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REVIEW

The fetal circulation

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Accumulating data on the human fetal circulation shows the similarity to the experimental animal physiology, but with important differences. The human fetus seems to circulate less blood through the placenta, shunt less through the ductus venosus and foramen ovale, but direct more blood through the lungs than the fetal sheep. However, there are substantial individual variations and the pattern changes with gestational age. The normalised umbilical blood flow decreases with gestational age, and, at 28 to 32 weeks, a new level of development seems to be reached. At this stage, the shunting through the ductus venosus and the foramen ovale reaches a minimum, and the flow through the lungs a maximum. The ductus venosus and foramen ovale are functionally closely related and represent an important distributional unit for the venous return. The left portal branch represents a venous watershed, and, similarly, the isthmus aorta an arterial watershed. Thus, the fetal central circulation is a very flexible and adaptive circulatory system. The responses to increased afterload, hypoxaemia and acidaemia in the human fetus are equivalent to those found in animal studies: increased ductus venosus and foramen ovale shunting, increased impedance in the lungs, reduced impedance in the brain, increasingly reversed flow in the aortic isthmus and a more prominent coronary blood flow.

KEY WORDS: circulation; blood flow; vein; artery; shunt; fetus

INTRODUCTION

Modern techniques, particularly ultrasound with its Doppler modalities, have opened a new era of fetal circulation. One of the consequences is that physiological data derived from human fetuses increasingly substitute reference values established on classical animal experiments. Many of the mechanisms described in these experiments have been shown to operate also in the human fetus, but in its own version. The following review is preferentially based on human data in the fetal period of development, with clinicians' priorities. The bibliographic references only selectively reflect a field that is growing by the day.

FETAL BLOOD VOLUME

Typically, the blood volume in the human fetus is 10 to 12% of the body weight compared to 7 to 8% in adults (Brace, 1993). One of the reasons for this difference is that the placenta contains a large pool of blood, a volume that is gradually reduced with the progress of gestation (Barcroft, 1946) (Figure 1). The calculated blood volume of 90 to 105 mL/kg in fetuses undergoing blood transfusion during the second half of pregnancy (Nicolaides *et al*., 1987) is probably an underestimation, and does not represent a physiologically normal group. Other studies indicate a volume of 110 to 115 mL/kg, which is more in line with experimental sheep studies (Brace, 1983; Yao *et al*., 1969). The estimated volume of 80 mL/kg contained within the fetal body is marginally more than that in adults. Compared to adults, the fetus is capable of a much faster regulation and restoration of the blood volume owing to high diffusion rates between fetal compartments (Brace, 1993).

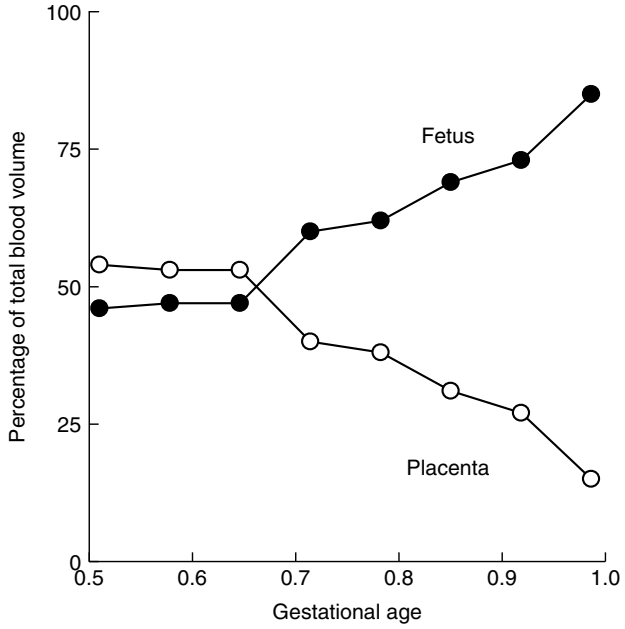

Figure 1—Distribution of blood volume between the placenta and fetal body in fetal sheep. Based on data from Barcroft J. 1946. *Researches on Pre-natal Life*. Blackwell Scientific Publications: Oxford

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BLOOD PRESSURE

The mean arterial pressure in human fetuses was reported to be 15 mm Hg at gestational weeks 19 to 21 (Castle and Mackenzie, 1986). Intrauterine recording of the intraventricular pressure in the human fetus suggests that the systemic systolic pressure increases from 15 to 20 mm Hg at 16 weeks to 30 to 40 at 28 weeks (Johnson *et al*., 2000). The results did not show any difference between the two ventricles, but variation was substantial. Similarly, there was no difference in diastolic ventricular pressure, which was $\leq$ 5 mm Hg at 16 to 18 weeks and showed a slight increase towards 5 to 15 mm Hg at 19 to 26 weeks. Umbilical venous pressure (after subtracting amniotic pressure) recorded during cordocentesis in 111 normal pregnancies undergoing prenatal diagnosis showed that the mean pressure increased with gestation from 4.5 mm Hg at 18 weeks to 6 mm Hg at term (Ville *et al*., 1994), which confirms previous studies reasonably well (Nicolini *et al*., 1989; Weiner *et al*., 1989).

CARDIAC FUNCTION

Once the structural details have been organised during the embryonic period, the fetal heart continues to grow in an adaptive interplay with the changing demands. The myocardium grows by cell division until birth and a continued growth thereafter comes with cell enlargement. The density of myofibrils increases particularly in early pregnancy, but the contractility continues to improve during the second half of pregnancy (Thornburg and Morton, 1994). The two ventricles seem to be histologically different, and show a different performance (Figure 2a) both in pressure/volume curves and with an intact peripheral vasculature (Reller *et al*., 1987; Thornburg and Morton, 1986). Typically, the fetal heart has very limited capacity to increase stroke volume by increasing end-diastolic filling pressure, the right ventricle even less than the left (Figure 2b), as they are already operating at the top of their function curves. The Frank–Starling mechanism does operate in the fetal heart, which is particularly apparent during fetal arrhythmias (Lingman *et al*., 1984). Adrenergic drive also shifts the function curve to increase stroke volume. However, increased heart rate may be the single most prominent means of increasing cardiac output in the fetus.

