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The role of doppler indices in predicting intra ventricular hemorrhage and perinatal mortality in fetal growth restriction

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Abstract

Objectives: The aim of this study is to determine whether Doppler indices predict intra-ventricular hemorrhage and perinatal mortality in fetal growth restricted pregnancies (FGR). **Material and Methods:** In this cohort study, 43 FGR fetuses underwent multi-vessel Doppler ultrasounds weekly or twice weekly after admission. Blood gases of the umbilical cord were analyzed immediately after delivery. Ultrasonography of the neonatal brain was performed after birth. Intra ventricular hemorrhage (IVH) and perinatal mortality were studied as outcomes. **Results:** The median gestational age at the diagnosis of fetal growth restriction was 31 weeks, and the median age at delivery was 33.4 weeks. Seven cases had IVH. The chance of IVH was about five times greater in cases of absent/reversed umbilical diastolic flow (AREDF). The predicting factors for IVH were gestational age at delivery, birth weight, and acidosis. Nine neonates died in the neonatal period. AREDF, the Ratio of Resistance Index of middle cranial artery to umbilical artery (Cerebral/Umbilical ratio MCA RI/UA RI), and absent/reversed "a" waves in ductus venosus (DV) were the Doppler indices predicting perinatal mortality. The other prognostic factors for perinatal mortality were gestational age at diagnosis and delivery, final amniotic fluid, Apgar score, and acidosis. **Conclusion:** Doppler indices, such as AREDF, can be predictors of IVH or perinatal death, and an absent or reversed "a" wave in the ductus venosus and the hypoxic index can be significant predictors of death in fetuses with fetal growth restriction. However, other important factors for IVH were gestational age at delivery and birth weight. The most important factors predicting perinatal mortality were gestational age, birth weight, acidosis, low AF, and low Apgar score.

Keywords: intraventricular hemorrhage, perinatal mortality, Doppler indices, fetal growth restriction

Introduction

Fetal growth restriction is a condition that places the fetus at risk for hypoxemia, acidemia, antepartum death, and intrapartum distress [1-3]. Perinatal mortality rates in growth-restricted neonates are six to ten times greater than those in normal age-matched controls [4]. These neonates are also at increased risk for a number of metabolic disturbances, including polycythemia, pulmonary transition difficulties, intra-ventricular hemorrhage (IVH), impaired cognitive function, and cerebral palsy [5]. Long-term morbidity and predisposition to adult-age chronic diseases, such as hypertension, obesity, and diabetes are increased in these pregnancies [6].

Predicting perinatal mortality and morbidity in cases of FGR is very important for the management of these pregnancies, especially with regard to the preterm fetus. Doppler indices were studied for several years [7-11]. Abnormal Doppler indices in fetuses with low weights, estimated via ultrasonography, were correlated with adverse perinatal events such as acidosis, IVH, mortality, and greater admission time in Neonatal Intensive Care Units [12-16]. The most common indices reported are S/D (ratio off-peak systolic blood flow velocity to diastolic velocity), the Pul-

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satility Index (PI), the Resistance Index (RI) of the umbilical artery (UA) and middle cerebral artery (MCA) [14-16], the hypoxic index (S/D of MCA / S/D of UA, MCA RI/UA RI) [17,18], and the Peak Systolic Velocities (PSV) of MCA [19]. Venous Doppler, such as those of the ductus venosus (DV) and the umbilical vein (UV) were used for detecting the outcome of FGR pregnancies [20,21].

The aim of this study is to determine which Doppler indices are better predictors of perinatal mortality and intra-ventricular hemorrhage in FGR pregnancies.

Material and method

Patients

This prospective cohort study was based on the evaluation of Doppler indices of 43 cases of FGR admitted to the perinatology ward in Shariati Hospital of Tehran University of Medical Sciences between October 2008 and November 2010. The study was performed after the Institutional Review Board and Ethics Committee approval was obtained. All were single pregnancies with estimated weights or abdominal circumferences below the 10th percentile of the normal growth curve, and umbilical artery Pulsatility Indices (PI) and Resistance Indices (RI) of more than two standard deviations (SD) of the mean age were enrolled in the study. The exclusion criteria were multi-fetus pregnancies, structural or chromosomal anomalies and intrauterine IVH.

All pregnant women were admitted prior to the termination of pregnancy (1 to 30 days), and the delivery time was decided based on fetal heart rate patterns as well as maternal and fetal clinical status. All fetuses with Gestational age lower than 34 weeks had received one course of betamethasone prior to the termination of pregnancy, and all those with preeclampsia had received magnesium sulphate prior to caesarian section or delivery.

