Ductus Venosus S-Wave/Isovolumetric A-Wave (SIA) Index and A-Wave Reversed Flow in Severely Premature Growth-Restricted Fetuses

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Objective. Ductus venosus (DV) Doppler waveforms show 2 periods of decreased velocity during isovolumetric relaxation (isovolumetric relaxation velocity [IRV]) and atrial contraction (A wave or end-diastolic velocity [EDV]). In intrauterine growth-restricted (IUGR) fetuses, both may become abnormal. The hypothesis for this study was that in severely premature IUGR fetuses, Doppler assessment of both the IRV and EDV allows a more accurate prediction of fetal outcome than absent/reversed end-diastolic flow (A/REDF) alone. ***Methods.*** Ductus venosus Doppler waveforms were serially studied in 49 severely premature IUGR fetuses from diagnosis until death or delivery. The DV waveforms were assessed for peak systolic velocity (PSV), IRV, and EDV and qualitatively for forward end-diastolic flow or A/REDF. The S-wave/isovolumetric A-wave (SIA) index [PSV/(IRV + EDV)] for each fetus was compared to fetal/neonatal outcomes. ***Results.*** There were 8 cases of fetal death (FD), 9 cases of neonatal death (ND), and 32 cases of neonatal survival (NS). A receiver operating characteristic (ROC) curve for the SIA index in all cases showed that values less than –1.25 correlated with FD and those greater than –1.25 correlated with live birth, with 100% sensitivity and 100% specificity. A second ROC curve of live births showed that values less than 2.07 correlated with NS and those greater than 2.07 correlated with ND with 67% sensitivity and 94% specificity. Ductus venosus A/REDF correlated with FD, ND, and NS with sensitivity values of 88%, 78%, and 32%, respectively. Of the 32 NSs, 11 (34%) had A/REDF with a median of 11 days before delivery. ***Conclusions.*** The SIA index is a novel Doppler parameter for assessment of severely premature IUGR fetuses that allows a much more accurate prediction of fetal outcome compared to A/REDF alone. ***Key words:*** Doppler ultrasound; ductus venosus; intrauterine fetal death; intrauterine growth restriction; isovolumetric relaxation; reversed flow; S-wave/isovolumetric A-wave index.

Abbreviations
A/REDF, absent/reversed end-diastolic flow; DV, ductus venosus; EDV, end-diastolic velocity; FD, fetal death; FF, forward flow; IR, isovolumetric relaxation; IRV, isovolumetric relaxation velocity; IUGR, intrauterine growth-restricted; ND, neonatal death; NS, neonatal survival; PDV, peak diastolic velocity; PSV, peak systolic velocity; ROC, receiver operating characteristic; SIA, S-wave/isovolumetric A-wave

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In severely premature intrauterine growth-restricted (IUGR) fetuses, gestational age and birth weight have long been recognized as important predictors of survival.[1–4] When gestational age and fetal birth weight data are excluded, then forward or absent/reversed end-diastolic blood flow in the ductus venosus (DV) is the best predictor of intact survival and neonatal mortality in IUGR fetuses between 28 and 31 weeks' gestation.[5] Other investigators perform cesarean delivery when there is DV reversed flow.[6]

However, we recently showed the presence of a transitional phase in severely preterm IUGR fetuses, in which absent/reversed end-diastolic flow (A/REDF) in the DV was present intermittently between periods of normal forward flow (FF), early in fetal cardiac decompensation. This transitional phase progressed to continuous absent and later reversed end-diastolic flow in the DV, ultimately resulting in cardiac failure and fetal death (FD). This previous study showed that intermittent A/REDF could persist for up to 57 days (median, 13 days), and continuous A/REDF could persist for up to 23 days (median, 7 days) before FD or delivery for nonreassuring fetal testing.[7] This is important because in IUGR fetuses between 25 and 29 weeks' gestation, each week of continued gestation decreases perinatal mortality by 48%.[8] Therefore, the use of A/REDF in the DV to determine the timing of delivery risks delivering the fetus weeks before necessary, essentially trading FD for neonatal death (ND).

