Fetal arterial and venous Doppler in growth restricted fetuses for the prediction of perinatal complications

Özgür Özyüncü[1], Burcu Saygan-Karamürsel[2], Didem Armangil[3], Lütfü S. Önderoğlu[1], Şule Yiğit[2], Melih Velipaşaoğlu[1], Özgür Deren[1]

[1]Maternal Fetal Medicine Unit, Department of Obstetrics and Gynecology and [3]Neonatology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, and [2]Department of Obstetrics and Gynecology, MESA Hospital, Ankara, Turkey

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Fetal arterial and venous Doppler is a useful tool for the monitoring of growth restricted fetuses. Our aim in this study was to compare outcomes when fetuses were grouped according to the combinations of the Doppler results and also according to each vessel Doppler. Deliveries during the period 2002-2008 were reviewed retrospectively and cases with a birth weight less than the 10th percentile were selected for the study. Cases with congenital malformations or chromosomal abnormalities were excluded. Cases were then grouped according to umbilical artery (UA), middle cerebral artery (MCA) and ductus venosus (DV) Doppler results. Two hundred fifty-five cases were selected for the study. The perinatal mortality rate was 9.8% (11 prenatal and 14 neonatal). In the presence of absent or reverse flow in UA, fetal death and neonatal complication rates were higher. In the fetuses having reverse or absent "a" wave, there were findings of metabolic deterioration. Absent-reverse UA end-diastolic flow increased the odds ratios of perinatal and fetal death, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), respiratory distress syndrome (RDS), and need for neonatal intensive care unit (NICU) (2.81, 5.94, 10.82, 5.79, 5.19, and 11.60, respectively). Absent/reverse "a" wave in DV increased the odds ratio of perinatal death, fetal death, neonatal death, RDS, and abnormal pH (19.89, 18.06, 12.50, 8.29, and 9.67, respectively). For prediction of fetal metabolic status, DV Doppler is a reliable tool. However, when perinatal complications are considered, this finding for intervention to delivery is a late point. Therefore, when reverse end-diastolic flow in the UA is observed, decision-to-delivery should be taken in order to avoid metabolic deterioration and increased postpartum death.

Key words: intrauterine growth restriction, Doppler, ultrasonography, perinatal death, perinatal morbidity.

Fetal growth restriction or intrauterine growth restriction (IUGR) is the inability of the fetus to obtain its growth potential. It is classically defined as a fetus with an estimated weight below the 10th percentile for gestational age[1] because the perinatal morbidity and mortality increase below that percentile[2]. This definition is controversial because some fetuses may be constitutionally small and may also be termed as IUGR. Therefore, IUGR may be termed as fetuses with an estimated fetal weight below the 10th percentile and presence of a pathophysiologic insult resulting from placental problems. This insult may manifest itself as oligohydramnios or abnormal fetal Doppler studies.

Fetal, neonatal, and perinatal mortality are affected by both the severity of growth

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restriction and the degree of prematurity. Small for gestational age (SGA) neonates have a higher risk of neonatal morbidity, particularly those born very preterm[3,4]. Increased risks of acidemia, respiratory distress syndrome (RDS), intracranial hemorrhage (ICH), and necrotizing enterocolitis (NEC) have also been described even for mildly preterm SGA neonates[5]. In addition, studies have shown a broad range of long-term outcomes in IUGR fetuses, including decreases in IQ[6], reduction in cognitive functions[7] and increased risk of cerebral palsy[8].

The optimal method(s) for monitoring the fetuses with suspected IUGR has not yet been established. The purpose of antenatal monitoring is to identify fetuses that are at highest risk of *in utero* demise that can benefit from intervention by preterm delivery. Fetal arterial and venous Doppler studies may help in identification of the fetuses at risk for perinatal complications or may help in prediction of the fetal acid base status or neonatal complications[9,10]. Therefore, Doppler velocimetry is recommended as the primary surveillance tool for monitoring pregnancies with IUGR[11]. It has been established by numerous randomized trials that the use of Doppler velocimetry can significantly reduce perinatal death. A meta-analysis of these trials reported that clinical management guided by Doppler ultrasonography reduced the odds ratio (OR) of perinatal death by 38%[12]. Absence or reversal of end-diastolic flow in the umbilical artery (UA) is suggestive of poor fetal condition, whereas normal or slightly decreased umbilical Doppler flow is rarely associated with significant morbidity and provides strong evidence of fetal well-being when delivery is delayed to achieve further fetal maturity[13]. The growth restricted fetus seems to be at highest risk of death when Doppler abnormalities are observed in the venous circulation (ductus venosus [DV] and umbilical vein)[14]. The temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the growth restricted fetus have been described as early abnormal Doppler findings in the UA and middle cerebral artery (MCA) followed by reversal of flow in the DV or pulsatile umbilical venous flow[15,16].