After birth, one to two milliliters blood was drawn from the double clamped umbilical cord for determination of the bicarbonate (HCO3), base deficit, and pH. Acidosis was considered to be present if the pH was below 7.27 in full-term fetuses or less than 7.25 in preterm fetuses [22,23].

A neonatologist determined the Apgar scores. The neonatologist was blinded to the results of the Ultrasonography and Doppler studies. All neonates with low Apgar scores or weights below 2,500 grams were admitted to the Neonatal Intensive Care Unit, and those with Apgar score of more than six, birth weights above 2,500 grams, and no resuscitation were admitted to the neonatology ward.

Ultrasound examination

One expert perinatologist performed all the Doppler studies. Doppler ultrasonography was performed on a patient in a supine position, using an Acuson Sequoia 512 US system (Mountain View, CA, USA) equipped with a broadband 4-5 MHz sector transducer.

The mechanical and thermal indices were kept below 1 (UNIT). We performed multi-vessel Doppler ultrasound of the fetuses (UA, UV, MCA, DV)_weekly or twice weekly with respect to the initial Doppler results. UA and UV Doppler waveforms were obtained from free loops of cord midway between the placenta and fetal abdomen. MCA Doppler waveforms were obtained at the level of the circle of Willis in the distal portion. RI, PI, SD, peak systolic velocities of UA and MCA, and hypoxic indices (MCA PI/ UA PI and MCA RI/UA RI) were also measured. The fetuses with PI-C/U ratios less than 1.08 and RI-C/U ratios less than 1 were considered as Hypoxic Index according to previous reports [17,24,25]. DV Doppler was obtained from a mid-sagittal or transverse section of the fetal abdomen. DV was considered abnormal if reduced, absent, or reversed “a” waves was detected. Doppler of the UV was considered abnormal in the presence of UV pulsatility without fetal respiration. When at least five consecutive uniform flow velocity waveforms with high signal-to-noise ratios and an insemination angle near zero were obtained during periods of fetal rest and apnea, the image was frozen and the waveforms were quantified or interpreted. We also measured amniotic fluid in pregnancies, and the last value before delivery was used for statistical analysis.

Ultrasound examination of the neonatal brain was performed by a radiologist with experience in neonatal imaging through anterior fontanels in coronal and parasagittal projections with a 7.5 MHz probe during the first twelve hours after birth until the seventh day after delivery and was graded from one to four [26]. [Grade I: germinal matrix hemorrhage only or germinal matrix hemorrhage plus intra-ventricular hemorrhage less than 10 percent of ventricular area. Grade II: intra-ventricular bleeding over 10-50% of ventricular area on the sagittal view. Grade III: intra-ventricular bleeding over >50% of the ventricular area or distending the ventricle. Grade IV IVH: parenchymal hemorrhage in any location, with or without intra-ventricular hemorrhage, also referred to as periventricular hemorrhage].

Statistical analysis

Statistical analysis was performed using the Software Package for the Social Sciences (SPSS version 11, Chicago, IL, USA). The normal distribution of the continuous variables was checked by one sample Kolmogorov-Smirnov test. The results were expressed as in terms of median (range) or frequency (percentage). Due to the abnormal distribution of most data, a Mann-Whitney U test was used to compare continuous variables between the two groups. Using univariate logistical regression analysis, the odds ratios and confidence intervals were estimated. P values equal to or less than 0.05 were considered statistically significant.

Results

The study consisted of 43 pregnant women with a diagnosis of FGR (table I.) Hypertension-related disorders were the most common maternal disease diagnosed in these pregnant women.

The median (range) of gestational age at delivery was 33.4 (27.6, 40.3) weeks. Thirty-four women had preterm deliveries. Twelve fetuses had absent or reversed diastolic flows of the UA (fig 1-2). The DV “a” wave was normal in 34 (fig 3), reversed in five (fig 4), and absent in three cases.

Table I. Maternal characteristics of pregnant women

Characteristics (N = 43)	
maternal age (years)	30 (21 - 54)
gestational age at diagnosis (weeks)	31 (23 - 40)
chronic HTN	14 (32.6)
PIH	5 (11.6)
preeclampsia	5 (11.6)
gestational diabetes	3 (7.0)
thrombophilia	3 (7.0)
hypo/ hyperthyroidism	3 (7.0)
others	4 (9.3)

N: number of patients, HTN: Hypertension, PIH: Pregnancy induced hypertension. Data presented as median (range)

