Venous Doppler Evaluation of the Growth-Restricted Fetus

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KEYWORDS

• Fetal growth restriction • Doppler • Ductus venosus
• Venous circulation • Fetal surveillance • Integrated testing

The incorporation of venous Doppler into the assessment of the fetal circulation has significantly enhanced the understanding of vascular dynamics in many fetal conditions. Fetal growth restriction (FGR) is a complication of placental insufficiency in which alterations in the venous vascular dynamics are important in the pathogenesis and progression to fetal compromise. In order to appreciate the value of venous Doppler evaluation in FGR, it is first important to appreciate the key features of venous circulation and the typical clinical progression at various gestational epochs.

THE VENOUS CIRCULATION AND FETAL NUTRIENT PARTITIONING

Because the fetus receives all its essential nutrients through the placental circulation, nutrient delivery, gas exchange, and blood flow are uniquely linked in fetal life. In the fetal circulation, nutrient delivery to essential organs and waste delivery to the placenta are accomplished by a series of shunt and watershed areas that ensure relative separation of blood streams of different nutritional content.[1] Blood rich in oxygen, fluid, and substrate reaches the fetal liver via the umbilical vein (UV). The ductus venosus (DV) arises from the UV, and its trumpet shape and relatively narrow diameter markedly accelerate UV blood flow toward the heart. Modulation of DV diameter regulates the proportion of UV blood that reaches the heart—under normal circumstances it is 25% of the UV flow. Of the remaining UV blood, 55% reaches the left liver lobe and 20% the right liver lobe through the portal circulation to continue to the heart through the hepatic veins after some of the essential nutrients have been metabolized in the liver.[2] An increase in the DV diameter increases the proportion of UV blood that reaches the heart directly, whereas the volume of blood reaching the left lobe of the liver is downregulated.[3,4]

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Clin Perinatol 38 (2011) 103–112
doi:10.1016/j.clp.2010.12.001 **perinatology.theclinics.com**
0095-5108/11/$ – see front matter

The accelerated DV blood stream joins the inferior vena cava and the 3 hepatic veins in the subdiaphragmatic venous vestibulum. Among the right atrial tributaries (venous vestibulum, superior vena cava, and coronary sinus), blood from the DV and left hepatic vein has the highest nutritional content. Because these blood streams enter the atria at different directions and velocities, they remain relatively separated so that the most saturated blood travels through the foramen ovale into the left atrium and the left ventricle. Accordingly, the right atrium and foramen ovale provide the second partition between enriched and depleted blood, whereas the left ventricular output supplies the myocardium and the brain through the vascular branches of the preductal aorta. The outputs of the individual ventricles come in contact at the aortic isthmus when the pulmonary artery carrying depleted blood and the aorta join at the ductus arteriosus. Beyond this point, the descending aorta carries mixed blood toward the fetal body and eventually the placenta.[1]

The proportion of UV blood bypassing the liver through DV-mediated shunting affects the glucose–insulinlike growth factor–insulin–mediated growth axis of the fetus, which is a primary determinant of longitudinal fetal growth.[1–3] Alterations in this shunting also affect the nutrient distribution to all downstream organs. Deceleration of the DV blood stream may also affect intracardiac partitioning of blood streams. A decline in the velocity of nutrient-rich blood directed toward the left atrium, a smaller foramen ovale aperture, or an increase in left ventricular pressure can restrict the amount of DV blood that enters the left ventricle. Therefore, the myocardium and brain may experience a decrease in nutrient and oxygen delivery.[1,5]

