cross-section, was placed under two-dimensional ultrasonic guidance immediately

proximal to the right atrium. Blood flow velocity waveforms were recorded on hard copies and only during fetal apnea, since fetal breathing movements modulate inferior vena cava blood flow (Chiba et al 1985). The inferior vena cava flow velocity waveform consists of three components (Reed et al 1990): the first and largest component represents forward flow during late diastole (atrial relaxation) and ventricular systole; the second component represents forward flow, which is coincident with early diastolic filling; the third component depicts reverse flow, reflecting atrial contraction (Fig.1). Analysis of at least three consecutive optimal Doppler flow recordings of the inferior vena cava was performed. Time-averaged velocity (cm/s), time-velocity integral (TVI;cm) and peak velocity (cm/s) during systole (S) and diastole (D) as well as TVI during reverse flow coincident with atrial contraction were measured. During forward flow, ratios for time-velocity integrals (TVI S/D) and peak velocities (peak S/D) were calculated. Time-velocity integral of reverse flow was expressed as a percentage of combined forward flow during systole and diastole. Data are presented as mean ± SD. Comparison of time-averaged velocity, TVI S/D, peak S/D and % reverse flow with gestational age was carried out using the Spearman rank correlation coefficient test. Comparison of the same flow velocity waveform parameters with fetal heart rate was performed by linear regression analysis.

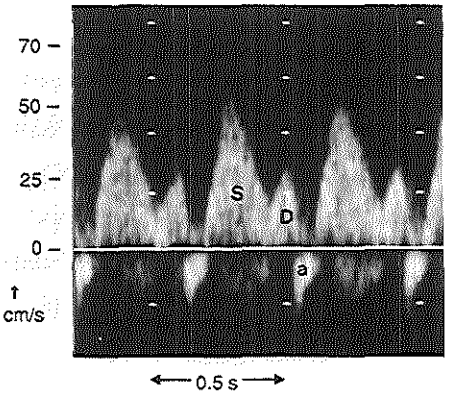

Figure 1: Flow velocity waveform recording from the fetal inferior vena cava at 27 weeks of gestation, representing systolic (S) and diastolic (D) forward flow and reverse flow(a) during atrial contraction.

RESULTS

The Toshiba SSA-270A depicts slightly lower values than the Hitachi EUB-450, but these differences never exceed 10% of the standard deviation per parameter. Technically acceptable flow velocity waveforms were collected in 13 out of 16 women (81%) at 19-22 weeks, 18 out of 22 women (82%) at 27-30 weeks and 17 out of 22 women (77%) at 36-39 weeks of gestation, leaving recordings from 48 women for further analysis. Table 1 presents the mean (± SD) values for time-averaged velocity (cm/s), peak S/D, TVI S/D and % reverse flow in the fetal inferior vena cava at 19-22, 27-30 and 36-39 weeks of gestation. A statistically significant positive correlation (r_s = 0.58; p<0.001) existed between time-averaged velocity and gestational age and a statistically significant negative correlation (r_s = 0.67; p<0.001) was established between % reverse flow and gestational age. Peak S/D and TVI S/D did not significantly change with gestational age. Reverse flow was absent in 5 out of 48 women (10%), all at 36-39 weeks of gestation. There was no statistically significant correlation between the different inferior vena cava flow velocity waveform parameters and fetal heart rate.

Table 1: Mean (± 1 SD) values for time-averaged velocity (cm/s), peak S/D, TVI S/D and % reverse flow in the fetal inferior vena cava at 19-22 weeks, 27-30 weeks and 36-39 weeks of gestation.

no. of women	gestational age (wks)	time-averaged velocity (cm/s)	peak S/D	TVI S/D	% reverse flow
13	19 - 22	14.2 ± 3.1	1.8 ± 0.3	3.5 ± 1.1	16.6 ± 6.2
18	27 - 30	23.1 ± 4.0	1.7 ± 0.3	3.7 ± 1.0	11.3 ± 3.7
17	36 - 39	25.6 ± 5.0	1.8 ± 0.2	3.7 ± 1.1	5.2 ± 3.6

S/D = systole /diastole; SD = standard deviation; TVI = time velocity integral

DISCUSSION

The purpose of the present study was to define changes in inferior vena cava blood flow patterns during the second half of normal pregnancy. Until recently, hemodynamic studies in human fetuses were mainly focused on intracardiac blood flow characteristics and attempted predictions of stroke volume or cardiac output (Maulik et al. 1984; Kenny et al. 1986; Reed et al. 1986).

Information about right heart filling through the vena cava, cardiac input or preload, has only been obtained in animals and human adults by way of pressure measurements (Wexler et al. 1968; Reuss et al. 1983; Appleton et al. 1987). These studies suggest a linear increase in time-averaged velocity and peak velocity in the inferior and superior vena cava with advancing gestational age.

The success rate in obtaining technically acceptable flow velocity waveforms in the fetal inferior vena cava was approximately 80% and not essentially different between the three gestational age periods studied.

The nearly two-fold increase in time-averaged velocity in the inferior vena cava may be accounted for by increased volume flow in this vessel, raised cardiac contractility and reduced cardiac afterload. Age-related reduction in afterload has been established as a result of the physiological decrease in placental vascular resistance during the second half of pregnancy (Trudinger et al. 1987; Reuwer et al. 1987).

The % reverse flow in the inferior vena cava demonstrated a three-fold reduction with advancing gestational age, which may be explained by the increase in ventricular compliance. Only data on % reverse flow obtained during the latter weeks of gestation were comparable with those obtained by Reed et al. (1990).

The ratios of systolic to diastolic flow both for peak velocity and time-velocity integral did not significantly change during the study period. Both this observation and slightly higher absolute values for the TVI S/D (3.4 $\pm$1.1 - 3.7 $\pm$ 1.1) are at variance with data reported by Reed et al. (1990), who found a reduction in the TVI S/D with advancing gestational age and an absolute value for this ratio of 2.8 $\pm$0.2. This discrepancy may be determined by the limited number of subjects and the different gestational age distribution in the latter study. However, we found a

rather large standard deviation for both the TVI S/D and the % reverse flow during all three gestational age periods. Preliminary data on the anatomical relationship between the fetal inferior vena cava and adjacent vessels, e.g. the ductus venosus and hepatic veins at the level of venous entrance into the right atrium, suggest that all three vessels constitute a funnel-like structure, in which the distance between the individual vessels only varies between 2 and 5 mm depending on gestational age.

This implies that at the sonographic scanning level employed by Reed et al. (1990) and ourselves, flow velocity waveform recordings may actually originate from the inferior vena cava, the ductus venosus or hepatic veins. This is further supported by our preliminary observation that waveforms obtained from well-defined sonographic images of the hepatic veins closely resemble those obtained at the venous entrance into the right atrium (Fig.2). Of interest is the observation that in contrast to the inferior vena cava and hepatic veins, waveforms originating from the ductus venosus do not display reverse flow.

We suggest that flow velocity waveform recordings obtained at the sonographic scanning level employed in the present study provide information on gestational age-related changes in venous return to the right atrium rather than changes in the inferior vena cava per sé. As a result, flow velocity waveform recording at the level of the inferior venous entrance into the right atrium may conceal the possible existence of behavioral state dependent changes in the individual venous vessels, in particular the inferior vena cava and hepatic veins. We propose that information on inferior vena cava flow velocity waveforms should be obtained more distal to the venous entrance into the right atrium.

SUMMARY

Fetal inferior vena cava flow velocity waveform recording was attempted at the entrance into the right atrium in 60 women at 19-22 weeks, 27-30 weeks and 36-39 weeks of gestation. Technically acceptable waveforms were collected in 48

women. A significant increase in time-averaged velocity and a significant decrease in percent reverse flow with advancing gestational age was established. A large standard deviation was observed for various inferior vena cava waveform parameters. From preliminary postmortem data it appeared that the inferior venous entrance into the right atrium represents a funnel-like structure composed of the inlet of the inferior vena cava, hepatic veins and the ductus venosus. It is suggested that waveform recording at the scanning level employed in the present study provides information on gestational age-related changes in venous return to the right atrium rather than changes in the inferior vena cava itself. It is proposed that information on inferior vena cava flow velocity waveforms should be obtained more distal to the venous entrance into the right atrium.

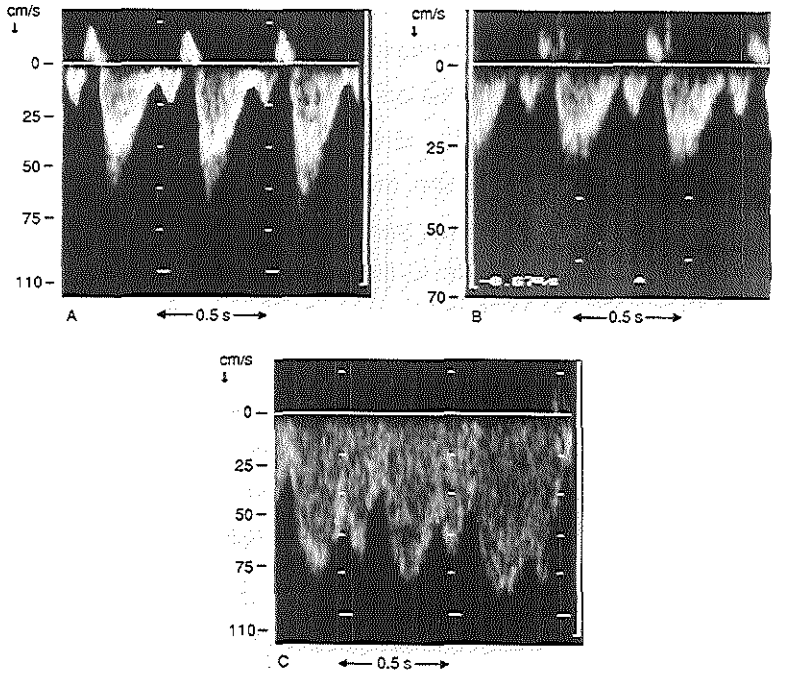

Figure 2: Flow velocity waveform recordings from the fetal "inferior vena cava" (A), left hepatic vein (B) and ductus venosus (C) at 38 weeks of gestation.

4.4.2 Ductus venosus blood flow velocity waveforms in the human fetus; a Doppler study

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INTRODUCTION

The ductus venosus is a blood vessel functioning exclusively in the fetal circulation. It is one of three links, which direct well-oxygenated blood almost directly from the umbilical vein to the fetal cerebrum and trunk. The ductus venosus forms a shunt, which maintains a circuit between the umbilical vein and the inferior vena cava, thus bypassing the hepatic micro-circulation (Rudolph 1983). In fetal sheep it was shown that more than half of the blood flow entering the fetus via the umbilical vein is shifted through the ductus venosus and preferentially streams through the foramen ovale to the left heart (Edelstone and Rudolph 1979). Moreover, umbilical cord compression decreases hepatic and pulmonary blood flow and increases the preferential distribution of blood flow through the ductus venosus as well as through the foramen ovale (Itskovitz et al. 1987).

No information is available on ductus venosus flow in the human fetus. For calculation of volume flow, data on both vessel diameter and flow velocity are needed. Whereas present ultrasound techniques do not allow accurate measurement of the vessel diameter of the ductus venosus,a preliminary study has demonstrated the possibility of recording flow velocity waveforms in this vessel. Normal data are needed before possible changes in ductus venosus flow velocity waveforms relative to pregnancy pathology can be assessed.

The objective of the present study was, therefore, three-fold:
i) to determine the success rate in obtaining technically acceptable blood flow velocity waveforms in the human fetal ductus venosus; ii) to investigate the correlation of ductus venosus blood flow velocity waveform characteristics with the cardiac cycle ; iii) to establish the relationship between the various blood flow velocity components and gestational age during the second half of normal pregnancy.

SUBJECTS AND METHODS

A total of 60 women gave informed consent to participate in the study. The study protocol was approved by the Hospital Ethics Committee. There were three gestational age groups : 19 - 22 weeks (n = 18), 27 - 30 weeks (n = 21) and 36 - 39 weeks (n = 21). These age groups were chosen to collect preliminary information on possible changes in ductus venosus flow velocity waveform during the second half of pregnancy. Each woman was included in the study only once. Gestational age was calculated from a reliable menstrual history and from an early ultrasonic measurement of fetal crown-rump length or biparietal diameter. Fetal growth was normal as documented by longitudinal fundal height measurements and confirmed by ultrasonic measurements of fetal upper-abdominal circumference. Birth weights were situated between the 10th and 90th percentile, according to Kloosterman's tables corrected for maternal parity and fetal sex (Kloosterman 1970). There were no structural anomalies.
Pulsed wave Doppler ultrasound recordings in the fetal ductus venosus were obtained by means of a combined curved-linear array two-dimensional real-time and pulsed Doppler system. The Toshiba SSA - 270A, manufactured by Toshiba Corporation, Medical Systems Division, Tokyo, Japan (Doppler carrier frequency 3.75 MHz), was used for the gestational age period 19 - 22 weeks (P.A.S.). The Hitachi EUB - 450, manufactured by Hitachi Medical Corporation, Tokyo, Japan (Doppler carrier frequency 3.5 MHz), was used for the gestational age period of 27 - 30 weeks and 36 - 39 weeks (T.W.A.H.). Intermachine variation was

calculated from five patients examined with both systems within a period of 30 minutes. From each patient at least six cycles with each Doppler system were investigated. In both systems the spatial peak temporal average power output was less than 100 mW/cm^2 in both imaging and Doppler modes according to manufacturers' specifications.

Two - dimensional ultrasound examinations were performed to confirm normal fetal cardiac anatomy. The fetal ductus venosus is localized in the liver, approximately between the right and left lobe. Its course is from caudal to cranial, from ventral to dorsal and slightly oblique to the left side. It originates from the ventral side of the umbilical sinus (also called :the left portal vein), and joins the inferior vena cava close to the right atrium (fig.5, chapter 4.2.1. page 97).

Its relationship to large surrounding vessels, such as the intra-abdominal umbilical vein, left portal vein and inferior vena cava, allowed determination of the flow direction of the ductus venosus in case the vessel course could not be clearly determined by two-dimensional real-time imaging. The specific nature of the waveform confirmed its origin from the ductus venosus. Only those waveform recordings were accepted in which the interrogation angle between the Doppler beam and assumed direction of blood flow was less than 30 degrees. The sample volume (2 - 4 mm) was placed at the most proximal part of the vessel, immediately above the umbilical sinus.

Blood flow velocity waveforms were recorded on hard copies and only during fetal apnea, since fetal breathing movements modulate venous blood flow (Marsal et al. 1984). Analysis of at least three consecutive optimal Doppler flow recordings of the ductus venosus was performed. Time-averaged velocity (cm/s) and peak velocity (cm/s) during systole (S) and diastole (D) were measured. The ratio for peak velocity (peak S/D) was calculated.

Data are presented as mean ± 1SD. Comparison of time-averaged velocity, peak systolic and peak diastolic velocity and peak S/D with gestational age was carried out using the Spearman rank correlation coefficient test. Comparison of the same flow velocity waveform parameters with fetal heart rate was performed by means of linear regression analysis.