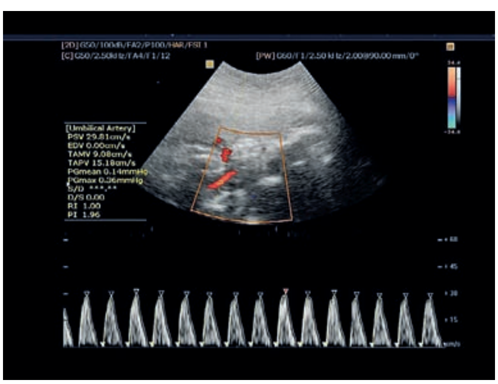

Fig 1. Doppler of Umbilical artery: absent diastolic flow

Forty-one patients had caesarian sections. Fetal distress was the most common indication of termination (28%), followed by reversed diastolic UA (16%), and maternal indications (16%). Reverse DV waves (7%), non-reactive NST (7%), absent-diastolic-flow-UA (5%), oligohydramnious (5%), and placental abruption (2%) were other indications. Two neonates died immediately after delivery before undergoing brain ultrasonography. Their gestational

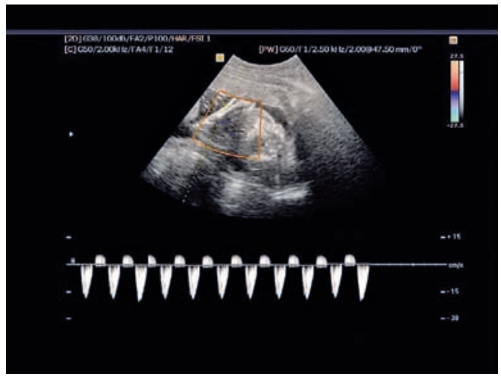

Fig 2. Doppler of Umbilical artery: reverse diastolic flow

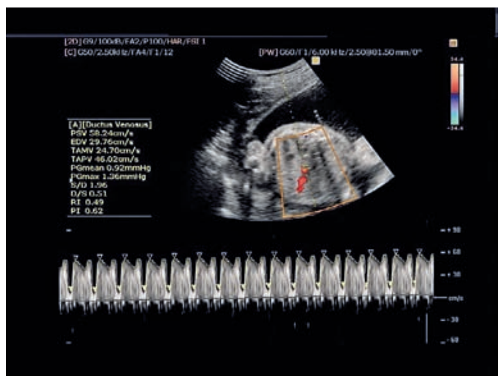

Fig 3. Doppler of Ductus Venosus: normal

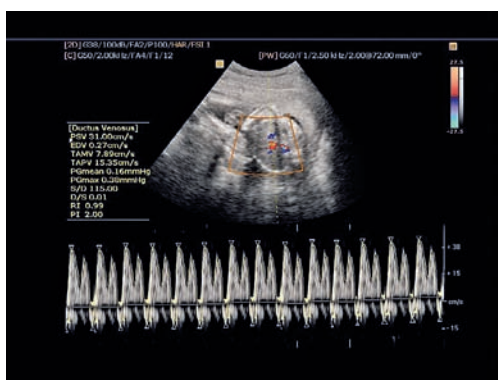

Fig 4. Doppler of Ductus Venosus: reverse ”a”wave

ages were 27wks and 4days and 28wks and 3days, and their birth weights were 620 and 500 grams, respectively. All 41 neonates underwent at least one brain sonography examination during the first 72 hours of life, and the results were normal in 34 (82.9%) and IVH in seven cases (16.2%) (Two with grade 3 and five with grades 1 and 2). Assessing the relationship between the last Doppler ultrasonographic indices obtained from the fetuses and the occurrence of IVH revealed that abnormal umbilical indices were more frequent in cases of IVH than in the normal group, although they were not statistically significant (table II).

Table II. Comparison of Doppler sonographic findings between IVH and normal brain sonography groups

	Normal group		IVH group		
	n/N	**%**	**n/N**	**%**	**P**
PI-UA> 95^{th}	20/30	66.7	4/5	80.0	1
RI-UA> 95^{th}	24/33	72.7	5/5	100	0.312
ARDF - UA	7/33	21.2	4/7	57.1	0.075
PSV- MCA > 95^{th}	0/25	0	1/5	20.0	0.167
PI-C/U ratio<1.08	18/30	60.0	4/4	100	0.273
RI-C/U ratio<1	18/33	54.5	5/5	100	0.136
ARDVAW	6/34	17.6	1/6	16.7	1

N: number of patients investigated, n: number of patients with pathological findings, ARDF: Absent/Reverse Diastolic Flow; ARDVAW: Absent/Reverse Ductus Venosus A Wave, PI-C/U: Pulsatility Index of MCA/pulsatility Index of UA; RI-C/U: Resistance Index of MCA/Resistance Index of UA, PSV:peak systolic velocity.

