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The fetal venous system, Part I: normal embryology, anatomy, hemodynamics, ultrasound evaluation and Doppler investigation

S. YAGEL*#, Z. KIVILEVITCH†#, S. M. COHEN*, D. V. VALSKY*, B. MESSING*, O. SHEN* and R. ACHIRON‡

**Obstetrics and Gynecology Ultrasound Center, Hadassah-Hebrew University Medical Centers, Mt Scopus, Jerusalem, †Ultrasound Unit, Negev Medical Center, Macabbi Health Services, Beer Sheba and ‡Ultrasound Unit, Department of Obstetrics and Gynecology, Chaim Sheba Medical Center, Tel Hashomer and Sackler School of Medicine, Tel Aviv, Israel*

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ABSTRACT

Since its introduction in the mid-1980s sonographic evaluation of the human fetal venous system has advanced dramatically. The venous system is well-recognized as a target for investigation in cases of circulatory compromise, and a broad spectrum of malformations affecting this system has been described. Appreciation of the normal embryology, anatomy and physiology of this system is essential to an understanding of structural anomalies and the sequential changes encountered in intrauterine growth restriction or other developmental disorders. We review the normal embryology, anatomy, and hemodynamics of the human fetal venous system, and provide an overview of Doppler investigation, as well as three- and four-dimensional ultrasound modalities and their application to this system. Copyright © 2010 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Sonographic investigation of the fetal venous system has developed rapidly since its introduction in the mid-1980s. Elucidation of normal venous anatomy, its role in normal fetal development and in the evaluation and management of intrauterine growth restriction, and other cardiovascular disorders, as well as its association as a part of complex structural anomalies, are the subjects of intensive research.

In addition to recognition of the normal and anomalous sonographic appearance of the fetal venous system, knowledge of its embryology and physiology is vital to better inform our management decisions, and provide appropriate parental counseling when an anomaly is encountered.

In this two-part review, Part I will comprise the embryology of the fetal venous system, continuing with normal fetal anatomy and hemodynamics, Doppler investigation of various vessels, and finally the application of three- and four-dimensional ultrasound (3D/4D-US) technology to this system. Part II will cover pathophysiology, the embryological basis and ultrasound appearance of anomalies, and Doppler flow studies in circulatory compromise, as well as 3D/4D-US in the evaluation of fetal venous malformations.

EMBRYOLOGY OF THE HUMAN VENOUS SYSTEM

The cardiovascular system is the first organ system to develop in the human embryo, and the heart begins to beat by day 23 of embryonic development. Three symmetric paired veins form the basis of the early venous system in the 4-week embryo (6 weeks' menstrual age (MA)), draining into the heart: the umbilical veins (UVs), vitelline veins (VVs) and cardinal veins (CVs). The UVs drain the chorion, the VVs the yolk sac, and the CVs the body of the embryo. All three pairs open to the right and left horn of the sinus venosus. Also at this stage the liver buds begin to develop from the ventral endodermal wall of the foregut. These cells invade mesenchymal tissue, called the septum transversum,

Correspondence to: Prof. S. Yagel, Hadassah University Hospital, Mt Scopus - Obstetrics and Gynecology, PO Box 24035, Jerusalem, Mt Scopus 91240, Israel (e-mail: simcha.yagel@gmail.com)

#S.Y. and Z.K. contributed equally to this article.

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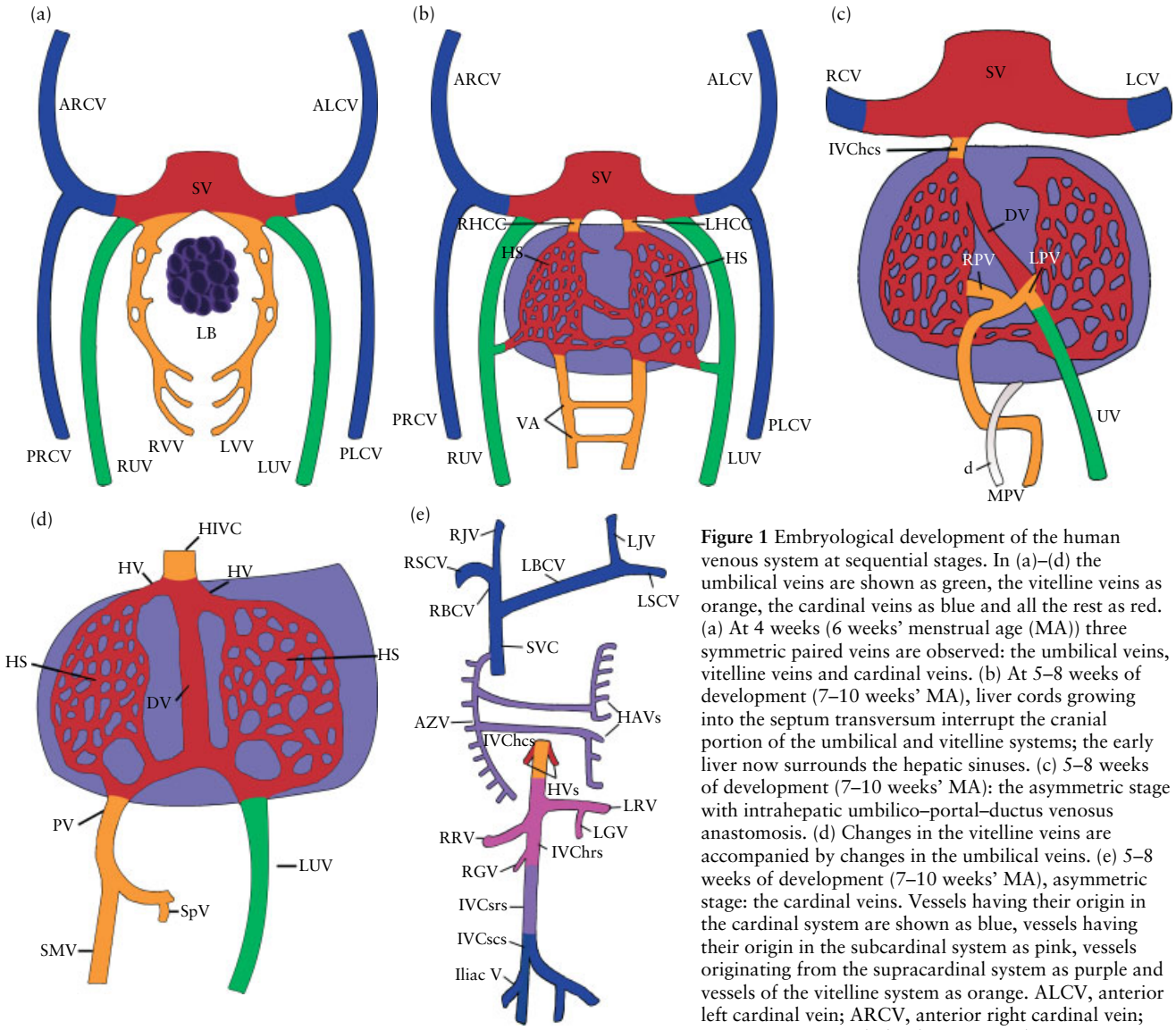