With the two ventricles pumping in parallel to the systemic circulation, the pressure difference between the ventricles is minimal compared to postnatal life (Johnson *et al*., 2000). Still, the difference in compliance of the great arteries and down stream impedance (upper body vs lower body and placenta) is visible in their pressure and velocity profiles. Some of the 'stiffness' of the fetal myocardium is attributed to the constraint of the pericardium, lungs and chest wall (Grant and Walker, 1996; Grant *et al*., 2001), all with low compliance since no air is introduced. However, with the shunts in operation and a metabolism capable of extracting oxygen at low saturation levels, the fetal heart appears to be a very flexible, responsive and adaptive structure.

CARDIAC OUTPUT AND CENTRAL DISTRIBUTION

In contrast to postnatal life, the systemic circulation is fed from the left and right ventricle in parallel, but with a small proportion of the right output being spared for the lungs. At mid-gestation, the combined cardiac output is 210 mL and increases to 1900 mL at 38 weeks (Rasanen *et al*., 1996) (Table 1). Doppler studies of this kind have shown that the right ventricular output is slightly larger than the left, and that pulmonary flow

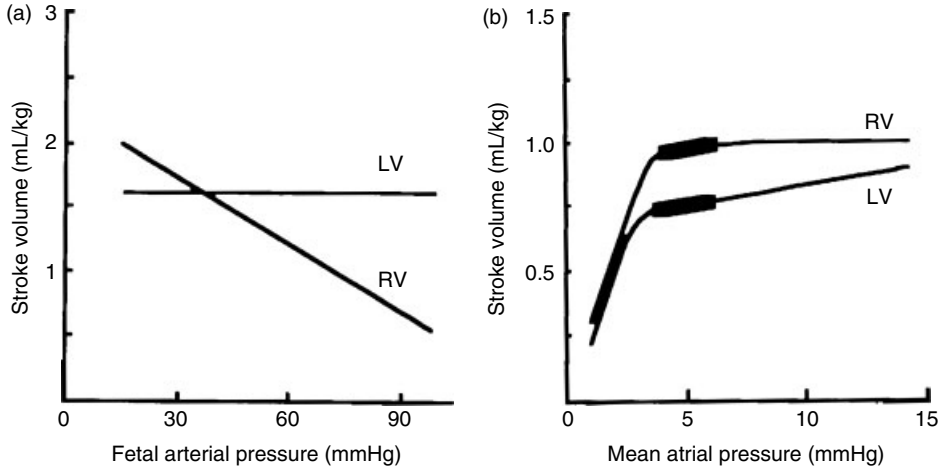

Figure 2—Difference in stroke volume for left and right ventricle (LV and RV) with increasing systemic blood pressure in late pregnancy (a). Difference between left and right ventricular stroke volume in relation to atrial pressure (b). Fetal ventricles work near the breaking point of their function curves (thick rule), and increased atrial pressure has little effect on stroke volume. Based on Thornburg KL, Morton MJ. 1986. Filling and atrial pressures as determinants of left ventricular stroke volume in unanaesthetized fetal lambs. *Am J Physiol* **251:** H961–H968; Thornburg KL, Morton MJ. 1994. Development of the cardiovascular system. In *Textbook of Fetal Physiology*, Thorburn GD, Harding R (eds). Oxford University Press: Oxford; Reller MD, Morton MJ, Reid DL, Thornburg KL. 1987. Fetal lamb ventricles respond differently to filling and arterial pressures and to in utero ventilation. *Pediatr Res* **22:** 519–532

Table 1—The combined cardiac output and its distribution to the left and right ventricle, foramen ovale, lungs and ductus arteriosus in normal human fetuses (Rasanen *et al*., 1996)

	% of combined cardiac output at gestational age		
	20 weeks	30 weeks	38 weeks
Combined cardiac output	210 (mL/min)	960 (mL/min)	1900 (mL/min)
Left ventricle	47	43	40
Right ventricle	53	57	60
Foramen ovale	34	18	19
Lungs	13	21	25
Ductus arteriosus	40	32	39

in the human fetus is larger (mean 13–25%) than in the classical fetal lamb studies ($\leqslant$ 10%). Interestingly, a developmental transition in fetal haemodynamics seems to occur at 28 to 32 weeks, when the pulmonary blood flow reaches a maximum (Rasanen *et al*., 1996). In another study, similar flow distribution was noted, but with less blood distributed to the fetal lungs, 11% (Mielke and Benda, 2001), which is more in line with the previous experimental studies.

The three shunts, ductus venosus, ductus arteriosus and foramen ovale, are essential distributional arrangements, making the fetal circulation a flexible and adaptive system for intrauterine life. Their haemodynamic properties and functional ranges constitute important determinants for the development of the fetal heart and circulation during the second and third trimester. The classical via dextra and sinistra continues to be a useful concept of blood flow distribution in the fetus (Figure 3).

In addition to the fetal shunts, the isthmus aorta has received increasing attention since it forms a watershed between the circulation of the upper body (including the brain) and that of the lower body (including the placenta) (Fouron *et al*., 1994; Makikallio *et al*., 2002; Teyssier *et al*., 1993). Another watershed is the section of the left portal vein situated between the main portal stem and the ductus venosus (Figure 3). This venous section normally directs umbilical blood to the right lobe of the liver. Under abnormal conditions, the flow may cease or be reversed, resulting in an increased admixture of splanchnic blood in the ductus venosus (Kiserud *et al*., 2003).

Oxygen saturation gives a picture of distribution and blending of flows in the central fetal circulation (Figure 3). The lowest saturation is found in the abdominal inferior vena cava (IVC), and the highest in the umbilical vein (Rudolph, 1985). Interestingly, the difference between the left and right ventricle is only 10%, increasing to 12% during hypoxaemia.