Doppler assessment of the DV in healthy fetuses shows a biphasic pattern of blood flow, with 2 peaks and 2 troughs. The first peak, the S wave, results from the large pressure gradient between the peripheral venous system and the empty right atrium during ventricular systole.[9] As such, this is usually the highest Doppler value in the DV. The opening of the atrioventricular valves and passive early filling of the ventricles in early diastole results in the second peak of FF, the D wave. At the end of ventricular systole but before diastole, there is a period of isovolumetric relaxation (IR) during which the increasing pressure of atrial distention approaches the waning pressure of systolic ejection. The IR can thus be visualized as a trough between the S and D waves (Figure 1, bottom). A second and usually much larger trough occurs with atrial contraction during late diastole, the A wave. This presumably results from closure of the foramen ovale with the crista dividens, thereby preventing direct blood flow from the DV to the left atrium.[10]

The guiding hypothesis for this study was that in severely premature IUGR fetuses, Doppler assessment of both the isovolumetric relaxation velocity (IRV) and end-diastolic velocity (EDV) allows a more accurate prediction of fetal outcome than A-wave absent or reversed flow alone.

Materials and Methods

Patient Characteristics

The patients included in this study were part of a database on IUGR fetuses, and their inclusion for this study was approved by the Wayne State University Human Investigation Committee. The patients had been included in a previous study.[7] We selected singletons with a diagnosis of IUGR that were studied with serial Doppler ultrasound examinations at intervals of every 48 hours or less and within 48 hours of delivery or FD. The fetuses had (1) an estimated weight below the 10th percentile confirmed by birth weight, (2) an umbilical artery pulsatility index greater than the 95th confidence interval of our reference range, (3) normal anatomy, and (4) Doppler assessment of the DV. Fetuses with an abnormal karyotype or suspicion of an infection were not included in the study.

Gestational age was based on certain last menstrual period or second-trimester ultrasound dating. Fetal weights were calculated and evaluated according to the reference range established by Hadlock et al.[11] Delivery was indicated in the presence of (1) nonreassuring fetal testing, (2) FD, or (3) worsening maternal or fetal conditions as determined by the managing physician. Nonreassuring fetal testing was defined by the presence of either continuous variable/late decelerations or a biophysical profile of 4 or less. When delivery was indicated and the fetus was less than 500 g, the patient was counseled on the poor prognosis and offered the option of nonintervention. Doppler ultrasound results were available to the managing physicians but were not used as indications for delivery. S-wave/isovolumetric A-wave (SIA) index values were not available to the managing physician.

We defined chronic hypertension as a blood pressure value of 140/90 mm Hg or higher diagnosed before 20 weeks' gestation or preconception. Preeclampsia was defined by hypertension and proteinuria that occurred after 20 weeks' gestation in a patient with previously normal blood pressure. Hypertension was defined as a blood pressure value of 140/90 mm Hg or higher on at least 2 occasions 6 hours apart. Proteinuria was defined as the presence of 300 mg of protein or more in a 24-hour urine specimen. We defined poor growth as an estimated fetal weight gain of 100 g or less over 2 weeks.

Doppler Studies

Pulsed wave Doppler ultrasound studies were performed in the absence of fetal breathing and fetal movements. Ductus venosus Doppler waveforms were serially studied from the time the diagnosis was made until delivery. The DV was sampled soon after its origin from the umbilical vein, either in a midsagittal longitudinal plane of the fetal trunk, as shown in Figure 1, top, or in an oblique transverse plane through the upper abdomen. Two sets of waveforms were obtained during each examination, at least 10 minutes apart from each other. Each set included at least 30 waveforms.

The DV waveforms were quantitatively assessed for peak systolic velocity (PSV), EDV, peak diastolic velocity (PDV), and IRV, as shown in Figure 1, bottom. A novel variable was developed that incorporates the pulsatility index with IRV. This end point, which we called the SIA index, is the proportion of the PSV to the sum of the IRV and the EDV [PSV/(IRV + EDV)]. Doppler values of reversed flow were entered as negative values. The SIA index for each examination was then compared to the fetal/neonatal outcome, gestational age at delivery or death, and fetal weight.