Figure 1 Embryological development of the human venous system at sequential stages. In (a)–(d) the umbilical veins are shown as green, the vitelline veins as orange, the cardinal veins as blue and all the rest as red. (a) At 4 weeks (6 weeks' menstrual age (MA)) three symmetric paired veins are observed: the umbilical veins, vitelline veins and cardinal veins. (b) At 5–8 weeks of development (7–10 weeks' MA), liver cords growing into the septum transversum interrupt the cranial portion of the umbilical and vitelline systems; the early liver now surrounds the hepatic sinuses. (c) 5–8 weeks of development (7–10 weeks' MA): the asymmetric stage with intrahepatic umbilico–portal–ductus venosus anastomosis. (d) Changes in the vitelline veins are accompanied by changes in the umbilical veins. (e) 5–8 weeks of development (7–10 weeks' MA), asymmetric stage: the cardinal veins. Vessels having their origin in the cardinal system are shown as blue, vessels having their origin in the subcardinal system as pink, vessels originating from the supracardinal system as purple and vessels of the vitelline system as orange. ALCV, anterior left cardinal vein; ARCV, anterior right cardinal vein; AZV, azygos vein; d, duodenum; DV, ductus venosus; HAVs, hemiazygos vein; HIVC, hepatic portion of the inferior vena cava; HS, hepatic sinus; HV(s), hepatic vein(s); Iliac V, iliac veins; IVChcs, inferior vena cava hepatocardiac segment; IVChrs, inferior vena cava hepatorenal segment; IVCscs, inferior vena cava sacrocardinal segment; IVCsrs, inferior vena cava sacrorenal segment; LB, liver buds; LBCV, left brachiocephalic vein; LCV, left cardinal vein; LGV, left gonadal vein; LHCC, left hepatic common cardinal vein; LJV, left jugular vein; LPV, left portal vein; LRV, left renal vein; LSCV, left subclavian vein; LUV, left umbilical vein; LVV, left vitelline vein; MPV, main portal vein; PLCV, posterior left cardinal vein; PRCV, posterior right cardinal vein; PV, portal vein; RBCV, right brachiocephalic vein; RCV, right cardinal vein; RGV, right gonadal vein; RHCC, right hepatic common cardinal vein; RJV, right jugular vein; RPV, right portal vein; RRV, right renal vein; RSCV, right subclavian vein; RUV, right umbilical vein; RVV, right vitelline vein; SMV, superior mesenteric vein; SpV, splenic vein; SV, sinus venosus; SVC, superior vena cava; UV, umbilical vein; VA, vitelline anastomoses. (Modified from Sadler[1] and Moore and Persaud[2]).

which will form the connective tissue of the future liver (Figure 1a)[1–3].

At between 4 and 6 weeks (6–8 weeks' MA), a complex pattern of vessel growth, anastomosis, and asymmetric degeneration occurs. The VV and UV systems, which represent the afferent venous vessels of the liver, are modified by their proximity to the developing liver in the septum transversum. The liver cords growing into the septum transversum interrupt the cranial portion of both veins between the liver and the heart with an extensive vascular network – the hepatic sinusoids. The growing hepatic sinusoids first become linked to both VVs, and by day 32 have tapped into the UV (Figure 1b).

By the 5th week of development (7th week MA), the left cranial part of the VV atrophies and disappears. The remaining right proximal VV, which will give rise to the hepatocardiac segment of the inferior vena cava (IVC), is connected to the intrahepatic efferent veins – the left (LHV), middle (MHV) and right (RHV) hepatic veins. Meanwhile, distal sections of the left and right VVs and the anastomoses between them become the portal vein (PV), while other segments of the right and left VVs collapse and disappear (Figure 1c).

These changes in the VVs are accompanied by changes in the UVs. The entire right UV and the left cranial segment of the left UV will atrophy and disappear; the left UV becomes the dominant conduit of blood from the placenta. During the 8th week of development (10th week MA), the intrahepatic portion of the VV, and more specifically the left portal branch, forms an anastomosis between the intrahepatic segment of the left UV and the ductus venosus (DV), which is formed by the coalescence of the hepatic sinusoids and drains into the hepatocardiac segment of the IVC (Figure 1d).