Therefore, when evaluating fetuses with Doppler ultrasonography in clinical practice, there may be numerous conditions with various severities. Other than the Doppler results, gestational age of the fetus is generally the main indicator. Therefore, neonatal outcomes in particular situations should be known for counseling and decision-making. Our aim in this study was to compare the neonatal outcomes and fetal acid base status when fetuses were grouped according to the combinations of the Doppler results and also according to each vessel Doppler results.

Material and Methods

Deliveries that took place in our institution between 2003 and 2008 were reviewed retrospectively with respect to birth weight. Pregnancies that resulted in birth of a newborn with a weight less than the 10th percentile for the gestational age (SGA) were selected. Among those pregnancies, singletons that had at least one Doppler examination within 10 days prior to delivery were recruited into the study group. Fetuses having any congenital malformation or chromosomal abnormalities and pregnancies complicated with maternal cardiac diseases, placental abruption or cord prolapsus were excluded. Pregnancies complicated with preeclampsia, HELLP syndrome and eclampsia were not excluded unless the indication for delivery was acute fetal distress. Pregnancies complicated with IUGR and resulting in intrauterine demise within the time period that fulfilled the above-mentioned criteria were also taken into the study group.

For all of these fetuses, Doppler examination results, fetal biometry and delivery data were obtained. Ultrasound examinations were performed with Siemens Sonoline Antares (Siemens AG, Germany). If analyzed, UA cord blood gas analysis results were also obtained. For the neonatal outcomes, need for neonatal intensive care unit (NICU), presence of RDS, bronchopulmonary dysplasia (BPD), NEC, intracranial hemorrhage (ICH), and neonatal death were obtained from the records of our Neonatology Department.

Cases were then grouped in three ways: First, cases were grouped according to the combined results of Doppler studies of the UA, MCA and DV. Group I was defined as normal cases

(MCA pulsatility index [PI] > UA PI), Group II as fetuses with redistribution (UA PI >MCA PI) with normal DV Doppler, and Group III as redistribution (UA PI > MCA PI) with increased DV PI. Secondly, cases were grouped according to the UA Doppler velocimetry only. Group I was defined as normal UA Doppler velocimetry, Group II as increased UA PI, Group III as absent UA end-diastolic flow, and Group IV as reverse UA end-diastolic flow. Finally, cases were grouped according to the DV Doppler velocimetry as Group I, normal DV PI; Group II, increased DV PI; and Group III, absent or reverse DV "a" wave.

For all of the situations, groups were compared for gestational age at delivery, birth weight, interval between date of birth and date of examination, fetal UA cord blood gas analysis (pH and base deficit), length of neonatal hospitalization, presence of fetal and neonatal death, need for NICU, and presence of RDS, NEC, sepsis, BPD, and ICH.

Data were analyzed with the SPSS 11.5 statistical package (SPSS, Chicago, IL, USA). Results are expressed as mean ± SD, or as median with interquartile range (IQR) when data were not normally distributed. Comparisons between groups were performed by ANOVA or the Kruskal–Wallis test for normally and non-normally distributed data, respectively. Significance among neonatal complications were compared between groups with chi-square test and if not appropriate then with Fisher's exact test. Level of significance was set at $p<0.05$ for this study.

Results

A total of 255 pregnancies were recruited into the study. General characteristics of the patients are summarized in Table I. The mean age of the patients was 29.66±5.9. Median gravidity and parity were 2 and 1, respectively. The mean gestational age at delivery was 254 days (36 weeks, 2 days). Median birth weight was 2050 g and the median interval between birth and last Doppler study was 3 days.

