*Fetal and Maternal Medicine Review 2003; **14**:1 57–95*
DOI: 10.1017/S0965539503001037

FETAL VENOUS CIRCULATION

TORVID KISERUD

Department of Obstetrics and Gynaecology, University of Bergen, Norway

INTRODUCTION

Ultrasound evaluation of the venous system is now a compulsory part of the haemodynamic assessment of the fetus. Once umbilical venous flow was introduced[1,2] and its pulsatile pattern discovered in the compromised fetus,[3] other sections of the venous system have been added or explored for possible diagnostic use: the inferior and superior vena cava,[4,5] ductus venosus,[6,7] hepatic veins,[8] pulmonary veins,[9,10] and intracranial veins.[11–13] The following presentation is not intended to be a complete review of the fetal venous circulation, which is growing by the day, but rather to focus on some central issues with an emphasis on physiologic principles. The reason for this focus is that, as clinicians, we tend to work according to pattern recognition, which is a necessary principle in daily life. However, in the long run as the fetal patient increasingly demands a more dynamic approach to solve the diagnostic riddles, we find ourselves digging deeper into the physiological mechanisms behind ultrasound images and recordings.

DEVELOPMENTAL ANATOMY

An increasing number of fetal venous malformations are diagnosed in utero and require a detailed knowledge of venous development, particularly when it comes to classifying the malformations.[14–16] At six weeks of gestation, the embryo has paired cardinal, hepato-cardinal, vitelline and umbilical veins draining directly or indirectly into the sinus venosus, a venous vestibulum to the primordial heart[17] (Figure 1). The venous system and the hepatic tissue form a meshwork below the sinus venosus.[18] As the liver grows, the umbilical circulation increasingly drains to the left umbilical vein, which nourishes both the liver parenchyma and a central stem towards the heart (the ductus venosus). After eight weeks of gestation, the ductus venosus is well defined,[19] the portal vein has replaced the proximal portion of the vitelline veins and the right hepato-cardinal vein has become the proximal portion of the inferior vena cava (IVC).

Address for correspondence: Torvid Kiserud, University of Bergen, Department of Obstetrics and Gynaecology, 5021 Bergen, Norway.

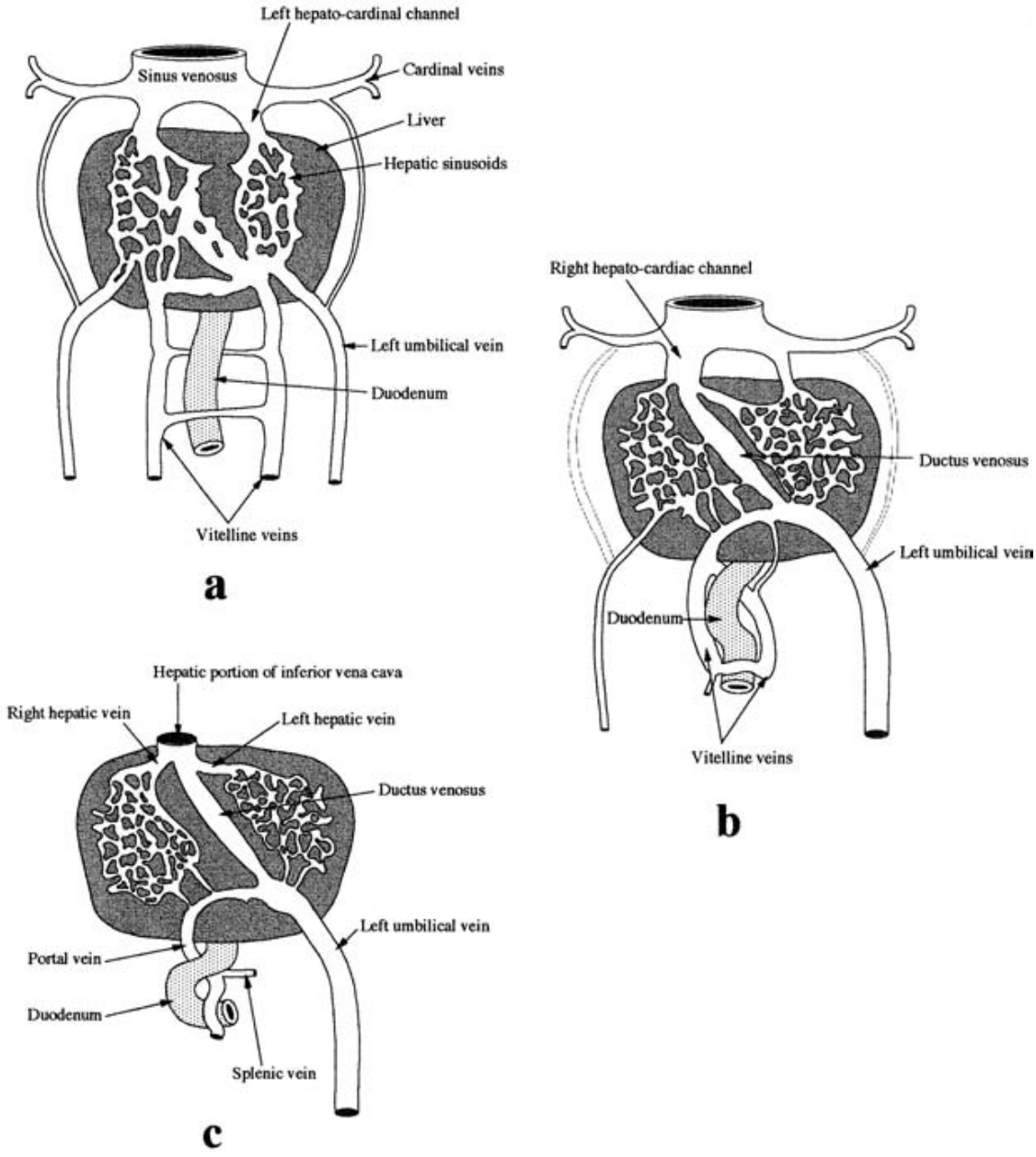

Figure 1 Panel **a**: After the sixth gestational week three major paired veins interact with the growing liver to form a meshwork. Panel **b**: A rapid development during the following days gives priority to the growth of the left umbilical vein and a defined ductus venosus. Panel **c**: After the eighth 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. **Reprinted with permission from Kiserud T: The ductus venosus in the human fetus. University of Trondheim, 1994**.

At this stage, the lateralisation is complete. The sinus venosus has been included in the atria with the coronary sinus and a single right-sided superior and inferior vena cava.

New anatomic studies of the human fetus have demonstrated details of the afferent and efferent venous system of the liver including the ductus venosus.[20,21] Compared to cast models from fetal sheep, the early anatomy in humans is different. Particularly, the course of the ductus venosus, its connection to the IVC and the very short course of the intrathoracic IVC are notable characteristics of the human fetus.

What is known during postnatal life as the left branch of the portal vein is formed as a transverse sinus and connected to the intraabdominal section of the umbilical vein.[21,22] For practical reasons, the entire venous section between the abdominal wall and the ductus venosus is labelled the intraabdominal umbilical vein[23] (Figure 2). On its way it supplies the left and medial portion of the liver with umbilical blood. The intraabdominal umbilical vein is a sizable vessel growing from 2.5 to 6 mm during the second half of pregnancy whereas the ductus remains a slender trumpet hardly ever exceeding 2 mm at its isthmus[24] (Figure 3).

The short section (1 cm or so) of the left portal branch between the ductus venosus and the main portal stem is of particular physiologic interest since it constitutes a watershed area[23,25] (Figure 2). Under normal conditions, umbilical blood flows towards the right portion of the fetal liver. However, during circulatory compromise, such as hypovolemia, deoxygenated portal blood may flow in the opposite direction towards the ductus venosus inlet.[25]

PHYSIOLOGICAL IMPORTANCE

Ultrasound examination of the human fetus in utero has brought new physiological data, which sometimes are quite different from the classical reference values based on animal experiments. Of particular interest is the umbilical circulation. Experimentally measured umbilical venous flow in the fetal sheep varies greatly (100–260 mL/min/kg) depending on gestation and the method applied.[25–27] When ultrasound made flow measurements possible in the human fetus, these values appeared to be at the lower range of those obtained in sheep.[1,2,28] This is not surprising since the fetal sheep has a higher growth rate, higher temperature, and lower haemoglobin concentration than the human fetus. A recent study of the human fetus showed that umbilical venous flow averages 22 mL/min at 18 weeks of gestation and 237 mL/min at 40 weeks with no decrease near term as reported in the early studies[24] (Figure 4). The corresponding normalised flow volume is 118 mL/min/kg at 18 weeks, and 64 mL/min/kg at term (Figure 5). These results are reproducible[29] and in agreement with studies on exteriorised human fetuses using electromagnetic flowmeters (mean of 110 mL/min/kg at 10–28 weeks)[30] and thermodilution studies at birth[31] (mean 75 mL/min/kg. In addition to this decline in normalised umbilical venous flow during the second half of pregnancy, the oxygen partial pressure is

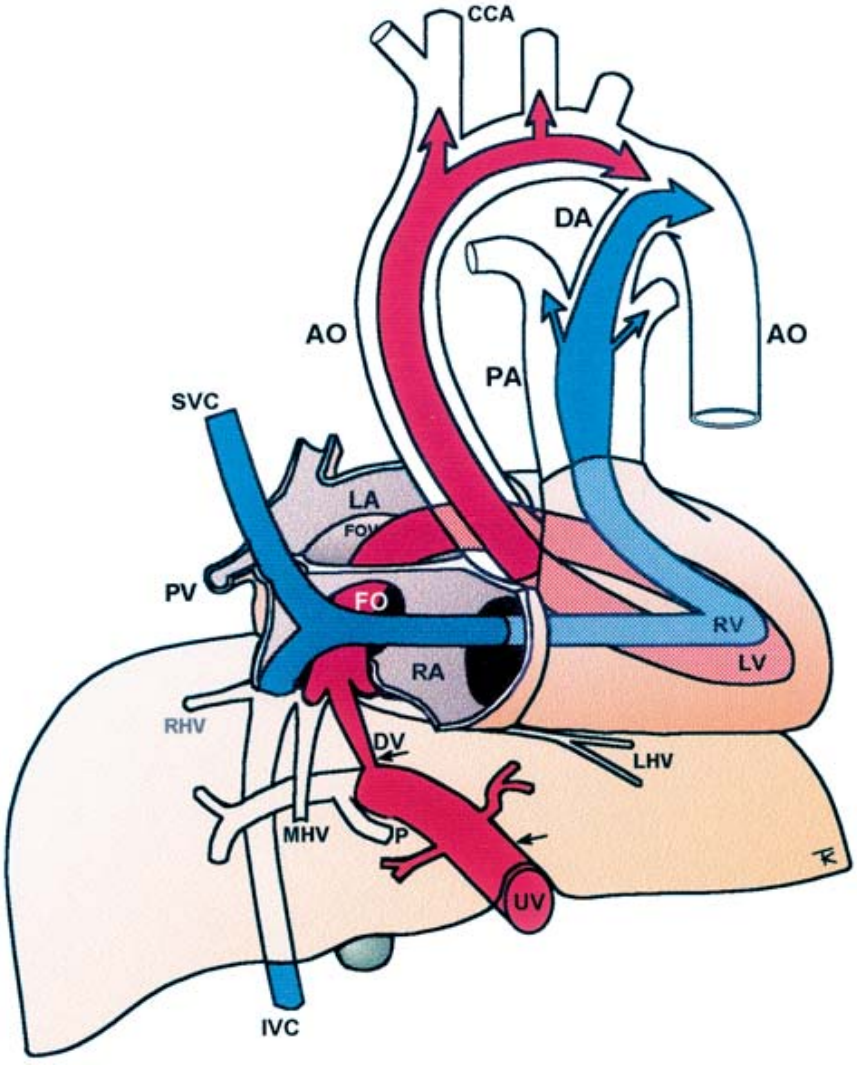

Figure 2 Circulatory pathways through the fetal liver and heart. Oxygenated blood (red) enters through the umbilical vein (UV) and is distributed to the liver or shunted through the ductus venosus (DV) and directed by a preferential streaming through the foramen ovale (FO) to the left atrium (LA) supplying the coronary and cerebral circuit by the aorta (AO) (*via sinistra*). Deoxygenated blood from the abdominal inferior vena cava (IVC) and superior vena cava (SVC) is predominantly directed to the right atrium to form the *via dextra* (blue) that bypasses the lungs by the ductus arteriosus (DA) and is the main provider of blood to the descending AO. CCA, common carotid arteries; FOV, foramen ovale valve; LHV, left hepatic vein; LV, left ventricle; MHV, medial hepatic vein; P, portal vein; PV, pulmonary vein; RHV, right hepatic vein; RV, right ventricle. **Printed with permission**[24]

reduced from 50 to 35 mmHg,[32] which is compensated by an increasing haemoglobin concentration during the same period.[33,34]

A still valued traditional concept of the central fetal circulation is that of the *via dextra* and *via sinistra*[34,35] (Figure 2). Deoxygenated blood from the superior vena cava (SVC) and the abdominal IVC follows predominantly the via dextra (the

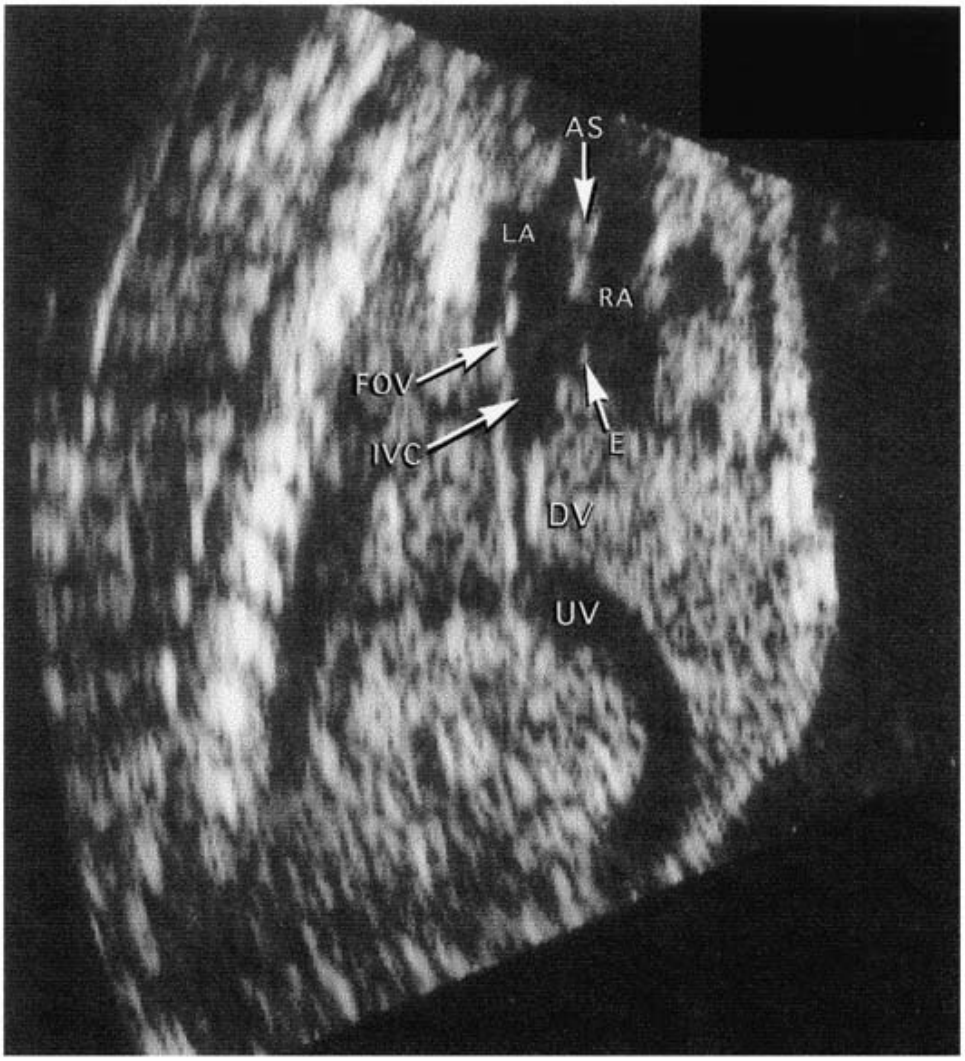

Figure 3 Sagittal ultrasound scan of a normal fetus at 30 weeks gestation showing the ductus venosus (DV) connecting the umbilical vein (UV) to the inferior vena cava (IVC). Only the proximal expanded left compartment of the IVC is exposed. The foramen ovale valve (FOV) on the left side and the Eustachian valve (E) on the right side form an extension of the IVC. The fetal atrial septum (AS) is situated further to the right side than is seen in postnatal life. Thus the preferential streaming of umbilical blood is guided into the LA. **Printed with permission from Kiserud T: The ductus venosus. Seminars in Perinatology, 2001; 25:11–20. WB Saunders Company**

right atrium, right ventricle, pulmonary trunk, ductus arteriosus, and descending aorta). On the other side, oxygenated umbilical blood is directed through the via sinistra (the ductus venosus, foramen ovale, left atrium, left ventricle, ascending aorta, isthmus aortae, and descending aorta). Two of the three fetal shunts involved in these arrangements, are on the venous side, the ductus venosus and foramen ovale. They operate closely together as a distributional unit; this has been shown with isotope labelled microspheres,[36–38] and with angiography[39] in exteriorised human fetuses and,