DOPPLER EXAMINATION OF FETAL VENOUS VESSELS

The venous vessels that have been evaluated in the context of FGR management include the UV, the DV, the inferior vena cava, and the hepatic veins. With the exception of the UV, all these vessels have a flow velocity pattern with several phases that are produced by atrial pressure-volume changes throughout the cardiac cycle (in the absence of fetal breathing movements). Venous forward flow is highest when intra-atrial pressure is low, and atrial size is most accommodating and lowest when the converse is true. Accordingly, venous forward flow is greatest during early atrial systole when the atria are relaxed and have the greatest dimensions and during ventricular systole when the rapid descent of the atrioventricular valve ring reduces intra-atrial pressures. On the other hand, when atrial pressure increases sharply during atrial systole or when the atrioventricular ring moves up during ventricular relaxation, forward flow in the venous system decreases. Therefore, every venous waveform has a systolic peak, a postsystolic trough, a diastolic peak, and a second trough during atrial systole. These phases of the waveform are called S, v, D, and a waves, respectively. The UV is typically protected from the cardiac pressure-volume changes and therefore has constant flow. The hepatic veins and inferior vena cava have lower forward velocities, and therefore, atrial systole may produce temporary reversal of blood flow in these vessels. Because of the marked acceleration of blood flow in the DV, it is the only venous vessel that has antegrade blood flow during all of these phases throughout gestation (**Fig. 1**).

Analysis of venous flow velocity waveforms can be used to quantify blood flow volume or to provide an estimate of cardiac preload (and forward cardiac function). Quantitative Doppler analysis is required to document the proportion of venous shunting at the DV and is typically reserved for research studies. Forward cardiac function can be estimated by relating measurements of angle-independent venous Doppler indices to reference ranges for gestation. Several Doppler indices have been

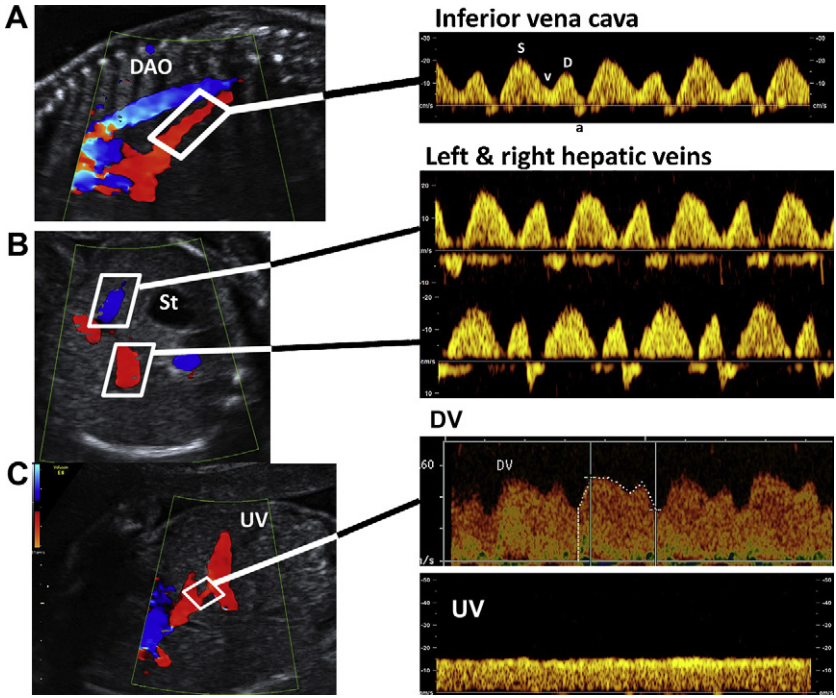

Fig. 1. The venous flow velocity waveform. With the exception of the UV all veins have a phasic flow pattern. (*A*) The inferior vena cava is best examined in a longitudinal view of the upper part of the fetal back where color Doppler identifies this vessel draining into the right atrium anterior to the descending aorta (DAO). When the sample gate is placed in the vessel in the region indicated by the white rectangle, the typical waveform is obtained showing forward flow during ventricular systole (S) and early diastole (D) with a brief decrease in forward flow during ascent of the atrioventricular ring (v) and physiologic flow reversal during atrial systole (a). (*B*) The hepatic veins are best examined in a transverse view of the upper abdomen (St, stomach). These vessels have a similar flow velocity waveform as the inferior vena cava. (*C*) The DV is readily identified by its origin from the UV. When the sample gate is placed in the area of the rectangle, the typical waveform is obtained, which has the highest blood flow velocities in the venous system and antegrade flow throughout the cardiac cycle. Placement of the sample gate in the intra-abdominal UV shows the constant flow velocity profile in this vessel.

described for venous vessels. Of these indices, the systole/a-wave ratio in the inferior vena cava provides the most accurate reflection of cardiac preload, whereas the pulsatility index for veins in the DV also reflects downstream blood flow resistance beyond the heart.[6] Because UV flow is normally constant and DV blood flow is antegrade throughout the cardiac cycle, pulsatile UV flow or absence/reversal of atrial systolic forward flow in the DV provides a descriptive qualitative measure of abnormal cardiac preload.