The CVs drain the embryo body, with the anterior and posterior ones draining the cranial and caudal parts of the body, respectively. Both veins empty into the common CVs – the third venous system entering the sinus venosus of the embryonic heart (Figure 1a). From the 5th week of development (7th week MA) the posterior branches are obliterated and only the most caudal part persists, giving rise to the common iliac vein and the most caudal segment of the IVC, the sacral segment. They are replaced by two pairs of veins, the subcardinal and the supracardinal veins. The subcardinal vein drains the kidney and gonads. By the 9th–10th week MA, the proximal left subcardinal vein obliterates and connects with the right branch, which then forms the renal–hepatic (suprarenal) segment of the IVC.

The supracardinal veins drain the thoracic wall and the iliac veins. The inferior portion of the left supracardinal vein obliterates and connects to the right subcardinal vein, forming the sacrorenal (prerenal) segment of the IVC. The superior segment of the supracardinal vein is divided into the left branch, called the hemiazygos vein, which forms a cross anastomosis to the right branch, called the azygos vein, which drains into the superior vena cava (SVC) (Figure 1e).

The IVC is, therefore, formed from four different embryonic sources in a caudocranial order (the first three have their origin from the posterior CV):

1) The most caudal, sacrocardinal segment is formed from the posterior CV;
2) The prerenal, sacrorenal segment from the right supracardinal vein;
3) The suprarenal, hepatic renal segment from the right subcardinal vein; and
4) The most cranial, hepatocardiac segment originates from the right VV.

During the same period the proximal left anterior CV regresses and disconnects from the sinus venosus. A shunt to the right anterior CV is then created, forming the left brachiocephalic vein. The right anterior CV is transformed into the right brachiocephalic vein. The segment between the junction of the left and right brachiocephalic veins and the right atrium develops meanwhile into the SVC.

Within the developing fetal liver afferent and efferent venous networks develop. The afferent system includes the UV, PV and DV, while the efferent comprises the hepatic veins. They form two apposing systems in the caudal and cranial portions of the liver, respectively (Figure 2)[1,3–5].

The pulmonary veins

During the 4th week of embryonic development (6th week MA, 4-mm embryo) blood coming from the developing lungs drains into the splanchnic plexus and then to the common CVs and the UV and VVs. These connections are maintained until the beginning of the 5th week, when the first pulmonary vein appears as a single dorsal invagination of the left atrium and meets the pulmonary venous plexus. This process continues, and as the atrial cavity develops through the 5th embryonic week, two right and two left branches of the pulmonary stem enter the atrial cavity via four orifices. These veins anastomose with the veins developing from the pulmonary mesoderm to form the definitive pulmonary veins[1,3]. The pulmonary venous plexus gradually loses its connection to the VVs and CVs.

Fetal venous anatomy

In the fetus oxygen- and nutrient-rich blood from the placenta is delivered through the UV and DV to the fetal heart. The intra-abdominal segment of the UV courses via the falciform ligament to merge with the left portal vein (LPV). This segment is also known as the umbilical segment of the LPV. It is similar in diameter to the LPV and is usually wider than the right portal vein (RPV). The intrahepatic point of separation between the UV and the PV is represented by the inferior branch of the LPV (LPVi)[4].

The LPV gives rise to the DV, which is aligned with the UV, just before turning almost 90° to the right to join the RPV. This portion of the LPV is also known as the pars transversa or portal sinus (PS), and it extends from the LPVi to the point of bifurcation of the main portal vein (MPV) to the RPV. The DV connects to the IVC distally, together with the LHV and MHV, just proximal to the entrance into the right atrium (Figure 2)[4].

The DV is a branchless, hourglass-shaped vessel narrowing to 1–2 mm, approximately one third of the width of the UV. Some investigators report a 'sphincter' regulating blood flow through the DV; an oxygen concentration-dependent mechanism may control the activity of this sphincter[6,7]. However, Mavrides *et al.*[8] in their histological study demonstrated that this narrowing zone consists of a multi-layered[4,8] shelf-like stricture, made of elastin, with no sphincter formation[4,8]. The rest of the DV is covered by a single layer of muscular elastin, and endothelial cells.

The RPV receives poorly oxygenated blood, primarily through the MPV. The greater volume and higher oxygen content of blood flowing through the left lobe of the liver as compared to the right results in a noticeably larger left than right lobe during fetal life. When the UV and DV atrophy after birth this situation is reversed.