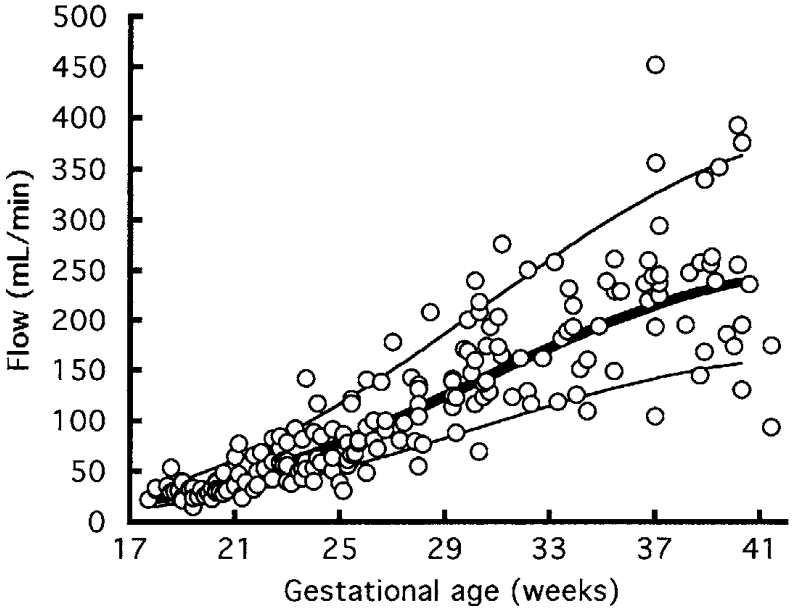

Figure 4 Blood flow in the intra-abdominal umbilical vein in 196 fetuses, (lines are 10th, 50th and 90th percentiles). **Printed with permission**[24]

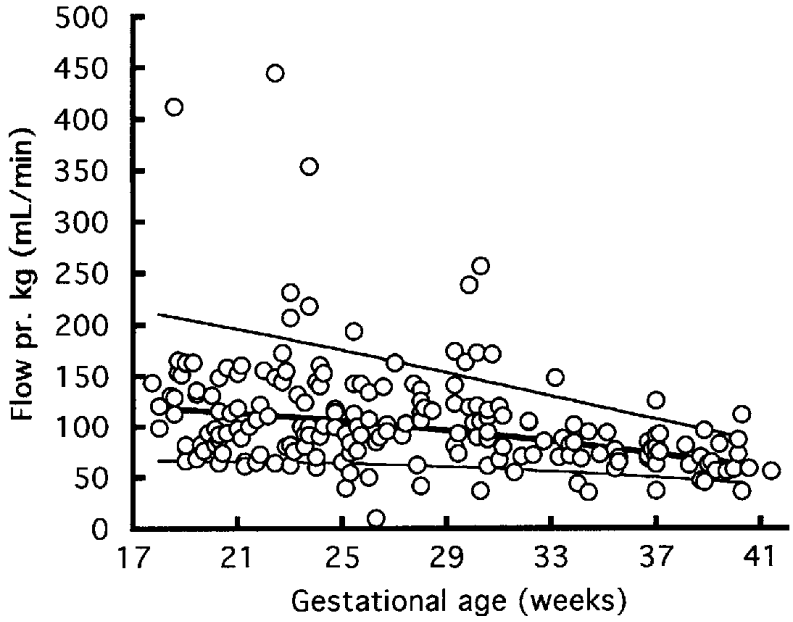

Figure 5 Blood flow per kg estimated body weight calculated for the intra-abdominal umbilical vein of 196 fetuses (lines are 10th, 50th and 90th percentiles). **Printed with permission**[24]

recently, also in utero using ultrasound.[6,40] The two pathways, the *via sinistra* and *via dextra*, have the proximal widened IVC in common (Figure 6). In addition to the phenomenon of laminar flow, the different directions, velocities, and positions of the two flows prevent an extensive mixing in the IVC.

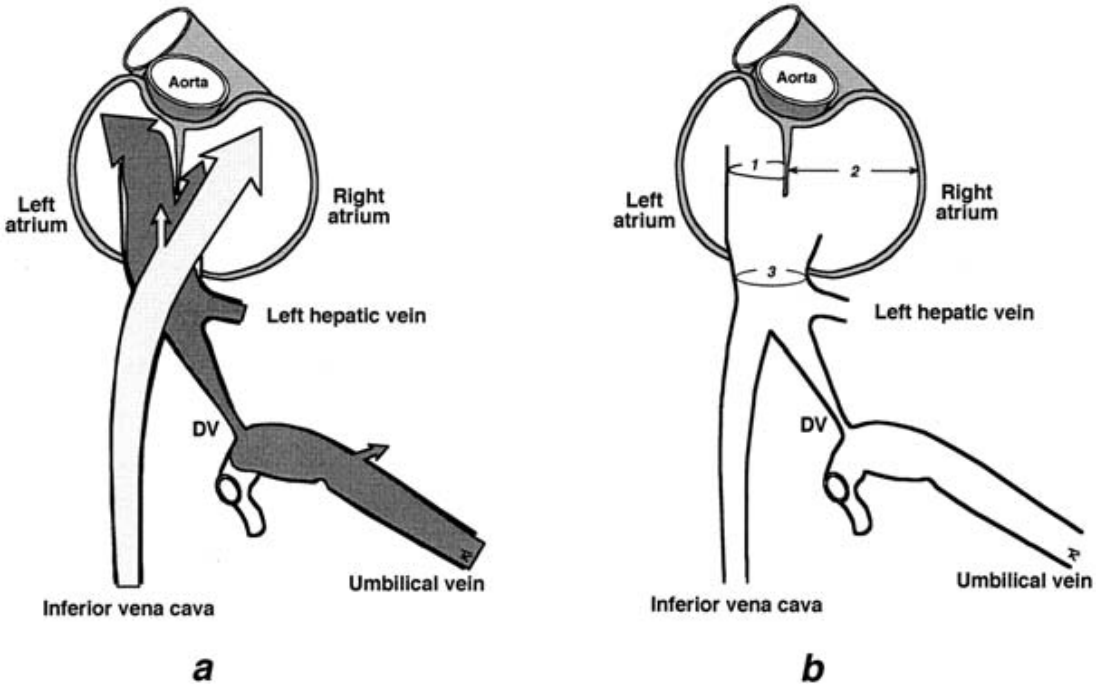

Figure 6 The ascending blood in the inferior vena cava enters the fetal heart between the foramen ovale flap and the Eustachian valve, and is divided into a left and right flow by the atrial septum (Panel ***a***). Blood from the abdominal inferior vena cava (light grey) enters the right atrium. Umbilical blood (dark grey) from the ductus venosus (DV) and left hepatic veins preferentially enters the left atrium passing the restricting section (1 in Panel ***b***). 2, transverse right atrial diameter; 3, inlet of the inferior vena cava. **Printed with permission**[131]

It is worth looking at the relationship between the IVC and the foramen ovale. The abdominal IVC is a slender structure during fetal life. As the IVC passes the liver, however, it increasingly widens, mainly in the left compartment,[40,41] to receive the hepatic and ductus venosus blood flow (Figure 6). The proximal portion of the IVC tilts 14 degrees forward compared to the descending aorta and forms an angle of 48 degrees with the ductus venosus.[40] The inlet into the fetal heart is ambiguous compared to the arrangement in later life. The fetal atrial septum is positioned slightly more to the right side than is seen during adult life. The consequence is that the interatrial septum resides on top of the IVC and divides with its crest, the crista dividens (Figure 3), the blood flow from the IVC into a right and left stream (Figure 6). The foramen ovale valve is attached to the atrial septum on the left side opposite to the insertion of the Eustachian valve (the IVC valve). The two thin valves form a tubular extension of the IVC between the atria (Figure 3 and 6). The foramen ovale valve is much longer and forms a ballooning "wind sock" to the left of the septum. After birth, there is only a small transfer of blood through the ductus venosus but a substantial increase in pulmonary venous return to the left atrium. The foramen ovale valve comes down to cover the orifice of the foramen ovale, and the IVC is from then on dedicated exclusively to the right atrium.

The blood that passes the ductus venosus has the highest velocity (i.e. kinetic energy) in the area,[6,7] sufficient to press open the foramen ovale valve and preferentially enter the left atrium (Figure 6). Flow from the left and medial hepatic veins has less kinetic energy and therefore comes next to the ductus venosus in supplying blood to the foramen ovale. This blood, however, represents another significant source of oxygen since the oxygen extraction in the liver rarely exceeds 10–15%.[42] The abundant volume of blood directed towards the foramen ovale provides a considerable spillover to the right side of the crista dividens of the atrial septum, and thus reduces the difference in saturation to just 10% between the left and the right ventricle.[26,43] However, during hypoxemia, the effect of preferential streaming through the foramen ovale seems to increase,[36,44] and the difference in saturation becomes 12%. An increased fraction of umbilical blood shunted through the ductus venosus (and foramen ovale) and a reduced pulmonary venous return to the left atrium are responsible for the shift in blend.

How much blood enters the left atrium through the foramen ovale? In fetal lambs, it is around 27% of the combined cardiac output.[25] In the human fetus, it has been calculated indirectly using measurements in the great arteries.[45–47] At 20 weeks, 34% of the combined cardiac output enters the foramen ovale.[47] At 30 weeks the proportion has come down to 18% and remains low for the rest of the pregnancy.[47] These studies used the time integral of the maximum velocity in the pulmonary arteries or ductus arteriosus to calculate flow, which carries a risk of overestimation (and thus underestimating the foramen ovale flow). Since the velocity changes from a flat to a more parabolic profile as the blood travels away from the heart, the maximum velocity is less likely to represent the mean velocity needed for the flow calculation.

To arrive in the left atrium, the umbilical blood has to be loaded with sufficient energy (kinetic energy and pressure) to pass the resistance of the ductus venosus or the hepatic vasculature, cross the IVC and enter the foramen ovale. Thus, the pressure (and kinetic energy) in the umbilical vein is vital for the fetus. In fetal sheep the porto-caval pressure gradient was measured to be 4 mm Hg,[48] and for the human fetus calculated to be 0–3.5 mm Hg during the cardiac cycle in the second half of pregnancy.[49] The pressure in the umbilical vein is 2.2 mm Hg (range 0–5) at 18–21 weeks gestation[50] and 5mm Hg (range 1–11) later in pregnancy.[51,52] It is regulated by the resistance in the portal vascular bed and the ductus venosus, and, on the other side, the arterial blood pressure that drives the blood through the placental vasculature. Compared to other fetal vascular beds, the placental circuit is relatively inert.[53] During experimentally induced hypoxaemia there is a general constriction of the fetal vascular beds (but less in the placenta), an increased arterial blood pressure directing a higher fraction of the combined cardiac output through the placenta, and an increased umbilical venous pressure. However, if the circulatory compromise involves a reduced umbilical pressure and flow, the portal vein represents another contributor to umbilical venous pressure regulation.[25]

The degree of shunting through the ductus venosus is regulated by diameter changes,[54] not only at the inlet but also along the entire length,[54,55] which should have a more profound effect on resistance. The vessel is influenced by α-adrenergic constriction, β-adrenergic relaxation, and relaxes under the influence of prostaglandin

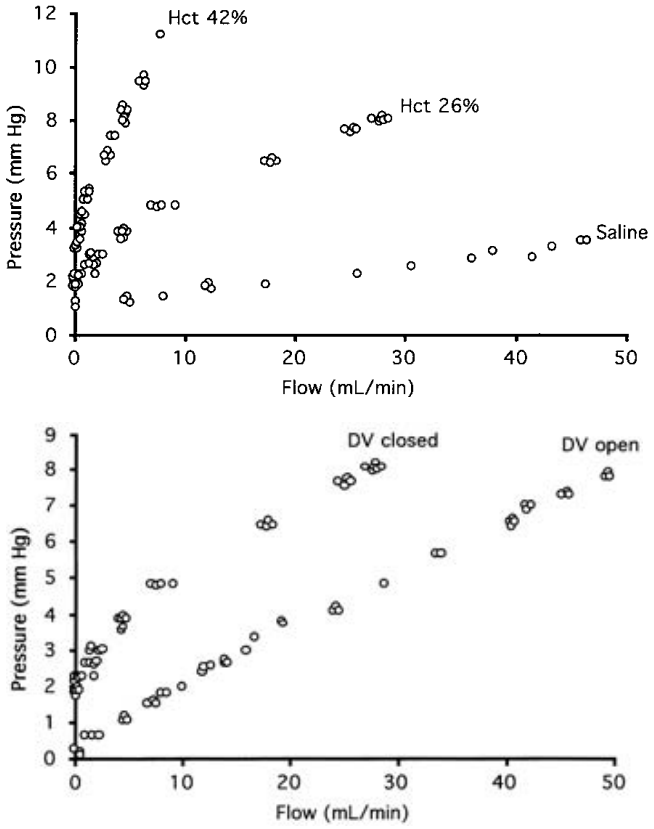

Figure 7 Upper panel: The effect of viscosity on resistance and closing pressure in a fetal lamb liver perfused through the umbilical vein. The ductus venosus was occluded. Resistance increased as the perfusate was changed from saline to blood of haematocrit (Hct) 26 and 42%. The linear relationship seen at high flow rates, however, is broken at low flow rates signifying a mounting resistance due to the escalating viscous friction. The closing pressure (at flow = 0) rises with increasing Hct. Lower panel: The effect of a patent ductus venosus is shown in the same preparation perfused with blood of haematocrit 26%. With the ductus venosus patent resistance was lower, closing pressure less, and flow greater at any pressure. At pressures above 7 mm Hg, more than half of the umbilical flow entered the liver parenchyma. Below 7 mm Hg more than half of the blood entered the ductus venosus. At very low pressures (< 3 mm Hg) the liver circuit had reached the closing pressure, and the umbilical blood exclusively entered the ductus venosus. **Printed with permission**[66]

E_1.[56–59] A recent study showed the relaxation effect of nitric oxide, the tonic α-adrenergic effect, and a substantial effect of hypoxaemia causing a 60% increase in the diameter of the isthmus.[54] This confirms that diameter regulation plays a central role in increasing the shunting observed during hypoxemia. Individual changes of the ductus venosus diameter have also been observed in serial measurements.[60]

There are indications that the fetal liver can modify the blood distribution by increasing its vascular resistance.[48,61–65] However, simple fluid dynamic forces have a substantial impact on the distribution.[66] High haematocrit (i.e. high viscosity) increases the closing pressure and resistance in the liver more than in the ductus venosus and shifts the distribution towards more shunting. Reduction in umbilical venous pressure augments this effect (Figure 7).

Table 1 The fraction of umbilical blood shunted through the ductus venosus observed in 193 low risk pregnancies[24]

	Degree of ductus venosus shunting (%)	
Gestational age (weeks)	50th percentile	(10th;90th percentiles)
18–19	28	(14;65)
20–24	25	(10;44)
25–28	22	(10;44)
29–32	19	(9;46)
33–36	20	(10;31)
37–41	23	(7;38)

Until recently, it was commonly believed that the shunting of oxygenated blood through the ductus venosus was crucial to fetal development. Experimental animal studies (and a study of previable exteriorised human fetuses) had shown that 50% of the umbilical venous return was shunted through the ductus venosus, a fraction that increased to 70% during hypovolemia[67,68] or hypoxemia.[36,44] More recent human data suggest reduced shunting.[24,69,70] Studies in low risk pregnancies found that roughly 30% of the umbilical blood was directed through the ductus venosus at mid-gestation.[24] The fraction was reduced to 20% at 30 weeks and remained unchanged until term (Table 1). In this study, small fetuses were shown to shunt marginally more through the ductus venosus. In another study, growth restricted fetuses had increased shunting through the ductus venosus.[71] Judged from dimension and flow, the ductus venosus plays a more prominent role in early compared to late pregnancy.[24,70]

Does agenesis of the ductus venosus indicate its physiological importance? As can be expected, an increasing number of case reports have linked ductus venosus agenesis to other malformations, chromosomal abnormalities, and intrauterine fetal death.[14,15,72–78] However, since the agenesis was found almost exclusively in fetuses referred for other reasons, and we do not know the incidence of ductus venosus agenesis in the normal population. The significance of absent ductus venosus shunting is still not known. In a series of 203 low risk pregnancies, one fetus had agenesis of the ductus venosus but experienced otherwise normal development, growth, and birth, suggesting that agenesis does exist in otherwise normal fetuses and may well be compatible with normal development.[24] This is supported by the fact that experimental occlusion of the ductus venosus had hardly any measurable effect on haemodynamics or oxygen distribution.[79,80]

The recent studies in human pregnancies showing an amazingly low degree of shunting through the ductus venosus,[24,70] have prompted the suggestion that it is the perfusion of the liver with umbilical blood that matters, and that the ductus venosus is important only during extreme acute conditions in the second half of pregnancy (e.g. fetal haemorrhage or hypoxemia). Tchirikov et al[81] provided further

support for this suggestion when they occluded the ductus venosus in fetal sheep and found that the liver grew more than in the controls. These fetal sheep also had a higher concentration of insulin-like growth factor-2 and showed an enhanced growth of most organs. Thus, the study confirmed the role of the fetal liver in fetal growth.[82] A subsequent ultrasound study of human pregnancies suggests that fetuses with a wide abdominal circumference (probably reflecting liver size) had higher umbilical venous flow but no difference in ductus venosus flow compared to fetuses with a smaller circumference.[83] This suggests increased liver perfusion in the large fetuses. In another study, cord haematocrit showed a strong and graded inverse association with birthweight and a graded association with lower concentrations of insulin-like growth factor-2.[84] The neonates with a haematocrit ≥ 0.50 had significantly higher levels of apolipoprotein-B, which persisted after adjustment for birthweight. The findings link liver perfusion to metabolic development, which is a topic of great interest in the search for mechanisms of intrauterine programming of adult diseases.