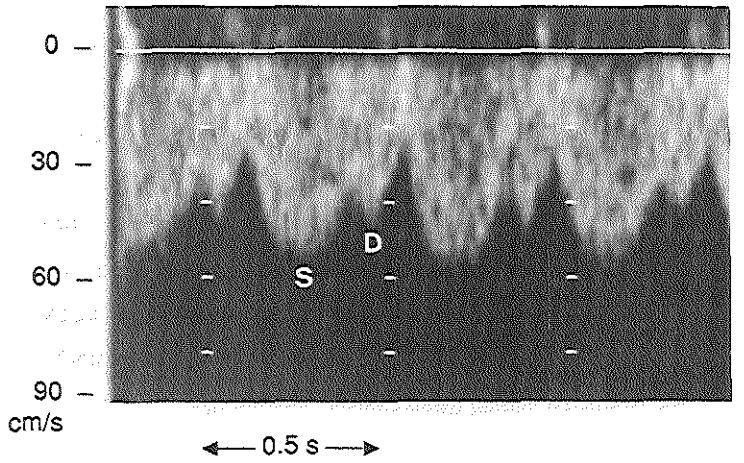

Figure 1: Normal ductus venosus flow velocity waveform pattern at 29 weeks of gestation, representing systolic (S) and diastolic (D) forward flow.

RESULTS

The ductus venosus flow velocity waveform depicts a pulsatile pattern, which consists of two forward components (fig.1). Whereas an exact determination of the time-relationship between the ductus venosus and the neighbouring inferior vena cava flow velocity waveform was not feasible, comparison of both waveforms suggests the two-component forward flow in the ductus venosus to represent the systolic and diastolic phase of the cardiac cycle. Faint Doppler shifts on the opposite channel were observed in the late diastolic phase of the cardiac cycle in 81 % (39 out of 48) of ductus venosus recordings. This observation was equally distributed over the three gestational age groups. Intermachine variation existed between the Toshiba SSA-270A and the Hitachi EUB-450; the first-mentioned shows slightly lower values, but these differences never exceed 16 % of the standard deviation per parameter. Technically acceptable ductus venosus flow velocity waveforms were collected in 14 out of 18 women (78 %) at 19 - 22 weeks, 18 out of 21 women (86 %) at 27 - 30 weeks and 16 out of 21 women (76 %) at 36 - 39 weeks of gestation, leaving recordings from 48 women for further analysis. In 41 (85.4 %) out of 48 women the ductus

venosus was actually visualized during the Doppler measurement. In the remaining seven women the course of this vessel was determined by its relationship to surrounding vessels.

Table 1 presents the mean (± SD) values for time-averaged velocity (cm/s), peak systolic and peak diastolic velocity (cm/s) and peak S/D. A statistically significant positive correlation with gestational age existed for: (i) the time-averaged velocity (r_s = + 0.50;p < 0.001); (ii) the peak systolic velocity (r_s = + 0.66;p < 0.001); (iii) the peak diastolic velocity (r_s = + 0.58;p < 0.001).

No such correlation could be established for peak S/D. Also, no statistically significant correlation could be demonstrated between the different ductus venosus flow velocity waveform parameters and fetal heart rate.

Table 1: Normal mean (± SD) values for time-averaged velocity (cm/s), peak systolic and peak diastolic velocity (cm/s) and peak S/D in the fetal ductus venosus at 19 - 22 weeks, 27 - 30 weeks and 36 - 39 weeks of gestation.

no. of women	gestational age (wks)	time-averaged velocity (cm/s)	peak systolic velocity (cm/s)	peak diastolic velocity (cm/s)	peak S/D
14	19 - 22	36.4 ± 8.0	47.1 ± 9.3	42.3 ± 8.8	1.12 ± 0.06
18	27 - 30	43.7 ± 6.9	55.4 ± 8.4	49.2 ± 6.9	1.13 ± 0.05
16	36 - 39	51.0 ± 7.4	64.2 ± 8.3	57.9 ± 8.4	1.13 ± 0.05

S/D = systole/ diastole.

DISCUSSION

The purpose of the present study was to establish the nature of the flow velocity waveform in the human ductus venosus and its change during advancing gestational age. Although studies have been performed on the anatomy of the human ductus venosus (Dickson 1957; Salzer 1970), in particular its much contested sphincter (Barclay et al. 1942; Chacko and Reynolds 1953), nothing is known about ductus venosus blood flow and its role in the human fetal circulation. It has been suggested that preferential streaming through the ductus venosus and the foramen ovale into the left ventricle as demonstrated in fetal lambs could also be present in the human fetus (Edelstone and Rudolph 1979).

To our knowledge this is the first study, in which the characteristics of the flow velocity waveform in the human ductus venosus have been described. Doppler assessment of the ductus venosus blood flow velocity waveform showed a very specific pattern with high peak velocities. Of interest is the abrupt change of a non-pulsatile flow pattern in the umbilical vein into a clearly pulsatile flow pattern in the ductus venosus. It is, therefore, very plausible to consider the pump-function of the fetal heart in the final formation of the ductus venosus blood flow velocity waveform. During ventricular systole the right atrium relaxes, which may cause a change in blood flow in the inferior vena cava as well as in the ductus venosus, resulting in a pulsatile profile. The absence of reverse flow in the ductus venosus, present in the inferior vena cava (Reed et al. 1990), could be the indirect result of the placental pressure gradient over the ductus venosus and umbilical vein. The ductus venosus is the only direct connection between the umbilical vein and the fetal circulation, so that a sufficient supply of well-oxygenated blood through the umbilical vein is directed through the ductus venosus under continuous pressure. This supports the view that the faint late-diastolic Doppler shift, observed in some recordings, is not reflecting reverse flow, but is determined by mechanical influence from surrounding tissues.

The results of this study show an increase of peak systolic, peak diastolic and time-averaged flow velocity in the ductus venosus with advancing gestation. This

comes as no surprise, since the same development has been demonstrated in other vessels, for example in the aorta descendens and the cardiac outflow tract (Marsal et al. 1984; Groenenberg et al. 1989). Several factors may play a role in the observed rise in flow velocities in the ductus venosus, such as increased volume flow, increased cardiac compliance and stroke volume or reduced afterload. Age-related reduction in afterload may occur in the human fetus as a result of the physiological decrease in placental vascular resistance (Trudinger 1987).

A striking observation is the high amplitude of the blood flow velocity waveform in the ductus venosus. Peak systolic velocities in the range of 40 - 80 cm/s indicate that ductus venosus velocities appear to be the highest when compared with umbilical vein, hepatic vein and inferior vena cava flow velocities (Gill et al. 1984, Huisman et al. 1991). Also of interest, is the fact that the peak S/D ratio remains rather constant during gestation. The similar rate of increase in peak systolic and peak diastolic velocity can be explained by an increase in volume blood flow through the ductus venosus with advancing gestation. This gestational age dependent increase occurs during both cardiac phases without the influence of other cardiac factors like compliance and stroke volume. Whether these observations will be helpful in discovering pathologic cases, needs further investigation.

SUMMARY

Successful human fetal ductus venosus flow velocity waveform recording was achieved cross-sectionally in 48 out of 60 women at 19 - 22 weeks, 27 - 30 weeks and 36 - 39 weeks of gestation. The ductus venosus shows a pulsatile flow pattern consisting of a systolic and diastolic forward component without a late diastolic reverse component such as demonstrated in the inferior vena cava. Peak systolic velocities as high as 40 - 80 cm/s were observed. A statistically significant increase in time-averaged velocity, peak systolic and peak diastolic velocity with advancing gestational age was established.

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Chapter 5
INFLUENCE OF FETAL VARIABLES ON VENOUS DOPPLER WAVEFORMS

5.1. Introductory remarks

For a proper interpretation of recorded Doppler data it is important to take into account the influence of intrinsic fetal factors. Variability in flow measurements can be caused by biological variance within the patient, different fetal behavioural states, fetal (breathing) movements and cardiac arrhythmia. Variation in Doppler recording due to within patient variance components have been extensively investigated in the reproducibility studies described in chapters 3.2 and 4.3. In this chapter we will focus on changes in venous return and venous blood flow velocities relative to different fetal physiologic conditions.

5.2 Fetal breathing movements and venous inflow

5.2.1 Changes in inferior vena cava blood flow and diameter during fetal breathing movements in the human fetus

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INTRODUCTION

Fetal breathing movements are caused by diaphragmatic contractions, resulting in intrathoracic and intraabdominal pressure changes (Mantell 1976). Combined real-time ultrasound and pulsed Doppler studies have demonstrated fetal breathing-dependent flow velocity modulation in the human fetus at arterial (Marsal et al. 1984; Trudinger 1987; van Eyck et al. 1990), cardiac (van Eyck et al. 1991) and venous level (Chiba et al. 1985).

Whereas increased flow velocities have been observed in the inferior vena cava (IVC) during the inspiratory phase of fetal breathing movements(Marsal et al. 1984; Chiba et al. 1985) no quantitive data are available with respect to modulation of blood flow velocity or vessel diameter during fetal breathing movements in this vein. In adults a momentary inspiratory collapse of the IVC was documented using two-dimensional echocardiography and M-mode (Natori et al. 1979; Mintz et al. 1981; Kircher et al. 1990). The degree of collapse (caval index) correlated well with right atrial pressure, allowing non-invasive indirect assessment of right heart function (Kircher et al. 1990). Such information would be also of interest in fetuses suffering from hydrops or growth retardation. In the latter instance, raised retrograde flow in the IVC during atrial contraction has been established suggesting increased ventricular pressure or decreased ventricular compliance (Reed et al. 1990).

The objective of the present study was to quantify modulation of IVC flow velocity waveforms and vessel diameter during fetal breathing movements in normal third trimester pregnancies.

SUBJECTS AND METHODS

A total of 57 women gave informed consent to participate in this study, of which the protocol was approved by the Hospital Ethics Committee. Gestational age was calculated on the basis of the last menstrual period combined with early

ultrasonic measurement of crown-rump-length or biparietal diameter. In all 57 women the pregnancy was uneventful resulting in the delivery of a normal infant with a birth weight between the 10th and 90th percentile, according to Kloosterman (1970). There were no macroscopically detectable congenital abnormalities.

Flow velocity recordings (n=40)

Modulation of fetal inferior vena cava (IVC) flow velocity waveforms was studied in 40 normal pregnancies at 27 - 32 weeks (n = 19) and 36 - 39 weeks (n = 21) of gestation. Oral administration of 50 gm of glucose induces fetal breathing activity within 30 to 120 minutes(Natale 1980). Fetal IVC flow velocity recordings were, therefore, made one hour after maternal oral administration of 50 gm dextrose (Dextro energy^{R}, CPC Benelux B.V., Loosdrecht, the Netherlands).
Fetal IVC waveform recordings were obtained by means of combined curved-linear array two-dimensional real-time and pulsed Doppler system with a carrier frequency of 3.5 MHz and a spatial peak temporal average power output of less than 100 mW/cm^2 according to manufacturer's specifications (Hitachi EUB-450, Hitachi Medical Corporation, Tokyo, Japan). The high-pass filter was set at 100 Hz. All measurements were performed by one examiner (TWAH) and with the women in semirecumbent position.
The fetal IVC was visualized in a sagittal view directly under the fetal spine, to the right of and parallel to the descending aorta. The sample volume (2 - 4 mm) was placed under two dimensional ultrasonic guidance immediately proximal to the right atrium(Huisman et al. 1991). Waveforms were only accepted if the interrogation angle between the Doppler beam and assumed direction of blood flow was less than 30 degrees. Fetal breathing movements were recognized by combined motion of fetal diaphragm, thorax and abdomen in two-dimensional real-time ultrasound. Continuous fetal breathing was considered present when the interval between two consecutive breathing movements was $\leq$ 6 seconds. At least three consecutive IVC waveforms were recorded on hard copies during

apnea. Since during breathing activity these three waveforms were not completed within three to five cardiac cycles, two to three hardcopies were collected during that particular breathing period. Waveforms were only recorded during high-amplitude fetal breathing movements. No distinction was made between the inspiratory and expiratory phase of the breathing cycle. After each individual analysis the three values per parameter were combined and the mean value was calculated for each fetus.

Using an XY-tablet and a microcomputer (Olivetti M24) with a specially designed programme the following parameters were calculated : time-averaged velocity (TAV;cm/s), time velocity integral (TVI; cm), peak velocity (cm/s) and percentage time velocity integral during reverse flow(Reed et al. 1990) (%REV = TVI during reverse flow / TVI during forward flow x 100%).

Vessel diameter recordings (n=30)

The vessel diameter changes in the IVC during apnea and FBM were studied in a group of 30 normal pregnancies using time motion recording (M-mode). Gestational age was 27 - 39 weeks (median 36 weeks). Recordings were obtained approximately 10 mm below the fetal diaphragm to avoid interference from diaphragmatic movements. The IVC was again visualized under the fetal spine in a sagittal scanning plane. Simultaneous real-time and M-mode recording should demonstrate IVC vessel wall reflections both during fetal breathing activity and apnea. Special effort was made to reduce any movement from the mother and examiner during recording and to ensure differentiation between fetal IVC and abdominal aorta. The transducer was angled laterally and medially to record maximum IVC vessel size. All recordings were performed by one examiner (TWAH). Also here, vessel diameter changes were studied one hour after maternal oral administration of 50 gm of dextrose (Dextro energy^{R}, CPC Benelux B.V., Loosdrecht, the Netherlands) to ascertain the occurrence of breathing movements. From hard copies IVC diameters during apnea and fetal breathing movements were measured using a ruler allowing a measuring accuracy of 0.25

millimeter. A maximum measuring error of 0 - 0.5 millimeters was accepted and the percentage collapse (caval index) was calculated. The "caval respiratory index" was defined as the percent decrease in diameter of the IVC with inspiration (Kircher et al. 1990).

Statistics

Data from all groups are presented as mean ± SD. Paired t-tests were used to compare flow velocity waveforms and caval respiratory indices obtained during fetal breathing movements and apnea. Using linear regression analysis comparison was made between time-averaged velocity, time velocity integral, peak velocity, percentage reverse flow, caval respiratory index and gestational age during fetal breathing activity. The Wilcoxon signed-rank test was applied to compare the standard deviations between the apneic and breathing-modulated data. P values < 0.05 were considered statistically significant.

RESULTS

IVC flow velocities

Maternal glucose loading induced regular fetal breathing movements in all 57 subjects. Modulation of IVC waveforms occurred in each instance and was characterized by near obliteration of the typical 3-component waveform pattern (systolic and early diastolic forward flow and late diastolic retrograde flow) resulting in a profile as demonstrated in figure 1. It was possible, however, to analyse these obliterated waveforms with sufficient accuracy for the parameters which are presented in table 1.

Absent reverse flow was observed during apnea in two fetuses at 27 - 32 weeks' gestation (10.5 %) and in five fetuses at 36 - 39 weeks' gestation (24 %). During breathing activity no reverse flow could be established in four cases (10 %).

