

# THE EFFECTS OF ABSENT OR REVERSED END-DIASTOLIC UMBILICAL ARTERY DOPPLER FLOW VELOCITY

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## SUMMARY

Abnormal umbilical artery flow with absent or reversed end-diastolic velocity (AREDV) during pregnancy is a strong indication of placental insufficiency. When AREDV occurs prenatally, a close follow-up or expeditious delivery should be contemplated. AREDV in the umbilical artery is associated with intraventricular hemorrhage, bronchopulmonary dysplasia, and perinatal mortality. It may be associated with respiratory distress syndrome, necrotizing enterocolitis, and long-term neurodevelopmental impairment. Available data suggest that women with high-risk pregnancies, such as preeclampsia, gestational hypertension and intrauterine growth restriction, should be evaluated with umbilical artery Doppler velocimetry to reduce the possibility of perinatal mortality and morbidity. [*Taiwan J Obstet Gynecol* 2009;48(3):225–231]

**Key Words:** absent or reversed end-diastolic velocity, fetal growth retardation, perinatal mortality, placental insufficiency, preeclampsia, pregnancy complications

## Introduction

Doppler velocity measurement has been extensively applied in prenatal diagnosis for more than two decades. Blood flow in numerous vessels has been investigated to predict fetal condition, especially in the umbilical artery [1–7]. Histopathologic studies suggest that abnormal umbilical artery Doppler velocimetry is correlated with a pathologic lesion of the placenta characterized by obliteration of arterioles in the tertiary stem villi; the umbilical artery flow velocity waveform is primarily determined by placental villous vascular architecture [8,9]. The increased placental vascular resistance is reflected as a decreased diastolic phase of the umbilical artery waveform; moreover, end-diastolic flow of the umbilical

artery vanishes and ultimately reverses in the progressively worsened condition, and absent or reversed end-diastolic velocity (AREDV) flow is finally present in the Doppler waveform [3,4,10,11]. AREDV during pregnancy is a strong indication of placental insufficiency. Previous studies have clarified that an increased umbilical artery systolic/diastolic ratio is a significant risk factor for progression of fetal acidosis, fetal distress, preterm delivery, low Apgar scores, and even perinatal death [12–15]. Mortality and morbidity (such as intraventricular hemorrhage [IVH], periventricular leukomalacia [PVL], bronchopulmonary dysplasia [BPD], respiratory distress syndrome [RDS], necrotizing enterocolitis [NEC], and long-term neurodevelopmental impairment) of fetuses with AREDV in the umbilical artery have been well discussed, especially in growth-restricted fetuses [1,2,10,16,17]. When AREDV occurs prenatally, close follow-up or expeditious delivery should be considered. High-risk pregnancies, such as preeclampsia and intrauterine growth restriction (IUGR), have abnormal development of the placenta vasculature which can be revealed in the abnormal Doppler velocimetry [9,18].



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We reviewed articles of neonatal complications related to abnormal umbilical artery Doppler ultrasonography.