All the fetuses had at least one UA Doppler analysis. Two hundred twenty-six had MCA Doppler analysis and 150 had DV Doppler analysis. There were a total of 11 prenatal deaths in the whole group. Neonatal data were obtained in all cases whereas blood gas analyses were available in 74% of the cases. The most common neonatal complications were NEC followed by neonatal sepsis and RDS (11.1%, 9.8% and 9%, respectively).

Among the 255 fetuses, when grouped according to the UA, MCA and DV, there were 157 fetuses in the first group, 48 in the second and 50 in the third group (Table II). The mean birth weight was 2344 g in Group I, 1634 g in Group II and 1255 g in Group III, and birth weight was significantly different between groups ($p<0.001$). The mean gestational age at birth was also significantly different between groups (37.00±2.7, 34.45±3.4 and 31.56±3.3 for Groups I, II and III, respectively). However, when fetal UA blood gas analyses were compared, pH and base deficits were not different between groups. There was only 1 fetal death in Group II and 9 in Group III, and this difference was found to be significant ($p<0.001$). There was no statistically significant difference between groups with respect to the postpartum deaths ($p=0.539$). Regarding the neonatal complications, Group III had significantly higher rates of need for NICU, RDS, NEC, sepsis, BPD, and ICH than Group I (Table II).

When all the fetuses were grouped according to the UA Doppler results, mean birth weights in Groups I, II, III and IV were 2380 g, 1643 g, 1223 g, and 1184 g, respectively (Table II). Mean birth weight, gestational age at delivery and pH were significantly different between groups except for Groups III and IV. Base deficit in Group IV was found to be significantly lower than in Groups I, II and III. Among fetal deaths, 5 occurred in Group II, 1 in Group III and 4 in Group IV. There was a statistically significant increase in the rate of intrauterine death as the end-diastolic flow decreased. However, regarding the postpartum deaths, there was no difference between groups. When neonatal outcomes were analyzed, the rates of need for NICU, RDS and BPD were significantly higher in Group IV than Groups I, II and III. The rate of NEC was significantly different between Groups I, II and III, but the difference was not present for Group IV. There were no differences between Group IV and the others regarding the rate of sepsis and ICH.

When patients were grouped according to the DV Doppler (Table III), the difference

Table I. General Characteristics of the Patients and Perinatal Outcome

Characteristics (n=255)	
Total no. of patients	255
Age (Mean±SD) (years)	29.66±5.898
Gravidity (Median (IQR))	2 (1-8)
Parity (Median (IQR))	1 (1-5)
Gestational age at delivery (Median (IQR)) (days)	254 (231-267)
Birth weight (Median (IQR))(g)	2050 (1380-2640)
Interval between last Doppler study and delivery (Median (IQR)) (days)	3 (1-7)
pH (n=171) (Mean±SD)	7.31±0.08
Base deficit (n=171) (Mean±SD)	-3.71±3.67
Prenatal death (n) (%)	11 (4.3%)
Number of abnormal pH	16 (6.3%)
Perinatal Complications (n=244) Length of neonatal hospitalization (Median(IQR)) (days)	3 (3-9)
NICU (%) (n)	145 (56.9%)
NEC (%) (n)	27 (11.1%)
Sepsis (%) (n)	24 (9.8%)
RDS (%) (n)	22 (9.0%)
Neonatal death (%) (n)	14 (5.5%)
ICH (%) (n)	9 (3.7%)
BPD (%) (n)	7 (2.9%)

BPD: Bronchopulmonary dysplasia. ICH: Intracranial hemorrhage. IQR: Interquartile range. NEC: Necrotizing enterocolitis. NICU: Need for Neonatal Intensive Care Unit. RDS: Respiratory distress syndrome. SD: Standard deviation.

