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Original Article

Ductus venosus Doppler and the postnatal outcomes of growth restricted fetuses with absent end-diastolic blood flow in the umbilical arteries

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ABSTRACT

Objective: We aimed to evaluate the outcomes of growth-restricted fetuses with absent end-diastolic velocity in the umbilical arteries (UA-AEDV), and investigate the relationship between Doppler flow velocity waveforms in the ductus venosus (DV) and the clinical features.

Materials and methods: This was a retrospective study of growth-restricted fetuses diagnosed with UA-AEDV delivered at our institution between 2013 and 2015. The time from diagnosis of UA-AEDV to delivery, postnatal survival, and developmental prognoses were the primary outcomes. The time lag between the occurrence of UA-AEDV and an abnormal increase in the DV pulsatility index (DV-PI) were investigated. We also examined the correlation between the DV-PI values immediately before birth and umbilical cord arterial pH at birth.

Results: The median gestational age at birth among the 18 subjects was 28^{+2} (24^{+0}–34^{+6}) weeks, and the observation period between the first detection of UA-AEDV and delivery ranged from 0 to 35 days with a median of 8 days. Among the 18 infants, 15 (83%) survived, among whom 2 were diagnosed with a developmental disability. Gestational age at delivery was significantly lower in the poor outcome group. A positive correlation (correlation coefficient, 0.68) was observed between the umbilical artery pH and the last measured DV-PI.

Conclusion: The time interval from initial detection of UA-AEDV to delivery is highly variable, and it is reasonable to manage these growth-restricted fetuses with UA-AEDV expectantly with careful surveillance for fetal well-being. Specifically, Doppler DV analysis is clinically valuable for their evaluation.

Introduction

Early-onset of fetal growth restriction (FGR) remains one of the most challenging issues in obstetrics and is a leading cause of perinatal morbidity and mortality. Fetal Doppler is a widely used method for evaluating FGR. Among a few parameters, Doppler velocimetry of the umbilical artery (UA) provides important information on placental function. Placental dysfunction is associated with a rise in UA vascular resistance with a progressive decrease in the diastolic phase. This change exposes the fetus to hypoxic conditions leading to life-threatening hemodynamic changes. In severe cases, UA end-diastolic flow ceases and ultimately reverses, conditions known as absent end-diastolic velocity (UA-AEDV) and reverse end-diastolic velocity (UA-REDV), respectively. Affected fetuses are at risk for acidosis, hypoxemia, perinatal mortality, and serious morbidity [1–5]. There is no in utero therapy that can effectively reverse placental insufficiency; therefore, when UA-AEDV occurs prenatally, prompt delivery may be considered [6]. However, the optimal timing of delivery in the presence of UA-AEDV is debatable. Many previous investigators have emphasized the substantial impact of gestational age at delivery, on neonatal mortality and morbidity rates in FGR [7–10]. For this reason, it is desirable that delivery is postponed as long as possible to minimize the risks of prematurity and organ injury.

Meanwhile, Doppler examination of the ductus venosus (DV) flow velocity waveform has been widely used for fetal surveillance. In clinical practice, the observation of increased pulsatility due to decreased velocity during atrial contraction (a-wave) can be considered a sign of fetal compromise [11,12]. A recent

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investigation of the longitudinal changes in vascular Doppler parameters described the typical progression pattern in FGR as an increased UA pulsatility index (PI), UA-AEDV followed by UA-REDV, an elevated DV-PI, and a reverse DV a-wave [13].

In this study, we aimed to investigate the perinatal and postnatal outcomes of severely growth-restricted fetuses with UA-AEDV, and the relationship between Doppler flow velocity waveforms in DV and the clinical features of these fetuses.

Materials and methods

Patients

We performed a chart review of patients diagnosed with FGR and UA-AEDV, managed at our institution between 2013 and 2015. The Kyushu University Hospital Ethical Review Board approved the study (Approval number 28-9). The US-estimated fetal body weight (BW, grams) was derived using an established formula for Japanese fetuses. The formula was based on biparietal diameter (BPD, cm), abdominal circumference (AC, cm), and femur length (FL, cm) and was defined as follows: $BW = (1.07 \times BPD^3) + (0.30 \times AC^2 \times FL)$ [14]. A fetus was defined as growth-restricted when the z-score of estimated weight was equal to or less than −1.5 standard deviation (SD) of the Japanese standard. Cases presenting with structural or chromosomal abnormalities and multiple fetuses were excluded from the study.

