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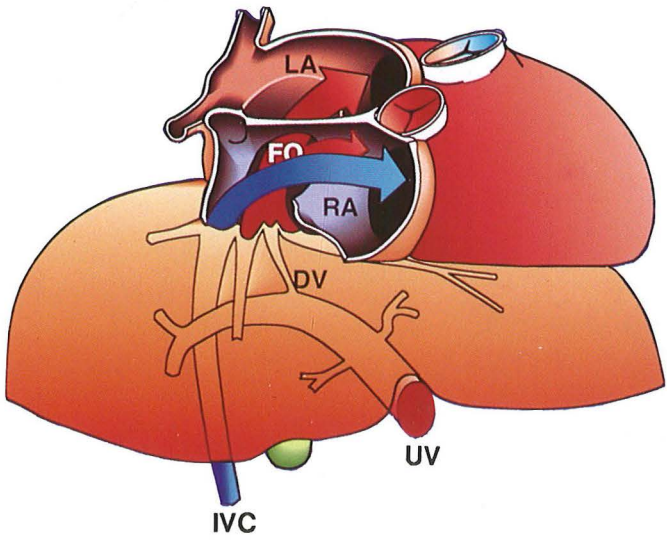
THE DUCTUS VENOSUS IN THE HUMAN FETUS

An ultrasonographic study of its functional anatomy, normal blood flow velocity and its changes during fetal disease



National Center for Fetal Medicine
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Trondheim – Norway

TAPIR

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CONTENTS

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Much of my knowledge in fetal physiology was acquired during my stay at Malmö General Hospital, University of Lund, Sweden, in 1989. My interest in fetal circulation and specifically the ductus venosus was aroused by the stimulating discussions with Professor Karel Maršál, one of the finest persons I have ever met. Although he is attached to another department, I have enjoyed a close relationship to Professor Bjørn Angelsen, Department of Medical Technology, University of Trondheim, and I admire his ability to shed light onto problems from unexpected angles.

The structures I have studied are densely woven together and rapidly change position (such as the foramen ovale valve), and the blood velocities of interest may have a swift variation. Their description, to a large extent, depends on the quality of the ultrasound equipment. I have been provided with what I believe has been the most appropriate equipment. Both the Doppler signals and the imaging unit of the Vingmed CFM 750 and

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After spending years on Ethiopian soil, I owe the African people deep gratitude for lending me some of their attitudes. They taught me to keep an open mind towards the stream of life, to question established knowledge, and to discover the finest wisdom in those who are most ignored. Their acceptance and concern for the most deprived of our kind included even me.

Finally, and most of all, I am grateful to those who are closest to me, and who with love have endured all my varied kinds of days.

Trondheim December 1993

Torvid Kiserud

SUMMARY

The ductus venosus is a small vessel that connects the fetal umbilical vein directly to the central venous system, bypassing the liver. Its specific function of distributing oxygenated blood has been described in the primate and in the fetal lamb. The question of how the oxygenated blood is distributed in the human fetus is a crucial one, and it was quite natural to explore this part of physiology in utero once appropriate technology was developed.

Aims: The initial purposes of the present studies were to identify the human ductus venosus in utero applying ultrasound techniques, to describe its functional relationship to the foramen ovale and the inferior venous inlet to the heart, to describe the normal blood flow velocity patterns in the ductus venosus, to establish a standardized measurement technique and to describe the reproducibility of such a velocimetry (Papers I and II).

Secondly, the aim was to explore the diagnostic possibilities provided by studying the changes in the ductus venosus blood flow velocity during states of hemodynamic compromise (Papers III and IV), and by exploring the possibilities of estimating the pressure gradient across the ductus venosus as a means for describing an essential parameter in fetal hemodynamics (Paper V).

Material and methods: 29 normal singleton pregnancies were included in a longitudinal study and examined every 3 - 4 weeks during gestational weeks 17 - 42 by applying 2D-imaging, color Doppler and pulsed Doppler to describe the ductus venosus and its blood flow velocity during fetal quiescence and during fetal breathing, and to record the blood flow velocity in the intra-abdominal portion of the umbilical vein (Papers I and V).

A reproducibility study was done in 27 pairs of observations to describe intra-observer variation of the ductus venosus velocimetry (Paper I). In 31 sets of observations, the sampling site was evaluated (inlet, mid portion and outlet of the ductus venosus) (Paper I).

103 normal fetuses (gestational age 17 - 40 weeks) were included in a cross-sectional study where 2D-imaging and color Doppler were used to describe the relationship between the ductus venosus and the foramen ovale, to record the angle of the ductus venosus, the abdominal and thoracic portion of the inferior vena cava, the left, medial and right hepatic vein and the direction of the ventricular septum (Paper II).

In 30 fetuses with known heart disease, the ductus venosus blood velocity and the umbilical vein blood velocity were recorded (Paper III).

In 38 cases of serious intra-uterine growth retardation (birthweight $\leq$ 2.5 centile) with no structural abnormality or chromosomal aberration, the ductus venosus blood velocity, the intra-abdominal umbilical vein dimension and blood velocity, and the umbilical artery blood velocity waveform were recorded (Paper IV).

Results: The ductus venosus could regularly be identified by ultrasonography during gestational weeks 17 - 42. It remained a narrow vein throughout the pregnancy and projected umbilical blood dorsally in a steep direction towards the left compartment of the inferior vena cava (IVC). A high maximum velocity (40 - 100 cm/s) comparable to the velocities otherwise seen on the arterial side, was found. There was a typical variation during the heart cycle much like that of the IVC and hepatic veins but without reversed

flow during atrial contraction. There were wide normal ranges for the ductus venosus velocity. The best reproducibility was achieved by standardizing the Doppler recording at the initial portion of the ductus venosus. Intra-observer reproducibility showed limits of agreement of ±13 cm/s (Paper I).

The foramen ovale received blood directly from the ductus venosus, left and medial hepatic vein and not as a transatrial flow from the right atrium (Paper II). A separate *left pathway* was described starting in the umbilical sinus, passing through the ductus venosus, the left compartment of the upper IVC, the foramen ovale and into the left atrium. The left and medial hepatic vein supplied this pathway. A *right pathway* was described starting in the abdominal portion of the IVC, projecting 14 degrees in the anterior direction to deliver the blood in the right atrium through the right compartment of the upper IVC. The right hepatic vein supplied this right pathway. The two pathways touched and crossed at an angle of 48 degrees in the proximal widened IVC (Paper II).

The pressure gradient between the umbilical vein and the IVC was estimated from the ductus venosus velocimetry and the umbilical vein velocimetry by means of the Bernoulli equation. The pressure gradient varied with the heart cycle and ranged between 0 - 3 mm Hg during the last half of the normal pregnancy (Paper V).

In the 30 cases of fetal cardiac disease, 8 (27%) had reduced peak blood velocity in the ductus venosus, and 18 (60%) had reduced minimum blood velocity. The changes were most commonly found in the cases with serious cardiac malformations (Paper III).

In the 38 cases of serious intra-uterine growth retardation, all the fetuses had a normal peak blood velocity in the ductus venosus in spite of the high frequency of placental compromise found in the group (68% with raised pulsatility index in the umbilical artery, 32% with absent or reversed end-diastolic flow in the umbilical artery, 76% with reduced umbilical vein flow, and 30% with pulsation in the umbilical vein). The reduced minimum blood velocity in the ductus venosus during atrial contraction found in 34% of the cases was another sign of hemodynamic compromise during serious growth retardation (Paper IV).

Conclusions: The ductus venosus can regularly be identified in the human fetus in utero by applying ultrasonographic techniques. During gestational weeks 18 - 40, the ductus venosus remains a slender vein projecting blood at a high velocity across the left compartment of the proximal IVC towards the foramen ovale. During intra-uterine life the foramen ovale seems to be functionally linked to the ductus venosus and left and medial hepatic vein to form a specific pathway of oxygenated blood to the left atrium.

The high blood flow velocity in the ductus venosus is maintained throughout the pregnancy with wide normal ranges and can be reliably recorded in a standardized procedure with fair reproducibility.

The blood flow velocity in the fetal ductus venosus reflects an important pressure gradient between the umbilical vein and the IVC. When the ductus venosus velocimetry is included in the hemodynamic evaluation we gain a more complete understanding of the fetal circulation as is shown in cases of fetal cardiac disease and in intra-uterine growth retardation. The method is promising and should be further evaluated for use in clinical obstetrics.

Ductus venosus velocimetry can be used as a non-invasive method of estimating the pressure gradient between the umbilical vein and the IVC in the fetus provided the methodological limitations are controlled.

LIST OF PAPERS

The present thesis is based upon the following Papers which will be referred to in the text by their respective Roman numerals:

I Kiserud, T., Eik-Nes, S. H., Hellevik, L. R., and Blaas, H.-G. (1992). Ductus venosus – a longitudinal Doppler velocimetric study of the human fetus. J Matern Fetal Invest, 2, 5-11.

II Kiserud, T., Eik-Nes, S. H., Blaas, H-G, and Hellevik, L. R. (1992). Foramen ovale: an ultrasonographic study of its relation to the inferior vena cava, ductus venosus and hepatic veins. Ultrasound Obstet Gynecol, 2, 389-396.

III Kiserud, T., Eik-Nes, S. H., Hellevik, L. R., and Blaas, H.-G. (1993). Ductus venosus blood velocity changes in fetal cardiac diseases. J Matern Fetal Invest, 3, 15-20.

IV Kiserud, T., Eik-Nes, S. H., Blaas, H.-G., and Hellevik, L. R. (1994). Ductus venosus blood velocity and the umbilical circulation in the seriously growth retarded fetus. Ultrasound Obstet Gynecol, 4, 109-114.

V Kiserud, T., Hellevik, L. R., Eik-Nes, S. H., Angelsen, B. A. J., and Blaas, H.-G. (1994). Estimation of the pressure gradient across the fetal ductus venosus based on Doppler velocimetry. Ultrasound Med Biol, 20, 225-232.

ABBREVIATIONS AND DEFINITIONS

BPD	The biparietal diameter of the fetal head including the outer-outer distance of the parietal bones
CI	Confidence intervals
CHD	Congenital heart defect
d	The mean difference of paired observations used to calculate limits of agreement in the assessment of reproducibility
Δp_{DV}	The pressure gradient across the ductus venosus representing the pressure difference between the umbilical vein and the inferior vena cava
D_{UV}	The diameter of the intra-abdominal portion of the umbilical vein measured as the inner width
DV	Ductus venosus (Arantii)
Eustachian valve	Also called the valve of the inferior vena cava. It extends in a vertical direction from the anterior edge of the inferior vena cava towards the right atrium
FO	Foramen ovale
fof	Foramen ovale flap
Gestational age	To create uniformity, the fetal age is referred to in completed weeks as assessed by ultrasonography. This applies also to the embryonic period.
Impedance	Resistance to pulsatile flow
Ispta	Spatial peak temporal average intensity (mW/cm^2) is a commonly used measure of the acoustic energy that the tissues are exposed to.
IUGR	Intra-uterine growth retardation
IUFD	Intra-uterine fetal death
IVC	Inferior vena cava
N	Nyquist limit: $N < prf / 2$. The highest Doppler frequency shift unambiguously recorded at a given pulse repetition frequency (prf)
Navier-Stokes equations	The basic equations that describe movements in fluids and the forces that govern these movements

Newtonian fluid	A fluid that has an unchanged viscosity with increasing shear rates (example: water)
Non-Newtonian fluid	A fluid that has a changing viscosity with different shear rates (example: blood)
MAD	Mean abdominal diameter in the fetus
PI	Pulsatility index: (systolic velocity – diastolic velocity) / mean velocity
ρ	Density of fluid
R	Viscous pressure drop in the generalized Bernoulli equation
Reynolds number	A number that expresses the risk of laminar flow developing into turbulence; it depends on vessel dimension, velocity and viscosity
SD	Standard deviation
SE	Standard error
SE(l)	Standard error of the limits of agreement
$t_{\alpha/2,n-1}$	The significance limit in the Student-t distribution
UA	Umbilical artery
UV	Umbilical vein
V_{min}	Maximum blood flow velocity in the ductus venosus during atrial contraction
V_{peak}	Peak of the maximum blood flow velocity in the ductus venosus measured during ventricular systole
V_{ta}	Time-averaged maximum blood flow velocity in the ductus venosus
V_{DV}	Maximum velocity tracing of the blood flow velocity in the ductus venosus
V_{UV}	Maximum blood velocity in the intra-abdominal portion of the umbilical vein

INTRODUCTION

Historical background

The ductus venosus is a tiny piece of vein hidden below the liver hilus in an area of a densely woven vasculature. It is amazing that it was described as a special vein as early as in the 16th century. Its description was attributed to the Italian anatomist Gulio Cesare Aranzio (1530 - 1580). This was the period of the awakening of modern medicine when thorough knowledge of anatomy was introduced as the foundation for all medical thinking. This tradition has been successfully maintained until the present century and poignantly expressed by the saying "A physician who does not know anatomy is not only useless, he is also dangerous."

Later examination of existing scripts, however, has revealed that the famous contemporary of Aranzio, the Dutch anatomist Vesalius, was the first to describe the ductus venosus (1561) and he included this information in his book published in 1563 (Franklin 1941).

The foramen ovale was accurately described by Galen (131 - 201) (reviewed by Patten 1931). But it was not until Harvey introduced the concept of the circulating blood that its physiological role in the fetus could be appreciated.

In 1766, Haller referred to experiments showing that air or fluid injected into the umbilical vein or inferior vena cava pass through the foramen ovale into the left atrium (reviewed by Barclay et al. 1944). He clearly understood and described the transfer of umbilical blood through the foramen ovale directly into the left atrium. A probably better known hypothesis was presented by Sabatier (1774) who suggested that all blood from the vena cava inferior, including that of the ductus venosus, entered the left atrium through the foramen ovale (reviewed by Dawes 1982). Wolff and Kilian had a slightly different concept and suggested that only two-thirds of the inferior vena cava blood entered the left side of the heart.

At the beginning of the present century, Pohlman opposed the idea of a direct transfer of blood from the inferior vena cava to the left atrium. After having conducted experiments

on fetal pigs, he proposed that all caval blood entered the right atrium before a portion continued through the foramen ovale to the left atrium. Barcroft, who in 1946 so vividly condensed the accumulated knowledge up to that time in his "Researches on pre-natal life", came to the conclusion that blood derived from the abdominal inferior vena cava, the hepatic veins and the ductus venosus mixed and was delivered directly either to the left of the atrial septum to feed a via sinistra, or to the right atrium to feed the via dextra. His conclusions were based on animal experiments that included measurement of oxygen tension and the newly introduced radioangiographic technique (Barclay et al. 1939, 1942a, 1944; Franklin et al. 1940; Barron 1944; Barcroft 1946). The results were later confirmed by others and the methods refined for a detailed study of fetal circulation (Dawes et al. 1954, 1959, 1960, 1961; Acheson et al. 1957; Peltonen and Hirvonen 1965). The same pattern of an inferior venous flow divided by the crista dividens into a left and right atrial inflow was found in pre-viable human fetuses (Lind and Wegelius 1949, 1954).

Experimental work during the 1970-80s applying isotope labeled microspheres in primates and sheep suggested that the fetal ductus venosus carried a considerable amount of blood to the thoracic portion of the inferior vena cava (Behrman et al. 1970; Edelstone and Rudolph 1979, Edelstone 1980) and that the blood derived from the ductus venosus formed a preferential streaming through the foramen ovale and the left atrium to ensure the oxygen supply to the myocard and brain (Behrman et al. 1970; Edelstone and Rudolph 1979; Rudolph 1985). This was, so to say, a modern version of Haller's hypothesis of 1766.

The introduction of ultrasound technique opened the door for a direct non-invasive study of the human fetus in utero (Campbell 1969; Campbell et al. 1973; Campbell and Wilkin 1975; Allen et al. 1980). In 1977, FitzGerald and Drumm reported on a new technique applying Doppler ultrasound to record blood flow velocity in the human fetus. This initiated a cascade of refined techniques and applications (McCallum et al. 1978; Gill 1979; Eik-Nes et al. 1980, 1982, 1984) to describe maternal and fetal circulation in great detail (Gill 1984; Marsál et al. 1984; Reuwer et al. 1984; Lingman and Marsál 1986; Wladimiroff et al. 1986; Huhta et al. 1987). During recent years, the improved ultrasound technology enabled researchers to expand their investigation to include early gestation (Huisman et al. 1992b; Rizzo et al. 1992; Wladimiroff et al. 1992), and to study details of the venous circulation (Reed et al. 1990; Gudmundsson et al. 1991; Wladimiroff et al. 1991) including that of the ductus venosus (Kiserud et al. 1991; Huisman et al. 1992c). The present work benefits greatly from being in the midst of that development.

Another leap forward came in 1976 when Holen, using Doppler velocimetry, estimated the pressure gradient across a mitral stenosis applying the Bernoulli principle. Especially for the otherwise inaccessible fetus in utero, such a non-invasive measurement of pressure offers an attractive perspective for potential uses.

Developmental anatomy

General considerations

Circulation is the single most rapid way of providing nourishment, gas exchange and exchange of water and electrolytes to tissues. This is also true for intra-uterine life, but the circulation has to be adjusted according to the needs at different levels of development. The umbilical circulation plays a dominating role during most of the pregnancy. At mid-pregnancy, 1/2 of the fetal blood volume is found in the placenta, and at the end of the pregnancy 1/3 - 1/6 is still contained in the placenta (Barcroft 1946; Yao et al. 1969).

Once the umbilical arteries leave the iliac arteries, they follow the cord to fuse together at the placental inlet and then branch up to supply 28-32 cotyledons (Ramsey and Donner 1980). The villous capillary bed drains into the umbilical vein which follows the cord back to the fetus.

The umbilical vein enters the abdomen to follow the inferior surface of the liver as the intra-abdominal portion of the umbilical vein. As the umbilical vein approaches the liver hilus, it gives off branches to the left and medial portion of the liver until it finally communicates with the transverse portion of the portal vein often called the portal sinus. A separate vague sinus at the level where the ductus venosus takes off is sometimes termed the umbilical sinus.

The ductus venosus is known as a narrow vein which connects the umbilical sinus to the hepatic veins and the inferior vena cava below the atrial inlet (Figure 1). The ductus venosus is branchless and has an isthmic inlet where it leaves the umbilical sinus dorsally and rather steeply in the cranial direction behind the liver but to a large extent surrounded by liver tissue (Barcroft 1946; Dawes 1968; Balique et al. 1984).

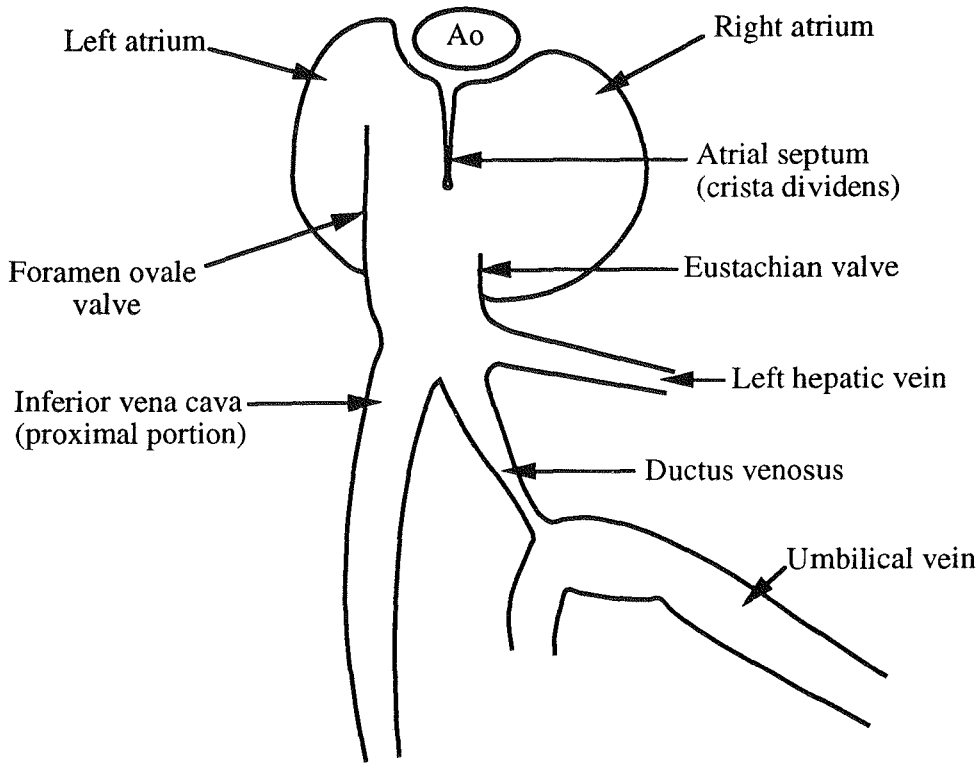

Figure 1: Details of the inferior venous inlet to the human fetal heart based on the ultrasound findings presented in Paper II. The distance from the confluence of the hepatic veins to the atrium is shorter in the human fetus than in fetal sheep. The ductus venosus connects the umbilical vein directly to the proximal portion of the inferior vena cava. Ao = Ascending aorta

The ductus venosus

During the early stages of intra-uterine life, however, the vascular system is arranged differently (Figure 2). The embryo of seven gestational weeks has paired vitelline and umbilical veins draining into the venous sinus (Sadler 1985). The venous system and the hepatic tissue form a meshwork. As the liver grows, the umbilical circulation becomes engrossed in the left umbilical vein which through the portal sinus nourishes both the liver parenchyma and a central stem towards the heart (the ductus venosus). At eight weeks' gestation, the ductus venosus is well defined (Chako and Reynolds 1953; Dickson 1957; Severn 1972; Lassau and Bastian 1983). During the rest of the

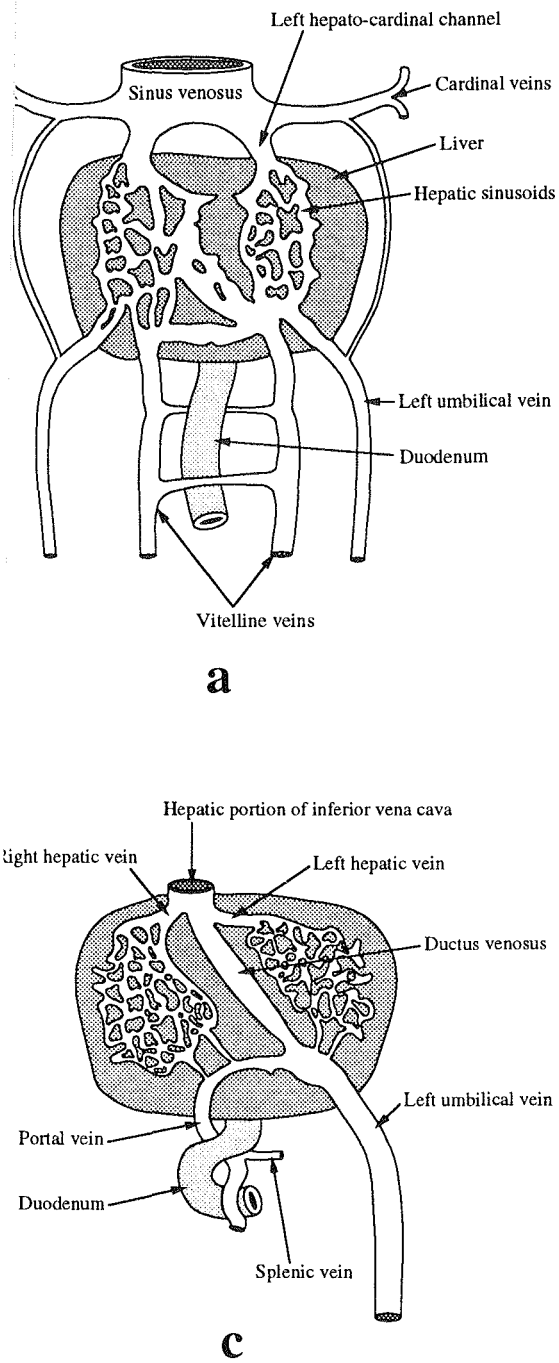

*Figure 2: **a)** After the sixth gestational week three major paired veins interact with the growing liver to form a meshwork. **b)** A rapid development during the following days gives priority to the growth of the left umbilical vein and a defined ductus venosus. **c)** After the eighth week the vitelline veins have been transformed into the superior mesenteric, splenic and portal veins communicating with the umbilical vein developed from the left side. The ductus venosus now forms a continuation of the umbilical vein towards the subcardial inferior vena cava.*

pregnancy, the ductus venosus shows a continuous growth of length but retains its shape of a trumpet with a narrow entrance (Chako and Reynolds 1953; Blanc 1960).

It has been suggested that a sphincter plays a role at the isthmic entrance (Barron 1942). Muscular and neural elements have been traced (Barclay et al. 1942b, 1944; Barron 1942, 1944; Chako and Reynolds 1953; Pearson and Sauter 1969, 1971; Oliveira et al. 1979) and based on histochemical studies, adrenergic activity has been suggested (Gennser et al. 1967; Ehinger et al. 1968; Coceani et al. 1984). These findings have not been reproduced by all investigators and have induced uncertainty whether such a sphincter function exists at all (Meyer and Lind 1965, 1966; Lind 1977).

The outlet of the ductus venosus is closely related to the left and medial hepatic vein both in the fetal lamb and in man (Barcroft 1946; Rudolph 1985; Champetier 1989). In the fetus, the medial hepatic vein is large, but during postnatal life it becomes relatively small in size and is often merely regarded as a branch of the left hepatic vein. The inferior vena cava widens at the level of the confluence where it receives the hepatic veins and the ductus venosus shortly before entering the fetal heart. The vessel is so wide that the term "infundibulum" has been suggested (Huisman et al. 1992a). The studies in fetal lambs suggest that the ductus venosus enters the left portion of the inferior vena cava, rather than the right portion (Rudolph 1985). In fetal lambs, an additional valve or membranous structure signifies a possible functional separation between the left and right hepatic venous inlet.

The foramen ovale

As the name indicates, the foramen ovale is a more or less elliptic opening of the posterior and lower portion of the fetal atrial septum. At nine weeks' gestation, its area corresponds in size to the area of the inferior vena cava (Patten, et al. 1929). At term, the orifice has diminished to 60% of the inferior vena cava cross section. During fetal life, the foramen ovale is partially closed by a thin valve on the left side of the septum. The valve balloons into the left atrium and its valve-like motion has been described during fetal life by applying M-mode ultrasound and 2D-imaging (Allen et al. 1982). The edge of the orifice formed by the atrial septum has been termed the crista dividens or limbus fossae ovalis (Franklin et al. 1940).

During fetal life, the crista dividens is positioned more toward the right atrium than in

postnatal life (Barclay et al. 1944; Barron 1944; Barcroft 1946; Dawes 1968; Rudolph 1985). Accordingly, the position of the foramen ovale inlet is adjusted to oppose the orifice of the inferior vena cava to form a more or less continuous tubular interatrial unit (Figure 1). The Eustachian valve (valve of the inferior vena cava) contributes to this functional unit by forming the anterior right wall of the interatrial tube, an extension of the inferior vena cava.

Postnatal development

The rearrangement of circulation into the postnatal pattern starts immediately after birth. After an instantaneous increase in blood pressure and heart rate, the first breaths are taken and the lungs are filled by air, pulmonary vascular resistance is reduced and the blood flow in the pulmonary arteries and veins increases dramatically (Barclay et al. 1944; Barron 1944; Barcroft 1946; Dawes et al. 1960; Dawes 1968, 1982; Lind 1977; Lind and Wegelius 1954; Peltonen and Hirvonen 1965; Rudolph 1985). The pressure drop in the pulmonary trunk is followed by a reduced or reversed blood flow in the arterial duct which then starts to close.

The umbilical venous flow subsides and the high amount of blood through the ductus venosus, left and medial hepatic vein is correspondingly reduced. The ductus venosus is obliterated within three months (Scammon and Norris 1918; Oliveira et al. 1979; Zink and van Petten 1980a). The net effect is a reduced flow towards the foramen ovale and a reversed pressure gradient across the foramen ovale flap causing the necessary apposition of the flap to the atrial septum (Dawes et al. 1955). During the following weeks and months the foramen ovale closes permanently (Scammon and Norris 1918; Patten 1931; Barclay et al. 1944; Barcroft 1946; Dawes 1982). The patent foramen ovale is a well known clinical problem in pediatrics, and may cause interatrial shunting (Long 1990). It is increasingly recognized, however, that the foramen ovale may remain patent into adult life and constitute a gate for emboli into the general circulation including that of the brain (Hart 1992; Kasper et al. 1992).

Probably based on the same mechanism as the one closing the arterial duct (Cytochrome P-450), the ductus venosus is obliterated (Coceani and Olley 1988; Adeagbo et al. 1989). But in contrast to the arterial duct, no trigger substance has been found that might cause

the sustained contraction of the sphincter of the ductus venosus. From clinical pediatric practice it is known that the ductus venosus is open during the first days of life, and is frequently used during catheterization and transfusion (Hirvonen et al. 1961; Rosen and Reich 1970; Sanders 1978). A recent ultrasound report describes blood flow in the ductus venosus in healthy neonates persisting sometimes beyond three weeks after birth (Loberant et al. 1992). However, the blood velocities described postnatally are lower than what is found during intra-uterine life .

