



Physiology of the fetal circulation

Torvid Kiserud^{a,b,*}

^a *Department of Obstetrics and Gynaecology, Institute of Clinical Medicine, University of Bergen, Bergen, Norway*

^b *Fetal Medicine Unit, Department of Obstetrics and Gynaecology, Haukeland University Hospital, Bergen, Norway*

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Foramen ovale;
Liver

Summary Our understanding of fetal circulatory physiology is based on experimental animal data, and this continues to be an important source of new insight into developmental mechanisms. A growing number of human studies have investigated the human physiology, with results that are similar but not identical to those from animal studies. It is time to appreciate these differences and base more of our clinical approach on human physiology. Accordingly, the present review focuses on distributional patterns and adaptational mechanisms that were mainly discovered by human studies. These include cardiac output, pulmonary and placental circulation, fetal brain and liver, venous return to the heart, and the fetal shunts (ductus venosus, foramen ovale and ductus arteriosus). Placental compromise induces a set of adaptational and compensational mechanisms reflecting the plasticity of the developing circulation, with both short- and long-term implications. Some of these aspects have become part of the clinical physiology of today with consequences for surveillance and treatment.

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Introduction

Many of the mechanisms described in animal experiments also occur in the human fetus, but with differences. The reasons for variation are many, e.g. a sheep fetus has a different anatomy compared with a human fetus, with a longer intrathoracic inferior vena cava (IVC), a smaller

brain, the fetal liver is positioned differently, two umbilical veins, a higher temperature, a lower Haemoglobin (Hgb), a higher growth rate and a shorter pregnancy. Ultrasound in obstetrics has been used increasingly to provide physiological data from human fetuses, and this is reflected in the present review.

Blood volume

The blood volume in the human fetus is estimated to be 10–12% of the body weight, compared with 7–8%

* Department of Obstetrics and Gynaecology, Haukeland University Hospital, N-5021 Bergen, Norway. Tel.: +47 55974200; fax: +47 55974968.

E-mail address: torvid.kiserud@kk.uib.no

in adults.¹ The main reason for this difference is the large pool of blood contained within the placenta; a volume that reduces as gestation progresses. The calculated blood volume of 90–105 ml/kg in fetuses undergoing blood transfusion during the second half of pregnancy² is probably an underestimate. Other studies have indicated a volume of 110–115 ml/kg, which is more in line with experimental sheep studies.³ The estimated volume of 80 ml/kg contained within the fetal body is marginally more than that in adults. Compared with adults, the fetus is capable of much faster regulation and restoration of the blood volume due to high diffusion rates between fetal compartments.¹

Arterial and venous blood pressure

The mean arterial pressure in human fetuses was measured to be 15 mmHg during cordocentesis at gestational weeks 19–21.⁴ Intra-uterine recording of the intraventricular pressure in the human fetus suggests that the systemic systolic pressure increases from 15–20 mmHg at 16 weeks to 30–40 mmHg at 28 weeks.⁵ There was no obvious difference between the left and right ventricles. This increase was also seen for diastolic pressure, which was ≤ 5 mmHg at 16–18 weeks and 5–15 mmHg at 19–26 weeks.

Umbilical venous pressure, recorded during cordocentesis and corrected for amniotic pressure, increased from 4.5 mmHg at 18 weeks to 6 mmHg at term.⁶

Cardiac performance

Structural details of the heart are organized during the embryonic period but are dependent on the physical environment, including blood flow, in order to develop normally. The myocardium grows by cell division until birth, and growth beyond birth is due to cell enlargement. The density of myofibrils increases particularly in early pregnancy and the contractility continues to improve during the second half of pregnancy.⁷ The two ventricles perform differently in pressure/volume curves and when tested with intact peripheral vasculature.⁸ The fetal heart has limited capacity to increase stroke volume by increasing diastolic filling pressure, the right ventricle even less than the left, as they are already operating at the top of their function curves. The Frank–Starling mechanism does operate in the fetal heart, which is

apparent during arrhythmias.⁹ 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.