in birth weights was found to be significant only for Groups I and III. The gestational age at delivery was significantly different between groups. In cord blood gas analysis, pH and base deficit were significantly lower in Group III than the others. Among the 10 fetal deaths, it was observed that 5 occurred in Group III, 4 in Group II and 1 in Group I. It was seen that the rate of fetal death was significantly higher in the fetuses having reverse or absent "a" wave (Group III). Similarly, the rate of postpartum exitus was also lower in the first group than the other groups. For the neonatal outcomes, the rate of NICU and NEC did not differ between groups, but the rate of RDS, sepsis and ICH were observed to be lower in Group I; however, this difference did not reach a statistically significant level between Groups I and III.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and ORs of some Doppler findings are summarized in Table III. Absent or reverse UA end-diastolic flow significantly increased the ORs of perinatal death (OR 2.806, 95% confidence interval [CI] 1.076-7.315, p=0.029), fetal death (OR 5.944, 95% CI 1.709-20.682, p=0.002), BPD (OR 10.821, 95% CI 2.293–51.051, p<0.001), NEC (OR 5.794, 95% CI 2.341–14.344, p<0.001), RDS (OR 5.195, 95% CI 1.962–13.757, p<0.001), and need for NICU (OR 11.607, 95% CI 2.697–49.957, p<0.001). Absent or reverse flow in UA end-diastolic velocity was found to have high specificity for perinatal complications but was found to be most sensitive for fetal death (45.5%), NEC (37.0%) and RDS (36.4%).

Absent or reverse "a" wave in DV significantly increased the OR of perinatal death (OR 19.89, 95% CI 5.031–78.608, p<0.001), fetal death (OR 18.06, 95% CI 4.271–76.332, p<0.001), neonatal death (OR 12.50, 95% CI 1.836–85.123, p=0.031), RDS (OR 8.29, 95% CI 1.523–45.069, p=0.026), and abnormal pH

(OR 9.67, 95% CI 1.695–55.143, p=0.021) rates. The sensitivity of this Doppler finding was found to be highest for detection of fetal death (45.5%).

Discussion

Fetal growth restriction is most commonly due to abnormal vascular development of the placenta. Defective trophoblast invasion and failure of physiologic transformation of uterine vessels result in progressive occlusive vasculopathy in the maternal and fetal vascular compartments of the placenta[17]. Abnormal vascular tone, as well as obliterative loss of fetal villous vessels, raises UA Doppler resistance. A decrease in end-diastolic velocity becomes apparent when some 30% of the placenta is affected and progresses to absent or reversed end-diastolic velocity when the damage extends to 60 to 70%[17]. Because fetal cardiovascular compromise progresses from arterial to venous flow, these changes have been termed early and late vascular responses, respectively[18]. Early Doppler changes include increase in the UA resistance with decreased MCA resistance resulting in preferential blood flow to the brain. This redistribution or "brain sparing effect" is a compensatory mechanism of the fetus to spare vital organs without any change in the metabolic status. In our results, it can be clearly seen that the pH and the base deficit did not change when redistribution was present (Table II). However, these physiologic changes do not mean that the fetus is not in danger. Birth weight was significantly lower in the fetuses that had redistribution. When compared with non-redistributed fetuses, due to the preferential blood flow, fetuses with redistribution developed more NEC and need for NICU (Table II). Increased rate of admission to the NICU was the result of preferential blood flow leading to NEC and preterm delivery leading to RDS.

However, as the vascular disease worsens with decompensation of the fetus, metabolic deterioration is observed. Late Doppler changes are usually in the venous system of the fetus but the absence or reverse flow in the UA blood flow is also considered a late finding[11,18]. As can be seen in Table II, nearly all outcomes except neonatal death are increased as the UA Doppler worsens. When absence and reverse flow in UA are compared separately, it was observed that only mean base deficit and the rate of fetal death were higher in the reverse flow group. This may be the result of the low number of fetuses in the reverse flow group (Group IV for UA), but it may also mean that absence and reverse flow are a continuum in the progress, which is only reflected in the base deficit. Therefore, absent flow in addition to reverse flow in the UA should be considered as late arterial Doppler findings.

In venous Doppler evaluation of the growth restricted fetuses, as a result of metabolic changes, both pH and base deficit, and as a consequence, rates of ICH, RDS and fetal neonatal and perinatal death are all increased (Table II). Absence or reversal of "a" wave in DV Doppler waveform is known to be a late finding[11,15,19], and our results were in concordance with the literature. The rate of neonatal sepsis unexpectedly did not increase as the Doppler findings worsened. Sepsis itself may not be a consequence of physiologic changes in the fetus; rather, it is a result of the increased admission to the NICU and increased rate of other complications.