In cases with absent/reversed umbilical diastolic flow, the chances of IVH was nearly five times greater, but was not significant (OR= 4.9; 95% CI: 0.9 – 27.5, p= 0.067). All IVH cases had PI-C/U ratios < 1.08 and RI-C/U ratios < 1. Both maternal and gestational ages were matched in the IVH and normal brain ultrasonography group. There was a statistically significant difference between the two groups in relation to gestational age and birth weight at delivery (table III). All IVH neonates were premature, with birth weights below 1,500 grams. The chance of IVH was 7.6 times more in cases with gestational ages less than 34 weeks when compared to cases with gestational ages greater than or equal to 34 weeks (OR= 7.6; 95%CI: 0.82 – 70.2, P = 0.074). The chances of developing IVH decreased by about 20% for each 100 gram increase in birth weight, (OR= 0.78; 95%CI: 0.63 – 0.98, P = 0.037). The odds ratio of IVH was twelve times more in the presence of umbilical cord acidosis when compared to cases without acidosis, (95%CI: 1.5 – 95.0; *P* 0.019). There was not a significant difference between the two groups regarding the PCO2 of the umbilical cord, (*P* = 0.527), base deficit (*P* = 0.132), HCO3 (*P* value= 0.188), and PO2 (*P* = 0.167). There were not statistically significant differences in one and five minute Apgar scores of <7 (*P* =0.069 and *P* = 0.226, respectively)

Table III. Comparison of maternal and neonatal characteristics between IVH ***and normal*** brain sonography groups

	Normal (n=34)	**IVH (n=7)**	**P**
Maternal age (year)	30 (21 – 54)	31 (24 – 38)	0.498
Gestational weeks at diagnosis	31.3 (25.7 – 40.0)	31.0 (23.0 – 33.1)	0.245
Gestational weeks at delivery	34.2 (28.0 – 40.3)	31.4 (28.0 – 34.0)	0.041
Preterm delivery:			0.145
28 -31.6 weeks	11 (32.4)	4 (57.1)	
32 – 33.6 weeks	4 (11.8)	2 (28.6)	
34 – 35.6 weeks	7 (20.6)	1 (14.3)	
≥36 weeks	12(35.3)	0	
Last AFI	7.8 (3.0 – 13.0)	6.0 (5.0 – 7.5)	0.082
Birth weight (gram)	1655 (660 – 2950)	1030 (400 – 1400)	0.021
acidosis	2 (5.9)	3 (42.9)	0.028
APGAR score minute 1	7 (3 – 9)	6 (1 – 8)	0.069
APGAR score minute 5	9 (6 – 10)	8 (2 – 10)	0.226

AFI (Amniotic Fluid Index) – Data presented as Median (Min.–Max.) or frequency (%)

Nine neonates died in the neonatal period. Six had early mortality (<12 hours), and three had late complications: one necrotizing entrocolitis, one IVH grade 3 and one due to pulmonary hemorrhage. UA indices were higher in those neonates that expired when compared to those that survived, although there was no significant relationship between the two groups (table IV). The odds ratio for death was 4.6 times higher in neonates with absent/reversed umbilical diastolic flows (95%CI: 0.98 – 22.03; P = 0.053) and 7.5 times higher with absent/reversed "*a*" waves in the DV (OR = 7.5, 95%CI: 1.3 – 42.5; P = 0.023). RI of MCA / RI of UA < 1 is the other Doppler abnormality that is significantly different between living and dead neonates. The significant predictors of perinatal mortality were lower gestational age at diagnosis and delivery (P < 0.001), lower final AFI (P 0.015), lower birth weight (P < 0.001), and lower Apgar scores in the first and fifth minutes after birth (P = 0.002 and P = 0.043, respectively), and acidosis (P < 0.001). Maternal hypertension-related disorders were more frequent among dead neonates than surviving neonates (89% versus 39%, P = 0.020). Three of seven neonates that died versus four of the 34 neonates that survived had IVH (P = 0.082) (table V).