	27 - 32 weeks		36 - 39 weeks	
	APN (x ± 1SD)	FBM (x ± 1SD)	APN (x ± 1SD)	FBM (x ± 1SD)
time-averaged velocity (cm/s)	26 ± 3	49 ± 11	29 ± 7	55 ± 9
peak velocity (cm/s)	49 ± 6	93 ± 18	54 ± 9	83 ± 11
time-velocity integral (cm)	11 ± 2	27 ± 9	13 ± 3	31 ± 9
percentage (%) reverse flow	12 ± 3	11 ± 4	10 ± 3	9 ± 4

Table 1: IVC Flow velocity waveform parameters during apnea and fetal breathing movements at 27 - 32 weeks and 36 - 39 weeks of gestation

APN = apnea; FBM = fetal breathing movements; x = mean value;
SD = standard deviation

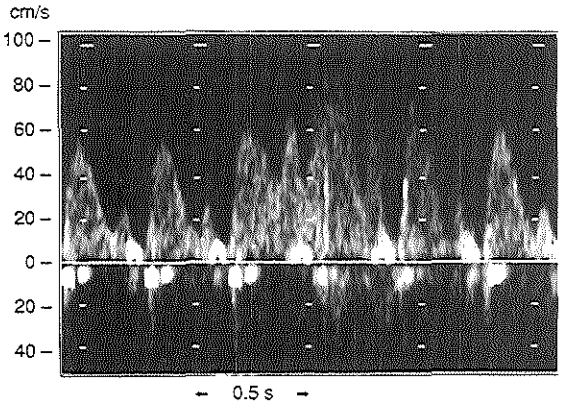

Figure 1: Normal IVC flow velocity waveforms modulated by a fetal breathing movement (FBM) in a 37 week old fetus.

A statistically significant increase ($p < 0.001$) for time-averaged velocity, peak velocity and time velocity integral in the IVC was demonstrated during breathing movements when compared with apnea (Table 1). This increase was in the range of 60 - 160 %. The percentage reverse flow during fetal breathing movements, if present, was not significantly different between the two states. The

changes observed for each flow velocity parameter were not statistically significantly different between the two gestational age groups. Standard deviation of all parameters was increased ($p < 0.01$) during breathing activity compared with the apneic phase in both groups.

IVC vessel diameters

In the group of 30 women studied by time motion recording, a temporary collapse of the IVC vessel wall during fetal breathing movements could be established in 27 fetuses (88%)(Fig.2). The vessel diameter collapse took place immediately beneath the diaphragm over a length of approximately 5 - 10 mm. This collapse occurred during downward movement of the diaphragm, indicating the inspiratory phase of the breathing cycle. Diameter measurement could be established with an estimation up to a quarter of a millimeter, leaving an estimation error in the range of 0 - 0.5 millimeters. This resulted in a maximum collapse estimation error of 17.5 %. Caval index, representing the percentage of vessel collapse during fetal breathing movement did not correlate with a gestational age. All data were, therefore, lumped together resulting in a mean value of 70.1 % ± 8.3 (range 50-83 %). During apnea IVC vessel pulsations demonstrated diameter reduction of only 14 % (range 11 - 19 %). This difference is statistically significant ($p < 0.001$).

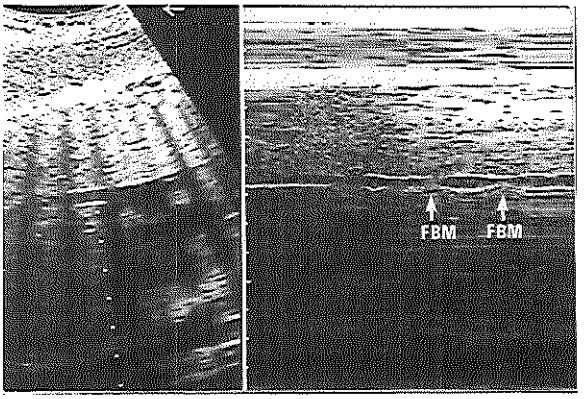

Figure 2: M-mode recording of the IVC vessel walls during fetal breathing activity.
Left: sample site (see arrow); Right: vessel diameter changes during apnea and during two fetal breathing movements (FBM).

DISCUSSION

This study demonstrates that fetal breathing movements influences fetal hemodynamics at the level of right atrium and inferior vena cava. Increased flow velocities were documented during breathing activity as compared with the apneic state in the range of 60 to 160 %, which is remarkably higher than in other cardiovascular structures. For instance, in the descending aorta a 2-40 % modulation was demonstrated (Marsal et al. 1984), in the ductus arteriosus 10-33 % (van Eyck et al. 1990) and in the foramen ovale 69-117 % (van Eyck et al. 1991). We hypothesize that this increase of flow velocities during breathing movements at the level of the IVC is caused by a raised pressure difference between thorax and abdomen resulting in a reduction in IVC vessel diameter and an increase of blood volume directed to the right atrium. Extra blood could originate from the hepatic vascular bed as it is squeezed into the IVC during the temporary increase of intra-abdominal pressure. This is in accordance with our preliminary observation that blood flow velocities in the hepatic veins were also greatly increased during fetal breathing movements (unpublished data). Also at the level of the foramen ovale raised flow velocities were established during fetal breathing activity. This was attributed to increased volume flow, since no diameter reduction could be detected at that particular level (van Eyck et al. 1991). It was proposed that the source of this additional volume flow could be either the IVC or the ductus venosus as part of fetal venous return. This study suggests that an increased amount of blood is drawn from the IVC into the right atrium.

In a previous study on inferior vena cava velocities during apnea, time-averaged velocity displayed a positive correlation and percentage reverse flow a negative correlation gestational age (Huisman et al. 1991). No such correlation could be established in the present study during fetal breathing activity. This and the presence of large standard deviation values in all breathing-modulated waveform parameters could be the result of several factors; firstly, distinct vessel diameter reductions (range 50 to 83 %) together with flow velocity increases in the range of 60 to 160 % were documented. Secondly, a breathing-related obliteration of the normal three component waveform, in particular the systolic and early

diastolic forward flow component, made it difficult to compare absolute flow velocity values. Finally, in this study no discrimination was made between fetal behavioral states or the type of fetal breathing movements (Nijhuis et al. 1982). Especially the depth of breathing is likely to be a component of considerable variance. Therefore, waveforms were only selected from a period of continuous high-amplitude breathing activity.

To our knowledge this is the first description of human fetal IVC vessel wall collapse during the inspiratory phase of fetal breathing movements. Unsuccessful recording was due to the inability to document both vessel walls, but also in these cases a clear collapse of the IVC during breathing movements could be observed. In adults this vessel size reduction was already postulated as early as 1941 by Holt. Brecher (1952) demonstrated in dogs that two stages could be observed in the response to application of negative pressure in the IVC: firstly a "depleting stage", characterized by a continuous reduction of the vein's filling state resulting in increased venous outflow and secondly a collapsed stage which occured during greater pressure gradients. Wexler et al. (1968) described the collapse of the human IVC in healthy adults during inspiration leading to an increase of flow velocity and a reduction of blood flow during the Valsalva maneuver. Veins coursing through the abdomen are often compressed by different organs and by the intraabdominal pressure, so that usually they are at least partially collapsed to an elliptical or slitlike state; veins inside the thorax are not collapsed, because the negative pressure inside the chest distends these veins (Guyton 1981). Venous pressure in the fetal IVC is higher than in the adult, but it is assumed that the fetal abdominal IVC vessel section is also slightly elliptical. Because of the limitations in ultrasonic diameter measurements an exact quantification of fetal IVC collapse was not the purpose of this study. The observed diameter changes, however, suggest a similar physiological explanation for the reduction of IVC vessel diameter in the fetus as in the adult. Some of the physical laws concerning fluid dynamics and laminar blood flow are thought to be different in circumstances with changes in vessel diameter. The fact, however, that very similar data have been observed in animals and adults, using accurate

measurement equipment, gives reason to extrapolate these physiologic explanations to the human fetus.

When in normal adults inspiration augments venous return, the increased blood flow is derived from the central capacitance venous system. As flow through the IVC increases and, therefore, intraluminal pressure decreases, the diameter of this highly compliant vessel decreases (Kircher et al. 1990). In adults with right heart dysfunction, however, the normal inspiratory increase in venous return is limited by cardiac enlargement and decreased right ventricular compliance (Natori et al. 1979). Flow in the IVC is impeded by increased right-sided cardiac filling pressures. This results on the one side in an increased IVC diameter and on the other side in a decrease of inspiratory caval collapse. In support of the presence of such a mechanism in the human fetus are our preliminary data obtained from four hydropic fetuses with congenital heart pathology (Ebstein's anomaly (2x), combined foramen ovale obstruction and aortic valve stenosis, supraventricular tachycardia). Vessel diameter study in these unborn infants with presumed increased right atrium pressure demonstrated no detectable collapse of the IVC during breathing movements. We suggest that in their case the increased heart volume and ascites may also play a role in the prevention of effective diaphragmatic contraction by mechanical interference and/or changes in thoracic-abdominal pressure gradient. More pathologic cases are needed to evaluate possible use of the caval index as a diagnostic tool for recognition of elevated right atrial pressure in the human fetus.

In conclusion, flow velocity waveforms in the inferior vena cava are markedly increased during fetal breathing movements. These changes are independent of gestational age and could be due to a raised pressure gradient between thorax and abdomen, resulting in a reduction in inferior vena cava vessel diameter and additional volume flow being directed to the right atrium. Inspiratory collapse of the inferior vena cava vessel wall as described in the adult, was documented for all normally developing fetuses. The significance of the "caval index" for the recognition of elevated right atrial pressure in abnormal human fetal development (hydrops, cardiac anomalies) needs further investigation.

SUMMARY

Breathing movements in the human fetus cause distinct changes in Doppler flow velocity measurements at arterial, venous and cardiac level. In adults breathing movements result in a momentary inspiratory collapse of the inferior vena cava vessel wall. The study objective was to quantify inferior vena cava flow velocity modulation during fetal breathing movements and to evaluate possible inferior vena cava vessel diameter changes in normal third trimester pregnancies.

We studied 57 women after oral administration of dextrose 50 gm. In 40 fetuses (n=19: 27-32 weeks and n=21: 36-39 weeks) fetal inferior vena cava waveforms were obtained during apnea and fetal breathing activity. In 30 fetuses (27-39 weeks) inferior vena cava vessel diameter changes were studied using M-mode during apnea and breathing movements. Peak and time-averaged velocities of inferior vena cava flow velocity waveforms showed a gestational age independent increase of 60 - 160 % during breathing activity. A temporary inferior vena cava vessel wall collapse (range: 50-83 %) was recorded, significantly different from vessel diameter changes during apnea (range: 11-19 %).

The marked increase of inferior vena cava flow velocities is due to a raised thoraco-abdominal pressure gradient, which may cause a reduction in vessel size and additional volume flow into the right atrium. The significance of the caval index for recognition of elevated right atrial pressure in abnormal human fetal development needs further investigation.

5.2.2. Changes in velocity waveforms from ductus venosus, hepatic veins and distal part of the inferior vena cava blood flow during fetal breathing movements in the human fetus

INTRODUCTION

It has been emphasized by many investigators that flow velocity waveforms are modulated by fetal breathing movements. After establishing the changes that take place in the inferior vena cava at the entrance into the right atrium (chapter 5.2.1), the other venous vascular sites as part of the venous return were also studied.

The objective of the present study was to describe and explain the modifications in flow velocity waveforms during fetal breathing activity in the ductus venosus, hepatic veins and distal part of the inferior vena cava.

MATERIAL AND METHODS

A total of 24 women with normal singleton pregnancies participated in this study. Gestational age ranged between 26 and 39 weeks of gestation (median 36 weeks). After informed consent was given, pulsed Doppler ultrasound was used to obtain flow velocities from the ductus venosus, hepatic veins and distal part of the inferior vena cava. Fetal breathing movements were stimulated by maternal glucose intake (see for details chapter 5.2.1.).

Fetal waveform recordings were obtained by means of combined curved-linear array two-dimensional real-time and pulsed Doppler system with a carrier frequency of 3.5 MHz and a spatial peak temporal average power output of less than 100 mW/cm^2 according to manufacturer's specifications (Hitachi EUB-450, Hitachi Medical Corporation, Tokyo, Japan). The high-pass filter was set at 100 Hz. All measurements were performed by one examiner (TWAH) and with the women in semirecumbent position. Waveforms were only accepted if the inter-

rogation angle between the Doppler beam and assumed direction of blood flow was less than 30 degrees. Fetal breathing movements were recognized by combined motion of fetal diaphragm, thorax and abdomen in two-dimensional real-time ultrasound. Waveforms were only recorded during continuous high-amplitude fetal breathing movements. Continuous fetal breathing was considered present when the interval between two consecutive breathing movements was $\leq$ 6 seconds. No distinction was made between the inspiratory and expiratory phase of the breathing cycle.

Specific attention was paid to placement of the sample volume. For the ductus venosus this was either near the point of inflow into the venous vestibulum (Huisman et al. 1992) or at its origin from the umbilical sinus. For the hepatic veins this was either close to their entrance near the right atrium or more distal to this point. For the distal part of the inferior vena cava the sample volume was placed below the venous vestibulum.

Quantification of breathing-related waveform changes was not performed, only a qualitative description will be provided.

RESULTS

ductus venosus

Waveforms were obtained from either the proximal part or the distal part or from both sites in the ductus venosus in 19 fetuses. Waveforms from the proximal part were characterized by obliteration of the two forward flow components (Fig.1) and by an increase of flow velocity similar to the changes demonstrated in the proximal part of the inferior vena cava (Huisman et al. 1993; chapter 5.2.1). A partial collapse of the vessel wall could be demonstrated in a few cases.

Waveforms from the distal part of the ductus venosus (the normal standardized site for Doppler recordings in this vessel) showed another type of breathing activity modulation. During a breathing cycle a decrease in peak systolic and/or peak diastolic flow velocity can be distinguished with either an increase or decrease of the end-diastolic flow component, reflecting atrial contraction (Fig.1).

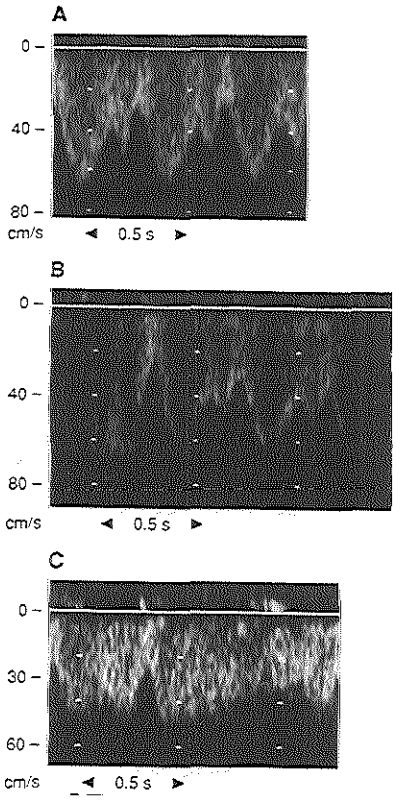

Figure 1: Waveforms obtained from the ductus venosus at its origin (distal part) during fetal apnea (upper panel), during breathing movements (lower panel) and at its most proximal part during breathing activity (middle panel).