When the two important Doppler findings (absent or reverse UA end-diastolic flow and absent or reverse "a" wave in DV) were analyzed in relation to neonatal outcomes, all of the perinatal complications were increased (Table III). However, in presence of absent or reverse UA end-diastolic flow, the increases in neonatal death, sepsis, ICH and abnormal pH rates did not reach a statistical significance. The highest ORs were need for NICU and BPD. In the presence of absent or reverse "a" wave in DV Doppler study, especially the OR for all perinatal mortality rates and abnormal pH rate increased more than the increase when there was UA abnormality. Unexpectedly, the ORs for neonatal complications were lower when compared to absent or reverse end-diastolic flow in UA. This is the result of increased fetal loss when these late findings are present, leading to a relatively lower number of survivors.

For the time being, there is no effective treatment option for vascular disease of the placenta. Therefore, we are left with two management options: to deliver the fetus accepting prematurity and related complications

Table II. Comparison of Cord Blood Analysis and Perinatal Complications Between Groups

Groups according to MCA, UA and DV PI				
	Group I (n=157)	Group II (n=48)	Group III (n=50)	p
Birth weight	2344.8 ± 612.9	1634.6 ±636.1	1255.7 ±552.5	<0.001(1-2)(1-3)(2-3)
GA at delivery	37.0±2.7	34.5±3.4	31.5±3.3	<0.001(1-2)(1-3)(2-3)
pH	7.32 ±.07	7.31±.08	7.29±.09	NS
Prenatal death (%)(n)	0(0)	2.1 (1)	18.0 (9)	<0.001(1-3)(2-3)
Neonatal death(%)(n)*	5.1(8)	6.4 (3)	9.8 (4)	NS
NICU (%)(n)*	45.2 (71)	80.8 (38)	90.2 (37)	<0.001(1-2)(1-3)
RDS (%)(n)*	3.2 (5)	10.6 (5)	31.7 (13)	<0.001(1-2)(1-3)(2-3)
NEC (%)(n)*	5.1 (8)	17.0 (8)	26.8 (11)	<0.001(1-2)(1-3)
Sepsis (%)(n)*	5.7 (9)	12.8 (6)	24.4 (10)	<0.05(1-3)
BPD (%)(n)*	0.6 (1)	4.3 (2)	9.8 (4)	<0.05(1-3)
ICH (%)(n)*	1.3 (2)	4.3 (2)	12.2 (5)	<0.05(1-3)
Groups according to Umbilical Artery Doppler				
	Group I (n=143)	Group II (n=77)	Group III (n=24)	Group IV (n=11)	p
Birth weight	2380.6±594.4	1643.8±671.7	1223.3±440.6	1184.5±645.6	<0.001(1-2)(1-3)(1-4)(2-3)
GA at delivery	37.13±2.6	34.11±3.6	32.05±3.7	30.62±2.5	<0.05(1-2)(1-3)(1-4)(2-3)(2-4)
pH	7.32±.07	7.31±.08	7.32±.04	7.22±.16	<0.05(1-2)(1-3)(1-4)(2-3)
Prenatal death (%)(n)	0 (0)	6.5 (5)	4.2 (1)	36.4 (4)	<0.001(1-2)(1-4)(2-4)(3-4)
Neonatal death(%)(n)*	4.9 (7)	8.3 (6)	0 (0)	28.6 (2)	NS
NICU (%)(n)*	44.1 (63)	76.4 (55)	91.3 (21)	100 (7)	<0.001(1-2)(1-3)(1-4)
RDS (%)(n)*	3.5 (5)	13.9 (10)	21.8 (5)	42.9 (3)	<0.05(1-2)(1-3)(1-4)
NEC (%)(n)*	4.2 (6)	15.3 (11)	39.1 (9)	14.3 (1)	<0.05(1-2)(1-3)(2-3)
Sepsis (%)(n)*	5.6 (8)	15.3 (11)	17.4 (4)	28.6 (2)	<0.05(1-2)
BPD (%)(n)*	0 (0)	4.2 (3)	13.0 (3)	14.3 (1)	<0.05(1-2)(1-3)(1-4)
ICH (%)(n)*	0.7 (1)	8.3 (6)	4.3 (1)	14.3 (1)	<0.05(1-2)
Groups according to Ductus Venosus Doppler				
	Group I (n=80)	Group II (n=56)	Group III (n=11)	p
Birth weight	1938.3±752.0	1475.1±684.9	1384.5±673.6	<0.001(1-2)
GA at delivery	35.24±3.4	33.28±3.9	30.52±2.7	<0.05(1-2)(1-3)(2-3)
pH	7.32±.09	7.31±.07	7.22±.16	<0.05(1-3)(2-3)
Prenatal death (%)(n)	1.3 (1)	7.1 (4)	45.5 (5)	<0.001(1-2)(2-3)
Neonatal death(%)(n)*	5.1 (4)	3.8 (2)	33.3 (2)	<0.05(1-2)(1-3)
NICU (%)(n)*	65.6 (52)	80.8 (42)	100.0 (6)	NS
RDS (%)(n)*	6.3 (5)	19.2 (10)	50.0 (3)	<0.05(1-2)(1-3)
NEC (%)(n)*	13.4 (11)	21.2 (11)	0 (0)	NS
Sepsis (%)(n)*	8.9 (7)	23.1 (12)	16.7 (1)	<0.05(1-2)
BPD (%)(n)*	2.5 (2)	7.7 (4)	16.7 (1)	NS
ICH (%)(n)*	1.3 (1)	11.5 (6)	16.7 (1)	<0.05(1-2)

