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Umbilical Artery Doppler Study as a Predictive Marker of Perinatal Outcome in Preterm Small for Gestational Age Infants

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Purpose: To evaluate the merit of umbilical artery Doppler study as a predictive marker of perinatal outcome in preterm small for gestational age (SGA) infants. **Materials and Methods:** A total of 218 patients at 27 - 36 weeks of gestational age (GA) who received antenatal umbilical artery Doppler velocimetry and delivered singleton infants with SGA. The ratio of peak-systolic to end-diastolic blood flow velocities (S/D) in the umbilical artery was measured in each patient. The patients were divided into 3 groups: the normal group with S/D ratios of less than 95th percentile (n = 134), elevated S/D ratio group of 95th or more percentile (n = 41), and those with absent/reversed end diastolic flow (n = 43). Maternal characteristics and neonatal outcomes of these groups were comparatively analyzed. **Results:** The gestational age (GA) at the time of diagnosis of SGA, the mean GA at delivery, and the mean birth weight showed statistically significant difference among three groups ($p < 0.001$). Also, poor perinatal outcome was significantly increased in infants with abnormal S/D ratio (13.4% vs. 31.7% vs. 67.4%, $p < 0.001$). Multivariate logistic regression analysis revealed umbilical artery Doppler study as a significant independent factor for prediction of poor perinatal outcome (odds ratio: 3.7, 95% confidence interval 1.4 - 9.5, $p = 0.007$). **Conclusion:** Antenatal umbilical artery Doppler velocimetry is shown as a significantly efficient marker in predicting perinatal outcome in preterm SGA infants.

Key Words: Preterm small for gestational age infant, umbilical artery Doppler velocimetry, perinatal outcome

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INTRODUCTION

Small for gestational age (SGA) occurs in approximately 5 - 10% of all pregnancies, and is one of critical obstetrical conditions that affect perinatal morbidity and mortality. The definition of SGA is not yet firmly established, nevertheless, it is commonly defined as birth weight or body weight, as estimated by ultrasonography, less than the 10th percentile for the gestational age, because fetal body weights less than this figure are often accompanied by increased perinatal morbidity and mortality rates.[1] In addition, infants born with SGA have increased risk of coronary heart disease and type 2 diabetes as adults.[2] However, not all SGA infants demonstrate poor neonatal outcomes, as some are constitutionally small but healthy infants. Therefore, it is important for obstetricians to identify such infants and distinguish them from true growth restricted babies, which is not always easy.

The application of umbilical artery Doppler velocimetry in high risk pregnancy with hypertension or presumed impaired fetal growth has been associated with a trend of reduction in perinatal deaths and also associated with fewer inductions of labor and admissions to hospital.[3] It is also available for evaluating the fetal-placental circulation in pregnancies which are suspected to have severe placental insufficiency.[4] The primary cause in 60% of pregnancies with fetal growth restriction (FGR) has been reported to be placental insufficiency.[4] When chorionic villi vessels are injured, which leads to reduction in umbilical artery blood flow, Doppler index increases and, in the end, there appears absent/reversed end diastolic blood flow.[5,6] In FGR fetuses, there exists strict

correlation between the umbilical artery Doppler waveform and increased incidence of perinatal complications[7] and, particularly, absent/reversed end diastolic umbilical artery blood flow has been shown to be associated with high perinatal mortality, long-term impairment of intellectual development, and neurodevelopmental delay.[8-12]

Compared to preterm appropriate for gestational age (AGA) infants, preterm SGA infants have comparatively higher risk of morbidity and mortality.[13,14] Of particular note is that, although the adverse neonatal outcomes of preterm SGA infants increase after the third trimester of pregnancy,[15] there is no difference in terms of neurodevelopmental outcome at 22 months after birth between preterm SGA and AGA infants.[16] To date, there are only a few studies carried out on the association of umbilical artery Doppler velocimetry in such preterm SGA infants with perinatal outcomes.

In the present study, we determined whether umbilical artery Doppler velocimetry can predict perinatal outcomes in preterm SGA infants delivered between 27 and 36 gestational weeks.