VENOUS DOPPLER RECORDING

Being a system of low pressures and velocities, venous blood flow recording is easily influenced by external forces and is more vulnerable to interference than arterial blood flow. Fetal breathing is recognized to have a substantial impact on the blood flow in the intraabdominal umbilical vein,[85–88] and Marsál et al[87] showed that the blood flow velocity during high amplitude respiratory movements can increase to 54% above the level during apnoea. Behavioural states also influence venous blood flow velocities.[89–91] The state of passive sleep is associated with lower velocities than during periods of active sleep. Such information should be kept in mind when the reference ranges reported in the literature and the recordings from individual patients are considered.

A straightforward description of the venous blood flow is done by inferring the time-averaged maximum velocity (V_{ta}) or intensity-weighted mean velocity (V_{mean}) from the Doppler signals. Since velocities in the umbilical vein are low, the fraction of velocities filtered out by the high-pass filter tends to skew the V_{mean} towards higher values. Interference from neighbouring vessels and vessel wall movements may also influence the assessment of V_{mean}, which is used for volume flow calculation: $\pi\,(D/2)^2\,V_{mean}$ where D denotes diameter.[1,2,24,28,86,92] To avoid such errors it is possible to use the more reproducible V_{ta} assuming that the velocity has a parabolic profile.[29,69,70,93–95] In that case $V_{mean} = 0.5\,V_{ta}$ and the blood flow can be calculated using:

$$\pi\,(D/2)^2\,0.5\,V_{ta}$$

The latter method gives slightly lower values (3–6%) than using the V_{mean}, but the method is probably more robust for clinical use. However, any acceleration or retardation of flow will change the velocity profile. There is now new theoretical

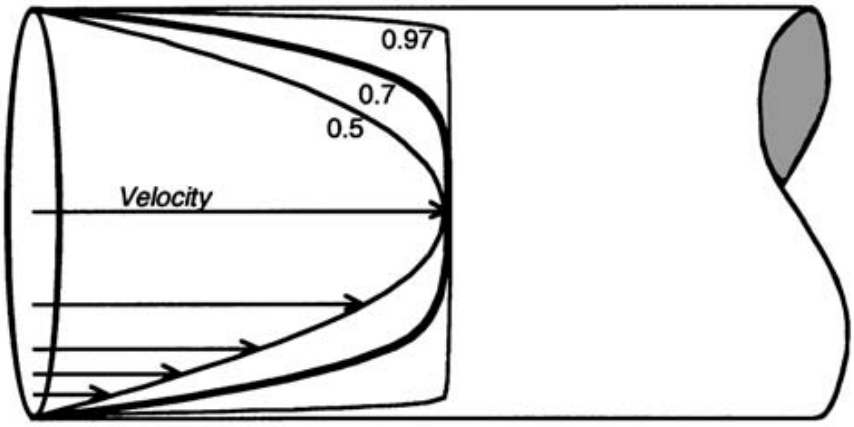

Figure 8 The blood velocity profile represents the velocity distribution across the vessel and is characterised by the V_{mean}/V_{max} ratio. The velocity profile in the ductus venosus inlet is partially blunted corresponding to a ratio of 0.7. The steady blood flow in the umbilical vein has a parabolic velocity profile (i.e. ratio 0.5). Accelerated blood at the cardiac outlets has a blunted profile (e.g. ratio 0.96). **Printed with permission**[98]

and experimental proof that the blood velocity profile at the ductus venosus inlet is partially blunted with a V_{mean}/V_{ta} ratio of 0.7. This figure, rather than 0.5, should be used when calculating volume flow.[96–98] (Figure 8).

Although both the V_{ta} and V_{mean} give valuable information on venous flow, other methods characterizing pulsatile venous blood flow velocity are used more frequently. The pattern of the blood flow velocity wave is basically the same for most main veins draining to the atria. There is a peak velocity during ventricular systole, a second peak corresponding to the passive filling during diastole, and a subsequent deflection of velocity (a-wave) caused by the atrial contraction during the active filling of the ventricles (Figure 9). Thus, the venous velocity waveform basically reflects cardiac function. As in adult and paediatric cardiology, the time integral under the three wave components can be calculated. A ratio of such integrals or peak velocities has the advantage of being independent of the angle of insonation, which otherwise is an important source of error.[4,5] A number of ratios based on the maximum velocity tracing have been suggested as exemplified in the case of the ductus venosus velocimetry[6–8,99,100] (Table 2).

The reproducibility of venous Doppler recordings is acceptable.[7,85,86,91,95,101] Velocimetry in the intraabdominal umbilical vein is reproducible with a coefficient of variation of 7%.[102] A comparison between the ultrasound method and steady state diffusion technique for assessing flow in the cordal section of the umbilical vein showed excellent agreement.[95] For the ductus venosus, which has high velocities, limits of agreement for the intraobserver variability were found to be ±13 cm/s, and the coefficient of variation was 9–15% for measurements done during the second half of pregnancy.[101] However, for the assessment of the a-wave, which is of particular interest at 10–14 weeks of gestation, the coefficient of variation of 27–29%[103,104] is

Table 2 Indices suggested in the literature to describe the ductus venosus blood flow velocity profile. Some of the indices are suggested also for other veins and are probably applicable for most pulsatile flow in the central venous system

Index	Reference
$\frac{V_{ta}}{S}$	Kiserud T et al. (1991)
$\frac{S}{D}$	Huisman TWA et al. (1992)
$\frac{S}{A}$	Oepkes D et al. (1993)
$\frac{S-A}{S}$	DeVore GR and Horenstein J (1993)
$\frac{S-A}{D}$	Hecher K et al. (1994)
$\frac{S-A}{V_{ta}}$	Hecher K et al. (1994)

A = minimum velocity during atrial contraction (a-wave); D = peak velocity during ventricular diastole; S = peak velocity during ventricular systole; V_{ta} = time-averaged maximum velocity.

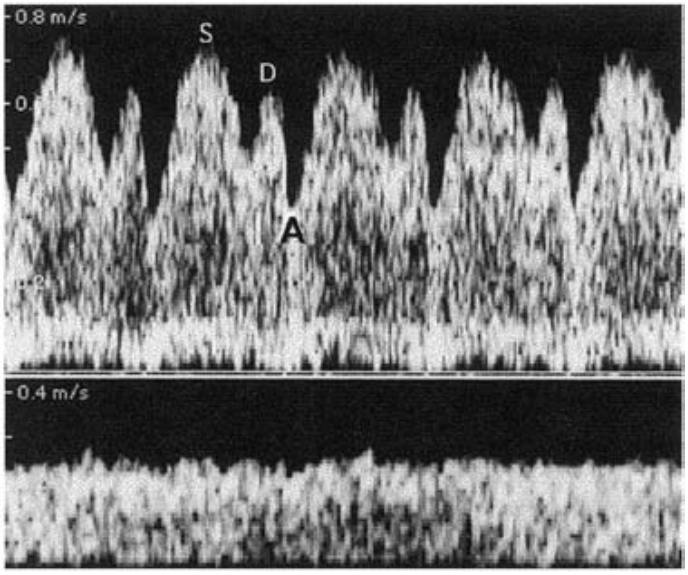

Figure 9 Typical blood velocity in the ductus venosus (upper Panel) and umbilical vein (lower Panel) of a fetus at 23 weeks gestation. A, nadir during atrial contraction (a-wave); D, peak during passive diastolic filling; S, peak during ventricular systole. **Printed with permission**[24]

unsatisfactory and reflects methodological problems.[105] Visual assessment of a zero or reversed velocity during the a-wave seems to perform better.[103]

The accuracy of volume flow estimations is mainly restricted by the error of diameter measurements, particularly in small vessels (Figure 10).[28,86,106,107] Figure 10 also illustrates the impact of repeat vessel diameter measurements on the flow

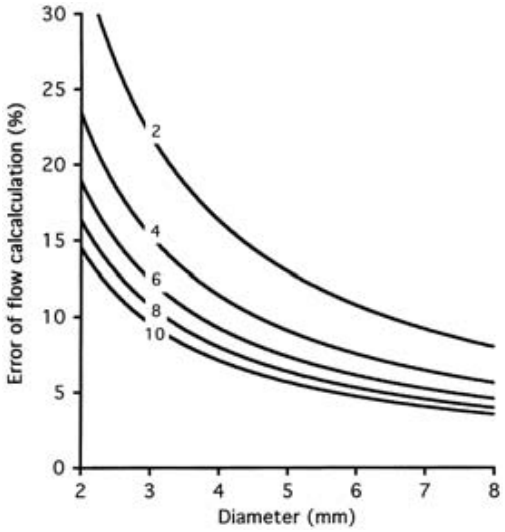

Figure 10 The error of flow calculation arising from the diameter measurement of the umbilical vein. Each line represents the upper 95% limit for the diameter calculated from 2–10 measurements. Thus, 95% of the observations will be equal or less than the line indicates. **Printed with permission**[106]

error.[106] A single measurement of a small umbilical vein, 3 mm, has an upper 95% confidence limit of 0.44 mm for the diameter error and a corresponding 29% flow error. When the diameter is based on six measurements, the corresponding limits are 0.18 mm and 12%, and for 10 measurements, 0.14 mm and 9%. This is a good method for controlling error, but as can be seen from Figure 10, there is a practical limitation to the method since further improvements require an exponential increase in the number of observations.

DETERMINANTS OF VENOUS PULSATION

The short velocity deflection of the umbilical venous velocity is commonly recognized as the atrial contraction wave (a-wave). However, pulsations may appear differently and have various causes.[108,109] Recent research has addressed this part of physiology. One important determinant is the direction of the pulse wave compared to the direction of the blood flow.[110] If the pressure wave travels in the same direction as the blood velocity (Figure 11), the pressure wave will impose a velocity increase (e.g. umbilical artery waveform), an effect also seen in the venous system (e.g. at the abdominal inlet).

When the pressure wave travels in opposite direction of the blood velocity (Figure 12), the pressure wave causes a deflection in the velocity (e.g. atrial contraction wave in the hepatic veins, ductus venosus and umbilical vein). Thus, deflections of velocity should be distinguished from pulsatile increments. The first being of clinical interest if found in the intra- or extraabdominal sections of the umbilical vein, whereas pulsatile increments in the same sections merely signify the impact of arterial pulsations with no known diagnostic implication.

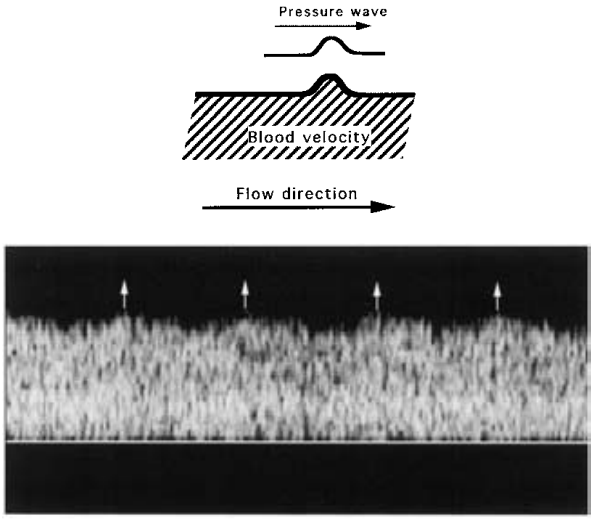

Figure 11 A pressure wave that travels in the same direction as blood flow causes a blood velocity increment (upper panel). The result is a velocity increment (arrow) observed in the umbilical vein, probably an impact of the neighbouring artery (lower panel). **Printed with permission**[110]

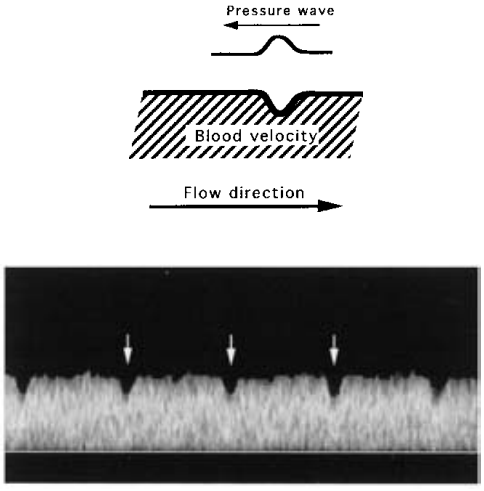

Figure 12 A pressure wave that travels in the opposite direction of flow causes a corresponding reduction in blood flow velocity (upper panel). The umbilical venous velocity inflection (arrow) due to an augmented atrial contraction represents an example of a pressure wave travelling against flow direction (lower panel). **Printed with permission**[110]

An augmented atrial contraction wave has become an important clinical marker. A high amplitude of this wave can be generated in the fetal atrium as a result of Frank-Starling mechanisms when the atrium is exceptionally distended during bradycardia (e.g. atrioventricular block), or when the atrial contraction comes at a time when the atrioventricular valves are closed (e.g. tachycardias), or during adrenergic drive.[111,112] Probably, the most powerful effect on the a-wave is during hypoxaemia.[113] Thus, the a-wave observed in the various sections of the venous system represents a method of surveillance that instantaneously reflects alteration in cardiac function.

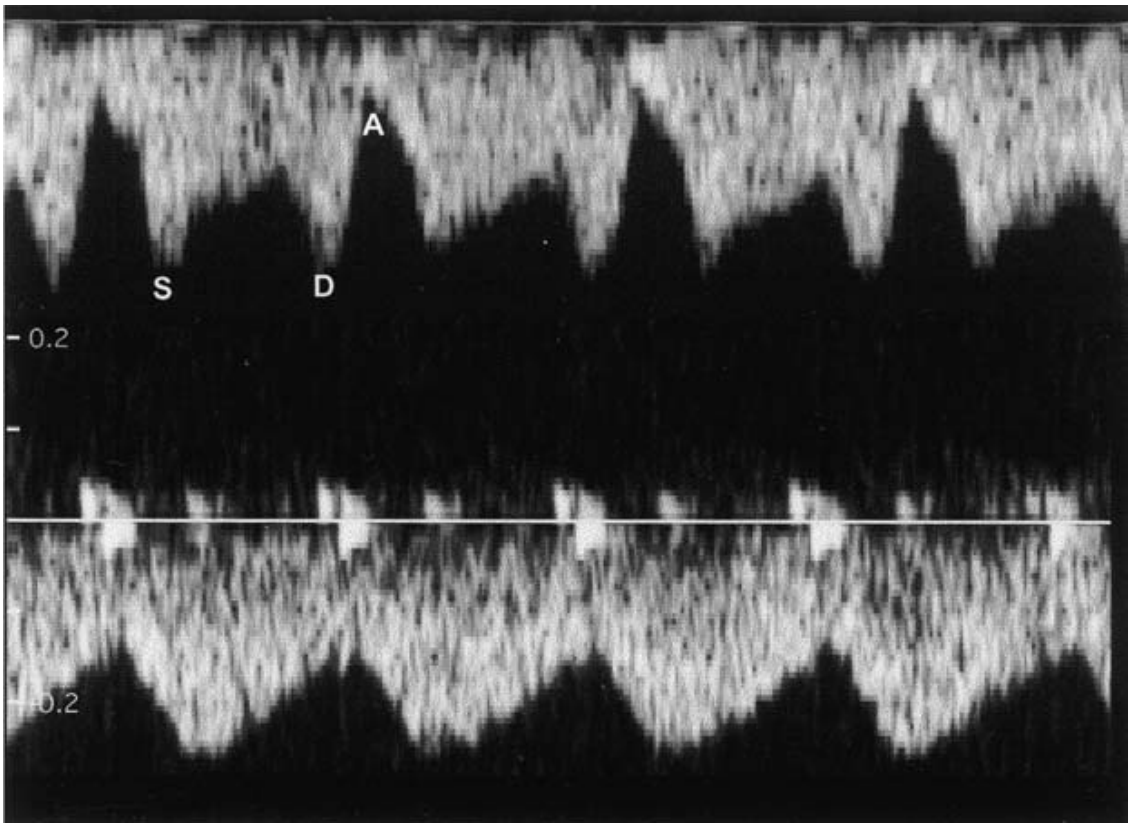

Figure 13 The pressure variation of the left atrium is reflected in the velocity recording of the pulmonary veins (upper Panel). With the loss of connection the pressure variation is not transmitted into the vein and the velocity pattern reflects the general pressure variation in the chest (typical for anomalous pulmonary venous drainage) (lower Panel). A, nadir during atrial contraction; D, diastolic peak; S, systolic peak.