Ultrasound examination

After the initial diagnosis of FGR, all patients underwent serial fetal ultrasound evaluation throughout their pregnancy. Doppler velocimetry was performed by experienced obstetricians with a Voluson E8 ultrasound system (GE Healthcare, Little Chalfont, UK). Flow velocity waveforms were obtained from the UA, middle cerebral artery (MCA), and DV. UA blood flow velocity waveforms were obtained from a free-floating loop of the umbilical cord. The angle of insonation was maintained as close to 0° as possible. Doppler velocimetry readings were accepted for analysis only after a clear, steady state was obtained. The presence of UA-AEDV or UA-REDV (UA-AREDV) was identified based on the visual evaluation of the blood velocity curve. In addition, blood flow signals of the DV were depicted in a mid-sagittal longitudinal plane of the fetal trunk using color Doppler. The angle between the ultrasound beam and the direction of the blood flow was maintained lower than 30°. The sample volume was limited to the isthmic portion of DV to avoid interference from blood flow in the inferior vena cava. A minimum of 5–10 successive waveforms were recorded and evaluated. The PI was calculated automatically by the machines using the following formula: PI = (Vs−Va)/Vmean, where Vs = peak velocity during ventricular systole, Va = minimum velocity during atrial contraction and Vmean = mean velocity during the cardiac cycle. An elevation in the DV-PI greater than 90th percentile of the Japanese standard was considered abnormal [15]. Concurrently, Doppler measurements were obtained from the MCA. The MCA resistance index (MRA-RI) was measured in an axial section of the fetal brain at the level of cavum septi pellucidi and thalamus.

Institutional management policy for preterm fetal growth restriction

Upon admission to our hospital for FGR, fetal well-being was assessed daily using cardiotocogram and ultrasonography. Fetal indications for emergent cesarean delivery included a non-reassuring pattern during non-stress test (NST) (recurrent severe variable decelerations, late decelerations, prolonged decelerations, and variability loss) and a low biophysical profiling score (BPS). When a reversed a-wave was found in the DV, prompt cesarean delivery was also indicated. UA-AREDV alone was not considered an indication for delivery. Interpretation of a low BPS was based on the established policy provided by Manning [16]; that is, a BPS of 6 in the presence of oligohydramnios (amniotic fluid pocket less than 2 cm), or scores of 4, 2 and 0 were considered as indications for emergent cesarean delivery if the gestational age was ≥32 weeks. A BPP of 4 in the presence of oligohydramnios or scores of 2 and 0 were considered indications for emergent cesarean delivery if the gestational age was ≥26 weeks. Blood gas was sampled from an umbilical cord segment clamped immediately after birth. Following delivery, neonatal care was assumed by an expert neonatology team.

Following discharge from the neonatal intensive care unit, neonates underwent follow-up examinations and developmental assessment using the Kyoto Scale of Psychological Development. This test is a standardized face-to-face instrument that is widely used in Japanese clinical settings to measure an individual's development in three areas, i.e., Postural-Motor, Cognitive-Adaptive, and Language–Social, providing an overall Developmental Quotient (DQ) and a DQ for each area [17,18]. A poor postnatal outcome was defined as postnatal death or a major developmental disability. A major developmental disability was defined as cerebral palsy (CP), intellectual disability (ID), and/or epilepsy. The diagnosis of CP was based on typical motor findings with or without additional signs of cognitive delay. ID was defined as an overall DQ of less than 70.

Study design

The time from diagnosis of UA-AEDV to delivery, gestational age at delivery, postnatal life prognoses, and major developmental disabilities were considered the primary outcomes for this study. The medical charts were reviewed and, in addition to the above data, the following information was recorded: gestational age at diagnosis of UA-AEDV, abnormally elevated DV-PI, progression to UA-REDV or reversed DV a-wave, the UA-RI, MCA-RI, and DV-PI immediately before delivery, the indications for delivery, and umbilical cord artery pH at birth. These findings in the favorable outcomes group were compared to those in the poor outcomes group.