The two ventricles pump in parallel (Fig. 1) and the pressure difference between them is minimal compared with postnatal life.⁵ However, experimental studies show some variation in pressure and velocity waves between the two sides, ascribed to the difference in compliance of the great arteries and downstream impedance (upper body vs lower body and placenta).¹⁰ Some of the 'stiffness' of the fetal myocardium is attributed to the constraint of the pericardium, lungs and chest wall,¹¹ all of which have low compliance before 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 distribution

The fetal systemic circulation is fed from the left and right ventricles in parallel. The left ventricle is predominantly dedicated to the coronary circulation and upper body, while the right ventricle is the main distributor to the lower part of the body, the placenta and the lungs. When using outer-inner diameter measurements of the vessels, the combined cardiac output (CCO) is reported to be 210 ml/min at mid-gestation and 1900 ml/min at 38 weeks¹² (Table 1). When using inner diameters, these numbers are lower.¹³ The right ventricular output is slightly larger than that of the left ventricle, and pulmonary flow in the human fetus is larger (mean 13–25%) than in the classical fetal lamb studies ($\leq 10\%$). Interestingly, a developmental transition in fetal haemodynamics seems to occur at 28–32 weeks when the pulmonary blood flow reaches a maximum with a simultaneous change in oxygen sensitivity in the pulmonary vasculature.^{12,14} Another study found that less blood was distributed to the fetal lungs (11%),¹³ which is more in line with previous experimental studies.

The three shunts (ductus venosus, ductus arteriosus and foramen ovale) are essential distributional arrangements that make the fetal circulation a flexible and adaptive system for intra-uterine life. A classical concept describes the pathway of oxygenated blood as the *via sinistra* (Fig. 1) leaving the umbilical vein through the ductus venosus to reach the foramen ovale, left ventricle and aorta, thus feeding the coronary