DUCTUS VENOSUS

The fetal ductus venosus is a slender trumpet-like shunt, connecting the intra-abdominal umbilical vein to the IVC at its inlet to the heart. The inlet, the isthmus, is the restrictive area with a mean diameter of 0.5 mm at mid-gestation and hardly ever exceeds 2 mm for the rest of a normal pregnancy (Kiserud *et al*., 1994b; Kiserud *et al*., 2000b). An umbilical venous pressure ranging from 2 to 9 mmHg (Ville *et al*., 1994), or rather: the portocaval pressure gradient, causes the blood to accelerate from mean 10 to 22 cm/s to 60 to 85 cm/s as it enters the ductus venosus and flows towards the IVC and foramen ovale (Bahlmann *et al*., 2000; Huisman *et al*., 1992; Kiserud *et al*., 1991). Since the well-oxygenated blood from the ductus venosus is loaded with the highest kinetic energy in the IVC, it will predominantly be this blood that presses open the foramen ovale valve to enter the left atrium, thus forming the 'preferential streaming' of the via sinistra.

While 30% of the umbilical blood is shunted through the ductus venosus at mid-gestation, the fraction is reduced to 20% at 30 weeks and remains so for the rest of the pregnancy, but with wide variations (Kiserud *et al*., 2000b) (Table 2). Interestingly, these results, which have been confirmed in another study (Bellotti

Table 2—The fraction of umbilical blood shunted through the ductus venosus during the second half of the human pregnancy (Kiserud *et al*., 2000b)

		Degree of ductus venosus shunting (%)	
Gestational age (weeks)	N	50th percentile	(10th; 90th percentiles)
18–19	34	28	(14;65)
20–24	45	25	(10;44)
25–28	34	22	(10;44)
29–32	32	19	(9;46)
33–36	21	20	(10;31)
37–41	27	23	(7;38)

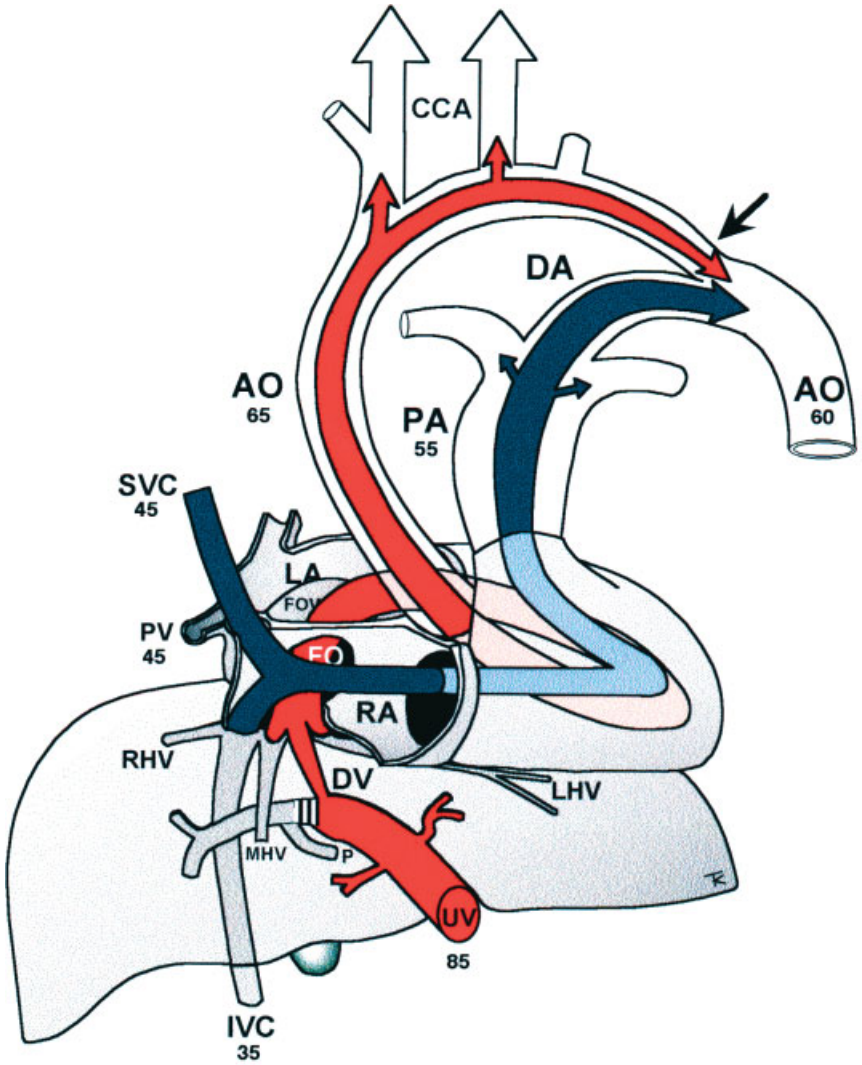

Figure 3—Pathways of the fetal heart and representative oxygen saturation values (in numbers). The via sinistra (red) directs well oxygenated blood from the umbilical vein (UV) through the ductus venosus (DV) (or left half of the liver) across the inferior vena cava (IVC), through the foramen ovale (FO), left atrium (LA) and ventricle (LV) and up the ascending aorta (AO) to join the via dextra (blue) in the descending AO. Deoxygenated blood from the superior vena cava (SVC) and IVC forms the via dextra through the right atrium (RA) and ventricle (RV), pulmonary trunk (PA) and ductus arteriosus (DA). The isthmus aortae (arrow) and the section of the left portal vein between the main stem (P) and the DV (striped area) represent watershed areas during hemodynamic compromise. CCA, common carotid arteries; FOV, foramen ovale valve; LHV, left hepatic vein; MHV, medial hepatic vein; PV, pulmonary vein; RHV, right hepatic vein

et al., 2000), are at variance with the experimental animal studies showing roughly 50% to be shunted through the ductus venosus (Behrman *et al*., 1970; Edelstone *et al*., 1978). The redistributional mechanisms of increased shunting during hypoxaemia found in animal experiments seem to operate in the human fetus as well (Kiserud *et al*., 2000a; Tchirikov *et al*., 1998).