Table IV. Comparison of Doppler sonographic findings between alive and dead groups

	Alive		Dead		
	n/N	%	n/N	%	P
PI-UA> 95th	21/31	67.7	4/5	80.0	1
RI-UA> 95th	24/33	72.7	7/7	100	0.175
ARDF - UA	7/33	21.2	5/9	55.6	0.090
PI-C/U ratio<1.08	19/30	63.3	4/5	80	0.640
RI-C/U ratio<1	17/32	53.1	8/8	100	0.016
ARDVAW	4/34	11.8	4/8	50.0	0.030

ARDF: Absent/Reverse Diastolic Flow; ARDVAW: Absent/Reverse Ductus Venosus A Wave

Discussion

Placental insufficiency results from various conditions. One of the most common conditions is maternal disease, such as chronic hypertension and preeclampsia [8,27]. In our study, hypertension-related disorders were the most common variety of disease in FGR pregnancies.

In respect to the increased mortality and morbidity in these pregnancies, the predicting factors are very important. IVH is an important cause of morbidity and mortality in very low-birth weight infants, and high-grade IVH is a known risk factor for severe perceptual, cognitive, and motor neurologic impairments [28,29]. Increasing resistance in the umbilical artery is the first change in the fetus in response to placental insufficiency. It can be diagnosed with rising PI, RI, and S/D of UA values in comparison with the normal value for a given gestational age. Progressing hypoxia results in cardiovascular changes, and the fetus attempts to send highly oxygenated blood to vital organs [30,31].

The Right and Left heart in a fetal state are parallel, so in order to compensate for hypoxia, a higher percent of the ductus venosus's blood goes to the right atrium and via the foramen ovale to the left atrium, which supplies highly oxygenated blood for the brain, heart, and adrenal glands [30-32]. The shift of blood to the brain is called brain sparing. This phenomenon is diagnosed via the

Table V. Comparison of maternal and neonatal characteristics between alive and dead groups

	Alive (n=34)	Dead (n=9)	P
Maternal age (year)	30 (21 – 54)	29 (25 – 38)	0.482
Gestational weeks at diagnosis	31.9 (25.6 – 40.0)	28.3 (23.0 – 30.0)	<0.001
Gestational weeks at delivery	34.2 (29.1 – 40.3)	28.4 (27.6 – 30.6)	<0.001
Last AFI	7.5 (3.0 – 13.0)	5.0 (3.0 – 9.0)	0.015
Birth weight (gram)	1655 (830 - 2950)	800 (400 - 900)	<0.001
APGAR score minute 1	7 (3 - 9)	4 (1 - 8)	0.002
APGAR score minute 5	9 (6 - 10)	7 (2 - 10)	0.043

AFI: Amniotic fluid Index

decline in PI, RI, and S/D in MCA levels [30-32]. This event has a few stages [33]. The first stage is decreasing PI and RI in MCA levels with a normal cerebroplacental ratio (CPR) [33]. In the second stage, centralization occurs, which can quantify the cereberoplacental ratio (CPR), and the decrease in this ratio is considered the hypoxic index as in previous articles. In recent articles the authors have demonstrated that the last change in MCA is normalization: the PI and RI of become normal. Therefore, it is possible that the changes in brain circulation can cause IVH in the neonatal period [34], and if this morbidity can be predicted, we can devise an intervention for reducing it. In the previous articles, no relationship between brain sparing and centralization with IVH was found [33-35]. Absent or reversed diastolic flow in UA was correlated with the IVH occurrence. Our study considers the relationship between multi-vessel Doppler indices and the occurrence of IVH. In our study, IVH in FGR neonates was more common in those neonates with abnormal Doppler indices. Hypoxic indices (MCA PI/UA PI <1.08 and MCA RI/UA RI<1), UA RI >95%, UA PI >95%, ARDF in the UA, and absent or reversed "a" waves in the DV were also more common in IVH groups, growth restricted neonate but the difference was not significant, so none of them could predict neonatal IVH. The important factors that predicted IVH in our study were acidosis in the umbilical cord, gestational age at delivery, and the weight of the neonate. Comparing with previous studies, our study showed the effect of birth weight on the occurrence of IVH, and each 100 grams of increased birth weight was able to reduce the incidence IVH by about 20%. Was it possible that the most important factor regarding IVH was prematurity, and none of our neonates with gestational ages greater than 34 weeks, except for one, had IVH. Is it possible that this was due to the pathogenesis of IVH. Etiology of IVH in preterm fetuses is different from that in preterm fetuses. In full-term fetuses, the most common cause of IVH is trauma, and the origin of this trauma is the choroid plexus [37,38]. In preterm fetuses, the origin of hemorrhage is the subependimal germinal plexus, which is very fragile and highly cellular [39-41]. It is prominent before 32 weeks [39]. Also, in neonates without brain sparing as compared to neonate with brain sparing, no IVH occurred, and it is possible that vasodilatation of the brain vessels has a preventive effect on FGR fetuses [36]. With the progression of hypoxia and in the presence of ARDF in UA, IVH is common. It is explained with a low afterload of the left ventricle and hypertension in the brain [42].