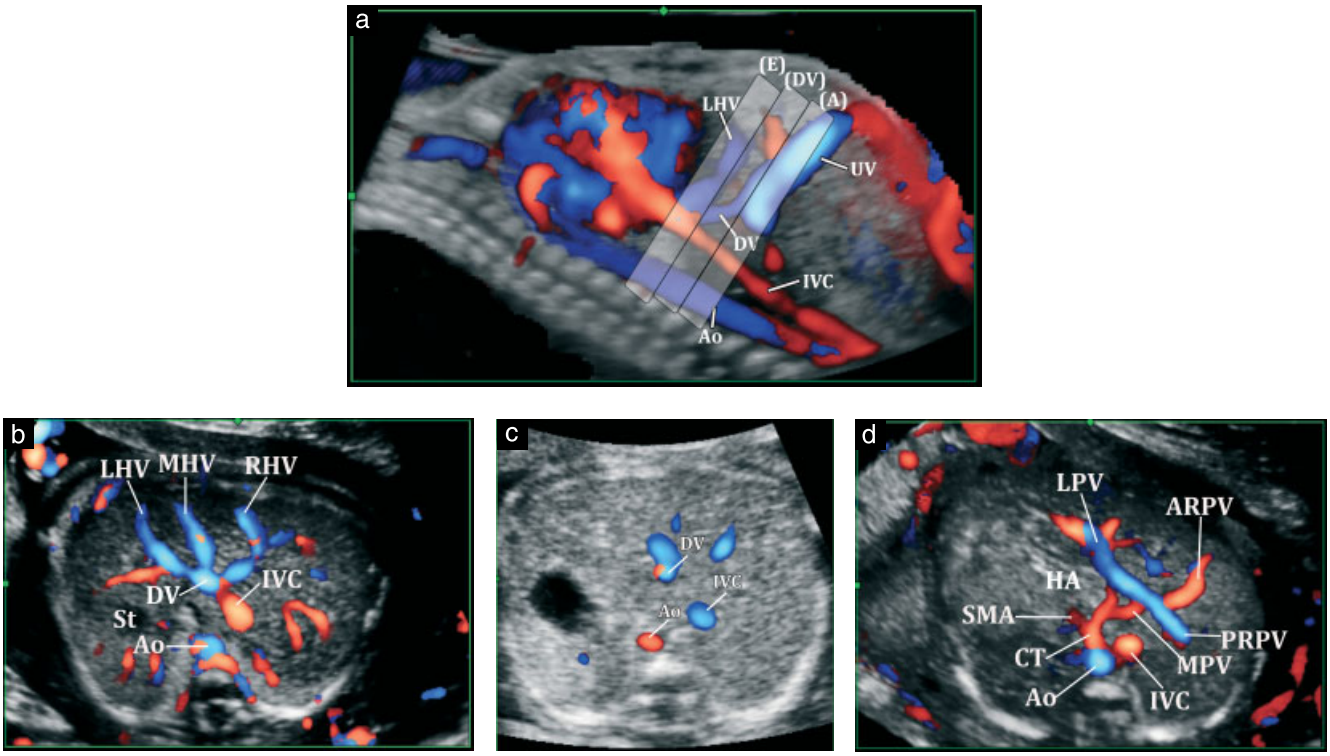

Figure 2 High-definition power flow Doppler imaging of the fetus in the mid-trimester, showing the normal fetal liver circulation as it appears from the end of the first trimester onwards. (a) Sagittal plane. Rectangles mark the planes of insonation for imaging the efferent (Rectangle [E]) and afferent (Rectangle [A]) venous systems and the mediating ductus venosus (DV) plane (Rectangle [DV]). (b–d) Transverse views of: hepatic (efferent) venous system (b), the DV plane, which links afferent and efferent systems (c) and the portal (afferent) venous system (d). Ao, aorta; ARPV, anterior right portal vein; CT, celiac trunk; HA, hepatic artery; IVC, inferior vena cava; LHV, left hepatic vein; LPV, left portal vein; MHV, middle hepatic vein; MPV, main portal vein; PRPV, posterior right portal vein; RHV, right hepatic vein; SMA, superior mesenteric artery; St, stomach; UV, umbilical vein.

The fetal portal system

Within the developing fetal liver two apposed venous systems develop, the afferent and efferent. The afferent venous system of the fetal liver (the UV, PV, PS and DV) and the efferent venous system (the hepatic veins) form two systems positioned in the caudal and cranial portions of the liver, respectively[4,5].

The MPV enters the liver in the porta hepatis or main fissure, posterior to the hepatic artery and the common hepatic duct. This fissure divides the liver into its right and left lobes. The site of connection of the MPV to the PS represents the anatomic point of division between its right and left branches, and is situated to the right and inferiorly to the origin of the DV.

The LPV is divided into three main branches – the inferior, superior and medial, (LPVi, LPVs and LPVm, respectively) – and lies approximately at the level of the origin of the LPVi. The right branch of the MPV becomes the RPV and bifurcates into two major branches, the anterior and posterior right portal veins (ARPV and PRPV, respectively), at varying distance from the MPV–PS junction (Figure 2).

The junction of the MPV and the PS displays a continuum of morphologic variation in the angle of communication, ranging from 90° to a completely parallel course and a disjunction of two paired vessels, the MPV/PRPV and LPV/ARPV, connected only by a thin bridging vessel. Among the variations three main subtypes can be identified[9,10]:

1) T-shaped, end-to-side anastomosis (the most common, identified in 68% of cases);
2) X-shaped, side to side anastomosis (12% of cases); and
3) H-shaped, parallel anastomosis (15% of cases) (Figure 3)[10].

The hepatic veins

The efferent venous drainage of the liver is situated topographically superiorly and apposed to the afferent system. It is trident-shaped and consists of three main hepatic veins – the RHV, LHV and MHV. The hepatic veins course anteriorly to the DV and open to the subdiaphragmatic vestibulum, a funnel-shaped dilatation of the hepatocardiac IVC segment. The vestibulum continues through the diaphragm to the right atrium[6]. Sonographically, all three branches can be depicted in the same plane, using a coronal, oblique, downward projection, as shown in Figure 2d.

Hemodynamics of the fetal venous system

The main function of the fetal venous system is to deliver blood rich with oxygen and nutrients from the placenta