The diameter in the ductus venosus is under tonic adrenergic control, and distends under the influence of nitroxide and prostaglandins (Adeagbo *et al*., 1982; Coceani *et al*., 1984; Kiserud *et al*., 2000a). The most pronounced response is seen during hypoxaemia, which causes a 60% increase of the diameter in fetal sheep (Kiserud *et al*., 2000a). Interestingly, the changes in diameter are not restricted to the isthmus, but include the entire length of the vessel, which makes a far greater impact on resistance (Kiserud *et al*., 2000a; Momma *et al*., 1984). Normally, the shunt is obliterated 1 to 3 weeks after birth, but a little later in premature neonates and cases with persistent pulmonary hypertension or cardiac malformation (Fugelseth *et al*., 1997, 1998; Fugelseth *et al*., 1999; Loberant *et al*., 1992). In contrast to the ductus arteriosus where oxygen triggers the closure, no trigger has been found for the ductus venosus (Coceani and Olley, 1988).

An equally important regulatory mechanism is that of fluid dynamics, that is, viscosity and pressure (Figure 4) (Edelstone, 1980; Kiserud *et al*., 1997). Since blood velocity in the ductus venosus is high, the blood has Newtonian properties with low viscosity (similar to water). In contrast, the liver tissue represents a huge capillary cross section with a low blood velocity. At low velocities, the blood is non-Newtonian with a correspondingly high viscosity (and resistance) and a

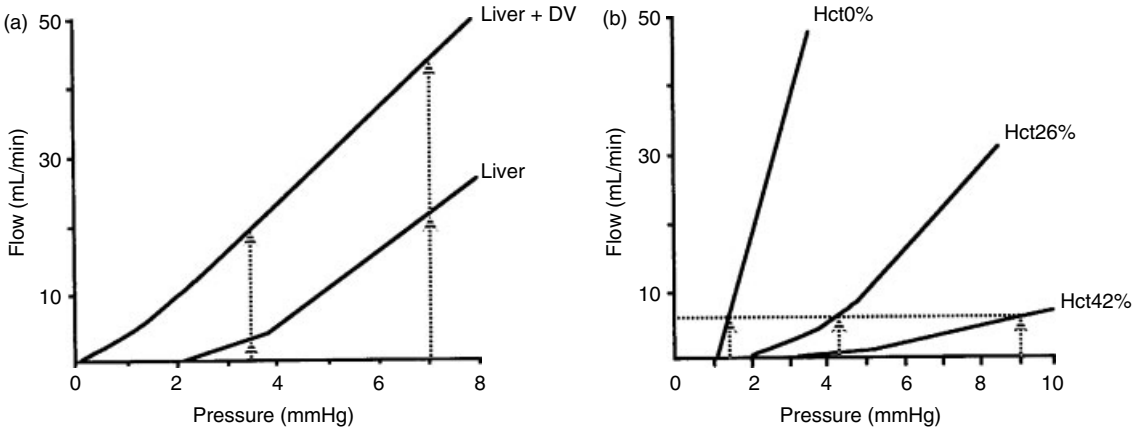

Figure 4—The umbilical flow distribution to the liver and ductus venosus (DV) varies with the umbilical pressure because viscosity plays a more prominent role at low blood velocity in the liver than in the ductus venosus (a). At 7 mm Hg the liver and ductus venosus receive 50% each of the umbilical flow, but at 3.5 mm Hg the distribution is 15 and 85%, respectively (stippled arrows). Note that the liver has an opening pressure of 2 mm Hg. Viscosity, that is, haematocrit (Hct), is a major contributor to resistance in the vascular bed of the liver (b). To perfuse the liver with 7 mL/min of blood with Hct 0, 26 or 42%, 1.4, 4.3 and 9 mm Hg is needed respectively (stippled arrows). Note the increasing opening (closing) pressure with increasing Hct. Based on data from Kiserud T, Stratford L, Hanson MA. 1997. 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* **177:** 86–90

closing pressure of 1 to 4 mm Hg. Accordingly, an increase in viscosity (i.e. haematocrit) causes a more pronounced reduction of the umbilical venous liver flow compared to that of the ductus venosus, thus increasing the fraction directed through the ductus venosus. Along the same line, variation in the umbilical venous pressure affects the two pathways differently. A reduction in venous pressure affects the liver perfusion more than the ductus venosus, resulting in a higher degree of shunting. On top of these fluid dynamic determinants comes the neural and endocrine regulation of the hepatic vascular bed, which has been difficult to demonstrate (Paulick *et al*., 1990, 1991).

The physiological significance of the ductus venosus function is unresolved. The low degree of shunting through the ductus venosus implies that 70 to 80% of the umbilical blood perfuses the liver, suggesting a higher developmental priority of the liver than the preferential streaming through the ductus venosus and foramen ovale (Kiserud *et al*., 2000b). Although there is a growing number of case reports connecting agenesis of the ductus venosus to chromosomal abnormalities, malformations, non-immune hydrops and intrauterine death (Contratti *et al*., 2001; Hofstaetter *et al*., 2000; Sivén *et al*., 1995; Volpe *et al*., 2002), agenesis is also found in normally grown fetuses (Kiserud *et al*., 2000b). Experimental obliteration of the vessel seems to have little haemodynamic effect (Amoroso *et al*., 1955; Rudolph *et al*., 1991), but causes an increase in insulin-like growth factor 2 and an increased growth of fetal organs (Tchirikov *et al*., 2001). It should also be borne in mind that the oxygen extraction in the liver is modest, 10 to 15% reduction in oxygen saturation (Bristow *et al*., 1981; Townsend *et al*., 1989), which makes the blood coming from the median and left hepatic vein an important contributor of oxygenated blood. Actually, the position and direction of the left hepatic venous blood under the Eustachian valve (inferior vena cava valve) favours this blood to be delivered at the foramen ovale (Kiserud *et al*., 1992). However, while the liver seems to have a high developmental priority, receiving most of the umbilical venous return, an increased shunting through the ductus venosus plays an important compensatory role during acute hypoxaemia and hypovolaemia (Behrman *et al*., 1970; Edelstone *et al*., 1980; Itskovitz *et al*., 1983, 1987; Meyers *et al*., 1991), and, probably, a prolonged adaptational role during chronic placental compromise.