A persistent ductus venosus is a rare but important clinical problem of a portocaval shunt (Barsky et al. 1989; Champetier et al. 1985; Wanless et al. 1985; Zientarski 1976). Its existence is closely connected to an altered liver function. Surgical closure of the ductus venosus in order to improve liver perfusion from the portal vein, however, often has not been a success. A persistent ductus venosus might be a sign of liver disease rather than a cause of liver disease. And the cause might be found in early fetal life.

Physiological background

Blood distribution to the atria

Sabatier suggested in 1774 that the blood from the inferior vena cava was completely and directly drained into the left atrium without an intermediary entrance in the right atrium (reviewed by Dawes 1982). It was inherent that the umbilical venous return of oxygenated blood was included in the inferior caval flow that was directed to the left atrium, while blood in the superior vena cava was directed into the right atrium, an assumption clearly expressed earlier by Haller (reviewed by Barclay et al. 1944). Sabatier's concept implied a difference in the distribution of oxygenated blood to the left and right sides of the heart and a higher oxygen supply to the coronary and carotid circulation. Wolff and Kilian modified the concept and suggested that 2/3 of the inferior vena cava blood entered the left atrium and 1/3 entered the right side (reviewed by Barcroft 1946).

The opposite view that all blood from the inferior vena cava entered the right atrium before further distribution to the left atrium through the foramen ovale, was promoted by Pohlman. Although Pohlman based his conclusions on experimental data, his

conclusions were criticized for the unphysiological conditions of his fetal pigs (Barclay et al. 1944; Dawes 1982). In postnatal life, both the superior and inferior vena cava enter the right atrium, and only there, a pattern that apparantly fits well with Pohlman's concept of prenatal circulation. Additionally, any opening in the atrial septum during postnatal life represents a possibility for shunting of blood across the atrial septum and is considered to be of clinical importance. Such thoughts may have enhanced the acceptance of Pohlman's concept of trans-septal flow which is commonly adopted in modern clinical literature on the fetal foramen ovale (Atkins et al. 1982; Wilson et al. 1989; van Eyck et al. 1990, 1991; Feit et al. 1991).

After Pohlman's pioneering experiments, years followed with systematic studies. To a large extent, the results of those studies supported Wolff and Kilian's concept. The findings by Huggett (reviewed by Barcroft 1946) that oxygen saturation in the carotid arteries of fetal sheep was higher than in the descending aorta but lower than was found in the umbilical vein was confirmed in later works (Barcroft et al. 1940, 1946; Dawes et al. 1954, 1961; Dawes and Mott 1959, 1964; Born et al. 1956; Cross et al. 1959). These results supported the idea of a direct transfer of umbilical blood to the left side of the heart to ensure the oxygen supply to the coronary arteries and cerebral circulation. These researchers found that the difference in oxygen saturation between the carotid artery and the descending aorta was not great (around 10%) and that it was modified during hypoxia, constriction of the aorta, constriction of the umbilical veins or during hemorrhage. The findings suggested that blood flow across the foramen ovale was of high priority.

The angiographic technique was introduced in the late thirties, and gave a dramatic new view into fetal circulation. The angiographic studies in fetal sheep and pre-viable human fetuses demonstrated that the inferior caval blood flow divided into a left (via sinistra) and a right branch (via dextra) separated by the crista dividens of the atrial septum (Franklin et al. 1940; Barclay et al. 1942a, 1944; Barcroft 1946; Lind and Wegelius 1949).

Studies in primates (Behrman et al. 1970) and fetal sheep (Edelstone and Rudolph 1979; Edelstone 1980; Itskovitz, LaGamma, and Rudolph, 1983; Itskovitz et al. 1987) where isotope labeled microspheres were applied gave further support to the concept of a preferential streaming of umbilical blood through the foramen ovale. Particularly during hypoxemia or reduced venous return, the preferential streaming could be demonstrated to maintain the umbilical blood supply to the left atrium (Behrman et al. 1970; Edelstone

and Rudolph 1979; Edelstone 1980; Edelstone et al. 1980; Itskovitz et al. 1983, 1987; Paulick et al. 1990a; Meyers et al. 1991).

In contrast to the normal pattern of a dominating right ventricle, the left ventricle seems to receive relatively more blood during states of reduced umbilical venous return, and the outputs from the two ventricles tend to be more equal in the growth retarded human fetus (Rizzo and Arduini 1991) . The preferential streaming is probably an important component in redistribution of blood within the fetal heart.

To understand the circulation in the fetal heart, several contributing factors have to be taken into account (Dawes 1982; Rudolph 1985). The cephalic venous return generally has a higher oxygen saturation than the abdominal inferior vena cava. The hemiazygos joins the coronary sinus and drains into the right atrium. Although the pulmonary circulation constitutes only 10% of the combined left and right cardiac output in the fetal sheep, it represents an additional admixture in the left atrium. Such contributions to the right and left atrium, representing different degrees of oxygen saturated blood, make the evaluation of the fetal cardiac circulation complicated (Dawes et al. 1954, 1968; Rudolph 1985).

Subdiaphragmatic blood distribution

The ductus venosus is assumed to play an important role in the concept of preferential streaming through the foramen ovale. Although early works suggested a modest blood flow through the ductus venosus (Franklin et al. 1940; Barclay et al. 1942a, 1944; Barcroft 1946), later studies suggested that 50% of the umbilical venous return was shunted directly through the ductus venosus into the inferior vena cava in the fetal primate and the fetal sheep (Behrman et al. 1970; Rudolph and Heymann 1970; Edelstone et al. 1978; Edelstone 1980). Applying a microsphere method, Rudolph et al. (1971) could show that 55% of the umbilical blood was shunted through the ductus venosus of the pre-viable human fetus. The range of the observed shunting, however, was huge (8 - 92%). There are possible errors attached to this method that might cause an overestimation of the ductus venosus flow. The microspheres were supposed to be trapped in the hepatic vasculature. Such an "embolization" could produce an increased resistance and cause a shift of flow to the ductus venosus. Further more, in the case of the fetal sheep, the paired umbilical veins might prevent a complete mixing of the injected bolus in the umbilical venous system and thus contribute to the variation of the results reported.

During induced hypoxemia, hemorrhage or partial clamping of the cord in animal preparations, the proportion of umbilical blood directed through the ductus venosus increases (Behrman et al. 1970; Edelstone et al. 1980; Itskovitz et al. 1983, 1987; Paulick et al. 1990a; Meyers et al. 1991) and maintains a preferential streaming through the foramen ovale. Such reports support the assumption that the ductus venosus is an important regulator of the umbilical venous return. The conclusion is further supported by the fact that the ductus venosus exists in a variety of species (Barron 1944; Barcroft 1946).

The lack of a ductus venosus in some species contradicts the conclusion that the ductus venosus is phylogenetically indispensable. For instance, the mature fetal pig lacks a well defined ductus venosus. But a number of low resistance channels of over 100 μ in diameter seem to transfer the umbilical blood to the inferior vena cava equally well as a normally functioning ductus venosus (Barnes et al. 1979; Silver et al. 1988). Occlusion of the ductus venosus in the mature fetal lamb was shown to increase blood flow through the left side of the liver, but did not alter the hemodynamics of heart and brain or the oxygen saturation in the carotid arteries or descending aorta (Amoroso et al. 1955; Rudolph et al. 1991). The experiments, however, did not address the problem of the function of the ductus venosus in earlier stages of the pregnancy or during serious hypoxia.

Assuming that 50% (or less) of the umbilical blood is directed through the ductus venosus, then the other 50% (or more) enters the liver vasculature, mainly the left and mid portion. A modest oxygen extraction from the circulating blood makes the left and medial portions of the liver an important source of oxygenated blood for further circulation (Bristow et al. 1981, 1982; Townsend et al. 1989). The anatomical arrangement of those vessels is believed to favor the preferential streaming through the foramen ovale in fetal sheep (Rudolph 1985). During hypoxia and reduced venous return in the umbilical vein, the liver seems to augment the blood redistribution through the ductus venosus by an increased vascular resistance (Edelstone and Rudolph 1979; Edelstone 1980; Edelstone et al. 1980; Itskovitz et al. 1983, 1987; Rudolph 1985; Paulick et al. 1990a; Meyers et al. 1991).

An autonomic regulation of fetal venous blood flow has been discussed. A constricting sphincter of the ductus venosus regulated by humoral or neural mediators would enhance the flexibility of blood distribution at the level of the liver and ductus venosus (Barron 1944; Barclay et al. 1944; Barcroft 1946; Born et al. 1956; Pearson and Sauter 1969, 1971; Zink and van Petten 1980b; Rudolph 1985; Paulick et al. 1990b, 1991). Although

in vitro studies have demonstrated both α- and β-adrenergic and cholinergic activity in the sphincteric tissue (Coceani et al. 1984), such sphincteric function has been difficult to show in vivo. Adrenergic and cholinergic agents introduced into the fetal circulation elicit complex hemodynamic responses and make any conclusion on the activity in the ductus venosus less reliable (Dawes et al. 1956; Dawes, 1968; Zink and van Petten 1980b; Paulick et al. 1991). Prostacycline and thromboxane have been suggested as influential upon the contractile elements of the ductus venosus and a cytochrome P-450-mediated mechanism to maintain patency in the ductus venosus much in the same way as in the ductus arteriosus (Adeagbo et al. 1982, 1984, 1989; Morin 1987; Coceani and Olley 1988; Paulick et al. 1990b).

The placenta circulation

The blood pressure in the umbilical artery is responsible for the perfusion of the placenta and the umbilical vein (Dawes 1962). The residual pressure found in the umbilical vein is needed to perfuse the hepatic vascular bed and the ductus venosus to make the blood reach the heart. The arterial pressure, however, is not uniform throughout the pregnancy; it shows an almost exponential development from low pressures in mid pregnancy to high pressures at term (Barcroft 1946; Dawes 1962). This information is, however, drawn from the fetal sheep. The mean arterial pressure in human fetuses was reported to be 15 mm Hg in weeks 19 - 21 (Castle and Mackenzie 1986) which suggests a similar pattern of pressure during human pregnancy but probably at a lower level than for the sheep.

Although no neural regulation of the placental vasculature seems to exist, there are reports that humoral substances such as angiotensin II and prostanoids influence impedance in the fetoplacental vascular bed (Hillier and Karim 1968; Novy et al. 1974; Hosokawa et al. 1985; Parisi and Walsh 1989). In vitro studies have traced local production and distribution of vasoactive substances in the vessels of the cord (Karim 1972; Haugen 1992). The implication of such findings for the in vivo situation for the human fetus still remains to be elucidated.

Induced hypoxemia regularly causes an increased systemic arterial pressure and an increased pressure in the umbilical vein (Born et al. 1956; Reynolds and Paul 1958; Dawes et al. 1959; Dawes, 1962, 1982; Assali et al. 1962; Cohn et al. 1974). This shows the close relationship between the placental circulation and the umbilical venous

return in the fetal lamb. The resistance in the umbilical circuit, however, has been reported to remain unchanged and the umbilical blood flow to increase (Dawes and Mott 1964).

In the growth retarded human fetus, an increased pulsatility index in the umbilical artery blood flow velocity is believed to reflect an increased placental impedance (Reuwer et al. 1984; Erskine and Ritchie 1985; Giles et al. 1985; Schulman et al. 1985; Trudinger et al. 1985; Laurin et al. 1987; Rochelson et al. 1987; Groenenberg et al. 1989; Maulik et al. 1989; Fok et al. 1990). Studies of embolization of the fetoplacental vascular bed in fetal sheep showed that resistance increased and umbilical blood flow decreased (Clapp et al. 1981), and that the pulsatility indices reflected the changes in the capillary cross section, vascular resistance and blood flow (Trudinger et al. 1987; Nimrod et al. 1989). In a mathematical model, however, Thompson (1990) estimated that the degree of embolization had to exceed 70% to cause any appreciable changes in the pulsatility indices. The relationship between umbilical vascular resistance and umbilical artery waveform indices was not reproduced, however, when angiotensin II was infused to raise the resistance to flow in the ovine umbilical circulation (Irion and Clark 1990). Trudinger suggested that the reduced diastolic blood flow velocity in the umbilical artery reflects the reduced vascular cross section at the level of the capillary bed rather than the vascular resistance (Trudinger et al. 1987). The embolization experiments were done with microspheres of 15 μm. The changes found in the placenta of small-for-date pregnancies included the arteries and were correlated to changes in the umbilical artery waveform (Giles et al. 1985; Fok et al. 1990).

Growth retarded fetuses are reported to have a reduced umbilical venous blood flow (Gill et al. 1984; Jouppila and Kirkinen 1984) and, accordingly, a reduced blood volume to be distributed in the liver and ductus venosus. In a state of imminent asphyxia or congestive fetal heart failure, pulsation in the umbilical vein might be found as an indicator of hemodynamic derangement (Lingman et al. 1986; Gudmundsson et al. 1991).

Additional compensatory mechanisms

Fetal respiratory movements do influence the blood flow pattern in the fetus (Dawes, et al. 1972, 1981; Marsál et al. 1984; Chiba et al. 1985; van Eyck et al. 1990, 1991; Spencer et al. 1991). Excessive carbon dioxide induces respiratory movements (Dawes 1968; Chapman et al. 1979; Connors et al. 1989) and may play an active role in

adjusting circulation to varying physiological demands. During respiratory movements the blood flow in the umbilical vein mounts, and may, during high amplitude respiratory movements, reach a 54% increase compared to the blood flow during apnea (Marsál et al. 1984). Such changes in blood flow volume might be an important means of modifying perfusion in the tissues.

Oxygen transport and extraction: More important than the oxygen saturation of the fetal blood is the actual oxygen uptake in the tissues. The tissues have a great ability to extract oxygen from the blood in the fetal sheep (Barcroft 1946; Acheson et al. 1957; Dawes 1961, 1968; Dawes and Mott 1964). Fetal blood with a low oxygen saturation tends to have an increased oxygen transport capacity. Even at an oxygen saturation of 50%, there is usually no reduction in oxygen uptake in the tissues (Acheson et al. 1957; Dawes and Mott 1959). These are powerful compensatory mechanisms to be considered when evaluating circulatory changes in the fetus.

Anaerobic energy supply: Once the oxygen of the umbilical blood is reduced below 50%, the fetus increasingly relies upon glycolysis and anaerobic metabolism (Dawes 1968). The ability of the fetal sheep, particularly the premature fetus, to survive total restriction of oxygen is remarkable. Fetal lambs seem capable of surviving sustained anoxia for 40 minutes in mid-pregnancy and term fetuses for a period of 10 - 15 minutes (Dawes et al. 1959).

Ultrasonographic examination

2D-imaging

Due to a period of rapid technical development, ultrasound imaging devices have become an indispensable part of obstetrical care. The gray scale technique and real-time operation of the machines enable the operator to do a detailed and instantaneous study of fetal structures. In general, the high frequency ultrasound transducer (for example 7 MHz) provides pictures of higher resolution but with a poorer penetration in the tissues than the low frequency transducer (e.g. 3 MHz), which has an impaired resolution but better penetration. During the course of pregnancy, the choice of equipment varies and is a trade-off between resolution and penetration.

Applying an ultrasound transducer of 3 MHz with an axial resolution of 0.5 mm, the accuracy of diameter measurement was reported to have SE = 0.25 mm in the case of the umbilical vein (Gill 1979; Gill et al. 1981). Eik-Nes et al. (1982, 1984) reported SD = 0.26 mm for the difference between observers in the case of the umbilical vein, and SD = 0.28 mm in the case of the fetal aorta. The intra-observer variation for the umbilical vein was SD = 0.2 mm and for the fetal aorta SD = 0.15 mm. Comparing M-mode to real-time technique, they found that the differences did not exceed 0.4 mm. Applying real-time equipment for measurements of intracardial orifices in the fetus, Beeby et al. (1991) reported that the inter-observer differences had SD = 0.6 - 2.0 mm and the intra-observer difference SD = 0.3 - 2.2 mm. These authors concluded that the method is of limited value when used for calculating fetal cardiac flow rates.

Computerized processing of the ultrasound signals has improved the image quality. Such postprocessing, however, requires time. During examination of the fetal heart with a frequency of 110 - 160 beats/min a high frame rate on the ultrasound machine is required in order to correctly visualize the rapidly moving structures. Such requirements restrict any extensive postprocessing. Under such circumstances the quality of the image will depend on a well focused unit. Mechanical sector scanners with annular array tend to have a narrower focus than the electronically focused units.

Doppler velocimetry

Both continuous and pulsed Doppler equipment is widely used in obstetric ultrasound evaluation. Continuous Doppler insonation has the advantage of recording all movements along the insonation axis, ensuring that the maximum velocity is included in the signals displayed – a commonly desired recording. The pulsed Doppler technique permits the observer to select signals from a specific depth of insonation (sample volume) as assigned by a pair of calipers on the 2D-image. Both techniques require that the cross section of the vessel be properly covered by the interrogating ultrasound to record all velocities in the vessel. The advantage of the pulsed Doppler technique is that it excludes signals from structures outside the sample volume. The subdiaphragmatic vasculature is densely woven and the velocimetric studies of the different vessels (inferior vena cava, ductus venosus, hepatic veins and renal arteries) take advantage of such a technique. By reducing the sample volume in the axial direction, even signals from small vessels can be specifically picked up. With the reduced sample volume, however, there is an increased risk of not recording all the velocities in the investigated vessel. It is important to be

aware of this risk when the maximum velocity is the reference velocity, or when the mean velocity in the vessel is to be calculated.

The reduced sample volume reduces interference in the axial direction but the lateral extension of the recorded volume remains unchanged. This is of importance particularly in the first trimester with the small distances between important vessels in the fetus.

Another disadvantage of the pulsed Doppler technique is the reduced ability to record high velocities at greater depth (Hatle and Angelsen 1982). This limitation, however, depends on the emitted Doppler ultrasound frequency: The higher Doppler frequency and the wider distance of sampling, the lower the maximum velocity that can be recorded. In a practical situation, at a depth of 7 cm velocities up to 0.87 m/s can be measured with a 5 MHz transducer, 2.17 m/s with a 2 MHz transducer and 4.34 m/s with 1 MHz transducer. But no such limit exists for the continuous Doppler.

Although information about the blood flow velocity in different fetal vessels is interesting information, information about the blood volume flow is more useful. In vitro experiments have shown a good correlation between the Doppler ultrasound measured flow and the true flow, but with a small systematic overestimation of 4.4% (Rasmussen 1987). For in vivo Doppler ultrasound measurements of blood flow, Rasmussen found a coefficient of variation of 5.6 - 9.4% for the fetal aorta and 6.8% for the fetal umbilical vein. The coefficient of variation for the pulsatility index in the descending aorta was 9.8% . Comparing Doppler ultrasound measurements to electromagnetic blood flow measurements in the descending aorta in the pig Eik-Nes et al. (1984) found a good correlation (R = 0.91) and no systematic error. For the fetal aorta there is a variation of diameter during the heart cycle. The error of not calculating aortic blood flow from the simultaneous diameter and velocity measurements is less than 8% and probably of little practical importance (Stahle et al. 1990).

Nimrod et al. (1989) found a satisfactory correlation (R = 0.89) between the peak systolic and diastolic velocity ratio based either on electromagnetic flow measurement or Doppler velocimetry in the umbilical artery of the fetal sheep. During acute embolization, the systolic/diastolic velocity ratio correlated (R = 0.86) with the placental vascular resistance.

The angle of insonation is an important factor affecting the accuracy of Doppler velocimetry (Gill 1979; Eik-Nes et al. 1982, 1984). With an insonation angle exceeding 60 degrees, the SD of the corrected flow measurements rapidly increases passing 20%.

The diameter measurements seem to be the most vulnerable point in Doppler based blood flow measurements (Eik-Nes et al. 1980, 1982; Gill et al. 1981; Beeby et al. 1991). This applies in particular to vessels of diameter 6 mm or less which are quite commonly found in the human fetus. With the previously mentioned variation in diameter measurement, the error of volume flow calculation in a vessel of 4 mm might mount to 25%.

Color Doppler visualization

Color Doppler provides information about velocity from a wider area of insonation and displays the direction and magnitude of velocity superimposed on the gray scale image. The flow towards the transducer and away from the transducer are coded by different colors (e.g. red and blue), and increasing velocities are usually coded by increasing intensities of colors or by different colors. Variance in velocities, which can be seen in turbulence, can be coded in a different color (e.g. green or yellow).

Like pulsed Doppler, color Doppler has an upper limit for recording velocities unambiguously. If the corresponding limit of the Doppler shift, called the Nyquist limit (N), is exceeded, the velocity will be ambiguously presented as aliasing and the velocities will be displayed as velocities of a different direction or as variance. No aliasing occurs if the Doppler shift does not exceed half of the pulse repetition frequency (prf): $N < prf/2$. In order to record higher velocities correctly, the pulse repetition frequency can be increased. Especially towards the end of the pregnancy, an increasing distance to travel for the Doppler pulse requires an expanded time between the pulses. Such accommodations restrict the value of the pulsed Doppler velocimetry and the color Doppler. The introduction of the autocorrelation principle into color Doppler technology reduced the processing time drastically, and improved the real-time imaging of flow (Taylor et al. 1988).

Safety

Ever since it was realized that Roentgen radiation and nuclear radiation have deleterious biological effects, there has been concern whenever the pregnant woman has been exposed to new techniques or agents. The question of whether the low energy levels

used in diagnostic ultrasound have any biological effect, is a pertinent one. An increasing number of studies have addressed the question (reviewed by Maulik 1989). The largest survey conducted is included in a Canadian report involving 340 000 patients and 1.2 million examinations (Environmental Health Directorate. Safety code 23, 1981). The report did not identify any adverse effect clearly attributed to the acoustic energy load. Dyslexia has been suggested as a result of intra-uterine exposure to ultrasound (Stark et al. 1984). This was not confirmed in a randomized trial (Salvesen et al. 1992a, 1992b, 1993). Neither were any other adverse effects on the human development demonstrated. In the trail of continued biosafety research, non-right-handedness was suggested as a possible result of ultrasound exposure in gestational week 17 - 20 (Salvesen et al. 1993). This possibility has not yet been addressed in any other study. It has been assuring that vigilance is maintained in the ultrasound centers resulting in a steadily growing list of publications on the issue of safety. So far, the investigations have not revealed any reproducible adverse effect in mammalian tissue by the ultrasound exposure of Ispta < 100 mW/cm^2, which corresponds to an energy setting hardly exceeded by any ultrasound equipment in general obstetrical use, including the Doppler ultrasound units. In 1988 the American Institute of Ultrasound in Medicine (AIUM) gave a revised recommendation for the levels of energy exposure for a safe ultrasound examination. The limit for the spatial peak temporal average intensity (Ipsta) in tissue was set to 100 mW/cm^2. Although cavitation in the tissues is a possible effect of ultrasound, more is known about the thermal effect. There is an increasing awareness of the rise of temperature in tissues exposed to Doppler ultrasound (Carsten et al. 1987; Abraham et al. 1989; Miller and Ziskin 1990). Although no new information has indicated any change in the advocated limits of energy for the ultrasound exposure, it has been recommended not to expose the human embryo to Doppler ultrasound (European Federation of Societies for Ultrasound in Medicine and Biology 1993) and to practice prudence in diagnostic ultrasound (Merritt et al. 1992).

Estimation of pressure gradient based on Doppler velocimetry

Although blood flow is the single most important information about the circulation that reflects physiological function, hemodynamics are not completely described unless pressure and resistance or impedance are included. Pressure and resistance to flow attract special interest in conditions such as arterial stenosis or valvular leakage. In 1976 Holen applied the knowledge condensed in the generalized Bernoulli equation to calculate

pressure gradients based on the non-invasive velocimetric method of Doppler ultrasonography. He showed that the generalized Bernoulli equation:

$$\Delta p = \tfrac{1}{2}\rho(V_2^2 - V_1^2) + \rho\int_1^2 \frac{\partial V}{\partial t}\, dx + R(V)$$

for practical clinical use could be simplified to $\Delta p = 4V_2^2$. He showed that the measurement was reproducible in the conditions where V_2 represented a high velocity compared to V_1. The method was further substantiated and quickly gained acceptance in a variety of circulatory studies and proved particularly useful in studying cardiac lesions such as valvular stenosis and regurgitation (Holen et al. 1977; Hatle et al. 1978; Hatle and Angelsen 1982; Skjaerpe et al. 1985; Skjaerpe and Hatle 1986). However, the method must be evaluated in regard to the physical conditions of intra-uterine life before it is applied to fetal circulation.

BASIC ASSUMPTIONS AND AIMS OF THE STUDIES

The aim of the present study was to identify by ultrasound the human ductus venosus in intra-uterine life, to describe its normal blood flow velocity pattern during the last half of pregnancy, to evaluate the reproducibility of the ductus venosus velocimetry, and to suggest a methodological standard (I).

Modern clinical work has commonly been based on the concept of the foramen ovale as a inter-atrial communication. This view contrasts with the concept advocated by the fetal physiologists that the foramen ovale receives its blood directly from the inferior vena cava. Fetal lamb studies have suggested a preferential streaming from the ductus venosus through the foramen ovale to the left heart. The present study addressed these issues and aimed to describe the functional relation between the ductus venosus and the foramen ovale in the human fetus. The position of the inferior vena cava and hepatic veins and their corresponding blood flow patterns were described to elucidate their function in the distribution of umbilical venous blood (II).

It was assumed that the ductus venosus blood velocity might reflect changes in central venous hemodynamics or alterations due to reduced umbilical venous return from the placenta. A corresponding alteration in the ductus venosus blood flow velocity would provide new possibilities to apply ductus venosus velocimetry as a diagnostic tool in assessing fetal hemodynamics. This question was addressed by investigating cases of fetal cardiac disease (III) and cases complicated by serious intra-uterine growth retardation (IV).

There is a close relationship between velocity and pressure in blood flow. Since the ductus venosus is a direct communication between the umbilical vein and the central venous system, the ductus venosus blood velocity was assumed to reflect the pressure gradient between the two venous systems. Measurement of the pressure gradient across the ductus venosus would probably represent vital information about the distribution of oxygenated umbilical blood in the fetus. The central venous pressure is another keystone in hemodynamics; this pressure could possibly be calculated as the difference between the umbilical pressure and the ductus venosus pressure gradient. The present study aimed at exploring the possibility of a non-invasive measurement of the pressure gradient across the ductus venosus based on Doppler velocimetry (V).

MATERIAL AND METHODS

Study populations

31 healthy pregnant women were recruited to be included in a longitudinal study of the ductus venosus (I and V) and to establish normal values for the umbilical vein blood velocity (V) and flow (IV), and normal values for the umbilical artery pulsatility index (PI) (IV). Because of deviations from the protocol, two were withdrawn from the study – one started smoking and one moved – leaving 29 for inclusion. Each of these 29 women had an uneventful pregnancy and delivery of a normal neonate. Gestational age was assessed by ultrasound before week 20 and the women were examined every 3-4 weeks until term.

In order to evaluate the sample site for the ductus venosus velocimetry, 33 unselected patients (gestational week 22 - 34) were studied (I). The intra-observer variation for the ductus venosus velocimetry was studied in 27 unselected patients (week 18 - 34) (I).

108 healthy pregnant women were included in a cross-sectional study to evaluate the topographic and functional relation between the ductus venosus, foramen ovale, inferior vena cava and hepatic veins (II). Five participants were withdrawn due to miscarriage or malformations detected after birth. The remaining 103 delivered normal babies. They were examined once (week 15 - 40).

30 cases (week 17 - 35) with known fetal cardiac disease (28 with congenital heart defects and two with supra-ventricular tachycardia) were included to explore the diagnostic possibilities of the ductus venosus velocimetry (III). 16 cases had abnormal karyotypes.

Of 53 cases of serious intra-uterine growth retardation (< 2.5 centile according to the ultrasound findings) 38 actually had a birthweight ≤ 2.5 centile (Keen and Pearse 1985; Yudkin et al. 1987), had no malformations or chromosomal aberrations, and were included for the evaluation of the ductus venosus velocimetry and umbilical circulation (IV). 22 women reported smoking, one had cardiolipin antibodies, one had protein C deficiency, one was under treatment for hypertension, and eight developed pregnancy-induced hypertension. There were seven intra-uterine fetal deaths and four postnatal deaths. The fetuses were examined 0 - 40 days before delivery.

Methods

Ultrasound equipment

A Vingmed CFM 750 ultrasound scanner (Vingmed Sound, Horten, Norway) was used throughout the study period. A 5 MHz annular array mechanical sector transducer carrying a 4 MHz Doppler unit was used with a spatial peak temporal average intensity (Ispta) set to 2 - 5 mW/cm^2 for the sector scan, 2 mW/cm^2 for the color flow, and 45 mW/cm^2 for the pulsed Doppler. Alternatively, a 3.75 MHz annular array transducer carrying a 2.5 MHz Doppler unit was applied with an Ispta setting of 2 - 6 mW/cm^2 for the sector scanner, 3 mW/cm^2 for the color flow, and 10 - 49 mW/cm^2 for the pulsed Doppler.

2D-imaging

Gestational age was assessed by biparietal diameter (BPD) before week 20 (I-V), or by crown-rump length (CRL) in early pregnancy (IV).

Intra-uterine growth was assessed by BPD and mean abdominal diameter (MAD) and rated according to a nomogram by Eik-Nes and Grøttum, Scan-Med a/s, Drammen, Norway (IV).

The inner diameter (D_{UV}) of the intra-abdominal portion of the umbilical vein was measured in a longitudinal section of the straight portion of the vein (IV).