The wave generated in the atrium is transmitted along transmission lines, the venous connections, to reach the periphery.[41,114,115] In the case of an interrupted transmission line, such as in total anomalous pulmonary veins where the pulmonary veins are not connected to the left atrium but to the portal system, the atrial wave will have no impact on the venous velocity pattern (Figure 13). The same phenomenon has been described in agenesis of the ductus venosus, which represents a breach in a prominent transmission line formed by the IVC, ductus venosus and umbilical vein.[115]

Once the wave is emitted from the atrium it will be modified during its course along the veins according to the local physical conditions.[60,116] One such determinant would be the stiffness of the vessel wall. In vitro experiments have shown that the stiffness varies from the ductus venosus outlet to its inlet, and to the intraabdominal umbilical vein.[117] The compliance and impedance vary accordingly. Mathematical modelling has shown that it is particularly the variation of impedance along the transmission line that changes the wave.[60,114]

The most powerful mechanism modifying the wave is reflection.[41,114,118] It is a well-known phenomenon in arterial haemodynamics,[119] but is equally valid in veins.[114]

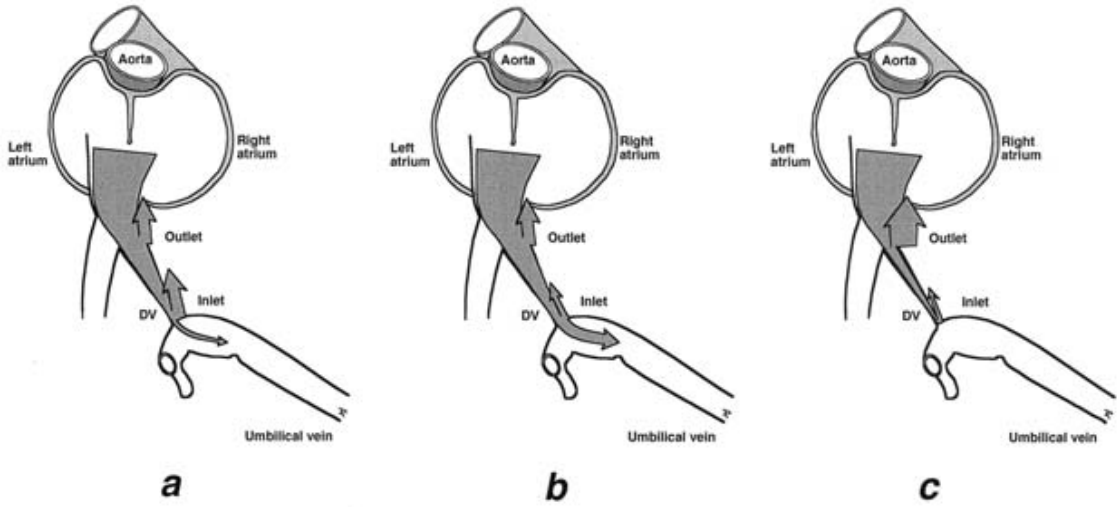

Figure 14 Panel ***a***: The IVC, ductus venosus, and umbilical vein act as a transmission line for the pulse waves in the opposite direction of venous blood flow. Under normal conditions, the large difference in impedance at the junction between the ductus venosus and umbilical vein (mainly due to differences in diameter) causes extensive wave reflection, and reduced transmission into the periphery with a correspondingly low probability of umbilical venous pulsation. Panel ***b***: Distension of the ductus venosus inlet (e.g. hypoxia) reduces the difference in diameter (and impedance) between the ductus venosus and umbilical vein and leads to less wave reflection and more transmission with an increased probability of umbilical venous pulsation. Panel ***c***: A squeezing of the ductus venosus *outlet* (e.g. bending position of the fetus) may represent a sufficient difference in impedance between the IVC and the ductus venosus causing extensive reflection and preventing pulse wave transmission down the system. Typically, there will be no pulsatile flow at the ductus venosus inlet until the fetus has changed position and the squeezing is relieved (cf. Figure 15). **Printed with permission**[118]

There is an analogy with the beam of light. When light hits an interface between media of different densities, some of the beam will be reflected and some transmitted. The pulse wave emitted from the atria will follow the transmission lines (i.e. veins) until it hits a junction (Figure 14a). Here the wave will be partially reflected and partially continue along the transmission line (e.g. IVC – ductus venosus junction, or ductus venosus-umbilical vein junction). The Reflex coefficient (R_c) determines the degree of reflection and depends on the impedance of the two sections of veins (e.g. Z_{DV}, ductus venosus, and Z_{UV}, umbilical vein):

$$\boldsymbol{R}_C = \frac{\textbf{Reflected wave}}{\textbf{Incident wave}} = \frac{Z_{UV} - Z_{DV}}{Z_{UV} + Z_{DV}}$$

In this case, Z_{UV} represents the terminal (distal) impedance in fluid dynamic terms, whereas Z_{DV} represents the characteristic impedance. From a practical point of view, the single most important determinant for impedance is the cross section of the vessel (A):

$$Z = \rho c/A$$

where ρ = density, and c = wave velocity. In the case of the ductus venosus-umbilical

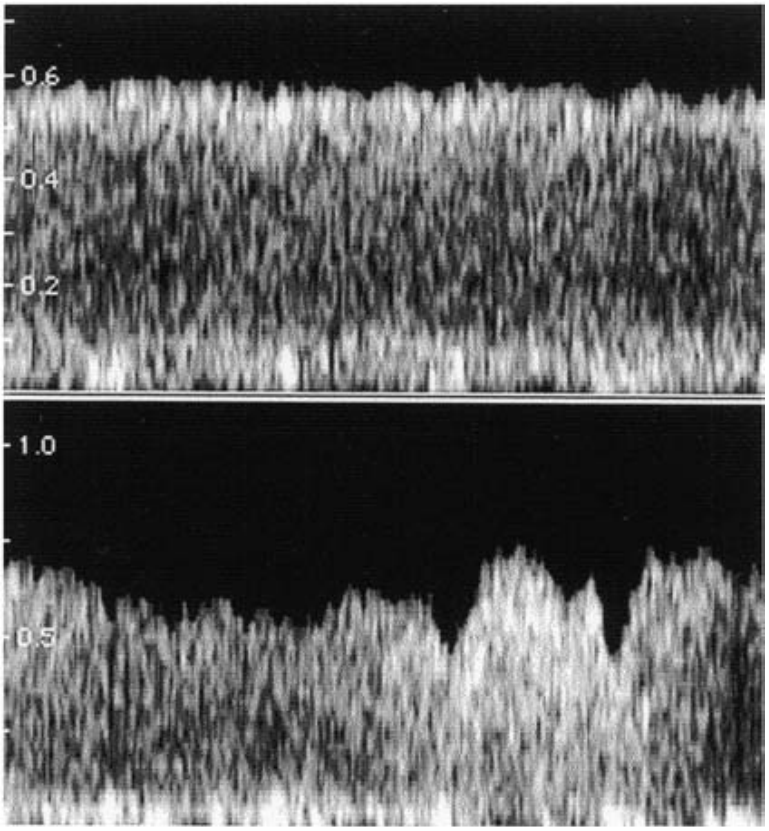

Figure 15 Doppler recording of the blood velocity at the inlet of the ductus venosus in a normal fetus at 34 weeks of gestation. The fetal position has caused a squeezing of the ductus venosus outlet (cf. Figure 14 c) (upper panel). A few minutes later the pulsatile flow is being restored with the change of fetal position (lower panel). **Printed with permission**[118]

vein junction, there is an extraordinary difference in cross section, and thus impedance; the ratio of the diameter of the umbilical vein and the ductus venosus being 4 (95% CI 2,6).[41] Correspondingly, most of the wave will be reflected and little energy transmitted further down. The small proportion of the energy transmitted to the umbilical vein is usually not sufficient to cause visible pulsation.

In extreme situations, such as during hypoxia, the ductus venosus distends in its entire length but particularly at the inlet, and the difference in vessel area between the two sections is reduced, less wave is reflected and more transmitted (Figure 14b). Thus, a larger proportion of the wave arrives in the umbilical vein and may induce pulsation, particularly if the a-wave was augmented in the first place.

In 3% of all recordings there is no pulsation in the ductus venosus, which is a normal phenomenon.[101] The pattern is caused by the position of the fetus bending forward and thus squeezing the IVC and ductus venosus outlet[41] (Figure 14c). The extensively reduced cross section causes a total reflection of wave at the level of the IVC-ductus venosus junction and hardly any pulse is transmitted further down until the squeeze has been released (Figure 15). A similar effect can probably be obtained by

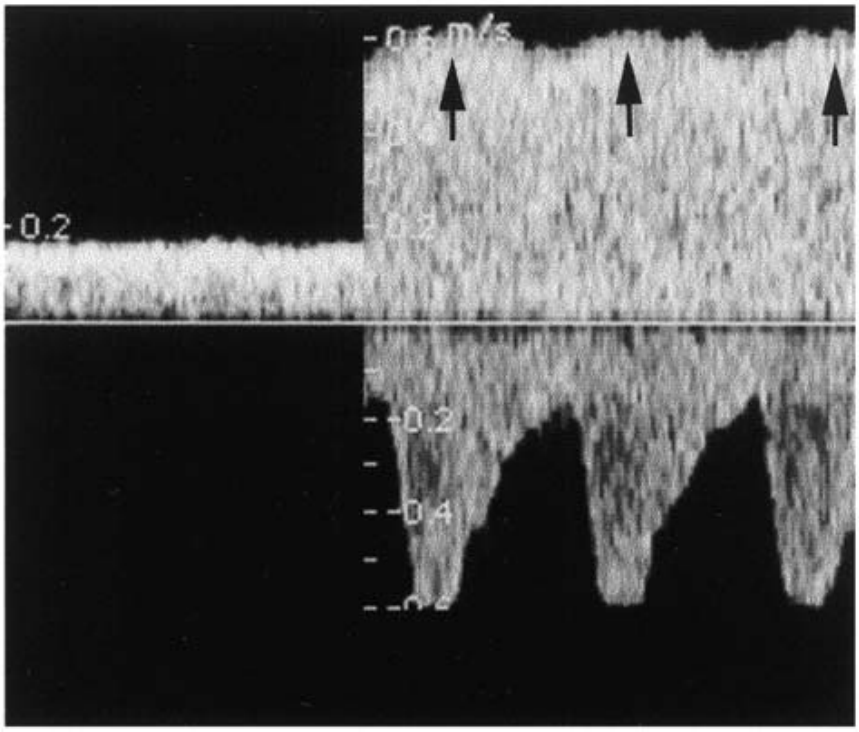

Figure 16 Doppler recording of the umbilical venous blood velocity at the fetal end of the cord (left panel) at 32 weeks of gestation. Due to a physiological constriction at the abdominal ring the velocity is accelerated (right panel). The low compliance leads to pulsation (arrows) imposed by the umbilical artery. Umbilical artery velocity recording below the zero line. **Printed with permission**[121]

the spontaneous variation in cross section sometimes seen in the proximal portion of the IVC.

Another determinant is the reservoir effect.[114] Whether a pulse that arrives in the umbilical vein induces velocity pulsation depends on the local compliance. The umbilical vein is a sizeable vessel and acts as a reservoir. The larger and more compliant the reservoir, the higher wave energy is required to induce a visible pulsation of the blood velocity. Accordingly, pulsation should be a rare event in late pregnancy, whereas the small vascular dimensions in early pregnancy predispose to pulsation. Pulsation in the umbilical vein is a normal phenomenon particularly before 13 weeks of gestation.[120] It follows that an increase in tone of the vessel wall (e.g. adrenergic drive, venous congestion) and reduced diameter (e.g. hypovolemia in fetal haemorrhage) may be accompanied by pulsation in the umbilical vein.

The effect of compliance is particularly well illustrated by the physiological stricture of the umbilical vein at the entrance through the abdominal wall.[121–123] Once the period of physiologic umbilical herniation has been completed, there is an increasing tightening of the umbilical ring causing a stricturing effect on the vein in quite a few fetuses during the following weeks and months. The stricture causes a high velocity, which, interestingly, often pulsates. Although the pulsation may be a velocity inflection caused by the a-wave, probably a more common waveform would

be a smooth increment of velocity (Figure 16) caused by the neighbouring umbilical arteries, a phenomenon that also can be traced in the umbilical cord.[124,125] Pulsation has also been traced in the left branch of the fetal portal vein,[91] which may be due to the smaller dimensions (i.e. compliance) of this section increasing the likelihood for pulsation even at a low wave energy.

It follows that pulsatile venous flow, both in precordial veins and in peripheral veins such as the umbilical vein and intracranial veins, is determined by cardiac function and the local physical properties of the vasculature. All determinants will vary with gestational age. Unless these facts are taken into account, we may misinterpret venous Doppler recordings.

FORAMEN OVALE

There have been several attempts to establish a method of assessing the fetal foramen ovale based on the postnatal concept that interatrial shunts flow in a transverse fashion.[126–129] Accordingly, the diameter of the foramen ovale orifice in the atrial septum was measured. However, as we have discussed in a previous section, the inferior venous return constitutes a rather vertical flow that is divided in a right and left arm at the level of the crista dividens (Figure 3 and 6a).[6,39,40] Patten et al[130] showed in 1929 that the restricting area for the blood that enters the foramen ovale actually was the horizontal section at the top of the "wind sock", between the foramen ovale flap and the atrial septum[130] (Figure 6b). Based on these principles, the area and diameter of the foramen ovale inlet to the left atrium have been determined.[131] Interestingly, the size of the foramen ovale is stable after 30 weeks of gestation, particularly when comparing with the IVC cross section (Figure 17). At mid-gestation the ratio between the area of the foramen ovale and the IVC is roughly 1, but at term it has been reduced to 0.5, reflecting the same pattern as has been seen for the pulmonary circulation and the ductus venosus flow: a developmental transition to less shunting at 30 weeks of gestation. The clinical testing of this method has just started and preliminary results seem to show that growth restricted fetuses have a relatively wider foramen ovale.[132]

PULMONARY VEINS

Compared to postnatal life, the pulmonary circulation represents a small proportion of the fetal circulation; animal experiments suggest around 8% of the combined cardiac output.[27] In the human fetus, recent studies suggest that the pulmonary flow may be slightly larger;[45–47] 13% at 20 weeks of gestation and 20–25% during the third trimester.[47] Doppler velocimetry of the pulmonary veins has not been used to quantify pulmonary flow but rather to study the velocity waveform, which is remarkably different from other precordial venous waveforms throughout pregnancy.[9,10,133] While the nadir during atrial contraction is easily recognised, the peak velocity during ventricular systole is blunted at an early stage of the cycle compared to other precordial

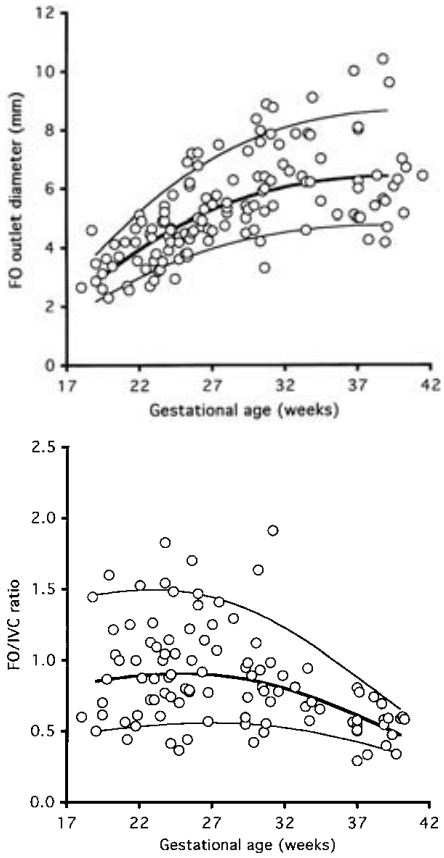

Figure 17 Foramen ovale (FO) outlet diameter (measurement 1 in figure 6b) in 135 fetuses shows less growth during the third trimester (upper panel). This fact is further visualised in the reduced ratio between the area of the FO and that of the inferior vena cava (IVC) seen in 102 observations (lower panel). Data are presented with 10th, 50th and 90th percentiles. **Printed with permission**[131]

veins (Figure 13). Since the pulmonary veins are connected to the left atrium, they have attracted attention in the hope that the wave analysis could specifically reflect left sided cardiac function. A lack of connection, i.e. totally anomalous pulmonary veins, leads to loss of the detailed velocity changes during the cardiac cycle, and the wave form represents the general pressure variation in the chest (Figure 13). It illustrates how important an open transmission link is for the wave propagation into the venous system.

However, the interpretation of the normal waveform has not been easy. An interesting contribution came with the study of fetuses with hypoplastic left heart syndrome with varying size of interatrial connection.[134] A closed foramen ovale makes the small atrium a secluded volume with a small compliance during ventricular systole. The early and acute downstroke during systole (Figure 18) reflects the low compliance and a corresponding quick increase in pressure. The other extreme, an abnormally large interatrial connection turns the right and left atrium in to a larger common compliant volume. In such cases a persisting sizeable velocity in the pulmonary vein during the entire ventricular systole reflects that compliance. Thus,

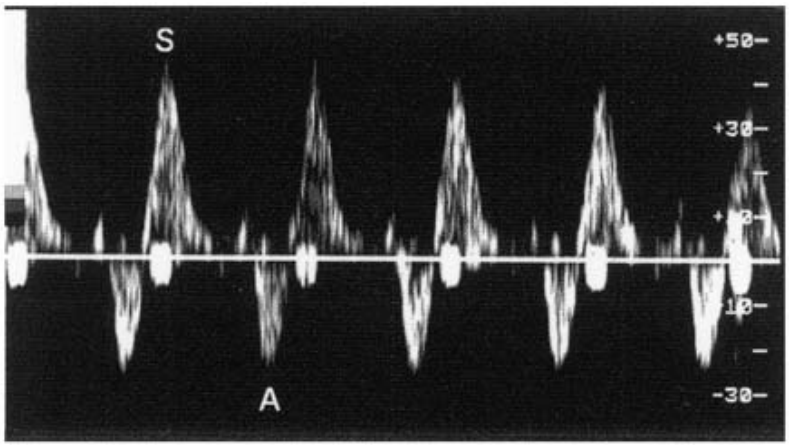

Figure 18 Pulmonary vein recording in a case of hypoplastic left heart syndrome with a closed foramen ovale. The acute downstroke during systole (S) indicate a low compliance of the left side. The reversed atrial contraction wave (A) further signifies an increased end-diastolic pressure. An open foramen ovale would have involved the right atrium with a different compliance reflected in a slower downstroke of S. **Printed with permission**[134]

the size of the foramen ovale is one of the important determinants of the pulmonary venous waveform.