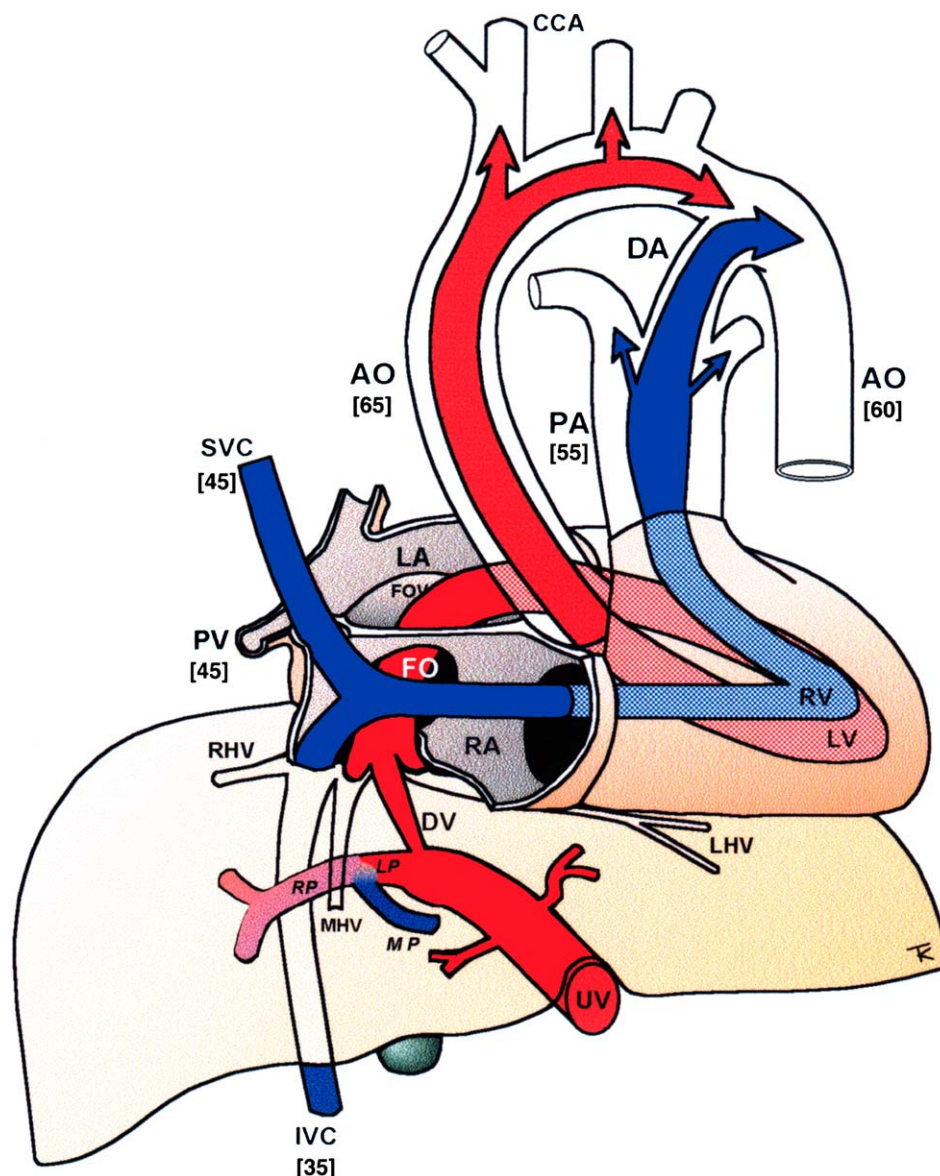


Figure 1 Pathways of the fetal heart and representative oxygen saturation values (in brackets). The via sinistra (red) directs well-oxygenated blood from the umbilical vein (UV) through the ductus venosus (DV) (or left half of the liver) across the inferior vena cava (IVC), through the foramen ovale (FO), left atrium (LA) and ventricle (LV) and up the ascending aorta (AO) to reach the descending AO through the isthmus aortae. De-oxygenated blood from the superior vena cava (SVC) and IVC forms the via dextra (blue) through the right atrium (RA) and ventricle (RV), pulmonary trunk (PA) and ductus arteriosus (DA). CCA, common carotid arteries; FOV, foramen ovale valve; LHV, left hepatic vein; LP, left portal branch; MHV, medial hepatic vein; MP, portal main stem; PV, pulmonary vein, RHV, right hepatic vein; RP, right portal branch. Copied and modified with permission from ref.¹⁶

and cerebral circuits. Conversely, a via dextra directs de-oxygenated blood from the caval veins through the tricuspid valve, pulmonary trunk and ductus arteriosus to reach the descending aorta, largely bypassing the pulmonary circuit.

Oxygen saturation gives a picture of distribution and blending of flows in the central fetal circulation (Fig. 1). The lowest saturation is found in the abdominal IVC, and the highest saturation is found in the umbilical vein.¹⁰ Interestingly, the

difference between the left and right ventricles is only 10%, and this increases to 12% during hypoxaemia. The small difference between the left and right ventricles is due to the abundant volume of oxygenated blood presented to the foramen ovale. In addition to the ductus venosus blood flow, the umbilical blood passing through the liver has had a modest reduction in saturation and represents another sizeable volume of oxygenated blood flowing in much the same direction as the ductus

Table 1 Combined cardiac output and distribution in human fetuses during the second half of pregnancy according to Rasanen et al.¹²

	% 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	25	21
Ductus arteriosus	40	32	39

venous towards the foramen ovale. In addition to some blending, the abundance of oxygenated blood will cause a spillover to the right side when reaching the foramen ovale with its crista dividens (limbus) (Fig. 2).

Ductus venosus and liver circulation

In the human fetus, the 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 of the ductus venosus, the isthmus, is the restrictive area with a mean diameter of 0.5 mm at mid-gestation and hardly exceeds 2 mm for the rest of a normal pregnancy.^{15,16} The umbilical venous pressure ranges from 2 to 9 mmHg⁶ (the portocaval pressure gradient), and causes the blood to accelerate from a mean of 10–22 cm/s in the umbilical vein to 60–85 cm/s as it enters the ductus venosus and flows towards the IVC and foramen ovale.^{17,18} The blood flow with the highest oxygenation, coming from the ductus venosus, also has the highest kinetic energy in the IVC and predominantly presses open the foramen ovale valve to enter the left atrium, i.e. the 'preferential streaming' described in animal studies.¹⁹

While 30% of the umbilical blood is shunted through the ductus venosus at mid-gestation, this fraction is reduced to 20% at 30 weeks and remains so for the rest of the pregnancy, but with wide variations (Fig. 3).¹⁶ These results are similar to those of another study,²⁰ but are at variance with experimental animal studies, admittedly using a different technique, which showed that approximately 50% was shunted through the ductus venosus.^{19,21} The redistributive mechanisms of increased shunting during hypoxaemia described in animal experiments also seem to operate in the human fetus.^{22,23}