The rate of perinatal mortality in our study was 20.9 % [9 of 43]. This rate in previous articles was 21.5-41.4% [43,44]. We had no intrauterine fetal death, but two fetuses experienced early mortality (<12 hours), and three had late complications, such as necrotizing entrocolitis, IVH grade 3, and pulmonary hemorrhage. These complications are frequent in premature neonates. Perinatal mortality was 4.6 times higher in cases of absent/reversed umbilical diastolic flow, and 7.6 times higher in neonates with absent or reversed "*a* "waves in the DV. In this way, our study was similar to previous studies [27,45-48]. Whenever previous articles showed high perinatal mortality in fetuses with high levels of PI and RI of UA [12-16], they compared pregnancies with high Doppler indexes and pregnancies without Doppler abnormalities. Thus, the results are due to placental insufficiency, resulting in high mortality and morbidity. We considered all fetuses with documented placental insufficiency and compared the pregnancies with mortality or short time morbidity in FGR neonates.

In previous studies, the cerebro-placental ratio was a predictor of adverse outcomes FGR. PI and RI were used for quantities centralization. We considered the cut-off to be 1 for RI and 1.08 for PI. In our study, CPR with respect to RI was a useful predictor of perinatal mortality in comparison to hypoxic index via the measurement of PI.

With respect to the sequence of cardiovascular changes in FGR pregnancies, venous changes are last, and reduced, absent, and reversed "*a*" waves in the DV are correlated with acidosis in the umbilical cord and so finally with stillbirth and perinatal mortality [27,28,45-48]. In our study, the odds ratio of perinatal mortality was 7.5 times higher in cases with absent or reversed "a" waves in the ductus venosus. All fetuses with reversed "a" waves in the DV had acidosis. In our study, we had no pulsatility in the umbilical vein, so it is possible that abnormality in the UV is the terminal deterioration of fetal circulation and that it appears after the abnormality in the ductus venosis. In a longitudinal survey of FGR [48], the pulsatility of UV was seen before the ductus venosus's absent or reversed "a" waves. It is possible that the pattern of changes was not consistent in all FGR pregnancies.

We note that very early onset placental insufficiency had a bad prognosis. This is reasonable because at the time the fetus is under stress and hypoxia is longer, mortality and morbidity become higher. The timing of termination in FGR pregnancies, especially in very preterm fetuses, is challenging. So multidisciplinity consists of multivessels fetal Doppler, and the behavior of the fetus via the Biophysical profile is important in deciding termination time [49]. The limitations of our study include a small case population. Also, we did not combine prenatal biophysical profiles with the color Doppler studies.

Conclusions

Among Doppler indices, absent/reversed umbilical diastolic flow could be a predictor of IVH or perinatal death, and absent or reversed "a" waves in the DV could be a significant predictor of death in FGR fetuses. It seems that despite Doppler indices, the most accurate prognostic factors for IVH and Perinatal mortality are the gestational ages at delivery time and birth weights of FGR fetuses.

In FGR pregnancies, the time of pregnancy termination, especially when it involves a preterm neonate, is still a subject for much discussion. According to our results, it seems to be reasonable to decide not to terminate the pregnancy of severely immature infants based on color Doppler studies.

Newborn acidosis is an important prognostic factor in the development of IVH and neonatal mortality and morbidity, which is accompanied by biophysical problems. It seems that combining the biophysical profile (BPP) and NST to decide the time for pregnancy termination is very important.