The UV can be conveniently examined in its free portion. This examination readily allows close to 0° insonation and therefore facilitates obtaining high-quality waveforms of high signal-to-noise ratio. The DV can be examined in a sagittal plane of the upper abdomen. In this view, the DV courses forward and upward toward the heart. Alternatively, the DV can be examined in a transverse view of the upper abdomen by tilting the transducer cephalad. The inferior vena cava is best examined in a sagittal plane next to the descending aorta and above the renal veins. The right,

middle, and left hepatic veins are best examined in a transverse view of the liver. Because all of these venous vessels have different blood flow velocities, color Doppler imaging is helpful in selectively identifying the vessel of interest and in increasing the reproducibility of measurements.[7] Because DV has the fastest blood flow in the venous system, choosing a velocity scale greater than 48 cm/s allows discrimination of motion artifacts and adjacent venous vessels with slower blood flow. In contrast, venous vessels and the inferior vena cava have lower velocities, accordingly the color imaging velocity scale should be reduced to depict the veins in their whole length and to allow placement of cursors with the smallest possible angle of insonation. Once the spectral Doppler sample gate has been placed over the vessel, the sweep speed should be adjusted to show no more than 5 to 6 waveforms. This adjustment ensures that all phases of the waveform are accurately assessed. For all the above-mentioned veins, the measured Doppler indices are higher if the vessels are sampled closer to the heart.[8] To provide reproducibility of assessment, the sampling site should correspond to the technique used to obtain the reference ranges. With advancing gestation, placental blood flow resistance, a major determinant of cardiac afterload, decreases significantly, whereas cardiac compliance and contractility increase. Accordingly, progressively efficient forward cardiac function results in a steady decline of venous Doppler indices with advancing gestation.[3,6,8]

The hallmark of abnormal venous flow velocity waveforms is a relative reduction of forward velocities during ventricular diastole, most apparent as abnormal a waves and to a lesser extent as abnormal D and v waves. These changes and the associated decrease in time-averaged maximum forward velocity result in an increase in most venous Doppler indices (**Fig. 2**).

CARDIOVASCULAR MANIFESTATIONS IN EARLY-ONSET FGR

The cardiovascular manifestations of FGR are determined by the gestational age and severity of the underlying placental disease. Early-onset placental dysfunction is associated with villous obliteration and fetal growth delay that is typically established by the second trimester.[9] Late-onset growth restriction presenting in the third trimester is associated with a lesser degree of placental vascular abnormality and accordingly does not present with the progressive cardiovascular deterioration described later.[9–11] Because venous Doppler parameters are typically normal in late-onset growth restriction, the primary value of venous Doppler evaluation is in early-onset FGR. In such cases of early-onset FGR, the vascular responses to placental dysfunction are subdivided into early and late based on their occurrence in the clinical progression and their association with fetal compromise.

Early Vascular Responses

A decline in UV blood flow volume detected by quantitative waveform analysis is the earliest recognizable Doppler sign of placental insufficiency predating clinical growth delay.[12] A compensatory increase in DV diameter increases UV blood diversion toward the heart.[4] Therefore, hepatic nutrient delivery is decreased, glycogen storage is depleted, and liver growth decreases producing a lagging abdominal circumference measurement as the first physical sign of FGR. Next, progressive villous obliteration increases placental blood flow resistance with a subsequent decrease in the ratio of cerebral and placental Doppler indices (decreased cerebroplacental Doppler ratio).[13] Once approximately 30% of the villous vasculature is affected, a threshold is reached to produce consistent elevation of the umbilical artery Doppler index.[14] Next, cerebral artery “brain sparing” refers to a significant reduction of the Doppler index as an