During normal conditions the foramen ovale represents a considerable inlet to the left atrium and the blood that enters is predominantly derived from the ductus venosus flow, which has a high kinetic energy.[6] The high kinetic energy is transformed into pressure once the velocity retards. Accordingly, the sizeable blood volume crossing the foramen ovale is expected to have a noticable impact on the pressure profile in the left atrium, and thus cause the blunted velocity pattern of the pulmonary vein during ventricular systole. A significant mitral regurgitation is expected to have a similar impact. The following determinants of the pulmonary venous velocity could be considered in the case of altered pulmonary venous velocity pattern:

1. Pulmonary volume flow
2. Foramen ovale size and flow
3. Left atrial compliance (size and muscle distensibility)
4. Atrial contraction, end-diastolic pressure (e.g. adrenergic drive, hypoxaemia)
5. Left ventricular size and performance
6. Mitral valve size and function (e.g. regurgitation)

DUCTUS VENOSUS

The recommended method for recording the blood velocity uses a large sample volume at the inlet in a near-sagittal scan at a minimum angle of insonation.[6,101] A second alternative is an oblique transection of the fetal abdomen.[7,101] During early pregnancy, the sample volume has to be adjusted to fit the dimensions.[135–138] Colour Doppler enhances the identification and the control of angle of interrogation.

In contrast to the neighbouring veins, the ductus venosus blood velocity is high and has no negative component during the last half of pregnancy[6–8,101,139] (Figure 9). The systolic peak velocity is 50–80 cm/s at 20 weeks gestation and 60–90 cm/s at 40 weeks. The same pattern is found in early second trimester but at lower velocities.[135–138,140] Below 15 weeks of gestation, a negative a-wave is increasingly seen in normal fetuses.[41] A reversed a-wave is more commonly found in fetuses with chromosomal aberrations and therefore has been suggested as a secondary screening tool in fetuses with increased nuchal translucency.[137,138,141] Similarly, an augmented a-wave has been associated with suboptimal cardiac function in early pregnancy.[142–144] The substantial variation between centres in the incidence of a negative a-wave in early pregnancy and the unacceptable intra- and interobserver variability[103,104] restrict ductus velocities from being accepted as a secondary method of screening at this stage.[105]

The waveform is usually described by a ratio, which has the advantage of being independent of the angle of insonation. A variety of ratios have been suggested (Table 2). Although the ratio between the V_{ta} and systolic peak was thought to reflect the ability to transfer umbilical blood through the ductus venosus during the cardiac cycle,[6] most ratios are used to describe cardiac function instead.[6–8,99,100] The Pulsalility Index for Veins ($PIV = (S - A)/V_{ta}$) suggested by Hecher et al. is probably the one most used and is a robust parameter for clinical work.[145]

An increased pulsatility is usually due to an augmented a-wave[6] (Figure 19). In fetuses with congenital heart defects this is a common finding, especially if the defect involves valves or ventricular function.[146] Similar changes are seen in the severely growth restricted fetus;[94,145,147–149] the systolic peak is maintained within normal ranges while the diastolic nadir is augmented, particularly in fetuses below 32 weeks of gestation.[94] Stress hormones and hypoxemia induce similar pressure variations in fetal sheep, and cause the same Doppler changes.[113,150,151] Although fetal reflexes and endocrine functions are not fully developed in the second trimester, the venous Doppler pattern induced by hypoxaemia is much the same as seen in older fetuses. This is mainly due to a direct hypoxic effect on the heart.[113] A correlation between increased pulsatility in the ductus venosus and acidosis has been demonstrated in compromised pregnancies[145,152] and the sign of an augmented or negative a-wave has been suggested as part of a scoring system to assess congestive heart failure.[153] A recent study has described an increased pulsatile waveform associated with the contractions of normal labour,[154] but it is not known yet whether such changes in labour can be related to hypoxaemia or acidosis.

In addition to an augmented a-wave, the waveform may deteriorate further. With increasing hypoxemia and acidosis, the myocardium becomes stiffer. A rapid systolic downstroke reflects a reduced compliance (of the ventricles and the atria). A corresponding augmented nadir *before* the atrioventricular valves open to permit the second wave of diastolic filling[113] (Figure 19), is seen in terminally ill fetuses, particularly in the very premature and growth restricted fetuses. Tricuspid or mitral regurgitation can impose similar changes on the velocity waveform by rapidly

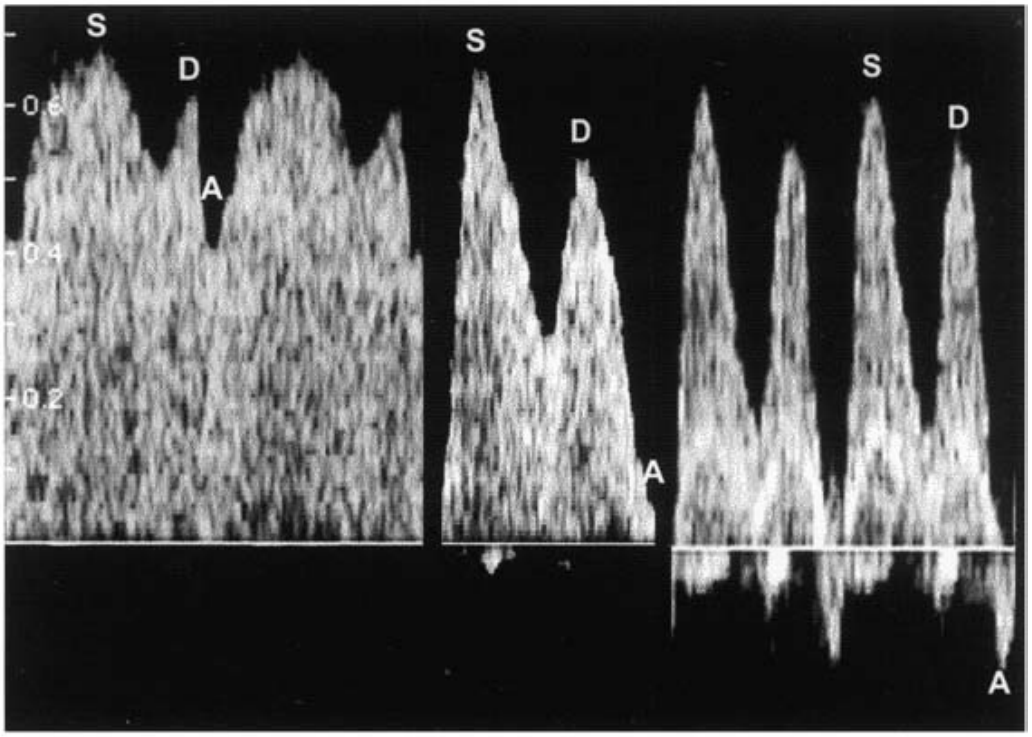

Figure 19 Compared to the normal pattern (left), changes in the ductus venosus blood velocity during placental compromise and hypoxemia consist mainly of an augmented atrial contraction wave (A) (centre). A further worsening would be a reversed A (right). Additionally, a quick downstroke and reduced velocity between the systolic (S) and diastolic (D) peak reflects a reduced compliance and deteriorating performance of the myocardium, seen in severe or preterminal cases.

increasing atrial pressure during systole. The effect will depend on the severity of regurgitation.

Compared to the popularity of the ductus venosus waveform analysis, the assessment of absolute blood velocity has attracted little attention. However, the unique shape and position of the ductus venosus has led investigators to suggest that velocities (V), derived from the narrow portion of the ductus venosus (DV) and the umbilical vein (UV), could be used to estimate the pressure gradient (Δp) between the umbilical vein and the IVC[49] using the Bernoulli equation, $\Delta p = 4\ (V^2_{DV} - V^2_{UV})$. During the last half of the pregnancy, the range for the pressure gradient across the ductus venosus was calculated to be 0–3.5 mm Hg during the heart cycle,[49] and 0–1.9 between gestational weeks 8–20.[155] Since velocities in the ductus venosus are considerably lower than the velocities experienced in adult valvular lesions, and the inner shape of the isthmus is smooth and tapering, there is a possibility of a convective pressure regain and a corresponding overestimate of Δp.[49,96,156,157] Mathematical modelling has suggested that there is $\leq 30\%$ energy dissipation.[157]

A simplified use of this concept would be to record the absolute velocity (the peak during systole or V_{ta}) assuming that the velocity reflects the Δp, the porto-caval or umbilico-caval pressure gradient.[6] High velocity can be expected in cases of

hepatic parenchymal diseases[158,159] (e.g. viral infections, mitochondrial diseases, and lymphoproliferative infiltration[159,160]) or as part of a hyperkinetic circulatory response to hypoxaemia.[161] Isoimmune anaemia may represent a combination of parenchymal liver changes and hyperkinetic circulation, both capable of increasing the Δp. The high ductus venosus velocity seen in cases of anaemia,[99,162,163] shows a further increase after a transfusion, followed by a fall in velocity the following day.[99] Alone, ductus venosus velocimetry is not a reliable test to predict fetal anaemia,[162,164] but could probably be part of a test battery.

Respiratory excursions substantially modify the velocity profile and should be avoided during standard recording. However, since the ductus venosus is interposed between the intrathoracic atria and the abdominal umbilical vein, ductus velocimetry has been suggested as an indicator of the thoraco-abdominal pressure difference and a quantitative measure of fetal respiratory force.[49] Velocity measurements during respiratory activity indicate pressure variations exceeding 20 mm Hg in the fetal chest. Changes in peak velocity, to assess respiratory pressure variation imposed on the fetal lungs, is a promising but largely unexplored technique.

Its physiological position in the circulation, and its extraordinary haemodynamic properties and regulatory mechanisms make the tiny ductus venosus different from all other venous sections, carrying the potential of unique diagnostic information.

THE INFERIOR VENA CAVA

Inferior vena cava velocimetry is regularly used to assess atrial function both in arrhythmias and in compromised fetuses. The relationship between the three components of the velocity wave has been used to describe changes in cardiac function with gestational age and during haemodynamic compromise. Reference ranges for the IVC velocities and ratios have been established for the second half of pregnancy.[8,165,166] A variety of veins contribute to the IVC at the level of the confluence immediately below the diaphragm and give a less reproducible velocity recording. It has been suggested that Doppler recording in the IVC should be standardized to a sampling site below the hepatic confluence.[166,167] Whether Doppler of the IVC or the ductus venosus is a better predictor of fetal acidosis is not resolved,[152,163] but the velocimetry has repeatedly been used to assess atrial function in compromised fetuses[4,5,145,165,168] and specifically arrhythmias.[4,5,169–173] Although the waveform in both the ductus venosus and IVC reflects cardiac function, the property and regulation of the two vessels are not the same and probably represent different diagnostic potential.

HEPATIC VEINS

The most striking difference to the adult liver anatomy is the well developed left fetal hepatic lobe. Correspondingly, the left and medial hepatic veins are large structures[22,174] that join the ductus venosus to form a more or less common inlet

to the left compartment of the IVC.[40,41] In adult life, however, the medial hepatic vein constitutes merely a branch of the left hepatic vein. Conversely, the right fetal hepatic vein drains into the IVC from the right side. This anatomical distinction is important in order to understand the physiological difference between the right pathway for deoxygenated blood delivery to the right atrium and the left pathway for oxygenated blood to the left heart[25,40] (Figure 2). Since it is difficult to record reproducible Doppler recordings in the IVC, the more accessible hepatic veins with an easier access have gained popularity[175] and normal ranges for velocity parameters have been established.[8] As in the IVC, the velocity profile in the hepatic veins reflects cardiac function and is thought to be a good indicator of diastolic performance.

SUPERIOR VENA CAVA

The fetal superior vena cava is a powerful vein directing blood to the right atrium. The inlet is situated on top of the foramen ovale near the atrial septum and is a major contributor to the via dextra (Figure 2). Theoretically, the blood flow velocity pattern in the fetal SVC should reflect the right atrial function more than the IVC since the IVC is engaged in a simultaneous blood delivery to both atria during fetal life. However, the waveform in the two veins is very similar,[4] and the Doppler examination of the SVC has been restricted to fetal cardiology. The vicinity to the ascending aorta has made it ideal for a simultaneous recording of ventricular and atrial events to differentiate various types of tachycardia.[176]

UMBILICAL VEIN

The value of Doppler velocimetry of the intraabdominal umbilical vein was recognized early[1,2,28] and many studies have used this as an adjuvant diagnostic method in fetal growth retardation,[3,29,95,124,177–183] anaemia,[178,184,185] hydrops,[186,187] discordant twins,[186–189] arrhythmia,[87,169] and congenital heart defects.[124,146,168] The umbilical venous flow reflects both the haemodynamic condition of the placenta and the conditions met in the liver vasculature, the ductus venosus, the central venous system and the heart. Traditionally, the measurement has been taken from the straight portion of the intraabdominal umbilical vein.

An alternative method, assessing venous flow in the umbilical cord, has recently been used successfully.[70,95,183] Improved ultrasound imaging and colour Doppler are good methods of controlling angle of insonation. The looping of the vein may be extensive and still constitute a limitation of the method. The results of flow assessment in this section of the umbilical vein are much the same as for intraabdominal measurements but do not show the relative decline with gestational age reported in other studies. A suggestion of using abdominal circumference (a commonly used ultrasound measurement) instead of estimated fetal weight when assessing relative umbilical blood flow is an interesting simplification.[95]

Another method of umbilical flow assessment has recently been suggested: averaging the flow estimation in the umbilical vein and arteries.[190] The method has produced higher flow values than most other studies and raises some questions concerning the accuracy of diameter measurements and the assessment of the arterial weighted mean blood velocity.

Although umbilical venous flow was reported to be increased in anaemic fetuses, the method did not reliably predict anaemia.[162,185] However, recent development[24,29,70,95] of the method seems to suggest it may be clinically useful such as in fetuses with growth deficit. The systematic variation between results from different centres still demands a standardisation of the method to ensure comparable measurements.[191]

Instead of volume flow assessment, the simpler measurement of velocity measurement alone could be an option. However, this has attracted limited clinical interest, apart from the pulsatile umbilical venous velocity (Figure 12). In 1986 Lingman et al. suggested that a pulsatile profile of the umbilical vein was a sign of imminent asphyxia.[3] Gudmundsson et al showed that the sign was associated with poor prognosis in hydrops fetalis,[186] and later this was shown also for cardiac malformations[146] and severe fetal growth restriction (FGR).[180] Huhta incorporated the sign in a scoring system for congestive heart failure.[153] Rizzo et al showed that pulsation is a common normal phenomenon in the first trimester, which gradually disappears after 12 weeks of gestation.[120] However, pulsation has been recorded in normal fetuses throughout pregnancy, especially in the deep portion of the portal vein[91] and at the abdominal wall.[121–123] There are apparently different sources of pulsation but the distinction has usually not been made in the literature. As mentioned in a previous section, inflections in an otherwise even velocity profile or replication of the ductus venosus velocity profile in the umbilical vein are probably severe signs of haemodynamic compromise involving an increased end-diastolic ventricular pressure, an increased central venous pressure and an altered compliance in the liver and central veins due to vascular distension, increased smooth muscle tone and vasoconstriction, or interstitial oedema. The transmission of the a-wave to the umbilical vein depends on a patent ductus venosus.[115] A distended ductus venosus inlet, and a reduced umbilical vein diameter compliance promote transmission.[114] Recognizing the a-wave in the umbilical vein and acknowledging the context of physiological condition and fluid dynamic properties of the area are equally important in the interpretation of the Doppler recording.