The Doppler examination of the ductus venosus is increasingly used to identify hypoxaemia, acidosis, cardiac decompensation and placental compromise, and is a promising tool for timing the delivery of critically ill fetuses (Baschat *et al*., 2001; Ferrazzi *et al*., 2002; Gudmundsson *et al*., 1997; Hecher *et al*., 1995a; Hecher *et al*., 2001; Kiserud *et al*., 1993; Kiserud *et al*., 1994a; Rizzo *et al*., 1994). An increased pulsatility, mostly caused by the augmented atrial contraction wave, signifies increased atrial contraction and end-diastolic filling pressure (Figure 5). Since the absolute blood velocity at the isthmus reflects the portocaval pressure gradient (Kiserud *et al*., 1994b), it is also a promising tool in the evaluation of fetal liver diseases, anaemia and conditions with increased venous return such as twin–twin transfusion syndrome (Hecher *et al*., 1995b).

FORAMEN OVALE

In neonatal and adult life, an atrial septum defect is commonly associated with a left-right or right-left shunting. It is conceivable that, even today, this concept is used to describe the function of the foramen ovale (Atkins *et al*., 1982; Wilson *et al*., 1989), but it is not a fair representation of the actual haemodynamics. Rather, it is a vertical blood flow that enters between the two atria from below (Barclay *et al*., 1944; Kiserud *et al*., 1991, 1992; Kiserud, 1999; Lind and Wegelius, 1949). This blood flow ends as a fountain as it hits the interatrial

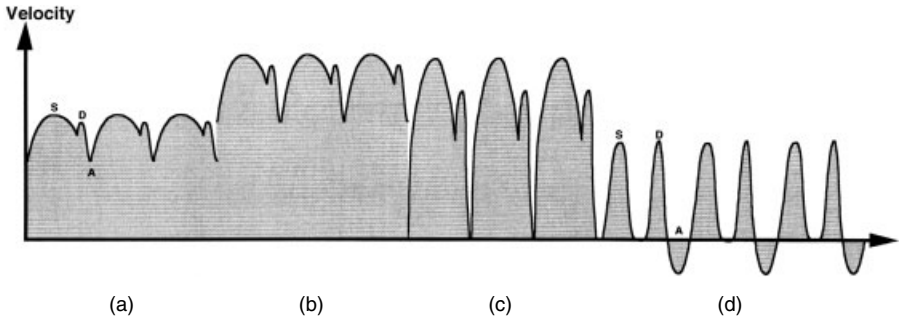

Figure 5—The blood velocity in the ductus venosus reflects the normal cyclic cardiac events (a) with a peak during ventricular systole (S), a peak during passive diastolic filling (D) and a deflection during atrial contraction (A). A general increase in velocities (b) reflects an increased portocaval pressure gradient (e.g. liver disease, anaemia). An additionally augmented atrial contraction wave (c) reflects increased end-diastolic pressure (e.g. increased preload, adrenergic drive) commonly seen in placental compromise. A further deterioration (d) would be a reversed A-wave. With increasing myocardial hypoxia and acidosis, the muscle is less compliant, causing a dichotomy of the S- and D-wave (e.g. preterminal placental compromise)

ridge, the crista dividens, and is divided into a left and right arm (Figures 6 and 7). The left arm fills the 'windsock', formed by the foramen ovale valve and the atrial septum, to enter the left atrium. The right arm is directed towards the tricuspid valve and joins the flow from the superior vena cava and coronary sinus to form the via dextra.

It is a delicate equilibrium easily influenced by changes in pressure on the two sides. An increased resistance and diastolic pressure of the left side is instantaneously reflected in an increased diversion of blood to the right side of the interatrial septum. In contrast to the hypertrophy of the left ventricle seen in aortic stenosis in adults, the fetal stenosis commonly leads to a shift of blood volume from left to right at the level of the foramen ovale with a corresponding development of the fetal heart, left hypoplasia and a compensatory growth of the right ventricle.

The developing ventricle responds to the demands of the afterload and is stimulated by the blood volume of the preload. However, for the left side of the heart, the

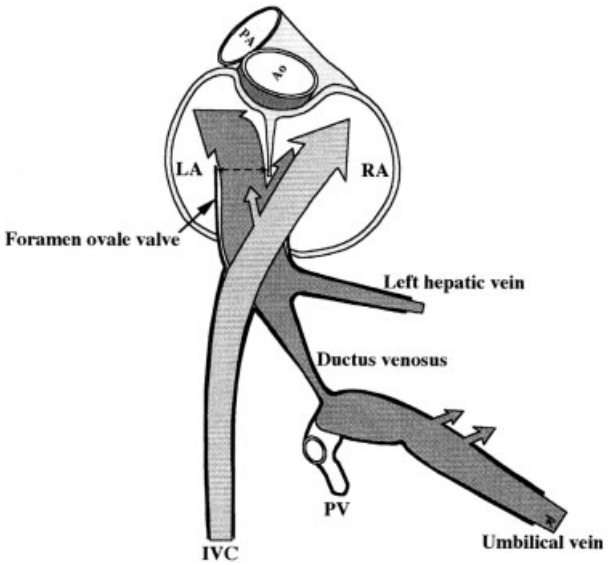

Figure 6—Flow distribution at the foramen ovale. The edge of the atrial septum (crista dividens) divides the ascending flow in two arms, to the right and left atrium (RA and LA). The horizontal diameter between the foramen ovale valve and the atrium (broken line) represents the restricting area into the LA. Position, direction and kinetic energy of the flow from the ductus venosus makes it predominantly enter the left atrium (dark gray). Conversely, blood from the inferior vena cava (IVC) enters the RA (light gray). Ao, aorta; PA, pulmonary trunk; PV, stem of the portal vein (From Kiserud and Rasmussen, 2001)