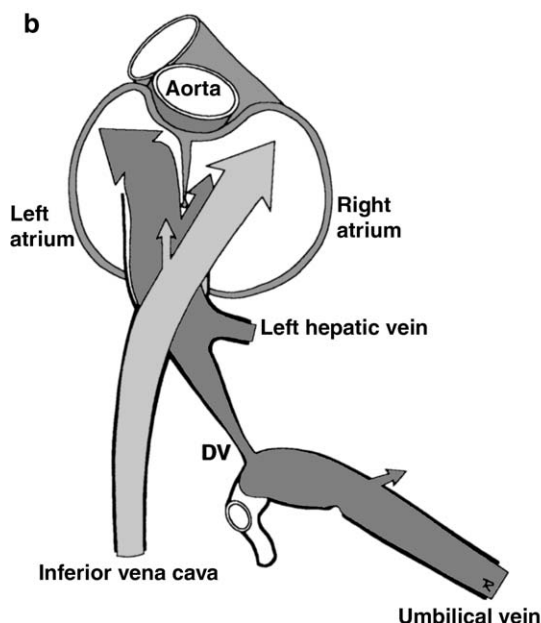
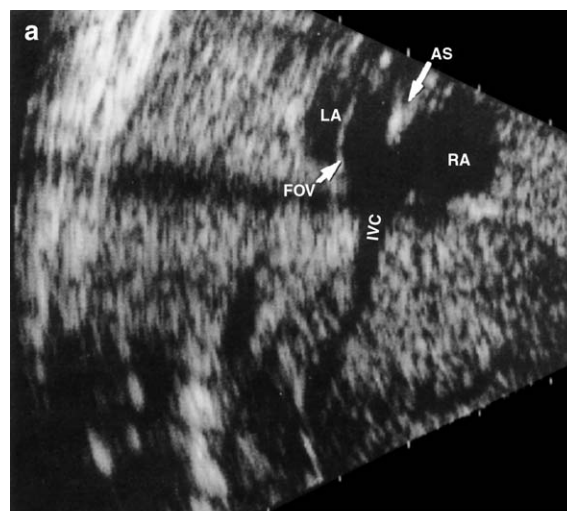


Figure 2 The foramen ovale acts as a flow distributor of the inferior venous inlet. (a) Ultrasound scan shows the inferior vena cava (IVC) and left and right atria (LA, RA). The atrial septum (AS) with its crista dividens (postnatal: limbus) faces the inlet of the IVC to divide the ascending column of blood. The terminal portion of the IVC expands, more to the left side, to receive blood from the liver and ductus venosus (DV). The high velocity, its position to the left and steep direction (b) makes the DV blood preferentially press open the foramen ovale valve (FOV) to enter the LA. IVC blood directed more anteriorly arrives predominantly in the RA. Increased pressure in LA or a premature apposition of FOV to the AS would divert more blood to the right. Reproduced with permission from ref.³⁶

The ductus venosus is under tonic adrenergic control, and distends under the influence of nitric oxide and prostaglandins.^{24,25} The most extensive dilatation is seen during hypoxaemia, leading to

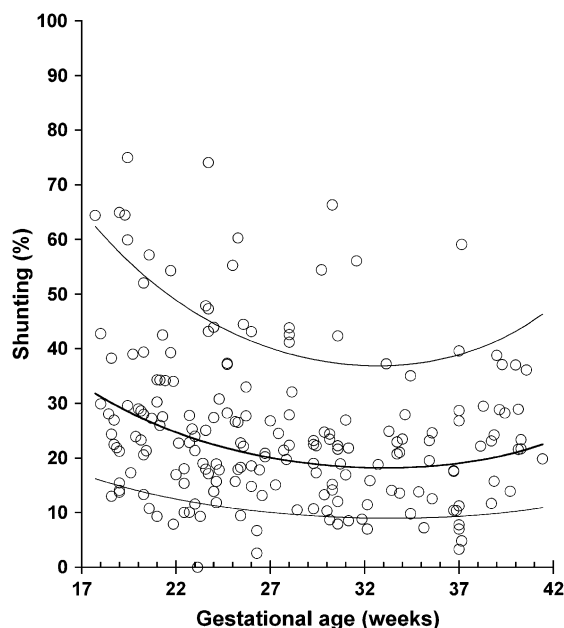


Figure 3 The fraction of umbilical venous return shunted through the ductus venosus in low-risk pregnancies is 30% at mid-gestation but approximately 20% at 30–40 weeks, signifying the developmental importance of the fetal liver receiving 70–80% of the umbilical blood. Reproduced with permission from ref.¹⁶