The position, direction, shape, length, and the inner width of the inlet and outlet of the ductus venosus were studied (I and V).

The topographic position of the ventricular septum, the left, medial and right hepatic veins were assessed in horizontal transections of the fetal torso, and their angle to the medial line was measured (II). The initial portion and the proximal portion of the ductus venosus were compared to the proximal portion of the inferior vena cava and the angle between them was noted (II). The abdominal portion and the proximal portion of the inferior vena cava were compared to the direction of the spine and the aorta and the angle between them was noted (II). The position of the atrial septum with the crista dividens,

the foramen ovale flap and the Eustachian valve were described in horizontal sections, coronary sections or oblique and tilted coronary sections (II).

Color Doppler

In addition to 2D-imaging, the color Doppler technique was applied to identify the umbilical artery (IV), umbilical vein (III-V) and the ductus venosus (I-V) in order to do the pulsed Doppler velocimetry. Color Doppler was specifically used to identify blood flow positions and directions in the ductus venosus, hepatic veins, inferior vena cava and foramen ovale (II).

To identify an atrioventricular regurgitation the color Doppler was applied with a filter of 0.49 m/s for the 3.75 MHz transducer and 0.27 m/s for the 5 MHz transducer (III-IV).

Doppler velocimetry

Blood flow velocity was recorded using pulsed Doppler technique at the smallest possible angle of insonation. The velocity values were corrected for the angle of interrogation in all measurements except for the umbilical artery.

The umbilical artery was identified by 2D-imaging and color Doppler in a free sling of the cord and pulsed Doppler signals were recorded with a liberal sample volume (IV). The simultaneous recording of a stable umbilical vein blood velocity ensured the state of fetal quiescence. The pulsatility index (PI) and the heart rate were calculated from the envelope tracing of the maximum Doppler frequency shift during 4 - 8 heart cycles. The calculations were done off line in the computer program Echodisp. PI above the 95% reference ranges was regarded as an elevated PI.

The umbilical vein was identified by 2D-imaging and color Doppler in the fetal abdomen (III - V). A wide sample volume was applied to cover the section of the vein in the straight portion. The Echodisp computer program was used to calculate the maximum velocity (V_{UV}) from the envelope of the maximum Doppler frequency shift during two seconds. Only signals acquired during fetal quiescence were included in the statistics. Assuming a parabolic velocity profile, the blood flow in the umbilical vein (IV) was calculated by:

$$\tfrac{1}{2} V_{UV} \cdot \pi \left(\tfrac{D_{UV}}{2}\right)^2$$

A value below the 95% reference ranges was considered to be reduced umbilical blood flow. Pulsation in the intra-abdominal umbilical vein was noted whenever there were increnations of the maximum velocity shift with a frequency corresponding to the heart rate (III - IV).

The ductus venosus was identified by 2D-imaging and color Doppler as a narrow extension of the abdominal umbilical vein (I - V). Identification was accepted when the ductus venosus was shown to connect the umbilical sinus to the inferior vena cava (I - V). The blood flow velocity was recorded at the isthmic inlet with a sample volume of 4 - 10 mm. An expanded sample volume was applied for simultaneous recordings of the IVC and the ductus venosus in order to compare the ductus venosus blood velocity pattern to the pattern found in the IVC (I). To assess the best sampling site, recordings were done at the inlet, the mid-portion and the outlet of the ductus venosus (I). Intra-observer variation for the standard procedure of the DV velocimetry was studied in pairs of observations (I). The participants left the examination room for a short period between the first and the second examination (median interval 24 min, range 4 - 52).

Estimation of pressure gradient

The pressure gradient across the ductus venosus (Δp_{DV}) was estimated by applying the Bernoulli equation (Holen et al. 1976)

$$\Delta p_{DV} = 4(V_{DV}^2 - V_{UV}^2)$$

based on the blood flow velocity measured in the ductus venosus (V_{DV}) and the blood flow velocity in the intra-abdominal umbilical vein (V_{UV}) (V). Estimation of the Δp_{DV} during respiratory movements was based on the V_{DV} only, neglecting the V_{UV} (Hatle et al. 1978) (V).

Statistical analysis

Normal blood velocity patterns in the ductus venosus and the estimated pressure gradients across the vessel were described by a linear regression and 95% confidence intervals for individual observations, probably more correctly termed prediction intervals (I and V). The results of the umbilical vein blood velocity were presented with a regression line and 95% confidence intervals for individual observations (prediction intervals) after a logarithmic transformation of the velocity values (V). The Shapiro-Francia test was applied to ensure a normal distribution of the data.

The 95% prediction intervals for the ductus venosus blood flow velocities, for the umbilical venous blood flow, and for the pulsatility index for the umbilical artery blood flow velocity were used as reference ranges in the study of fetal cardiac diseases (III) and in the study of IUGR (IV).

The results of the measurements of the angle of the ventricular septum, inferior vena cava, ductus venosus and hepatic veins were presented with their mean values and SD (II).

The reproducibility (intra-observer variation and variation according to site of sampling) was assessed by the limits of agreement (I) (Bland and Altman 1986; Bailey et al. 1989; Sarmandal et al. 1989). The limits of agreement express the ranges for the mean difference (d) between pairs of observations and are calculated as the 95% CI of d (d $\pm 1.96SD = [l_1; l_2]$). The standard error of the limits of agreement (SE(l)) is t-distributed and calculated by

$$SE(l) = \sqrt{3(SD)^2/n}\,.$$

Thus, the 95% CI for l_1 and l_2 (referred to as the true limits of agreement) can be calculated:

$$\left[l_1 - t_{\alpha/2,n-1}SE(l);\ \ l_1 + t_{\alpha/2,n-1}SE(l)\right].$$

$t_{\alpha/2,n-1}$ is the significance limit.

Fisher's exact test was applied to assess the difference in distribution between groups in the study of cardiac malformations (III) and in the study of IUGR (IV).

RESULTS AND COMMENTS

Description of the ductus venosus: location, shape and size

The present study showed that the ductus venosus could regularly be identified in the human fetus applying ultrasound imaging and color Doppler techniques (I-II). The ductus venosus was visualized in an oblique transection of the upper fetal abdomen, or even better in a mid-sagittal section. It was recognized as a slender trumpet-like communication between the umbilical sinus and the inferior vena cava. The direction seemed to be slightly to the left side and the inclination increased by 5 degrees until it entered the left side of the inferior vena cava at an angle of 48 degrees (II). The entrance into the inferior vena cava was closely linked to the left and medial hepatic vein (II).

Of the geometrical measurements of the ductus venosus the following were obtained: length N = 75, isthmic width N = 60, and outlet width N = 24) (V). The results were incomplete especially after 34 weeks but might indicate a continuous but modest growth during the last half of the pregnancy (V). At 18 - 23 weeks' gestation, the ductus venosus measurements were: length 7.1 ±1.7 mm, isthmic inlet 0.8 ±0.3 mm and outlet 1.6 ±0.4 mm. And at 31-40 weeks the corresponding measures were: length 13.6 ±3.3 mm, isthmic inlet 1.2 ±0.5 mm, and outlet 2.6 ±0.8 mm.

The accuracy of such measurements may be questioned. When measuring the fetal aorta and umbilical vein, the accuracy was reported to be within the level of 0.4 mm (Eik-Nes et al. 1982, 1984). The measurements of the ductus venosus have obvious limitations, especially with the isthmic portion which has an inner diameter around 0.8 mm at 20 weeks. and hardly exceeded 2 mm during the rest of the pregnancy.

Normal blood flow velocity in the ductus venosus

Doppler velocimetry was possible in all instances (184 observations) and a high velocity was demonstrated during the last half of the pregnancy that was comparable to the velocity otherwise only seen on the arterial side (I). Typically, there was a variation in maximum velocity during the heart cycle much in the same way as seen in the inferior vena cava. A peak velocity (V_{peak}) was described during the ventricular systole, another

peak during the ventricular diastole and a nadir (V_{min}) during the atrial contraction. In contrast to the blood velocity in the inferior vena cava and hepatic veins, the ductus venosus blood flow velocity remained orthograde during the atrial contraction. In 11% of the recordings, however, there was a less obvious or absent peak during the ventricular diastole and in 3% there was no nadir (I).

63 observations were done during fetal respiratory movement. The ductus venosus blood flow velocity showed substantial variations. Towards the end of the pregnancy, velocities exceeding 200 cm/s were noted during fetal inspiratory movements. Such velocity changes indicate that fetal respiratory movements may have a tremendous impact on fetal circulation.

Ductus venosus velocimetry: standardization and reproducibility

The recording of the ductus venosus blood velocity was done with a pulsed Doppler unit to reduce interference from other vessels. The sample volume was kept wide (4 - 10 mm) to ensure that the maximum velocity was included in the recording. The sample volume was placed at the initial part of the ductus venosus. In order to ensure identification and to have the right direction for angle correction, efforts were made to visualize the ductus venosus by 2D-imaging and by color Doppler to show the vascular continuity from the umbilical vein to the inferior vena cava . Of the 184 measurements of blood velocity, 71 were made with an angle correction < 30 degrees. These results did not differ from the rest (I).

The intra-observer variation was studied with the standardized technique of velocity recording at the ductus venosus entrance (I). The limits of agreement were [-13; 12] for the V_{peak} and [-15; 12] for the V_{min} measured in cm/s. The corresponding coefficient of variation was 8.7% for V_{peak} and 15.0% for V_{min} (cm/s).

In the study of reproducibility according to sample site, the most uniform results were achieved when recording at the isthmic entrance or in the mid-portion of the ductus venosus (I). There was no difference in the mean results gained at the entrance and in the mid-portion, but the limits of agreement were rather wide: [-20; 20] for V_{peak} and [-16; 20] for V_{min} (cm/s). There was a slight reduction (11%) in the velocities measured at the outlet compared to the inlet, and the limits of agreement increased. The results show that

wide ranges of variation have to be accepted for the ductus venosus velocimetry and that the best repeatability is found in the initial portion of the vessel.

The individual measurements varied considerably during the pregnancy although the measurements were standardized to be done during fetal quiescence (I). The presented studies emphasize the wide biological variations and the methodological limitations that must be considered when ductus venosus velocimetry is put in to clinical use.

The relationship between the ductus venosus and the foramen ovale

In the cross-sectional study which included 103 healthy singleton pregnancies, a close relationship between ductus venosus and the foramen ovale was described (II). As mentioned previously, the course of the ductus venosus was rather steep upwards and dorsally, slightly to the left side where it joined the left and posterior portion of the inferior vena cava. The inferior vena cava widened substantially at the level of the inlet of the ductus venosus and hepatic veins. A continuous blood flow could be traced from the umbilical vein through the ductus venosus, traversing the left compartment of the inferior vena cava, and filling the tube formed by the foramen ovale flap and the atrial septum (Figure 3a). This seemed to constitute a well defined left pathway which crossed and touched the blood stream from the abdominal inferior vena cava which traveled along the right compartment of the inferior venous inflow (Figures 3b and c). Turbulence could be traced in the interface between the two pathways (Figure 12 in II). The degree of mixture of the two streams probably depends on the position, the direction and the velocity in the two streams. The present results suggest that in the human fetus, there is a preferential streaming from the umbilical vein to the left atrium much in the same way as has been described in the fetal sheep and it may constitute an important way of ensuring oxygenated blood supply to the coronary and cerebral circulation in the human fetus. Furthermore, the present results deem it unlikely that the venous blood first enters the right atrium and than continues to the left atrium by a transatrial flow, as has been assumed in recent publications (Atkins et al. 1982; Wilson et al. 1989; van Eyck et al. 1990, 1991; Feit, et al. 1991).

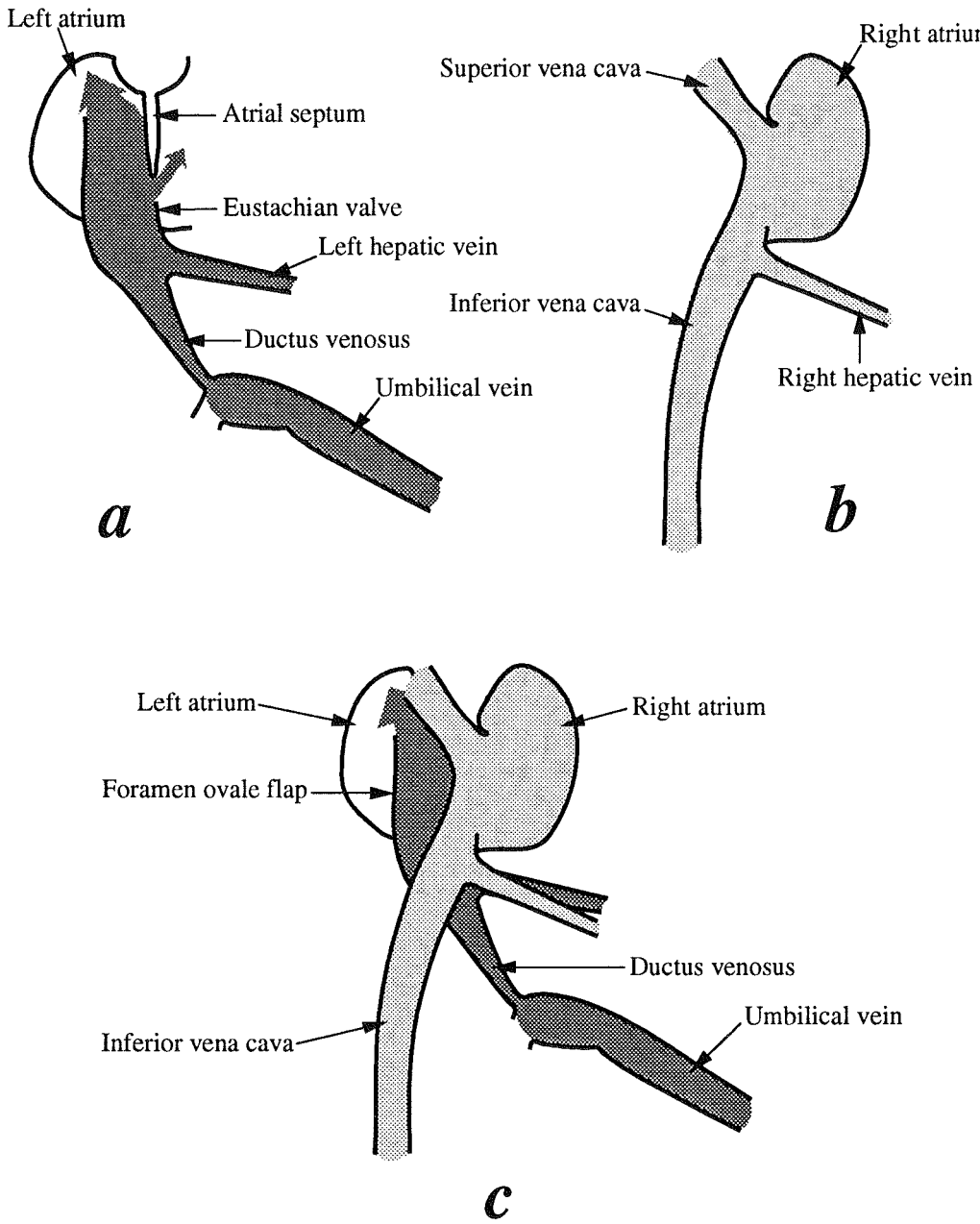

Figure 3: ***a)*** *A left pathway for oxygenated blood was described as starting in the umbilical vein, passing the ductus venosus and traversing through the left compartment of the inferior vena cava in the posterior direction to enter the foramen ovale and the left atrium. An overflow to the right atrium was recorded below the atrial septum.* ***b)*** *A right pathway for deoxygenated blood was described as starting in the abdominal inferior vena cava, passing through the right compartment of the inferior vena cava to direct the blood anteriorly into the right atrium.* ***c)*** *The two pathways touched and crossed at average angle of 48 degrees in the proximal portion of the inferior vena cava.*

The hepatic veins – location and blood flow direction

The results of the study support the assumption that there is a functional difference between the left and the right portion of the liver (II). The left and medial hepatic veins joined more or less completely as they entered the left portion of the proximal inferior vena cava together with the ductus venosus (Figure 4). The direction of these vessels pointed towards the foramen ovale flap. The flow direction into the foramen ovale seemed to be facilitated by the position of the heart which turned 45 degrees toward the left side. An oblique coronary transection could visualize that the left and medial hepatic vein drained into the foramen ovale (Figure 11. in II). This was achieved by the left portion of the Eustachian valve which separated the venous inlet from the right atrium. By using color Doppler imaging the blood flow from the left and medial hepatic vein could be followed into the foramen ovale.

The study also showed that the right hepatic vein joined the right portion of the inferior vena cava (Figure 10 in II). Again the results from animal studies seem to be reproduced in the human fetus. In fetal sheep, the left and mid portion of the liver receives a large proportion of the oxygenated umbilical blood and delivers the blood into the inferior vena cava after a modest oxygen extraction. The right part of the liver receives most of the portal blood mixed with umbilical blood. As a result, the blood that leaves the right part of the liver has a lower oxygen saturation than blood from the left side of the liver. Thus the topographical arrangement of the hepatic veins and their blood flow patterns described in the present study supports a similar functional arrangement in the human fetus as is described in fetal sheep.

The inferior vena cava

Although the abdominal portion of the inferior vena cava initially seems to run parallel to the aorta in the sagittal section, the present study revealed that the proximal portion of the inferior vena cava turns forward, 21 degrees anteriorly compared to the direction of its inferior portion, and 13 - 14 degrees compared to the spine and aorta (II). By insonating in a sagittal direction along the abdominal inferior vena cava and its right sub-diaphragmatic portion, color Doppler imaging showed the blood flow projecting into the right atrium to join the superior vena cava flow. This pathway seemed to constitute a

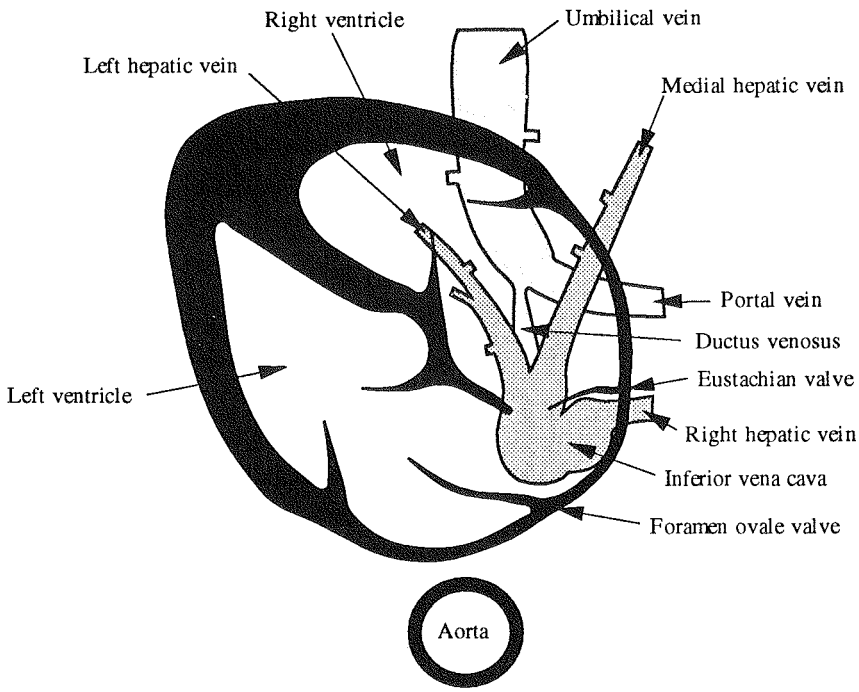

Figure 4: A transverse view illustrates the results of the study on the location and direction of the fetal heart and the subdiaphragmatic venous system. The ventricular septum points 45 degrees to the left of the mid-sagittal plane. The proximal portion of the inferior vena cava seems to be divided functionally in a left and right compartment. The left and medial hepatic veins together with the ductus venosus are connected to the left compartment, and the right hepatic vein to the right compartment.

separate right functional unit draining deoxygenated blood into the right atrium avoiding extensive mixture with the umbilical blood following the left pathway towards the left atrium.

It was not possible to assess the degree of mixture of the two streams employing the existing technology. During the color Doppler recording a spillover from the left pathway into the right atrium was often recorded (Figure 9 in II). Judging from the color flow patterns, it is tempting to suggest that the oxygenated blood delivered by the ductus

venosus, left and medial hepatic veins is abundant for the left side. What is not received by the left atrium could spill over to the right side. Such a thought is not in contradiction with the relatively high oxygen saturation found on the right side. Probably, the mechanisms of distributing oxygenated and deoxygenated blood in each of their compartments of the heart is most important during periods of increased oxygen demand or during reduced delivery of oxygenated umbilical blood.

Estimation of the pressure gradient across the ductus venosus

In 158 of the observations done in the longitudinal study of 29 normal pregnancies, paired observations of the blood flow velocity in the ductus venosus and the intra-abdominal portion of the umbilical vein were made in order to estimate the pressure gradient across the ductus venosus (V). The pressure gradient varied during the heart cycle in accordance with the changing ductus venosus velocity, and was found to be between 0 - 3 mm Hg with hardly any change of range during gestational week 18 - 40. Comparing these results with the existing pressure measurements in fetal lambs and human fetuses (Barcroft 1946; Dawes et al. 1955; Dawes 1968; Rudolph 1985; Castle and Mackenzie 1986; Nicolini et al. 1989; Weiner et al. 1989), the values seem to be within reasonable ranges. A final confirmation of how well the estimation based on Doppler velocimetry reflects the actual pressure across the human ductus venosus will first be known when the direct and simultaneous measurements of velocity and pressures in utero can be made.

58 observations during fetal respiratory exercise showed large variations of the pressure gradient. During expiratory movements, the pressure gradient across the ductus venosus could reduce to values below zero. During inspiratory movements, however, pressure gradients exceeding 20 mm Hg were sometimes estimated during the last weeks of the pregnancy.

Such a pressure estimation ($\Delta p_{DV} = 4(V_{DV}^2 - V_{UV}^2)$) is based on assumptions and simplifications and has inherent possibilities for errors. The generalized Bernoulli equation

$$\Delta p_{DV} = \tfrac{1}{2}\rho(V_{DV}^2 - V_{UV}^2) + \rho \int_{UV}^{DV} \frac{\partial V}{\partial t}\, dx + R(V)$$

takes into account some of those possibilities. The second term

$$\rho \int_{UV}^{DV} \frac{\partial V}{\partial t}\, dx$$

represents the inertia with a similar pressure development as that expressed in the first term of convective pressure, but with a small time lag (Hatle et al. 1978). Angelsen discussed this in the case of mitral stenosis and showed that it can be omitted (Hatle and Angelsen 1982).

The last term, R(v), represents the viscous pressure loss and, when it is omitted, might cause a corresponding underestimation of the pressure gradient. In the case of the ductus venosus, R(v) was estimated to be in the order of 0.1 mm Hg applying Navier-Stokes equations (the basic equations for movements in fluids) (Fung 1981, 1984). In the calculations, an average ductus venosus geometry for 34 weeks' gestation was assumed (length 15 mm, inlet 1.5 mm and outlet 3 mm), and a flat velocity profile at the entrance was believed to develop into a parabolic profile during the course of the ductus venosus. The velocity was set to 75 cm/s and the calculation was done for a Newtonian fluid.

Another major factor which could influence the pressure estimation was the convective pressure recovery along the ductus venosus. In the case of the mitral stenosis, it was deemed unnecessary to include this factor in the estimation. In the ductus venosus, however, the isthmus appeared as a discrete stricture which might permit a recovery of pressure. In that case, the Δp_{DV} deducted from the velocimetry would be systematically overestimated. Assuming the mentioned geometrical pattern at 34 weeks, a blood flow velocity of 0.75 m/s at the inlet, and a blunt velocity profile which evolves into a parabolic profile along the course of the ductus venosus would result in a 50% reduction in velocity at the outlet, and a convective pressure recovery in the order of 1.7 mm Hg as estimated by the Navier-Stokes equations (Fung, 1981, 1984) for a Newtonian fluid. Actually, the maximum velocities recorded at the ductus venosus outlet was not reduced by 50% compared to the velocities at the isthmic inlet. The velocity reduction was around 11% (I). The diverging shape of the ductus venosus and the non-Newtonian properties of blood both tend to give an elongated velocity profile with high axial velocities. Such a velocity profile seems more in agreement with the measured velocity values and implies that the error in pressure estimation of 1.7 mm Hg due to convective pressure regain, probably is much too high.

Turbulence is another important factor which drastically increases viscous resistance. The development of turbulence depends on the properties of the wall, dimensions of the vessel, viscosity and velocity. The Reynolds number expresses this relationship (Fung

1984). Values above 2 300 are usually associated with the development of turbulence. For the isthmic portion of the ductus venosus with diameter ≤ 2.5 mm and velocity ≤ 0.9 m/s (extremes of normal ranges) the Reynolds number remains below the critical value. Higher velocity (such as during respiration) and increased diameter of the vessel will probably be associated with turbulence. Pulsatile velocity, however, tends to counteract the development of turbulence. The appearance of turbulence tends to further reduce any overestimation of the Δp_{DV}. From this discussion it can be inferred that the methodological limitations have to be defined and quantified before the suggested method of pressure estimation across the ductus venosus can be accepted as another parameter in assessing fetal hemodynamics.

Diagnostic possibilities with ductus venosus velocimetry

Blood velocity and pressure gradient. The distribution of the oxygenated blood returning through the umbilical vein depends on the pattern of resistance in the ductus venosus and liver vasculature, on the pressure established in the umbilical vein and on the central venous pressure met in the heart and IVC. Any alteration in the gradient between those two pressures would possibly cause a change in the ductus venosus blood flow velocity and accordingly afford a new diagnostic possibility (Kiserud 1991). The estimated pressure gradient of 0 - 3 mm Hg across the ductus venosus gives an idea of the normal ranges that exist for the perfusion of the ductus venosus and hepatic vascular bed (V). Once the methodological limitations for such a pressure estimation are quantified and controlled, this information about pressure could be incorporated in the hemodynamic evaluation of the fetus. It would be especially useful when combined with the umbilical venous pressure measured during cordocentesis (V). Taking into account the methodological limitations of the pressure estimation, the information about the velocity changes alone could probably serve as a valuable indicator of altered pressures in the central venous circulation. This issue is addressed in the following three sections.

Altered central venous hemodynamics in fetal cardiac diseases (III). In the 30 cases of fetal cardiac disease included in the study, it was shown that the ductus venosus V_{peak} was maintained within normal ranges in 22 fetuses and reduced in eight cases, 27%. During atrial contraction, however, a reduced V_{min} was found in 19 cases, 63%. This concerned especially the heart malformations involving the pump function (i.e. dysfunction of the atrioventricular valves or outlet tracts) as 13 (81%) of those 16

cases had a reduced or reversed V_{min}. A reduced V_{min} was less commonly associated with isolated VSD and ASD (6/12 cases, 50%).

Pulsation in the intra-abdominal umbilical vein was associated with reduced or reversed V_{min} in all 12 cases. Umbilical vein pulsation in the last half of the pregnancy is generally regarded as a sign of serious hemodynamic derangement (Gudmundsson, et al., 1991; Lingman, et al., 1986). The reduced or reversed V_{min} in the ductus venosus might reflect the serious hemodynamic situation in a similar way. Such a reduced V_{min} might be caused by an increased end-diastolic pressure in the ventricles.

Regurgitation in the atrioventricular valves would cause an increased atrial pressure and possibly alter the pressure gradient across the ductus venosus. The three cases of atrioventricular regurgitation actually had a reduced V_{peak} and V_{min}. The results support the hypothesis that an altered atrial pressure may cause changes in the ductus venosus blood flow velocity.

Altered umbilical venous return in serious IUGR (IV). In the 38 cases of serious IUGR included in the study, the placental circulation was commonly altered. The elevated pulsatility index of the umbilical artery in 26 cases, 68%, and absent end-diastolic flow, ARED, in 12 cases, 32%, probably reflect the increased vascular impedance of the placenta in those cases. And the low umbilical blood flow in 25 of 33 cases, 76%, reflects a reduced placental blood flow. In spite of such an impairment in the umbilical circulation, the ductus venosus V_{peak} was maintained within normal ranges. The results support the assumption that the ductus venosus blood flow is part of a preferential streaming through the human fetal foramen ovale and is kept within normal ranges as long as possible even during the most serious derangement of umbilical circulation.

However, during atrial contraction, a reduced V_{min} was found in 13 cases (34%). This probably reflects an increased end-diastolic ventricular pressure due to reduced compliance in the course of an increased after-load.

The point might be raised that small fetuses would normally have lower umbilical blood flow values which correspond to their body size (Dawes 1968; Eik-Nes et al. 1980; Gill 1979). Two possibilities might be valid: a natural small growth potential induces a corresponding small circulatory supply, or an impaired placental circulation causes a corresponding restriction in growth. The altered pulsatility index in the umbilical artery in the majority of our cases is suggestive of an increased placental impedance and

impaired function as the cause of restricted growth. However, even in the highly selected group of IUGR in the present study, the population probably is heterogenic and might include small and healthy fetuses with normal placentas, small fetuses due to altered placental hemodynamics, and small fetuses due to other states of impaired placental function not associated with increased placental impedance.