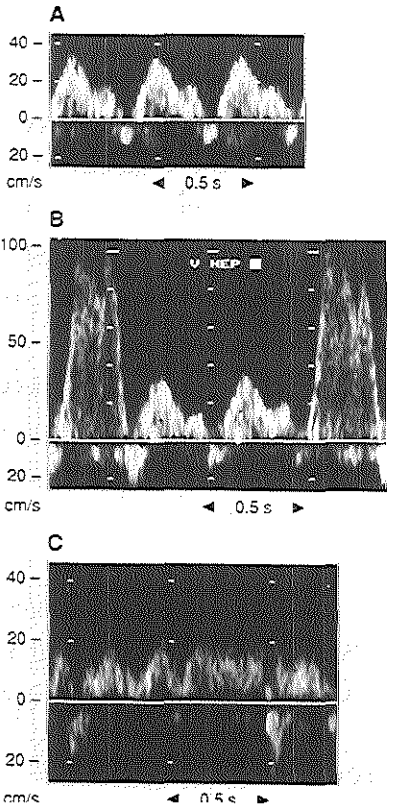

Figure 2: Waveforms obtained from a hepatic vein at its proximal part close to the entrance into the venous vestibulum during fetal apnea (upper panel), during breathing movements (middle panel) and at a point more distal in the vessel during breathing activity (lower panel).

hepatic veins

In 19 fetuses waveforms originating from a hepatic vein were obtained from either the proximal part close to the entrance into the venous vestibulum or a distal part or from both sites without distinction between right, middle or left hepatic vein. Waveforms from the proximal part were characterized by obliteration of the normal flow pattern (Fig.2) and by an increase of flow velocity similar to the changes demonstrated in the proximal part of the inferior vena cava

(chapter 5.2.1). A partial collapse of the vessel wall could be demonstrated in most cases.

Waveforms from a more distal part of the hepatic vein showed a different type of breathing related modulation. Obliteration of the systolic and diastolic peak velocities was often combined with an increase of the reverse flow component, coincident with right atrial contraction (Fig.2).

distal part of the inferior vena cava

In 11 fetuses Doppler waveform recording was performed in the distal part of the inferior vena cava. This breathing-related waveform is characterized by an obliteration of the systolic and diastolic peak velocities similar to that seen in the distal part of the hepatic veins. It is also sometimes associated with an increase of the reverse flow component, coincident with right atrial contraction (Fig.3).

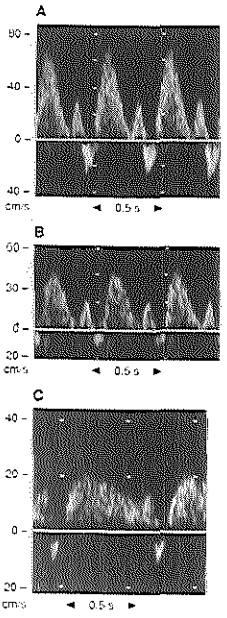

Figure 3: Waveforms obtained from the proximal part of the inferior vena cava (upper panel), compared with waveforms from the distal part of the inferior vena cava during fetal apnea (middle panel) and during breathing activity (lower panel).

DISCUSSION

To our knowledge there is only one report on flow velocity waveform modulation in the ductus venosus during fetal breathing movements (Kiserud et al. 1992). An increase in velocities was demonstrated similar to the changes seen at the proximal part of the inferior vena cava. These observations are in agreement with the results of the present study, in which a breathing-related increase in venous flow velocity was documented for the proximal part of the hepatic veins and the ductus venosus. It is hypothesized that this increase in flow velocities during breathing activity is caused by a raised pressure difference between thorax and abdomen. This pressure gradient results in a sucking force which leads to partial collapse of the venous vessel walls and an increase of blood volume directed towards the right atrium. This mechanism is in accordance with a breathing related rise in flow velocity established at foramen ovale level (van Eyck et al. 1991). This velocity increase was attributed to increased volume flow, since no diameter reduction could be detected at that particular level.

With the downward movement of the diaphragm during the inspiratory phase of the breathing cycle the intra-abdominal pressure will rise. Flow velocity waveform recording distal to the partially collapsing venous vessel wall merely demonstrated a reduction in flow velocity. This may be determined by the increase in intra-abdominal pressure and the functional obstruction of the collapsing vessel wall.

It has been demonstrated that in the umbilical vein the end of the inspiratory movement is associated with an increase in flow velocity towards the initial baseline value (Trudinger and Cook 1989). It was suggested that the decrease in intra-abdominal pressure following the inspiratory phase once again allows blood flow to return to the fetus from the free-floating part of the umbilical vein (Trudinger and Cook 1990). It was also reported that the percentage reduction in venous flow velocity was significantly higher than the percentage increase in venous flow velocity during breathing activity (Koppelaar and Wladimiroff 1993). Since the inspiratory and expiratory phase of the breathing cycle were found to be virtually equal in duration, this study suggests a net reduction in venous flow

velocity values during fetal breathing movements. Diameter measurements at this particular level, however, have been characterized by large measurement errors resulting in a low reproducibility. Therefore, the net result of the actual umbilical venous blood flow remains uncertain.

5.3 Fetal behavioural states and venous inflow

5.3.1 Ductus venosus flow velocity waveforms relative to fetal behavioural states in normal term pregnancy

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INTRODUCTION

It has been demonstrated that fetal behavioural state dependent changes occur at both arterial and cardiac level in normal human fetuses at term (van Eyck et al. 1985 and 1987; van der Mooren et al. 1989; Rizzo et al. 1990). A significant decrease of the pulsatility index in blood flow velocities during active sleep (fetal behavioural state 2F) as compared with passive sleep (fetal behavioural state 1F) has been observed in the descending aorta and internal carotid artery. This observation suggests increased perfusion of the fetal skeletal musculature and brain to meet raised energy requirements during state 2F (van Eyck et al. 1985 and 1987). During this active sleep period blood flow velocities also appeared to be reduced in the ductus arteriosus (van der Mooren et al. 1989), but raised at foramen ovale level (van Eyck et al. 1990), suggesting increased blood flow to the left heart through the latter shunt. The question arises as to whether these behavioural state dependent flow velocity changes are a result of changed cardiac preload.

The ductus venosus acts as an important shunt for oxygen rich blood to be directed through the foramen ovale into the left heart. Recent reports have pointed out the possibility of ductus venosus flow velocity waveform recording in the human fetus in late pregnancy (Huisman et al. 1992; Kiserud et al. 1991).
The purpose of the present study, therefore, was (i) to establish between patients and within patient variance in blood flow velocity waveforms in the human ductus venosus and (ii) to assess the influence of quiet and active sleep states on these waveforms in normal term fetuses.

MATERIAL AND METHODS

A total of 29 women with normal singleton pregnancies at 36 to 39 weeks of gestation gave informed consent to participate in the study. The study protocol had been approved by the Hospital Ethics Committee. Their gestational age had been calculated from the last menstrual period and confirmed by ultrasonic measurements of fetal crown-rump length or biparietal diameter. The median maternal age was 27.8 years (range 21 to 37). All participants were non-smokers and, except for iron tablets, no medication was prescribed. Subsequent birth weight was between the 10th and 90th percentile corrected for maternal parity and fetal sex (Kloosterman 1970). There were no structural anomalies.
Doppler ultrasound recordings in the fetal ductus venosus were obtained by means of a combined curved-linear two-dimensional real-time and pulsed Doppler system, the Hitachi EUB - 450 manufactured by Hitachi Medical Corporation Tokyo, Japan. The Doppler and real-time carrier frequency was 3.5 MHz and the high-pass filter was set at 100 Hz. The spatial peak temporal average power output was less than 100 mW/cm^2 in both imaging and Doppler modes according to manufacturers' specifications. All Doppler recording was performed by one examiner (TWAH).
Two-dimensional ultrasound examination was carried out to confirm normal fetal cardiac anatomy. The fetal ductus venosus is localized in the liver, approximately

between the right and left lobe. Its course is from caudal to cranial, from ventral to dorsal and sometimes slightly oblique to the left or right side. It originates from the ventral side of the umbilical sinus (also called the umbilical portion of the left portal vein) and joins the inferior vena cava close to the right atrium. The sample volume (4 mm) was placed under two-dimensional ultrasonic guidance immediately above the umbilical sinus as described previously (Huisman et al. 1992). Only those waveform recordings were accepted in which the corrected interrogation angle between the Doppler beam and assumed direction of blood flow was less than 30 degrees.

Reproducibility study

The reproducibility of waveform recording in the ductus venosus was investigated in 10 women. In each fetus three recordings of three to five waveforms were made during the most prevalent fetal behavioural state, that is active sleep state or state 2F, at time intervals of approximately 10 minutes. The presence of behavioural state 2F was confirmed after each recording. Hard copies of ductus venosus measurements did not reveal the identity of the patient, nor the date or time of recording. After collecting the hardcopies, they were coded with numbers, shuffled in a random order and all analyzed in one session. Waveform analysis was performed by two separate observers (TWAH and ChB) at different occasions without knowing each other's results.

Behavioural state study

Ductus venosus flow recording was attempted in fetuses of 19 othet women during fetal behavioural states 1F and 2F according to the classification of Nijhuis et al. (1982).

In order to establish these behavioural states the following parameters were recorded: (i) the fetal heart rate, which was recorded with a Doppler ultrasound cardiotocograph (Hewlett Packard); (ii) fetal eye movements, which were observed by ultrasonic visualisation of the fetal eye lens in a transverse scanning plane through the orbits using the two-dimensional real-time scanner.

Immediately after establishing the presence or absence of eye movements the transducer was moved in a sagittal scanning plane of the fetal trunk to confirm presence of body movements. Flow velocity waveform recordings were only performed when a clear fetal behavioural state had been identified and when this state had been present over a period of at least three minutes. In order to avoid interference the cardiotocograph was switched off during the Doppler recording. Blood flow velocity waveforms were recorded on hard copies and only during fetal apnea, since fetal breathing movements modulate venous blood flow (Marsal et al. 1984).

Data analysis

Waveform analysis was performed using a graphics tablet and a microcomputer (Olivetti M24, Olivetti B.V., Leiden, the Netherlands). The ductus venosus blood flow velocity waveform consists of a systolic (S) and diastolic (D) forward component without a late diastolic reverse flow component (Huisman et al. 1992). Time-averaged velocity (cm/s) and peak velocity (cm/s) during systole (S) and diastole (D) were calculated together with the ratio for peak velocities (peak S/D). Period time (msec) was established from the time interval between peak systoles from two consecutive cardiac cycles.

Statistical analysis

In the reproducibility study data were analyzed by a "components of variance" analysis, using module ONEWAY of the SPSSPC statistical package. This analysis yielded the variance component due to differences between patients and the variance component due to within patient variation. Also the variance in waveform analysis between observers was calculated. The variance components are expressed by their square root representing the standard deviation. The coefficient of variation in the measurement of the parameter was defined as the within patient, between patient or interobserver component as percentage of the mean value.

The two-tailed Student's t-test for paired comparisons was used to test the H_0-

hypothesis that there is no difference in the individual waveform components between behavioural state 1F and 2F. The tests were based on the averages per patient. In each state approximately 10 waveforms were averaged. Differences between the measurements in the two states were plotted against the mean of the two measurements. Statistical significance was considered to be present if $p < 0.01$. Data are presented as mean (SD).

RESULTS

Data from the reproducibility study are presented in table 1. Within patient coefficient of variation was lower than 10 %. For all parameters the interobserver coefficient of variation in waveform analysis was approximately 1.5 %.

Table 1: Data from the reproducibility study on ductus venosus waveform recording in 10 normal fetuses.

flow velocity parameter	mean value	between patient SD (coefficient of variation)	within patient SD (coefficient of variation)	interobserver SD (coefficient of variation)
time-averaged velocity (cm/s)	47.0	6.4 (13.6 %)	4.1 (8.7 %)	0.64 (1.4 %)
peak systolic velocity (cm/s)	60.0	8.1 (13.5 %)	5.4 (9.0 %)	0.89 (1.5 %)
peak diastolic velocity (cm/s)	54.2	8.3 (15.3 %)	5.3 (9.8 %)	0.93 (1.7 %)
peak S/D ratio	1.15	0.03 (2.6 %)	0.05 (4.3 %)	0.003 (0.3 %)

SD = standard deviation; S/D = systolic / diastolic; interobserver SD is meant for analysis of waveforms

Data from the behavioural state study are presented in table 2. Doppler signals could not be obtained in four women, leaving 15 women for further analysis. Failure was either due to fetal position or fetal breathing movements both in state 1F and 2F. The mean number of technically acceptable blood flow velocity waveforms obtained at the level of the fetal ductus venosus for all 15 women was 19 (11) in state 1F and 26 (10) in state 2F, resulting in a total number of 682 waveforms.

Peak systolic, peak diastolic and time-averaged velocity demonstrated a statistically significant decrease ($p < 0.001$) in state 1F as compared with state 2F (Fig.1 and 2). Differences did not tend to increase or decrease if mean level changed. Peak systolic/diastolic ratio and period time were not statistically different between the two behavioural states.

Table 2: Data from ductus venosus waveform recording in fetal behavioural state (FBS) 2F as compared with state 1F in 15 normal fetuses; mean values (SD)

flow velocity parameter	FBS 2F	FBS 1F	difference
time-averaged velocity (cm/s)	56.1 (9.2)	38.3 (7.1)	31.7 %
peak systolic velocity (cm/s)	70.1 (9.5)	47.6 (7.7)	32.1 %
peak diastolic velocity (cm/s)	61.6 (9.9)	42.7 (8.1)	30.7 %
peak S/D ratio	1.12 (0.08)	1.14 (0.07)	1.8 %
period time (ms)	436 (36)	428 (34)	1.8 %

SD = standard deviation; S/D = systolic/ diastolic

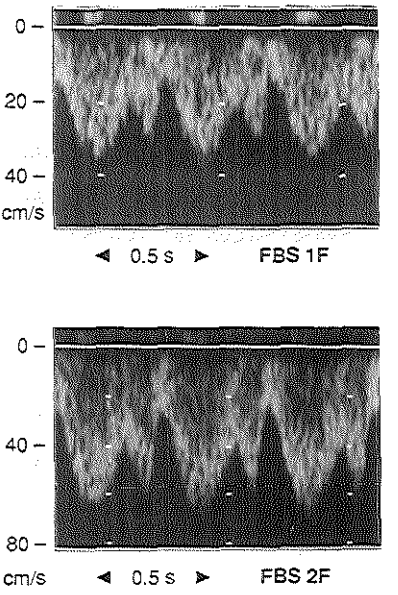


Figure 1: Flow velocity waveforms obtained from the ductus venosus of a 36 week-old fetus during fetal behavioural state (FBS) 1F and 2F.

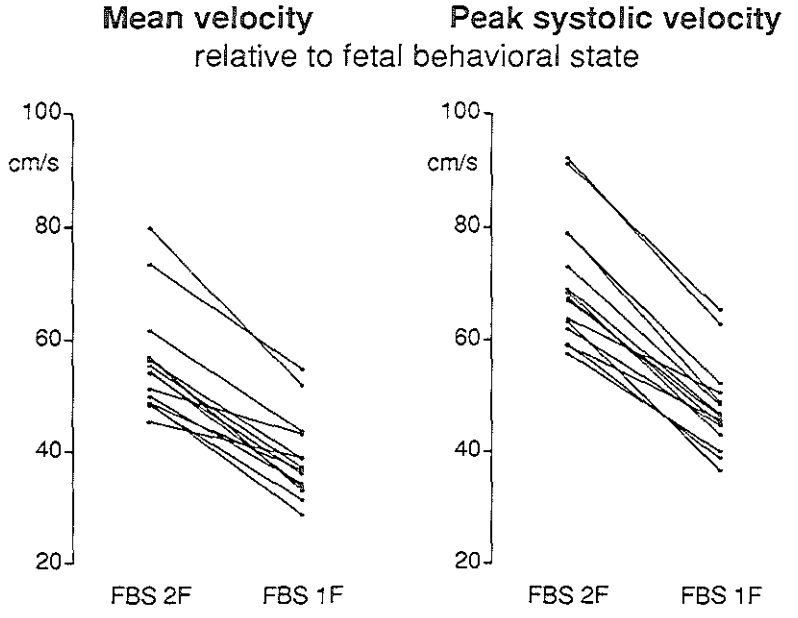


Figure 2: Ductus venosus mean velocity (right graph) and peak systolic velocity (left graph) relative to fetal behavioural state.