a 60% increase of the diameter in fetal sheep.²⁵ However, the changes in diameter are not restricted to the isthmus but also include the entire length of the vessel, which has a far greater impact on resistance.^{25,26} The shunt obliterates within 1–3 weeks of birth in term infants, although this takes longer in premature births and in cases with persistent pulmonary hypertension or cardiac malformation.^{27–29} In contrast to the ductus arteriosus where increased oxygen tension triggers the closure, no trigger has been found for the ductus venosus.²⁴

Equally important to the active regulatory mechanism is the passive regulation based on fluid dynamics, i.e. viscosity and pressure.³⁰ Blood velocity in the ductus venosus is high and has Newtonian properties with low viscosity (similar to water). In contrast, liver tissue represents a huge capillary cross-section with a low blood velocity. At low velocities, the blood is non-Newtonian with an accordingly high viscosity (and resistance) and a closing pressure of 1–4 mmHg. It follows that an increase in haematocrit leads to increased viscous resistance in the low-velocity venous liver flow and has little effect on the high-velocity flow in the ductus venosus. Thus, the change in haematocrit alone leads to a shift of umbilical venous flow from the liver to the ductus venosus.

Along the same lines, variation in the umbilical venous pressure affects the two pathways differently.³⁰ A reduction in venous pressure reduces liver perfusion more than ductus venosus flow, as a further reduction in an already low velocity in the large cross-section of the portal vasculature implies a considerable increase in viscous resistance. The result is a higher degree of shunting.

In addition to these fluid dynamic determinants, the neural and endocrine regulation of the hepatic vascular bed also play a role.³¹ The portal vasculature shows a more pronounced constricting response to adrenergic stimulation compared with the ductus venosus.³² It all combines to make a distribution system that is extremely sensitive to both active and passive regulation, which is in line with the substantial normal variation of shunting seen in human fetuses.^{16,33}

The physiological role of the ductus venosus is not well understood. The shunting seems more prominent in early pregnancy than after 30 weeks of gestation. The low degree of shunting through the ductus venosus during the last 8–10 weeks of pregnancy implies that approximately 80% of the umbilical blood perfuses the liver, signifying a very high developmental priority of the umbilical liver perfusion compared with the ductus venosus.¹⁶ However, during hypoxic challenges, the priority seems to be different. Fetuses maintain a higher degree of ductus venosus shunting, probably as a redistributive adaptation to hypoxic pressure, ensuring oxygenation of the heart and brain.²¹ The cost for responding to such needs could be permanently altered liver development.³⁴

It should be borne in mind that oxygen extraction in the liver is rather modest (10–15% reduction in oxygen saturation),³⁵ which means that blood coming from the median and left hepatic vein are important contributors of oxygenated blood. Actually, the position and direction of the left hepatic venous blood under the Eustachian valve (IVC valve) favour this blood to be delivered at the foramen ovale.³⁶

Although agenesis of the ductus venosus has been linked to abnormalities and fetal demise,³⁷ agenesis is also found in fetuses that have exhibited normal growth.¹⁶ Experimental obliteration of the vessel seems to have little haemodynamic effect,³⁸ but causes an increase in insulin-like growth factor 2 and increases the growth of fetal organs.³⁹ Recent studies have indicated that the fetal umbilical flow to the liver towards the end of pregnancy is influenced by the maternal nutritional state and diet.⁴⁰ Umbilical venous flow constitutes 75% of the venous supply to the liver, with the remaining 25% coming from the main portal

stem.⁴¹ In human fetuses, the arterial supply to the liver is not known but it seems to have a more prominent role during compromise.⁴²

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.^{43,44} Increased pulsatility, mainly caused by the augmented atrial contraction wave, signifies increased atrial contraction due to adrenergic drive, or increased venous filling pressure, or both.