Additionally, the DV waveforms were qualitatively assessed for flow during the A-wave: FF or A/REDF. To fulfill the criteria of FF or A/REDF, the waveforms at each set had to be similar between the 2 sets; ie, all of the waveforms in each set had FF or A/REDF, as recently reported.[7] To maintain consistency, the worst of the 2 values was used for data analysis. Finally, the time in days between identification of A/REDF and delivery or diagnosis of FD was calculated.

Data were analyzed with SPSS version 15.0 statistical software for Windows (SPSS Inc, Chicago, IL). Because of unequal variances, primary analysis was by Kruskal-Wallis nonparametric 1-way analysis of variance and post hoc analysis by the Mann-Whitney *U* test. Two receiver operating characteristic (ROC) curves were developed to determine the optimal SIA index cut points to predict FD and neonatal survival (NS).

Results

Forty-nine fetuses met the entry criteria, whose characteristics are reported in Tables 1 and 2. There were 8 cases of FD, 9 cases of ND, and 32 cases of NS at the time of discharge from the hospital. In all 8 FD cases, fetal weight was less than 500 g, and the patients declined any intervention. All fetuses with the exception of those that died in utero were born by cesarean delivery. A total of 169 studies were performed (median, 3 per patient; range, 1–9).

Kruskal-Wallis nonparametric 1-way analysis of variance comparing the SIA index, fetal weight, and gestational age at delivery or death to the fetal outcome (NS, ND, or FD) showed that all 3 variables were statistically significant ($P < .001$). Post hoc analysis by the Mann-Whitney *U* test

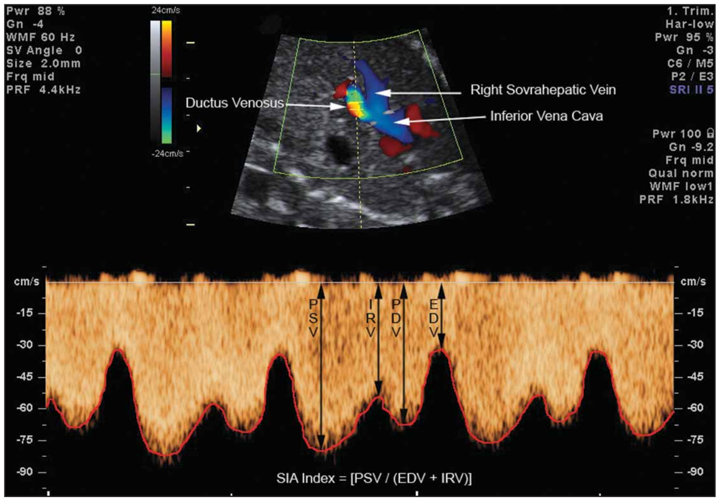


Figure 1. Top, Sagittal section of the fetal body showing the venous vestibulum at the confluence of the inferior vena cava, the DV, and the right sovrahepatic vein. The sample volume is placed in the DV. Bottom, Flow velocity waveforms of the DV.

Table 1. Characteristics of the Study Population (N = 49)

Characteristic	Median (Range)
GA at study entry, wk	26.3 (18.6–32.5)
GA at delivery, wk	
Total population	28.3 (23.1–33.6)
FD (n = 8)	25.5 (23.1–29)
ND (n = 9)	25.5 (24.1–28.6)
NS (n = 32)	29.3 (26.4–33.6)
Birth weight, g	
Total population	617 (282–1465)
FD (n = 8)	360 (282–472)
ND (n = 9)	528 (440–660)
NS (n = 32)	830 (400–1465)

GA indicates gestational age.

Table 2. Maternal and Fetal Comorbidities of the Study Population (N = 49)

Parameter	n
Comorbidities preceding pregnancy	
None	29
Human immunodeficiency virus	1
Lupus	1
Hyperthyroid	1
Chronic hypertension	17
Comorbidities in pregnancy	
None	16
Chronic hypertension	17
Preeclampsia	19
HELLP	6
Antiphospholipid syndrome	1
Cocaine use	1
Indication for delivery	
IUFD	8
NRFT	27
Preeclampsia	9
HELLP	4
Poor growth	3
Abruption	2

More than 1 comorbidity and indication for delivery were present in the same patient. HELLP indicates hemolysis, elevated liver enzymes, and low platelet count; IUFD, intrauterine FD; and NRFT, nonreassuring fetal testing.

showed that all 3 variables differentiated NS from ND, with gestational age having the lowest *P* value ($P < .001$). All 3 variables differentiated NS from FD equally ($P < .001$); however, the SIA index and fetal weight but not gestational age differentiated between ND and FD, with the SIA index having the lowest *P* value ($P < .001$). Statistical analysis findings are summarized in Table 3.

