The Effects of Absent or Reversed End-diastolic Umbilical Artery Doppler Flow Velocity

Kuo-Gon Wang[1,2], Chen-Yu Chen[1,3]*, Yi-Yung Chen[1]

[1]*Department of Obstetrics and Gynecology, Mackay Memorial Hospital,* [2]*Taipei Medical University, and* [3]*Mackay Medicine, Nursing and Management College, Taipei, Taiwan.*

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].

Correspondence to: Dr Chen-Yu Chen, Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail: f122481@ms1.mmh.org.tw
Accepted: December 4, 2008

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 ≥ 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 FDFV 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.

References

1. Fleischer A, Schulman H, Farmakides G, Bracero L, Blattner P, Randolph G. Umbilical artery velocity waveforms and intrauterine growth retardation. *Am J Obstet Gynecol* 1985; 151:502–6.
2. Rochelson BL, Schulman H, Fleischer A, et al. The clinical significance of Doppler umbilical artery velocimetry in the small for gestational age fetus. *Am J Obstet Gynecol* 1987; 156:1223–6.
3. Trudinger BJ, Cook CM, Giles WB. Fetal umbilical artery velocity waveforms and subsequent neonatal outcome. *Br J Obstet Gynaecol* 1991;98:378–84.
4. Devoe LD, Gardner P, Dear C, Faircloth D. The significance of increasing umbilical artery systolic-diastolic ratios in third-trimester pregnancy. *Obstet Gynecol* 1992;80:684–7.
5. Hecher K, Campbell S, Doyle P, Harrington K. Nicolaides K. Assessment of fetal compromise by Doppler ultrasound investigation of the fetal circulation: arterial, intracardiac, and venous blood flow velocity studies. *Circulation* 1995; 91:129–38.
6. 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;16:407–13.
7. Ferrazzi E, Bozzo M, Rigano S, et al. Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. *Ultrasound Obstet Gynecol* 2002;19:140–6.
8. Giles WB, Trudinger BJ, Baird PJ. Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation. *Br J Obstet Gynaecol* 1985;92:31–8.
9. Kingdom JC, Burrell SJ, Kaufmann P. Pathology and clinical implications of abnormal umbilical artery Doppler waveforms. *Ultrasound Obstet Gynecol* 1997;9:271–86.
10. Gudmundsson S, Marsal K. Umbilical and uteroplacental blood flow velocity waveforms in pregnancies with fetal growth retardation. *Eur J Obstet Gynecol Reprod Biol* 1988;27: 187–96.
11. Wang KG, Chen CP, Yang JM, Su TH. Impact of reverse end-diastolic flow velocity in umbilical artery on pregnancy outcome after the 28th gestational week. *Acta Obstet Gynecol Scand* 1998;77:527–31.
12. Berkowitz GS, Mehalek KE, Chitkara U, Rosenberg J, Cogswell C, Berkowitz RL. Doppler umbilical velocimetry in the prediction of adverse outcome in pregnancies at risk for intrauterine growth retardation. *Obstet Gynecol* 1988;71: 742–6.