In early pregnancy, the augmented a-wave in the ductus venosus is associated with an increased risk of chromosomal aberration and has been suggested as a secondary screening test.^{45,46}

Foramen ovale

A defect in the atrial septum is commonly associated with left-right or right-left shunting in post-natal life. It is conceivable that this concept is carried over to describe the function of the foramen ovale in the fetus,⁴⁷ but this is not a fair representation of the actual haemodynamics. Rather, the inferior venous inlet to the heart should be viewed as a column of blood that ascends between the two atria from below.^{36,48} This column hits the interatrial ridge, the crista dividens, and is divided into a left and right arm (Fig. 2). The left arm fills the 'windsock', formed between 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*.

This is an equilibrium easily influenced by changes in pressure on the two sides. Increased

resistance and pressure of the left side is instantaneously reflected in increased diversion of blood to the right side. In contrast to the hypertrophy of the left ventricle seen in aortic stenosis in adults, fetal stenosis commonly leads to a shift of blood volume from left to right at the level of the foramen ovale, with corresponding development of left-sided hypoplasia and 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 foramen ovale is an important limiting factor, particularly in cases of a maldeveloped foramen or a premature closure.⁴⁹ Under physiological conditions, it is not the oval-shaped hole of the septum that constitutes the restricting area for the flow to the left atrium, but the horizontal area between the foramen ovale valve and the atrial septum above the foramen ovale.⁵⁰ Interestingly, the growth of this area is somehow blunted after 28–30 weeks of gestation compared with the cross-section of the IVC. This effect coincides with changes in fetal lung perfusion¹² and ductus venosus shunting,¹⁶ and may signify a transition into a more mature circulatory physiology.

Ductus arteriosus and pulmonary circulation

The ductus arteriosus constitutes a wide muscular vessel connecting the pulmonary arterial trunk to the descending aorta (Fig. 4).⁵¹ During the second trimester, the velocity in the ductus arteriosus increases more than that in the pulmonary trunk, reflecting the development of the wind-kessel function of the pulmonary trunk.⁵² During the

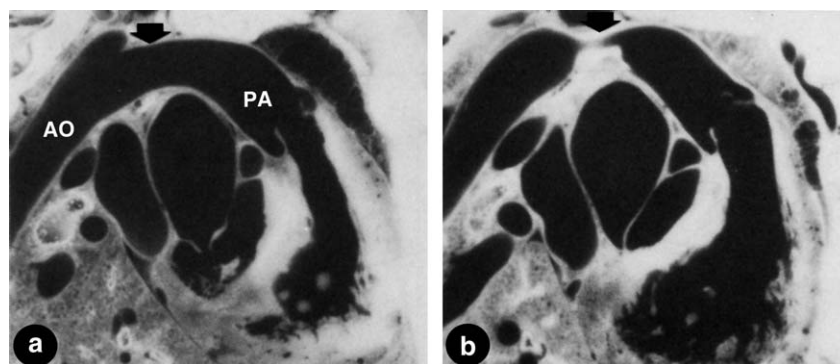


Figure 4 (a) The ductus arteriosus (arrow) is a sizeable connection between the pulmonary trunk (PA) and the aorta (AO) in fetal rats. (b) Indomethacin induces severe constriction. Reproduced with permission from ref.⁵¹

second half of pregnancy, 40% or less of the CCO is directed through the ductus arteriosus^{12,13} (Table 1). The lungs receive 13% of the CCO at mid-gestation and 20–25% after 30 weeks,¹² which is more than that reported in fetal sheep experiments¹⁰ and a more recent human study.¹³ Normally, the shunt closes 2 days after birth,⁵³ but a patent duct is a common clinical problem. An increase in oxygen tension is regarded as the main trigger for its closure.²⁴ The vessel is under the general influence of circulating substances, particularly prostaglandin E₂, which is crucial in maintaining patency.⁵⁴ Sensitivity to prostaglandin antagonists is at its highest in the third trimester and is enhanced by glucocorticoids and fetal stress.⁵⁵ Nitric oxide has a relaxing effect prior to the third trimester. The increased reactivity of the ductus arteriosus in the third trimester makes it vulnerable to prostaglandin synthase inhibitors, such as indomethacin, which may cause severe and longlasting constriction.^{55,56}