Next, we investigated the relationship between the DV waveform abnormalities and clinical features. Specifically, we determined the time from occurrence of UA-AEDV to the development of an elevated DV-PI and assessed the association of this period with the postnatal outcome. Further, we examined the correlations of DV-PI and MCA-RI values immediately before birth with the umbilical cord arterial pH at birth.

Statistical analysis

Data is reported as median with range when data is not normally distributed. Intergroup comparisons were performed using the chi-square and Mann–Whitney test for categorical and continuous outcomes, respectively. Correlations were analyzed using Spearman's correlation coefficient. A P value of less than 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Twenty patients with FGR and UA-AEDV were encountered. Two fetuses died in utero, and these cases were omitted from our study because the cause of death was extremely low birth weight (230 g

and 125 g, respectively). The remaining 18 viable fetuses were the subjects of our analysis.

Table 1 shows clinical features of the 18 cases. The median age of patients was 35 years (range, 23–46). Three women had already been diagnosed as hypertensive at the onset of pregnancy. Seven developed preeclampsia. The median gestational age at diagnosis of FGR and UA-AEDV were 23^{+6} (17^{+1}–31^{+4}) and 27^{+0} (23^{+0}–34^{+3}) weeks, respectively. Among the 18 cases with UA-AEDV, 12 (67%) progressed to UA-REDV thereafter.

Table 2 shows the perinatal and postnatal outcomes of the 18 cases. The median gestational age at delivery was 28^{+2} (24^{+0}–34^{+6}) weeks, and all fetuses were delivered by cesarean section. The period between detection of UA-AEDV and delivery ranged from 0 to 35 days with a median of 8 days. The indications for emergent cesarean section included HELLP syndrome (n = 2), placental abruption (n = 1), abnormal fetal heart rate pattern on NST (n = 9), a low BPS score (n = 4), and reverse flow in the DV a-wave (n = 2). In all cases except for one involving placental abruption, Doppler examination was performed within 24 h before delivery. Two fetuses were examined within 12 h of delivery, and 15 fetuses immediately before. The median neonatal body weight was 616 g (range, 286–1425 g). Among the 18 infants, 15 (83%) survived, and three died. Among the 15 survivors, two were diagnosed as developmentally delayed (ID, 2; CP, 1; epilepsy, 1; including overlap). In total, five cases showed poor postnatal outcomes (death or developmental delay).

Table 1
Maternal profiles and demographics of 18 pregnancies.

Characteristic	Median (range) or number (%)
Maternal age at delivery (years)	35 (23–46)
Parity	0 (0–4)
Primiparous	10 (56%)
Multiparous	8 (44%)
Pregnancy after ART	1 (6%)
Maternal complications	
Hypertension	3 (17%)
Thyroid disorder	2 (11%)
Asthma	1 (6%)
Other obstetric complications	
Preeclampsia	7 (39%)
Preterm threatened labor	0 (0%)
GA at diagnosis of FGR (wks)	23^{+6} (17^{+1}–31^{+4})
GA at UA-AEDV (wks)	27^{+0} (23^{+0}–34^{+3})
Z-score of the estimated weight at the instant of UA-AEDV	−3.2 (−2.2 to −4.0)
Progression to UA-REDV	12 (67%)

GA: Gestational age, ART: Assisted reproductive technology, FGR: Fetal growth restriction, UA-AEDV: umbilical artery absent end-diastolic velocity, UA-REDV: umbilical artery reversed end-diastolic velocity.

Table 2
Perinatal and postnatal outcomes of 18 pregnancies.