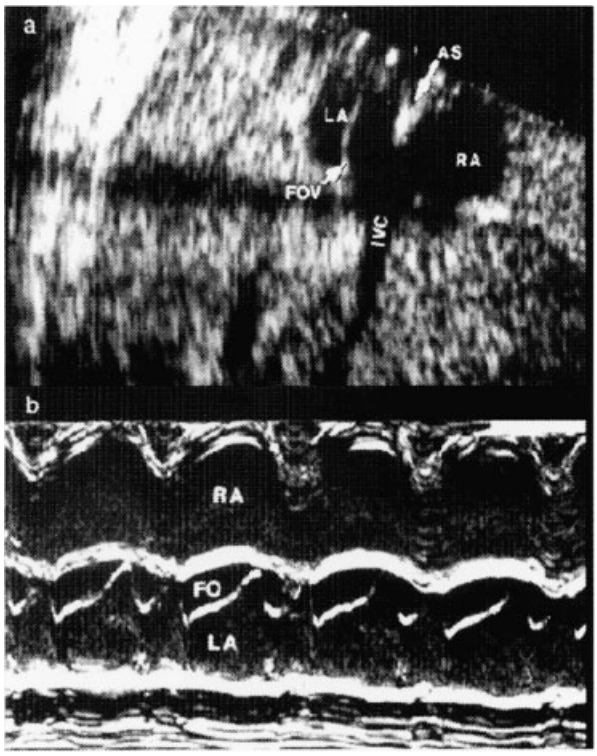

Figure 7—Ultrasound scan (a) showing that the fetal atrial septum (AS), at the level of the foramen ovale, is situated more towards the right atrium (RA) than in postnatal life, opposing the inferior vena cava (IVC). The entrance to the left atrium (LA) is formed as a 'windsock', delineated by the foramen ovale valve (FOV) towards the left, and the AS towards the right. M-mode (b) shows the changes in diameter of this 'windsock' (FO) during the heart cycle. From Kiserud T, Rasmussen S. 2001. Ultrasound assessment of the fetal foramen ovale. *Ultrasound Obstet Gynecol* **17:** 119–124

foramen ovale is an important limiting factor, particularly in cases of a maldeveloped foramen or a premature closure (Lenz *et al*., 2002). Under physiological conditions, it is not the area of the ovally shaped hole of the septum that constitutes the restricting area for the flow to the left atrium, but rather the horizontal area between the foramen ovale valve and the atrial septum above the foramen ovale (Figure 5) (Kiserud and Rasmussen, 2001). Interestingly, the growth of this area is somehow blunted after 28 to 30 weeks of gestation compared to the cross section of the IVC (Figure 8). The effect coincides with changes in fetal lung perfusion (Rasanen *et al*., 1996) and ductus venosus shunting (Kiserud *et al*., 2000b), and may signify a transition into a more mature circulatory physiology.

DUCTUS ARTERIOSUS

This shunt is a wide muscular vessel connecting the pulmonary arterial trunk to the descending aorta (Figure 3). During the second trimester, 40% or less of the combined cardiac output is directed through the ductus arteriosus (Mielke and Benda, 2001; Rasanen *et al*., 1996) (Table 1). Normally, the shunt closes 2 days after birth (Huhta *et al*., 1984), but a patent duct is a common clinical problem. The vessel is under the general influence of circulating substances, particularly prostaglandin E_2, which is crucial in maintaining patency (Clyman *et al*., 1978). The sensitivity to prostaglandin antagonists is at its highest in the third trimester and is enhanced by glucocorticoids or fetal stress (Clyman, 1987; Moise *et al*., 1988). Nitric oxide has a relaxing effect also before the third trimester.

The ductus arteriosus bypasses the pulmonary circuit, but the distribution between these two pathways depends heavily on the impedance of the pulmonary vasculature, which is under Prostaglandin I_2 control in addition to a series of substances (Coceani *et al*., 1980). In an elegant study, Rasanen *et al*. showed how the reactivity in the pulmonary vascular bed increased in the third trimester (Rasanen *et al*., 1998). While fetuses at gestational age 20 to 26 weeks showed no changes during maternal hyperoxygenation, fetuses at 31 to 36 weeks had a lower impedance in the pulmonary arteries assessed by the pulsatility index, and an increased pulmonary blood flow. Correspondingly, the blood flow in the ductus arteriosus was reduced.

The increased reactivity of the ductus arteriosus in the third trimester makes it vulnerable to prostaglandin synthase inhibitors such as indomethacin, which may cause a severe and long-lasting constriction, resulting in a congestive heart failure (Huhta *et al*., 1987; Moise *et al*., 1988).

ISTHMUS AORTAE

Fetal sheep studies have shown that roughly 10% of the combined cardiac output in the fetus passes through the isthmus aortae (Rudolph, 1985). The flexibility of the central fetal circulation is particularly visible in the isthmus aortae. In cases of reduced output from the left ventricle (e.g. critical aorta stenosis and hypoplastic left heart syndrome), the aortic arch is fed by blood from the ductus arteriosus in a reversed fashion through the isthmus.