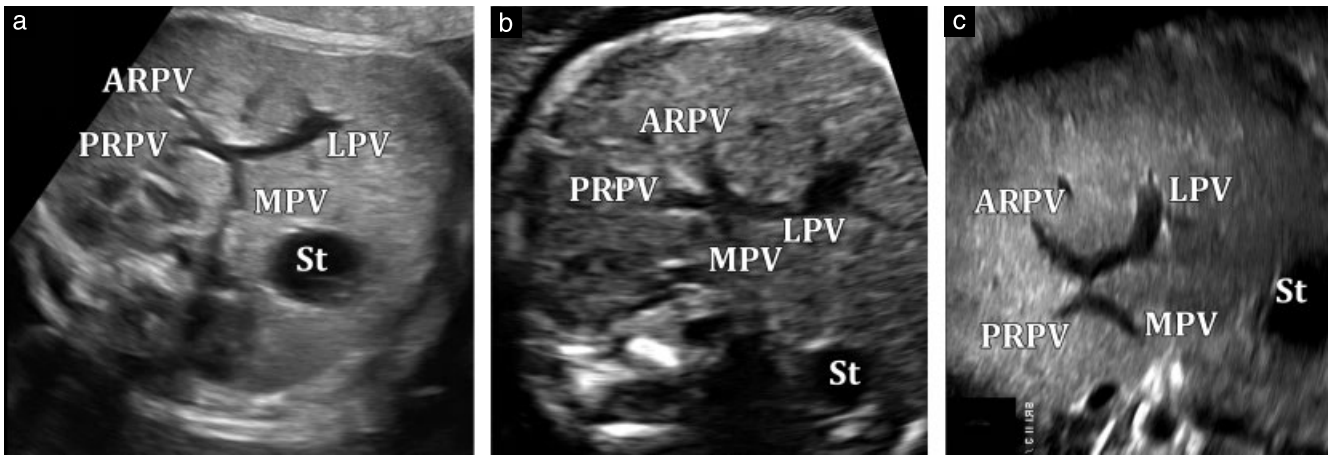

Figure 3 Gray-scale ultrasound images showing normal anatomic variants in the connections of the intrahepatic portal veins. The three main types of the main portal vein (MPV)–portal sinus junction are identified. (a) Type 1, a T-shaped, end-to-side anastomosis. (b) Type 2, an X-shaped, side-to-side anastomosis. (c) Type 3, an H-shaped, parallel anastomosis. ARPV, anterior right portal vein; PRPV, posterior right portal vein; LPV, left portal vein; St, stomach.

to the fetal heart. The DV plays a critical role in this important function. The venous system represents one component of the four that comprise the fetomaternal vascular system, the others being the heart, the placenta, and the arterial system. Their function individually and as part of an integrated system depends on the healthy performance of each component.

In order to facilitate smooth blood flow towards the heart, low placental resistance and improved cardiac contraction must work in synergy. A pressure gradient is created between the atria and ventricles which reduces the preload in the venous circulatory system and allows blood to flow toward the heart. This pressure gradient is further accentuated by the physiologic stenosis of the DV. At this point blood velocity increases from 15–17 cm/s in the intrahepatic segment of the UV to 65–75 cm/s in the DV, causing an increase in the umbilicocaval pressure gradient[11].

The fetal venous system and the other elements of the fetal circulation demonstrate their physiologic interdependence during fetal breathing movements. It has been shown that change in the pressure gradient between the intra-abdominal and intrathoracic cavities created by fetal breathing movements alters blood flow in the venous system[12,13]. During inspiration the pressure gradient between the abdominal cavity (as it contracts inwards) and thoracic cavity (as it expands outwards) rises from some 0–3 mmHg to about 22 mmHg. This raises the pressure gradient between the UV and the thoracic segment of the IVC (umbilicocaval pressure gradient), and in turn flow velocity in the UV rises. The opposite effect is observed during expiration[12,13].

Intrathoracic pressure variations caused by fetal breathing movements have been shown to affect both venous return to the heart and the arterial system[14]. When blood flow to the heart decreases, changes are observed in placental blood flow on the fetal side of the interface. Increased venous preload prevents the placenta from emptying, increasing resistance and causing a drop in arterial diastolic flow. Additionally, ineffective filling of the cardiac ventricles from decreased venous return causes a drop in arterial systolic blood flow. The diastolic phase of the cardiac cycle shows the most marked effects. An increase in venous flow to the heart, on the other hand, is accompanied at the next heart beat by a rise in systolic and diastolic arterial blood flow. The placenta therefore is a system capable of transmitting pressure changes occurring within the heart and thorax. The changes in intracavitary pressure and flow velocities at inspiration and expiration are summarized in Figure 4.

Fetal blood volume has been estimated at approximately 10–12% of body weight, as compared to 7–8% in the adult[15,16]. The variation between the fetus and adult comes from the large reservoir of blood in the placenta. The proportional volume of blood in the placenta decreases as gestation progresses. Doppler-based estimates of fetal cardiac output indicate that about one third of combined cardiac output is sent to the placenta at 20–32 weeks' gestation, a proportion that declines to about a fifth after 32 weeks[17,18].

In-utero human studies have shown that fetal umbilical venous flow increases with advancing pregnancy from 33–54 mL/min at 20–23 weeks' gestation to 221–320 mL/min at 36–38 weeks. However when blood flow is calculated per unit of weight, umbilical venous flow decreases from 117–125 mL/min/kg at 20–23 weeks to 63–104 mL/min/kg at 36–38 weeks' gestation[19,20].

Animal[21] and human[22] studies have shown that under normal conditions 70–75% of the blood flow in the UV is distributed to the liver, while only 25–30% flows to the DV. Of the blood volume flowing to the liver approximately 75% supplies the left lobe and 25% the right. This constitutes 50% of the blood supply to the right liver lobe, while the remainder is supplied by the PV. The fetal liver is thus divided into two physiologically different lobes, the left, supplied by blood rich in oxygen and nutrients, and the right, which receives a mixed supply of blood. The LPV represents a watershed between the