Characteristic	Median (range) or number (%)
GA at delivery (wks)	28^{+2} (24^{+0}–34^{+6})
Time from diagnosis of AEDV to delivery (days)	8 (0–35)
Delivery mode	
Cesarean	18 (100%)
Vaginal	0 (0%)
Indication for delivery	
HELLP syndrome	2 (11%)
Placental abruption	1 (6%)
Deteriorated fetal condition	15 (83%)
Non-reassuring on NST	9
Low BPS	4
Reversed DV a-wave	2
Neonatal birth weight (grams)	616 (286–1425)
Apgar score at 1 min	6.5 (0–8)
Apgar score at 5 min	8 (2–10)
Umbilical cord artery pH	7.29 (6.74–7.39)
Cord artery pH <7.10	1 (6%)
Postnatal life prognosis	
Alive	15 (83%)
Dead	3 (17%)
Long-term prognosis	
Intellectual disability	2[a]
Cerebral palsy	1[a]
Epilepsy	1[a]
Hearing loss	0
Sight loss	0

GA: Gestational age, AEDV: absent end-diastolic velocity, NST: Non-stress test, BPS: Biophysical profile score, DV: Ductus venosus.
[a] There is some overlap.

Fig. 1 shows the period between first detection of UA-AEDV and delivery in all 18 cases. The first occurrence of an abnormally elevated DV-PI is also shown. In seven cases (cases 1, 9, 12, 14, and 16–18) the DV-PI values did not increase until delivery. Among these, six infants showed favorable postnatal outcomes. In six cases, DV-PI values increased before UA-AEDV was diagnosed (cases 2, 3, 4, 5, 6, and 13). Among these, there were three with a poor outcome.

Table 3 shows a comparison of perinatal factors between the poor and favorable outcome groups, including gestational age at diagnosis of UA-AEDV, age at delivery, time from diagnosis of UA-AEDV to delivery, and Doppler findings immediately before delivery. Gestational age at delivery was significantly earlier in the poor outcomes group, suggesting the significant impact of gestational age at delivery on neonatal mortality and morbidity rates. No statistically significant difference was observed in Doppler findings before delivery; however, DV-PI tended to be higher in the poor outcomes group.

Fig. 2 shows the correlation between Doppler findings immediately before delivery and the UA pH at birth. A significant correlation between the UA pH and last measured DV-PI was observed. In contrast, there was no correlation between the UA pH and last measured MCA-RI.

Discussion

The ideal time to interrupt a pregnancy in cases of FGR with severe placental insufficiency is still a complex subject. Clinicians are left with two management options: to deliver the fetus accepting prematurity and related complications or to wait permitting organ maturation for as long as possible until intrauterine fetal metabolic deterioration develops. Because gestational age at delivery is the most important factor determining perinatal outcomes [7–10], clinicians must balance the risk of prematurity against ongoing fetal acidemia and hypoxemia when monitoring fetuses with severely abnormal Doppler findings. Additionally, treatment results of immature infants differ substantially among different countries [19]; therefore, optimal management for FGR should be reviewed in each country.

In our study, the time interval between UA-AEDV and delivery was variable. Three cases had a time interval exceeding 20 days, the longest of which was 35 days (Case 11). Previously, Muller et al. reported that the mean observation period between diagnosis of UA-AEDV and delivery was 8.9 days with a range of one to 40 days in their 35 fetuses [20]. Turan described the sequence of Doppler abnormalities that occurred during the interval from diagnosis of FGR to delivery in their study of 104 cases [13]. In this study, the median intervals from the occurrence of UA-AEDV and UA-REDV to delivery were 10 and five days, respectively. Our results were nearly identical to the results of these two previous investigations. In addition, it is particularly notable that our series did not include a case with acidemia except for one case of sudden placental