*Cases with intrauterine demise are excluded.

Numbers in the superscript parenthesis are the p-value indicating significance between groups.

BPD: Bronchopulmonary dysplasia. DV: Ductus venosus. EDF: End-diastolic flow. GA: Gestational age. ICH: Intracranial hemorrhage. MCA: Middle cerebral artery. NEC: Necrotizing enterocolitis. NICU: Need for Neonatal Intensive Care Unit. PI: Pulsatility index. RDS: Respiratory distress syndrome. SD: Standard deviation. UA: Umbilical artery.

Table III. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, Odds Ratio and Confidence Interval with p values of Absent or Reverse Flow in UA and Absent or Reverse "a" Wave in DV for Perinatal Complications

		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Odds Ratio	CI (95% CI)	p
A/R UA EDV	Perinatal death	28.0	87.8	20	96.7	2.806	1.076 – 7.315	0.029*
	Prenatal death	45.5	87.7	14.3	97.7	5.944	1.709 – 20.682	0.002*
	Neonatal death	14.3	87.8	6.7	99.0	1.202	0.256 – 5.655	0.815
	BPD	57.1	89.0	13.3	98.1	10.821	2.293 – 51.051	<0.001*
	Sepsis	25.0	89.1	20.0	97.0	2.722	0.985 – 7.523	0.092
	NEC	37.0	90.8	33.3	95.2	5.794	2.341 – 14.344	<0.001*
	RDS	36.4	90.1	26.7	96.2	5.195	1.962 – 13.757	<0.001*
	NICU	19.3	98.0	93.3	77.6	11.607	2.697 – 49.957	<0.001*
	ICH	22.2	88.1	6.7	99.0	2.112	0.418 – 10.676	0.355
	Abnormal pH	18.8	87.7	13.7	97.8	1.652	0.431 – 6.334	0.460
A/R DV "a" Wave	Perinatal death	38.9	93.2	43.8	94.6	19.89	5.031 - 78.608	<0.001*
	Prenatal death	45.5	92.1	31.3	96.2	18.06	4.271 - 76.332	<0.001*
	Neonatal death	28.6	93.2	18.2	98.4	12.50	1.836 - 85.123	0.031*
	BPD	14.3	92.4	9.1	99.2	4.13	0.415 - 41.146	0.276
	Sepsis	5.3	91.7	9.1	99.1	1.24	0.137 - 11.276	0.846
	NEC	4.5	91.5	9.1	99.1	0.83	0.769 - 0.898	0.589
	RDS	17.6	93.4	27.3	97.4	8.29	1.523 - 45.069	0.026*
	NICU	8.1	92.5	72.7	82.2	0.72	0.642 - 0.797	0.189
	ICH	12.5	92.4	9.1	99.2	3.51	0.360 - 34.293	0.310
	Abnormal pH	23.1	93.5	33.3	96.7	9.67	1.695 - 55.143	0.021*