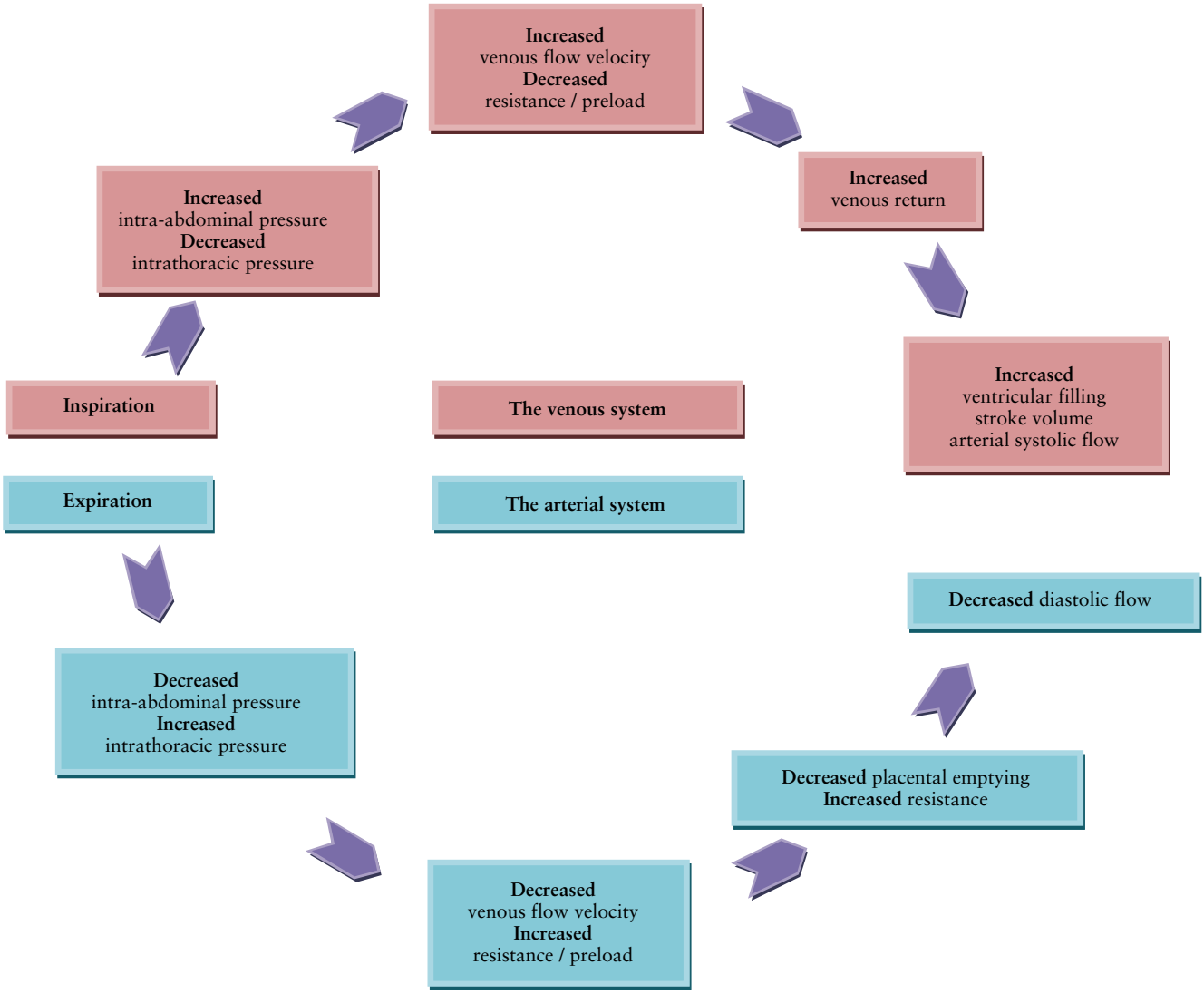

Figure 4 Venous–placental–arterial interaction during fetal breathing movements.

umbilical and portal circulations, in the words of Kiserud *et al.*[23].

The thoracic IVC blood flow is uniquely characterized by a double streaming of flow. It is composed of high-velocity DV flow, running along the left dorsal portion of the IVC, and directed by the crista dividends toward the foramen ovale, and low-velocity IVC flow, which runs on the right-ventral portion of the IVC and is directed toward the tricuspid valve. The final result is a preferential supply of high-quality placental blood to the most essential organs, the heart and the brain[11,24–26].

Doppler waveforms of the normal fetal venous system

Doppler waveforms of the fetal precordial veins mirror the heart cycle. Their typical three-peak form represents the ventricular systolic phase (S), passive diastolic phase (D), and active diastolic phase (A). As opposed to the IVC and hepatic veins (HVs), DV blood flows forward throughout the entire heart cycle, assuring a constant high-quality blood supply to the heart. Various methods have been proposed for evaluating venous system preload index, similarly to the arterial system[27–30]. A gradual decrease in preload index with progression of pregnancy has been consistently shown[28,31]. Doppler investigation of the most commonly investigated vessels is described below (Figure 5).

Umbilical vein

Umbilical vein Doppler patterns are evaluated in the intra-abdominal portion of the vein (Figure 5). Although linear forward flow reflects the normal functioning of a positive umbilicocaval pressure gradient, pulsatile flow may be considered a normal feature until 15 weeks' gestation, before the low-resistance placental vascular bed is established by the second trophoblast invasion[32]. As mentioned above, UV pulsations are also associated with fetal breathing movements in the second half of pregnancy. Van Splunder *et al.*[33] showed that, proceeding from the free loop of the UV to the intrahepatic, porto-umbilical connection, the retrograde atrial contraction waveform