MATERIALS AND METHODS

A retrospective study was conducted from a chart review of pregnancies who delivered a SGA infant at 27 - 36 weeks of gestation at the Department of Obstetrics and Gynecology, Ajou University Hospital, between 1997 and 2006. SGA was defined as those infants with a birth weight of less than the 10th percentile in the distribution curve for the calculated gestational age.[17] Those pregnancies excluded from this study were multiple pregnancies, those patients who did not receive umbilical artery Doppler velocimetry, pregnancies with evidence of congenital malformations of the fetus, chromosomal abnormalities, hydramnios, and TORCH infections. Ultrasonography of pregnancies was conducted with ATL HDI-UM9 (Advanced Technology Laboratories, Bothell, Wash, USA), Aloka SSD-5500 (Aloka Ltd, Tokyo, Japan). Five identical umbilical artery Doppler velocimetry waveforms were obtained from midpoint between the fetal abdominal wall and the placental insertion site of the umbilical cord. The patients were divided into 3 groups: Group 1 (or control group), in whom the S/D ratio, which was derived from measurement of the peak systolic velocity and minimum end-diastolic velocity, was less than the 95th percentile, Group 2 with equal to or greater than 95th percentile S/D ratio, and Group 3 in whom the end-diastolic blood flow was absent or reversed. All patients less than 34th weeks of gestation were treated with steroids. Maternal characteristics and neonatal outcomes were analyzed and compared between the above groups.

The parameters analyzed in this study were maternal age, obstetrical history, gestational age at the time of diagnosis of SGA, gestational age at the time of delivery, time interval between the times of SGA diagnosis and delivery, mode of delivery, incidence of cesarean section due to fetal distress, and incidence of severe preeclampsia and oligohydramnios. Also, neonatal gender, birth weight, incidence of Apgar scores of less than 7 at 5 minutes, neonatal intensive care unit (NICU) admission and duration of admission, duration of ventilator care, perinatal death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and periventricular leukomalacia (PVL) were analyzed. After delivery, all neonates underwent chest and abdominal X-ray exams, brain and abdominal ultrasound exams and, in cases where intracranial hemorrhage was suspected, diagnosis was confirmed by brain computerized tomography (CT). Poor perinatal outcome was defined as the presence of any 1 of the followings; perinatal death, RDS, BPD, grade 3 or above IVH, NEC, and PVL.

Results obtained were expressed as mean ± SD, and statistical analysis was done by Chi-square, independent T-test, ANOVA test and logistic regression utilizing the SPSS for Windows (version 12.0, SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered to be statistically significant.

RESULTS

Two hundred and eighteen infants met the inclusion criteria over the study period (Table 1). There were 134 infants in Group 1, 41 infants in Group 2, and 43 infants in Group 3.

The weeks of gestation at the time of diagnosis of SGA in the Groups 1, 2, and 3 were 34.1 ± 1.9, 33.5 ± 2.6, and 31.7 ± 2.2 weeks, respectively. Gestational age at the time of delivery was 35.0 ± 1.5, 34.0 ± 2.4, and 32.0 ± 2.2 weeks, respectively, for the same 3 groups, and it was the shortest in Group 3 ($p < 0.001$). The incidence of severe preeclampsia in the 3 groups were 31.3% (42/134), 26.8% (11/41), and 53.5% (23/43), being statistically higher in Group 3 ($p = 0.015$), however, there was no significant difference in oligohydramnios between the 3 groups. The time intervals from the diagnosis of SGA to delivery were 8.7, 5.9, and 3.7 days, being significantly shorter in Group 3 ($p = 0.002$), but no significant difference was observed between the 3 groups in terms of cesarean section rates due to fetal distress (Table 2).

The mean birth weights of infants at the time of delivery in Group 1, 2, and 3 were 1904.0 ± 342.5, 1629.0 ± 375.1, and 1151.2 ± 364.9 g, respectively, Group 3 being the lowest ($p < 0.001$). There was no statistical difference between the groups in terms of neonatal gender or NICU admission rates, however, we were able to observe significant increase in the rate of less than 7 Apgar score at 5 minutes, duration of NICU care and ventilator care, and perinatal death as Doppler index was becoming poorer ($p < 0.001$). Also, there was significant difference in poor perinatal outcome between Group 1, 2, and 3 (13.4%, 31.7%, and 67.4%, respectively, $p < 0.001$, Table 3).

The multivariate regression analysis revealed that gestational age (OR; 0.4, 95% CI 0.4 - 0.6, $p < 0.001$) and umbilical artery S/D ratio (OR; 3.7, 95% CI 1.4 - 9.5, $p = 0.007$) were statistically significant independent factors for prediction of poor perinatal outcome (Table 4).