BPD: Bronchopulmonary dysplasia. DV: Ductus venosus. EDV: End-diastolic volume. ICH: Intracranial hemorrhage. NEC: Necrotizing enterocolitis. NICU: Need for Neonatal Intensive Care Unit. RDS: Respiratory distress syndrome. UA: Umbilical artery.
*Statistically significant

or wait to permit organ maturation for as long as possible until intrauterine fetal metabolic deterioration develops. Accepting prematurity in an IUGR fetus is a risky option because the outcome in a premature fetus with growth restriction is worse than prematurity alone[3,5]. At this time, the point at which intrauterine decompensation occurs is not clear. Considering the placental and cerebral arterial changes as the time of intervention is not appropriate

because those changes occur early in the pathogenesis of fetal growth restriction. In the Growth Restriction Intervention Trial study[20], when UA abnormalities are taken as the time to intervention point, growth restricted infants randomized to early delivery did better than infants randomized to "wait for deterioration", especially after 33 weeks.

Changes in the venous system, especially in the DV, are a more reliable finding because DV changes occur late in the progression of placenta-based fetal growth restriction[16, 18, 21]. However, DV alone is also not enough when neonatal outcomes are considered. Prematurity is a very strong factor in predicting poor neonatal outcome. In a multicenter study conducted by Baschat et al.[22], beyond 27 weeks, DV abnormality emerges as the statistically important fetal cardiovascular predictor of neonatal complication. Before this, the impact of gestational age is so important that DV Doppler alone does not provide sufficient stratification of risk. The final step in progression, reversal of the DV "a" wave, indicates risk for fetal cardiac, hepatic, and generalized metabolic failures[23], which relates with perinatal death. Therefore, DV velocity, forward or absent/reversed, is likely a reliable trigger for intervention in severe fetal growth restriction beyond 27 weeks of gestation[22]. In our results, when this abnormal finding is present, nearly half (45.5%) of the fetuses died *in utero* and nearly one-third (33.2%) of the survivors died after birth (Table II). The same intrauterine death rate is also true when there is absent or reverse UA end-diastolic velocity, but because the rate of abnormal pH did not increase, there were more postpartum survivors. Additionally, when we performed a subgroup analysis among fetuses with reverse flow in UA, the rate of prenatal death, neonatal death and perinatal death did not differ significantly ($p=0.721$, $p=0.476$ and $p=0.500$, respectively) in the presence or absence of reverse "a" wave. If this is true and the perinatal death rate did not differ, why do we wait for the occurrence of metabolic deterioration? To deliver the fetus before reverse "a" wave occurs may be a more reliable intervention time when neonatal complications are considered.

There are several weak points to this study. One of the most important is that blood gas analysis was not available for all the fetuses. Nearly 25% of blood gas analyses were unavailable. However, in the most important group, "absent or reverse "a" wave in the DV", there were 11 fetuses, and among those, blood gas analysis was available for all the liveborn neonates. Therefore, the absence in the other groups may not be very important. The other weak point in our study is the heterogeneity of the mothers. Pregnants with preeclampsia, eclampsia and HELLP syndrome were also included into the study. Nevertheless, because the pathogenesis of IUGR in both situations is similar, the difference would not be important unless acute complications are excluded. Lastly, because of the design of the study, the findings are not correlated with the biophysical testing and cardiotocography results. However, our aim was to correlate Doppler findings with neonatal complications.

In conclusion, the results in our study showed that in estimation of the neonatal outcomes, results of all three Doppler examinations should be considered together. However, for the prediction of fetal metabolic status, DV Doppler is a more reliable tool. When perinatal complications, especially perinatal death, are considered, reversed "a" wave in the DV Doppler waveform for intervention-to-delivery is a late point. Therefore, decision-to-delivery should be taken at the point when reverse end-diastolic flow in the UA is observed, in order to avoid metabolic deterioration and increased postpartum death. However, it must be remembered that the gestational age is the major determinant in the perinatal outcome of growth restricted fetuses and must be considered when decision-to-delivery is imminent.

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