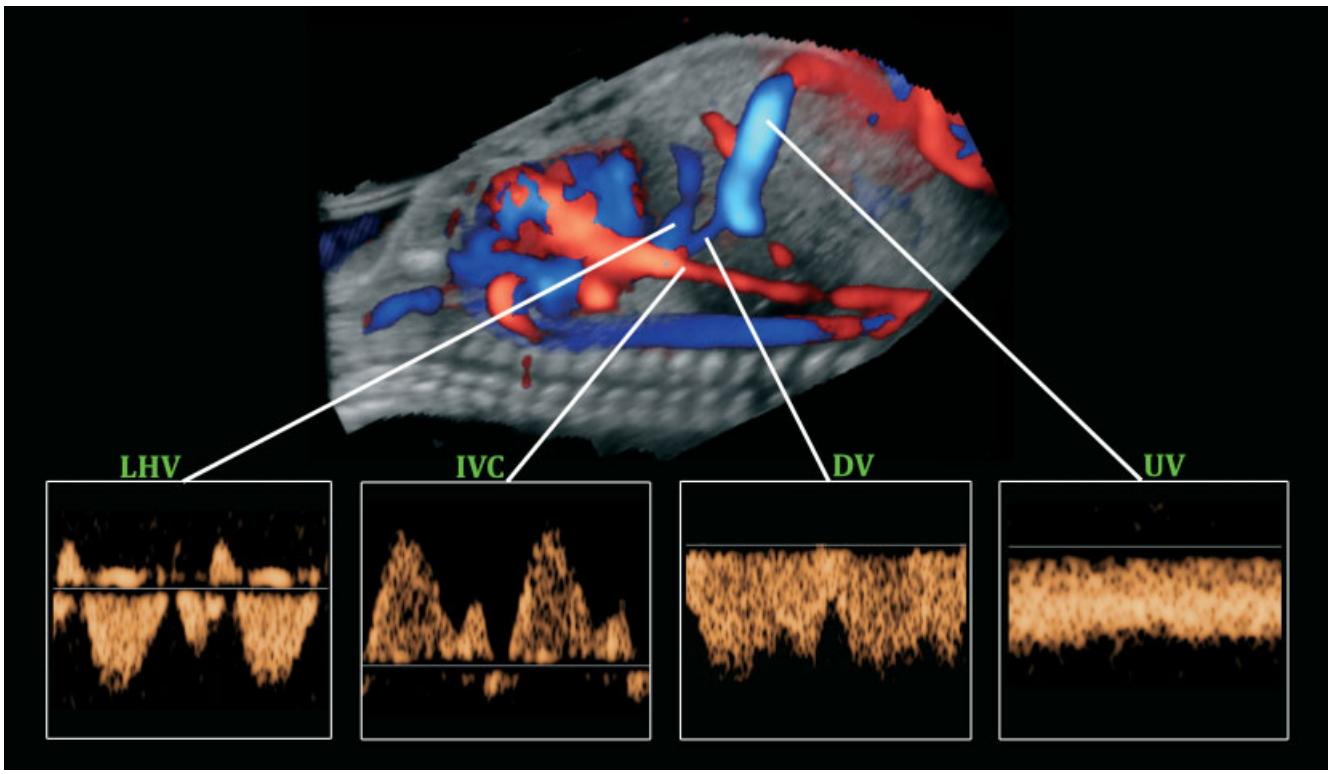

Figure 5 High-definition power flow Doppler image of the fetal circulation showing normal Doppler waveforms in the left hepatic vein (LHV), inferior vena cava (IVC), ductus venosus (DV) and umbilical vein (UV).

propagation is more pronounced and the incidence of pulsations increased from 19.6 to 78.4%, respectively.

Ductus venosus

The DV is sampled at its inlet with a large sample volume in a near-sagittal scan at a low angle of insonation[11]. Alternatively, DV flow can be sampled in an oblique transverse section of the fetal abdomen. Normally, about 30% of blood is shunted through the DV at 20 weeks' gestation, while about 20% of blood is so shunted at 30 weeks[19,22,34]. Changes in DV flow are seen in hypoxia and hypovolemia in experimental animal models and in human fetuses[35–39]. These changes are discussed in detail in Part II.

Inferior vena cava

The IVC is usually sampled in the fetal abdomen, caudal to the hepatic confluence and DV outlet, to avoid interference from neighboring vessels (Figure 5). Reference ranges for normal IVC flow parameters have been established. It is normal to observe a negative a-wave in the IVC because of the vessel's normally lower velocities[40–43]. The rate of flow reversal is estimated as the percentage of the total forward flow (S + D waves), and decreases as pregnancy advances from 16% at 16 weeks' gestation to 7% at term[41].

The IVC is the preferred vessel for postnatal evaluation of small-for-gestational-age neonates and is familiar to pediatricians, so it is often sampled in the fetus[34].

Hepatic and portal veins

The HVs, while easy to sample, have not been widely studied[44–46]. As compared with the DV and IVC, the HVs show a lower increase in peak velocity and decrease in resistance indices with advancing gestational age. This renders them less suitable as targets for monitoring fetal well-being. The waveform is similar to that of the IVC, presenting a characteristic reversed a-wave. The signs of cardiac compromise observed in the HV are similar to those apparent in the DV and IVC[34,45,46].

The portal system

The MPV exclusively supplies the right liver lobe, delivering 50% of the right lobe venous blood supply. This constitutes only 20% of all the venous supply to the liver, the remainder coming from the UV and the main trunk of the LPV. As mentioned above, the LPV is the watershed of the fetal venous circulation, as the meeting point between the umbilical and portal systems, bridging to the DV[23,47]. Under normal conditions its flow is directed toward the right liver lobe. The higher velocity of the UV, and higher umbilicocaval pressure gradient, prevent blood from the MPV from flowing toward the DV[48,49].