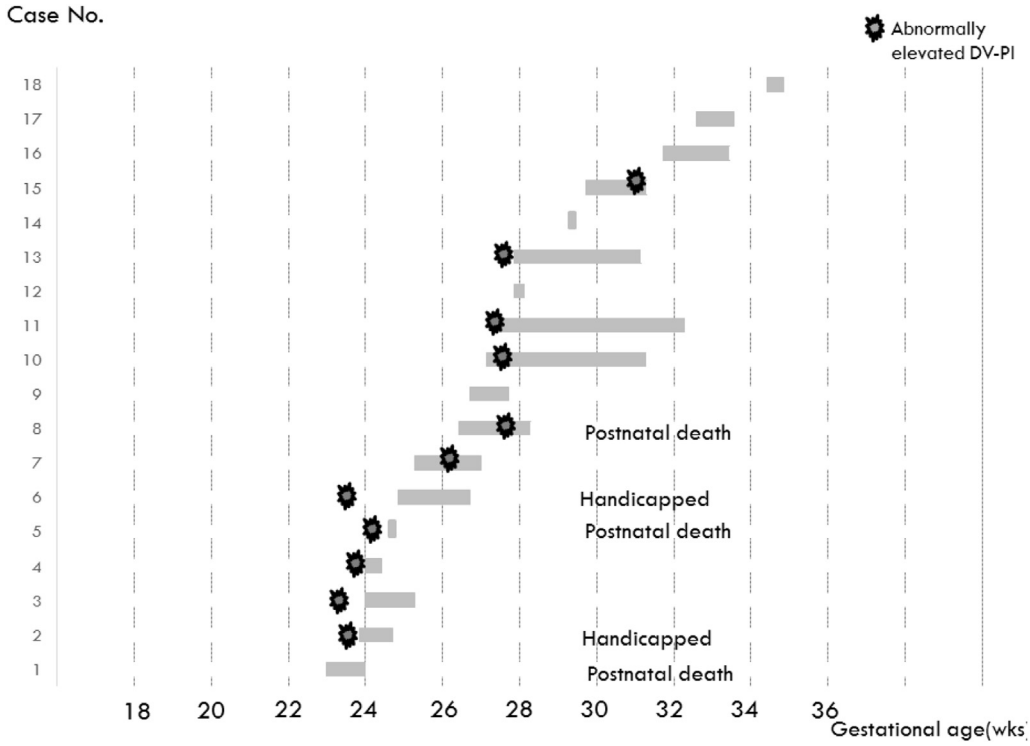

Fig. 1. The observation period between the first occurrence of the absent blood flow in the umbilical artery during diastole and delivery in all 18 cases.

Table 3
Comparison of perinatal data between patients with poor vs. favorable outcomes.

Variable	Poor outcome group (n = 5)	Favorable outcome group (n = 13)	P value
GA at UA-AEDV (wk)	24^{+5} (23^{+0}–26^{+3})	27^{+6} (24^{+0}–34^{+3})	0.02[a]
Time from diagnosis of UA-AEDV to delivery (d)	7 (0–13)	9 (0–35)	NS
Progression to UA-REDV, n (%)			NS
HELLP syndrome, n (%)	0 (0%)	2 (15%)	NS
Placental abruption, n (%)	0 (0%)	1 (8%)	NS
DV-PI value before delivery	1.20 (0.58–1.38)	0.76 (0.36–2.88)	NS (0.20)
UA-RI value before delivery	1.22 (1.00–1.36)	1.06 (1.00–1.19)	NS
MCA-RI value before delivery	0.65 (0.59–0.68)	0.68 (0.55–0.87)	NS
GA at delivery (wk)	24^{+5} (24^{+0}–28^{+2})	31^{+1} (24^{+3}–34^{+6})	0.03[a]
Birth weight (g)	424 (316–484)	842 (426–1425)	NS

GA: gestational age, UA-AEDV: umbilical artery absent end-diastolic velocity, UA-REDV: umbilical artery reverse end-diastolic velocity, DV-PI: pulsatility index of ductus venosus, UA-RI: resistance index of umbilical arteries, MCA-RI: resistance index of middle cerebral artery.
[a] Statistically significant.

abruption. We believe an expectant management with close fetal monitoring for FGR with UA-AEDV to prolong the gestational age in even by a short time is reasonably acceptable.

In general, pregnancies with UA-AEDV are believed to have a high perinatal mortality and morbidity. Vasconcelos investigated the neonatal outcomes in fetuses with UA-AREDV in 2010. In that report, perinatal death was observed in 26 (42%) among 62 [21]. Gerber et al. retrospectively investigated the short and long-term morbidity and mortality of fetuses with UA-AREDV in 2006 [22]. In their study, among the 27 patients managed expectantly under strict surveillance, death occurred in six (22%), and a major disability was observed in two. In our study, 15 infants survived (83%), and among the survivors, only two (13%) demonstrated a major developmental disability. The postnatal prognosis we observed seemed favorable in spite of the comparatively severe condition of our study subjects. An investigation by Brodszki showed similarly positive outcomes. That study described the outcomes of growth-restricted fetuses with UA-AREDV delivered before the 30th gestational week due to fetal indications [23] and reported a high survival rate (38/42, 90%). These findings suggest that the prognosis of fetuses with UA-AREDV is not as poor as many believe, and proper decision-making regarding the timing of delivery may contribute to favorable outcomes.