VENOUS DOPPLER IN PLACENTAL COMPROMISE

Fetal growth restriction is a frequent clinical challenge and a growing battery of diagnostic procedures and surveillance tools are now in use. Recent developments justify a separate section on the issue. Fetal growth restriction is commonly associated with placental compromise. Although flow is low in FGR,[177–179] the umbilical venous pressure is maintained within normal limits.[192] There is an increased incidence of

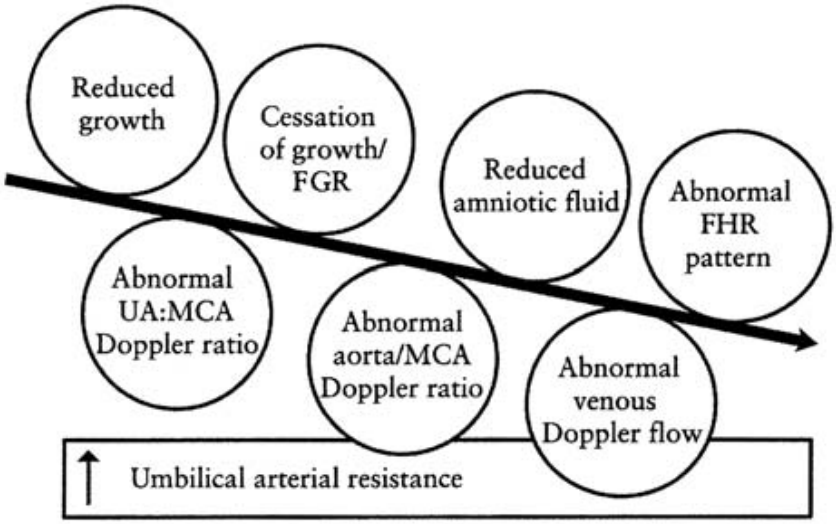

Figure 20 Sequential changes in placental compromise. Although individual variation should be kept in mind, this has proved a useful approach to the clinical development of severe fetal growth restriction (FGR). **Printed with permission**[203]

hypoxaemia and acidosis in these fetuses.[152,163,193] Chronic hypoxaemia is expected to induce a pattern of reduced flow in the inferior compared to the superior vena cava,[25] a higher degree of shunting through the ductus venosus[71] and the foramen ovale, reduced flow through the fetal lungs, and an increased difference in pO_2 between the left and right heart.[25] Viscosity (i.e. haematocrit) tends to be higher in growth restricted fetuses compared to normal fetuses[194] with a higher concentration of catecholamines[195] and atrial natriuretic peptide,[196] an augmented endothelin-1 response to cordocentesis,[197] and an augmented cortisol response to hypoxaemia.[198] When there is abnormal placental vascular development, an increased pulsatility of the blood flow in the umbilical artery can be expected. When a Doppler recording shows absent or reversed end-diastolic flow in the umbilical artery, the obstetrician has identified a group of fetuses where 1/3 may die.[199] It is also known that the outcome improves if the Doppler findings are taken into account in the management.

What exactly to do at this stage is less clear. A second tool, Doppler examination of the fetal middle cerebral artery, which probably reflects compensatory responses of the brain circuit, has been suggested as a separate indicator of acidosis and adverse outcome.[200–202] Biophysical profile, cardiotocography with computerised calculation of short time variation of the fetal heartrate, and uterine artery waveform changes are commonly in use.[203] Another important tool, venous Doppler, seems to emerge as a useful means of timing delivery.

Based on the assumption that there is a sequence of circulatory events in the physiology of placental compromise[204] (Figure 20), growth restricted fetuses have been studied serially until delivery.[205–207] It was already known that an augmented a-wave in the ductus venosus, IVC or in a hepatic vein was a common finding in severe

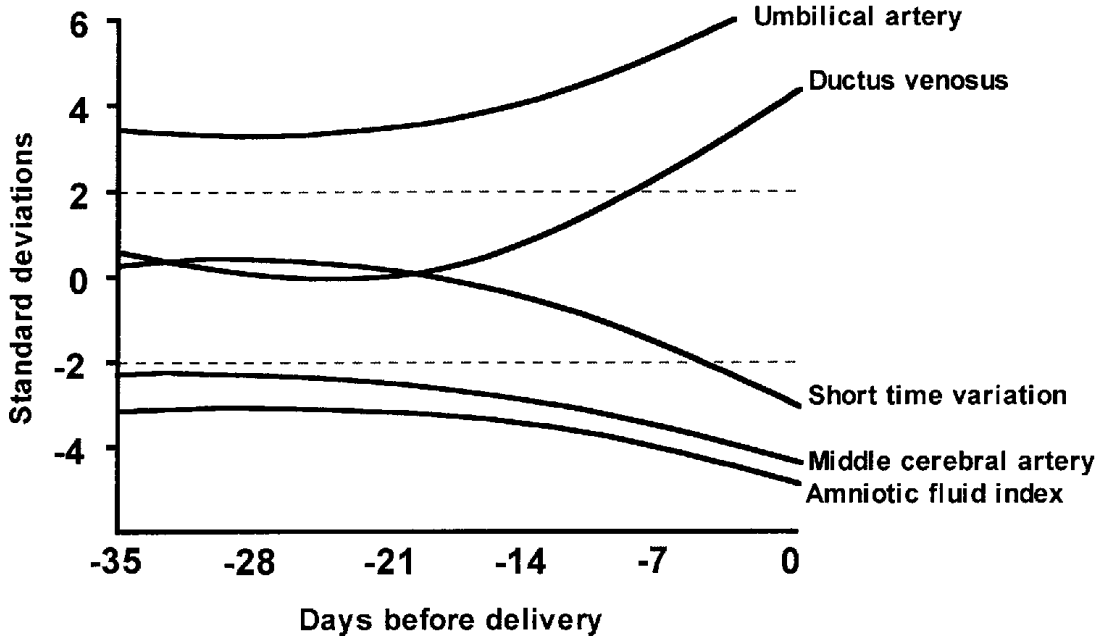

Figure 21 Serial observations of cases with severe fetal growth restriction delivered ≤ 32 weeks of gestation. Changes in the Pulsatility Index of the umbilical and middle cerebral arteries together with oligohydramnios were commonly found 3–5 weeks before delivery. Alterations in venous Doppler (ductus venosus) and short time variation were the most striking findings during the last two weeks before delivery, indicating that these two parameters in particular may be suitable for the final timing of delivery. **Modified and reproduced with permission**[206]

FGR, particularly in the fetus before 32 weeks of gestation.[145,147,165,180,208] Although there were wide individual variations, Hecher et al[206] reported recently patterns of change in the last weeks before delivery. In a group of fetuses delivered before 32 weeks of gestation, reduced amniotic fluid and increased umbilical artery pulsatility were common findings 4–5 weeks before delivery, whereas abnormal venous Doppler was rare. In the subsequent weeks the middle cerebral artery changed and, days before delivery, venous Doppler changes had become evident (Figure 21). Although most parameters (including the umbilical artery pulsatility) showed changes during the last two weeks before delivery, the changes were most prominent in the short term variation of the fetal heart rate and the ductus venosus blood flow pulsatility, suggesting those parameters to be particularly useful for timing delivery.

For the group of growth restricted fetuses delivered after 32 weeks of gestation, Hecher at al found less abnormal parameters 4–5 weeks before delivery than in those delivered before 32 weeks. Although changes were observed in the last days before delivery, particularly in the ductus venosus and umbilical artery, these were less pronounced in the older fetuses. These findings have been confirmed in studies with slightly different designs.[205,207] It follows that Doppler parameters can probably be used in a more organised fashion, particularly in the surveillance and decision making in cases of FGR. However, further studies are needed to evaluate the benefits and disadvantages of different strategies.

CONCLUSION

Doppler examination of the fetal venous circulation provides valuable diagnostic information. This is of equal importance to the arterial circulation. Quantitative venous flow assessment has brought new insight into fetal physiology, both for the umbilical circulation and for the distributional details in the liver and heart. The technology appears ready for clinical use. Waveform analysis of precordial venous flow has been incorporated into clinical evaluation, particularly for the severely growth restricted fetus. Thus, valuable information on fetal cardiac function has become available. Study of the fetal venous circulation holds the promise of an improved strategy of surveillance and decision making in high risk pregnancies. Hopefully, the physiological background and haemodynamic mechanisms explained in this review will help the interpretation of venous recordings, allowing them to be used to their full potential.

REFERENCES

1 Gill RW. Pulsed Doppler with B-mode imaging for quantitative blood flow measurement. *Ultrasound Med Biol* 1979; **5**: 223–35.

2 Eik-Nes SH, Brubakk AO, Ulstein MK. Measurement of human fetal blood flow. *Br Med J* 1980; **280**: 283–84.

3 Lingman G, Laurin J, Marsál K, Persson P-H. Circulatory changes in fetuses with imminent asphyxia. *Biol Neonate* 1986; **49**: 66–73.

4 Reed KL, Appleton CP, Anderson CF, Shenker L, Sahn DJ. Doppler studies of vena cava flows in human fetuses; insights into normal and abnormal cardiac physiology. *Circulation* 1990; **81**: 498–505.

5 Kanzaki T, Chiba Y. Evaluation of the preload condition of the fetus by inferior vena caval blood flow pattern. *Fetal Diagn Ther* 1990; **5**: 168–74.

6 Kiserud T, Eik-Nes SH, Blaas H-G, Hellevik LR. Ultrasonographic velocimetry of the fetal ductus venosus. *Lancet* 1991; **338**: 1412–414.

7 Huisman TWA, Stewart PA, Wladimiroff JW. Ductus venosus blood flow velocity waveforms in the human fetus - a doppler study. *Ultrasound Med Biol* 1992; **18**: 33–37.

8 Hecher K, Campbell S, Snijders R, Nicolaides K. Reference ranges for fetal venous and atrioventricular blood flow parameters. *Ultrasound Obstet Gynecol* 1994; **4**: 381–90.

9 Better DJ, Kaufman S, Allen LD. The normal pattern of pulmonary venous flow on pulsed Doppler examination of the human fetus. *J Am Soc Echocardiol* 1996; **9**: 281–85.

10 Laudy JAM, Huisman TWA, Ridder MAJ, Wladimiroff JW. Normal fetal pulmonary venous blood flow velocity. *Ultrasound Obstet Gynecol* 1995; **6**: 277–81.

11 Pooh RK, Pooh KH, Nakagawa Y, Maeda K, Fukui R, Aono T. Transvaginal doppler assessment of fetal intracranial venous flow. *Obstet Gynecol* 1999; **93**: 697–701.

12 Dubiel M, Breborowic GH, Laurini R, Gudmundsson S. Blood velocity in the fetal vein of Galen and the outcome of high-risk pregnancy. *Europ J Obstet Gynecol Reprod Biol* 2001; **99**: 14–18.

13 Laurichesse-Delmas H, Grimaud O, Moscoso G, Ville Y. Color Doppler study of the venous circulation in the fetal brain and hemodynamic study of the cerebral transverse sinus. *Ultrasound Obstet Gynecol* 1999; **13**: 34–42.

14 Hofstaetter C, Plath H, Hansmann M. Prenatal diagnosis of abnormalities of the fetal venous system. *Ultrasound Obstet Gynecol* 2000; **15**: 231–41.

15 Achiron R, Hegesh J, Yagel S, Lipitz S, Cohen SB, Rotstein Z. Abnormalities of the fetal central veins and umbilico-portal system: prenatal ultrasonographic diagnosis and proposed classification. *Ultrasound Obstet Gynecol* 2000; **16**: 539–48.

16 Morgan G, Superina R. Congenital absence of the portal vein: two cases and a proposed classification system for portasystemic vascular anomalies. *J Pediatr Surg* 1994; **29**: 1239–241.

17 Sadler TW. Langman's medical embryology. 5th ed. Baltimore, Hong Kong, London, Sydney: Williams & Wilkins; 1985.

18 Lassau JP, Bastian D. Organogenesis of the venous structures of the human liver: a hemodynamic theory. *Anat Clin* 1983; **5**: 97–102.

19 Chako AW, Reynolds SRM. Embryonic development in the human of the sphincter of the ductus venosus. *Anat Rec* 1953; **115**: 151–73.

20 Mavrides E, Moscoso G, Carvalho JS, Campbell S, Thilaganathan B. The human ductus venosus between 13 and 17 weeks of gestation: histological and morphometric studies. *Ultrasound Obstet Gynecol* 2002; **19**: 39–46.

21 Mavrides E, Moscoso G, Carvalho JS, Campbell S, Thilaganathan B. The anatomy of the umbilical, portal and hepatic venous system in the human fetus at 14–19 weeks of gestation. *Ultrasound Obstet Gynecol* 2001; **18**: 598–604.

22 Chinn DH, Filly RA, Callen PW. Ultrasonographic evaluation of fetal umbilical and hepatic vascular anatomy. *Radiology* 1982; **144**: 153–57.

23 Kiserud T. Naming veins: by morphology, physiology or sociology. *Ultrasound Obstet Gynecol* 2001; **18**: 562–63.

24 Kiserud T, Rasmussen S, Skulstad SM. Blood flow and degree of shunting through the ductus venosus in the human fetus. *Am J Obstet Gynecol* 2000; **182**: 147–53.

25 Rudolph AM. Distribution and regulation of blood flow in the fetal and neonatal lamb. *Circ Res* 1985; **57**: 811–21.

26 Dawes GS. Foetal and Neonatal physiology. Chicago: Year Book Medical Publishers, Inc.; 1968.

27 Jensen A, Berger R. Regional distribution of cardiac output. In: Hanson MA, Spencer JAD, Rodeck CH, eds. *Fetus and neonate. Physiology and clinical application*. Cambridge: Cambridge University Press: 1993: 23–74.

28 Gill RW, Trudinger BJ, Garrett WJ, Kossoff G, Warren PS. Fetal umbilical venous flow measured in utero by pulsed Doppler and B-mode ultrasound. *Am J Obstet Gynecol* 1981; **139**: 720–25.

29 Boito S, Struijk PC, Ursem NTC, Stijnen T, Wladimiroff JW. Umbilical venous volume flow in the normally developing and growth-restricted human fetus. *Ultrasound Obstet Gynecol* 2002; **19**: 344–49.

30 Assali NS, Rauramo L, Peltonen T. Measurement of uterine blood flow and uterine metabolism. *Am J Obstet Gynecol* 1960; **79**: 86–98.

31 Stembera ZK, Hodr J, Janda J. Umbilical blood flow in healthy newborn infants during the first minutes after birth. *Am J Obstet Gynecol* 1965; **91**: 568–74.

32 Soothill PW, Nicolaides KH, Rodeck CH, Campbell S. The effect of gestational age on blood gas and acid-base values in human pregnancy. *Fetal Therapy* 1986; **1**:**4**: 166–73.

33 Nicolaides KH, Soothill PW, Clewell WH, Rodeck CH, Mibashan RS, Campbell S. Fetal haemoglobin measurement in the assessment of red cell isoimmunisation. *Lancet* 1988; **1**: 1073–1075.

34 Barcroft J. Research on pre-natal life. Oxford: Blackwell Scientific Publications; 1946: 292.

35 Hanson MA, Kiserud T. Circulation. In: Harding R, Bocking A, eds. *Developmental physiology*. Cambridge: Cambridge University Press; 2001: 70–93.

36 Behrman RE, Lees MH, Peterson EN, de Lannoy CW, Seeds AE. Distribution of the circulation in the normal and asphyxiated fetal primate. *Am J Obstet Gynecol* 1970; **108**: 956–69.

37 Edelstone DI, Rudolph AM. Preferential streaming of ductus venosus blood to the brain and heart in fetal lambs. *Am J Physiol* 1979; **237**: 724–29.

38 Rudolph AM, Heymann MA, Teramo K, Barrett C, Räihä N. Studies on the circulation of the previable human fetus. *Pediatr Res* 1971; **5**: 452–65.

39 Lind J, Wegelius C. Angiocardiographic studies on the human foetal circulation. *Pediatrics* 1949; **4**: 391–400.

40 Kiserud T, Eik-Nes SH, Blaas H-G, Hellevik LR. Foramen ovale: an ultrasonographic study of its relation to the inferior vena cava, ductus venosus and hepatic veins. *Ultrasound Obstet Gynecol* 1992; **2**: 389–96.

41 Kiserud T. Hemodynamics of the ductus venosus. *Eur J Obstet Gynecol Reprod Biol* 1999; **84**: 139–47.

42 Bristow J, Rudolph AM, Itskovitz J, Barnes R. Hepatic oxygen and glucose metabolism in the fetal lamb. *J Clin Invest* 1982; **71**: 1047–1061.

43 Dawes GS, Mott JC. Changes in O2 distribution and consumption in foetal lambs with variations in umbilical blood flow. *J Physiol (Lond)* 1964; **170**: 524–40.

44 Edelstone DI, Rudolph AM, Heymann MA. Effect of hypoxemia and decreasing umbilical flow on liver and ductus venosus blood flows in fetal lambs. *Am J Physiol* 1980; **238**: 656–663.

45 Mielke G, Benda N. Cardiac output and central distribution of blood flow in the human fetus. *Circulation* 2001; **103**: 1662–668.

46 Sutton MSJ, Groves A, MacNeill A, Sharland G, Allen G. Assessment of changes in blood flow through the lungs and foramen ovale in the normal human fetus with gestational age: a prospective Doppler echocardiographic study. *Br Heart J* 1994; **71**: 232–37.

47 Rasanen J, Wood DC, Weiner S, Ludomirski A, Huhta JC. Role of the pulmonary circulation in the distribution of human fetal cardiac output during the second half of pregnancy. *Circulation* 1996; **94**: 1068–1073.

48 Paulick RP, Meyers RL, Rudolph CD. Venous responses to hypoxemia in the fetal lamb. *J Dev Physiol* 1990; **14**: 81–88.

49 Kiserud T, Hellevik LR, Eik-Nes SH, Angelsen BAJ, Blaas H-G. Estimation of the pressure gradient across the fetal ductus venosus based on Doppler velocimetry. *Ultrasound Med Biol* 1994; **20**: 225–32.

50 Castle B, Mackenzie IZ. In vivo observations on intravascular blood pressure in the fetus during mid-pregnancy. In: Rolfe P, ed. *Fetal physiological measurements.* London, Boston, Durban, Singapore, Toronto, Wellington: Butterworths; 1986. 65–69.

51 Nicolini U, Fisk NM, Talbert DG, Rodeck CH, Kochenour NK. Intrauterine manometry: technique and application to fetal pathology. *Prenat Diagn* 1989; **9**: 243–54.

52 Weiner CP, Heilskov JRN, Pelzer GRN, Grant SRN. Normal values for human umbilical venous and amniotic fluid pressure and their alteration by fetal disease. *Am J Obstet Gynecol* 1989; **161**: 714–17.