Fetal respiratory force (V). The high blood velocities recorded in the ductus venosus during fetal respiratory movements were used to estimate the pressure difference between the umbilical vein and the IVC. Applying the Bernoulli equation, pressure gradients up to 22 mm Hg were estimated during fetal inspiratory movements in late pregnancy. By a slight approximation, such a pressure gradient might be regarded as the difference between the intra-thoracic pressure and the abdominal pressure, and could possibly reflect and quantify the fetal respiratory force. It is therefore suggested as a measure for fetal muscular respiratory capability that can be described both in the normal and the sick fetus.

POSSIBLE IMPLICATIONS AND FUTURE DEVELOPMENT

The results of the present studies call attention to the ductus venosus as an important distributor of umbilical blood in the human fetus. The studies demonstrated the close relation between the ductus venosus function and the umbilical arteries, the placenta, the umbilical vein, the hepatic circulation and the inferior venous inflow to the heart including the foramen ovale. These sections of fetal circulation put together could be discussed as a single functional unit responsible for the renovation of the fetal blood and its distribution back to the fetus (Figure 5). It might help in understanding some of the assumed principles which govern one of the most important hemodynamic units in the human fetus, and it offers the opportunity to speculate on and suggest future areas of research and clinical applications.

As a pregnancy proceeds, the fetal heart generates an increasing systemic blood pressure (Barcroft 1946; Dawes 1962). Normally, this arterial pressure suffices to perfuse the placenta, bring the oxygenated blood to the umbilical vein and back to the fetus (Dawes 1968). The oxygenated blood in the umbilical vein has a low but sufficient blood pressure to perfuse the liver parenchyma and accelerate the blood in the ductus venosus in parallel. It seems that the pressure in the umbilical vein, or more specifically the pressure drop from the umbilical vein to the left and right atrium, is a key issue in fetal circulation.

Induced hypoxemia in the fetal lamb causes increased arterial pressure and elevated pressure in the umbilical vein (Born et al. 1956; Reynolds and Paul 1958; Dawes 1968; Behrman et al. 1970; Edelstone 1980; Edelstone et al. 1980; Paulick et al. 1990a). Provided resistance remains unchanged, the net effect of this would be an increased flow through the ductus venosus and the liver. In the human fetus with anemia, that might be the case. The ductus venosus blood velocity is elevated in those fetuses and is reduced after intra-uterine transfusion (Oepkes et al. 1993). Serial ductus venosus velocimetric examinations may offer a possibility of surveying anemic fetuses or fetuses at risk for developing anemia (Figure 6).

Partial or complete clamping of the umbilical cord reduces or stops the umbilical venous return and evokes an initial rise in the arterial blood pressure in fetal sheep (Barcroft, 1946; Dawes, 1968). In the human fetus, a compromised placental circulation with an increased impedance probably requires an increase in the arterial pressure to maintain

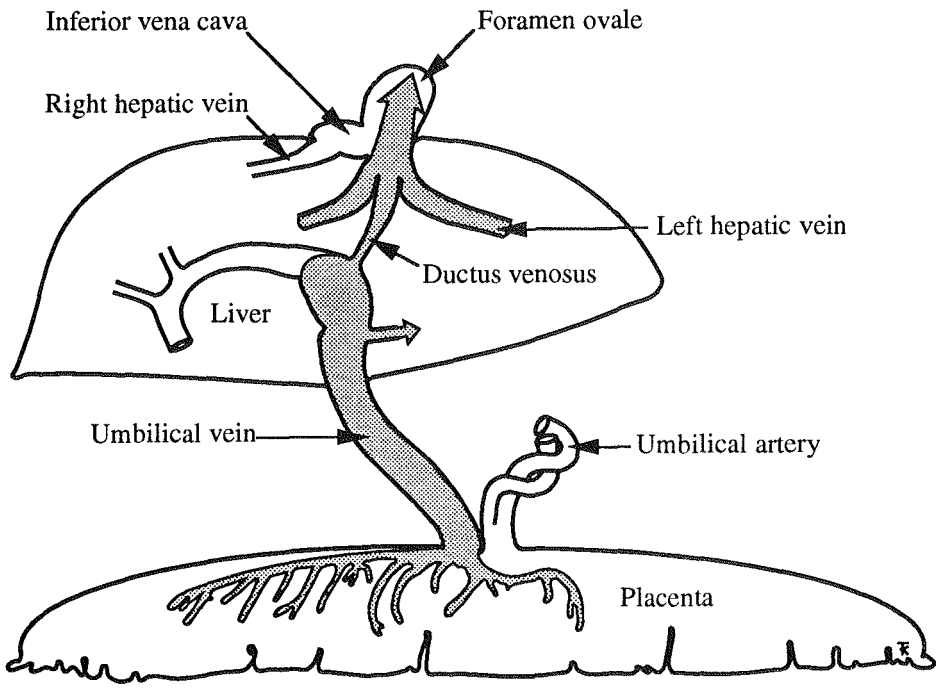

Figure 5: Oxygenated blood (gray) returns from the placenta to the fetus through the umbilical vein. The blood is distributed to the hepatic vasculature or shunted through the ductus venosus to be directed with a high velocity across the inferior vena cava towards the foramen ovale. The umbilical venous pressure is essential to maintain such a flow pattern. On one side, the pressure in the umbilical vein depends on the umbilical arterial pressure and the placental impedance, and on the other hand, on the vascular resistance in the liver and the ductus venosus.

perfusion and to maintain the umbilical venous pressure. A further deterioration of the placental vasculature would bring the fetus to the point where the increase in the arterial pressure is not sufficient to maintain the umbilical venous return and the venous pressure. An additional mechanism is then available, the hepatic vasculature might increase resistance (Rudolph, 1985). As a result, the umbilical venous pressure might improve and the blood flow velocity in the ductus venosus be maintained at the expense of the hepatic circulation. Such mechanisms might be responsible for the pattern of circulation in serious IUGR described in the present study (IV). All the fetuses in the study maintained normal peak blood flow velocity in the ductus venosus. A reduced blood velocity in the ductus venosus during atrial contraction in these fetuses might

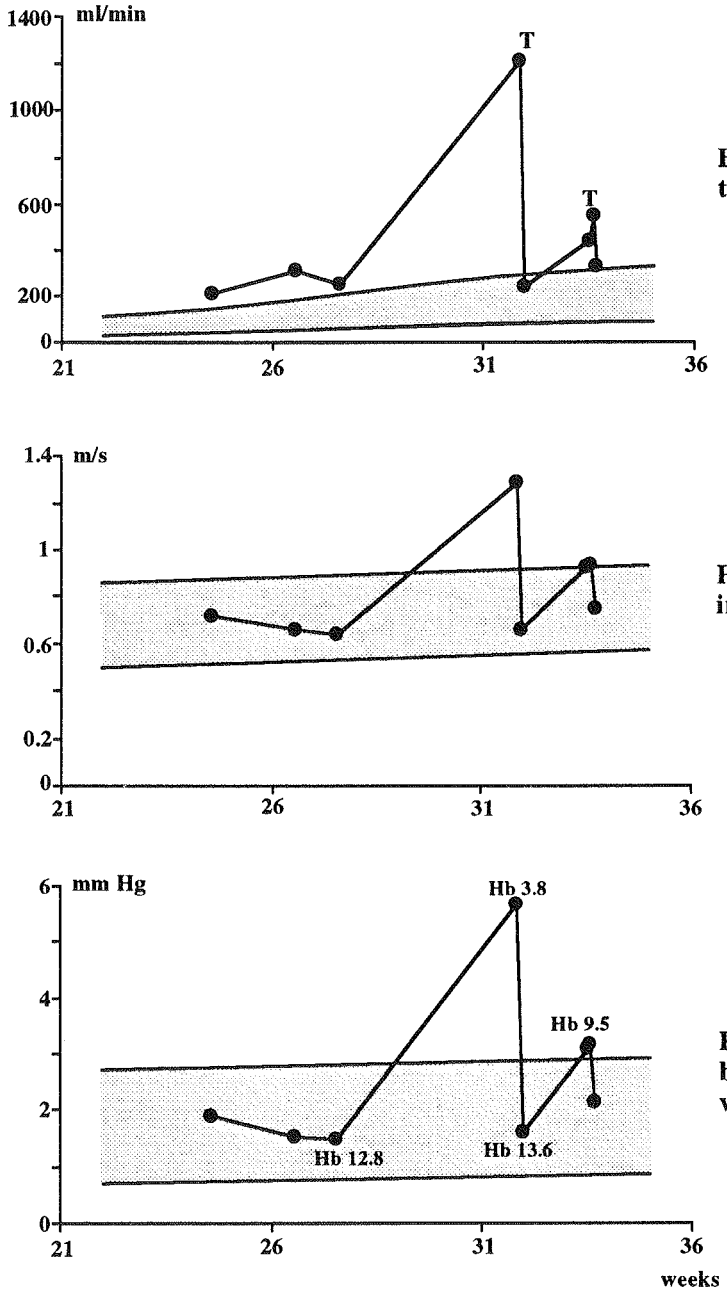

Figure 6: Serial Doppler measurements in a pregnancy complicated by Rhesus-immunization. As the fetus developed anemia, the umbilical venous flow, the blood flow velocity in the ductus venosus and the estimated pressure drop between the umbilical vein and the inferior vena cava (IVC) increased. A day after the intra-uterine transfusion (T) the measurements had returned to normal levels. Gray zones = normal ranges with 95% limits. IVC = inferior vena cava.

reflect an increased end-diastolic pressure in the ventricles and is suggestive of increased afterload and maybe arterial hypertension.

Another possible cause of an altered ductus venosus blood flow velocity is an increased central venous pressure. That could be the case in cardiac failure due to structural cardiac malformations or functional changes with secondary congestive heart failure. Teleologically speaking, an increased central venous pressure demands an increase in arterial pressure to achieve an increase in the pressure of the umbilical vein and thus ensure the required pressure drop and blood velocity across the ductus venosus. The recipient fetus in the so called twin-twin transfusion syndrome might be in such a state. An atrioventricular regurgitation (found in such fetuses and in fetuses with cardiac diseases) might cause an increased atrial pressure which demands an increased umbilical venous pressure to maintain normal distribution across the ductus venosus.

Another diagnostic possibility of the above suggested model is to be found in the liver circulation. Since the ductus venosus and the portal vasculature of the liver are circulated in parallel, a disease which involves the liver parenchyma might cause an increase in the hepatic vascular resistance. A corresponding portal hypertension in the fetus is synonymous with an increased umbilical pressure with a corresponding accelerated blood flow velocity in the ductus venosus.

A refinement of the diagnostic possibilities would be the estimation of the pressure gradient across the ductus venosus. Not only would such a pressure be of interest per se, it could also be combined with the pressures measured in the umbilical vein during cordocentesis to calculate central venous pressure, another important piece of information concerning the fetal circulation.

How important the ductus venosus actually is in the human fetus remains unanswered and awaits reliable techniques of volume flow measurements in small vessels. Studies of the hemodynamics and oxygen saturation during occlusion of the ductus venosus in the mature fetal sheep, however, suggest that the contribution from the ductus venosus is not indispensable during the last weeks of pregnancy (Amoroso et al. 1955; Rudolph et al. 1991). The well preserved peak blood flow velocity in the ductus venosus during serious growth retardation might indicate that this blood flow is of importance during serious fetal compromise.

Fetal breathing movements have been described in detail both in the sheep and in humans (Barcroft 1946; Dawes et al. 1970, 1972; Marsál 1977) and its influence on different

parts of the fetal circulation has been described (Dawes et al. 1981; Marsál et al. 1984; Spencer et al. 1991; van Eyck et al. 1991; Huisman et al. 1993). The high velocities of the ductus venosus blood flow and correspondingly high estimated pressure gradients described in the present work might indicate that fetal respiratory movements are of importance to increase umbilical blood delivery through the foramen ovale. Future studies might reveal to what extent respiratory movement is a complementary circulatory function to the ductus venosus.

Huisman et al. (1992b) could identify ductus venosus blood flow as early as 9 - 10 weeks. The ductus venosus blood flow might have a more dominant hemodynamic function in the second trimester than in late pregnancy. The pattern of hemodynamic compromise in our presented cases of IUGR (IV) could evoke such an idea. The gross changes in the venous circulation were seen mainly before week 32, as were the serious outcomes.

A further area of research is the possible sphincter function or any expansion in diameter in the ductus venosus in vivo mediated by neural or humoral stimulation as has long been discussed in the literature (Gennser et al. 1967; Ehinger et al. 1968; Coceani et al. 1984; Coceani and Olley 1988).

There is an increasing interest to study the ductus venosus blood flow velocity in a variety of clinical conditions (DeVore and Horenstein 1993; Huisman 1993; Oepkes et al. 1993; Soregaroli et al. 1993) In any case, the challenges that the tiny ductus venosus affords us, are not in proportion to its size.

CONCLUSIONS

Identification of the ductus venosus in utero: The present studies have shown that the human ductus venosus can regularly be identified in utero during the last half of the pregnancy by applying ultrasonography. The ductus venosus is visualized by 2D-imaging and color Doppler as a narrow connection between the umbilical sinus and the inferior vena cava. It runs in a steep cranial and dorsal direction to join the left compartment of the widened proximal part of the inferior vena cava.

Ductus venosus blood flow velocity: Through pulsed Doppler recording it was shown that the blood flow in the ductus venosus has a remarkably high velocity with a characteristic pattern which reflects the heart cycle. The velocity ranged between 40-100 cm/s and was always in an orthograde direction during gestational week 18-40. Although the velocity usually could be described with a peak during the ventricular systole, another peak occurred during the ventricular diastole and a nadir during the atrial contraction. 13% of the recordings showed only one single peak and a nadir. In 3% of the recordings an even velocity pattern was noted without any peak or nadir.

Standardization and reproducibility of the ductus venosus velocimetry: The study showed that the ductus venosus blood flow velocity had wide limits of variation in normal pregnancies as expressed in the 95% reference ranges established for the peak velocity, the minimum velocity and the time-averaged maximum velocity during gestational week 18 - 40. A standardized recording procedure was developed and included:

1. Accurate identification of the ductus venosus by gray scale imaging
2. Identification of the ductus venosus blood flow by color Doppler
3. Pulsed Doppler recording of the blood flow velocity at the isthmic portion of the vessel.

Intra-observer variation had limits of agreement of ±13 cm/s. The most uniform results were achieved when the recording was done at the initial portion of the ductus venosus.

The functional relationship between the foramen ovale, the inferior vena cava and the ductus venosus: The present studies have described a functional link between the ductus venosus and the foramen ovale in the human fetus in utero:

1. There is a direct delivery of blood from the inferior vena cava to the left atrium

without an intermediate entrance to the right atrium.

2. The blood which is delivered to the left atrium through the foramen ovale preferentially comes from the ductus venosus, left and medial hepatic vein in a defined left pathway.
3. The high blood flow velocity found in the ductus venosus seems to give the oxygenated umbilical blood the necessary momentum to follow this pathway and reach the left atrium.
4. A right pathway starting in the abdominal part of the inferior vena cava, points increasingly forward to direct low oxygenated blood into the right atrium. The right hepatic vein seemed to contribute to this right pathway.

Diagnostic possibilities with ductus venosus velocimetry: Doppler velocimetry in seriously growth retarded fetuses showed that the ductus venosus blood flow velocity had a high priority and the peak blood velocity was maintained within normal ranges even during substantial impairment of the placental circulation. A sign of hemodynamic compromise was described in the reduced ductus venosus blood velocity during atrial contraction commonly occurring together with pulsation in the umbilical vein. Such a sign was also frequently noted in fetal cardiac diseases and was suggested as a diagnostic possibility in the fetal hemodynamic evaluation. Ductus venosus velocities were particularly affected in the serious congenital heart defects and showed a reduced or reversed blood velocity during atrial contraction. The results of the studies in growth retarded fetuses and in fetuses with cardiac diseases suggest that the ductus venosus velocimetry is a possible new parameter in the evaluation of the fetal hemodynamics.

Estimation of the pressure gradient between the umbilical vein and the IVC: The ductus venosus blood velocity probably reflects an important pressure gradient between the umbilical vein and the IVC. The present study suggests a method to estimate the pressure gradient across the ductus venosus applying the Bernoulli equation. The method makes it possible to calculate the central venous pressure by subtracting the ductus venosus pressure gradient from the umbilical venous pressure. Once methodological limitations are controlled, such information about pressure gradient in the venous return might become a useful component of the fetal hemodynamic evaluation.

Evaluation of fetal respiratory function: Fetal respiratory exercise had a substantial impact on the blood flow velocity in the ductus venosus. Especially during inspiratory movements, velocities up to 220 cm/s were noted. By applying the Bernoulli equation, such velocities are estimated to correspond to pressure gradients above 20 mm

Hg and indicate the remarkable force fetal respiratory activity has on fetal hemodynamics. Such measurements have a potential to be used in evaluating the fetal respiratory force.

The ultrasonographic examination of the ductus venosus in utero seems to afford new information about an important fetal hemodynamic principle and offers a variety of diagnostic possibilities for a refined evaluation of the sick fetus.

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CORRECTIONS

Paper I

Page 9, second column, second paragraph, last line "as can be judged by Figs. 7 and 8" *should be* "as can be judged by Figs. 8 and 9".

Page 10, Table 2., last line "(–21; 26) (–21; 50)" *should be* "(–26; 26) (–35; 48)".

Page 11, Reference 19., last line "307-310." *should be* "307-310; 1986".

Page 11, Reference 22., last line "1412-1414; 1901" *should be* "1412-1414; 1991".

Paper V

Page 228, Fig. 4, upper panel "N = 163" *should be* "N = 184".

Paper I

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Ductus Venosus—A Longitudinal Doppler Velocimetric Study of the Human Fetus

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Abstract. Based on the knowledge that the ductus venosus (DV) is an important regulator of venous blood in fetal lambs, the aim of this study was to describe the DV in the human fetus. In a longitudinal study that included 29 normal women, ultrasonography was applied including color Doppler and pulsed Doppler velocimetry every 3 to 4 weeks in the last half of pregnancy. The DV was identified in all examinations. Of 60 measurements of the inner diameter, none exceeded 2 mm. Of a total of 416 maximum velocity tracings, 184 observations were included for analysis. The DV waveform was typical, with no reversed blood flow during atrial contraction. The peak velocity was remarkably high, 65 to 75 cm/s (18 to 40 weeks) with wide 95% confidence limits. Intraobserver variation had wide limits of agreement (−13; 12). The results show that the DV can regularly be identified using sonographic techniques. The direction and high velocity support the theory that the DV delivers oxygenated blood for the preferential blood stream to the left atrium.

Key words: Ductus venosus–Fetus–Human–Ultrasonography–Doppler velocimetry.

The fetus depends on the oxygenated blood that returns from the placenta. This blood stream follows the umbilical vein (UV) into the abdomen and the umbilical sinus, otherwise called the portal sinus, which branches into the liver. In addition, the umbilical sinus is connected directly to the thoracic portion of the inferior vena cava (IVC) by the ductus venosus (DV), also called ductus Arantii, attributed to the Italian Gulio Cesare Aranzio, 1530–1589 [1]. The DV is described as a narrow vessel reaching a length of 20 mm and width of 2 mm at term [2]. The discussion about whether a sphincter or a lip regulates the blood flow in the DV has still not been settled [3–5]. Together with the foramen ovale (FO) and the ductus arteriosus, the DV regulates the fetal blood distribution [6]. Animal studies have shown that in normal conditions, 50%, and in the state of hypoxia, 60% of the umbilical blood may bypass the liver through the DV to be directly delivered into the IVC [7–10]. Since Sabatier (1774), Wolff (1776), and Kilian (1826), there has been a theory that this blood to a large extent is admitted to the left atrium by the FO [10]. This theory was later confirmed in fetal lamb experiments [11–13]. Thus, well-oxygenated blood is delivered to the left ventricle, supplying vital organs such as the heart and the brain through the ascending aorta. It has been suggested that a similar blood distribution is found in the human fetus [4, 10, 11]. Since the human brain develops beyond that of other species in relative size and function it may be especially dependent on a steady supply of oxygenated blood. Although the DV in the human fetus has been depicted on ultrasonography, little is known of its function in utero [14–16].

Being a direct connection between the umbilical vein and the heart makes the DV of special interest regarding central venous pressure in the fetus. Since the blood velocity in the DV depends on a pressure gradient between the UV and the atrium, the DV velocimetry could indirectly provide information on an altered pressure difference between the atrium and the UV. This would be of interest in clinical problems such as hydrops, congenital heart disease, growth retardation, and fetofetal transfusion.

The aim of this study was to describe the DV and its blood velocity in normal human pregnancies.

Methods

Thirty-one healthy pregnant women participated in the longitudinal study. They were recruited according to a protocol approved by the committee of ethics and gave informed consent in writing. Each participant was a

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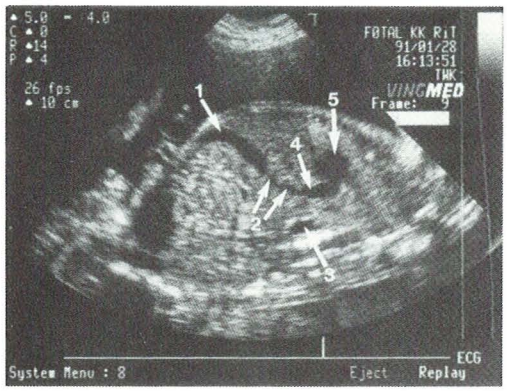

Fig. 1. Near sagittal midsection of fetus. The UV (1) is connected by the DV (2) to the IVC (4). Aorta (3). Right atrium (5).

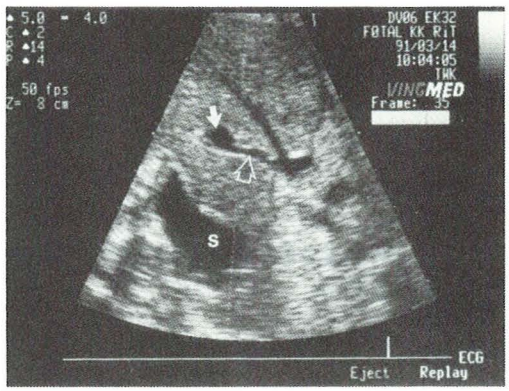

Fig. 2. Oblique transverse section of a fetus showing the DV (open arrow) connecting the UV (filled arrow) to the IVC. A hepatic vein is also seen. Stomach (S).

nonsmoker, had a normal obstetrical history, an uneventful actual pregnancy, and a normal routine ultrasound scan at the 17th to 20th week of gestation. Gestational age was assessed by ultrasonography. Criteria for later exclusion were complications such as growth retardation (< 5 centile at birth), pregnancy-induced hypertension, bleeding, or any serious complication leading to hospitalization.

Starting in the 17th week of gestation, the participants were examined every third to fourth week until term. Each session lasted 20 to 50 minutes. A Vingmed 750 CFM ultrasound scanner (Vingmed Sound, Horten, Norway) was applied for two-dimensional imaging (2D-imaging), color flow mapping, and pulsed Doppler examination. For the 2D-imaging, 5 and 3.75 MHz mechanical sector transducers were applied with a spatial peak temporal average intensity (Ispta) set to 5 and 6 mW/cm^2 respectively. The pulsed Doppler frequencies were 4 and 2.5 MHz with Ispta settings of 45 and 10 mW/cm^2 respectively.

The DV was identified either in the midsagittal section from the anterior, or paravertebrally from the posterior (Fig. 1). An oblique transverse section of the upper abdomen could also be applied (Fig. 2). Identification of the DV was accepted when the luminal connection between the umbilical sinus and IVC was visualized. The inner diameter of the narrowest portion was measured. Color Doppler was added to enhance visualization and assessment of the angle of insonation (Fig. 3). Pulsed Doppler signals were collected with a sample volume of 4 to 10 mm just above the inlet of the DV. Signals were recorded both in fetal quiescence and under respiratory movements. For the purpose of comparison, Doppler signals were recorded in the hepatic veins. In 12 examinations, a recording of the DV and IVC was done simultaneously with an expanded sample volume to assess the relation of the blood flow pattern to the heart cycle. The flow pattern in the IVC has a known relationship to the heart cycle [17, 18].

All the signals were transferred to a computer for later analysis. From each session, one stable tracing of at least four heart cycles at a rate of 120 to 150, representing the best visualized image of the DV and the smallest angle of insonation, was admitted for statistical analysis. Maximum velocity tracing was applied to estimate the peak velocity (V_{peak}), the time averaged maximum velocity (V_{ta}) and minimum velocity (V_{min}).

To assess the effect of the sample site, 33 observations were made in unselected patients (22nd to 34th week). The velocities at the standard site above the inlet of the DV were compared with the velocities at the midportion and the outlet.

Intraobserver variations for the standard procedure of DV velocimetry were studied in 27 pairs of observations in unselected patients (18th to 34th week). The participants left the examination room for a short period between the first and the second examination (median interval 24 minutes, range 4 to 52).

To evaluate the variation in these two parts of the study, the correlation coefficient, the coefficient of

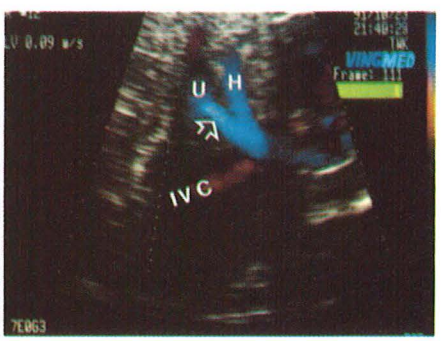

Fig. 3. Color Doppler showing the DV blood velocity direction (open arrow) from UV (U) to the IVC. Hepatic vein (H).

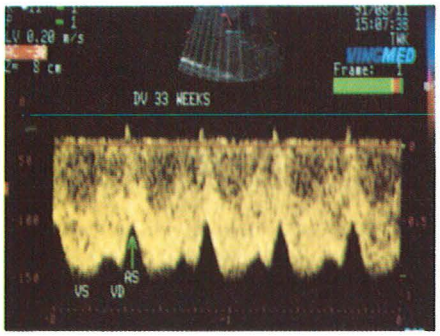

Fig. 4. A typical DV Doppler velocimetric recording. A velocity peak in the ventricular systole (VS), another peak in the ventricular diastole (VD), and a trough during atrial systole (AS).

variation and the limits and true limits of agreement were calculated [19, 20]. Based on the mean difference (d) and standard deviation (SD) the limits of agreement (d ± 1.96 SD) could be calculated. By adding the 95% confidence interval of these limits, the true limits of agreement were established.

Results

Of the 31 participants in the longitudinal study, two were withdrawn (one moved and one started smoking), leaving 29 to be analyzed. The women's mean age was 27 years (range 21 to 40). At delivery, mean gestational age was 40 weeks/3 days (range 37/5 to 42/2). Mean birth weight was 3659 g (range 2950 to 4350 g). There was one cesarean section due to maternal age and one due to suspected asphyxia during labor. Both babies, however, had normal Apgar scores and pH. The rest of the children all had uneventful deliveries and Apgar ≥ 9.

Combining 2D-imaging and color flow mapping, the DV could be identified in all examinations (Fig. 1 to 3). It could be described as a narrow trumpet-like structure throughout the pregnancy. The inner width was measured in 60 examinations (18 to 35 weeks) and the narrowest portion of the DV never exceeded 2 mm. It was visualized in the midsagittal section or slightly towards the left side, pointing posteriorly and obliquely upwards. Often it was slightly bowed, with the bow becoming steeper towards the IVC, projecting its fountain-like jet into the posterior part of the thoracic IVC. The color flow signals in the DV had a constant forward direction and a higher intensity than the neighboring venous signals of lower velocity and periodic zero or negative flow.

A total of 416 pulsed Doppler recordings from the DV were successfully obtained in all 187 examinations with up to four registrations in each session. The signals from three examinations were lost during a computer breakdown. In the remaining 184 sessions, one recording from each session was used for further analysis. The pulsed Doppler frequency shift was found to have a characteristic pattern (Fig. 4). In the 12 instances of simultaneous recording, the DV showed the same relation to the heart cycle that the IVC has (Fig. 5). The maximum velocity tracing had a peak during the ventricular systole, another peak during the ventricular diastole and the lowest velocity during the short contraction of the atrium (V_{min}). In contrast to the IVC, no reversed flow was encountered in the DV under standard conditions. Although the described pattern was predominant, in 47 observations (11% of 416) the peak during ventricular diastole was less obvious or missing, leaving the wave with a single peak and a trough. And in another 13 recordings (3% of 416), the trough was inconspicuous or absent, leaving the tracing almost even throughout the heart cycle (Fig. 6).

In contrast to the DV pattern, the blood velocity in 52 observations of the hepatic veins regularly revealed zero flow or reversed flow during atrial contraction.

DV velocity was recorded under respiratory movements in 63 observations. The velocity was extensively influenced by fetal breathing movements (Fig. 7). V_{peak} and V_{min} were reduced by expiratory movements, and transient zero flow or even reverse flow

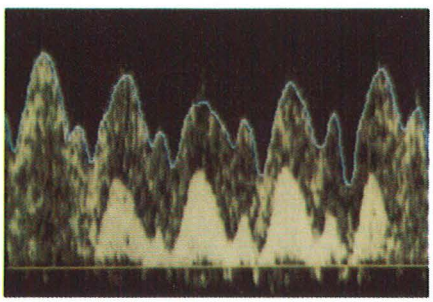

Fig. 5. Simultaneous recording of the IVC (low velocity) and the DV (high velocity) with an expanded sample volume.