13. Burke G, Stuart B, Crowley P, Scanaill SN, Drumm J. Is intrauterine growth retardation with normal umbilical artery blood flow a benign condition? *BMJ* 1990;300:1044–5.
14. Trudinger BJ, Cook CM, Giles WB, Ng S, Fong E, Connelly A, Wilcox W. Fetal umbilical artery velocity waveforms and subsequent neonatal outcome. *Br J Obstet Gynaecol* 1991;98: 378–84.
15. Yoon BH, Oh IH, Lee PR, Kim WJ, Syn HC, Kim SW. Is an abnormal Doppler umbilical artery waveform ratio a risk factor for poor perinatal outcome in the non-small for gestational age fetus? *Am J Perinatol* 1993;10:245–9.
16. Soregaroli M, Bonera R, Danti L, Dinolfo D, Taddei F, Valcamonico A, Frusca T. Prognostic role of umbilical artery Doppler velocimetry in growth-restricted fetuses. *J Matern Fetal Neonatal Med* 2002;11:199–203.
17. Hartung J, Kalache KD, Heyna C, et al. Outcome of 60 neonates who had ARED flow prenatally compared with a matched control group of appropriate-for-gestational age preterm neonates. *Ultrasound Obstet Gynecol* 2005;25:566–72.
18. Alfirevic Z, Neilson JP. Doppler ultrasonography in high-risk pregnancies: systematic review with meta-analysis. *Am J Obstet Gynecol* 1995;172:1379–87.
19. Vergani P, Locatelli A, Doria V, Assi F, Paterlini G, Pezzullo JC, Ghidini A. Intraventricular hemorrhage and periventricular leukomalacia in preterm infants. *Obstet Gynecol* 2004; 104:225–31.
20. 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.
21. Volpe JJ. Intraventricular hemorrhage in the premature infant—current concepts, part I. *Ann Neurol* 1989;25:3–11.
22. Wilcox GR, Trudinger BJ. Fetal platelet consumption: a feature of placental insufficiency. *Obstet Gynecol* 1991;77:616–21.
23. Steiner H, Staudach A, Spitzer D, Schaffer KH, Gregg A, Weiner CP. Growth deficient fetuses with absent or reversed umbilical artery end-diastolic flow are metabolically compromised. *Early Hum Dev* 1995;41:1–9.
24. Phelan JP, Korst LM, Ahn MO, Martin GI. Neonatal nucleated red blood cell and lymphocyte counts in fetal brain injury. *Obstet Gynecol* 1998;91:485–9.
25. Viscardi RM, Sun CC. Placental lesion multiplicity: risk factor for IUGR and neonatal cranial ultrasound abnormalities. *Early Hum Dev* 2001;62:1–10.
26. Eronen M, Kari A, Pesonen E, Kaaja R, Wallgren EI, Hallman M. Value of absent or retrograde end-diastolic flow in fetal aorta and umbilical artery as a predictor of perinatal outcome in pregnancy-induced hypertension. *Acta Paediatr* 1993;82:919–24.
27. Gaziano EP, Knox H, Ferrera B, Brandt DG, Calvin SE, Knox GE. Is it time to reassess the risk for the growth-retarded fetus with normal Doppler velocimetry of the umbilical artery? *Am J Obstet Gynecol* 1994;170:1734–41.
28. Yoon BH, Lee CM, Kim SW. An abnormal umbilical artery waveform: a strong and independent predictor of adverse perinatal outcome in patients with preeclampsia. *Am J Obstet Gynecol* 1994;171:713–21.