### Intraventricular Hemorrhage

IVH is an important cause of morbidity and mortality in very low-birth-weight infants, and high-grade IVH is a significant risk factor for severe perceptual, cognitive and motor neurologic impairment [19]. AREDV in the umbilical artery causes an enhanced right ventricular afterload which induces greater output to the left ventricle (redistribution of fetal blood flow) and increases cerebral perfusion [20,21]. In this condition, cerebral vasodilatation increases vascular wall strain and mechanical forces, which may contribute to IVH. On the other hand, AREDV in the umbilical artery also causes fetal hypoxia, acidemia, platelet depletion, and elevated nucleated red blood cells; this may cause hemorrhagic placental endovasculitis, infarction, and may subsequently increase the risk of brain injury [22–25]. Eronen et al [26] prospectively studied the flow velocities of the umbilical artery, descending aorta and aortic arch of 65 pregnant women with gestational hypertension between 24 and 34 gestational weeks, and 42 live-born infants (23 with and 19 without AREDV) were analyzed. They found that neonates with AREDV had an increased incidence of IVH ( $p=0.03$ ). Gaziano et al [27] observed the relationship between umbilical artery Doppler velocimetry and neonatal outcomes in 90 surviving neonates out of 100 IUGR infants, and found that the incidence of IVH (20% vs. 6%) was higher in the abnormal Doppler group (mean systolic/diastolic ratio  $\geq 2$  SD) ( $p=0.05$ ). Yoon et al [28] performed a study of umbilical artery velocimetry in 72 pregnant women with preeclampsia and found that women with abnormal umbilical artery velocimetry (pulsatility index  $> 2$  SD) had a significantly higher incidence of IVH ( $p<0.05$ ). Karsdorp et al [29] assessed the outcome of antenatal umbilical artery Doppler velocimetry in three groups: 214 children with forward end-diastolic velocity (FEDV), 178 with absent end-diastolic velocity (AEDV), and 67 with reversed end-diastolic velocity (REDV); they also found an increased incidence of IVH in the AREDV group ( $p=0.02$ ). More recently, Baschat et al [30] evaluated the relationship between neonatal IVH and Doppler flow in 113 IUGR fetuses, of whom 15 (13.3%) had IVH, and 51 (45.1%) had umbilical artery AREDV; the relative risk was 4.9-fold greater for IVH in subjects with AREDV. In contrast, several studies demonstrated that when the effects of prematurity and IUGR were considered, AREDV in the umbilical artery appeared to be a poor indicator of IVH [31,32].

### Periventricular Leukomalacia

PVL is the most important determinant of neurologic morbidity in children who are born prematurely and is considered a sonographic marker for cerebral palsy [33,34]. Unlike IVH, however, studies discussing the relationship between umbilical artery AREDV and PVL are limited, and several studies failed to find an association between AREDV and PVL [17,32]. In theory, blood-gas analyses from cordocentesis or immediately after birth have found a strong correlation between AREDV and acidemia in IUGR fetuses [23]; moreover, studies of preterm fetal and newborn metabolic acidosis also suggested a higher risk of severe PVL [35]. Further large prospective studies are necessary to verify the impact of AREDV in PVL, since it is an important predictor of neurodevelopmental impairment.

### Bronchopulmonary Dysplasia

BPD is one of the most common respiratory complications in premature infants. The predisposing factors for BPD include lung immaturity, airway inflammation, perinatal infection, oxygen toxicity, and barotrauma resulting from mechanical ventilation [36–38]. Furthermore, BPD is a significant risk factor for neurodevelopmental impairment [39,40]. Studies discussing the relationship between umbilical artery AREDV and BPD are scanty; nevertheless, a positive correlation has been found [17,26]. Eronen et al [26] prospectively studied the flow velocities of the umbilical artery, descending aorta and aortic arch of 65 pregnant women with gestational hypertension between 24 and 34 weeks' gestation, and 42 live births (23 with and 19 without AREDV) were analyzed. They found that neonates with AREDV had an increased incidence of BPD ( $p=0.03$ ). Hartung et al [17] reviewed the outcomes of 60 neonates with AREDV flow prenatally, of whom 44 (61%) survived, and they found a statistically significant increase in BPD compared with the control group ( $p=0.002$ ).

### Respiratory Distress Syndrome

RDS is one of the leading causes of mortality and morbidity among premature neonates. Despite findings in numerous studies, the relationship between AREDV in the umbilical artery and RDS is still controversial. Yoon et al [28] performed a study of umbilical artery velocimetry in 72 pregnant women with preeclampsia and found that women with abnormal umbilical artery velocimetry (pulsatility index  $> 2$  SD) had a significantly