Table 1. Characteristics of Study Population

Characteristics	Median (Range) or n* (%)
Maternal age (yrs)	29.7 (20 - 41)
Parity	1 (1 - 2)
GA at delivery (wks)	34 (27 - 36)
Birth weight (g)	1,830 (450 - 2,510)
Mode of delivery	
Vaginal delivery	66 (30.3)
Cesarean delivery	152 (69.7)
Perinatal outcome	
Poor	60 (27.5)
Favorable	158 (72.5)
Perinatal death	10 (4.6)

GA, gestational age.
*n = 218

DISCUSSION

In the present study, we observed that poor umbilical artery Doppler index in preterm SGA pregnancies is associated with increased incidence of adverse perinatal outcome, and that umbilical

Table 2. Maternal Outcome according to Umbilical Artery S/D Ratio

	Group 1 (n = 134)	Group 2 (n = 41)	Group 3 (n = 43)	p value
Nulliparity	80 (59.7%)	22 (53.7%)	21 (48.8%)	NS
Preeclampsia, severe	42 (31.3%)	11 (26.8%)	23 (53.5%)	0.015
GA at dx. of IUGR (wks)	34.1 ± 1.9	33.5 ± 2.6	31.7 ± 2.2	< 0.001*
GA at delivery (wks)	35.0 ± 1.5	34.0 ± 2.4	32.0 ± 2.2	< 0.001†
Period from diagnosis to delivery (d)	8.7	5.9	3.7	0.002‡
Oligohydramnios	18 (13.4%)	10 (24.4%)	12 (27.9%)	0.056
C/S for fetal distress	24 (17.9%)	5 (12.1%)	6 (13.9%)	NS

S/D, systolic/diastolic; GA, gestational age; dx., diagnosis; IUGR, intrauterine growth restriction; C/S, cesarean section; NS, not significant.
*Statistical significance between Group 1 and 3 and 2 and 3.
†‡Statistical significance between Group 1 and 3.
Data are expressed as mean ± SD or number (percentage) unless otherwise indicated.

Table 3. Neonatal Outcome according to Umbilical Artery S/D Ratio

	Group 1 (n = 134)	Group 2 (n = 41)	Group 3 (n = 43)	*p* value
Gender				NS
Male	53	17	25	
Female	81	24	18	
Birth weight (g)	1904.0 ± 342.5	1629.0 ± 375.1	1151.2 ± 364.9	< 0.001†
Apgar score < 7 at 5 min	12 (9.0%)	5 (12.2%)	16 (37.2%)	< 0.001
Perinatal death	2 (1.5%)	1 (2.4%)	7 (16.3%)	< 0.001
Ventilator care (d)	0.2	1.3	9.2	< 0.001*
Admission to NICU	123 (91.8%)	40 (97.6%)	43 (100%)	NS
Hospital days in NICU (d)	14.0 ± 10.9	24.0 ± 21.0	41.3 ± 36.0	< 0.001‡
Poor perinatal outcomes§	18 (13.4)	13 (31.7)	29 (67.4)	< 0.001

S/D, systolic/diastolic; NICU, neonatal intensive care unit; NS, not significant.
*Statistical significance between Group 1 and 3 and 2 and 3.
†‡Statistical significance between all groups.
§Presence of any one of the following; perinatal death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), grade 3 or above intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), periventricular leukomalacia (PVL).
Data are expressed as mean ± SD or number (percentage) unless otherwise indicated.

Table 4. Factors Affecting the Poor Perinatal Outcome

Predictive value	Coefficient SE	*p* value	OR (95% CI)
UAS/D	0.48	0.007	3.7 (1.4 - 9.5)
GA	0.73	< 0.001	0.4 (0.4 - 0.6)

SE, standard error; OR, odds ratio; CI, confidence interval; UAS/D, umbilical artery systolic/diastolic ratio; GA, gestational age.

artery Doppler index is an independent factor of prediction for perinatal outcome, irrespective of gestational age. In particular, Group 3, which showed absent/reversed end diastolic blood flow, was associated with the worst perinatal outcome which was in agreement with previously reported results.[7-11,18]