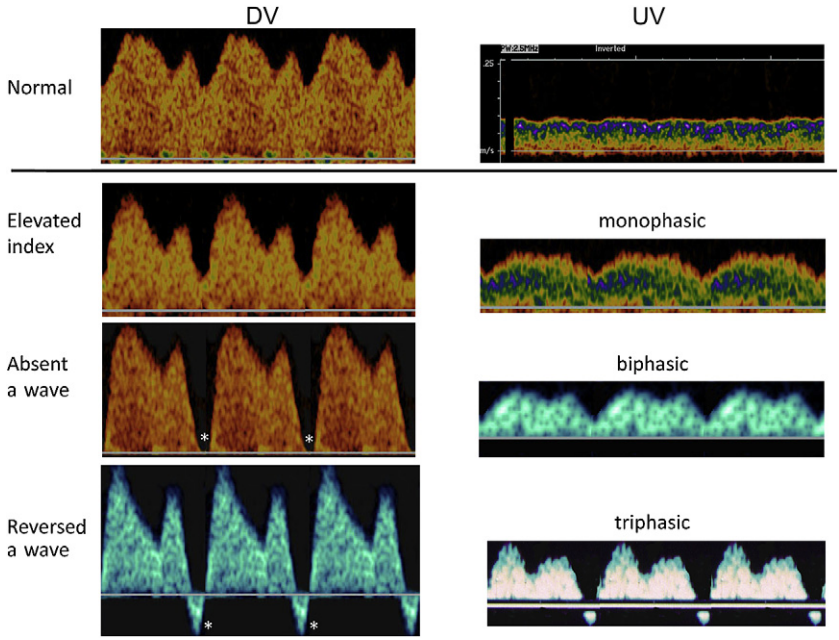

Fig. 2. Abnormal DV and UV flow velocity waveforms. Growth-restricted fetuses with increased placental blood flow resistance may develop abnormal venous flow as an advanced cardiovascular manifestation. This abnormal flow may manifest as a decrease in the a wave or a decrease in a, v, and D waves. In extreme circumstances, both a and v waves may be reversed. (*) In the UV, elevations of central venous pressure and worsening placental dysfunction may be reflected by progressive pulsatility. Monophasic, biphasic, and triphasic pulsations may be observed in association with deterioration of precordial venous Doppler parameters. These changes are attributable to a variable mixture of increased placental blood flow resistance, decreased cardiac compliance, and decreased contractility.

autoregulatory response to worsening placental function.[15] These early vascular responses contribute to preferential perfusion of vital fetal organs and placenta at the expense of the bowel, lungs, and lower body. These responses are thought to be compensatory, mediated through central and peripheral autoregulation, and not associated with dramatic physiologic dysfunction and/or fetal acidemia.[9]

Late Vascular Responses

Loss of forward flow during end diastole in the umbilical artery indicates that the fetus is developing late cardiovascular responses. In this setting, 60% to 70% of the placental villous vasculature is abnormal and there is a progressive decline in placental metabolic function and a marked increase in blood flow resistance.[6,9,14,16] Under these circumstances, a progressive decline in venous forward velocities is observed in all venous vessels. The DV Doppler indices increase. Next, forward velocity during atrial contraction is lost and may reverse. When the DV a wave is absent, UV pulsations may progress to a biphasic, or even a triphasic, pattern.[9,17] Late Doppler findings result from altered forward cardiac function and abnormal organ autoregulation, generally signifying the onset of compromise.[16] The DV blood flow abnormalities result from several mechanisms. These mechanisms include impaired preload handling (deficient cardiac filling because of a dysfunctional myocardium),

impaired afterload handling (deficient cardiac emptying against a high placental blood flow resistance), and increased retrograde transmission of cardiac pressures because of progressive dilation of the DV.[8,9] During these conditions, the fetus is at a high risk for acidemia, deterioration of biophysical parameters, and stillbirth (**Fig. 3**).[18–21]