DISCUSSION

The flow velocity in the ductus venosus reflects the pressure gradient between the umbilical vein and the right atrium. Volume flow will be directed from the ductus venosus through the foramen ovale into the left heart and as such the ductus venosus is responsible for the supply of well-oxygenated blood to the fetal brain.

The present study demonstrates a good within patient reproducibility as compared with behavioural state dependent differences for waveforms originating from the ductus venosus. Between observer variation in waveform recording was not the purpose of this study. Differences between the observers in waveform analysis turned out to be negligible compared to the variability within patients. The relatively lower coefficient value for the peak systolic/diastolic ratio is determined by the very small differences in variance for both the between patient and within patient component. The ratio itself is composed of two separate measurements with their own variabilities, but it remains remarkable constant throughout pregnancy despite different fetal behavioural states.

A decrease of approximately 30 % was established for both the ductus venosus peak systolic and peak diastolic velocity as well as time-averaged velocity during behavioural state 1F. This decrease may be determined by either a dilatation of the ductal diameter, a reduction in volume flow through the ductus venosus or a combination of both.

Only a few reports have appeared on diameter changes of the ductus venosus by vasoactive agents and these were limited to animal experiments (Adeagbo et al. 1982; Morin 1987). These reports focused on the postnatal patency or closure of the ductus venosus rather than on the physiological process of dilatation and constriction during fetal life. Anatomical descriptions of a ductus venosus sphincter have been followed by reports which deny existence of such a structure (Chacko and Reynolds 1953; Meyer and Lind 1966;Ferraz and Junqueira 1975). Elastic collagen fibres can be found at the transition zone in the umbilical sinus to the ductus venosus vessel wall. Only a few smooth muscle cells were observed,

but they are mainly situated around the inlet in the umbilical sinus. Influence of prostaglandins would be of primary importance in the postnatal closure of the ductus venosus, rather than in the process of acute response to fetal behavioural state change. The presence of an autonomic nervous
mechanism in the regulation of the observed behavioral state dependent blood flow velocity changes seems more likely. Descriptions of functional alpha-adrenergic nerves in the origin of the ductus venosus in fetal lambs have appeared, as well as nerves originating from the phrenic nerves in the proximal and distal part of the human ductus venosus adventitial layer (Pearson and Sauter 1971).

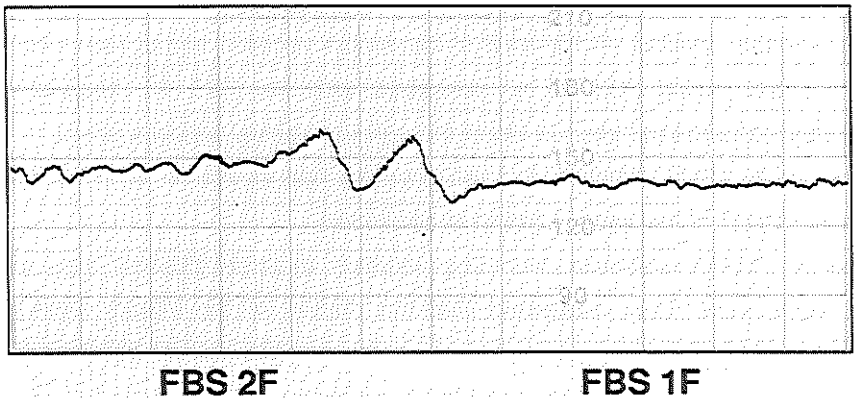
Peak velocity may indicate how the fetus manages to build up the necessary velocity to shunt blood from the umbilical sinus to the right atrium, whereas time-averaged maximum velocity may estimate the volume of flow through the ductus reaching this velocity. Accurate determination of volume flow by ultrasound may be prone to errors, mainly caused by inaccuracies in the determination of vessel diameter. This is particularly so for a narrow, venous vessel (± 5 mm at term) like the ductus venosus. The equal reduction in peak systolic and peak diastolic flow velocity during fetal behavioural state 1F suggests decreased volume flow through the ductus venosus during this behavioural state. If this is true, a redistribution of volume flow at the level of the umbilical sinus should be considered. More volume flow through the ductus venosus during behavioural state 2F as compared with state 1F would be consistent with earlier reports on a behavioural state related rise in volume flow at foramen ovale (van Eyck et al. 1990) and mitral valve level (Rizzo et al. 1990). Increased volume flow through the left heart would be necessary to ensure raised cerebral blood flow during behavioural state 2F as has been demonstrated in animal studies (Richardson et al. 1985) and has also been suggested from data on reduced vascular resistance at cerebral level in the human fetus (van Eyck et al. 1987).

It can be concluded that an acceptable within patient reproducibility for ductus venosus waveform recordings can be obtained. Peak systolic, peak diastolic and time-averaged velocities in the ductus venosus displayed an approximately 30 %

decrease suggesting reduction of volume flow during fetal behavioural state 1F. The fetal behavioural state should be taken into account in future studies on ductus venosus flow velocity waveforms in normal term pregnancies.

SUMMARY

The objective of this study was to assess the influence of fetal behavioral states on human ductus venosus flow velocity waveforms in normal term fetuses.
The relationship between ductus venosus flow velocities and behavioral states was investigated in 19 normal term fetuses. Time-averaged, peak systolic, peak diastolic velocity, peak S/D ratio and period time were calculated from Doppler recordings obtained during passive sleep (behavioral state 1F) and active sleep (state 2F).
An decrease of approximately 30 % was established for peak systolic, peak diastolic velocity and time-averaged velocity during behavioral state 1F.
Fetal behavioral state dependent changes were observed suggesting a redistribution of umbilical venous blood through the ductus venosus shunt during the passive sleep state as compared with the active sleep state.



5.3.2 Inferior vena cava flow velocity waveforms relative to fetal behavioural states and sample site in normal term pregnancy

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INTRODUCTION

It has been demonstrated that fetal behavioural state dependent changes occur at both arterial and cardiac level in normal human fetuses at term (van Eyck et al. 1985, 1987, 1990; van der Mooren et al. 1989; Rizzo et al. 1990).
During the active sleep period (fetal behavioural state FBS 2F) blood flow velocities appear to be reduced in the ductus arteriosus (van der Mooren et al. 1989), but raised at foramen ovale level (van Eyck et al. 1990), suggesting increased blood flow to the left heart through the latter shunt. The question arises as to whether these FBS dependent flow velocity changes are a result of changed cardiac preload. At the level of the ductus venosus higher flow velocities were recorded during FBS 2F as compared with the FBS 1F, suggesting a redistribution of umbilical venous blood through the ductus venosus shunt (Huisman et al. 1993). Whether this redistribution has an impact on inferior vena cava flow as part of the venous return is not known.
Rizzo et al. (1992) evaluated recording variation at three different sites in the inferior vena cava. They suggested that the portion of the inferior vena cava situated between the entrance of the renal vein and the ductus venosus is the site of choice to record velocity waveforms. However, we believe that a more proximal site remains the most informative place to assess fetal hemodynamics, since together with the inflow from the ductus venosus and hepatic veins at the

level of the venous vestibulum, Doppler measurements at the entrance of the right atrium will represent total venous return (Huisman et al. 1992).
The objective of the present study, therefore, was to assess the influence of fetal behavioural states on flow velocity waveforms obtained from both the proximal and distal part of the inferior vena cava in normal term fetuses.

MATERIAL AND METHODS

A total of 13 women with normal singleton pregnancies at 36 to 39 weeks of gestation gave informed consent to participate in the study. The study protocol had been approved by the Hospital Ethics Committee. Their gestational age had been calculated from the last menstrual period and confirmed by ultrasonic measurements of fetal crown-rump length or biparietal diameter. All participants were non-smokers and, except for iron tablets, no medication was prescribed. Fetal birth weight was situated between the 10th and 90th percentile according to Kloosterman's tables (1970) corrected for maternal parity and fetal sex. There were no structural anomalies.
Doppler ultrasound recordings in the fetal inferior vena cava were obtained by means of a combined curved-linear two-dimensional real-time and pulsed Doppler system, the Hitachi EUB - 450 manufactured by Hitachi Medical Corporation Tokyo, Japan. The Doppler and real-time carrier frequency was 3.5 MHz and the high-pass filter was set at 100 Hz. The spatial peak temporal average power output was less than 100 mW/cm^2 in both imaging and Doppler modes according to manufacturers' specifications. All Doppler recording was performed by one examiner (TWAH).
Two-dimensional ultrasound examination was carried out to confirm normal fetal cardiac anatomy. The inferior vena cava is situated to the right of and parallel to the descending aorta in a sagittal scanning plane, which included the right atrium. The sample volume (4 mm) was placed under two-dimensional ultrasonic guidance at two different locations: (i) immediately proximate to the right atrium

as described previously (Huisman et al. 1991); (ii) below the venous vestibulum in a more distal part of the inferior vena cava (Huisman et al. 1992). Only those waveform recordings were accepted in which the corrected interrogation angle between the Doppler beam and assumed direction of blood flow was less than 30 degrees.

Flow velocity waveforms from the inferior vena cava were recorded during FBS 1F and 2F according to the classification of Nijhuis et al. (1982).

These behavioral states are defined as follows:

State 1F - quiescence, which can be regularly interrupted by brief gross body movements, which mostly are startles; eye movements are absent; stable heart-rate pattern with a small oscillation band width (< 10 bpm); isolated accelerations do 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; eye movements almost continually present; a heart-rate pattern with a wider oscillation band width (> 10 bpm) than in state 1F and frequent accelerations during movements (Nijhuis et al. 1982).

In order to establish these behavioral states the following parameters were recorded: (i) the fetal heart rate, which was recorded with a Doppler ultrasound cardiotocograph (Hewlett Packard, carrier frequency 1 MHz); (ii) fetal eye movements, which were observed by ultrasonic visualisation of the fetal eye lens in a transverse scanning plane through the orbits using the two-dimensional real-time scanner. Immediately after establishing the presence or absence of eye movements the transducer was moved in a sagittal scanning plane of the fetal trunk to confirm presence of body movements. Flow velocity waveform recordings were only performed when a clear fetal behavioral state had been identified and when this state had been present over a period of at least three minutes. Since fetal behavioral state 2F (active sleep period) is the most prevelant state (Nijhuis et al. 1982). Doppler recordings to compare the proximal with the distal measurement site were collected in state 2F.

In order to avoid interference the cardiotocograph was switched off during the

Doppler recording. Blood flow velocity waveforms were recorded on hard copies and only during fetal apnea, since fetal breathing movements modulate venous blood flow (Marsal et al. 1984).

Waveform analysis was performed by an independent examiner (IPvS) using a graphics tablet and a microcomputer (Olivetti M24, Olivetti B.V., Leiden, the Netherlands). The inferior vena cava blood flow velocity waveform consists of a systolic (S) and early diastolic (D) forward component with a late diastolic reverse flow component (Reed et al. 1990)). Time-averaged velocity (cm/s) and peak velocity (cm/s) during systole (S) and diastole (D) were calculated together with the ratio for peak velocities (peak S/D). Percentage reverse flow was calculated from the time velocity integral during the retrograde flow component as percentage of the time velocity integral during the total forward flow component. Period time (msec) was established from the time interval between peak systoles from two consecutive cardiac cycles.

The two-tailed Student's t-test for paired comparisons was used to test the H_0-hypothesis that there is no difference in the individual waveform components between behavioral state 1F and 2F. Also, the H^0-hypothesis was tested that there is no difference in waveform parameters between the proximal and distal portion of the inferior vena cava in state 2F. The tests were based on the averages per patient. Differences between the measurements in the two states were plotted against the mean of the two measurements. Statistical significance was considered to be present if $p < 0.01$. Data are presented as mean $\pm$ SD.

RESULTS

No Doppler signals from both inferior vena cava locations could be obtained in three women, leaving 10 women for further analysis. Failure was either due to fetal position or fetal breathing movements both in state 1F and 2F.

No statistically significant difference between state 1F and 2F could be demonstrated for the inferior vena cava flow velocity both in the proximal and distal part

of this vessel for all parameters. Differences did not tend to increase or decrease if mean level changed. Also, period time for waveforms obtained in the proximal part (417 (23) ms vs. 414 (22) ms) and in the distal part (443 (19) ms vs. 436 (16) ms) was not statistically different between the two behavioral states.
Statistically significantly higher values were recorded in the proximal part of the inferior vena cava for peak systolic, diastolic and time-averaged velocity ($p < 0.001$) when compared with the distal part of this vessel during state 2F. No significant difference could be demonstrated for the peak S/D ratio between the two sites. Since only two fetuses showed a reversed flow component in the waveform obtained in the distal part of the inferior vena cava, this parameter was not tested.

DISCUSSION

In the previous chapter (5.3.1) fetal behavioral state dependent changes were observed in the ductus venosus flow velocity waveform suggesting a redistribution of umbilical venous blood through the ductus venosus shunt during the passive sleep state as compared with the active sleep state. No statistically significant changes in flow velocity values could be detected at the level of the inferior vena cava during different behavioural states. This means that only at ductus venosus level a redistribution may take place, while flow velocity waveforms from the other venous vessels responsible for venous return may not reflect behavioural state related changes. However, in chapter 4.3 it was already pointed out that changes in fetal inferior vena cava flow velocities should be interpreted only when these changes exceed the changes caused by within patient variability. Both in the proximal and distal part of this vessel a considerable within and between patient variation components in flow velocity waveform parameters was documented. A possible behavioural state dependent modulation may be within the range of these variabilities.
A large difference in flow velocity values was observed between the two

measurement sites. Flow at the entrance of the right atrium is formed by the combined flows of the hepatic veins, inferior vena cava and ductus venosus (Huisman et al. 1992). The latter vessel displays relatively high velocities, because of the large pressure gradient between the intraabdominal part of the umbilical vein and the right atrium. Therefore, we speculate that the higher flow velocities in the proximal part of the inferior vena cava compared with the distal part may be due to the high-velocity flow component from the ductus venosus. This observation is in contrast with a report by Rizzo et al. (1992a), who found no marked differences between mean values of Doppler indices obtained at the proximal portion of the inferior vena cava and those obtained at the distal portion between the entrance of the ductus venosus and the renal vein. However, they only compared ratios of peak velocities and time velocity integrals. Also in our study, peak S/D ratio was not essentially different when comparing the two sites. The presence of a reversed flow component in the distal part of the inferior vena cava could only be determined in two fetuses. Rizzo et al. (1992a) reported higher incidences of retrograde flow at their two distal sampling sites (up to 58 %). A possible explanation for this discrepancy may be the more proximal placement of the sample volume just below the entrance of the ductus venosus using colour Doppler mapping in the latter study. In our study, after ultrasonic visualization of the venous vestibulum (containing the entrance of the ductus venosus) and the distal portion of the inferior vena cava, the sample volume was placed more distally along this vessel correcting for the angle insonation. Absence of retrograde flow component at this latter location may be the result of the relatively larger distance between this site and the right atrium compared with the other group, which may minimize reversed flow during right atrial contraction. Also a higher vessel compliance at the distal part of the inferior vena cava, caused by absence of surrounding liver tissue, may be a factor in the underlying mechanism. Since the percentage reversed flow in the inferior vena cava flow velocity waveform is considered to be a useful parameter in the evaluation of fetal hemodynamics and cardiovascular pathology (Reed et al. 1990; Gudmundsson et al. 1991; Rizzo et al. 1992b), we suggest that Doppler recor-

ding should be performed in the more proximal part of this vessel.