MPV blood flow is directed towards the right branch, with a monophasic (sometimes pulsatile) waveform. Blood volume and velocity increase gradually from 20 weeks' gestation to term. Velocity almost doubles from 8.4 to 14.9 cm/s. The flow volume increases from 5 to 41 mL/min, and when calculated per unit of weight, from

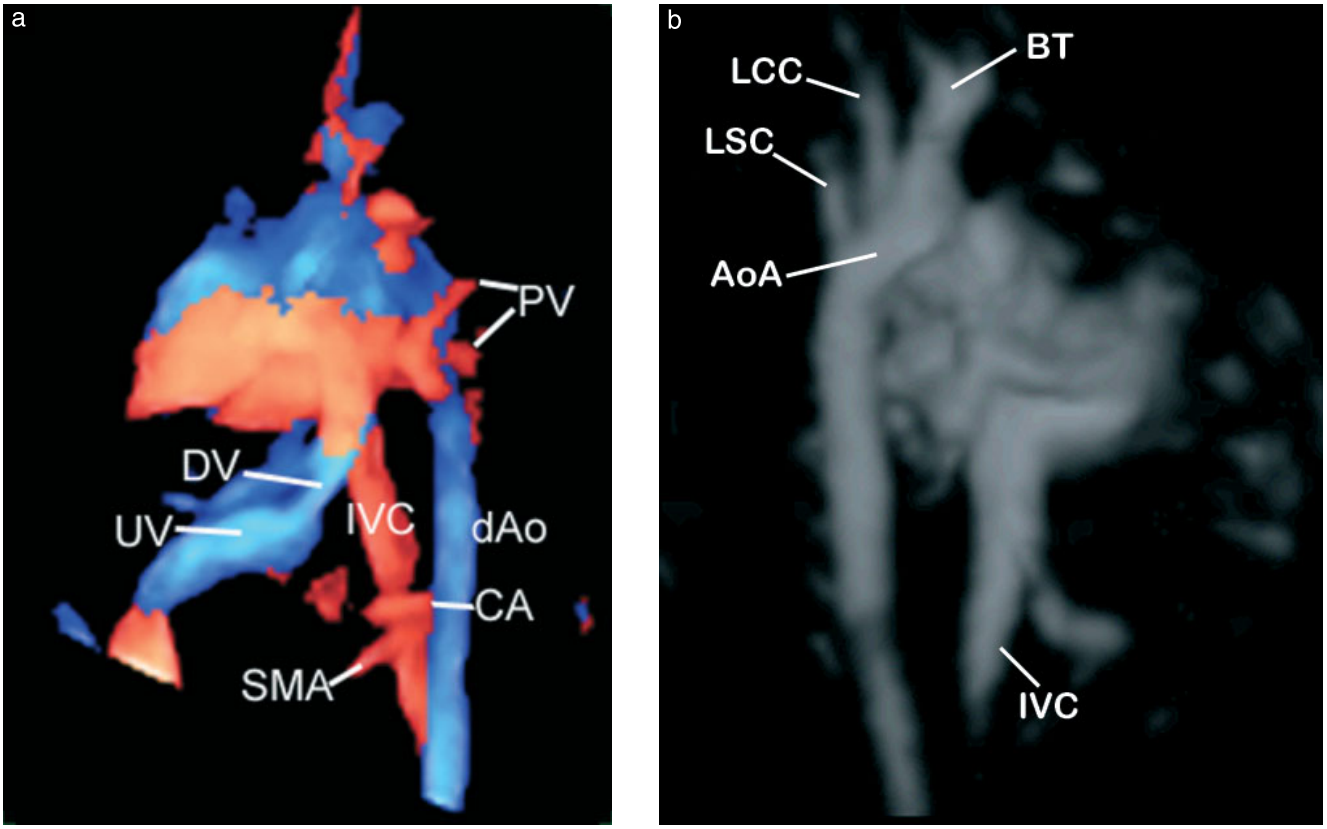

Figure 6 The normal heart and great vessels imaged by high-definition power-flow Doppler (a) and by B-flow ultrasound (b). AoA, aortic arch; BT, brachiocephalic trunk; CA, celiac artery; dAo, descending aorta; DV, ductus venosus; IVC, inferior vena cava; LCC, left common carotid; LSC, left subclavian; PV, pulmonary veins; SMA, superior mesenteric artery; UV, umbilical vein. (Reproduced with permission from Yagel *et al.*[51]).

10 to 13 mL/min/kg. This is in contrast to UV blood flow, indicating a preferential flow to the liver as pregnancy progresses[50].

The pulsatility of the waveform diminishes as the vessel is sampled distally from the insertion of the MPV toward the right and left branches. The nature of these pulsations is not clear. They may originate from adjacent pulsation of the hepatic artery, or represent the reverse propagation of the atrial contraction (a-wave) to the portal system. The latter origin is supported by the fact that it has been shown that in hemodynamically compromised fetuses, accentuation of LPV peak velocity mirrored the DV a-wave[23].

3D/4D ULTRASOUND IN THE EVALUATION OF THE FETAL VENOUS SYSTEM

3D/4D-US modalities were recently reviewed[51]. Spatio-temporal image correlation, B-flow, 3D power Doppler, 3D high-definition power-flow Doppler, multiplanar reconstruction, 3D rendering, inversion mode, virtual organ computer-aided analysis and tomographic ultrasound imaging have been applied to the evaluation of the normal and anomalous fetal venous systems and have been extensively described over the last decade[52–61]. They have been shown to have utility in improving anatomic evaluation of this system, and most recently have been applied to functional evaluation. Specific applications are shown in Figure 6.

CONCLUSIONS

Understanding the normal embryology of the venous system is essential to appreciating the complex malformations that occur in it. Ultrasonography has been shown to be an effective tool for imaging the normally developing venous system, and may have more to offer than does traditional embryology. Over the years many ultrasound images of the venous system have appeared in the literature. The embryological and anatomic knowledge accumulated from these images potentially surpasses that of traditional embryological illustrations, as it is based on hundreds of ultrasound images from dozens of imaging planes in many subjects. Ultrasound has also shown us rare variants of anatomy, and shown others to be not as rare as previously believed. Two-dimensional-US, 3D/4D-US, color and power Doppler are all effective tools in the ultrasound evaluation of the venous system, adding to our understanding of its complex anatomy and assisting in providing cogent advice to patients.

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