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 the control of prostaglandin I₂ and modified by a series of substances.²⁴ In an elegant study, Rasanen et al. showed how reactivity in the pulmonary vascular bed increased in the third trimester.¹⁴ While fetuses at gestational age 20–26 weeks showed no changes during maternal hyperoxygenation, fetuses at 31–36 weeks had lower impedance in the pulmonary arteries assessed by the pulsatility index, and increased pulmonary blood flow. Correspondingly, the blood flow in the ductus arteriosus was reduced.

Brain circulation

Differences in circulation physiology between animal experiments and human fetuses are likely to be greatest when concerning the brain, as the human brain is relatively larger than in other species. In a study of human previable fetuses weighing 12–272 g (probably corresponding to 10–20 weeks of gestation), it was found that the brain received approximately 15% of the systemic venous return (equal to the CCO less the pulmonary circuit).³³ The proportion directed to the brain increased with low arterial pH, increased pCO₂ and reduced placental perfusion. A study of the primate *Macaca mulatta* at an advanced stage of gestation found that 16% of the CCO was distributed to the brain, and this fraction increased to 31% during hypoxic challenge.²¹ Both of these studies

reflect redistributive preferences to the brain during hypoxaemia and acidosis. Clinical obstetrics has taken advantage of such 'brain-sparing' mechanisms, and uses the increased diastolic blood velocity recorded in the middle cerebral artery as a marker of compensatory redistribution of blood to the brain.⁵⁷

Fetoplacental circulation

In the fetal sheep, 45% of the CCO is directed to the umbilical arteries and placenta.⁵⁸ This percentage is less in exteriorized human fetuses, but it increases from 17% at 10 weeks to 33% at 20 weeks of gestation.³³ These results overestimate the placental fraction as the CCO calculation was based on systemic venous return, not including the pulmonary venous return. Secondly, the measurements were not performed under strict physiological conditions. Doppler studies of low-risk pregnancies have found similar results; one-third of the fetal CCO is directed to the placenta at 20–32 weeks of gestation,^{59,60} but this decreases to approximately one-fifth beyond 32 weeks of gestation.⁶⁰

The introduction of Doppler ultrasound made it possible to assess umbilical venous blood flow⁶¹ in the human fetus in utero. Recent longitudinal observations in low-risk pregnancies have found that the umbilical blood flow increases from a mean of 36 ml/min at 20 weeks to 265 ml/min at 40 weeks of gestation.⁶² Umbilical flow normalized for fetal weight is at its highest (117 ml/min/kg) at 25 weeks and at its lowest at 41 weeks (63 ml/min/kg) of gestation. These results are in accordance with earlier studies applying thermodilution at birth.⁶³ The fact that human umbilical flow is considerably lower than that in the fetal sheep is not disconcerting as fetal sheep have a higher growth rate, a higher temperature and a lower Hgb.

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 effect⁶⁴ and nitric oxide has a vasodilatory effect,⁶⁵ but the exact role of humoral regulation is not fully understood.⁶⁶ Placental blood flow has been found to be fairly stable and chiefly determined by arterial blood pressure.¹⁰ The substantial increase in the vascular cross-section during late gestation accounts for a reduction in impedance and the corresponding fall in umbilical artery pulsatility seen in longitudinal studies.⁶⁷ Placental vasculature is believed to account for 55% of the umbilical

resistance.⁶⁸ The waveform recorded by Doppler measurement in the umbilical artery reflects this downstream impedance and is used extensively to identify placental compromise.⁶⁹

Watershed areas and the compromised circulation

The watershed area in the brain circulation has long been used to explain certain lesions of neonates, and a concept of a watershed at the isthmus of the aorta, the left portal vein and the foramen ovale with its crista dividens has been proposed recently.

It has long been known that fetuses with critical aorta stenosis or hypoplastic left heart syndrome direct ductus arteriosus blood in a retrograde direction through the isthmus aortae to feed the aortic arch. Recent studies have highlighted the isthmus aortae as a watershed between the aortic arch and the ductus arteriosus in anatomically normal fetuses.^{70,71} 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 with various degrees of reversed flow was suggested to be an indicator of placental compromise.