It can be concluded that no behavioural state dependent changes were observed both in the proximal and distal portion of the inferior vena cava. Since considerable variation in flow velocities has been documented for this vessel, a possible modulation during different behavioural states may be obscured by these waveform variabilities.

5.4 Fetal arrhythmias and venous inflow

5.4.1 Doppler evaluation of venous return during fetal arrhythmias

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Submitted

INTRODUCTION

Little is known about fetal cardiovascular hemodynamics in cases of arrhythmias, because only non-invasive methods to measure blood flows can be applied. Whereas the frequently encountered supraventricular extrasystolic beats do not seem to cause profound circulatory consequences (Allan et al. 1983), supraventricular tachycardia and complete heart block induce marked changes in the fetal circulation (Stewart 1989).

A large number of reports has been dedicated to describe a variety of treatment procedures in tachycardia with very little information on the exact underlying mechanism and with relatively poor results. Recently, better understanding of the physiology of fetal arrhythmias has lead to higher success rates in treatment (Kleinman et al.1985; Wladimiroff and Stewart 1985). However, the mechanism and time-relation of the resolution of hydrops after successful treatment remains poorly understood.

Combined real-time and Doppler ultrasound allows study of fetal heart rate and flow velocity in different types of arrhythmia. Recently, evaluation of venous blood flow into the right atrium has been investigated (Reed et al. 1990; Huisman et al. 1991), but no data exist on venous Doppler parameters before and after treatment of tachycardia.

The purpose of this study was, therefore, twofold: (i) to describe the changes in flow velocity at the level of the ductus venosus, inferior vena cava, hepatic veins and umbilical vein in various cases of fetal arrhythmia; (ii) to evaluate these changes before and after fetal therapy for tachycardia.

MATERIAL AND METHODS

In our department two-dimensional directed M-mode echocardiography is the method of choice to determine fetal arrhythmias and has been previously described (Stewart 1989). The M-line is directed through the structures to be examined. Atrial systole is identified by movement of the atrial wall towards the atrial septum or aortic root and ventricular systole inferred from opening of the arterial valve, or onset of ventricular wall motion towards the septum.

With this method, a total of 22 fetuses was examined and diagnosed to have a fetal arrhythmia. The group consisted of ten cases with supraventricular extrasystoles (SVE), 8 fetuses with supraventricular tachycardia (SVT) and 4 cases with bradycardia (1 sinus bradycardia, 3 complete congenital heart block (CCHB)). After diagnosis and determination of fetal heart rates, patients were asked to participate in this study. All patients gave informed consent to the protocol, which was approved by the Hospital Ethics Committee.

Patients with fetal SVT were examined before and at different time-intervals after prescribed antiarrhythmic drugs. Time-intervals were approximately one to three days, one week, two weeks and one month after the beginning of treatment or after change in type of drug. Before and after Doppler recording the fetal heart rate was controlled by two-dimensional ultrasound and M-mode.

Pulsed wave Doppler ultrasound recordings in the fetal ductus venosus, inferior vena cava, hepatic veins and umbilical vein were obtained by means of a combined curved-linear array two-dimensional real-time and pulsed Doppler system. The Toshiba SSA-270A, manufactured by Toshiba Corporation, Medical Systems Division, Tokyo, Japan (Doppler carrier frequency 3.75 MHz) and the

Hitachi EUB - 450, manufactured by Hitachi Medical Corporation, Tokyo, Japan (Doppler carrier frequency 3.5 MHz), were used. The Toshiba SSA-270A depicts slightly lower values than the Hitachi EUB-450, but these differences never exceed 10 % of the standard deviation per parameter. The spatial peak temporal average power output of both systems was less than 100 mW/cm^2 in both imaging and Doppler modes according to manufacturers' specifications.

Two - dimensional ultrasound examinations were performed to confirm normal fetal cardiac anatomy.

Flow velocity waveforms from the inferior vena cava were obtained in a sagittal scanning plane directly under the fetal spine, to the right of and parallel to the descending aorta. The sample volume (3 to 4 mm) was placed immediately proximal to the right atrium allowing detailed information on venous return (Huisman et al. 1991).

The fetal ductus venosus is localised in the liver, approximately between the right and left lobe. Its course is from caudal to cranial, from ventral to dorsal and slightly oblique to the left side. It originates from the ventral side of the umbilical sinus (also called :the left portal vein), and joins the inferior vena cava close to the right atrium. Its relationship to large surrounding vessels, such as the intra-abdominal umbilical vein, left portal vein and inferior vena cava, allowed determination of the flow direction of the ductus venosus in case the vessel course could not be clearly determined by two -dimensional real-time imaging. The specific nature of the waveform confirmed its origin from the ductus venosus. The sample volume (3 to 4 mm) was placed at the most proximal part of the vessel, immediately above the umbilical sinus.

Three hepatic veins can be identified: left, middle (or sagittal) and right hepatic vein. Since no differences in blood flow between these veins is presumed to be present, Doppler flow velocity waveforms were obtained from the most accessible hepatic vein. This was done either in a transverse to oblique or in a sagittal scanning plane.

Flow velocity waveforms from the umbilical vein were documented at two locations: in a free-floating loop and at the first part of the intraabdominal route.

The latter site was visualized in a transverse scanning view.
For all recording sites only those waveforms were accepted in which the interrogation angle between the Doppler beam and assumed direction of blood flow was less than 30 degrees.
Blood flow velocity waveforms were recorded on hard copies and only during fetal apnea, since fetal breathing movements modulate venous blood flow (Marsal et al. 1984). Analysis of at least three consecutive optimal Doppler flow recordings of the inferior vena cava, ductus venosus and hepatic veins was performed. The umbilical vein waveform was analysed at three points of the continuous flow component or at three cardiac cycles reflected by pulsations.
Peak systolic(S) and peak diastolic(D) velocities were calculated together with their ratio (peak S/D ratio). Percentage reversed flow was calculated from time velocity integral of the retrograde flow component as percentage of time velocity integral of the total forward flow component (Reed et al. 1990).

RESULTS

Supraventricular extrasystoles (n=10)
During SVE's diastolic forward flow in the ductus venosus is interrupted by retrograde flow (Fig. 1a: R). During the post extrasystolic beat (PES) peak systolic velocity increased compared with normal with a resultant slight increase in the peak S/D ratio. Diastole is prolonged, which is reflected by increased diastolic time velocity integral. During SVE's the early diastolic forward flow component in the inferior vena cava is interrupted by reversed flow (Fig. 1b: R). In 2 cases this reversed flow component displayed a peak velocity of approximately 50 cm/s, while peak sytolic velocity of the normal forward flow component only amounted for 35 cm/s. The post extrasystolic beat is characterized by a prolonged diastole with an increased late-diastolic reversed flow and in 4 cases also an early-diastolic reversed flow component. Umbilical venous pulsations are present during the premature atrial contractions (Fig. 1c).

Bradycardia (n=4)

One fetus with sinus bradycardia (heart rate ± 68 beats/min.) demonstrated high percentages of retrograde flow in the inferior vena cava (Fig. 2a: R). This is caused by the fact that the very first (D1) as well as the very last part (D3) of the prolonged diastolic phase is characterized by a reversed flow component. Peak S/D ratio was slightly lower than in normal fetuses, reflecting a high-velocity diastolic forward component.

Three fetuses with complete heart block (CCHB) displayed atrial rates in the range of 130 and 156 beats/min; ventricular rates ranged from 53 to 60 beats / min. Inferior vena cava and ductus venosus flow velocity waveforms demonstrated high velocity retrograde flow components during ventricular contraction (Fig. 3a and 3b: VR). Reversed flow during atrial contractions (R) remained approximately unchanged compared with the normal IVC waveform. Waveforms are characterized by irregular systolic and diastolic flow patterns due to the asynchronous atrial and ventricular contractions. Umbilical venous pulsations with varying amplitudes are also present in these fetuses (Fig. 3c).

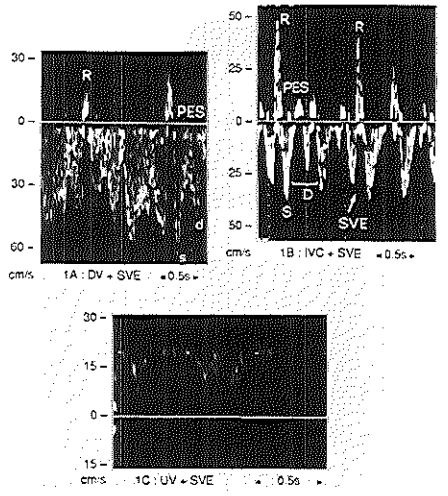


Figure 1: Flow velocity waveforms in the ductus venosus (1A), the inferior vena cava (1B) and umbilical vein (1C) during supraventricular extrasystole (SVE).

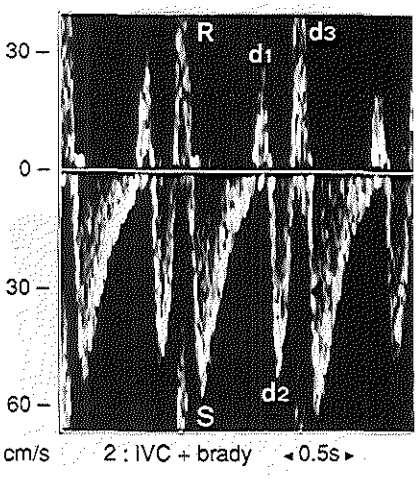


Figure 2: Flow velocity waveforms in the inferior vena cava in a fetus with sinus bradycardia (± 68 beats/min.).

Supraventricular tachycardia (n=8)

Table 1 describes eight patients with fetuses suffering from SVT.

Tachyarrhythmia related changes are mainly occurring during cardiac diastole, which is characterized by complete reversal of flow velocity in the ductus venosus, inferior vena cava and hepatic veins (Fig. 4 a, 4b and 4c: R). Umbilical venous pulsations of various amplitude are also present (Fig. 4d).

Table 2 presents the response of the flow velocity waveforms of these fetuses to the antiarrhythmic treatment. Immediately after cardioversion to (sometimes a period of) normal sinus rhythm the abnormal retrograde flow component disappeared. In almost all fetuses diastolic flow patterns remained disturbed during the following days or, even, weeks (Fig. 5a and 5b).

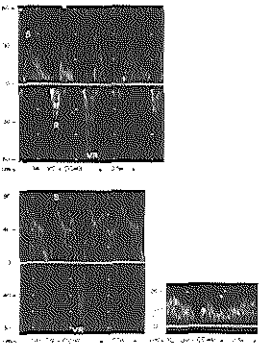


Figure 3: Flow velocity waveforms in the inferior vena cava (3A), ductus venosus (3B) and umbilical vein (3C) in a fetus with complete congenital heart block.

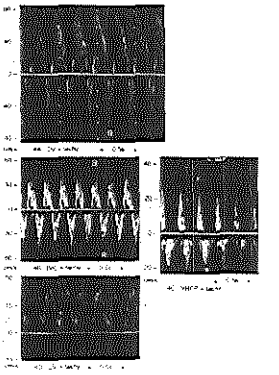
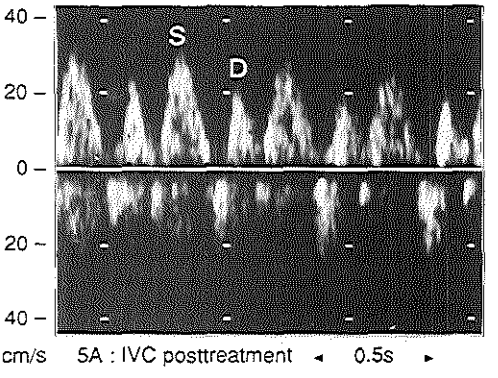


Figure 4: Flow velocity waveforms in the ductus venosus(4A),inferior vena cava(4B) hepatic vein (4C) and umbilical vein (4D) during fetal supraventricular tachycardia.



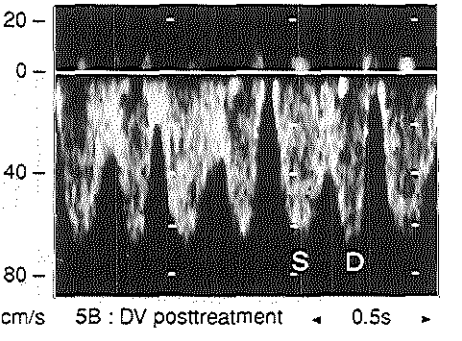


Figure 5: Flow velocity waveforms in the inferior vena cava (5A) and ductus venosus (5B) approximately 7 days after successful treatment of the tachycardia.

This was reflected by abnormal peak systolic/diastolic ratios; normally peak S/D ratio for the inferior vena cava ranges between 1.6 and 2.0, while in these affected fetuses it was in the range of 1.2 to 1.5. Ductus venosus peak S/D ranges between 1.1 and 1.2, while in this group it sometimes was around 1.0.