In the case of hypoxemia, the fraction of blood DV shunts from the umbilical vein increases to maintain cerebral and myocardial oxygenation [24]. Recent reports have indicated a relationship between the degree of acidemia and the values of DV waveform indices occurring in severe FGR cases secondary to chronic placental insufficiency. However, studies investigating an association between DV flow and postnatal outcomes are still scarce, particularly the ones focusing on pregnancies with UA-AEDV. Muller et al. studied 33 viable born fetuses with UA-AREDV and compared short-term outcomes between the groups with positive (n = 23) and reverse DV flow (n = 10) [20]. Their results showed that the incidence of intraventricular hemorrhage and respiratory distress syndrome were significantly higher, and ventilation

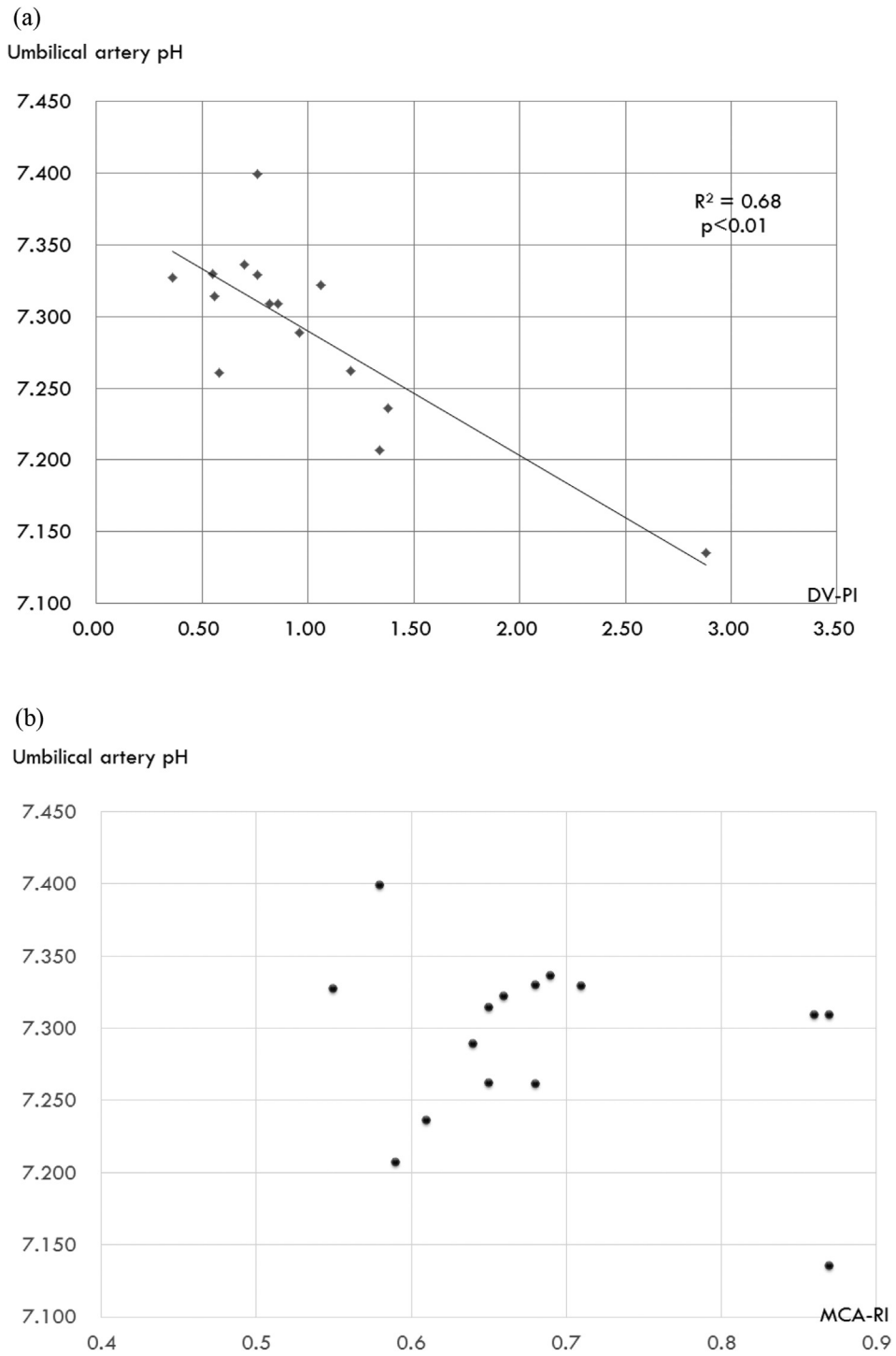

Fig. 2. Correlation between the umbilical artery pH at birth and the last measured ductus venosus pulsatility index (a) and middle cerebral resistance index (b) in 17 cases (except for one case of placental abruption).

duration was significantly longer in the group with reverse DV flow. In a study by Alves et al. investigating the short-term postnatal outcomes of 103 pregnancies with UA-AREDV, 20 cases with reverse DV flow on the day of delivery and 83 cases with positive DV flow were compared [25]. Postnatal death, intraventricular hemorrhage, and pulmonary hemorrhage were frequently found in the former group. In our study, only two cases exhibiting reverse DV flow were included. One of these two infants (Case 6), who was born at 26 weeks of gestation with a birth weight of 476 g, was subsequently diagnosed with a developmental delay. Hence, moving forward, the risk of reverse DV flow is recognizable. Furthermore, reverse DV flow has been demonstrated to be a risk factor not only for postnatal morbidity but also for impending fetal death by some studies [26,27], and these studies indicate that reverse DV flow should prompt intervention in FGR. In contrast, absence of correlation has been also demonstrated between increased DV-PI (without reverse flow) and fetal outcomes before 32 gestational weeks, even in cases of severe FGR due to placental insufficiency [28]. Elevated DV-PI without reverse flow during atrial contraction alone should be managed expectantly.