Similarly, the direction of flow in the left portal vein (Fig. 1) is suggested to reflect compromised venous return demanding a compensatory increase of blood from the main portal stem to maintain portal and umbilical pressure, with the result being a cessation of umbilical venous flow to the left portal branch, and, at a more advanced stage of compromise, reversed flow that permits splanchnic blood to enter the ductus venosus.⁷²

A third watershed, the foramen ovale (Fig. 2), differs from the two former watersheds. It distributes blood to the left and right atria by dividing the ascending venous blood into two arms at the crista dividens. The horizontal area between the foramen ovale valve and the atrial septum is thought to be the restricting area for flow to the left atrium.⁵⁰ In cases with increased venous return (e.g. arteriovenous malformation), an increased volume of blood is diverted to the right side, leading to increased growth of the right ventricle. In cases of abnormally small foramen ovale, the left side of the heart develops less in size (one of the possible mechanisms leading to hypoplastic left heart syndrome).

These concepts are in need of detailed studies to make them clinically relevant.

Circulatory regulation

Circulatory responses to hypoxaemia and hypovolaemia have been particularly well studied in animals during the last trimester of pregnancy,⁷³ 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 insults.^{74,75} A hypoxic insult in late pregnancy activates a chemoreflex mediated by the carotid bodies (and, to a lesser extent, the aortic bodies), causing an immediate vagal effect with reduced heart rate and a sympathetic vasoconstriction.⁷⁶ This is followed by endocrine responses (e.g. adrenaline 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 mechanisms, and increased concentrations of adrenocorticotrophic hormone, cortisol, atrial natriuretic peptide, neuropeptide Y and adrenomedullin orchestrate a circulatory redistributive pattern that maintains placental circulation and gives priority to the adrenal glands, myocardium and brain⁷³ (Fig. 5). In clinical medicine, this translates into a frequently visualized coronary circulation,⁷⁷ a shift in left–right ventricular distribution,⁷⁸ a cerebral circulation with high diastolic flow,⁵⁷ and an increased impedance in the pulmonary circulation⁷⁹ during circulatory compromise.

Sustained hypoxia forces an adaptational shift to less oxygen demand, reduced DNA synthesis

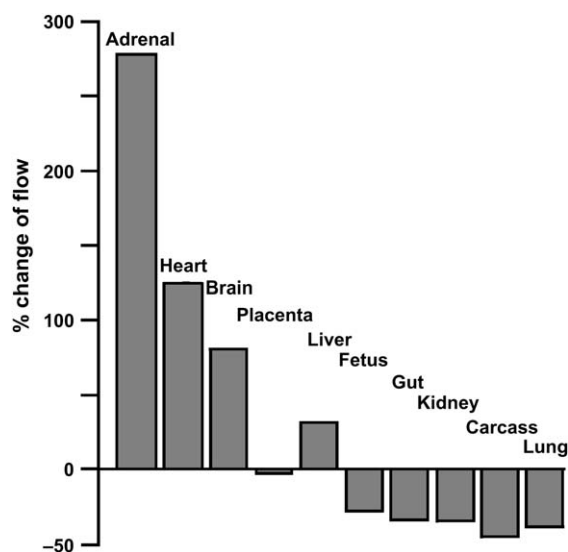


Figure 5 Redistribution of fetal combined cardiac output during acute hypoxaemia caused by reduced uterine blood flow. Based on ref.⁵⁸

and growth, with a gradual return towards normal concentrations of blood gases and endocrine status,⁸⁰ although with a residual deviation that may have a longlasting effect on 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.⁸¹

Practice points

- Which of the two ventricles takes a larger volume load?
- From where comes the blood in the left atrium?
- How much of the umbilical venous return is shunted through the ductus venosus in the human fetus?
- In what sense is the aortic isthmus a watershed?

Research directions

- More information on human fetal circulation is expected to substitute animal experimental studies as the basis for clinical medicine.
- More detailed adaptational pattern is expected to give a better background for fetal surveillance.
- More detailed knowledge of human fetal responses and adaptation is expected to unveil the mechanisms involved in in utero conditioning of health risk in adult life.

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