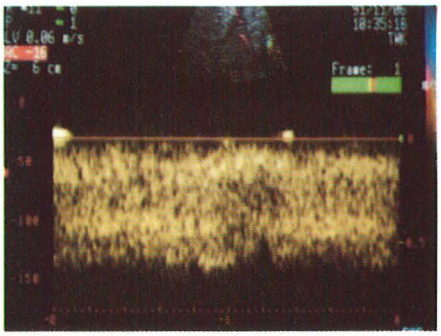

Fig. 6. DV Doppler velocimetry showing almost no changes during the heart cycle.

was recorded. Peak velocity up to 200 cm/s was seen during inspiratory movements.

Data from the 184 observations in the longitudinal study had a linear regression. V_{peak} had a mean of 65 cm/s in the 18th week increasing to 75 cm/s in the 40th week (Fig. 8). In 71 observations, the angle correction was < 30 degrees. The mean in this group did not differ from the rest but the 95% confidence intervals were smaller (Fig. 9). V_{ta} was slightly less than V_{peak} (Fig. 10). The velocity during atrial contraction, however, was clearly lower but never reached the level of zero (Fig. 11).

The individual measurements varied considerably throughout the pregnancy as was obvious in the nine fetuses randomly picked from the longitudinal study group (Fig. 12). The intraobserver variation is shown in Table 1.

The effect of the sampling site is shown in Tables 2 and 3. At the outlet into the IVC, maximum velocity tracing was not possible in 10 cases due to noise, admixture of different velocities, or uncertain angle correction. The calculations were based on the remaining 23 observations.

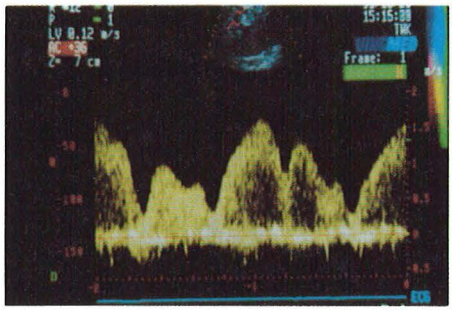

Fig. 7. DV Doppler velocimetry during respiratory movements.

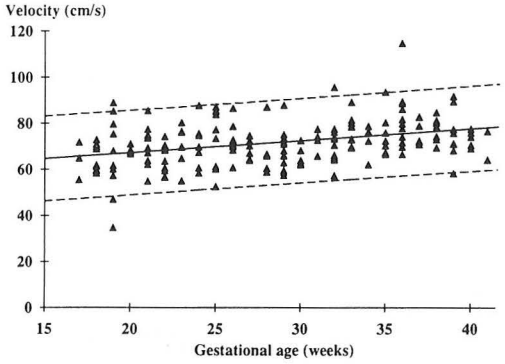

Fig. 8. DV peak velocity in 184 observations of 29 fetuses. Linear regression line with 95% confidence limits.

Discussion

The improved ultrasound equipment of today, especially the Doppler technique, has made detailed investigation of the fetal vascular system possible [18, 21]. Our results show that a small vessel like the DV can regularly be visualized and described in vivo. The ultrasound image of the DV seems to be in agreement with previous reports on anatomical studies [2]. We found that the DV continues to be a narrow trumpet-like vessel throughout the pregnancy with the narrowest portion ≤ 2 mm. Since the DV is a small vessel in an area where a number of vessels are encountered, we required that the DV, in contrast to other veins, be identified in the 2D-image by the luminal connection between the two major veins, the UV and the IVC (Fig. 2). This could be applied to the color Doppler imaging as well. The study revealed a high blood velocity otherwise found mostly on the arterial side. Respiratory movements had a pronounced influence on

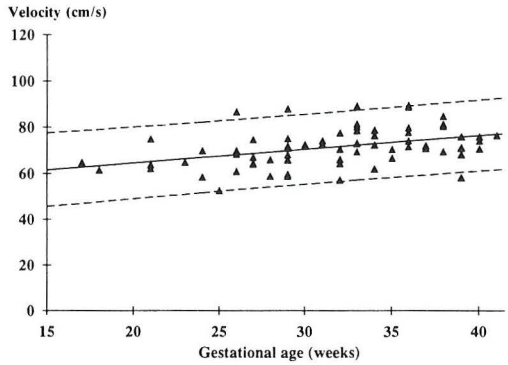

Fig. 9. DV peak velocity in 71 observations with an angle correction of < 30 degrees. Linear regression line with 95% confidence limits.

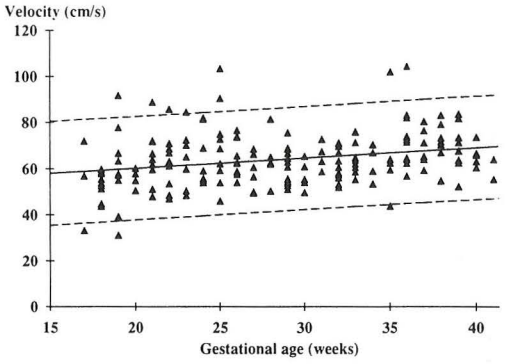

Fig. 10. DV time averaged maximum velocity in 184 observations of 29 fetuses. Linear regression line with 95% confidence limits.

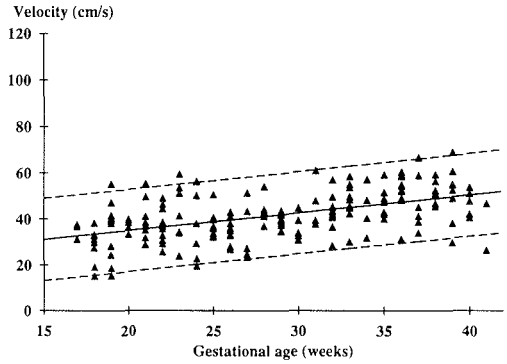

Fig. 11. DV maximum velocity during atrial contraction (V_{min}) in 184 observations of 29 fetuses. Linear regression line with 95% confidence limits.

the velocities in the DV (Fig. 7). The velocity pattern was closely related to that of the IVC and hepatic veins and was influenced by the heart cycle in the same manner. Typically, however, the DV had no reversed flow in fetal quiescence, in contrast to the neighboring vessels. Our study shows that the DV may regularly be identified with 2D-imaging, color Doppler and pulsed Doppler recording. Especially when angle correction is necessary, color Doppler will be of indispensable help. A more reliable identification, however, is achieved by combining the three methods. It is important to ensure the identity of the DV because the neighboring hepatic veins are closely situated and become confluent with the DV at the IVC outlet, and are therefore potential sources of error at the time of blood velocity measurement.

There was a wide normal variation in the maximum velocity recordings throughout the pregnancy, as seen

Table 1. Intraobserver variation of V_{peak} and V_{min} in 27 pairs of observations.

	V_{peak}	V_{min}
Correlation coefficient	0.9	0.9
Coefficient of variation (%)	8.7	15.0
Differences (mean)	−0.7	−1.7
SD	6.5	6.9
Limits of agreement	(−13; 12)	(−15; 12)
True limits of agreement	(−16; 14)	(−18; 14)

in Figs. 8 to 12, and in the liberal limits of agreement in the intraobserver study (Table 1). As for the sampling site, the Doppler signals at the midportion gave results with a distribution much the same as found at the standard inlet (Tables 2 and 3). However, the true limits of agreement between the paired observations of V_{peak} and for V_{min} suggest that the sites may not be used interchangeably without impairing the accuracy of the method. The measurements at the DV outlet show hardly any agreement with the inlet recordings and cannot substitute the standard measurement. Apparently this type of recording is vulnerable and requires meticulous technique. We suggest standardizing the sampling site at a location immediately above the inlet of the DV, applying an expanded sample volume to ensure the recording of the highest velocity. A reduced sample volume may sometimes be necessary to avoid interference.

Extensive angle correction may alter the measurement accuracy. In our study, an angle correction of ≥ 30 degrees had a negligable impact on the results as can be judged by Figs. 7 and 8.

Although the DV velocity had a typical pattern most of the time, other less typical tracings were encountered in 14% and should probably be regarded as normal variants (Fig. 5). These patterns show that it may be inappropriate to rely on the velocity pattern

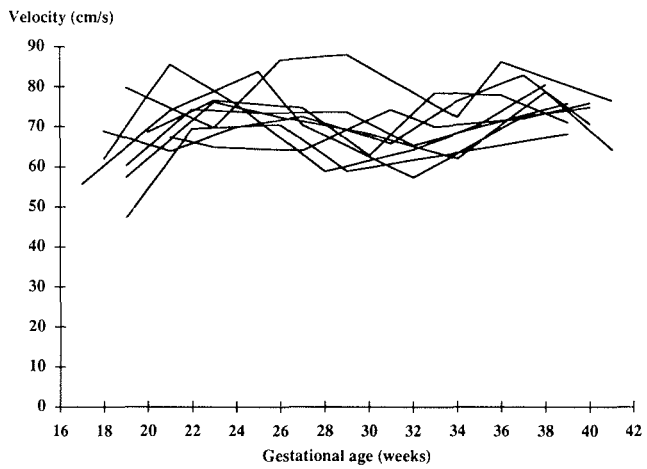

Fig. 12. DV peak velocity in 9 fetuses showing the individual variation throughout the pregnancy.

Table 2. Variation of V_{peak} according to site of sampling in 33 sets of observations.

Site of sampling	Inlet	Midportion	Outlet
V_{peak} (cm/s)	76	76	68
SD	14	13	13
Mean difference to inlet		0.1	6.3
SD		10	15
Correlation coefficient		0.7	0.4
Coefficient of variation (%)		13	21
Limits of agreement		(−20; 20)	(−24; 36)
True limits of agreement		(−21; 26)	(−21; 50)

alone to identify the DV. Whether such velocity patterns represent activity in a sphincter or not, is left to speculation.

The limits of agreement were chosen to describe the variation of the measurements, since correlation coefficient and coefficient of variation may not describe the degree of agreement in paired observations [19, 20]. For example, a measurement in week 18 of V_{min} = 18 cm/s and another measurement of V_{min} = 3 cm/s may both represent the same blood velocity because the lower limit of agreement is −15. The lowest velocity in this case is at the lower limit of agreement. This way of describing variation may guide us to a better understanding of the limitations of the method and prompt us to introduce robust criteria when applying the method in a clinical situation.

Studies on fetal lambs have focused on the DV as an important regulator of fetal venous circulation [3–12]. In the fetal lamb, half of the umbilical blood bypasses the liver through the DV. And in a state of asphyxia this fraction increases. This blood streams preferentially through the FO as shown in fetal sheep [13]. Our results support the hypothesis that the DV plays a similar role in the human fetal circulation. The amount of blood entering the DV, however, cannot be measured using our technique. The color Doppler technique only gives information about velocity and direction, but will not demonstrate admixture of blood from different sources in the way that angiographic methods do. But the high velocity of the DV blood flow pointing in the oblique posterior direction supports the theory that this blood preferentially passes the FO.

Table 3. Variation of V_{min} according to site of sampling in 33 sets of observations.

Site of sampling	Inlet	Midportion	Outlet
V_{min} (cm/s)	47	45	31
SD	14	15	13
Mean difference to inlet		2.2	15
SD		9	13
Correlation coefficient		0.8	0.6
Coefficient of variation (%)		20	33
Limits of agreement		(−16; 20)	(−11; 40)
True limits of agreement		(−21; 26)	(−21; 50)

A high velocity implies a corresponding pressure gradient. It is suggested that the DV velocimetry reflects the pressure gradient between the UV and the atriae [22]. In fetal sheep the UV pressure is 15 mmHg [6]. The human UV pressure is reported to be only 5 mmHg [23, 24]. Once pressure measurements with reproducible results are established, there is a possibility of calculating central venous pressure based on umbilical pressure recording and velocimetry of the UV and DV. The knowledge of central venous pressure would shed new light on normal and altered fetal hemodynamics.

Assuming that a high velocity is necessary to make the oxygenated blood cross the FO, the velocimetry of the DV could be used to indicate how well the fetus manages this regulation in a state of disease [22]. This means that a low V_{peak} may indicate a hemodynamic compromise. However, it may be equally important to maintain a high velocity throughout a major part of the heart cycle to achieve the desired volume of blood to cross the FO. Comparing the V_{ta} to V_{peak} may give a rough idea of how well this is done. During atrial contraction the DV velocity is at its minimum (V_{min}). One could speculate that V_{min} is a sensitive indicator of any changes in atrial function. An altered umbilical pressure, challenged by the normal atrial pressure rise, would also influence the V_{min}. According to such a concept, V_{min} would be vulnerable and reflect early changes in atrial function or umbilical venous return. As discussed above, wide limits of agreement for the DV velocimetry imply that liberal ranges for the normal measurement should be accepted and that an abnormal velocity should be interpreted with caution. This applies particularly to V_{min}, having a lower true limit of agreement −18. At 20 weeks, this could mean almost zero velocity of V_{min}. That would make the DV velocity resemble IVC and hepatic vein velocities. Such a case emphasizes the importance of a reliable identification of the vessel. A negative velocity of the V_{min} would, however, probably be a robust indicator of altered hemodynamics.

We conclude that the DV seems to be of importance in the human fetus. The high blood velocity recorded in the vessel shows broad normal variations and considerable intraobserver variation. Taking this into account, the DV velocimetry still has a promising diagnostic potential.

Acknowledgment. The text was revised by Nancy Lea Eik-Nes.

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Paper II

Ultrasound Obstet. Gynecol. 2 (1992) 389–396

Foramen ovale: an ultrasonographic study of its relation to the inferior vena cava, ductus venosus and hepatic veins

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Key words: FORAMEN OVALE. BLOOD FLOW. HUMAN FETUS. ULTRASONOGRAPHY. DOPPLER

ABSTRACT

According to the literature, oxygenated blood from the ductus venosus and hepatic veins may either enter the right atrium before flowing through the foramen ovale to the left atrium, or flow directly from the ductus venosus and the hepatic veins to the foramen ovale, bypassing the right atrium. To address this problem, 103 normal fetuses were examined by two-dimensional imaging, M-mode and color Doppler at an average gestational age of 27 weeks (range, 15–40 weeks). The position of the ventricular septum and foramen ovale, and the angle and flow direction of the inferior vena cava, ductus venosus and hepatic veins were recorded. Two pathways for blood were described: 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 at an angle of 13° to the long axis of the spine. The left and medial hepatic veins enter the left ductus venosus–foramen ovale pathway, and the right hepatic vein enters the right inferior vena cava–right atrium pathway. This supports the hypothesis that oxygenated blood from the ductus venosus and left hepatic veins flows directly through the foramen ovale to the left atrium avoiding extensive mixture in the inferior vena cava and an intermediate entrance to the right atrium.

INTRODUCTION

The foramen ovale is one of the three physiological shunts in the fetus. It can be described as an opening in the posterior and lower part of the atrial septum in the fetal heart. At the moment of birth, the fetal circulation is transformed into the neonatal pattern of increased pulmonary flow; the umbilical venous flow is discontinued, and the thin foramen ovale-flap (also called the mobile septum primum) covers this opening from the left side[1]. Studies in the fetal lamb have shown that blood from the ductus venosus and hepatic veins preferentially enters the left heart via the foramen ovale to supply the coronary arteries and brain with oxygenated blood[2–4]. Some studies have shown that in the human fetus the ductus venosus delivers blood with a high velocity[5,6] into the inferior vena cava in a posterior and oblique direction. This favors the direct injection of oxygenated blood through the foramen ovale[5], avoiding extensive mixing with the deoxygenated blood otherwise entering the right atrium via the inferior vena cava. Recent literature on the foramen ovale, however, commonly relates to a different concept: the oxygenated blood first enters the right atrium and then flows through the foramen ovale to the left atrium[7–9].

The aim of the study presented here was to describe the relationship between the ductus venosus, hepatic veins, inferior vena cava and the foramen ovale in the human fetus.

METHODS

A total of 108 healthy pregnant women were included in a cross-sectional study after giving their informed consent. Twenty-nine participants were recruited from the low-risk, and 79 from the high-risk antenatal clinic when referred for ultrasonographic evaluation that included fetal echocardiography. Gestational age was assessed from a routine ultrasound scan at 17–20 weeks. All the fetuses included had normal anatomy, assessed by the routine scan and by the fetal echocardiographic examination. The newborn infants were examined by a pediatrician. Fetuses with growth below the fifth centile were not included. Five participants were withdrawn, one due to a miscarriage at 20 weeks, and three after the neonatal examination (one case of muscular ventricular septum defect, two cases of secundum atrial septum defect, and one case of atresia of the small intestine). The remaining

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Table 1 Results of the angle measurements of the inferior venous inlet to the fetal heart

Observation	*Direction*	*n*	*Mean* (degrees)	*Standard deviation*
Ventricular septum	left from mid-line	51	45	11
Distal vs. proximal inferior vena cava	sagittal plane	48	21	8
Inferior vena cava vs. aorta	sagittal plane	49	14	4
Inferior vena cava vs. spine	sagittal plane	49	13	5
Ductus venosus (proximal) vs. inferior vena cava	sagittal plane	57	48	9
Ductus venosus (distal) vs. inferior vena cava	sagittal plane	39	55	12
Left hepatic vein	left from mid-line	29	27	14
Medial hepatic vein	right from mid-line	28	29	9
Right hepatic vein	right from mid-line	16	70	8

103 had a median birth weight of 3440 g (range, 1210–4710 g) at a median gestational age of 39 weeks (range, 28–43 weeks). The ultrasound measurements included in the study were carried out at an average gestational age of 27 weeks (range, 15–40 weeks).

Each participant was examined once with a Vingmed CFM 750 ultrasound scanner (Vingmed Sound, Horten, Norway) for two-dimensional imaging, M-mode and color Doppler imaging. A 5 MHz sector scanner carrying a 4 MHz Doppler unit was used; its spatial peak temporal average intensity (I_{SPTA}) was set to 2 mW/cm^2 for the sector scan, 10 mW/cm^2 for the M-mode, and to 2 mW/cm^2 for the color flow. Alternatively, a 3.75 MHz sector scanner carrying a 2.5 MHz Doppler unit was applied with an I_{SPTA} setting of 2 mW/cm^2 for the sector scan, 9 mW/cm^2 for the M-mode, and 3 mW/cm^2 for the color flow. Only information obtained during fetal apnea was included in the study.

The cardiac position was examined in a transection providing a four-chamber view. The angle between the ventricular septum and the mid-sagittal plane through the sternum and long axis of the spine was recorded.

The foramen ovale was depicted in several transverse sections, and in an oblique coronal section including the foramen ovale, the foramen ovale-flap and the inferior vena cava. The M-mode was used to record the movements of the foramen ovale-flap during the heart cycle.

The inferior vena cava was examined in a sagittal section. The angle between the distal and the proximal portions was noted. For this and the subsequent measurements, a mid-luminal line was drawn parallel to the walls of the vessel. The angles between the proximal portion of the inferior vena cava and the long axis of the spine, and between the inferior vena cava and the aorta were recorded. The proximal portion of the inferior vena cava and the connection to the atria was studied in transverse and longitudinal sections, and the site for the inlet of the veins and the ductus venosus noted.

The ductus venosus was studied in a near mid-sagittal section and the angles between both the distal and the proximal ductus venosus and the proximal inferior vena cava were measured.

The hepatic veins were assessed in a transection, including their outlet into the inferior vena cava below the diaphragm, in order to record the main stem of the left, medial and right hepatic veins. Their angle to the mid-sagittal plane was recorded and their inlet to the inferior vena cava examined.

The blood flow directions were assessed using color Doppler imaging of the proximal inferior vena cava and right atrium, the ductus venosus, hepatic veins, foramen ovale and the left atrium.

RESULTS

The results of the angle measurements for the ventricular septum, inferior vena cava, ductus venosus and hepatic veins are listed in Table 1. Figures 1 and 2 provide a visual summary of the results. The angles showed no significant correlation with gestational age. Generally, the variation was considerable, as can be appreciated in the example of the angle of the inferior vena cava compared to the spine (Figure 3).

Two-dimensional and color Doppler images of the inferior vena cava–foramen ovale unit were obtained in all cases and the results are summarized as below:

(1) The inferior vena cava was found to widen in the proximal portion and to enter into the atria in a slightly anterior direction (Figure 4). An extension of the inferior vena cava continued into the lumen of the atria itself like a short interatrial tube (Figure 5). On the right side, the Eustachian valve (otherwise called the valve of the inferior vena cava) formed the wall connected to the atrial septum. On the left side, the foramen ovale-flap formed the wall extending well into the left atrium and continued as a partial tubal extension in the left atrium (Figure 4). The atrial septum resided above the middle of the inferior vena cava with an easily visible crest, known as the crista dividens (otherwise known as the septum secundum or limbus fossae ovalis). Thus the inferior vena cava–foramen ovale complex could be described as a Y-shaped unit with a long branch to the left atrium and a short branch to the right atrium. The cleft between the two branches was the crista dividens (the atrial septum) (Figure 4).

(2) In the sagittal planes, two separate pathways could be described (Figure 2). A right *inferior vena cava–right atrium pathway* was visualized by the distal inferior vena cava, the right portion of the proximal inferior vena cava, and the right atrium (Figure 6). Blood flow could be traced along this pathway straight into the right atrium (Figure 7). The right hepatic vein was connected to this pathway in the

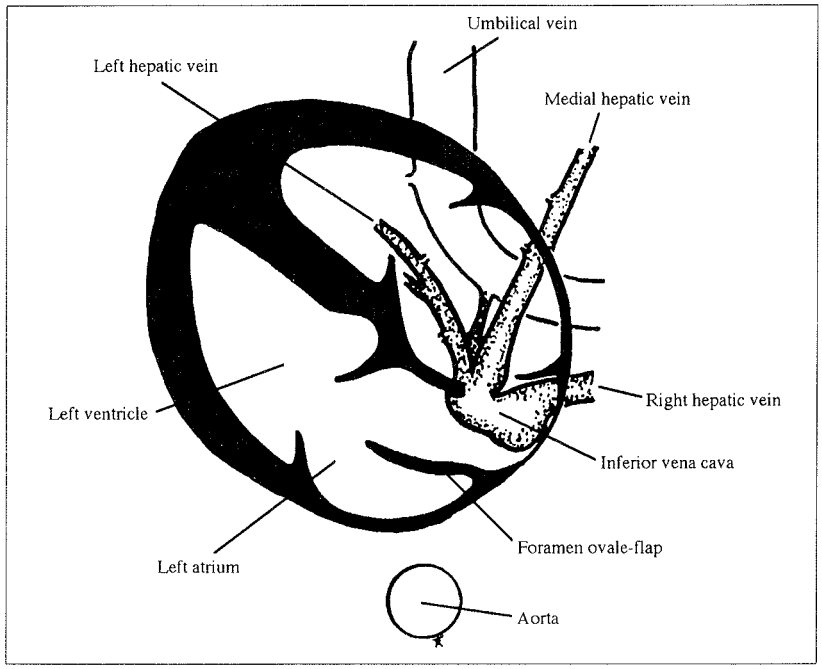

Figure 1 Transectional view of the heart superimposed on the venous inlet below the diaphragm. The position of the ventricular septum and the main stems of the hepatic veins are adjusted according to the angle measurements representing mean values compared to a mid-sagittal plane. The ductus venosus connects the umbilical vein to the left portion of the inferior vena cava together with the left hepatic vein and medial hepatic vein

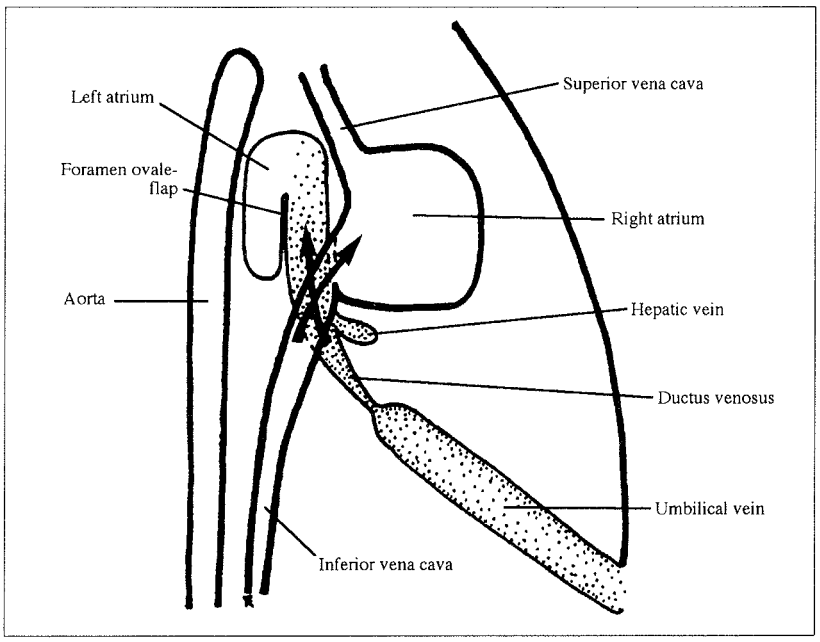

Figure 2 Sagittal view of the ductus venosus–foramen ovale and inferior vena cava–right atrium pathways crossing in the proximal portion of the inferior vena cava. The right portion of the inferior vena cava projects into the right atrium. The left pathway starts in the umbilical vein, passes through the ductus venosus and the inferior vena cava to enter directly into the foramen ovale and the left atrium

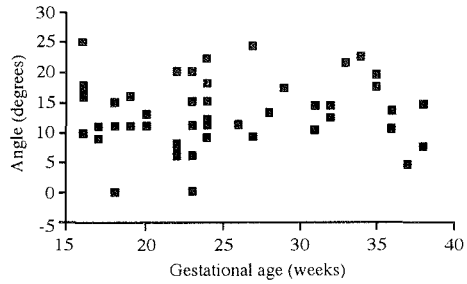

Figure 3 Results of angle measurements of the upper part of the inferior vena cava in relation to the spine in 49 fetuses. No correlation with increasing gestational age was found

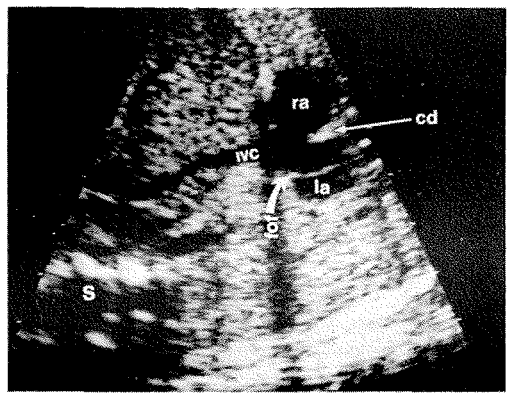

Figure 4 An oblique coronal section shows that the inferior vena cava (IVC) widens in a Y-shape. One branch goes to the right atrium (ra), and the other branch to the left side of the crista dividens (cd). In this section the foramen ovale-flap (fof) divides the left atrium (la) in two. The position of the spine is shown by 'S'

right portion of the proximal inferior vena cava (Figure 1). In a plane slightly to the left of the abdominal inferior vena cava, a left *ductus venosus–foramen ovale pathway* was visualized by the umbilical sinus, the ductus venosus, the left portion of the proximal inferior vena cava, the foramen ovale and the left atrium (Figure 8). The blood flow visualized along this pathway distended the foramen ovale-flap like a spinnaker during most of the heart cycle (Figures 4 and 9). M-mode recordings in eight cases showed that the foramen ovale-flap moved towards the septum during the short atrial contraction and caused a substantial reduction in the foramen ovale diameter in the transverse section. The flow seemed mainly to feed the left atrium but to some extent even the right atrium (Figure 9). The left and medial hepatic veins were connected to the left ductus venosus–foramen ovale pathway in the left portion of the proximal inferior vena cava following along a groove fenced off from the right atrium by the Eustachian valve and the atrial septum until arriving in the left atrium (Figures 1, 10 and 11).

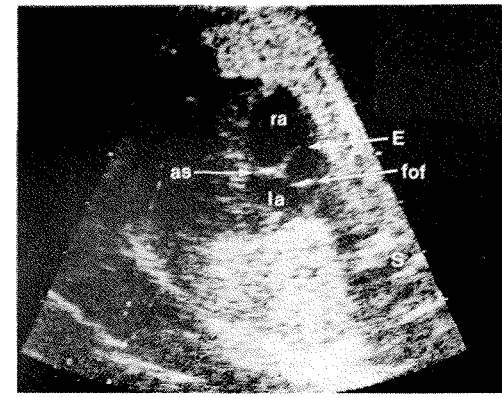

Figure 5 Transverse section of the heart immediately above the diaphragm shows the inferior vena cava continuing as a tube between the left atrium (la) and the right atrium (ra). The walls are formed by the Eustachian valve (E) and the foramen ovale-flap (fof). The position of the atrial septum and the spine are shown by 'as' and (S), respectively

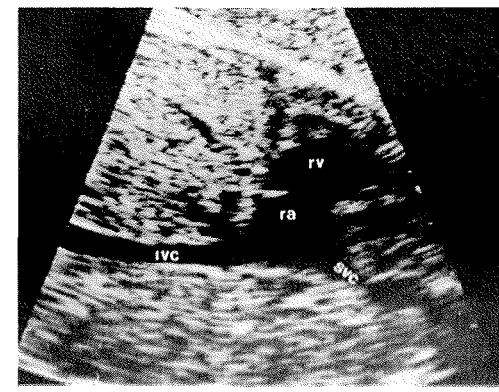

Figure 6 Sagittal insonation showing the inferior vena cava (IVC) entering the right atrium (ra). The ductus venosus cannot be seen in this section. The position of the right ventricle and superior vena cava are shown by 'rv' and 'SVC', respectively

The proximal inferior vena cava was described in a left and right portion with an elliptic cross-section (Figures 1 and 10). The inlet of the left and the medial hepatic veins to the left side, and the right hepatic vein to the right, made this division more distinct. Color Doppler imaging showed different velocity patterns in the two halves. The two pathways had the proximal inferior vena cava in common but traversed this short portion at different directions and in different sites (Figure 2). In the interface between the two pathways, turbulence could be recorded (Figure 12).