Two ROC curves were developed to determine the optimal SIA index cut points for predicting FD and NS. The first ROC curve compared FD to live births (ND and NS) and showed a cut point of –1.25 with 100% sensitivity and 100% specificity, with SIA index values less than –1.25 indicating stronger evidence of FD (Figure 2A). The second ROC curve compared ND to NS and showed a cut point of 2.07 with 67% sensitivity and 94% specificity, with SIA index values greater than 2.07 indicating stronger evidence of ND (Figure 2B).

Qualitative assessment of the ultrasound data (FF or A/REDF) showed that at the time of the last ultrasound examination before delivery or death, 7 of 8 fetuses that resulted in FD (88%) had A/REDF; 7 of 9 fetuses that resulted in ND (78%) had A/REDF; and 7 of 32 fetuses that resulted in NS (22%) had A/REDF. When all ultrasound data were assessed qualitatively, 8 of 8 fetuses that resulted in FD (100%) had A/REDF at some point, with a median time of 5 days and a mean of 14 days before death; 7 of 9 fetuses that resulted in ND (78%) had A/REDF at some point, with a median time of 3 days and a mean of 7 days before delivery; and 11 of 32 fetuses that resulted in NS (34%) had A/REDF at some point, with a median and mean time of 11 days before delivery. When fetuses that resulted in FD and ND were combined and compared to fetuses that resulted in NS, the use of qualitative DV assessment resulted in sensitivity of 88%, specificity of 66%, a positive predictive value of 58%, and a negative predictive value of 91%.

Discussion

The hypothesis driving this study was that Doppler assessment of both the IRV and EDV allows a more accurate prediction of fetal outcome than A-wave absent or reversed flow alone in severely premature growth-restricted fetuses. To test this hypothesis, we performed serial quantitative measurements of the 4 DV Doppler ultrasound variables in 49 IUGR fetuses between 23.1 and 33.6 weeks' gestation at the time of

Table 3. Means and SDs of Results (N = 49)

Parameter	FD (n = 8)	ND (n = 9)	NS (n = 32)	Post Hoc *P*
SIA index	–7.1 ± 3.2	3.3 ± 4.3	1.3 ± 0.9	A[a]B[a]C[a]
EGA, wk	25.2 ± 1.9	25.7 ± 1.2	29.5 ± 2	AB[a]
Fetal weight, g	363 ± 73	538 ± 85	856 ± 336	AB[a]C

A indicates $P < .001$ for NS versus ND; B, $P < .001$ for NS versus FD; C, $P < .001$ for ND versus FD; and EGA, estimated gestational age.
[a]Variable with lowest *P* value for end point.

delivery and compared these results to fetal outcomes. We found that (1) the SIA index was most sensitive at distinguishing FD from ND; (2) gestational age, the SIA index, and fetal weight distinguished between FD and NS equally; and (3) gestational age was most sensitive at distinguishing between ND and NS. The use of the PDV did not provide additional statistical significance.

Additionally, we were able to develop an ROC curve that showed that an SIA index of less than –1.25 correlated with FD with 100% sensitivity and 100% specificity. A second ROC curve showed that an SIA index of greater than 2.07 correlated with ND with 67% sensitivity and 94% specificity.