Recent studies have highlighted the isthmus aortae as a watershed between the aortic arch and the ductus arteriosus–descending aorta (Figure 3) (Fouron *et al*., 1994; Makikallio *et al*., 2002; Sonesson and Fouron,

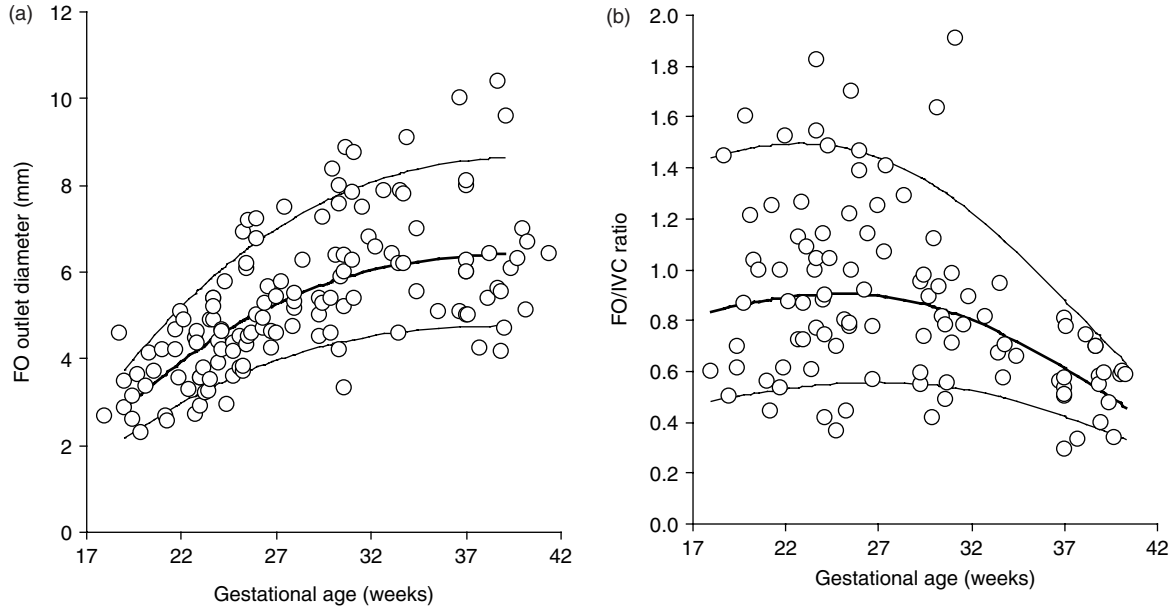

Figure 8—The horizontal diameter of the foramen ovale (FO) hardly grows after 30 weeks of gestation in normal pregnancies (a). The reduced functional importance after 30 weeks of gestation is also reflected in the ration of the horizontal area of the foramen ovale (FO) and inferior vena cava (IVC) (b). From Kiserud T, Rasmussen S. 2001. Ultrasound assessment of the fetal foramen ovale. *Ultrasound Obstet Gynecol* **17:** 119–124

1997; Teyssier *et al*., 1993). Since this watershed also reflects the difference in impedance between the cerebral circuit and that of the placenta and lower fetal body, the blood velocity pattern across the isthmus has been suggested as an indicator of placental compromise. With increasing downstream impedance below the isthmus aortae (and a reduced impedance in the cerebral circuit), the orthograde blood velocity is changed to biphasic and finally retrograde more or less during the entire cycle (Bonnin *et al*., 1993).

FETOPLACENTAL CIRCULATION

In the fetal sheep, 45% of the combined cardiac output is directed to the umbilical arteries and placenta (Jensen *et al*., 1991). In the exteriorised human fetus it is less, but increases from 17% at 10 weeks to 33% at 20 weeks of gestation (Rudolph *et al*., 1971). The results are overestimating the placental fraction since the combined cardiac output calculation was based on the systemic venous return, not including the pulmonary venous return. On the other hand, the measurements were not performed under strict physiological conditions.

The introduction of Doppler ultrasound made it possible to assess umbilical venous blood flow (Eik-Nes *et al*., 1980; Gill, 1979; Gill *et al*., 1981; Lingman and Marsál, 1986), and, recently, also arterial flow (Goldkrand *et al*., 2000) or a combination of arterial and venous flow(Lees *et al*., 1999) in the human fetus *in utero*. Umbilical blood flow is 35 mL min^{-1} at 20 weeks and 240 at 40 weeks of gestation (Figure 9) (Kiserud *et al*., 2000b). The corresponding normalised flow is 115 mL min^{-1} kg^{-1} at 20 weeks and 64 at 40 weeks. These results have been confirmed in a similar study (Boito *et al*., 2002) and are in accordance with earlier studies applying thermodilution at birth (Stembera *et al*., 1965), but at some variance with others (Barbera *et al*., 1999; Bellotti *et al*., 2000). The human umbilical flow is considerably lower than that in the fetal sheep. That is not disconcerting since the fetal sheep grows at a higher rate, has a higher temperature and lower haemoglobin.

At mid-gestation, as much as 50% of the total fetal blood volume may be contained within the placenta, but the fraction is reduced to 20 to 25% at term in fetal sheep (Barcroft, 1946) (Figure 1). In the human at birth, the fraction is 33% (Yao *et al*., 1969).