29. Karsdorp VH, van Vugt JM, van Geijn HP, Kostense PJ, Arduini D, Montenegro N, Todros T. Clinical significance of absent or reversed end diastolic velocity waveforms in umbilical artery. *Lancet* 1994;344:1664–8.
30. 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;19:334–9.
31. Adiotomre PN, Johnstone FD, Laing IA. Effect of absent end diastolic flow velocity in the fetal umbilical artery on subsequent outcome. *Arch Dis Child Fetal Neonatal Ed* 1997; 76:35–8.
32. Spinillo A, Montanari L, Bergante C, Gaia G, Chiara A, Fazzi E. Prognostic value of umbilical artery Doppler studies in unselected preterm deliveries. *Obstet Gynecol* 2005;105: 613–20.
33. Graziani LJ, Pasto M, Stanley C, et al. Neonatal neurosonographic correlates of cerebral palsy in preterm infants. *Pediatrics* 1986;78:88–95.
34. Graham M, Levene MI, Trounce JQ, Rutter N. Prediction of cerebral palsy in very low birthweight infants: prospective ultrasound study. *Lancet* 1987;2:593–6.
35. Low JA, Froese AF, Galbraith RS, Sauerbrei EE, McKinven JP, Karchmar EJ. The association of fetal and newborn metabolic acidosis with severe periventricular leukomalacia in the preterm newborn. *Am J Obstet Gynecol* 1990;162:977–81.
36. Groneck P, Speer C. Inflammatory mediators and bronchopulmonary dysplasia. *Arch Dis Child Fetal Neonatal Ed* 1995;73:1F–3F.
37. Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotraumas and oxygen toxicity explain interhospital variation in rates of chronic lung disease? *Pediatrics* 2000;105:1194–201.
38. Jobe AH, Ikegami M. Prevention of bronchopulmonary dysplasia. *Curr Opin Pediatr* 2001;13:124–9.
39. Hack M, Wilson-Costello D, Friedman H, Taylor GH, Schluchter M, Fanaroff AA. Neurodevelopment and predictors of outcomes of children with birth weights of less than 1000 g: 1992–1995. *Arch Pediatr Adolesc Med* 2000;154: 725–31.
40. Walsh MC, Morris BH, Wrage LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798–804.
41. Gonzalez JM, Stamilio DM, Ural S, Macones GA, Odibo AO. Relationship between abnormal fetal testing and adverse perinatal outcomes in intrauterine growth restriction. *Am J Obstet Gynecol* 2007;196:48–51.
42. Torrance HL, Mulder EJ, Brouwers HA, van Bel F, Visser GH. Respiratory outcome in preterm small for gestational age fetuses with or without abnormal umbilical artery Doppler and/or maternal hypertension. *J Matern Fetal Neonatal Med* 2007;20:613–21.
43. Santulli TV, Schullinger JN, Heird WC, et al. Acute necrotizing enterocolitis in infancy: a review of 64 cases. *Pediatrics* 1975;55:376–87.
44. Caplan MS, MacKendrick W. Necrotizing enterocolitis: a review of pathogenetic mechanisms and implications for prevention. *Pediatr Pathol* 1993;13:357–69.
45. Beeby PJ, Jeffrey H. Risk factors for necrotising enterocolitis: the influence of gestational age. *Arch Dis Child* 1992;67:432–5.
46. McDonnell M, Wilkinson AR. Necrotising enterocolitis: perinatal approach to prevention, early diagnosis and management. *Semin Neonatol* 1997;2:291–6.

47. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. Morbidity and mortality among very-low-birth weight neonates with intrauterine growth restriction. *Am J Obstet Gynecol* 2000;182:198–206.
48. Dorling J, Kempley S, Leaf A. Feeding growth restricted preterm infants with abnormal antenatal Doppler results. *Arch Dis Child Fetal Neonatal Ed* 2005;90:F359–63.
49. Manogura AC, Turan O, Kush ML, et al. Predictors of necrotizing enterocolitis in preterm growth-restricted neonates. *Am J Obstet Gynecol* 2008;198:638.e1–5.
50. Valcamonico A, Danti L, Frusca T, Soregaroli M, Zucca S, Abrami F, Tiberti A. Absent end-diastolic velocity in umbilical artery: risk of neonatal morbidity and brain damage. *Am J Obstet Gynecol* 1994;170:796–801.
51. Wilson DC, Harper A, McClure G, Halliday HL, Reid M. Long term predictive value of Doppler studies in high risk fetuses. *Br J Obstet Gynaecol* 1992;99:575–8.
52. Kirsten GF, Van Zyl JI, Van Zijl F, Maritz JS, Odendaal HJ. Infants of women with severe early pre-eclampsia: the effect of absent end-diastolic umbilical artery Doppler flow velocities on neurodevelopmental outcome. *Acta Paediatr* 2000; 89:566–70.
53. Weiss E, Stefan U, Berle P. Blood flow velocity waveforms of the middle cerebral artery and abnormal neurological evaluations in live-born fetuses with absent or reverse end-diastolic flow velocities of the umbilical arteries. *Eur J Obstet Gynecol Reprod Biol* 1992;45:93–100.
54. Vossbeck S, de Camargo OK, Grab D, Bode H, Pohlandt F. Neonatal and neurodevelopmental outcome in infants born before 30 weeks of gestation with absent or reversed end-diastolic flow velocities in the umbilical artery. *Eur J Pediatr* 2001;160:128–34.
55. Schreuder AM, McDonnell M, Gaffney G, Johnson A, Hope PL. Outcome at school age following antenatal detection of absent or reversed end diastolic flow velocity in the umbilical artery. *Arch Dis Child Fetal Neonatal Ed* 2002;86: 108–14.
56. Valcamonico A, Accorsi P, Battaglia S, Soregaroli M, Beretta D, Frusca T. Absent or reverse end-diastolic flow in the umbilical artery: intellectual development at school age. *Eur J Obstet Gynecol Reprod Biol* 2004;114:23–8.
57. Dobbing J. Undernutrition and the developing brain: the use of animal models to elucidate the human problem. *Psychiatr Neurol Neurochir* 1971;74:433–42.
58. Smart JL, Dobbing J. Vulnerability of developing brain, II: effects of early nutritional deprivation on reflex ontogeny and development of behavior in the rat. *Brain Res* 1971; 28:85–95.
59. Rees S, Bocking AD, Harding R. Structure of the fetal sheep brain in experimental growth retardation. *J Dev Physiol* 1988; 10:211–25.
60. Tolsa CB, Zimine S, Warfield SK, et al. Early alteration of structural and functional brain development in premature infants born with intrauterine growth restriction. *Pediatr Res* 2004;56:132–8.
61. Ducey J, Schulman H, Farmakides G, et al. A classification of hypertension in pregnancy based on Doppler velocimetry. *Am J Obstet Gynecol* 1987;157:680–5.
62. Brosens IA, Robertson WB, Dixon HG. The role of the spiral arteries in the pathogenesis of pre-eclampsia. *Obstet Gynecol Annu* 1972;1:177–91.
63. Sibai BM, Taslimi M, Abdella TN, Brooks TF, Spinnato JA, Anderson GD. Maternal perinatal outcome of conservative management of severe preeclampsia in midtrimester. *Am J Obstet Gynecol* 1985;152:32–7.
64. Fairlie FM, Moretti M, Walker JJ, Sibai BM. Determinants of perinatal outcome in pregnancy-induced hypertension with absence of umbilical artery end-diastolic frequencies. *Am J Obstet Gynecol* 1991;164:1084–9.
65. Thornton JG, Hornbuckle J, Vail A, Spiegelhalter DJ, Levene M; GRIT study group. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. *Lancet* 2004;364: 513–20.
66. Giles WB, Bisits A. Clinical use of Doppler in pregnancy: information from six randomized trials. *Fetal Diagn Ther* 1993;8:247–55.
67. Divon MY. Randomized controlled trials of umbilical artery Doppler velocimetry: how many are too many? *Ultrasound Obstet Gynecol* 1995;6:377–9.
68. Neilson JP, Alfirevic Z. Doppler ultrasound for fetal assessment in high risk pregnancies. *Cochrane Database Syst Rev* 2000;(2):CD000073.
69. Goffinet F, Paris-Llado J, Nisand I, Bréart G. Umbilical artery Doppler velocimetry in unselected and low risk pregnancies: a review of randomised controlled trials. *Br J Obstet Gynaecol* 1997;104:425–30.
70. Burrell SJ, Kingdom JC. The use of umbilical artery Doppler ultrasonography in modern obstetrics. *Curr Opin Obstet Gynecol* 1997;9:370–4.
71. Bricker L, Neilson JP. Routine Doppler ultrasound in pregnancy. *Cochrane Database Syst Rev* 2000;(2):CD001450.