Interestingly, six cases in our series exhibited abnormally elevated DV-PI before the development of UA-AEDV. FGR tended to be diagnosed early in these cases, and three of these six had a poor outcome (Cases 2, 5, and 6). Although it is possible that the appearance of an elevation in DV-PI prior to UA-AEDV is a predictor of poor postnatal outcomes, we believe this sequence to be a characteristic pattern of early-onset FGR. The study by Turan discussed above described a typical such progression sequence as elevated UA-PI, reduced cerebroplacental ratio, UA-AEDV, UA-REDV, elevated DV-PI, and reverse DV a-wave. However, they also reported that among the sub-group of fetuses with severe early-onset placental dysfunction, an elevated DV was the initial finding in 24% cases [13]. Early-onset FGR can carry a risk for parallel progression of UA and DV Doppler abnormalities. Late-onset FGR is less likely to progress in this fashion. Early onset severe FGR may tend to show signs of cardiovascular deterioration, and UA-AEDV in such fetuses sometimes reflects fetal cardiac dysfunction rather than increased placental vascular resistance.

In this study, a significant positive correlation between the UA pH and last measured DV-PI was observed. We included cases involving preeclampsia, eclampsia, and HELLP syndrome in our analysis and excluded cases with acute complications such as placental abruption. Previously, Muller found a significant correlation between UA pH or UA base excess and the highest or last measured DV-PI [20]. For fetuses with UA-AEDV, it is expected that the fetal acidemic state can be estimated by carefully monitoring DV-PI.

In conclusion, the time interval from initial detection of UA-AEDV to delivery is highly variable, and it is reasonable to manage growth-restricted fetuses with UA-AEDV expectantly with careful surveillance for fetal well-being to prolong the gestational age and promote fetal maturation. Fetal surveillance may be facilitated by DV Doppler as it is a useful tool for estimation of the fetal acidemic state and evaluation of the underlying FGR condition. The optimal timing of delivery in FGR cannot be stated with certainty given the currently available data. Controlled trials employing longitudinal cardiotocograms and Doppler studies are necessary to address this question.

Conflict of interest

The authors have no financial interest to declare in relation to the content of this article.

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