Table 1: Patient characteristics

pat nr.	gestational age	type arrhythmia and FHR (beats/min)	fluid collections	treatment and dose
1	35 +3	PSVT; 235	absent	digoxin 3 x 0.25 mg/d
2	27 +3	PSVT; 230	absent CTR: 0.51	digoxin 3 x 0.25 mg/d day 4: change flecainide 3 x 100 mg/d
3	23 +2	PSVT; 260	absent	digoxin 3 x 0.25 mg/d day 7: change flecainide 3 x 100 mg/d
4	26	PSVT; 83 / 290	absent CTR:0.50	digoxin 3 x 0.25 mg/d
5	35 +6	SVT; 215 - atrial flutter;430 - 2:1 conduction	CTR:0.61; ASA, R heart ↑	digoxin 3 x 0.25 mg/d
6	31 +4	PSVT; 294	CTR:0.66; ASA,R heart↑ ascites, skin edema, pericard effusion	flecainide 3 x 100 mg/d
7	26 +6	PSVT; 230	CTR: 0.63; ascites, skin edema	flecainide 3 x 100 mg/d
8	32 +2	PSVT; 290	CTR: 0.65 ascites, pericard and pleural effusion	flecainide 3 x 100 mg/d day 6: change digoxin 3 x 0.25 mg/d

Table 2 : Flow velocity waveforms and disturbances before and after treatment for SVT, relative to fetal response

pat. nr.	flow velocity waveforms + disturbances	response after 1 - 3 days P.T.	response after ± 7 days P.T.	response after ± 14 days P.T.	response after 4-11 weeks fetal outcome
1	IVC:rf 75; PSV 75 DV: rf 50; PSV 55 UV: min. pulsations	NSR, slight PE IVC: no abn.rf PSV 25; abn.DP	NSR, PE gone some SVE IVC + DV: normalized	NSR, no abn.	37 +6: CS because of periods SVT; ♀ 3300 g, no abn. ther. digoxin
2	IVC:rf 30; PSV 30 DV: rf 60; PSV 25 V Hep: rf 30; PSV 20 UV: min. pulsations	PSVT, no fluid collections, flow p. unchanged day 4: change to flecainide	NSR, ASA IVC: no abn.rf PSV 30; abn.DP DV: no abn.rf PSV 40; abn.DP V Hep:no abn.rf PSV 20; abn.DP	NSR, IVC: PSV 40 slight abn.DP DV: PSV 30 slight abn.DP V Hep: PSV 25 slight abn.DP	day 75: flow p.normalized. 38 +5:vag.del. ♂ 3470 g, NSR, no abn. ther. flecainide
3	IVC:rf 80; PSV 40 DV: rf 35; PSV 80 UV: large pulsations	PSVT, slight asc./ pl.eff.; flow p. unchanged	day 7: PSVT change to flecainide	NSR, fluid collections gone; IVC: no abn.rf PSV 35; abn.DP DV: no abn.rf, PSV 70; abn.DP UV: min. puls.	day 74: flow p. norm. 39 +4:vag.del. o 2950 g, NSR ther. digoxin
4	IVC:rf 50; PSV 60 DV: rf 40; PSV 80 UV: large pulsations	PSVT, hydrocele flow p. unchanged	NSR, freq. SVE's IVC: no abn. rf flow p. normal, PSV 30 DV: no abn. rf, flow p. normal, PSV 55 UV:no pulsation	NSR, some SVE's flow p. normalized	day 56: flow p. nl. 38 +5: vag. del. ♂ 4050 g, ileostomy because of meconium ileus; CF.
5	IVC:rf 60; PSV 60 DV: rf 70; PSV 75 UV: min. pulsations	mostly NSR-+SVE IVC: no abn.rf PSV 40; abn.DP DV: no abn.rf PSV 60; abn.DP V Hep:no abn.rf PSV 25; abn.DP	mostly NSR + SVE R heart ↓; CTR 0.56 IVC: flow p. normalized, PSV 40 DV: flow p. normalized, PSV 65	mostly NSR+-SVE low level dig. 4 x 0.25 mg/d IVC: normal flow p. PSV 50 DV: normal flow p. PSV 60	39 +4: vag. del. ♀ 3600 g, no abn. ther. digoxin

pat. nr.	flow velocity waveforms + disturbances	response after 1 - 3 days P.T.	response after ± 7 days P.T.	response after ± 14 days P.T.	response after 4-11 weeks;fetal outcome
6	IVC:rf 40; PSV 50 UV: min. pulsations	NSR, fluid collections unchanged high level flec 2 x 100 mg/d IVC: no abn.rf PSV 35; abn.DP DV: no abn.rf PSV 65; abn.DP	NSR, fluid unchanged; IVC: PSV 40 abn. DP DV: PSV 75 abn.DP V Hep: PSV 15 abn.DP UV: min. puls.	NSR, fluid ↓ IVC: PSV 50 abn. DP DV: PSV 65 flow p. normalized V Hep: PSV 25 abn.DP UV: min. puls.	day 31: fluid gone flow p. norm. 37: vag. del. ♀ 2500 g, no abn. ther. digoxin
7	IVC:rf 70; PSV 40 DV: rf 60; PSV 80 UV: min. pulsations	periods NSR, fluid collections unchanged; IVC: rf 20; PSV 40 abn.DP DV: no abn.rf PSV 40 abn.DP V Hep:nl.flow p	NSR, fluid IVC: PSV 35 flow p. normalized DV: PSV 70 slight abn.DP	NSR, fluid collections gone; IVC: PSV 50 flow p. normal DV: PSV 80 flow p. normal V Hep: PSV 35 flow p. normal	day 78: flow p. norm. 37 +2: vag. del. ♀ 4220 g , no abn. ther. flecainide
8	IVC:rf 60; PSV 70 DV: rf 25; PSV 65 UV: large pulsations	SVT, fluid collections gone, low level flec 4 x 100 mg/d day 6: slight asc. change to digoxine	SVT+periods NSR asc. gone IVC: rf 15; PSV 30 abn.DP DV: no abn.rf PSV 80 abn.DP UV: min. puls.	NSR, no fluid collections IVC:rf 20; PSV 35 slight abn. DP DV: PSV 45 slight abn.DP V Hep:rf 15; PSV 30 slight abn. DP UV: no puls.	day 18: NSR+ periods SVT; asc.+ pl.eff. IVC + DV + UV: flow p. idem 33 +5: CS ♂ 3000 g WPW; ther. digoxin + propranolol

Abbreviations:

fluid ↓ = decrease of fluid collections
abn.DP = abnormal diastolic flow pattern
IVC = inferior vena cava
DV = ductus venosus
UV = umbilical vein
V Hep = hepatic vein
R heart ↓ = decrease of right heart volume
R heart ↑ = increased right heart volume
PSV = peak systolic veolocity (cm/s)
min. puls. = minimal pulsations
SVE = supraventricular extrasystole
SVT = supraventricular tachycardia
flow p. = flow pattern
vag. del. = vaginal delivery
PE = pericard effusion
pl.eff. = pleural effusion
asc. = ascites
rf = reverse flow (cm/s)
P.T. = post treatment
ASA = atrial septum aneurysm
nl. = normal
ther. = therapy
NSR = normal sinus rhythm
freq. = frequent
dig. = digoxine
flec. = flecainide
CF = cystic fibrosis
CS = caesarean section

DISCUSSION

Combined two-dimensional ultrasonography and M-mode allow the most accurate description of the type and severity of arrhythmia, despite one report on diagnosis of fetal arrhythmias by Doppler ultrasound (Chan et al. 1990). Only a few reports have appeared which documented venous velocity waveforms by Doppler recording during this particular condition. Reed et al. (1990) described the changes in inferior vena cava waveforms during different types of arrhythmia. Our observations on inferior vena cava waveform modulation are in agreement with their report. Especially in the fetuses with premature atrial contractions and complete heart block the increase of the reverse flow component during altered cardiac contractions is interesting. It reflects an overfilled right atrium contracting when right ventriclar pressure is high or the ventricle is not relaxed. When the atrial contraction occurs with the atrioventricular valves still closed during ventricular systole, very high-velocity retrograde flow components are formed, which are called "cannon a waves" by Reed et al.(1990). The same group also reported on umbilical vein flow velocities in the same patients (Indik et al. 1991). They associated the high percentage reversed flow with the occurrence of umbilical venous pulsations. No data exist on ductus venosus flow velocity waveform modulation during arrhythmias except for one case of fetal tachycardia described by Kiserud et al.(1991). The disturbed diastolic phase in the ductus venosus waveform is the direct result of the different right atrial contraction pattern. Normally without any retrograde flow component, the ductus venosus flow velocity waveform during arrhythmia reflects the influence of an atrial contraction of an overfilled heart chamber resulting in reversed flow.

To our knowledge this is the first report on Doppler assessment of venous inflow before and after successful treatment of fetal supraventricular tachycardia. The disappearance of the enormous reversed flow component in the fetal inferior vena cava, ductus venosus and hepatic veins in case of a paroxysmal or permanent normal sinus rhythm is remarkable. This significant change in blood flow reflects the influence of the cardiac relaxation time on venous return. In fetuses with tachycardia blood is pooled in the central venous system and the

right atrium, since the ventricles demonstrate shortened periods of filling during the abnormally fast heart rhythm. In the diastolic phase of the cardiac cycle this increased end-diastolic pressure results in a backward surge of right atrial blood into the venous vessels. Inadequate forward flow will eventually lead, in most untreated cases, to development of cardiac decompensation reflected by fetal hydrops and asphyxia.

The normalization of flow velocity waveforms after the return of normal sinus rhythm is also variable. In our study this is demonstrated by the interval from an abnormal to a normal peak systolic/diastolic ratio in the inferior vena cava and ductus venosus waveform. Successful anti-arrhythmic agents like digoxin and flecainide may interrupt the abnormally fast heart rhythm, but there might still be aberrant pathways or abnormal conductance which influence the contraction force of the right atrium myocardium. We suggest that different factors play a role in the recovery of the fetal circulatory function.

Almost no data exist about human fetal electro-physiology or myocardial performance (Kleinman and Copel 1991). Knowledge has been acquired from neonates and animals, but the variable response and tolerance of fetal myocardium to various pharmaco-therapeutic regimes suggests different types of mechanism which lead to SVT. The influence of gestational age and increasing maturity may also play a role.

The role of the placenta as a barrier for drug transport into the fetal circulation and as a compensating force for an abnormal venous pressure has not been solved yet. The hydropic fetus, presumably due to hydrops of the placenta and altered placental perfusion states, has considerably less absorption of maternally-administered medications than the non-hydropic fetus (Younis and Granat 1987; Weiner et al. 1988; Gembruch et al. 1989; Hansmann et al. 1991).

The discussion about the presence and disappearance of fluid collections in hydropic fetuses remains speculative. Ascites, pleural and pericardial effusion and skin edema have been diagnosed as signs of the fetal struggle with abnormal heart rate. These symptoms are probably a better measure of fetal cardiac response to the tachycardia then venous waveforms.

It can be concluded that during fetal arrhythmias venous return blood flow is altered. The diastolic phase of the cardiac cycle is mainly disturbed by the change in right atrial filling patterns, reflected by increased retrograde flow components. After successful treatment of fetal tachycardia normalization of blood flow velocity waveforms is often slow, suggesting the variable response of the fetal myocardium to periods of abnormal conductance.

SUMMARY

The objective of this study was to describe the changes in venous flow velocity in various cases of fetal arrhythmia and to evaluate these changes before and after fetal therapy for tachycardia.

By means of Doppler ultrasonography a group of 22 fetuses was studied, consisting of ten cases with supraventricular extrasystoles, eight fetuses with supraventricular tachycardia, before and after successful treatment, and four cases of bradycardia. Flow velocity waveform recordings were obtained from the ductus venosus, inferior vena cava, hepatic veins and umbilical vein.

Peak systolic and diastolic velocity and their ratio were calculated. Presence of reversed flow and umbilical venous pulsations were noted.

All fetal arrhythmias were characterized by increased retrograde flow components and disturbed diastolic flow patterns. In most cases umbilical venous pulsations of varying amplitude were present. In the fetuses with tachycardia diastolic flow patterns remained disturbed after successful treatment, reflected by abnormal peak systolic to peak diastolic ratios in the inferior vena cava and ductus venosus waveform.

In conclusion, premature atrial contractions and complete heart block will increase the reverse flow component during the altered right atrial contractions, reflecting an overfilled right atrium contracting when right ventriclar pressure is high or the ventricle is not relaxed. The normalization of flow velocity waveforms after the return of normal sinus rhythm is in most cases slow suggesting the variable response of the fetal myocardium to periods of abnormal conductance.

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Chapter 6
GENERAL CONCLUSIONS

In this thesis combined two-dimensional real-time and Doppler ultrasound was used to study the fetal circulation in early and late pregnancy. In particular venous inflow hemodynamics was investigated, because venous return is of great importance to cardiac performance. Present transvaginal Doppler techniques allow detailed information on fetal waveform characteristics and velocities as early as 10 weeks of gestation. Transvaginal waveform recording was successful up to approximately 14 weeks' gestation. Afterwards, waveform recording was always carried out using the transabdominal approach because of increasing fetal size.

Flow velocity waveforms obtained at various cardiovascular levels in late first and early second trimester fetuses display an acceptable reproducibility in the individual patient, except for the acceleration time, whereas all parameters depict larger variabilities for between patient values. The possible clinical significance of an early single flow velocity measurement will therefore be limited.

At 10-12 weeks, end-diastolic flow velocities were always absent in the fetal descending aorta and umbilical artery, but were present in 58 % of the intra-cerebral artery waveforms, suggesting a relatively low cerebral vascular resistance compared with that at the fetal trunk and umbilical placental level.

The pulsatility index at all three levels decreased significantly with advancing gestational age, suggesting a reduction in fetal and umbilical placental vascular resistance during the late first and early second trimester of normal pregnancy. This may be due to the unplugging of the trophoblast at 13 to 14 weeks of gestation. These Pulsatility Index changes are independent of the reduction in FHR observed at this stage of early pregnancy.

A pulsatile flow pattern was observed in the ductus venosus and inferior vena cava, whereas only the latter demonstrated a retrograde flow component during right atrial contraction. The reduction in inferior vena cava flow reversal with

advancing gestational age may be a result of raised ventricular compliance or increased ventricular relaxation rate as well as reduction in afterload. The time-averaged flow velocity in the ductus venosus is 2.7 and 3.2 times higher than that in the inferior vena cava and umbilical vein in early pregnancy. The marked difference in flow velocity between the ductus venosus and inferior vena cava may result in a tendency not to mix and supports the assumption that two channels of venous return exist: inferior vena cava blood flow will be channeled to the tricuspid valve and ductus venosus blood flow will be mainly directed towards the foramen ovale.

This is supported by our study on the anatomical relationships between the venous vessels in the fetal hepatic region in the second half of pregnancy. The abdominal inferior vena cava terminates in a funnel-like venous structure, a subdiaphragmatic vestibulum, which contains the orifices of the hepatic veins as well as the ductus venosus. It is suggested that information on blood flow velocities in the individual vessels in the hepatic and subdiaphragmatic area should be obtained more distally to the right atrium and not at the level of the venous vestibulum.

In second and third trimester fetuses an acceptable within patient reproducibility for venous waveform recordings was obtained. Venous Doppler waveforms, however, should be interpreted with caution, since they are subject to variation on the basis of variable sample placement and angle insonation or biological variations in fetal hemodynamics.

The inferior vena cava flow velocity waveform displays a systolic and early diastolic forward component with reversed flow during late diastole. Waveform recording at the level of the inferior venous entrance into the right atrium provides information on changes in venous return rather than changes in the inferior vena cava per sé.

The ductus venosus shows a pulsatile flow pattern consisting of a systolic and diastolic forward component without the late diastolic reverse component demonstrated in the inferior vena cava. Ductus venosus peak systolic velocities as high as 40 - 80 cm/s were observed. A statistically significant increase in time-averaged velocity, peak systolic and peak diastolic velocity in the inferior vena

cava and ductus venosus with advancing gestational age was established. This may be caused by increased volume flow, increased cardiac compliance and stroke volume or reduced afterload. Age-related reduction in afterload may occur in the human fetus as a result of the physiological decrease in placental vascular resistance.

The influence on venous flow velocity waveforms of various fetal intrinsic factors such as fetal breathing movements, behavioural states and arrhythmias was studied in late pregnancy. Flow velocity waveforms in the hepatic venous vasculature close to the right atrium are markedly increased during fetal breathing movements. These changes are independent of gestational age and could be due to a raised pressure gradient between thorax and abdomen, resulting in a reduction in venous vessel diameter and additional volume flow being directed towards the right atrium. The significance of the inspiratory collapse of the fetal inferior vena cava ("caval index") for the recognition of elevated right atrial pressure in abnormal human fetal development needs further investigation.

Flow velocity waveform recording distal to the partially collapsing venous vessel wall merely demonstrated a reduction in flow velocity. This may be determined by the increase in intra-abdominal pressure and the functional obstruction of the collapsing vessel wall.