53 Wood CE. Local and endocrine factors in the control of the circulation. In: Hanson MA, Spencer JAD, Rodeck CH, eds. *Fetus and Neonate. Physiology and clinical application*. Cambridge: Cambridge University Press; 1993. 100–15.

54 Kiserud T, Ozaki T, Nishina H, Rodeck C, Hanson MA. Effect of NO, phenylephrine and hypoxemia on the ductus venosus diameter in the fetal sheep. *Am J Physiol* 2000; **279**: 1166–171.

55 Momma K, Ito T, Ando M. In situ morphology of the ductus venosus and related vessels in the fetal and neonatal rat. *Pediatr Res* 1992; **32**: 386–89.

56 Coceani F, Adeagbo ASO, Cutz E, Olley PM. Autonomic mechanisms in the ductus venosus of the lamb. *Am J Physiol* 1984; **247**: 17–24.

57 Adeagbo ASO, Coceani F, Olley PM. The response of the lamb ductus venosus to prostaglandins and inhibitors of prostaglandin and thromboxane synthesis. *Circ Res* 1982; **51**: 580–86.

58 Adeagbo ASO, Bishai I, Lees J, Olley PM, Coceani F. Evidence for a role of prostaglandine I2 and thromboxane A2 in the ductus venosus of the lamb. *Can J Physiol Pharmacol* 1984; **63**: 1101–105.

59 Momma K, Takeuchi H, Hagiwara H. Pharmacological constriction of the ductus arteriosus and ductus venosus in fetal rats. In: Nora J, Takao A, eds. *Congenital heart disease. Causes and processes.* Mount Kisco: Futura; 1984. 313–27.

60 Bellotti M, Pennati G, Pardi G, Fumero R. Dilatation of the ductus venosus in human fetuses: ultrasonographic evidence and mathematical modeling. *Am J Physiol* 1998; **275**: 1759–767.

61 Edelstone DI. Regulation of blood flow through the ductus venosus. *J Dev Physiol* 1980; **2**: 219–38.

62 Paulick RP, Meyers RL, Rudolph CD, Rudolph AM. Venous and hepatic vascular responses to indomethacin and prostaglandin E1 in the fetal lamb. *Am J Obstet Gynecol* 1990; **163**: 1357–363.

63 Paulick RP, Meyers RL, Rudolph CD, Rudolph AM. Umbilical and hepatic venous responses to circulating vasoconstrictive hormones in fetal lamb. *Am J Physiol* 1991; **260**: 1205–213.

64 Zink J, van Petten GR. The effect of norepinephrine on blood flow throught the fetal liver and ductus venosus. *Am J Obstet Gynecol* 1980; **137**: 71–77.

65 Edelstone DI, Merick RE, Caritis SN, Mueller-Heubach E. Umbilical blood flow and its distribution before and during autonomic blockade in fetal lambs. *Am J Obstet Gynecol* 1980; **138**: 703–707.

66 Kiserud T, Stratford L, Hanson MA. Umbilical flow distribution to the liver and ductus venosus: an in vitro investigation of the fluid dynamic mechanisms in the fetal sheep. *Am J Obstet Gynecol* 1997; **177**: 86–90.

67 Itskovitz J, LaGamma EF, Rudolph AM. Effects of cord compression on fetal blood flow distribution and O_2 delivery. *Am J Physiol* 1987; **252**: 100–109.

68 Meyers RL, Paulick RP, Rudolph CD, Rudolph AM. Cardiovascular responses to acute, severe haemorrhage in fetal sheep. *J Dev Physiol* 1991; **15**: 189–97.

69 Kiserud T, Rasmussen S, Skulstad SM. Distribution of umbilical blood through the ductus venosus. *J Soc Gynecol Invest* 1998; **5**: 156–57.

70 Bellotti M, Pennati G, De Gasperi C, Battaglia FC, Ferrazzi E. Role of ductus venosus in distribution of umbilical flow in human fetuses during second half of pregnancy. *Am J Physiol* 2000; **279**: 1256–263.

71 Tchirikov M, Rybakowski C, Hünecke B, Schröder HJ. Blood flow through the ductus venosus in singleton and multifetal pregnancies and in fetuses with intrauterine growth retardation. *Am J Obstet Gynecol* 1998; **178**: 943–49.

72 Jørgensen C, Andolf E. Four cases of absent ductus venosus: three in combination with severe hydrops fetalis. *Fetal Ther* 1994; **9**: 395–97.

73 Sivén M, Ley D, Hägerstrand I, Svenningsen N. Agenesis of the ductus venosus and its correlation to hydrops fetalis and the fetal hepatic circulation. *Ped Path Lab Med* 1995; **15**: 39–50.

74 Avni EF, Ghysels M, Donner C, Damis E. In utero diagnosis of congenital absence of the ductus venosus. *J Clin Ultrasound* 1997; **25**: 456–58.

75 Gembruch U, Baschat AA, Gortner L. Prenatal diagnosis of ductus venosus agenesis: a report of two cases and review of the literature. *Ultrasound Obstet Gynecol* 1998; **11**: 185–89.

76 Contratti G, Banzi C, Ghi T, Perolo A, Pilu G, Visenti A. Absence of the ductus venosus: report of 10 new cases and review of the literature. *Ultrasound Obstet Gynecol* 2001; **18**: 605–609.

77 Shih JC, Shyu MK, Hsieh MH, Yang JH, Huang SF, Lin GJ, et al. Agenesis of the ductus venosus in a case of monochorionic twins which mimics twin-twin transfusion syndrome. *Prenat Diagn* 1996; **16**: 243–46.

78 Brozot ML, Schultz R, Patroni LT, Lopes LM, Armbruster Moraes E, Zugaib M. Trisomy 10: ultrasound features and natural history after first trimester diagnosis. *Prenat Diagn* 2001; **21**: 672–75.

79 Rudolph CD, Meyers RL, Paulick RP, Rudolph AM. Effects of ductus venosus obstruction on liver and regional blood flows in the fetal lamb. *Pediatr Res* 1991; **29**: 347–52.

80 Amoroso EC, Dawes GS, Mott JC, Rennick BR. Occlusion of the ductus venosus in the mature foetal lamb. *J Physiol* 1955; **129**: 64–65.

81 Tchirikov M, Kertschanska S, Schroder HJ. Obstruction of ductus venosus stimulates cell proliferation in organs of fetal sheep. *Placenta* 2001; **22**: 24–31.

82 Tchirikov M, Kertschanska S, Sturenberg HJ, Schroder HJ. Liver blood perfusion as a possible instrument for fetal growth regulation. *Placenta* 2002; **23**: 153–58.

83 Haugen G, Godfrey K, Shore S, Kiserud T, Hanson M. Fetal hepatic blood flow and liver size. *J Soc Genecol Invest* 2002; **9**: 126A.

84 Haugen G, Godfrey K, Shore S, Kiserud T, Breier B, Hanson M. Relation of fetal hematocrit to concentrations of insulin-like growth factor-2 and apolipoprotein-B in umbilical cord serum. *J Soc Genecol Invest* 2002; **9**: 296A.

85 Eik-Nes SH, Marsál K, Brubakk AO, Ulstein M. Ultrasonic measurements of human fetal blood flow in aorta and umbilical vein: Influence of fetal breathing movements. In: Kurjak A, ed. Recent advances in ultrasound diagnosis. Proceedings of the International Symposium on Recent Advances in Ultrasound Diagnosis. *Exerpta Medica*; 1980: 233–240.

86 Eik-Nes SH, Marsál K, Kristoffersen K. Methodology and basic problems related to blood flow studies in the human fetus. *Ultrasound Med Biol* 1984; **10**: 329–37.

87 Marsál K, Lindblad A, Lingman G, Eik-Nes SH. Blood flow in the fetal descending aorta; intrinsic factors affecting fetal blood flow, i.e. fetal breathing movements and cardiac arrhythmia. *Ultrasound Med Biol* 1984; **10**: 339–48.

88 Chiba Y, Utsu M, Kanzaki T, Hasegawa T. Changes in venous flow and intratracheal flow in fetal breathing movements. *Ultrasound Med Biol* 1985; **11**: 43–49.

89 van Eyck J, Stewart PA, Wladimiroff JW. Human fetal foramen ovale flow velocity waveforms relative to behavioral states in normal term pregnancy. *Am J Obstet Gynecol* 1990; **163**: 1239–242.

90 Huisman TWA, Brezinka C, Stewart PA, Wladimiroff JW. Ductus venosus flow velocity waveforms relative to fetal behavioural states. *Br J Obstet Gynecol* 1994; **101**: 220–24.

91 van Splunder IP, Huisman TWA, Stijnen T, Wladimiroff JW. Presence of pulsations and reproducibility of waveform recording in the umbilical and left portal vein in normal pregnancies. *Ultrasound Obstet Gynecol* 1994; **4**: 49–53.

92 Eik-Nes SH, Marsal K, Kristoffersen K. Transcutaneous measurment of human fetal blood flow – Methodological studies. In: Kurjak A, Kratochwil A, eds. Recent advances in ultrasound diagnosis. Proceedings of the 4th European Congress on Ultrasonics in Medicine. Amsterdam: *Excerpta Medica*; 1981: 209–19.

93 Fung YC. Biomechanics. New York, Berlin: Springer-Verlag; 1993: 568.

94 Kiserud T, Eik-Nes SH, Blaas H-G, Hellevik LR, Simensen B. Ductus venosus blood velocity and the umbilical circulation in the seriously growth retarded fetus. *Ultrasound Obstet Gynecol* 1994; **4**: 109–14.

95 Barbera A, Galan HL, Ferrazzi E, Rigano S, Józwik M, Pardi G. Relationship of umbilical vein blood flow to growth parameters in the human fetus. *Am J Obstet Gynecol* 1999; **181**: 174–79.

96 Pennati G, Redaelli A, Bellotti M, Ferrazzi E. Computational analysis of the ductus venosus fluid dynamics based on Doppler measurements. *Ultrasound Med Biol* 1996; **22**: 1017–1029.

97 Pennati G, Bellotti M, Ferrazzi E, Bozzo M, Pardi G, Fumero R. Blood flow through the ductus venosus in human fetuses: calculation using Doppler velocimetry and computational findings. *Ultrasound Med Biol* 1998; **24**: 477–87.

98 Kiserud T, Hellevik LR, Hanson MA. The blood velocity profile in the ductus venosus inlet expressed by the mean/maximum velocity ratio. *Ultrasound Med Biol* 1998; **24**: 1301–306.

99 Oepkes D, Vandenbussche FP, van Bel F, Kanhai HHH. Fetal ductus venosus blood flow velocities before and after transfusion in red-cell alloimmunized pregnancies. *Obstet Gynecol* 1993; **82**: 237–41.

100 DeVore GR, Horenstein J. Ductus venosus index: a method for evaluating right ventricular preload in the second-trimester fetus. *Ultrasound Obstet Gynecol* 1993; **3**: 338–42.

101 Kiserud T, Eik-Nes SH, Hellevik LR, Blaas H-G. Ductus venosus – a longitudinal doppler velocimetric study of the human fetus. *J Matern Fetal Invest* 1992; **2**: 5–11.

102 Rasmussen K. Precision and accuracy of Doppler flow measurements. In vitro and in vivo study of the applicability of the method in human fetuses. *Scand J Clin Lab Invest* 1987; **47**: 311–18.

103 Mavrides E, Holden D, Bland JM, Tekay A, Thilaganathan B. Intraobserver and interobserver variability of transabdominal Doppler velocimetry measurements of the fetal ductus venosus between 10 and 14 weeks of gestation. *Ultrasound Obstet Gynecol* 2001; **17**: 306–10.

104 Prefumo F, De Biasio P, Venturini PL. Reproducibility of ductus venosus Doppler flow measurements at 11–14 weeks of gestation. *Ultrasound Obstet Gynecol* 2001; **17**: 3001–3005.

105 Hecher K. Assessment of ductus venosus flow during the first and early second trimester: what can we expect? *Ultrasound Obstet Gynecol* 2001; **17**: 285–87.

106 Kiserud T, Rasmussen S. How repeat measurements affect mean diameter of the umbilical vein and the ductus venosus. *Ultrasound Obstet Gynecol* 1998; **11**: 419–25.

107 Kiserud T, Saito T, Ozaki T, Rasmussen S, Hanson M. Validation of diameter measurements by ultrasound. Intra-observer and inter-observer variation assessed in vitro and in the fetal sheep. *Ultrasound Obstet Gynecol* 1999; **13**: 52–57.

108 Huhta JC. Deciphering the hieroglyphics of venous Doppler velocities. *Ultrasound Obstet Gynecol* 1997; **9**: 300–301.

109 Kiserud T. In a different vein: the ductus venosus could yield much valuable information. *Ultrasound Obstet Gynecol* 1997; **9**: 369–72.

110 Kiserud T. Venous flow in IUGR and cardiac decompensation. In: Yagel S, Gembruch U, Silverman N, eds. *Fetal cardiology*. London: Dunitz Publishers; 2003. (in press)

111 Reuss ML, Rudolph AM, Dae MW. Phasic blood flow patterns in the superior and inferior venae cavae and umbilical vein of fetal sheep. *Am J Obstet Gynecol* 1983; **145**: 70–76.

112 Hasaart TH, de Haan J. Phasic blood flow patterns in the common umbilical vein of fetal sheep during umbilical cord occlusion and the influence of autonomic nervous system blockade. *J Perinat Med* 1986; **14**: 19–26.

113 Kiserud T, Jauniaux E, West D, Ozturk O, Hanson MA. Circulatory responses to acute maternal hyperoxaemia and hypoxaemia assessed non-invasively by ultrasound in fetal sheep at 0.3–0.5 gestation. *Br J Obstet Gynaecol* 2001; **108**: 359–64.

114 Hellevik LR, Stergiopulos N, Kiserud T, Rabben SI, Eik-Nes SH, Irgens F. A mathematical model of umbilical venous pulsation. *J Biomech* 2000; **33**: 1123–130.

115 Kiserud T, Crowe C, Hanson M. Ductus venosus agenesis prevents transmission of central venous pulsations to the umbilical vein in the fetal sheep. *Ultrasound Obstet Gynecol* 1998; **11**: 190–94.

116 Acharya G, Kiserud T. Ductus venosus blood velocity and diameter pulsations are more prominent at the outlet than at the inlet. *Eur J Obstet Gynecol Reprod Biol* 1999; **84**: 149–54.

117 Hellevik LR, Kiserud T, Irgens F, Steriopulos N, Hanson M. Mechanical properties of the fetal ductus venosus and umbilical vein. *Heart Vessels* 1998; **13**: 175–80.

118 Kiserud T. Fetal venous circulation – an update on hemodynamics. *J Perinat Med* 2000; **28**: 90–96.

119 Nichols WW, O'Rourke MF. McDonald's Blood flow in arteries. Theoretical, experimental and clinical principles. 4 ed. London: Arnold; 1998: 564.

120 Rizzo G, Arduini D, Romanini C. Umbilical vein pulsation: a physiological finding in early gestation. *Am J Obstet Gynecol* 1992; **167**: 675–77.

121 Skulstad SM, Kiserud T, Rasmussen S. Degree of fetal umbilical venous constriction at the abdominal wall in a low risk population at 20–40 weeks of gestation. *Prenat Diagn* 2002; **22:** 1022–1027.

122 Skulstad SM, Rasmussen S, Iversen O-E, Kiserud T. The development of high venous velocity at the fetal umbilical ring during gestational weeks 11–19. *Br J Obstet Gynaecol* 2001; **108**: 248–53.

123 Kilavuz Ö, Vetter K. The umbilcal ring – the first rapid in the fetoplacental venous system. *J Perinat Med* 1998; **26**: 120–22.

124 Nakai Y, Miyazaki Y, Matsuoka Y, Matsumoto M, Imanaka M, Ogita S. Pulsatile umbilical venous flow and its clinical significance. *Br J Obstet Gynaecol* 1992; **99**: 977–80.

125 Nakai Y, Imanaka M, Nishio J, Ogita S. Umbilical cord venous pulsation in normal fetuses and its incidence after 13 weeks gestation. *Ultrasound Med Biol* 1994; **21**: 443–46.

126 Tan J, Silverman NH, Hoffman JIE, Villegas M, Schmidt KG. Cardiac dimensions determined by cross-sectional echocardiography in the normal human fetus from 18 weeks to term. *Am J Cardiol* 1992; **70**: 1459–467.

127 Phillipos EZ, Robertson MA, Still KD. The echocardiographic assessment of the human fetal foramen ovale. *J Am Soc Echocardiogr* 1994; **7**: 257–63.

128 Feit LR, Copel JA, Kleinman CS. Foramen ovale size in the normal and abnormal human fetal heart: an indicator of transatrial flow physiology. *Ultrasound Obstet Gynecol* 1991; **1**: 313–19.

129 Wilson AD, Rao PS, Aeschlimann S. Normal fetal foramen ovale flap and transatrial Doppler velocity pattern. *J Am Soc Echo* 1989; **3**: 491–94.

130 Patten BM, Sommerfield WA, Paff GH. Functional limitations of the foramen ovale in the human foetal heart. *Anat Rec* 1929; **44**: 165–78.

131 Kiserud T, Rasmussen S. Ultrasound assessment of the fetal foramen ovale. *Ultrasound Obstet Gynecol* 2001; **17**: 119–24.