DISCUSSION

At first glance, the arrangement of the venous inlet to the heart, with a number of vessels in different directions, and a wide proximal inferior vena cava appears compli-

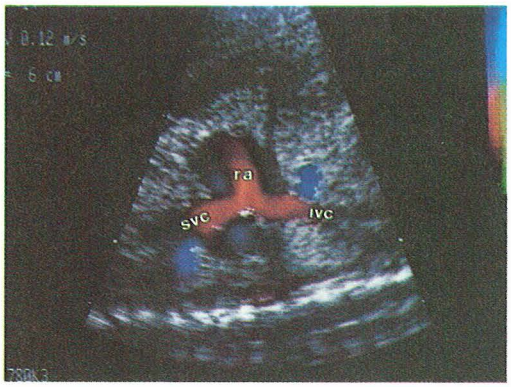

Figure 7 Color Doppler imaging shows blood flow from the inferior vena cava (IVC) and superior vena cava (SVC) entering the right atrium (ra). The ductus venosus cannot be seen in this section

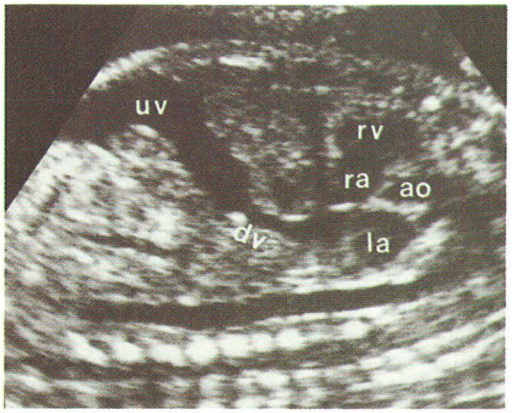

Figure 8 Sagittal section showing the umbilical vein (uv), and ductus venosus (dv) connected to the left atrium (la) divided off from the right atrium (ra). The distal inferior vena cava was not seen in this section. The position of the aorta and right ventricle are shown by 'ao' and 'rv', respectively

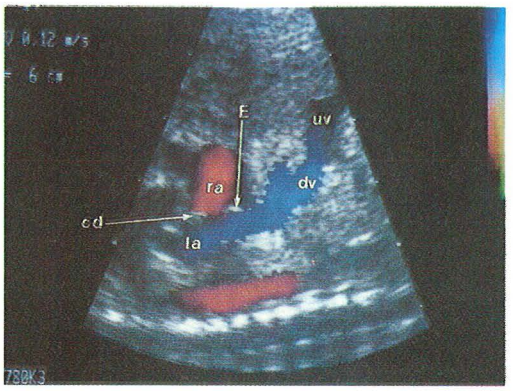

Figure 9 Color Doppler traces blood flow from the umbilical vein (uv) through the ductus venosus (dv) into the left atrium (la) divided off from the right atrium (ra) by the Eustachian valve (E) and the crista dividens (cd). Some blood appears to enter the right atrium above the Eustachian valve

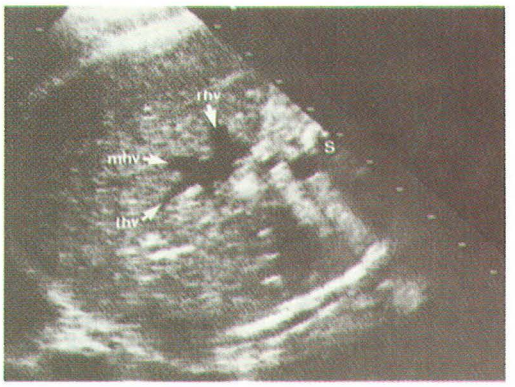

Figure 10 Cross-section of the venous inlet below the diaphragm. Left hepatic vein (lhv) and medial hepatic vein (mhv) enter together in the left side of the inferior vena cava. The right hepatic vein (rhv) enters the right side. The position of the spine is shown by 'S'

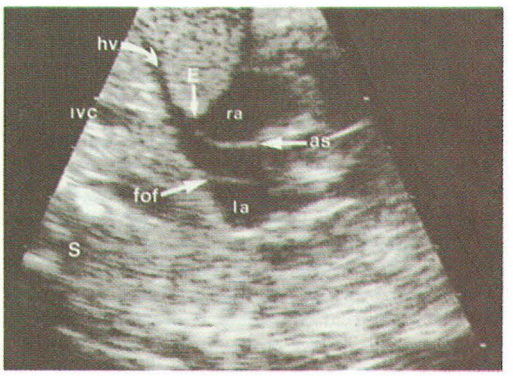

Figure 11 Oblique section showing a hepatic vein (hv) directly connected to the foramen ovale and divided off from the right atrium (ra) by the atrial septum (as) and Eustachian valve (E). Inferior vena cava: IVC; left atrium: la; foramen ovale-flap: fof; spine: S

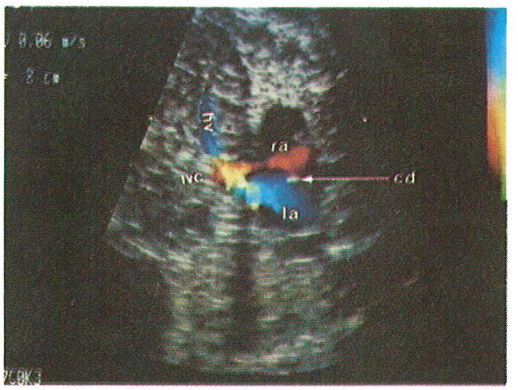

Figure 12 The two pathways cross and touch in the proximal portion of the inferior vena cava (IVC). Color Doppler shows turbulence (yellow) at their interface. Crista dividens: cd; hepatic vein: hv; left atrium: la; right atrium: ra

cated, and might easily lead to the conclusion that the blood is mixed extensively in the proximal portion of the inferior vena cava and the atria. The anatomical arrangement and the blood flow pattern, however, suggest a logical order where oxygenated and deoxygenated blood each flow into their respective compartments just as well as food and air are organized in the crossing pathways in the throat. This study shows that, in the human fetus, the inferior vena cava is closely connected to the foramen ovale in a vertical Y-shaped unit (Figure 4). The atrial septum resides in the middle with the crista dividens separating the short branch that leads to the right atrium from the long branch that leads to the left atrium. The inferior vena cava is actually extended into a short interatrial tube formed on the right side by the Eustachian valve (Figure 5) and on the left side by the foramen ovale-flap. These sonographical findings in the live human fetus are in agreement with the early descriptions made by Sabatier, Kilian and Wolff (reviewed in ref. 10) and the later angiographic studies describing the inferior venous inflow to the heart as a vertical fountain dividing into a right and left portion[11–14]. Such an arrangement permits the blood to enter the left atrium directly from the inferior vena cava. Our color Doppler recordings support this view by showing flow directed mainly vertically (Figures 7 and 9). The hypothesis, that blood is delivered directly to the left heart circumventing the right atrium, was challenged early by Pohlmann (reviewed in ref. 10). His opposing theory suggests that the inferior vena cava blood first enters the right atrium and then flows through the foramen ovale to reach the left atrium. Such a concept is still referred to in ultrasound studies[7,8] and may be valid especially in postnatal life when transatrial blood flow is of clinical interest[9]. According to the present observations in healthy fetuses, however, the blood seems to flow directly from the inferior vena cava either to the left or to the right atrium, rather than follow a transverse course through the foramen ovale.

Is there a difference between the blood that goes to the left atrium and the blood that goes to the right atrium? Sonographically, it was possible to observe a separate right inferior vena cava–right atrium pathway in a sagittal section (Figures 2 and 6) projecting blood from the distal inferior vena cava slightly anteriorly into the right atrium (Figure 7). The blood in the distal inferior vena cava has a low oxygen saturation[15] and seems to pass through the right portion of the proximal inferior vena cava and mainly enters the right atrium together with the superior vena cava blood. By insonation in a sagittal section slightly to the left, a separate left ductus venosus–foramen ovale pathway can be visualized (Figures 2 and 8) bypassing the inferior vena cava–right atrium pathway at the level of the proximal inferior vena cava at an angle of 48°. The umbilical blood is accelerated in the ductus venosus[5] and directed toward the foramen ovale (Figure 9) through the left portion of the proximal inferior vena cava. These observations are in agreement with the results obtained from fetal lambs[2–4]. Oxygenated umbilical blood follows a preferential stream through the foramen ovale to reach the left heart and brain.

The position and direction of the hepatic veins seem to favor a functional division of the proximal inferior vena cava. The left and medial hepatic vein join the ductus venosus in the left side of the proximal inferior vena cava (Figures 1 and 10), and the right hepatic vein joins the right side. This is in concordance with fetal lamb studies[4] and supports the hypothesis that the left and medial hepatic veins join the ductus venosus to supply the preferential bloodstream to the left atrium.

It has been of special interest to note that the left and medial hepatic veins, at least in some sections, seem to be directly connected to the foramen ovale and the left atrium, following along a groove-like structure in the inferior vena cava, and divided off from the right atrium by the atrial septum and the Eustachian valve (Figure 11). Such a design possibly reduces the risk of admixture of deoxygenated blood from the right portion of the inferior vena cava.

Although a separate left ductus venosus–foramen ovale pathway and a right inferior vena cava–right atrium pathway can be defined, a certain mixture is probably unavoidable since both pathways have the proximal portion of the inferior vena cava in common. Traversing their respective left and right compartments, the blood flows have an interface where turbulence can be traced (Figure 12). One could speculate that even this contact might be of some hemodynamic importance; at least some of the hepatic vein flow has a more horizontal route (Figures 1, 10 and 11). According to hydrodynamic principles, such a crossing 'jet' could make the ascending inferior vena cava blood flow deviate more anteriorly when touching at the crossing point. This might particularly become true during fetal respiration which causes a substantial increase in the blood velocities[16,17].

Methodological restrictions should be kept in mind when evaluating the results of our study. Color Doppler ultrasonography shows the velocity and direction of flow in a one-section plane, but it does not discriminate between contributions from different sources in the way that angiography does. Additionally, the spatial resolution of color Doppler imaging is inferior to that of two-dimensional ultrasonography. A high number of vessels in the area may interfere with the signals. The right pulmonary vein, the superior vena cava and the coronary sinus are especially close to the foramen ovale and may contribute to the flow recorded near the atrial septum and foramen ovale. The two-dimensional measurements that we made showed a substantial variation. The variation reflects not only intraobserver variation but also biological variation, including considerable differences in position of the fetal torso (bending forward, stretching out, twisting, etc.). Additionally, the interpretation of the direction of the vessels themselves may represent a source of error. Their natural course is often not straight and may cause arbitrary angle measurements. Although a portion of the vein is found to be reasonably straight and suitable for assessment of the angle, it is the last portion into the inferior vena cava

that determines the flow direction of interest. The last portion, however, is often given an additional final curve in the posterior direction, that is not always possible to catch in an angle measurement. The data, however, do give an impression of the arrangement of vessels as shown in Figures 1 and 2.

It is tempting to speculate on the inferior vena cava–foramen ovale relation as a Y-shaped unit. One can imagine that the long left branch, which mainly consists of the thin foramen ovale-flap, is distended in a manner similar to a spinnaker due to a large amount of high-velocity umbilical blood directed towards the flap by the ductus venosus and hepatic veins. Dawes and colleagues described a pressure gradient between the proximal inferior vena cava and the left atrium of 0.2–1.0 mmHg in the fetal lamb before birth[1]. Based on the increased pressure in the left atrium during the short atrial contraction, they deduced that the foramen ovale-flap probably was closed during the same period. In both our two-dimensional and M-mode recordings, the foramen ovale-flap was found to be extended during the whole cardiac cycle with the exception of the short period of atrial contraction. During that contraction, the foramen ovale-flap and the crista dividens met; however, in contrast to the inferior vena cava[18], there is a forward flow in the ductus venosus[17] even during atrial contraction. This increases the proportion of oxygenated blood in the proximal inferior vena cava. By these arrangements, one can imagine the foramen ovale branch to be flooded abundantly with oxygenated blood. The left heart receives from this flood according to the peripheral demand. The overflow spills directly over to the right side causing an improved oxygen saturation even in the right atrium. Such a view does not contradict the results obtained from studies on the fetal lamb[4,15]. After birth, the umbilical circulation is interrupted and the 'wind' towards the spinnaker subsides. On the other side, the pulmonary vein flow increases. The pressure gradient between the inferior vena cava and the left atrium drops[1] and thus the foramen ovale-flap comes down to the septum.

A better knowledge of the blood delivery through the inferior vena cava–foramen ovale complex into the fetal heart may deepen the understanding of the developing normal fetal heart and developmental disorders. The inferior vena cava–foramen ovale unit seems to be a flexible device for blood distribution to the heart. The upper part of this unit is wide and there is a broad contact between the two branches under the crista dividens. Even minor pressure changes between the two atria could be immediately equilibrated by the vertical fountain. A reduction of the left heart output would instantly give an increased overflow to the right atrium at the level of the inferior vena cava–foramen ovale unit causing an increased volume load on the right side.

In conclusion, this study supports the hypothesis that the human fetal inferior venous return is arranged in a Y-shaped inferior vena cava–foramen ovale unit. The left branch seems to be fed by blood from a left ductus venosus–foramen ovale pathway; on the opposite side the right branch of the Y seems to receive the blood flow from a right inferior vena cava–right atrium pathway. The two pathways cross and touch in the common widened proximal portion of the inferior vena cava. The left and medial hepatic veins contribute to the ductus venosus–foramen ovale pathway passing through the left part of the inferior vena cava to reach the foramen ovale. The direction of these vessels, the arrangement of the Eustachian valve and the septum, the high volume of oxygenated blood, and the high blood velocity probably constitute the physical prerequisites for a functioning left ductus venosus–foramen ovale pathway, avoiding extensive admixture with deoxygenated blood in the inferior vena cava. Our study supports the hypothesis that blood is injected directly from the ductus venosus and hepatic veins into the foramen ovale, rather than intermediately brought to the right atrium before entering the foramen ovale.

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Paper III

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Ductus Venosus Blood Velocity Changes in Fetal Cardiac Diseases

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Objective: The ductus venosus (DV) directs oxygenated umbilical blood by a high velocity jet directly into the inferior vena cava (IVC) and foramen ovale for preferential distribution to the left heart. Because the DV connects the umbilical vein (UV) directly to the IVC, it has been suggested that the DV velocimetry might reflect the pressure gradient between the UV and the atria. On the assumption that fetal cardiac disorders may alter the pressure gradient across the DV and accordingly alter the DV blood velocity, the present study aimed to describe the DV blood velocity in fetal cardiac disorders.

Methods: Of the 30 cases of fetal cardiac disorders included, 28 fetuses had congenital heart defects (CHD) (12 with isolated septal defects; 16 with ventricular inlet or outlet disorders), and two had supraventricular tachycardia. Each was examined once at gestational age 17–35 weeks. 2D-ultrasonography, color Doppler, and pulsed Doppler were used to make a hemodynamic assessment.

Results: Eight fetuses had reduced DV peak velocity; 19 had reduced DV velocity during atrial contraction (13 of the 19 had reversed blood flow). Malformations involving ventricular inlet or outlet were more commonly associated with reduced DV velocity during atrial contraction (13/16) than were isolated septal defects (5/12).

Conclusion: A substantial proportion of antenatally detected fetal cardiac disorders had an altered DV velocity. The blood flow during atrial contraction seems to be particularly vulnerable, especially in CHD directly involving ventricular pump function. The results indicate that DV velocimetry may be valuable in fetal hemodynamic assessment.

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Key words: Ductus venosus velocimetry–Fetal cardiac disorders–Doppler–Ultrasonography

In the fetal lamb, oxygenated blood flows from the placenta through the umbilical vein (UV) into the portal sinus (otherwise called umbilical sinus).[1–3] Half of the blood stream enters the liver parenchyma and the other half circumvents the liver through the ductus venosus (DV) directly into the thoracic inferior vena cava (IVC) (Fig. 1).[3–5] In the state of hypoxia, the proportion directed through the DV increases to 70%.[3,6] A sphincter in the DV has been discussed as a possible regulatory mechanism.[1,7–10] It seems possible that the liver itself plays an active role in regulating venous return.[3–6] The DV blood streams preferentially through the foramen ovale (FO) to the left heart to supply the myocard and the brain.[3,11,12] A similar pattern of hemodynamic regulation is believed to exist in the human fetus.[2,3,8]

It has been shown that high velocity blood in the human DV is directed posteriorly to enter the IVC and FO, and a typical velocity pattern has been described.[13,14] The pattern in the DV reflects the cardiac cycle much in the same way as the IVC and the hepatic veins, but with a positive velocity also during atrial contraction (Fig. 2). As the DV connects the UV directly to the IVC, it has been suggested that the DV velocimetry could reflect the pressure gradient between the UV and the atria.[14] A reduced umbilical venous pressure would cause a reduced velocity in the DV and, accordingly, a reduced direct injection of oxygenated blood. On the other side, an increased atrial pressure or otherwise altered atrial hemodynamics would also reduce the DV velocity.[13] This is the background for the hypothesis that changes in the fetal heart itself may alter the pressure gradient and the DV velocity pattern.

We set out to test the hypothesis that fetal cardiac disorders would cause an altered DV velocity. Our aim

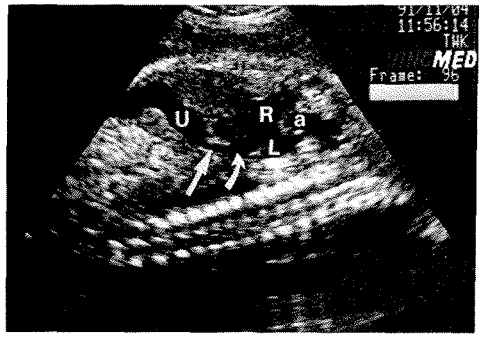

Fig. 1. Ductus venosus (straight arrow) connects the umbilical sinus (U) to the thoracic vena cava inferior (curved arrow) and left atrium (L). Right atrium (R). Aorta (a).

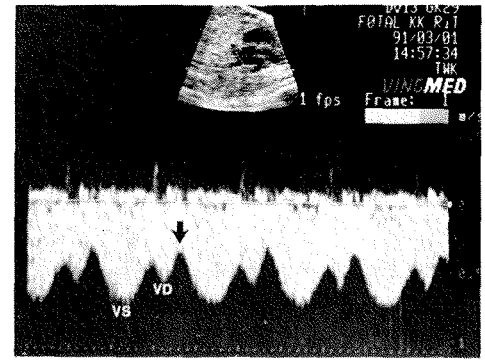

Fig. 2. Typical normal Doppler velocimetric recording of ductus venosus blood flow in week 29. V_{peak} during ventricular systole (VS); another peak during ventricular diastole (VD); a trough during atrial contraction, V_{min} (black arrow).

was to describe the DV velocity in fetuses with a known cardiac disease in order to describe the pattern of velocity changes in relation to the cardiac lesion. We were also interested in exploring the possibilities of the DV velocimetry as an indicator of fetal cardiac diseases in general.

Material and Methods

Thirty pregnancies with gestational age 17–35 weeks, with a known fetal cardiac disease, were consecutively examined as part of a hemodynamic evaluation during the period including May 1990 to January 1992 (Table 1). They were recruited either from the local pregnant population or referred from other hospitals. Gestational age had been assessed by ultrasonography around week 18. Twenty-eight fetuses had congenital heart defects (CHD) and two had supraventricular tachycardia (SVT). The CHDs consisted of 12 cases of septal disorders and 16 cases with disorder of the ventricular inlet or outlet, with or without septal defects. Eleven fetuses had edema or effusion into a body cavity. Sixteen cases were of known abnormal karyotype and 18 had additional structural malformations. The diagnoses were confirmed by neonatal assessment or by autopsy.

A Vingmed 750 CFM ultrasound scanner (Vingmed Sound, Horten, Norway) was applied combining sector scan, color Doppler and pulsed Doppler. A 5 MHz sector scanner carrying a 4 MHz Doppler unit was used with a spatial peak temporal average intensity (Ispta) set to 5 and 45 mW/cm^2, respectively. Alternatively, a 3.75 MHz sector scanner carrying a 2.5 MHz Doppler unit was applied with an Ispta setting of 6 and 10 mW/cm^2, respectively.

The DV was identified near the midsagital section or in an oblique transection of the fetus demonstrating a luminal connection between the UV and the IVC.[14] Color Doppler ensured the identification and insonation angle for correction of the velocity values. Pulsed Doppler signals were recorded with a sample volume 4–10 mm placed immediately above the DV inlet.[14] The Doppler frequency shifts were stored on a computer for later analysis of the maximum velocity tracing to evaluate peak velocity (V_{peak}) during ventricular systole and the lowest velocity (V_{min}) recorded during the atrial contraction. Stable tracings representing at least four heart cycles in fetal quiescence were used for the analysis, and only one tracing from the first examination of each patient was included. The recordings were compared with the normal values established in a previous study applying the same technique.[14]

In addition, velocity recordings from the UV, the umbilical artery, the tricuspid, and the mitral valve were part of the assessment. An atrioventricular regurgitation was defined as significant when it was holosystolic.

Fisher's exact test was applied to test the significance of differences.

Results

The results of Doppler velocimetry and outcome for the 30 fetuses are presented in Table 2. Of a total of 30 patients, eight had a reduced V_{peak} in the DV (Fig. 3). The V_{min} in the DV during atrial contraction, however, was reduced (below the 95% confidence limit) in 19 of the cases (Fig. 4).

In the CHD group of 28 cases (nos. 1–28), seven had a reduced V_{peak}, 18 had a reduced V_{min}, and nine had a reversed flow (Fig. 5). In the subgroup of 12 cases of isolated septal defects (nos. 1–12), V_{peak} was reduced in three, V_{min} was reduced in five and one had regurgitation. In the subgroup of 16 cases of structural malformations involving ventricular inlet or outlet (nos. 13–28) the DV V_{peak} was reduced in four, V_{min} was reduced in 13, and regurgitation in eight cases. The difference in number of reduced V_{min} between the

Table 1. Pregnancies with a known fetal cardiac disease.

No.	Cardiac diagnosis	Gest age	Other malformations	Karyotype	Hydrops
1	ASD	31	Omphalocele	Normal	Pleural effusion
2	VSD	31	CCA, right hydronephrosis	T18	
3	VSD	20	Right renal agenesia, club foot, SUA	69XXX	
4	VSD	29	Spina bifida, club foot	T18	
5	VSD	21	Spina bifida, omphalocele, renal dysplasia	69XXX	
6	VSD	17	Cystic hygroma	T21	Edema, ascites
7	VSD	19	Cystic hygroma	Normal	
8	ASD, VSD	19	Cystic hygroma, renal dysplasia	Not known	Pleural effusion, ascites
9	ASD, VSD	18		T21	Ascites, enlarged liver
10	AVSD, VSD	19		pT14	Edema
11	AVSD	31		T21	Ascites
12	AVSD	19		T21	
13	VSD, corrected TGA, PA, ASD, isomerism	31	Duodenal atresia	Normal	
14	VSD, trunc, pulmonary window	33		Normal	
15	VSD, hypoplastic RV, TA, PA	36	Esophageal atresia, anal atresia, oligodactyly	T18	
16	VSD, hypoplastic LV, TI, DIRV, block 2 : 1	31		Normal	Pericardial effusion
17	VSD, PA	32	VACTERL association, SUA	Normal	
18	VSD, PA	19	Holoprosencephalon, renal dysplasia	T13	Ascites, pericardial effusion
19	Coarctation of aorta	18		pT18	Edema, pericardial effusion
20	Coarctation of aorta, VSD	33	Holoprosencephalon	Normal	
21	Coarctation of aorta	34		Normal	
22	ASD, coarctation of aorta	31	Goldenhar syndrome	Normal	
23	ASV, VSD, overriding aorta	32	Diaphragmatic hernia	T18	
24	Fallot	18	Epigastric omphalocele, bladder exstrophy	T13	
25	ASD, VSD, TA	21	Dandy Walker cyst, SUA	pT18	
26	SV, SA, trunc, block 3 : 1	19		Normal	Pleural effusion, ascites
27	Tricuspid atresia	19		Normal	Neck edema
28	ASD, VSD, common AV-valve	18	Diaphragmatic hernia	T18	
29	SVT (214)	30			
30	SVT (240)	23			

ASD = atrial septal defect, AVSD = atrioventricular septal defect, CCA = corpus callosum agenesia, DIRV = double inlet right ventricle, LV = left ventricle, PA = pulmonary atresia, pT = partial trisomy, RV = right ventricle, SA = single atrium, SUA = single umbilical artery, SV = single ventricle, SVT = supraventricular tachycardia, T = trisomy, TA = tricuspid atresia, TGA = transposition of the great arteries, TI = tricuspid insufficiency, VACTERL = association including vertebral, anal, cardiac, tracheal, esophageal, renal and limb dysgenesis, VSD = ventricular septal defect

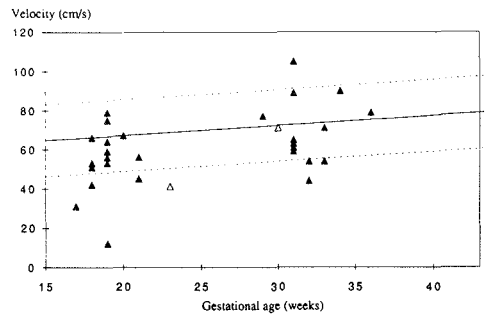

Fig. 3. Ductus venosus V_{peak} in 30 fetuses with cardiac disorders compared with regression line (solid line) and 95% confidence limits for normals (broken lines). Structural cardiac malformations (filled triangles); supraventricular tachycardia (empty triangles).

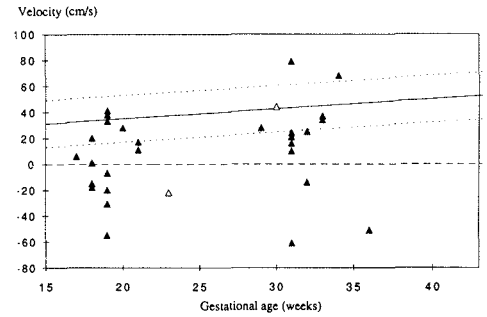

Fig. 4. Ductus venosus V_{min} during atrial contraction in 30 fetuses with cardiac disorders compared with regression line (solid line) and 95% confidence limits for normals (broken lines). Structural cardiac malformations (filled triangles), supraventricular tachycardia (empty triangles), zero velocity (horizontal broken line).

Table 2. Results and outcome.

No.	DV Vpeak (cm/s)	DV Vmin (cm/s)	AV regurgitation	UV pulsation	Outcome
1	60	**21**			Early neonatal death
2	64	**21**		Yes	Early neonatal death
3	67	28			TOP
4	77	28			TOP
5	**45**	**11**			TOP
6	**31**	**6**		Yes	TOP
7	53	33			TOP
8	**12**	**−7**		Yes	TOP
9	66	20			TOP
10	79	39			TOP
11	89	79			Live birth
12	59	38			TOP
13	61	**16**			Infant death
14	71	37			Live birth
15	79	**−51**		Yes	Early neonatal death
16	105	**−61**	Yes	Yes	Neonatal death
17	**44**	**−14**		Yes	Neonatal death
18	64	**−20**			TOP
19	**42**	**−16**		Yes	TOP
20	**54**	34			IUFD
21	90	68			Live birth
22	64	**10**			IUFD
23	**54**	**25**			Early neonatal death
24	51	**−16**		Yes	TOP
25	56	**17**			TOP
26	75	**−55**	Yes	Yes	TOP
27	56	**−31**		Yes	TOP
28	52	**1**	Yes	Yes	TOP
29	71	44			Live birth
30	41	**−22**		Yes	Live birth

Velocity below the 95% confidence limit is shown in bold numbers. AV = atrioventricular, DV Vpeak = ductus venosus peak velocity, DV Vmin = ductus venosus minimum velocity, IUFD = intrauterine fetal death, TOP = termination of pregnancy, UV = umbilical vein.

subgroups was statistically significant ($P < 0.05$). When only the DV regurgitation was taken into account, there was still a statistically significant difference between the two groups—nos. 1–12 and nos. 13–28 ($P < 0.05$).

Pulsation in the UV was found in 12 cases having a corresponding negative DV V_{min} value in nine of the cases (Table 2). The remaining three cases of UV pulsation had DV V_{min} below normal values but still positive velocity.

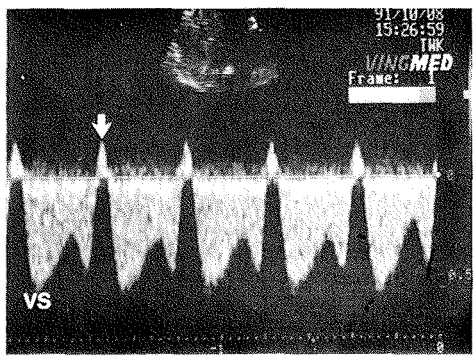

Fig. 5. Ductus venosus blood flow velocity in case 24 with Fallot's tetralogy, week 18. V_{peak} during ventricular systole (VS), V_{min} shows regurgitation during atrial contraction (arrow).