Resistance to flow is mainly determined by the peripheral vascular bed of the placenta. This vasculature has no neural regulation and catecholamines have little effect on the vasculature. Endothelin and prostanoid have a constricting effect (Poston, 1997), nitric oxide vasodilates (Sand *et al*., 2002), but the exact role of humoral regulation is not fully known (Poston *et al*., 1995). The placental blood flow has been found to be fairly stable and is chiefly determined by the arterial blood pressure (Rudolph, 1985). The substantial increase in vascularisation during late gestation accounts for a low impedance and the corresponding high diastolic blood velocity in the umbilical arteries, but placental vasculature is believed to account for 55% of the umbilical

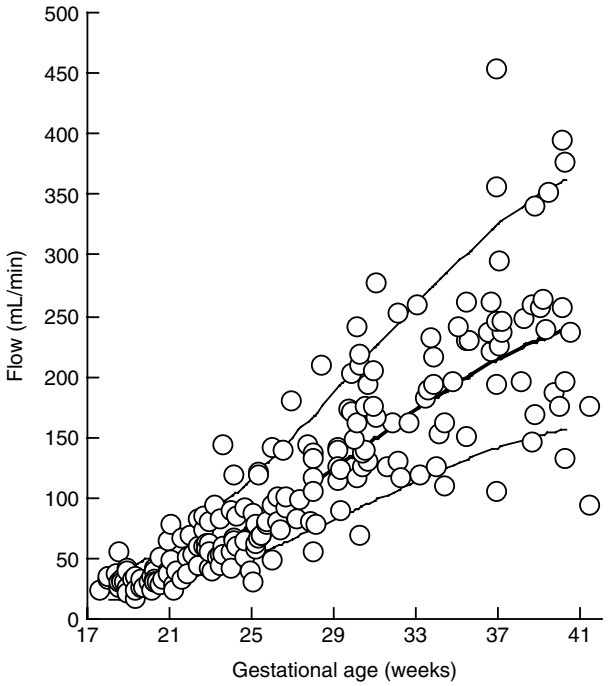

Figure 9—Normal umbilical blood flow assessed in the intra-abdominal umbilical vein during the second half of pregnancy. From Kiserud T, Rasmussen S, Skulstad SM 2000b. Blood flow and degree of shunting through the ductus venosus in the human fetus. *Am J Obstet Gynecol* **182** 147–153

resistance (Adamson, 1999). The waveform recorded by Doppler measurement in the umbilical artery reflects this downstream impedance and is extensively used to identify placental compromise (Alfirevic and Neilson, 1995). On the venous side, recent studies have shown that a tightening of the umbilical ring at the level of the abdominal wall causes various degrees of venous stricture after the period of umbilical herniation (7–12 weeks) with venous blood velocity exceeding 100 cm/s in some fetuses (Skulstad *et al*., 2001; Skulstad *et al*., 2002).

CIRCULATORY REGULATION

The regulation mechanisms and responses to hypoxaemia and hypovolaemia are particularly well studied in animal experiments during the last third of pregnancy (Iwamoto, 1993), but, even during mid-gestation and earlier, there seem to be neural and endocrine responses in addition to the prominent direct effect on cardiac function caused by hypoxic insult (Iwamoto *et al*., 1989; Kiserud *et al*., 2001). A hypoxic insult in late pregnancy activates a chemoreflex mediated by the carotid bodies (to a lesses extent the aortic bodies), causing an immediate vagal effect with reduced heart rate and a sympathetic vasoconstriction (Giussani *et al*., 1993; Giussani *et al*., 1996; Hanson, 1988; Hanson, 1997). This is followed by endocrine responses (e.g. adrenalin and noradrenaline), maintaining vasoconstriction (α-adrenergic), increasing heart rate (β-adrenergic) and reducing blood volume with renin release and increased angiotensin II concentration. The responses involve angiotensin–vasopressin

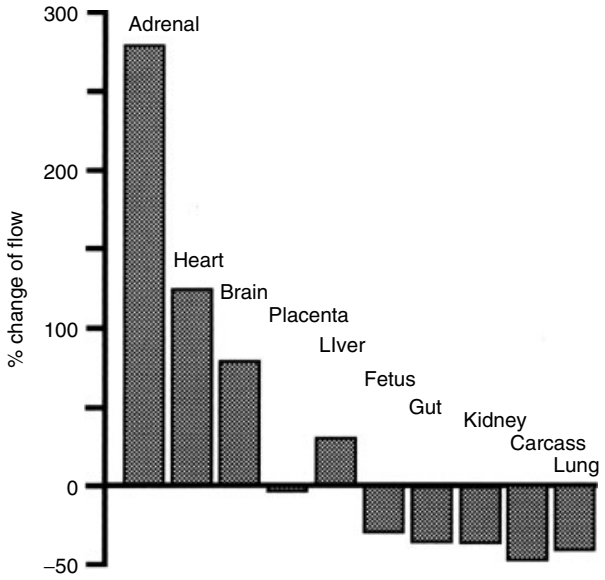

Figure 10—Redistribution of organ blood flow (% of control) during fetal hypoxia caused by reduced uterine flow. Based on data from Jensen A, Roman C, Rudolph AM. 1991. Effect of reduced uterine flow on fetal blood flow distribution and oxygen delivery. *J Dev Physiol* **15:** 309–323

mechanisms, and an increased concentrations of ACTH, cortisol, atrial natriuretic peptide, neuropeptide Y and adrenomedullin are in play to orchestrate a circulatory redistributional pattern that maintains placental circulation and gives priority to the adrenal glands, myocardium and brain (Iwamoto, 1993) (Figure 10). In clinical medicine, this translates into frequently visualised coronary circulation (Baschat *et al*., 1997; Baschat *et al*., 2000; Chaoui, 1996; Gembruch and Baschat, 1996), shift in left-right ventricular distribution (Rizzo *et al*., 1995), cerebral circulation with high diastolic flow (Wladimiroff *et al*., 1987) and increased impedance in the pulmonary circulation (Rizzo *et al*., 1996) during circulatory compromise.

A sustained hypoxia forces an adaptational shift to less oxygen demand (Bocking *et al*., 1988; Bocking, 1993), reduced DNA synthesis (Hooper *et al*., 1991) and growth, with a gradual return towards normal concentrations of blood gasses and endocrine status (Challis *et al*., 1989), though with a residual deviation that may have a long-lasting effect on the fetal and newborn life. There is an increasing awareness that even subtle differences in the development of autocrine, paracrine, endocrine and metabolic functions induced by nutritional or circulatory variations during pregnancy could have lasting effects with increased risks of cardiovascular and endocrine diseases in adult life (Barker and Sultan, 1995).

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