These findings show that the SIA index is a physiologically relevant indicator of worsening cardiac disease. Ductus venosus blood flow is directed toward the heart throughout the entire cardiac cycle in healthy fetuses, even in early pregnancy (Figures 1, top, and 3A). Placental insufficiency results in increased peripheral vascular resistance and increased end-diastolic pressure. As this condition worsens, blood flow during atrial systole approaches stasis and ultimately results in reversal of flow, manifested as a decreased EDV (Figures 3B and 4A). With increasing myocardial hypoxia and acidosis, the cardiac muscle is less compliant, and decreased blood flow during IR results in absent or even reversed blood flow, manifested as a decreased IRV (Figures 3C and 4, B and C). A simple histogram of the ROC curve data (Figure 5) shows 3 separate zones: zone 1 consists of fetuses with SIA index values of 2.07 or greater, which are likely to result in ND; zone 2 consists of fetuses with SIA index values greater than –1.25 and less than 2.07, which are likely to result in NS; and zone 3 consists of fetuses with SIA index values of –1.25 or less, which are likely to result in FD.

Mathematically, this relationship is explained by the combination of the EDV and IRV in the denominator of the SIA index. As placental insufficiency worsens, the EDV approaches 0 and progresses to negative values. The SIA index remains positive throughout this period because the IRV compensates for the decreasing EDV values. Even though A/REDF is present at this time, these fetuses are likely to survive. It is only when the IRV begins to decline with decreased cardiac

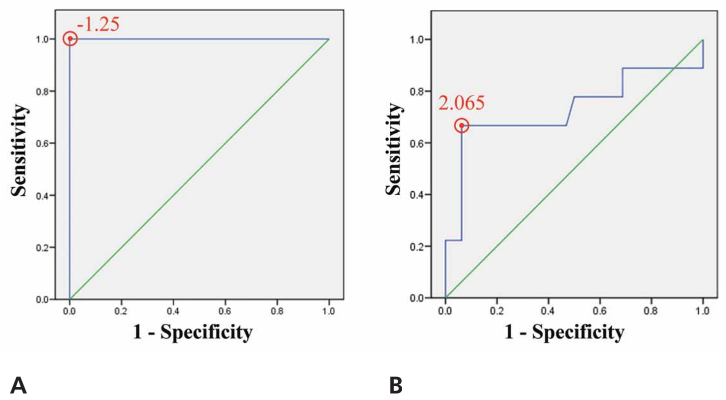
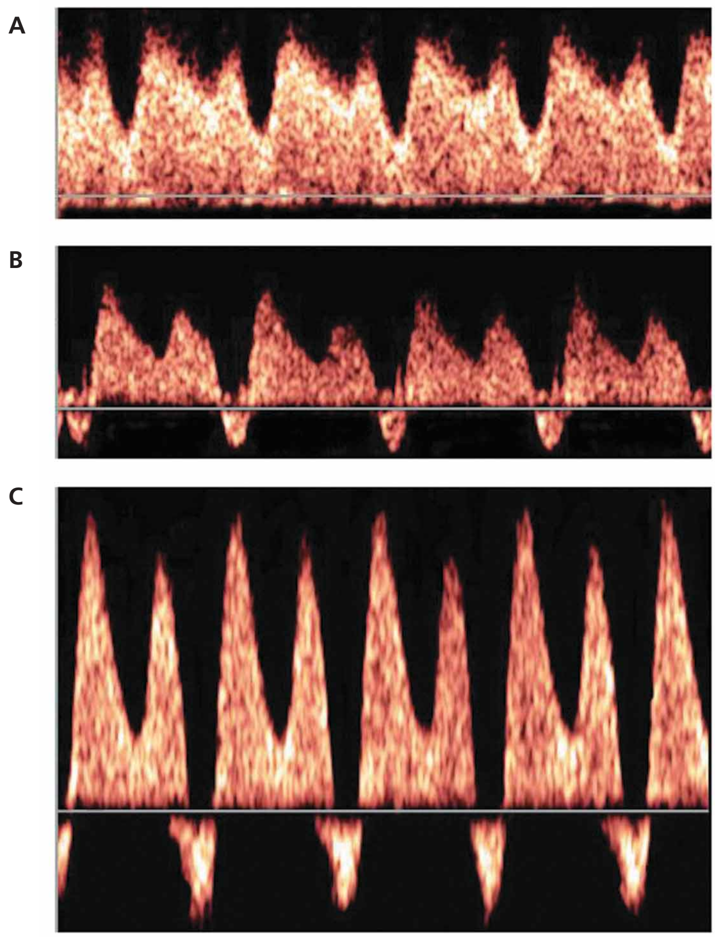