Previous studies showed that, in pregnancies accompanied by FGR, the umbilical artery Doppler velocimetry can discriminate those at high risk for adverse perinatal outcome and predict neonatal outcome.[7,18-21] It has also been emphasized that FGR with normal umbilical artery Doppler velocimetry is a disease entity different from those with abnormal umbilical artery Doppler blood flow,[22] which may be managed by outpatient care,[23] and that SGA fetuses with normal umbilical artery S/D ratios do not show increased morbidity compared to AGA pregnancies.[24] In addition, it has been reported that, if the umbilical artery S/D ratio and amniotic fluid volume are normal, adverse outcomes will occur only during delivery of the baby, and therefore, close antenatal surveillance may be unnecessary.[25] Furthermore, in cases of SGA fetuses with normal umbilical artery Doppler velocimetries, the frequency of fetal surveillance could be reduced from twice weekly to fortnightly, because no differences in neonatal outcomes were detected between antenatal cares provided twice a week and every two weeks.[26] In an extensive series, Seyam et al. demonstrated that pregnancies with normal umbilical artery Doppler blood flow are associated with decreased risk for oligohydramnios (31.3% vs. 60.2%, $p = 0.037$), neonatal birth weight of less than 10th percentile (37.5% vs. 73.8%, $p = 0.004$), and NICU admissions (0% vs. 26.5%, $p = 0.02$), compared to pregnancies with abnormal Doppler blood flows.[18] In our study, we were able to demonstrate that those pregnancies with nor-

mal umbilical artery Doppler index showed decreased risk for poor perinatal outcomes such as low birth weight, less than 7 Apgar scores at 5 minutes, ventilator care frequency, and NICU admission duration. Thus, the umbilical artery Doppler study appears to assist clinicians in distinguishing constitutionally small infants from those with FGR.

However, McCowan et al. found that, among 109 babies with normal umbilical artery blood flow velocity waveforms out of 186 SGA babies, 49% showed low ponderal indices, 26% were hypoglycemic at the time of birth, and 35% received NICU care, thus concluding that not all SGA babies with normal umbilical artery Doppler waveforms result in favorable outcomes.[27] In a similar study, 129 SGA fetuses with normal umbilical artery Doppler velocimetry were compared with normal pregnancies, and there was a higher incidence of NICU admissions (15.5% vs. 3.9%; $p < 0.001$) and neonatal morbidity (2.3% vs. 0%; $p = 0.04$), and suboptimal neurodevelopmental outcome in the SGA group.[28]

Therefore, in light of the above conflicting data available, a better method is needed to assess the well-being of the FGR fetus, such as an integrated antenatal test which combines a biophysical profile and Doppler study employing other vessels.[29]

One of the key points in this study that is different from many previous studies is that we diagnosed the SGA status of the infant not by antenatal ultrasound assessment, but by birth weight measured after birth. This method would eliminate possible errors in birth weight measurement, especially for infants who are truly larger than SGA weights estimated, since neonatal birth weight less than the 10th percentile is associated with poor perinatal outcome compared to FGR diagnosed antenatally.[1] Another different aspect of this study was that all subjects studied were preterm deliveries before 37 weeks of gestation. As deliveries are specifically differentiated from term pregnancies, the narrowing of the scope of study subjects would make the results more credible.

In a recent study, Spinillo et al. reported that, in pregnancies of less than 35 weeks accompanied by FGR, the umbilical artery Doppler study is unrelated to infant outcome if FGR is not present even after adjusting for gestational age and birth weight (OR: 3.2, 95% CI 1.18 - 8.66), although the absent/reversed umbilical artery end-diastolic flow is an independent predictor for increased risk of either neonatal death or cerebral palsy.[30] Similarly, our present results showed that there was a significantly increased incidence of neonatal death and duration of admission for NICU care in preterm SGA infants with umbilical artery absent/reversed end diastolic flow. However, we also observed that the NICU admission rates were high in all the three study groups, irrespective of the Doppler index values. This is most likely due to the fact that all subjects in this study were preterm SGA infants, therefore, they were babies with smaller birth weights, regardless of other neonatal complications.

In this study, 1 of the drawbacks besides its retrospective nature is that, although umbilical artery Doppler velocimetry studies were conducted in pregnancies that showed evidence of FGR, other additional waveforms, such as the middle cerebral artery or the ductus venosus, were not evaluated when pregnancies showed normal umbilical artery Doppler waveforms, and therefore, they are not available for comparison.

From the results of this study, we could conclude that the absent/reversed end diastolic flow, as detected by antenatal umbilical artery Doppler in preterm SGA infants, is associated with increased risk for poor perinatal outcome. More specifically, we confirmed in the present study that gestational age and umbilical artery Doppler velocimetry were independent predictors for perinatal outcome. Although there exists presently no method to overcome SGA in utero, umbilical artery Doppler velocimetry is expected to assist clinicians in predicting perinatal outcome and managing preterm SGA fetuses, and also formulating antenatal surveillance guidelines for such conditions.

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