A fetal behavioural state dependent decrease of 30 % was observed in the ductus venosus peak systolic, peak diastolic and time-averaged velocity, suggesting a redistribution of umbilical venous blood through the ductus venosus shunt during the passive sleep state as compared with the active sleep state in the term fetus. The fetal behavioral state should be taken into account in future studies on ductus venosus flow velocity waveforms in normal term pregnancies. No behavioural state dependent changes were observed both in the proximal and distal portion of the inferior vena cava. Possible modulation in relation to behavioural states may, however, be obscured by considerable variation in flow velocities as demonstrated in the present study.

Finally, during fetal arrhythmias venous return blood flow is altered. The diastolic phase of the cardiac cycle is mainly disturbed by the change in right atrial filling patterns, reflected by increased retrograde flow components. After successful treatment of fetal tachycardia normalization of blood flow velocity waveforms is often slow, suggesting a variable response of the fetal myocardium to periods of abnormal conductance.

Summary

Chapter 1

In this introductory chapter it is pointed out that study of venous return in the human fetus is dependent on non-invasive methods and variation by fetal intrinsic variables. The objectives of the present thesis are focused on Doppler assessment of venous blood flow velocities in the human fetus relative to gestational age, fetal heart rate and rhythm, fetal breathing movements and fetal behavioural states.

Chapter 2

This chapter describes the acquisition of knowledge on fetal hemodynamics, in particular embryological, anatomical and physiological factors that have influenced research on venous return. It is pointed out that most information has been acquired from animal experiments, so that a need for accurate data on the human fetal circulation still remains. The non-invasive Doppler techniques available for obtaining this information are discussed, comparing the significance of both the transabdominal and transvaginal approach.

Chapter 3

In this chapter various aspects of fetal cardiovascular performance are discussed using Doppler ultrasonography in women with late-first and early-second trimester pregnancies. A reproducibility study displays an acceptable biological variation for individual flow velocity waveform parameters in the fetus. Examination of peripheral arteries demonstrates that the afterload conditions are characterized by a high resistance at fetoplacental level. This is reflected by the absence of end-diastolic flow in flow velocity waveforms from the umbilical artery and fetal descending aorta before 14 weeks of gestation. At 12 to 13 weeks Doppler

velocity waveforms from the fetal intracerebral artery display an end-diastolic flow component, which suggests a low resistance fetal cerebral circulation in the presence of a high afterload resistance.

Data on atrioventricular flow velocity waveforms at 10 to 14 weeks of gestation suggest low compliance of the fetal ventricles reflected by late-diastolic filling dominance.

This is also supported by the higher percentages of retrograde flow in inferior vena cava waveforms from first trimester fetuses as compared with the second and third trimester. Moreover, study of preload parameters demonstrates that time-averaged velocity in the inferior vena cava is markedly lower than in the ductus venosus, supporting the assumption that two channels of venous return exist side by side.

Chapter 4

This chapter begins with a detailed study of the anatomy of the fetal (peri)hepatic vasculature. The presence of a funnel-like venous structure at venous inflow level, named venous vestibulum, was established. This contains the orifices of the hepatic veins, the inferior vena cava itself and the ductus venosus. The anatomical complexity of all these veins may produce variable Doppler flow velocity waveforms at venous inflow level. A reproducibility study demonstrates acceptable within patient variance in inferior vena cava and ductus venosus flow recordings. In the following sub-chapters normal values for inferior vena cava and ductus venosus flow velocity parameters throughout the second half of pregnancy are documented. A statistically significant increase in time-averaged and peak systolic velocity with advancing gestation is observed.

Chapter 5

In this chapter the influence of various intrinsic factors is discussed in relation to normal venous flow velocity parameters. Variability in flow measurements can be caused by (i) biological variance within the patient; (ii) fetal (breathing) movements; (iii) different fetal behavioural states and (iv) cardiac arrhythmia. Variation in Doppler recording due to within patient variance components has been extensively investigated in the reproducibility studies described in chapters 3.2 and 4.3.

Firstly, the role of fetal breathing movements was examined in second and third trimester fetuses. Maternal glucose administration induced fetal breathing activity and inferior vena cava, ductus venosus and hepatic vein flow velocity waveforms were documented. These waveforms, which were obtained close to the right atrium, demonstrate a significant increase in peak systolic, diastolic and time-averaged velocity during fetal breathing movements. These changes are independent of gestational age and could be due to a raised pressure gradient between thorax and abdomen, resulting in a reduction in venous vessel diameter and additional volume flow being directed towards the right atrium. The breathing-related reduction of the inferior vena cava vessel diameter or "inspiratory collapse" had already been observed in the adult. The significance of this collapse of the fetal inferior vena cava (also called: "caval index") for the recognition of elevated right atrial pressure in abnormal human fetal development needs further investigation. Flow velocity waveform recording distal to the partially collapsing venous vessel wall merely demonstrates a reduction in flow velocity. This may be determined by the increase in intra-abdominal pressure and the functional obstruction of the collapsing vessel wall.

Secondly, we focused on changes in venous return and venous blood flow velocities relative to different fetal behavioral states. During the passive sleep state (FBS 1F) a significant decrease in ductus venosus blood flow velocity is observed compared with the active sleep state (FBS 2F), while inferior vena cava flow parameters do not demonstrate any changes. It is suggested that a redistribution of venous blood flow takes place at the level of the ductus venosus

relative to the fetal behavioural state.

Finally, during cardiac arrhythmias marked changes in preload flow components occur, in particular during the diastolic filling phase. The main alteration was the appearance or increase of the retrograde flow component coincident with right atrial contraction. These changes were also investigated in fetuses suffering from supraventricular tachycardia, who were successfully treated with maternal therapy of digoxine or flecanide. Normalization of the reversed flow component, but in particular the diastolic flow characteristics, of ductus venosus and inferior vena cava blood flow velocity waveforms is often slow, suggesting a variable response of the fetal myocardium to periods of abnormal conductance.

Samenvatting

Hoofdstuk 1

In dit inleidend hoofdstuk wordt gewezen op het feit dat onderzoek naar de veneuze return in de humane foetus afhankelijk is van non-invasive methoden en van variaties bepaald door foetale intrinsieke faktoren.
De doelstellingen van dit proefschrift concentreren zich op de evaluatie van veneuze bloedstroom snelheden in de humane foetus door middel van Doppler echografie in relatie tot de zwangerschapsduur, foetale hart frequentie en ritme, foetale ademhalingsbewegingen en foetale gedragstoestanden.

Hoofdstuk 2

Dit hoofdstuk beschrijft de methoden ter verkrijging van kennis omtrent de foetale hemodynamiek, in het bijzonder de embryologische, anatomische en fysiologische faktoren die onderzoek naar de veneuze return hebben beinvloed. Er wordt op gewezen dat de meeste informatie is vergaard in dierexperimentele proeven, zodat er een noodzakelijkheid blijft bestaan voor accurate gegevens over de humane foetale circulatie. De non-invasieve Doppler technieken die bekend zijn om deze informatie te verkrijgen worden besproken, waarbij de plaats en noodzakelijkheid van enerzijds de transabdominale en anderzijds de transvaginale benadering worden vergeleken.

Hoofdstuk 3

In dit hoofdstuk worden de verschillende aspekten van foetaal cardiovasculair functioneren met behulp van Doppler echografie beschreven bij vrouwen gedurende het eerste en vroeg tweede zwangerschapstrimester. Een reproduceerbaarheidsstudie demonstreert een acceptabele biologische variantie binnen de veschillende bloedstroomsnelheids parameters in de individuele foetus.

Onderzoek van de perifere arteriën laat zien dat afterload kondities worden gekenmerkt door een relatief hoge vasculaire weerstand op foeto-placentair niveau. Dit wordt weerspiegeld in de afwezigheid van eind-diastolische flow in het bloedstroomsnelheidsprofiel van de arteria umbilicalis en de foetale aorta descendens vòòr de zwangerschapsduur van 14 weken. In de zwangerschaps-periode van 12 - 13 weken vertoont Doppler echografie van de intracerebrale arterie altijd de aanwezigheid van een eind-diastolische flow component, hetgeen een relatief lage vaatweerstand in de foetale cerebrale circulatie onder omstandigheden van hoge afterload vaatweerstand suggereert.
Onderzoek naar de foetale cardiale functie bij 10 tot 14 weken zwangerschaps-duur suggereert een lage compliantie van de foetale ventrikels gekenmerkt door dominantie van de laat-diastolische vullingsgraad. Dit wordt gesteund door het hogere percentage van retrograde flow in de foetale vena cava inferior in het eerste zwangerschapstrimester vergeleken met het tweede en derde trimester. Bovendien heeft studie naar de "preload" parameters laten zien dat de gemiddel-de bloedstroom snelheid in de vena cava inferior beduidend lager ligt dan de ductus venosus. Dit steunt de veronderstelling dat twee kanalen van veneuze return naast elkaar bestaan.

Hoofdstuk 4

Dit hoofdstuk begint met een gedetaileerde studie naar de anatomie van het foetale (peri)hepatische bloedvatenstelsel. De aanwezigheid van een trechter-vormige veneuze structuur, veneus vestibulum genaamd, werd vastgelegd, welke de openingen van de hepatische venen, de vena cava inferior zelf en de ductus venosus bevat. De anatomische complexiteit van al deze venen zou mogelijk variatie in de Doppler bloedstroom snelheidsprofielen registratie kunnen veroor-zaken. Een reproduceerbaarheidsstudie laat een acceptabele intrapatient variatie in vena cava inferior en ductus venosus stroomsnelheidsmetingen zien. In de daaropvolgende subhoofdstukken worden de normaal waarden van de vena cava inferior en ductus venosus stroomsnelheids parameters gedurende de tweede helft van de zwangerschap gedocumenteerd. Een statistisch significante toename

in gemiddelde en piek systolische snelheden met toenemende zwangerschapsduur wordt vastgesteld.

Hoofdstuk 5

In dit hoofdstuk wordt de invloed van verschillende intrinsieke faktoren onderzocht in relatie tot normale veneuze stroomsnelheids parameters. Variabiliteit in flow metingen kunnen worden veroorzaakt door: (i) biologische variatie binnen de patient; (ii) door foetale (ademhalings) bewegingen; (iii) verschillen in foetale gedragstoestand en (iv) cardiale arritmiëen. Variatie in Doppler registratie die te danken is aan intrapatient variatie zijn reeds beschreven in hoofdstukken 3.2 en 4.3.

Ten eerste werd de rol van foetale ademhalingsbewegingen in het tweede en derde zwangerschapstrimester onderzocht. Maternale glucose toediening induceerde foetale ademhalings aktiviteit. Bloedstroomsnelheidsprofielen van de vena cava inferior, ductus venosus en hepatische venen werden vervolgens vastgelegd. Deze profielen, die dicht bij het rechter atrium werden verkregen, vertonen een significante toename in piek systolische, diastolische en gemiddelde snelheid tijdens foetale ademhalingsbewegingen. Deze veranderingen zijn onafhankelijk van de zwangerschapsduur en kunnen mogelijk worden verklaard door een verhoogde drukgradiënt tussen thorax en abdomen, resulterend enerzijds in een afname van de veneuze vaatwand diameter en anderzijds in een additionele bloedstroom die in de richting van het rechter atrium wordt geleid.

Deze ademhalingsafhankelijke afname van de vena cava inferior vaat diameter of "inspiratoire collaps" is reeds eerder beschreven bij de volwassene. De klinische relevantie van deze collaps van de vena cava inferior vaatwand (ook genoemd: "caval index") voor de diagnose van verhoogde rechter atriale druk tijdens abnormale foetale ontwikkeling dient verder te worden onderzocht. Bloedstroomsnelheids metingen distaal van de gedeeltelijk collaberende veneuze vaatwanden laten slechts een afname van de stroomsnelheid zien. Dit zou bepaald kunnen worden door de gelijktijdige toename van de intra-abdominale druk en de

functionele obstructie van de collaberende vaatwand.

Ten tweede was het onderzoek geconcentreerd op veranderingen in veneuze bloedstroomsnelheden die gerelateerd zijn aan de verschillende foetale gedragstoestanden. Tijdens de passieve slaaptoestand (FBS 1F) wordt een significante afname van de bloedstroomsnelheid in de ductus venosus vastgesteld, vergeleken met de actieve slaaptoestand (FBS 2F), terwijl de vena cava inferior flow parameters deze verandering niet vertonen. Dit suggereert dat een redistributie van veneuze bloedstroom plaats vindt op het niveau van de sinus umbilicalis en de daaruit ontspringende ductus venosus, welke gerelateerd is aan de foetale gedragstoestand.

Tenslotte vinden tijdens cardiale arritmiëen opmerkelijke veranderingen plaats in de zogenaamde "preload" stroomcomponenten, in het bijzonder gedurende de diastolische vullingsfase. De meest in het oog springende verandering is verschijning of toename van de retrograde flow component tegelijkertijd met de contractie van het rechter atrium. Deze veranderingen werden ook onderzocht bij ongeborenen, die leden aan supraventriculaire tachycardie, en die via de moeder succesvol behandeld waren met digoxine of flecainide. Normalisatie van de retrograde flow, maar vooral de diastolische flow karakteristieken in de ductus venosus en vena cava inferior is vaak langzaam, hetgeen een variabele respons van het foetale myocard suggereert op perioden van abnormale prikkelgeleiding.

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Curriculum vitae

De auteur van dit proefschrift werd op 5 april 1963 geboren te Amsterdam. Van 1975 tot 1981 werd de middelbare school bezocht, het Erasmiaans Gymnasium te Rotterdam, alwaar het eindexamen Gymnasium ß in 1981 werd behaald.
Door de numerus clausus werd in augustus 1981 met de geneeskunde studie aangevangen aan het Rijks Universitair Centrum te Antwerpen (RUCA) in België. Na het behalen van het kandidaatsdiploma werd in 1985 gestart met de doctoraalfase aan het Universitair Instituut Antwerpen (UIA). De medische studie werd afgesloten met het verkrijgen van het doctoraal diploma in februari 1988 (met onderscheiding) en het artsdiploma op 30 juni 1989 (met onderscheiding) aan de Universiteit van Antwerpen.
In april, mei en juni 1989 was de schrijver werkzaam als docent anatomie, fysiologie en pathologie aan de verpleegopleiding "de Driemaster" in Rotterdam.
Van 1 november 1989 tot 31 mei 1993 werkte hij als arts in opleiding voor onderzoeker (AIO) onder leiding van Prof.Dr. J.W. Wladimiroff binnen de vakgroep verloskunde/gynaecologie van de faculteit der geneeskunde aan de Erasmus Universiteit Rotterdam (hoofd Prof.Dr.A.C. Drogendijk). In deze periode werd tevens regelmatig routine obstetrisch en structureel echoscopisch onderzoek verricht.
Vanaf 1 juni 1993 werkt de promovendus als arts-assistent-geneeskunde-niet-in-opleiding binnen de afdeling obstetrie/gynaecologie van het Academisch Ziekenhuis Rotterdam - Dijkzigt (hoofd Prof.Dr.A.C.Drogendijk) en werd een opleidingsplaats obstetrie/gynaecologie verworven voor 1994 aan het Academisch Ziekenhuis Groningen (hoofd Prof.Dr.J. Aalders).

Age, si quid agis