The three cases of atrioventricular regurgitation (nos. 16, 26, and 28) had reduced DV V_{min} and two had reversed flow during atrial contraction. The third one (no. 28) had V_{min} 1 cm/s.

Of the two cases of SVT, one fetus had reduced V_{peak} and reversed V_{min} during the tachycardia. Velocities improved, however, after conversion to normal rhythm (Fig. 6). A total of four cases (nos. 16, 26, 29, and 30) had altered rhythm and three of them were combined with reversed DV flow during atrial contraction (Table 2).

Chromosomal aberration was identified in 16 cases of CHD, and 10 of them had an altered DV velocity pattern. This was not statistically different from the group of 11 cases of CHD with a normal karyotype and seven instances of DV velocity alteration.

Hydrops or effusion in a body cavity occurred in 11 cases. Three of them had reduced V_{peak} and eight had reduced V_{min}.

Umbilical artery velocimetry revealed one case of diastolic zero-flow (no. 8) and one case of diastolic

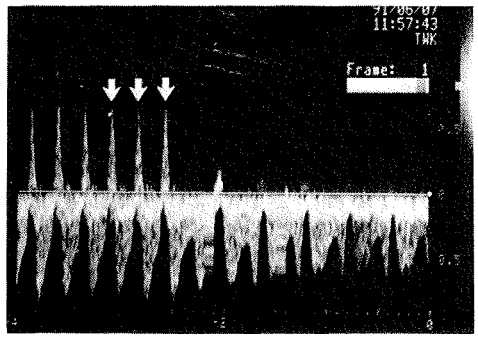

Fig. 6. Ductus venosus blood flow velocity in case 30 with supraventricular tachycardia in week 23. Reversed flow (arrows) is recorded during atrial contraction at the time of tachycardia. The regurgitation disappears after conversion to normal rhythm.

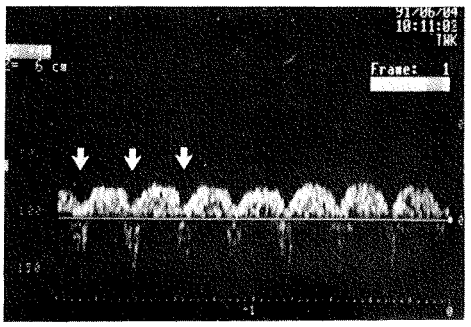

Fig. 7. Intraabdominal umbilical vein pulsation (arrows) corresponding to the ductus venosus regurgitation during tachycardia in case 30.

reversed flow (no. 24). The remaining 28 fetuses had normal wave forms.

Sixteen pregnancies were terminated. The remaining group of CHD had a perinatal mortality of 6/12. Three are still alive. The two cases of SVT had an uneventful course after birth.

Discussion

CHD is not easily detected antenatally and the detected cases are usually of a serious type.[15,16] This has to be considered when evaluating our results. CHD seems to influence the blood flow in the DV. About 3/4 of the fetuses with CHD managed to maintain a normal V_{peak} and thereby maintain a normal oxygen transport to the left heart in a major part of the cycle (Fig. 2). However, during the short period of atrial contraction, 18 of the 28 fetuses with a CHD had a reduced or reversed DV blood velocity, in contrast to the normal fetuses with no negative DV flow under standard conditions.[14] This supports the hypothesis that the short period of atrial contraction is the most vulnerable phase of the DV flow, and suggests that this phase is a sensitive indicator of altered hemodynamics.[13]

There was a wide variety of structural abnormalities. The group of septal defects without ventricular inlet or outlet disorder (nos. 1–12) had DV regurgitation during the atrial contraction in one of the cases. The more complicated cases, including changes in atrioventricular valves or great arteries (nos. 13–28), had regurgitation in the DV during atrial contraction in half of the cases. Compared with the normal population, this is a substantial alteration of the DV flow pattern. Malformations of the AV valves, the great arteries and their valves had a statistically higher impact on the DV velocity than the septal defects alone. Thus, the malformations directly involving the pump function itself seem especially capable of altering the DV flow.

Cardiac arrhythmia was recorded in four cases, and three of them had DV regurgitation. This is an interesting finding, but the numbers are too small to draw a conclusion.

Regurgitation in the AV valves was recorded in three cases and was associated with reversed DV blood flow during atrial contraction. From a theoretical point of view, a holosystolic mitral or tricuspid regurgitation may raise the atrial pressure and reduce the DV flow at least during atrial contraction, as illustrated in the three cases. The numbers are, however, too small for any conclusion.

Hydrops or effusion in a body cavity occurred in 11 of the cases but only eight of them had altered DV velocity indicating an altered pressure gradient between the UV and the atria, at least during the atrial contraction. However, three cases of hydrops had normal DV velocity (at least at the time of examination), suggesting that hydrops may be due to other causes. This is further emphasized by the fact that four of the 11 cases of DV regurgitation had no hydrops. However, an altered pressure gradient may play a central role in many fetuses developing hydrops as seen in our study.

Umbilical vein pulsation has been described as a possible indicator of hemodynamic derangement in the hydropic fetus.[17] In our patients, umbilical vein pulsation was recorded in 12 cases and nine of these were associated with a regurgitation through the DV during atrial contraction (Figs. 5–7). The remaining three had a reduced velocity during atrial contraction (V_{min}). This supports the theory that the atrial systole in these cases gives a reversed pulse down the DV into the umbilical sinus and UV.[13,14]

The outcome in the study group is poor. Aside from 16 terminations of pregnancy, the remaining group had a high mortality. Our group is selected and the numbers too small to permit any conclusion on the DV flow changes as a prognostic sign.

An indicator of CHD would be of help in clinical work. The rate of antenatally detected CHD is known to be low, and serious malformations are more frequently detected than minor ones.[15,16] Could DV velocimetry be applied as a simple test for fetal heart dis-

ease? The sensitivity of a DV V_{min} below the 95% CI, however, is 64% (100% × 18/28) for the CHD in our study group of antenatally detectable cardiac malformations. The sensitivity is, however, improved to 81% (100% × 13/16) when considering only the malformations involving AV valves and great arteries. This group of CHD is of special interest as it may heavily influence the counseling as well as the management of the pregnancy and of the newborn. However, there are a few facts to be considered when evaluating the DV velocimetry. A high proportion of chromosomal aberrations and other malformations could, per se, be a cause of the hemodynamic changes recorded in the fetuses, or could at least have an additive effect, reducing the importance of the DV velocimetry itself. Furthermore, intraobserver variation has to be taken into account as expressed in the limits of agreement for V_{min} {−15; 12 cm/s} and true limits of agreement {−18; 14 cm/s} indicating the reproducibility.[14] These are liberal limits, evoking caution when interpreting the measurements. Negative V_{min}, however, would be a more robust criterium than just reduced V_{min}. It is easily recognized and thus clinically more applicable. In our selected group of CHD, negative V_{min} has a sensitivity of 30% (100% × 9/28) which is low. It is also low, 50% (100% × 8/16), in the group of serious malformations (ventricular inlet and outlet involvement). Applying reversed DV blood flow as a diagnostic criterium may be too crude. As can be deducted from Figure 4, there is a slight increase of velocity during the course of pregnancy, making a regurgitation less probable towards the last weeks. DV velocimetry can be applied in a hemodynamic evaluation of CHD but the measurements should be interpreted with caution. A broader study is needed to see whether the low sensitivity of today's screening for CHD can be improved by adding a measurement like the DV velocimetry.

Assuming that the DV blood velocity is important for the preferential bloodstream through the FO, the DV velocimetry may give valuable information on the state of the oxygen transport to the left side and may elucidate hemodynamic changes in CHD and arrhythmias in the fetus. Our study shows that a substantial proportion of the fetuses with a CHD has an altered DV blood velocity in contrast to the normal ones.

Acknowledgments. The text was revised by Nancy Lea Eik-Nes.

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Paper IV

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Ductus venosus blood velocity and the umbilical circulation in the seriously growth-retarded fetus

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Key words: INTRAUTERINE GROWTH RETARDATION, DUCTUS VENOSUS, BLOOD FLOW, DOPPLER ULTRASOUND

ABSTRACT

Based on the assumption that the ductus venosus is a regulator of oxygenated blood in the fetus, the present study investigated the blood flow velocity of the ductus venosus in relation to the umbilical circulation in the seriously growth-retarded fetus. The study group of 38 fetuses (gestational week 17–39) had no chromosomal aberrations or structural malformations and had an ultrasonographic biometry of < 2.5th centile and birth weight of ≤ 2.5th centile. Of the 38 fetuses seven died in utero *and four died postnatally. The ultrasonographic examination included pulsed Doppler measurement of the umbilical artery pulsatility index (PI), the umbilical vein dimension and blood flow velocity, and the peak and maximum blood flow velocities of the ductus venosus. The majority of fetuses had a raised PI in the umbilical artery (26/38) and reduced blood flow in the umbilical vein (25/33). Despite such changes in the umbilical circulation, a normal peak velocity in the ductus venosus was maintained in all fetuses. During the atrial contraction, however, 13 fetuses had reduced or reversed blood velocity in the ductus venosus. Reduced ductus venosus velocity during atrial contraction seemed to be a serious finding linked to raised PI and absent or reversed end-diastolic flow in the umbilical artery, and umbilical vein pulsation. The results support the assumption that the blood flow of the ductus venosus is a preferential bloodstream in the human fetus that is maintained within normal ranges as long as possible during placental hemodynamic compromise.*

INTRODUCTION

The ductus venosus has long been discussed as being a main distributor of oxygenated blood in the fetus[1–4]. It is a narrow, trumpet-shaped vein with an isthmic entrance, which remains narrow throughout the last half of pregnancy[5,6]. The geometrical properties of the ductus venosus and its anatomical position as the only direct communication between the umbilical vein and the central venous system indicate specific hemodynamic tasks in intrauterine life. Studies in fetal lambs have shown that half of the oxygenated blood returning from the placenta is directed through the ductus venosus, forming the preferential bloodstream through the foramen ovale to the left heart[7–9]. Recent work supports the assumption that a similar pattern of blood flow distribution exists in the human fetus[10]. In the human ductus venosus, well-oxygenated blood is accelerated into a high-velocity jet towards the foramen ovale[11,12]. Additionally, the left and medial hepatic veins deliver reasonably well-oxygenated blood to the same preferential bloodstream[10,13]. During induced hypoxia in the fetal lamb, pressure in the umbilical vein increases, and there is an increased proportion of umbilical blood flowing through the ductus venosus rather than through the liver[14,15]. In such cases in the fetal lamb, the ductus venosus is reported to shunt 70% of the umbilical blood directly into the thoracic inferior vena cava. A similar shift from the hepatic flow to the ductus venosus is seen when the cord is partially clamped or during acute hemorrhage[15–17]. It is reasonable to believe that the umbilical venous return is regulated along the same principles in the human fetus. Since intrauterine growth retardation (IUGR) is thought to be associated with placental compromise and hypoxia, the described pattern of blood redistribution could possibly be found in such patients.

The present study aimed to investigate the blood flow velocity in the ductus venosus, and its relation to the umbilical circulation in the seriously growth-retarded fetus.

METHODS

Patients were recruited from the high-risk clinic at the National Center for Fetal Medicine. They were included

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in the study according to a protocol approved by the regional committee of ethics. The criteria for inclusion, based on observations using ultrasound, were: singleton pregnancy, gestational age assessed before week 20, normal anatomy assessed by routine ultrasound examination, and fetal biometry below the 2.5th centile. To assess intrauterine growth, the biparietal diameter and mean abdominal diameter were compared to nomograms established by Eik-Nes and Grøttum (Scanmed, Drammen, Norway). Exclusion criteria were birth weight of > 2.5th centile, malformations detected after birth and chromosomal aberrations. A total of 53 patients were recruited, but 13 were later excluded, due to an actual birth weight of > 2.5th centile. Another two cases were excluded because of malformations detected after birth (clubfoot, hypospadia), leaving 38 fetuses in the study.

In the study group of 38 cases, 22 women were smokers, one had anti-cardiolipin antibodies, one had protein C deficiency, one was under treatment for hypertension, and eight developed pregnancy-induced hypertension. The general policy of our department during the study period was not to deliver by Cesarean section below a gestational age 26 weeks and 0 days. One patient, however, had a Cesarean section performed at 23 weeks on maternal indications, and another at 25 weeks on fetal indications at a different hospital.

Hemodynamic evaluation was by means of a Vingmed CFM 750 ultrasound scanner (Vingmed Sound, Horten, Norway). A 5-MHz sector scanner carrying a 4-MHz Doppler unit was used with a spatial peak temporal average intensity set to 2 mW/cm^2 for the sector scan, 2 mW/cm^2 for the color flow, and 45 mW/cm^2 for the pulsed Doppler. Alternatively, a 3.75-MHz transducer carrying a 2.5-MHz Doppler unit was applied with a setting of spatial peak temporal average intensity of 2 mW/cm^2 for the sector scanner, 3 mW/cm^2 for the color flow, and 49 mW/cm^2 for the pulsed Doppler.

A sling of the umbilical artery was identified by two-dimensional imaging and color Doppler, and pulsed Doppler signals were recorded. The PI was calculated from 4–8 heart cycles. The PI for the umbilical artery was considered elevated if it was above the 95% reference ranges. The normal ranges were based on a longitudinal study which included 290 observations in 59 normal pregnancies. Fetal heart rate was calculated from the signals of the umbilical artery or the ductus venosus.

The maximum blood flow velocity in the umbilical vein (V_{uv}) was recorded in the straight intra-abdominal portion and corrected for angle of insonation. The inner diameter (D_{uv}) was measured at the same level. Velocity calculation in the umbilical vein was based on the maximum Doppler shift during 2–4 s. The velocity and the recorded diameter were used to calculate the umbilical venous blood flow by the formula $\frac{1}{2}V_{UV} \cdot \pi(\frac{D_{uv}}{2})^2$, assuming that the velocity had a parabolic profile. Umbilical blood flow below the 95% reference ranges for normal fetuses was considered to be reduced. Umbilical vein pulsation in fetal quiescence was recorded when decrements of the maximum velocity with a frequency corresponding to that of the heart rate occurred in the intra-abdominal portion of the vessel.

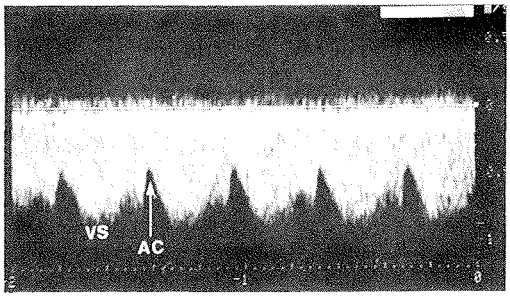

Figure 1 Normal ductus venosus blood velocity recorded by pulsed Doppler ultrasound in week 26. The maximum velocity varied during the heart cycle with the peak velocity in the ventricular systole (VS) and the minimum during atrial contraction (AC)

The ductus venosus was identified in a mid-sagittal section or an oblique transection of the fetal abdomen. The angle of insonation was determined by color Doppler according to a previously described technique[11], and pulsed Doppler signals were recorded from the isthmic portion of the ductus venosus. Peak velocity was defined as the maximum velocity during ventricular systole (Figure 1), and minimum velocity was defined as the lowest maximum velocity recorded during atrial contraction. Peak velocity and minimum velocity were calculated from at least four heart cycles. Blood velocities below the 95% reference ranges[11] for normal fetuses were considered to be reduced.

The Doppler signals were stored and analyzed off-line. Only signals obtained during fetal quiescence were included for analysis. In the case of repeated examinations, only the last set of recordings before birth was included in the statistics. Fisher's exact test was used to assess differences in distribution between groups.

RESULTS

The 38 babies (23 females and 15 males) included in the study were born at a median gestational age of 35 weeks 2 days (range 18 weeks 0 days to 39 weeks 6 days) with a median birth weight of 1550 g (range 105–2380 g). Of the 31 liveborn babies, eight were delivered vaginally and 23 by Cesarean section. The arterial cord pH at birth was measured in 28 newborns, median 7.29 (range 7.14–7.39). The Apgar score was ≤ 7 in five cases. The total mortality was 11 (29%). There were seven cases of intrauterine fetal death in weeks 18–27, and four babies died postnatally. One of these was delivered by Cesarean section at 23 weeks, and survived for an hour. The other three were delivered at 25, 27 and 30 weeks, and survived for four days, 9 months and 6 weeks, respectively. The median gestational age at birth for the 11 who died was 25 weeks 6 days (range 18 weeks 0 days to 30 weeks 3 days) compared to 36 weeks 6 days (range 29 weeks 5 days to 39 weeks 6 days) for the 27 who survived. The

Doppler velocimetry included in the present report was performed at median 2 days (range 0–34 days) before delivery.

The blood velocity of the umbilical artery was recorded in all 38 fetuses (Figure 2). The PI was elevated in 26 (68%). Absent or reversed end-diastolic flow was noted in 12 fetuses (32%). The mean heart rate was 140 beats/min (range 119–160). Reduced minimum velocity of the ductus venosus was more commonly found among the fetuses with elevated umbilical artery PI (12/26, 46%) than among the fetuses with normal PI (1/12, 8%; $p < 0.05$) (Figure 2). All deaths occurred in the group of fetuses with elevated umbilical artery PI (Figure 2).

Blood flow calculation of the umbilical vein was possible in 33 of 38 cases (Figure 3). Reduced blood flow was found in 25 cases (76% of 33). Raised PI in the umbilical artery was more common in the group with reduced umbilical vein blood flow (19/25, 76%), than in the group with normal umbilical vein blood flow (2/8, 25%; $p = 0.01$) (Figure 3). Reduced minimum blood velocity of the ductus venosus was combined with reduced umbilical blood flow in 9/25 cases (36%) compared to 1/8 (13%) in fetuses with normal umbilical flow ($p = 0.18$). Umbilical vein pulsation was encountered in 11 (30%) of 37 fetuses.

Blood velocity recordings of the ductus venosus were obtained for all 38 fetuses. The peak blood velocity in the ductus venosus was normal for all cases (Figure 4). However, during atrial contraction 13 (34%) had a reduced blood velocity in the ductus venosus, and six (16%) of these had reversed flow (Figures 5 and 6). Umbilical vein pulsation was more often found among fetuses with reduced minimum velocity in the ductus venosus (9/13, 69%) than among the fetuses with normal minimum velocity in the ductus venosus (2/24, 8%; $p < 0.01$) (Figure 5). Also absent or reversed end-diastolic flow in the umbilical artery was more commonly associated with reduced minimum velocity in the ductus venosus (10/13, 77%) than with normal minimum velocity in the ductus venosus (2/25, 8%; $p < 0.01$) (Figure 5). All seven intrauterine fetal deaths and 2/4 postnatal deaths occurred in the group of fetuses with reduced ductus venosus velocity during atrial contraction (Figure 7).

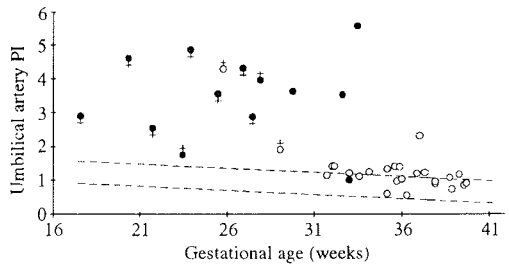

Figure 2 Pulsatility index (PI) in the umbilical artery in 38 seriously growth-retarded fetuses (circles). Filled circle, reduced ductus venosus minimum velocity; cross below circle, intrauterine fetal death; cross above circle, postnatal death; dashed lines, 95% references ranges

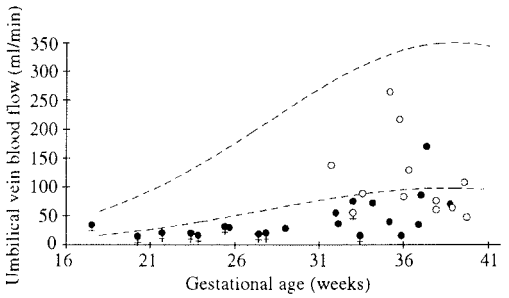

Figure 3 Umbilical venous blood flow in 33 seriously growth-retarded fetuses (circles). Filled circle, raised pulsatility index of the umbilical artery; cross below the circle, reduced ductus venosus minimum velocity; dashed lines, 95% reference ranges

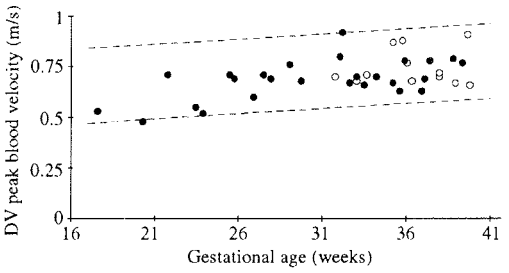

Figure 4 Peak velocity of the ductus venosus (DV) blood flow recorded during ventricular systole in 38 seriously growth-retarded fetuses (circles). Filled circle, increased pulsatility index in the umbilical artery; dashed lines, 95% reference ranges

DISCUSSION

In the present study a highly selected group of pregnancies complicated with IUGR was examined to shed light on the function of the ductus venosus and its relation to the umbilical circulation. Among the 38 cases, 68% had increased PI in the umbilical artery and 32% had absent or reversed end-diastolic flow. A reduced umbilical vein blood flow was found in 76% of our patients. This is a well-documented pattern for IUGR[18-22].

Under normal conditions, the peak blood velocity in the ductus venosus is described to be remarkably high, ranging from 50 to 100 cm/s in the last half of pregnancy[11,12]. It is interesting that the ductus venosus peak velocity was maintained within normal ranges in the entire group of fetuses with IUGR in spite of a compromised umbilical circulation (Figure 4). This result supports the assumption that the pattern of redistribution described in the fetal lamb also operates in the human fetus: an increased proportion of umbilical blood passes through the ductus venosus during hypoxia and in the state of reduced umbilical vein flow[4,7,14-17].

During the short period of atrial contraction, however, a different pattern was displayed, as 34% of the cases had a reduced minimum velocity in the ductus venosus. This finding is similar to the changes found in fetuses with heart disease[23]. The deep trough during atrial contraction may represent an increased end-diastolic filling pressure. A reversed blood flow in the ductus venosus during atrial contraction was found in 16% of the cases. It has previously been suggested that this is a sign of hemodynamic compromise[6,23], and is comparable to umbilical vein pulsation[24].

In the present study, 30% of the cases had umbilical vein pulsation. However, among the cases of reduced ductus venosus blood flow velocity during atrial contraction, 69% were associated with umbilical vein pulsation (Figure 5). Although umbilical vein pulsation seems to be a normal phenomenon in the first trimester[25], the phenomenon is associated with compromised fetal hemodynamics in late pregnancy[24]. The present study supports that assumption.

As can be deduced from the present data (Figures 2, 3, 5 and 7), signs of hemodynamic compromise were more common before 31 weeks than later in pregnancy. Early cases probably represent a more serious disease with early signs. Such signs might also reflect a more vulnerable phase in fetal life when the fetal circulation operates on a lower level of blood pressure[26].

The relationship between hemodynamic changes and mortality cannot adequately be evaluated in the present study due to small numbers, the fact that the department's policy was less active before 26 weeks and 0 days, and that the postnatal deaths occurred in the very young neonates (Figure 7), known to have a high complication rate due to prematurity. It is interesting to note that the seven intrauterine fetal deaths were associated with reduced minimum velocity in the ductus venosus (7/7), increased PI in the umbilical artery (7/7), absent or reversed end-diastolic flow in the umbilical artery (6/7), and umbilical vein pulsation (7/7) (Figures 2, 5 and 7).

During recent years, the assumed increased placental impedance and the changes it causes to the umbilical artery blood velocity waveform have attracted much attention[27,28]. Equally interesting, however, is the information on the venous blood return from the placenta[4,26]. To have a more complete understanding of the regulatory dynamics of the umbilical circulation, it might be useful to include the umbilical arteries, the placenta, the umbilical vein, the liver, the ductus venosus and the foramen ovale in the evaluation. Together they could be considered as a unit that regulates the oxygenated umbilical blood flow and blood distribution (Figure 8). On the one hand, arterial blood pressure, umbilical artery dimension and placental impedance regulate the input to the umbilical vein. On the other hand, the umbilical vein pressure, liver resistance and ductus venosus modify the output. The present study showed that there was a close relationship between the signs indicating an increased placental impedance and a reduced umbilical blood flow in serious IUGR (Figure 3). According to the fetal lamb studies, hypoxia or reduced umbilical vein flow leads to a redistribution of the umbilical venous blood flow, increasing the proportion that is directed through the ductus venosus at the expense of hepatic blood flow. This may be caused by an increase in the hepatic vascular

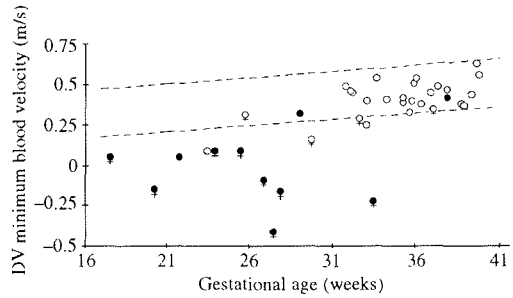

Figure 5 Minimum velocity of the ductus venosus (DV) blood flow recorded during atrial contraction in 38 seriously growth-retarded fetuses (circles). Filled circle, umbilical vein pulsation; cross below the circle, absent or reversed end-diastolic flow in the umbilical artery; dashed lines, 95% reference ranges

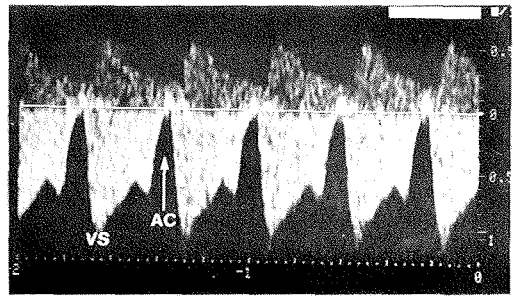

Figure 6 Doppler velocimetry of the ductus venosus in a fetus with a serious growth retardation (27 weeks). Normal peak velocity was maintained during ventricular systole (VS), but during atrial contraction (AC) the velocity was reduced below normal values. Signals above the line represent interference, probably from a branch of the celiac trunk

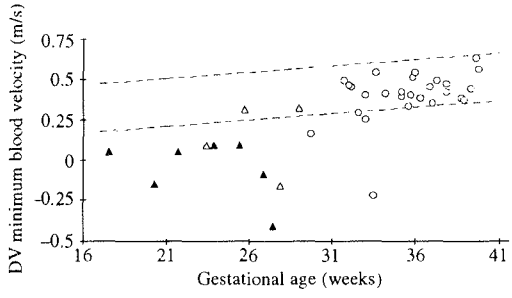

Figure 7 Minimum velocity of the ductus venosus (DV) blood flow recorded during atrial contraction in 38 seriously growth-retarded fetuses (circles and triangles). Filled triangle, intrauterine fetal death; empty triangle, postnatal death; dashed lines, 95% reference ranges

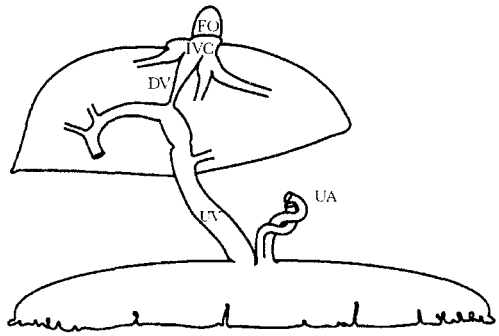

Figure 8 Diagram illustrating blood flow. The umbilical arteries (UA) pump the blood through the placenta. The umbilical vein (UV) receives the oxygenated blood with a residual pressure sufficient to perfuse the liver parenchyma and the ductus venosus (DV) in parallel. The ductus venosus projects a high-velocity stream across the left side of the inferior vena cava (IVC), to enter the foramen ovale (FO) as a preferential stream

resistance or by reduced umbilical vein blood pressure[14–17]. The net effect of this redistribution is a higher proportion of highly oxygenated blood passing through the foramen ovale at the expense of the hepatic perfusion. Although it has not been possible in the present study to assess the hepatic circulation, our results support the theory presented above by showing that the ductus venosus blood flow maintains its normal peak velocity even in the most compromised hemodynamic states of IUGR (Figure 4). The results suggest that the ductus venosus blood flow has a high priority and is involved in an important redistribution once the oxygenated umbilical venous return is jeopardized.

How important the ductus venosus blood flow actually is still remains to be determined. Occlusion of the ductus venosus in the mature fetal lamb does not cause any measurable change in oxygen saturation in the aorta or carotid arteries[29,30]. Whether such results indicate that the ductus venosus is of less importance during the last weeks of pregnancy is not known. Perhaps it indicates that the ductus venosus is not indispensable, but that the fetus with an occluded ductus venosus has less capacity to endure placental compromise. Further studies may provide an answer.