higher incidence of RDS ( $p < 0.01$ ). Gonzalez et al [41] performed a retrospective cohort study of 151 pregnancies with IUGR, of which 24 cases had AREDV in the umbilical artery (17 with AEDV and seven with REDV); they found that an umbilical artery with AREDV in the presence of IUGR was associated with a significantly increased incidence of RDS (odds ratio, OR, 6.5; 95% confidence interval, CI, 1.8–23.3). In contrast with previous studies, Karsdorp et al [29] assessed the outcome of antenatal umbilical artery Doppler velocimetry in three groups: 214 children with FEDV, 178 with AEDV, and 67 with REDV. They found that umbilical artery AREDV did not increase the risk of RDS. Hartung et al [17] reviewed the outcomes of 60 neonates with AREDV flow prenatally, of whom 44 survived (61%), and they found that there was no statistically significant increase in RDS compared with the control group. Torrance et al [42] performed a retrospective study of umbilical artery Doppler velocimetry in 187 IUGR infants before 30 weeks' gestation. They found no significant increase in incidence of RDS in the infants with abnormal umbilical artery Doppler velocimetry, and concluded that lung maturation is not related to placental insufficiency.

## Necrotizing Enterocolitis

The pathogenesis of NEC is not well understood and factors thought to increase the risk of intestinal injury include prematurity, intestinal ischemia, enteral feeding, and bacterial colonization [43,44]. Recent studies have shown that IUGR may be an additional risk factor of NEC [45–47]. In fetuses with AREDV in the umbilical artery, especially combined with IUGR, circulatory redistribution increases blood flow to the brain (the brain-sparing effect) and decreases blood flow to the viscera. Fetal hypoxia combines with increased mesenteric vascular resistance to predispose to intestinal ischemic injury; this may contribute to the development of NEC [48]. Dorling et al [48] performed a meta-analysis of 14 case series between 1987 and 2002 to compare the NEC rate in AREDV infants with controls and found that nine studies reported a higher incidence of NEC in the study groups, with an OR of 2.13 (95% CI, 1.49–3.03) in all 14 studies. Hartung et al [17] reviewed the outcomes of 60 neonates with AREDV flow prenatally, of whom 44 survived (61%) and were compared with the control group. They found a statistically significant increase in intestinal complications (NEC or operation;  $p < 0.01$ ) in the AREDV group. However, more recent studies found contrasting results. Gonzalez et al [41] performed a study of 151 pregnancies with IUGR over 7 years, of which 24 had AREDV, and they found that there was

no significant association between AREDV and NEC (OR, 1; 95% CI, 0.1–9.8). Manogura et al [49] prospectively studied the umbilical artery, middle cerebral artery, ductus venosus and umbilical vein flow of 404 neonates, of whom 39 (9.7%) had NEC, and they found that the neonates with NEC had higher placental resistance with significantly increased umbilical artery pulsatility index (4.91 vs. 4.17;  $p = 0.023$ ). Nevertheless, further advanced analysis of placental resistance failed to demonstrate a progressive relationship, and there was no significant correlation between AEDV or REDV and NEC ( $p = 0.079$  and 0.520). The authors analyzed their different outcomes with some previous studies and pointed to: (1) incomplete observations in previous studies because of confined single arterial beds (umbilical or mesenteric arteries), (2) underpowered studies because of the low incidence of NEC, (3) missed determination of the relationship of abnormal Doppler progression and gestational age, and (4) metabolic status at birth not been taken into account. They concluded that placental insufficiency may predispose patients to NEC but is not the primary cascade of events leading to NEC.

## Perinatal Mortality

According to our review, AREDV in the umbilical artery is associated with IVH and BPD, and may be related to RDS and NEC. IVH is a major risk factor for neonatal death and, together with BPD, is an important complication in the very premature infant. Therefore, we would expect to see an increased incidence of perinatal mortality. This is supported by a number of studies. Eronen et al [26] prospectively studied the flow velocities of the umbilical artery, descending aorta and aortic arch of 65 pregnant women with gestational hypertension between 24 and 34 gestational weeks, and 42 live births (23 with and 19 without AREDV) were analyzed. In contrast to no mortality in fetuses without AREDV, the mortality rate with AREDV was 30% ( $p = 0.01$ ). Yoon et al [28] analyzed the umbilical artery velocimetry in 72 pregnant women complicated with preeclampsia and found that women with an abnormal umbilical artery velocimetry (pulsatility index  $> 2$  SD) had a significantly higher incidence of perinatal death ( $p < 0.000001$ ). Karsdorp et al [29] assessed the outcome of antenatal umbilical artery Doppler velocimetry in three groups: 214 children with FEDV, 178 with AEDV, and 67 with REDV; the OR for perinatal mortality in pregnancies complicated by AEDV flow was 4.0 and by REDV flow was 10.6, compared with the FEDV group. Valcamonico et al [50] analyzed 20 surviving IUGR infants with antenatal AREDV in the umbilical artery and 26 IUGR