132 Heling K-S, Chaoui R, Hartung J, Kalache K, Bollmann R. Perfusion through the foramen ovale in normal and in pregnancies complicated by IUGR and heart defects. *Arch Perinat Med* 1999; **5**: S13.

133 Paladini D, Palmieri S, Celantano E, Guida F, Salviati M, Morra T, et al. Pulmonary venous blood flow in the human fetus. *Ultrasound Obstet Gynecol* 1997; **10**: 27–31.

134 Lenz F, Machlitt A, Hartung J, Bollmann R, Chaoui R. Fetal pulmonary venous flow pattern is determined by left atrial pressure: report of two cases of left heart hypoplasia, one with patent and the other with closed interatrial communication. *Ultrasound Obstet Gynecol* 2002; **19**: 392–95.

135 Huisman TWA, Stewart PA, Wladimiroff JW, Stijnen T. Flow velocity waveforms in the ductus venosus, umbilical vein and inferior vena cava in normal human fetuses at 12–15 weeks of gestation. *Ultrasound Med Biol* 1993; **19**: 441–45.

136 Montenegro N, Matias A, Areias JC, Barros H. Ductus venosus revisited: a Doppler blood flow evaluation in first trimester of pregnancy. *Ultrasound Med Biol* 1997; **23**: 171–76.

137 Borrell A, Antolin E, Costa D, Farre MT, Martinez JM, Fortuny A. Abnormal ductus venosus blood flow in trisomy 21 fetuses during early pregnancy. *Am J Obstet Gynecol* 1998; **179**: 1612–617.

138 Matias A, Gomes C, Flack N, Montenegro N, Nikolaides KH. Screening for chromosomal defects at 11–14 weeks: the role of ductus venosus blood flow. *Ultrasound Obstet Gynecol* 1998; **12**: 380–84.

139 Bahlmann F, Wellek S, Reinhardt I, Merz E, Welter C. Reference values of ductus venosus flow velocities and calculated waveform indices. *Prenat Diagn* 2000; **20**: 623–34.

140 Prefumo F, Risso D, Venturini PL, De Biasio P. Reference values for ductus venosus Doppler flow measurements at 10–14 weeks of gestation. *Ultrasound Obstet Gynecol* 2002; **20**: 42–46.

141 Antolín E, Comas C, Torrents M, Muñoz A, Figueras F, Echevarrías M, et al. The role of ductus venosus blood flow assessment in screening for chromosomal abnormalities at 10–16 weeks of gestation. *Ultrasound Obstet Gynecol* 2001; **17**: 295–300.

142 Bilardo CM, Müller MA, Zikulnig L, Schipper M, Hecher K. Ductus venosus studies in fetuses at high risk for chromosomal or heart abnormalities: relationship with nuchal translucency measurement and fetal outcome. *Ultrasound Obstet Gynecol* 2001; **17**: 288–94.

143 Matias A, Huggon I, Areias JC, Montenegro N, Nicolaides KH. Cardiac defects in chromosomally normal fetuses with abnormal ductus venosus blood flow at 10–14 weeks. *Ultrasound Obstet Gynecol* 1999; **14**: 307–10.

144 Montenegro N, Matias A, Areias S, Castedo S, Barros H. Increased fetal nuchal translucency: possible involvement of early cardiac failure. *Ultrasound Obstet Gynecol* 1997; **10**: 265–68.

145 Hecher K, Campbell S, Doyle P, Harrington K, Nicolaides K. Assessment of fetal compromise by Doppler ultrasound investigation of the fetal circulation. *Circulation* 1995; **91**: 129–38.

146 Kiserud T, Eik-Nes SH, Hellevik LR, Blaas H-G. Ductus venosus blood velocity changes in fetal cardiac diseases. *J Matern Fetal Invest* 1993; **3**: 15–20.

147 Rizzo G, Capponi A, Arduini D, Romanini C. Ductus venosus velocity waveforms in appropriate and small for gestational age fetuses. *Early Hum Dev* 1994; **39**: 15–26.

148 van Splunder P, Stijnen T, Wladimiroff JW. Fetal atrioventricular, venous, and arterial flow velocity waveforms in the small for gestational age fetus. *Pediatr Res* 1997; **42**: 765–75.

149 Nakata M. Doppler-velocity waveforms in ductus venosus in normal and small-for-gestational-age fetuses. *J Obstet Gynaecol Res* 1996; **22**: 489–96.

150 Tchirikov M, Eisermann K, Rybakowski C, Schröder HJ. Doppler ultrasound evaluation of ductus venosus blood flow during acute hypoxia in fetal lambs. *Ultrasound Obstet Gynecol* 1998; **11**: 426–31.

151 Gudmundsson S, Gunnarsson G, Hökegård K-H, Ingmarsson J, Kjellmer I. Venous Doppler velocimetry in relationship to central venous pressure and heart rate during hypoxia in ovine fetus. *J Perinat Med* 1999; **27**: 81–90.

152 Rizzo G, Capponi A, Talone P, Arduini D, Romanini C. Doppler indices from inferior vena cava and ductus venosus in predicting pH and oxygen tension in umbilical blood at cordocentesis in growth-retarded fetuses. *Ultrasound Obstet Gynecol* 1996; **7**: 401–10.

153 Huhta J. Right ventricular function in the human fetus. *J Perinat Med* 2001; **29**: 381–89.

154 Krapp M, Denzel S, Katalini A, Berg C, Smrcek JM, Geipel A, et al. Normal values of fetal ductus venosus blood waveforms during the first stage of labor. *Ultrasound Obstet Gynecol* 2002; **19**: 556–61.

155 van Splunder IP, Stijnen T, Wladimiroff JW. Fetal pressure gradient across the ductus venosus in early pregnancy using Doppler ultrasonography. *Ultrasound Obstet Gynecol* 1995; **6**: 334–39.

156 Pennati G, Bellotti M, Ferrazzi E, Rigano S, Garberi A. Hemodynamic changes across the human ductus venosus: a comparison between clinical findings and mathematical calculations. *Ultrasound Obstet Gynecol* 1997; **9**: 383–91.

157 Hellevik LR, Kiserud T, Irgens F, Ytrehus T, Eik-Nes SH. Simulation of pressure drop and energy dissipation for blood flow in a human fetal bifurcation. *ASME J Biomech Eng* 1998; **120**: 455–62.

158 Kiserud T, Eik-Nes SH. Doppler velocimetry of the ductus venosus. In: Maulik D, ed. *Doppler Ultrasound in Obstetrics and Gynecology*. New York, Berlin: Springer-Verlag; 1996: 403–22.

159 Kiserud T. Ductus venosus blood velocity in myeloproliferative disorders. *Ultrasound Obstet Gynecol* 2001; **18**: 184–85.

160 Smrcek JM, Baschat AA, Germer U, Gloeckner-Hofmann K, Gembruch U. Fetal hydrops and hepatosplenomegaly in the second half of pregnancy: a sign of myeloproliferative disorder in fetuses with trisomy 21. *Ultrasound Obstet Gynecol* 2001; **17**: 403–409.

161 Kiserud T, Eik-Nes SH. The fetal ductus venosus. In: Copel JA, Reed KL, editors. *Doppler ultrasound in obstetrics and gynecology*. New York: Raven Press; 1994.

162 Oepkes D, Brand R, Vandenbussche FP, Meerman RH, Kanhai HHH. The use of ultrasonography and Doppler in the predication of fetal haemolytic anaemia: a multivariate analysis. *Br J Obstet Gynaecol* 1994; **101**: 680–84.

163 Hecher K, Snijders R, Campbell S, Nicolaides K. Fetal venous, intracardiac, and arterial blood flow measurements in intrauterine growth retardation: relationship with fetal blood gases. *Am J Obstet Gynecol* 1995; **173**: 10–15.

164 Hecher K, Snijders R, Campbell S, Nicolaides K. Fetal venous, arterial, and intracardiac blood flow in red blood cell immunization. *Obstet Gynecol* 1995; **85**: 122–28.

165 Rizzo G, Arduini D, Romanini C. Inferior vena cava flow velocity waveforms in appropriate- and small-for-gestational-age fetuses. *Am J Obstet Gynecol* 1992; **166**: 1271–280.

166 Huisman TWA, Stewart PA, Wladimiroff JW. Flow velocity waveforms in the fetal inferior vena cava during the second half of normal pregnancy. *Ultrasound Med Biol* 1991; **17**: 679–82.

167 Rizzo G, Caforio L, Arduini D, Romanini C. Effect of sampling site on inferior vena cava flow velocity waveforms. *J Matern Fetal Invest* 1992; **2**: 153–56.

168 Indik JH, Chen V, Reed KL. Association of umbilical venous with inferior vena cava blood flow velocities. *Obstet Gynecol* 1991; **77**: 551–57.

169 Lingman G, Dahlström JA, Eik-Nes SH, Marsál K, Ohlin P, Ohrlander S. Hemodynamic evaluation of fetal heart arrhythmias. *Br J Obstet Gynecol* 1984; **91**: 647–52.

170 Gembruch U, Krapp M, Baumann P. Changes of venous blood flow velocity waveforms in fetuses with supraventricular tachycardia. *Ultrasound Obstet Gynecol* 1995; **5**: 394–99.

171 Gembruch U, Redel DA, Bald R, Hansmann M. Longitudinal study in 18 cases of fetal supraventricular tachycardia: Doppler echocardiographic findings and pathophysiologic implications. *Am Heart J* 1993; **125**: 1290–301.

172 Lingman G, Lundström N-G, Marsál K, Ohrlander S. Fetal cardiac arrhythmia. Clinical outcome of 113 cases. *Acta Obstet Gynecol Scand* 1986; **65**: 263–67.

173 Chan FY, Woo SK, Ghosh A, Tang M, Lam C. Prenatal diagnosis of congenital fetal arrhythmias by simultaneous Doppler velocimetry of the fetal abdominal aorta and inferior vena cava. *Obstet Gynecol* 1990; **76**: 200–205.

174 Champetier J, Yver R, Tomasella T. Functional anatomy of the liver of the human fetus: application to ultrasonography. *Surg Radiol Anat* 1989; **11**: 53–62.

175 Hofstaetter C, Gudmundsson S, Dubiel M, Marsál K. Fetal right hepatic venous blood velocity in normal and high-risk pregnancies. *Eur J Ultrasound* 1996; **4**: 153–60.

176 Villazon E, Fouron JC, Fournier A, Proulx F. Prenatal diagnosis of junctional ectopic tachycardia. *Pediatr Cardiol* 2001; **22**: 160–62.

177 Gill RW, Kossoff G, Warren PS, Garrett WJ. Umbilical venous flow in normal and complicated pregnancies. *Ultrasound Med Biol* 1984; **10**: 349–63.

178 Jouppila P, Kirkinen P. Umbilical vein blood flow as an indicator of fetal hypoxia. *Br J Obstet Gynaecol* 1984; **91**: 107–10.

179 Laurin J, Lingman G, Marsál K, Persson P-H. Fetal blood flow in pregnancies complicated by intrauterine growth retardation. *Obstet Gynecol* 1987; **69**: 895–902.

180 Kiserud T, Eik-Nes SH, Blaas H-G, Hellevik LR, Simensen B. Ductus venosus blood velocity and the umbilical circulation in the seriously growth retarded fetus. *Ultrasound Obstet Gynecol* 1994; **4**: 109–14.

181 Nakai Y, Imanaka M, Nishio J, Ogita S. Umbilical venous pulsation associated with hypercoiled cord in growth-retarded fetuses. *Gynecol Obstet Invest* 1997; **43**: 6–7.

182 Rizzo G, Capponi A, Soregaroli M, Arduini D, Romanini C. Umbilical vein pulsation and acid-base status at cordocentesis in growth-retarded fetuses with abscent end-diastolic velocity in the umbilical artery. *Biol Neonate* 1995; **68**: 163–68.

183 Ferrazzi E, Rigano S, Bozzo M, Bellotti M, Giovannini N, Galan H, et al. Umbilical vein blood flow in growth-restricted fetuses. *Ultrasound Obstet Gynecol* 2000; **16**: 432–38.

184 Kirkinen P, Jouppila P, Eik-Nes SH. Umbilical vein blood flow in rhesus-isoimmunization. *Br J Obstet Gynaecol* 1983; **90**: 640–43.

185 Rightmire DA, Nicolaides KH, Rodeck CH, Campbell S. Fetal blood velocities in Rh isoimmunization: relationship to gestational age and fetal hematocrit. *Obstet Gynecol* 1986; **68**: 233–36.

186 Gudmundsson S, Huhta JC, Wood DC, Tulzer G, Cohen AW, Weiner S. Venous Doppler ultrasonography in the fetus with nonimmune hydrops. *Am J Obstet Gynecol* 1991; **164**: 33–37.

187 Tulzer G, Gudmundsson S, Wood DC, Cohen AW, Weiner S, Huhta JC. Doppler in non–immune hydrops fetalis. *Ultrasound Obstet Gynecol* 1994; **4**: 279–83.

188 Rizzo G, Arduini D, Romanini C. Cardiac and extracardiac flows in discordant twins. *Am J Obstet Gynecol* 1994; **170**: 1321–327.

189 Gramelli D, Ludovici G, Paita Y, Merialdi A, Vadora E. Spontaneous remission of double pulsatile umbilical venous flow in twin-twin transfusion syndrome: a case report. *Ultrasound Obstet Gynecol* 1995; **5**: 138–40.

190 Lees C, Albaiges G, Deane C, Parra M, Nicolaides KH. Assessment of umbilical arterial and venous flow using color Doppler. *Ultrasound Obstet Gynecol* 1999; **14**: 250–55.

191 Ferrazzi E. Measurement of venous blood flow in the human fetus: adream comes true, but now for some standardization. *Ultrasound Obstet Gynecol* 2001; **18**: 1–4.

192 Ville Y, Sideris I, Hecher K, Snijders RJM, Nicolaides KH. Umbilical venous pressure in normal, growth-retarded, and anemic fetuses. *Am J Obstet Gynecol* 1994; **170**: 487–94.

193 Soothill PW, Nicolaides KH, Campbell S. Prenatal asphyxia, hyperlactaemia and erythroblastosis in growth retarded fetuses. *Br Med J* 1987; i:1051–1053.

194 Jouppila P, Kirkinen P, Puukka R. Correlation between umbilical vein blood flow and umbilical blood viscosity in normal and complicated pregnancies. *Arch Gynecol* 1986; **237**: 191–97.

195 Jones CT, Robinson JS. Studies on experimental growth retardation in sheep. Plasma catecholamines in fetuses with small placentae. *J Develop Physiol* 1983; **5**: 77–87.

196 Capponi A, Rizzo G, De Angelis C, Arduini D, Romanini C. Atrial natriuretic peptide levels in fetal blood in relation to inferior vena cava velocity waveforms. *Obstet Gynecol* 1997; **89**: 242–47.

197 Rizzo G, Capponi A, Rinaldo D, Arduini D, Romanini C. Release of vasoactive agents during cordocenteseis: difference between normally grown and growth-restricted fetuses. *Am J Obstet Gynecol* 1996; **175**: 563–70.

198 Robinson JS, Jones CT, Kingston EJ. Studies on experimental growth retardation in sheep. The effect of maternal hypoxaemia. *J Develop Physiol* 1983; **5**: 89–100.

199 Alfirevic Z, Neilson JP. Doppler ultrasonography in high-risk pregnancies: Systematic review with meta-analysis. *Am J Obstet Gynecol* 1995; **172**: 1379–387.

200 Dubiel M, Gudmundsson S, Gunnarsson G, Marsál K. Middle cerebral artery velocimetry as a predictor of hypoxemia in fetuses with increased resistance to blood flow in the umbilical artery. *Early Hum Dev* 1997; **47**: 177–84.

201 Hershkovitz R, Kingdom JC, Geary M, Rodeck CH. Fetal cerebral blood flow redistribution in late gestation: identification of compromise in small fetuses with normal umbilical artery Doppler. *Ultrasound Obstet Gynecol* 2000; **15**: 209–12.

202 Severi FM, Bocchi C, Visenti A, Falco P, Cobellis L, Florio P, et al. Uterine and fetal cerebral Doppler predict the outcome of third-trimester small-for-gestational age fetuses with normal umbilical artery Doppler. *Ultrasound Obstet Gynecol* 2002; **19**: 225–28.

203 Harrington KF. Making best and appropriate use of fetal biophysical and Doppler ultrasound data in the management of the growth restricted fetus. *Ultrasound Obstet Gynecol* 2000; **16**: 399–401.

204 Romero R, Kalache KD, Kadar N. Timing the delivery of the preterm severly growth-restricted fetus: venous Doppler, cardiotochography or the biophysical profile? *Ultrasound Obstet Gynecol* 2002; **19**: 118–21.

205 Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G, et al. Temporal sequence of abnormal Doppler changes in peripheral and central circulatory systems of the severely growth-restricted fetus. *Ultrasound Obstet Gynecol* 2002; **19**: 140–46.

206 Hecher K, Bilardo CM, Stigter RH, Ville Y, Hackelöer BJ, Kok HJ. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. *Ultrasound Obstet Gynecol* 2001; **18**: 564–70.

207 Baschat AA, Gembruch U, Harman CR. The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsen. *Ultrasound Obstet Gynecol* 2001; **18**: 571–77.

208 Gudmundsson S, Tulzer G, Huhta J, Marsál K. Venous Doppler in the fetus with absent end-diastolicflow in the umbilical artery. *Ultrasound Obstet Gynecol* 1997; **7**: 262–67.