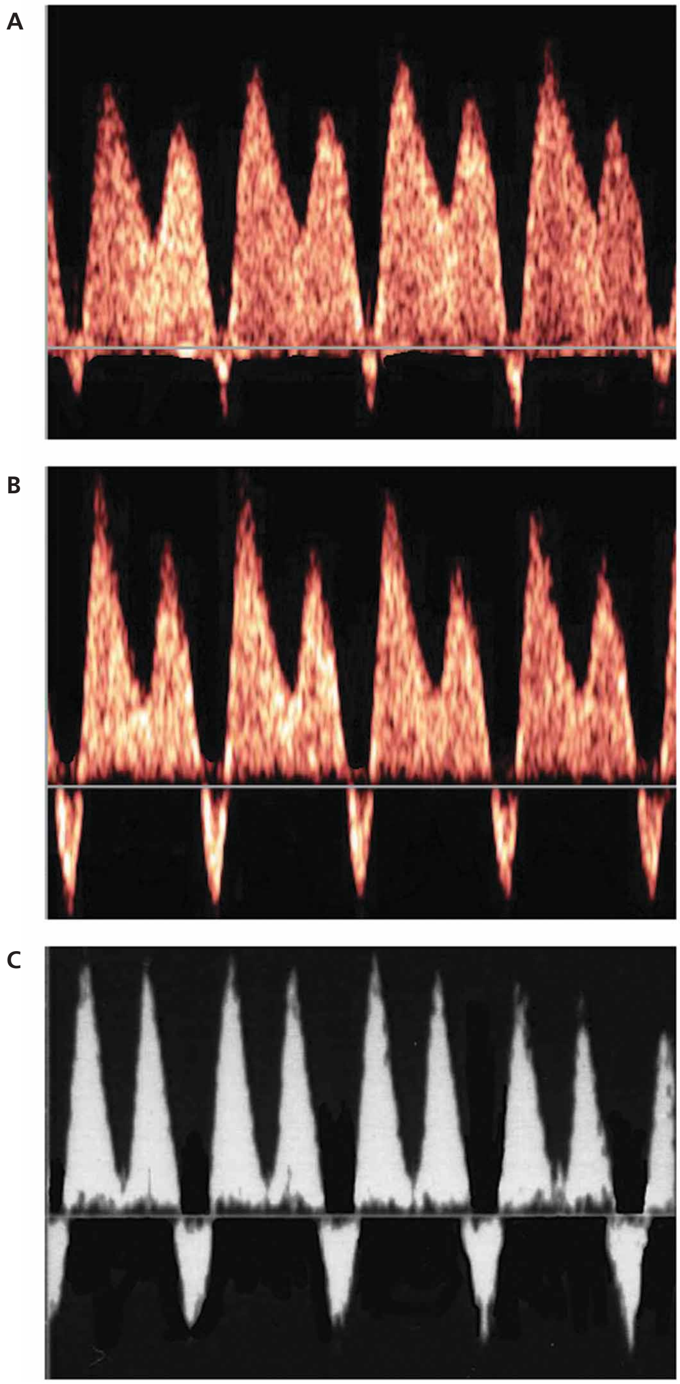
Figure 2. Receiver operating characteristic curves for the SIA index in severely premature IUGR fetuses. **A**, Receiver operating characteristic curve for the SIA index in all fetuses comparing FD to live birth. Smaller values indicate stronger evidence of FD. **B**, Receiver operating characteristic curve for the SIA index in all live births comparing NS to ND. Smaller values indicate stronger evidence of NS.

Figure 3. Flow velocity waveforms of the DV in an IUGR fetus at 13 days (**A**), 7 days (**B**), and 48 hours (**C**) before intrauterine death at 25 weeks' gestation. The patient declined intervention because of fetal weight less than 500 g.



wall compliance that the EDV negative value approaches the positive IRV value. At this time, the denominator decreases, and the SIA index surpasses 2.07, resulting in increased risk of ND.