infants with positive diastolic flow velocity, divided into two control groups (10 with a normal Doppler pattern and 16 with reduced but present end-diastolic flow). They found an increased rate of perinatal mortality in the AREDV group than in the two control groups (26% vs. 6% and 4%). Our previous study [11] observed the outcomes of 30 fetuses with REDV in the third trimester and found three stillbirths and 12 neonatal deaths, resulting in a perinatal mortality rate of 50%. More recently, Spinillo et al [32] conducted a cohort study of 582 neonates with gestational ages between 24 and 35 weeks and also found that the risk of neonatal death was associated with increased umbilical artery resistance in IUGR fetuses based on univariate stratified analysis ( $p=0.045$ ).

## Neurodevelopment

The association of umbilical artery Doppler velocimetry and long-term neurodevelopmental outcome in children is controversial. Two studies [51,52] failed to demonstrate the relationship between abnormal umbilical artery flow velocity waveforms and long-term neurodevelopmental sequelae. Wilson et al [51] carried out a study of 40 children with abnormal umbilical artery flow velocity waveforms and followed their neurologic development at 5 years of age, finding no significant difference in neurologic impairment between normal and abnormal waveform groups. Kirsten et al [52] performed another umbilical artery Doppler study of 242 pregnant women with severe preeclampsia before 34 weeks' gestation, of whom 68 (28%) had AEDV. They followed 193 surviving infants at 6-monthly intervals until 4 years of age, and concluded that there was no difference in the developmental quotients and motor outcomes between the infants with absent end-diastolic velocities and those in the control groups. However, other studies [32,50,53–55] have described an association between AREDV in the umbilical artery and adverse neurologic sequelae. Weiss et al [53] performed a study to examine the neurologic outcome of 37 newborns with antenatal AREDV in the umbilical artery, and found a greater risk of neurologic sequelae during the first 6 months of age in infants with AREDV than in the control group (11 vs. 3). Valcamonico et al [50] studied 20 surviving IUGR infants with antenatal AREDV in the umbilical artery and 26 IUGR infants with positive diastolic flow velocity, divided into two control groups (10 with normal Doppler pattern and 16 with reduced but present end-diastolic flow). They performed neurologic examinations at 3, 6, 9, 12, 18 and 24 months of age and found a higher incidence of permanent neurologic

sequelae in the study group than in the two control groups (35% vs. 0% and 12%). Nevertheless, a recent follow-up study over 8 years by the same authors revealed no difference in the intelligence quotient between the study group and the two control groups, and the authors concluded that AREDV cannot be a reliable predictor of intellectual development at school age [56]. Vossbeck et al [54] performed another study to examine the neurodevelopmental outcome of 40 preterm infants, under 30 weeks' gestation, with umbilical artery AREDV compared with 40 gestational age-matched controls. The Kaufman Assessment Battery for Children or the Bayley Scales of Infant Development was performed at 13–100 months of age, and the authors found that infants with AREDV had an increased risk of permanent neurodevelopmental impairment compared with controls: 44% vs. 25% had mental retardation ( $p=0.033$ ), and 38% vs. 19% had severe motor impairment ( $p=0.073$ ). Schreuder et al [55] assessed 76 children at 5–12 years of age who had antenatal umbilical artery Doppler measurements; 40 had FEDV, 27 had AEDV, and nine had REDV. They found that the mental ability and neuromotor function of the REDV group were worse than those of either the FEDV or AEDV groups. Comparing REDV with the FEDV and AEDV groups, the British Ability Scales general conceptual ability mean scores were 87.7 vs. 101 and 101.1, respectively, and the Quick Neurological Screening Test mean scores were 32.8 vs. 21.5 and 23.2, respectively. The authors suggested that REDV, but not AEDV, represents intrauterine decompensation and increases the risk of neurologic sequelae. More recently, Spinillo et al [32] carried out a cohort study of 582 neonates born between 24 and 35 weeks' gestation, and evaluated the relationship between umbilical artery Doppler flow velocities and the infants' neurodevelopmental outcome at 2 years. Among the 21 infants of IUGR, 13 cases of neonatal death or cerebral palsy occurred in pregnancies with AREDV in the umbilical artery ( $p=0.01$ ). The authors concluded that AREDV in the umbilical artery is an independent predictor of cerebral palsy or neonatal death in preterm infants complicated by IUGR.