It is concluded that the ductus venosus peak velocity is maintained at a high level, even in advanced stages of IUGR, indicating the high priority of blood flow in this vessel. A sign of hemodynamic compromise, however, was found in reduced ductus venosus blood velocity during atrial contraction. In addition, serious IUGR was associated with absent or reversed end-diastolic flow and increased PI in the umbilical artery, umbilical vein pulsation and reduced umbilical venous flow. By including the ductus venosus velocimetry, hemodynamic evaluation offers a more complete understanding of the umbilical circulation and its capacity of redistribution, as is shown in the present cases of intrauterine growth retardation.

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●*Original Contribution*

ESTIMATION OF THE PRESSURE GRADIENT ACROSS THE FETAL DUCTUS VENOSUS BASED ON DOPPLER VELOCIMETRY

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Abstract—In the fetus, the umbilical vein is directly linked to the inferior vena cava by the narrow ductus venosus. Thus, the ductus venosus blood velocity probably reflects the pressure gradient between the umbilical vein and the central venous system. In a longitudinal study that included 29 normal fetuses, pulsed Doppler velocimetry was carried out in the umbilical vein and the ductus venosus during the last half of the pregnancy. By applying the Bernoulli equation, we estimated the pressure gradient across the ductus venosus to vary between 0–3 mm Hg during the heart cycle; it remained within those ranges during gestational weeks 18–40. During fetal inspiratory movement, pressure gradients up to 22 mm Hg were estimated. The estimated ductus venosus pressure gradient seems to be within ranges compatible with known umbilical venous pressures, and may provide a new opportunity to understand central venous hemodynamics and respiratory force in the fetus once methodological limitations are controlled.

Key Words: **Fetus, Doppler, Ultrasound, Blood flow velocity, Blood pressure, Venous pressure, Ductus venosus, Estimation.**

INTRODUCTION

The advent of ultrasound has given a great boost to fetal medicine. The Doppler modality opened the way to study the fetal circulation (Fitzgerald and Drumm 1977) and soon became an important tool for investigating fetal blood flow in greater detail (McCallum et al. 1978; Gill 1979; Eik-Nes et al. 1980), promoting an increase in knowledge of human fetal physiology (Campbell et al. 1983; Wladimiroff et al. 1986; Lingman and Maršál, 1986). A further advancement in understanding the fetal circulation was the measurement of blood pressure during fetoscopic (Castle and Mackenzie 1986) or ultrasound guided cordocentesis (Nicolini et al. 1989; Weiner et al. 1989).

The central venous pressure is generally accepted as a key to understanding central blood circulation and the underlying hemodynamic changes in disease. In the human fetus, information about the pressure in the atria or caval veins would allow us to understand normal and altered hemodynamics. Such pressures have been measured in fetal sheep under experimental conditions, but technical limitations prevent us from recording the corresponding pressures in human fetuses. The special vascular arrangement in the fetus, however, might offer a possibility to estimate pressures using indirect methods.

The umbilical vein is directly linked to the central venous system by the ductus venosus. Angiographic studies in the fetal lamb showed that the umbilical blood that passed the ductus venosus to a large extent followed the inferior caval blood through the foramen ovale (Barclay et al. 1942). Later studies suggested that 50% of the umbilical blood bypasses the liver through the ductus venosus (Edelstone et al. 1978) and is delivered directly to a preferential streaming through the foramen ovale to ensure oxygen supply to the coronary and cerebral circulation (Behrman et al. 1970; Edelstone and Rudolph 1979). A similar pattern has recently been demonstrated in the human fetus *in utero* (Kiserud et al. 1992b). A high blood flow velocity in the human ductus venosus indicates a marked pressure gradient between the umbilical vein and the inferior vena cava (Kiserud et al. 1991; Huisman et al. 1992a).

The close relationship between pressure and ve-

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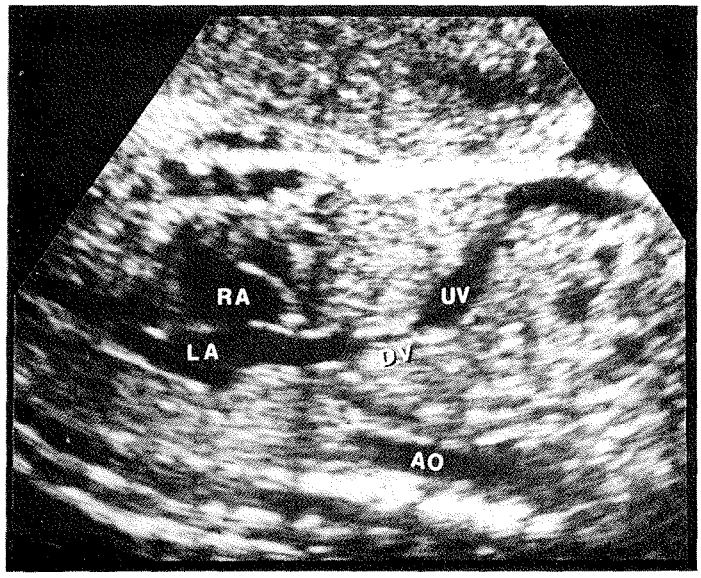

Fig. 1. Sagittal insonation in a fetus of 25 weeks showing the umbilical vein (UV) and the ductus venosus (DV) which points through the inferior vena cava towards the left atrium (LA). Aorta (AO). Right atrium (RA).

locity affords the possibility of estimating a pressure gradient based on velocity measurements (Holen et al. 1976). The location of the human ductus venosus, its isthmic shape and high velocity, make it suitable for Doppler velocimetry and pressure calculation (Kiserud et al. 1992a).

The aim of the present study was to explore the possibilities of estimating the pressure gradient between the umbilical vein and the inferior vena cava using the umbilical vein and the ductus venosus blood velocities obtained by Doppler ultrasonography.

MATERIAL AND METHODS

Thirty-one healthy pregnant women were recruited from the low risk antenatal clinic for a longitudinal study. Written informed consent was given in accordance with a protocol approved by the regional committee of ethics. The participants were nonsmokers, had a normal obstetrical history and the present singleton pregnancy was uneventful. The routine ultrasound scan at the 17th–20th week of gestation showed a normal fetus. Gestational age was assessed by ultrasonography. Criteria for later exclusion were complications such as growth retardation (<5 centile at birth), pregnancy-induced hypertension, bleeding or any structural malformation detected after birth.

Starting from week 17, the participants were examined every 3–4 weeks until term. A Vingmed 750 CFM ultrasound scanner (Vingmed Sound, Horten, Norway) was applied for 2D-imaging, colour flow imaging and pulsed Doppler examination. A 5 MHz mechanical sector transducer carrying a 4 MHz Doppler unit was applied with the spatial peak temporal average intensities (Ispta) set to 5 and 45 mW/cm^2, respectively. Alternatively, a 3.75 MHz mechanical sector transducer carrying a 2.5 MHz Doppler unit was used with the Ispta settings of 6 and 10 mW/cm^2. It has been recommended that the calculated intensity of focused Doppler ultrasound in the fetal tissues not exceed an Ispta of 100 mW/cm^2 (American Institute of Ultrasound in Medicine Bioeffects Committee 1988).

The ductus venosus was identified by 2D-imaging and colour Doppler in a midsagittal insonation (Fig. 1) or an oblique transection of the upper abdomen. The pulsed Doppler shift was recorded during fetal quiescence and at the smallest possible angle of interrogation. The velocities were corrected for the angle of insonation. The maximum velocity envelope representing at least four heart cycles was used to calculate the ductus venosus blood velocity (V_{DV}), the peak velocity during ventricular systole, the minimum velocity during atrial contraction and the time-averaged maximum velocity (Fig. 2). The same technique was applied

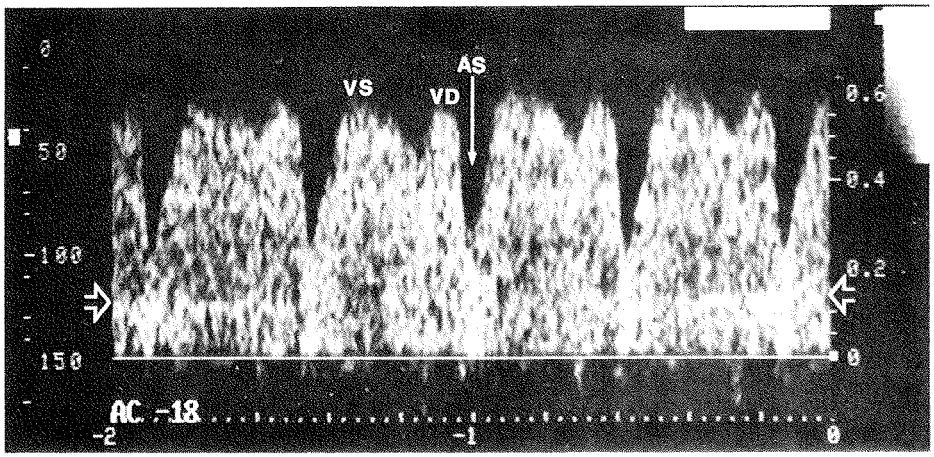

Fig. 2. Pulsed Doppler recording of the ductus venosus blood velocity (m/s) during 2 s in a fetus of 17 weeks. A velocity peak is found during ventricular systole (VS), another peak during ventricular diastole (VD), and a minimum during atrial systole (AS). Umbilical vein velocity interference (open arrows). Angle correction (AC).

to record the blood velocity in the ductus venosus during respiratory movements in the same group of participants. Respiratory movements were identified during 2D-imaging by diaphragmatic movements. Concomitant velocity changes in the umbilical vein or the inferior vena cava, as previously described (Maršál et al. 1984), confirmed the continued breathing activity during Doppler velocimetry. The length of the ductus venosus, its inner diameter at the isthmic inlet and at the outlet were measured (Fig. 3).

The straight portion of the abdominal umbilical vein was identified by 2D-imaging either in a midsagittal or an oblique transection of the fetal abdomen. The blood velocity in the umbilical vein was recorded during fetal quiescence by applying the pulsed Doppler technique at the smallest possible angle of insonation with a sample volume covering the section of the vein. The velocities were corrected for the angle of insonation. The time-averaged maximum velocity (V_{UV}) in the umbilical vein was calculated from the maximum velocity envelope representing at least two seconds.

The pressure gradient across the ductus venosus (Δp_{DV}) was estimated applying the Bernoulli equation $\Delta p_{DV} = 4(V_{DV}^2 - V_{UV}^2)$ (Holen et al. 1976). Estimation of the Δp_{DV} during respiratory movements was based on the V_{DV} only, neglecting the V_{UV} (Hatle et al. 1978).

RESULTS

Of the 31 participants, one moved and one started smoking and were accordingly withdrawn from the study, leaving 29 to be analysed. The women's mean age was 27 years (range 21–40). At delivery, mean gestational age was 40 weeks/3 days (range 37/5–42/2). Mean birth weight was 3 659 g (range 2950–4350). All neonates had Apgar ≥ 9.

The results of the ductus venosus blood velocity recordings have been presented previously (Kiserud et al. 1992a). The peak velocity ranged between 0.5–0.9

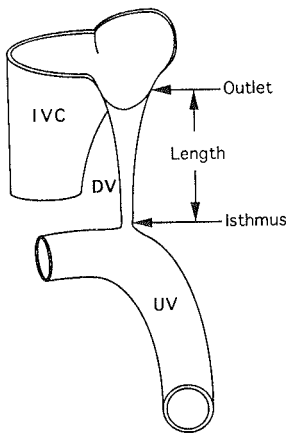

Fig. 3. The ductus venosus (DV) connects the umbilical vein (UV) to the left portion of the inferior vena cava (IVC). The DV is shaped like a trumpet with an isthmus at the entrance and a wider outlet.

m/s (Fig. 4), the minimum velocity ranged between 0.2–0.6 m/s, and the time-averaged velocity between 0.4–0.8 m/s. The results of the umbilical vein velocimetry are presented in Fig. 4. The estimated Δp_{DV} ranged between 0–3 mm Hg and showed a similar profile during the cardiac cycle as was found for the ductus venosus blood velocity itself (Fig. 5). The results of the estimated maximum Δp_{DV} during ventricular systole, the time-averaged Δp_{DV} and the minimum Δp_{DV} during atrial contraction showed hardly any changes during gestational weeks 18–40 (Fig. 6).

In the 58 observations during fetal respiratory exercise in the 29 participants, large variations in Δp_{DV} were noted, particularly at the end of the pregnancy, ranging from below 0 mm Hg during expiratory movements to 22 mm Hg during high amplitude inspiratory movements. The geometrical measurements of the ductus venosus are presented in Fig. 7.

DISCUSSION

The blood flow in the human ductus venosus has a high velocity, which makes it ideal for Doppler velocimetry. In this study, a method is suggested to estimate the pressure gradient between the umbilical vein and the inferior vena cava based on a simplified model (Fig. 3) applying the Bernoulli equation to the velocities obtained from the umbilical vein and the ductus venosus (Fig. 5). During fetal quiescence, the estimated Δp_{DV} varied from 0 mm Hg to 3 mm Hg with the time-averaged Δp_{DV} of 0.5–2.5 mm Hg during the last half of the pregnancy (Fig. 6). During respiratory exercise, however, the fetus achieved as much as a 10-fold increase in the pressure gradient during inspiration, emphasising the powerful additional force fetal respiratory movements exert on fetal circulation. The blood velocity in the umbilical vein was ignored in the calculation of the Δp_{DV} during respiratory movements for two reasons. A simultaneous recording of the velocity in the ductus venosus and the umbilical vein during fetal movement is a difficult task with the equipment available today. Secondly, the velocity increment in the umbilical vein during fetal breathing movements was described to be 19% (range 6–54%) (Maršál et al. 1984). Thus, the blood velocity in the umbilical vein during inspiratory movements on average contributes only 0.3 mm Hg to the pressure calculation, and would not exceed 0.8 mm Hg. This is negligible compared to the total Δp_{DV}, which is calculated to be in the order of 20 mm Hg during high amplitude inspiration.

The results show a decrease in the number of geometrical observations after 34 weeks. Of the geometrical measurements, the outlet measurement had the lowest priority throughout the pregnancy. One reason for this was the limited examination time at each session. In addition, fetal movements reduced the active examination time even more toward the end of the pregnancy. The Doppler velocimetry was given higher priority than, and sometimes done at the expense of, the geometrical measurements. These practical restrictions are reflected in the results (Fig. 7). In the present study, the ductus venosus at 18 weeks seemed roughly to be 5 mm long, 0.6 mm wide at the isthmus and 2 mm wide at the outlet. At 34 weeks, the ductus venosus was 15 mm long, 1.5 mm wide at the isthmus and 3 mm at the outlet. The error of vessel diameter measurements in the fetus is reported not to exceed 0.4 mm (Eik-Nes et al. 1982). For larger measurements, such as the length of the ductus venosus, a similar error is to be expected and tolerated. For the isthmus diameters ranging between 0.5–2.3 mm, however, the measurements do not permit firm conclusions. Although the data are incomplete, and the ultrasound measurements have a limited accuracy, the results might give an impression of the geometrical pattern that is in agreement with earlier anatomical reports

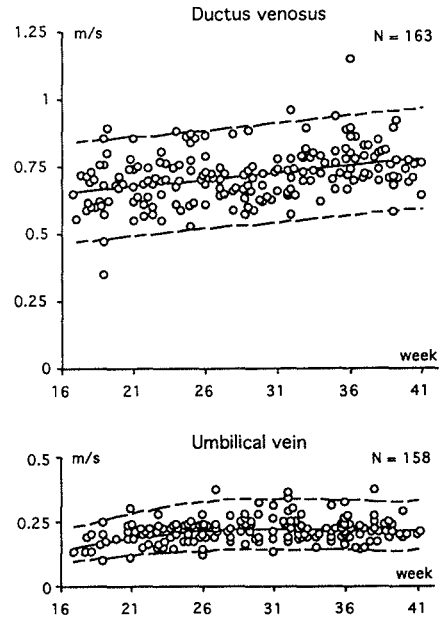

Fig. 4. Ductus venosus peak blood velocity recorded during ventricular systole in 29 normal fetuses during the last half of the pregnancy (upper panel). The maximum blood velocity in the intraabdominal umbilical vein in the same individuals (lower panel). Regression line with 95% CI (broken lines).

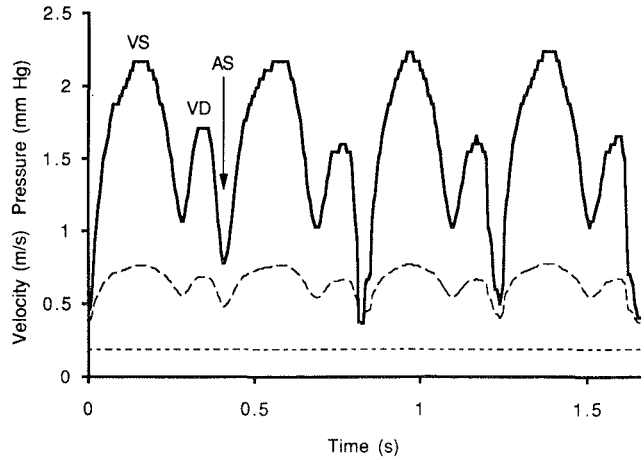

Fig. 5. The estimated pressure gradient across the ductus venosus (solid line) during four heart cycles based on the blood velocity in the ductus venosus (broken line) and the umbilical vein (dotted line) in a fetus of 19 weeks. A peak value is found during ventricular systole (VS), another peak during ventricular diastole (VD), and a minimum during atrial systole (AS).

(Barclay et al. 1944; Chako and Reynolds 1953). Blanc (1960) found that the orifice of the ductus venosus was patent for a probe of 1.5 mm in 100 out of 107 stillborns and infants less than 48 h of age.

The estimated Δp_{DV} is comparable to the reported pressure (p_{UV}) in the human umbilical vein, 2.2 mm Hg (range 0–5) in week 18–21 (Castle and Mackenzie 1986), 4.5 mm Hg (3.2–5.8 95% CI) (Nicolini et al. 1989) and 5.3 mm Hg (range 1–11) (Weiner et al. 1989), and would allow reasonable central venous pressure (p_{IVC}) values to be estimated based on a simple subtraction: $p_{IVC} = p_{UV} - \Delta p_{DV}$. The problem, however, is that the reported pressures measured by cordocentesis were taken from the placental end and not the intraabdominal end of the umbilical vein, or from the cord at a distance from the fetal abdomen not specified. There is no report on the pressure drop along the human umbilical vein, but in fetal sheep it is believed to be 5 mm Hg. Dawes (1968) summarised the results of the studies on mature fetal sheep, and described the venous pressure in the placental end of the umbilical vein to be 15 mm Hg, in the abdominal umbilical vein 10 mm Hg and the pressure drop across the ductus venosus and liver to be 10 mm Hg. Later studies suggested a lower pressure in the umbilical sinus in the fetal lamb, 4.7 ± 0.5 mm Hg, and a pressure gradient across the ductus venosus of 3.1 ± 0.5 mm Hg (Paulick et al. 1990) which comes closer to the human results. Dawes et al. (1955) reported the pressure gradient from the thoracic inferior vena cava across the foramen ovale to the left atrium to be 0.2–1.2 mm Hg during the heart cycle in fetal sheep. Rudolph (1985) described a ventricular end-diastolic pressure of 3–5 mm Hg in the fetal sheep. Taking into account all the pressures reported, the estimated Δp_{DV} in the present study seems to be within reasonable ranges. But there is still a need for further data on the pressure in the umbilical vein and on the pressure drop along the cord in the human fetus before the central venous pressure can reliably be estimated. The fetal ductus venosus in sheep has a different shape than that found in man. It is slightly more kinked in the isthmic portion (Barclay et al. 1944) than is the human ductus venosus (Kiserud et al. 1992b). Thus, both the differences in anatomy and the pressures reported leave the question open regarding the extent to which the results from the sheep are applicable to the human ductus venosus.

The velocity (V_1) recorded across a valvular lesion usually is much higher than the velocity recorded for V_2 in the Bernoulli equation, $\Delta p = 4(V_1^2 - V_2^2)$. This justifies a pressure estimation based on the reduced equation $\Delta p = 4V_1^2$ (Hatle et al. 1978). Under normal conditions in the last half of the pregnancy, the fetal V_{UV} contributes little when calculating Δp_{DV} as can be deducted from Fig. 5. This is especially true during fetal inspiratory movements sometimes producing V_{DV} of more than 2 m/s. However, in the early second trimester (Huisman et al. 1992b) or in the sick fetus, as in cardiac diseases (Kiserud et al. 1993), the velocities in the ductus venosus may be low, making the V_{UV}

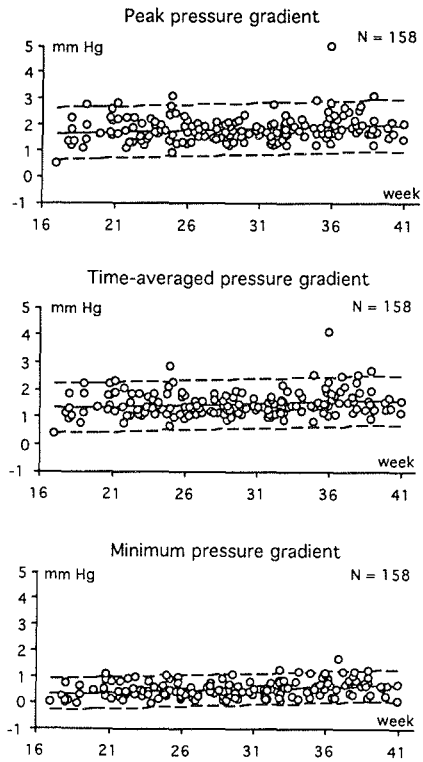

Fig. 6. The estimated pressure gradient across the ductus venosus in 29 normal fetuses during the last half of the pregnancy recorded during ventricular systole (upper panel), time-averaged during the whole heart cycle (mid-panel), during atrial systole (lower panel). Regression line with 95% CI (broken lines).

relevant when calculating low pressure gradients. And in the case of anemia, the umbilical vein velocity may increase (Kirkinen et al. 1983). Thus, in the fetus, it is probably more adequate to apply the full Bernoulli equation, $\Delta p_{DV} = 4(V_{DV}^2 - V_{UV}^2)$, to ensure that the varying impact of the umbilical vein blood flow velocity is included.

The limits of agreement for the reproducibility of the ductus venosus velocimetry is reported to be ±0.14 m/s (Kiserud et al. 1992a). This is at the magnitude of the umbilical vein blood velocity, and exemplifies how little the umbilical vein velocity may contribute in the pressure estimation compared to possible sources of error. The reproducibility of the umbilical vein velocimetry itself is reported to be good, provided the insonation is kept at a low angle (Gill et al. 1981).

The proposed pressure estimation is a simplification with an inherent possibility of errors. Such errors may result in an underestimation of the Δp_{DV} due to viscous pressure loss, or an overestimation due to convective pressure recovery. In the generalised Bernoulli equation

$$\Delta p_{DV} = \frac{1}{2}\rho(V_{DV}^2 - V_{UV}^2) + \rho \int_{UV}^{DV} \frac{\partial V}{\partial t}\, dx + R(V),$$

the blood density, ρ, was set to 1.06×10^3 kg m^{-3}. The second term represents the inertia, which in our case was dropped based on the same premises as discussed by Hatle (1978). The last term, $R(V)$, depends on the geometrical properties of the ductus venosus, the velocity profile and viscosity of the blood, and represents a viscous pressure loss that might cause an underestimation of the Δp_{DV} once it is omitted. In our case, a flat velocity profile (plug flow) at the isthmic entrance was assumed to develop into a more or less parabolic velocity profile as the blood traversed the

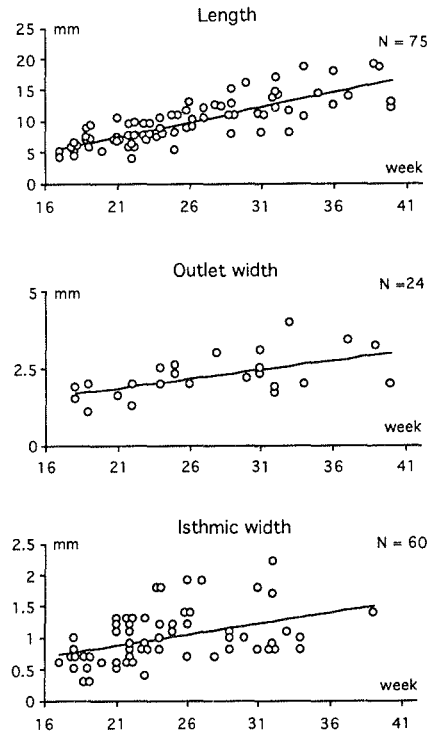

Fig. 7. Results of the measurements of the ductus venosus dimensions in 29 normal fetuses during the last half of the pregnancy presented with a linear regression line.

ductus venosus. With the average geometry found at 34 weeks (length 15 mm, isthmic width 1.5 mm and outlet 3 mm), a maximum velocity of 0.75 m/s with parabolic velocity profile in a Newtonian fluid, the viscous pressure drop was estimated to be in the order of 0.1 mm Hg (Fung 1981).

Another important factor that could influence the pressure estimation is the convective pressure recovery along the ductus venosus. In the case of mitral stenosis, it was deemed unnecessary to include it. In the ductus venosus, however, the geometrical properties are different and might very well permit a recovery of pressure and cause a corresponding overestimation of the Δp_{DV}. Assuming the mentioned geometrical pattern at 34 weeks, a flat velocity profile that develops into a parabolic profile in the course of the ductus venosus, a convective pressure recovery in the order of 1.7 mm Hg could be estimated applying the Navier–Stokes equation for a Newtonian fluid (Fung 1981). It implies a reduction of the blood flow velocity by 50% at the ductus venosus outlet. It also implies a gross overestimation of the Δp_{DV} applying the Bernoulli equation on the ductus venosus velocity. Blood, however, is not considered Newtonian fluid, and the diverging shape of the ductus venosus probably tends to give an elongated velocity profile maintaining high central velocities and rather stagnant peripheral velocities. Such velocity properties could easily give a reduced convective pressure recovery along the axial flow, and correspondingly cause a lesser overestimation than the 1.7 mm Hg suggested above. Besides, velocity measurements done at different locations in the ductus venosus indicate a different velocity pattern than the 50% reduction calculated above. Doppler velocimetry at the entrance, in the mid-portion and at the outlet showed that the maximum velocity was maintained through the length of the ductus venosus, but with a slight reduction (11%) of the velocity at the outlet (Kiserud et al. 1992a). Thus, it is assumed that the pressure recovery based on convective flow, at least for the central velocities, might be considerably less than was estimated above. Accordingly, the central velocity laminae maintain their momentum towards the foramen ovale. Actually, colour Doppler can be used to trace such flow velocities passing through the foramen ovale into the left atrium. How much the velocities are reduced along the last part of this route has not yet been assessed.

A further point could be brought up. Through the years, there has been a discussion on whether there is an active sphincter of the ductus venosus or not. A sphincter with similar properties as were described for the ductus arteriosus was described by Adeagbo et al. (1990). How active such a sphincter is during intrauterine life is not known, but adrenergic activity has been traced in the ductus venosus in the fetal lamb (Coceani 1984). A sphincter activity would, however, vary the isthmic diameter and cause an unpredictable viscous and convective pressure drop.

The discussion, so far, has assumed a laminar blood flow in the ductus venosus. Turbulent flow would, however, be associated with substantially higher resistance and, accordingly, less overestimation of the pressure drop in our case. For blood, a Reynolds number above 2300 is often associated with turbulence (Fung 1984). The smoothness and shape of the ductus venosus contribute to keeping the critical value high. Under conditions as mentioned previously (isthmic diameter of 1.5 mm and velocity of 0.75 m/s) including a viscosity of 0.01 Pa·s, a Reynolds number is calculated to 1200, a value fully in agreement with laminar flow. During high amplitude inspiratory movement, a velocity of 2 m/s would give a Reynolds number of 3200 with a risk of turbulence. During such respiratory movements, however, the ductus venosus diameter probably tends to decrease in the same way as the umbilical vein and the inferior vena cava do (Maršál et al. 1984). With the isthmus squeezed to 1 mm and the velocity maintained at 2 m/s, a turbulent flow could be avoided because the corresponding Reynolds number would be 2100. A constricting sphincter would easily amplify this effect. On the other hand, a widening of the isthmus to 2.5 mm would probably cause turbulence with a Reynolds number of 5300.

The presently suggested pressure estimation has the potential to aid in establishing more knowledge of normal fetal circulatory physiology, and in a number of conditions such as hydrops, congestive heart failure, placental compromise, hypoxia, anemia, liver diseases, vascular malformations and twin–twin transfusion syndrome. An evaluation of the relationship between the blood flow velocity and the pressure gradient in the ductus venosus in the fetal lamb would give an indication of the extent to which the principle is applicable to the ductus venosus in general. But it would be more important to gain further information on the pressure in the human umbilical vein and inferior vena cava, to establish the ductus venosus pressure gradient as a hemodynamic parameter for the evaluation of the fetus.

SUMMARY

The present study suggests that the ductus venosus velocimetry combined with the umbilical vein velocimetry can be used to estimate the pressure gradient across the ductus venosus when the Bernoulli equation is applied. The normal pressure gradient across the ductus venosus seems to be in the range of 0–3 mm

Hg during the last half of the pregnancy, but may increase up to 22 mm Hg during inspiratory movements. The method may be incorporated in the fetal hemodynamic evaluation, provided the methodological limitations are controlled.

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