THE ROLE OF VENOUS DOPPLER IN FGR MANAGEMENT

The main management goals in FGR are the prevention of stillbirth and delivery based on an accurate assessment of fetal versus neonatal risks. In the absence of disease-specific surveillance regimens, the risk for unanticipated stillbirth in FGR pregnancies is increased when the managing obstetrician chooses delayed delivery.[22] Prevention of stillbirth in this setting requires adjustment of the monitoring interval in recognition of the anticipated rate and severity of deterioration.[23,24] When the risks of iatrogenic prematurity are not taken into account, neonatal morbidity and mortality in FGR are

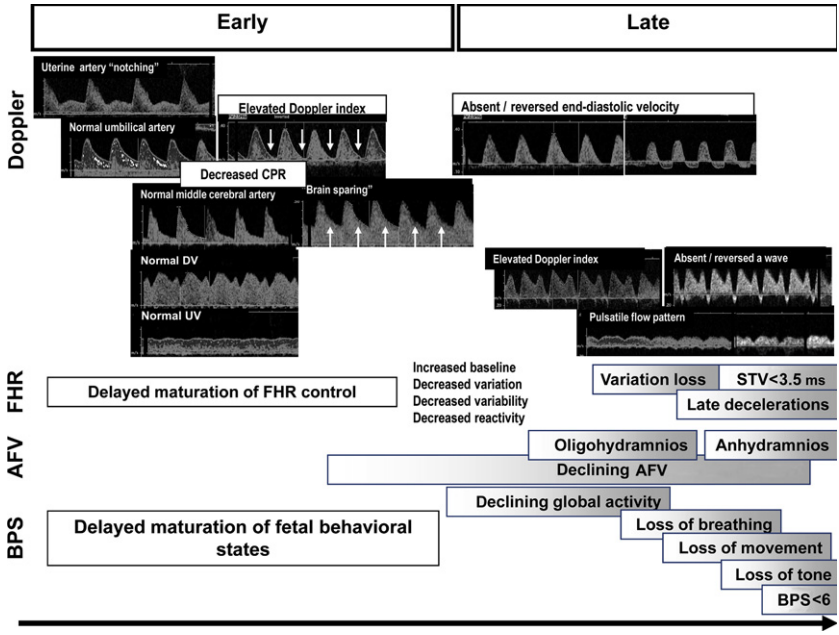

Fig. 3. Progressive deterioration of behavioral and cardiovascular parameters in placental dysfunction. This figure summarizes the early and late responses to placental insufficiency. Doppler variables in the placental circulation precede abnormalities in the cerebral circulation. Fetal heart rate (FHR), amniotic fluid volume (AFV), and biophysical parameters (biophysical profile score [BPS]) are still normal at this time, and a computerized analysis of the fetal behavioral patterns is necessary to document a developmental delay. With progression to late responses, venous Doppler abnormality in the fetal circulation is characteristic, often preceding the sequential loss of fetal dynamic variables and frequently accompanying the decline in AFV. The decline in biophysical variables shows a reproducible relationship with the acid-base status. Because the BPS is a composite score of 5 variables, an abnormal BPS of less than 6 often develops late and may be sudden. Absence or reversal of the DV a wave, decrease of the short-term variation (STV) of the computerized FHR analysis, spontaneous late decelerations, and an abnormal BPS are the most advanced testing abnormalities. If adaptation mechanisms fail and the fetus remains undelivered, stillbirth ensues (*arrows* indicate trend direction).

increased with early obstetric intervention.[22,25] In combination with the umbilical artery, venous Doppler surveillance is helpful in choosing fetal monitoring intervals and thereby potentially improving the timing of delivery.