Conflict of interest: None

References

1. Regnault TR, Galan HL, Parker TA, Anthony RV. Placental development in normal and compromised pregnancies-- a review. Placenta 2002; 23 Suppl A: S119-129.
2. Holmes RP, Soothill PW. Intra-uterine growth retardation. Curr Opin Obstet Gynecol 1996; 8: 148-154.
3. Soothill PW, Nicolaides KH, Campbell S. Prenatal asphyxia, hyperlacticaemia, hypoglycaemia, and erythroblastosis in growth retarded fetuses. Br Med J (Clin Res Ed) 1987; 294: 1051-1053.
4. Gardosi J, Mul T, Mongelli M, Fagan D. Analysis of birthweight and gestational age in antepartum stillbirths. Br J Obstet Gynaecol 1998; 105: 524-530.
5. Bernstein I GS. Intrauterine growth restriction. SG G, editor. New York: Churchill-Livingstone Publishers; 2007.
6. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ 1989; 298: 564-567.
7. Breeze AC, Lees CC. Prediction and perinatal outcomes of fetal growth restriction. Semin Fetal Neonatal Med 2007; 12: 383-397.
8. Pires P, Latham AE, Mabessone SK, et al. Fetal and placental Doppler velocimetry in hypertensive pregnant women and perinatal outcomes according to gestational age. Radiol Bras 2010; 43: 155-160.
9. Mari G. Doppler ultrasonography in obstetrics: from the diagnosis of fetal anemia to the treatment of intrauterine growth-restricted fetuses. Am J Obstet Gynecol 2009; 200: 613.e1-9.
10. Hecher K, Bilardo CM, Stigter RH, et al. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet Gynecol 2001;18: 564-570.
11. Arabin B, Becker R, Mohnhaupt A, Entezami M, Weitzel HK. Prediction of fetal distress and poor outcome in intrauterine growth retardation--a comparison of fetal heart rate monitoring combined with stress tests and Doppler ultrasound. Fetal Diagn Ther 1993; 8: 234-240.
12. Chang TC, Robson SC, Spencer JA, Gallivan S. Prediction of perinatal morbidity at term in small fetuses: comparison of fetal growth and Doppler ultrasound. Br J Obstet Gynaecol 1994; 101: 422-427.
13. Marsal K. Obstetric management of intrauterine growth restriction. Best Pract Res Clin Obstet Gynaecol 2009; 23: 857-870.
14. Sterne G, Shields LE, Dubinsky TJ. Abnormal fetal cerebral and umbilical Doppler measurements in fetuses with intrauterine growth restriction predicts the severity of perinatal morbidity. J Clin Ultrasound 2001; 29: 146-151.
15. FitzGerald DE, Drumm JE. Non-invasive measurement of human fetal circulation using ultrasound: a new method. Br Med J 1977; 2: 1450-1451.
16. Trudinger BJ, Giles WB, Cook CM, Bombardieri J, Collins L. Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. Br J Obstet Gynaecol 1985; 92: 23-30.
17. Arbeille Ph LP, Fignon A, Locatelli A, Maulik D. Fetal hemodynamics and flow velocity indices. Copel JA, Reed KL, editors. New York: Raven Press Ltd; 1994.
18. Jugovic D, Tumbri J, Medic M, et al. New Doppler index for prediction of perinatal brain damage in growth-restricted and hypoxic fetuses. Ultrasound Obstet Gynecol 2007; 30: 303-311.
19. Mari G, Hanif F, Kruger M, et al. Middle cerebral artery peak systolic velocity: a new Doppler parameter in the assessment of growth-restricted fetuses. Ultrasound Obstet Gynecol 2007; 29: 310-316.
20. Ozcan T, Sbracia M, d'Ancona RL, Copel JA, Mari G. Arterial and venous Doppler velocimetry in the severely growth-restricted fetus and associations with adverse perinatal outcome. Ultrasound Obstet Gynecol 1998; 12: 39-44.
21. Baschat AA, Gembruch U, Reiss I, Gortner L, Weiner CP, Harman CR. Relationship between arterial and venous Doppler and perinatal outcome in fetal growth restriction. Ultrasound Obstet Gynecol 2000; 16: 407-413.
22. Victory R, Penava D, da Silva O, Natale R, Richardson B. Umbilical cord pH and base excess values in relation to neonatal morbidity for infants delivered preterm. Am J Obstet Gynecol 2003; 189: 803-807.
23. Ertan AK, Tanriverdi HA, Meier M, Schmidt W. Perinatal risk factors for neonatal intracerebral hemorrhage in preterm infants. Eur J Obstet Gynecol Reprod Biol 2006; 127: 29-34.
24. Gaziano E, Gaziano C, Brandt D. Doppler velocimetry determined redistribution of fetal blood flow: correlation with