Figure 4. Flow velocity waveforms of the DV in an IUGR fetus at 16 days (**A**), 4 days (**B**), and 24 hours (**C**) before intrauterine death at 23.1 weeks' gestation. The patient declined intervention because of fetal weight less than 500 g and a gestational age of 23 weeks.

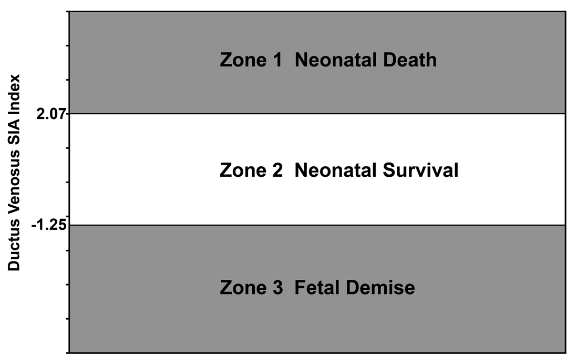


As cardiac failure progresses, the EDV and IRV values continue to decline until their sum is negative, and the SIA index value becomes negative, at which time FD is likely.

It has been proposed that the presence of DV A/REDF in IUGR fetuses may predict imminent FD and warrants immediate delivery.[12] Here we show that qualitative analysis of DV A/REDF accurately predicted both FD and ND within 48 hours of delivery or death with sensitivity of 88% and 78%, respectively. However, the use of DV A/REDF as an indicator for delivery in this study would have resulted in a false-positive rate of 34% and a false-negative rate of 11%. On the basis of a previous study showing a 48% decrease in neonatal mortality for each week of gestation between 25 and 29 weeks,[8] qualitative assessment of DV blood flow would have increased the risk of neonatal mortality by 75% for 34% of those fetuses that survived.

On the basis of the above findings, we think that when DV A/REDF is identified in IUGR fetuses between 25 and 30 weeks, delivery is not always immediately necessary. After 30 weeks' gestation, if there is a question of whether to deliver or continue the pregnancy, we would advocate delivery because fetuses most often survive by that time. Similarly, IUGR fetuses delivered before 25 weeks' gestation rarely survive.[13] Between these gestational ages, the SIA index may allow the prediction of fetal outcome and may assist in the timing of delivery. Those fetuses in IUGR stages I and II[14] with abnormal Doppler findings, including umbilical artery or

Figure 5. Critical values for the SIA index in severely premature IUGR fetuses.



middle cerebral artery PSV, but normal DV EDV could be followed with serial Doppler assessments of the DV SIA index. Delivery would be precipitated when the SIA index approaches either 2 at its upper limit, because of an increased risk of ND, or –1.25 at its lower limit, because of an increased risk of FD. For fetuses in which DV A/REDF is identified (IUGR stage III), the SIA index could be used to distinguish those fetuses likely to survive after delivery (SIA index <2) from those fetuses that would not benefit from aggressive management. Additionally, patients offered expectant management because of fetal weight less than 500 g or gestational age less than 25 weeks could be counseled regarding the likelihood of FD based on the SIA index.

A limitation of this retrospective study was that we were not able to perform Doppler assessments of blood flow in the DV on a daily basis to allow a more accurate assessment of Doppler parameters within 24 hours of delivery or death in all fetuses. Additionally, the limited numbers of cases prevented the delineation of IUGR fetuses in which no apparent cause could be found from IUGR associated with preeclampsia or chronic hypertension. This is important, as we have recently reported.[15]

The strength of this study was our ability to follow premature fetuses with serial DV Doppler ultrasound examinations from the onset of abnormal blood flow to FD, allowing observation of the natural process of progressive placental insufficiency. A novel finding of this study was that those fetuses destined not to survive, regardless of intervention, could be identified. This may prevent the increased maternal morbidity and mortality associated with aggressive management, such as cesarean delivery.

In conclusion, we have identified a novel parameter, the SIA index, which allows a more accurate prediction of fetal outcome compared to A/REDF alone. Although prospective assessment of the SIA index is required to verify its clinical use and to further refine the critical values for FD, ND, and NS, it may provide the clinician with additional information in the management of severely premature IUGR fetuses.

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