Previous animal models have reported that increased placental impedance generates abnormally small brain weight and results in delayed development [57–59]. Furthermore, the mechanisms and hypotheses of AREDV predisposing to IVH may also result in long-term neurologic damage [20–25]. One human study by Tolsa et al [60] examined the cause of the relationship between the severity of abnormal umbilical artery blood flow and neurodevelopmental impairment in infants. The authors used magnetic resonance imaging to measure brain tissue volumes in 14 premature infants with placental

insufficiency (indicated by abnormal Doppler measurements) and IUGR, and in 14 infants of matched gestational age with adequate fetal growth. Infants with IUGR had a significant decrement in intracranial volume (429.3 vs. 475.9 mL;  $p < 0.01$ ) and in cerebral cortical gray matter (149.3 vs. 189.0 mL;  $p < 0.01$ ) at term when compared with the control group. Besides, the attention-interaction availability in IUGR infants was significantly worse than that of the control group. The authors suggested that placental insufficiency with IUGR has adverse structural and functional effects on brain development.

## Conclusion

A large study in Europe by Karsdorp et al [29] assessed the outcome of antenatal umbilical artery Doppler velocimetry and indicated that the perinatal mortality was 40% for AEDV, and even up to 70% for REDV. High-risk pregnancies, such as preeclampsia and gestational hypertension, have abnormal development of the placenta vasculature which can be revealed in abnormal umbilical artery Doppler velocimetry [9,28,61]. Preeclampsia predisposes to the increase in vascular resistance because of inadequate trophoblastic invasion of the maternal spiral arteries, and thus diminishes uteroplacental perfusion which results in an increased incidence of fetal hypoxia, IUGR, and even perinatal mortality [62–64]. Thus, umbilical artery wave velocity is an important predictor of poorer perinatal outcomes in pregnant women with preeclampsia or hypertension [28,61]. Furthermore, AREDV in the umbilical artery is known to be correlated with IUGR and many neonatal complications such as those reviewed in this article [29]. Nevertheless, several studies revealed that when the effects of prematurity and IUGR are taken into consideration, AREDV in the umbilical artery appears to be a poor indicator [31,32,49]. Larger prospective clinical studies are required to provide adequate evidence to exclude these confounding factors.

Although there are many methods of monitoring fetal health such as the non-stress test, contraction stress test, biophysical profile, amniotic fluid volume and Doppler velocimetry of fetal vessels, with the current information, we still cannot give detailed guidance to determine the optimal timing for delivery of a preterm infant, especially those with IUGR [65]. The challenge for obstetricians is to balance the possibility of prematurity with the risk of long-term neurodevelopmental sequelae. It has been well established that the clinical use of umbilical artery Doppler velocimetry in high-risk pregnancies results in a reduction of perinatal morbidity

and mortality [18,66–68]; but routine screening of umbilical artery Doppler velocimetry in low-risk or unselected pregnancies reveals no benefit to mothers or neonates [69–71]. Besides, this review is limited to discussing the effects of abnormal flow in the umbilical artery, although other vessel flow abnormalities, such as middle cerebral artery, aortic isthmus or ductus venosus, are also of value.

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