growth restriction in diamniotic monochorionic and dizygotic twins. Am J Obstet Gynecol 1998; 178: 1359-1367.
25. Khan IA, Wahab S, Khan RA, Ullah E, Ali M. Neonatal Intracranial Ischemia and Hemorrhage : Role of Cranial Sonography and CT Scanning. J Korean Neurosurg Soc 2010; 47: 89-94.
26. Volpe JJ. Intraventricular hemorrhage and brain injury in the premature infant. Neuropathology and pathogenesis. Clin Perinatol 1989; 16: 361-386.
27. Baschat AA, Gembruch U, Weiner CP, Harman CR. Qualitative venous Doppler waveform analysis improves prediction of critical perinatal outcomes in premature growth-restricted fetuses. Ultrasound Obstet Gynecol 2003; 22: 240-245.
28. Leech RW, Kohnen P. Subependymal and intraventricular hemorrhages in the newborn. Am J Pathol 1974; 77: 465-475.
29. Vergani P, Locatelli A, Doria V, et al. Intraventricular hemorrhage and periventricular leukomalacia in preterm infants. Obstet Gynecol 2004; 104: 225-231.
30. Harrington K, Thompson MO, Carpenter RG, Nguyen M, Campbell S. Doppler fetal circulation in pregnancies complicated by pre-eclampsia or delivery of a small for gestational age baby: 2. Longitudinal analysis. Br J Obstet Gynaecol 1999; 106: 453-466.
31. Baschat AA, Gembruch U, Harman CR. The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. Ultrasound Obstet Gynecol 2001; 18: 571-577.
32. Wladimiroff JW, Tonge HM, Stewart PA. Doppler ultrasound assessment of cerebral blood flow in the human fetus. Br J Obstet Gynaecol 1986; 93: 471-475.
33. Baschat AA, Gembruch U, Viscardi RM, Gortner L, Harman CR. Antenatal prediction of intraventricular hemorrhage in fetal growth restriction: what is the role of Doppler? Ultrasound Obstet Gynecol 2002; 19: 334-339.
34. Ment LR, Oh W, Ehrenkranz RA, Philip AG, Duncan CC, Makuch RW. Antenatal steroids, delivery mode, and intraventricular hemorrhage in preterm infants. Am J Obstet Gynecol 1995; 172: 795-800.
35. Bada HS, Hajjar W, Chua C, Sumner DS. Noninvasive diagnosis of neonatal asphyxia and intraventricular hemorrhage by Doppler ultrasound. J Pediatr 1979; 95: 775-779.
36. Mari G, Abuhamad AZ, Keller M, Verpairojkit B, Ment L, Copel JA. Is the fetal brain-sparing effect a risk factor for the development of intraventricular hemorrhage in the preterm infant? Ultrasound Obstet Gynecol 1996; 8: 329-332.
37. Wehberg K, Vincent M, Garrison B, Dilustro JF, Frank LM. Intraventricular hemorrhage in the full-term neonate associated with abdominal compression. Pediatrics 1992; 89: 327-329.
38. Mao C, Guo J, Chituwo BM. Intraventricular haemorrhage and its prognosis, prevention and treatment in term infants. J Trop Pediatr 1999; 45: 237-240.
39. Gould SJ, Howard S. Glial differentiation in the germinal layer of fetal and preterm infant brain: an immunocytochemical study. Pediatr Pathol 1988; 8: 25-36.
40. Rorke LB. Anatomical features of the developing brain implicated in pathogenesis of hypoxic-ischemic injury. Brain Pathol 1992; 2: 211-221.
41. Volpe JJ. Intraventricular hemorrhage in the premature infant--current concepts. Part I. Ann Neurol 1989; 25: 3-11.
42. al-Ghazali W, Chita SK, Chapman MG, Allan LD. Evidence of redistribution of cardiac output in asymmetrical growth retardation. Br J Obstet Gynaecol 1989; 96: 697-704.
43. Mari G, Hanif F, Treadwell MC, Kruger M. Gestational age at delivery and Doppler waveforms in very preterm intrauterine growth-restricted fetuses as predictors of perinatal mortality. J Ultrasound Med 2007; 26: 555-559.
44. Baschat AA, Cosmi E, Bilardo CM, et al. Predictors of neonatal outcome in early-onset placental dysfunction. Obstet Gynecol 2007; 109: 253-261.
45. Romero R, Kalache KD, Kadar N. Timing the delivery of the preterm severely growth-restricted fetus: venous Doppler, cardiotocography or the biophysical profile? Ultrasound Obstet Gynecol 2002; 19: 118-121.
46. Bilardo CM, Wolf H, Stigter RH, et al. Relationship between monitoring parameters and perinatal outcome in severe, early intrauterine growth restriction. Ultrasound Obstet Gynecol 2004; 23: 119-125.
47. Baschat AA, Guclu S, Kush ML, Gembruch U, Weiner CP, Harman CR. Venous Doppler in the prediction of acid-base status of growth-restricted fetuses with elevated placental blood flow resistance. Am J Obstet Gynecol 2004; 191: 277-284.
48. Turan OM, Turan S, Gungor S, et al. Progression of Doppler abnormalities in intrauterine growth restriction. Ultrasound Obstet Gynecol 2008; 32: 160-167.
49. Baschat AA. Integrated fetal testing in growth restriction: combining multivessel Doppler and biophysical parameters. Ultrasound Obstet Gynecol 2003; 21: 1-8.