Choice of Monitoring Intervals

In the patient carrying a growth-restricted fetus, if delivery is not yet an option, the interval between surveillance visits needs to be shortened if there are signs of disease acceleration and/or deterioration of fetal metabolic status. Although the achievement of developmental milestones is delayed in FGR, the 5-component biophysical profile score retains a close relationship with the fetal pH from 20 weeks onward.[26] However, dynamic variables depend on the current acid-base status and do not provide an estimate of the range of clinical progression. Doppler parameters, on the other hand, have a less-close relationship with fetal pH but define the rate and severity of disease progression. Because biophysical parameters and venous Doppler parameters are independent of each other until the point of final common deterioration, incorporation of venous Doppler evaluation into FGR surveillance provides an estimate of the degree of fetal acidemia, risk of stillbirth, and disease acceleration.[11,27]

In early-onset FGR with elevated umbilical artery Doppler resistance and positive end-diastolic velocity, the overall perinatal mortality is 5.6%. This percentage increases to 11.5% when end-diastolic velocity is absent or reversed and when venous Doppler indices are still normal. Perinatal mortality increases almost 4-fold to 38.8% when venous Doppler indices become abnormal, predominantly because of an increase in the rate of stillbirths. In a setting of a 25% stillbirth rate, abnormal venous Doppler findings have 65% sensitivity and 95% specificity for the prediction of stillbirth.[28] Depending on the cutoff (2 vs 3 SDs) and the combination of veins examined, for the prediction of acidemia, the sensitivity ranges from 70% to 90% and the specificity from 70% to 80%.[29,30] In this prediction, DV and inferior vena cava perform similarly but rates of false-positive test results are reduced if either vessel is combined with UV Doppler.[30] The accuracy of prediction is improved by serial observations that document a progressive increase in venous Doppler indices.[18]

When early-onset FGR is diagnosed first, the rate of progression of the umbilical artery Doppler waveform defines the anticipated rate of progression. Loss of end-diastolic velocity within 2 weeks is likely to result in a rapidly progressive clinical picture progressing to abnormal venous Doppler parameters within 4 weeks. In contrast, a more gradual loss of end-diastolic velocity over 4 weeks is associated with a longer latency period of 6 weeks to venous Doppler deterioration.[11]

Based on these associations with clinical variables, umbilical artery Doppler and venous Doppler are the most helpful techniques in determining monitoring intervals when delivery is not yet an option. In the presence of positive umbilical artery end-diastolic velocity, clinical deterioration is unlikely to occur within 1 week. On the other hand, when umbilical artery end-diastolic velocity is absent, at least twice-weekly surveillance is necessary. Reversal of umbilical artery end-diastolic velocity and/or increasing venous Doppler indices, mandate higher testing frequency, up to daily testing. Reversal of DV a wave increases the risk for an abnormal biophysical profile score within 1 to 8 days,[19,20] and at the authors' center, at least daily testing is performed in this setting.

Choice of Thresholds for Delivery

Because there is no effective prenatal treatment of FGR, the principal obstetric intervention is delivery when the risks of prolonged monitoring and fetal deterioration

exceed the neonatal risks.[22] Although it was long thought that fetal deterioration itself would result in an adverse neonatal outcome, gestational age at delivery is a critical determining factor for outcome in FGR.[18,22,25,31] The effect of gestational age seems so great that reversal of DV a wave only becomes an independent risk factor for neonatal morbidity and mortality after 27 weeks' gestation.[32] The Growth Restriction Intervention Trial (GRIT) in Europe evaluated the effect of delivery timing on perinatal mortality and neurodevelopment. In the absence of a specific management plan and delivery trigger, immediate delivery, when concerns about fetal well-being arose, was associated with a higher rate of prematurity-related neonatal mortality.[22] On the other hand, delayed delivery without a specific monitoring plan carries the risk of unanticipated stillbirth. At present, there is no randomized treatment trial that has evaluated the performance of specific monitoring regimens and delivery triggers in improving outcomes in FGR. However, based on observational data, delivery thresholds need to be high at 24 to 26 weeks of gestation because of the high neonatal mortality at this gestational epoch. Until 28 weeks of gestation, each day in utero potentially increases survival by 2%/day.[32] Thereafter, survival benefits per day decline and thresholds for delivery may be lower. Accordingly, reversed DV a wave may be tolerated at 26 weeks' gestation until the biophysical profile score deteriorates, although the same finding may trigger delivery at 32 weeks' gestation. The Trial of Umbilical and Fetal Flow in Europe has just completed enrollment, and it is hoped that the results will provide answers to the question of delivery timing in FGR.

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