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Early intervention in management of very preterm growth-restricted fetuses: 2-year outcome of infants delivered on fetal indication before 30 gestational weeks

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KEYWORDS: Doppler ultrasound; intrauterine growth restriction; umbilical artery; very preterm infant

ABSTRACT

Objectives *To describe the outcome of growth-restricted fetuses with absent or reversed end-diastolic flow (ARED) in the umbilical artery delivered on fetal indication before 30 gestational weeks.*

Methods *Between 1998 and 2004, 42 fetuses with intrauterine growth restriction (IUGR) and ARED in the umbilical artery were delivered liveborn by Cesarean section on fetal indication before 30 gestational weeks. The median gestational age at delivery was 27 + 1 (range, 24 + 4 to 29 + 5) weeks. An additional four fetuses died* in utero *at a median gestational age of 24 + 2 (range, 23 + 5 to 25 + 4) weeks. Neonatal morbidity, infant mortality and major neurological morbidity of liveborn infants were compared with those in two control groups: all 371 liveborn infants delivered at < 30 weeks during the corresponding time period (Group A) and a subset of these, 42 matched infants without IUGR (Group B).*

Results *Thirty-two fetuses (7%) were delivered within 48 h of the occurrence of ARED (25 absent, seven reversed end-diastolic flow). The remaining 10 fetuses (five absent, five reversed end-diastolic flow) were monitored for a median of 6.5 (range, 3–18) days before delivery. One infant died in the neonatal period and three during the first year of postnatal life (2-year survival 90%). The incidence of chronic lung disease was higher in the ARED Group than in Control Groups A and B (*$P = 0.001$ *and* $P = 0.03$*, respectively). There were no differences between the groups in the occurrence of necrotizing enterocolitis, cerebral hemorrhage or retinopathy of prematurity. Cerebral palsy was diagnosed in 14% of the index group compared with 11% and 17% of Control Groups A and B (*$P > 0.05$*).*

Conclusions *Very preterm growth-restricted fetuses with umbilical artery ARED delivered on fetal indication, in most cases before the occurrence of severe changes in the ductus venosus velocity waveforms and/or fetal heart rate tracings, showed high 2-year survival and low morbidity.*

INTRODUCTION

Intrauterine growth restriction (IUGR) and severe prematurity are both associated with an increase in perinatal morbidity and mortality[1]. When severe IUGR is diagnosed early in gestation, the clinician is faced with the difficult problem of deciding on possible delivery on fetal indication. The risk of intrauterine death has to be weighed against the potential risks of iatrogenic very preterm delivery. With no evidence-based management protocols available, timing of the delivery of a very preterm growth-restricted fetus remains so far an unsolved issue.

Abnormal umbilical artery blood flow in a small-for-gestational age (SGA) fetus indicates IUGR due to placental insufficiency[2]. Although severe changes in umbilical artery flow (i.e. absent or reversed end-diastolic flow (ARED)) after 32–34 gestational weeks are considered an indication for immediate delivery by most clinicians, additional information, e.g. flow characteristics of fetal cerebral arteries and central venous vessels, is essential to facilitate management and decision making in very preterm fetuses[3]. Numerous studies have established that Doppler velocimetry changes in the circulation of severely growth-restricted fetuses develop in a time-dependent, sequential fashion[4–7]. Delivering even the very

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preterm fetus before late Doppler changes (i.e. absent or reversed flow during the a-wave in the ductus venosus) or severe fetal heart rate (FHR) changes occur has been the management policy at the Department of Obstetrics and Gynecology in Lund during the past 10 years.

The long-term combined effects of IUGR and extreme prematurity on postnatal development are to a large extent unknown. The aim of this study was to describe the perinatal, neonatal and long-term outcome of growth-restricted fetuses with severely abnormal umbilical artery blood flow delivered very preterm on fetal indication.

METHODS

This was a retrospective study of fetuses with ARED in the umbilical artery delivered on fetal indication before 30 gestational weeks at the Department of Obstetrics and Gynecology in Lund, a Level 3 perinatological center serving the Southern Swedish Health Care Region with a population of 1.3 million inhabitants and about 17 000 deliveries per year. Approximately eight to 10 growth-restricted fetuses with ARED in the umbilical artery are managed and delivered in the department per year. About two-thirds of them are referred to Lund from the central hospitals of the region.

Since 1998, the clinical protocol for management of very preterm fetuses with IUGR has been based on the following general principles: active attitude to avoid severe fetal hypoxia and deterioration of fetal condition; if possible, to wait until at least 25 weeks of gestational age before delivery; and to await the effect of antenatal steroid treatment. The decision whether and when to deliver is based on a thorough analysis and discussion within the perinatal team, and with the approval of the parents. The decision is made individually based on all available clinical information on the mother, the pregnancy and on the condition of the fetus (e.g. Doppler velocimetry, cardiotocography (CTG) preferably with computerized analysis of short-term FHR variability, ultrasound examination of fetal size and growth). When possible, repeated examinations are performed to enable assessment of the progress of the pathological process. In singletons, the aim is to avoid any of following: occurrence of low variability (< 5 beats per min), silent pattern and/or late decelerations in the FHR records, occurrence of absent or reversed flow in the ductus venosus corresponding to the atrial contraction (a-wave), pulsations in the umbilical vein, and/or reversed flow in the umbilical artery lasting more than 1 day. In twins, the decision is usually very much guided by the gestational age with respect to the survival chances of the unaffected fetus. The active neonatal care of very preterm infants delivered at ≥ 23 weeks of gestation comprises early surfactant administration and early initiation of enteral feeding using human milk exclusively.

Index group (ARED Group)

During the period 1998–2004, 46 fetuses with ARED flow in the umbilical artery before 30 gestational weeks were managed. There were four cases of intrauterine death. The remaining 42 fetuses (ARED Group) met the following inclusion criteria: estimated fetal weight more than 2 SD below the mean of the Swedish reference population[8], presence of ARED in the umbilical artery, liveborn delivery on fetal indication before 30 completed weeks of gestation, no malformations or abnormal karyotype known before birth, and absence of twin-to-twin transfusion syndrome.

Gestational age was determined by routine ultrasound assessment of fetal size at 17–18 postmenstrual weeks. In seven fetuses the gestational age was found to be ≥ 14 (range, 14–49) days shorter according to fetal biometry than according to the last menstrual period.

Fetal and placental circulation in the ARED Group was monitored with Doppler ultrasound by recording flow velocity signals from the umbilical artery in a free loop of the umbilical cord, the umbilical vein (both in its intra-abdominal part and in a free loop of umbilical cord), the fetal middle cerebral artery, the ductus venosus and from both maternal uterine arteries. Doppler velocimetry was performed transabdominally using either an Aspen (Acuson, Mountain View, CA, USA) or an HDI 5000 (Philips Medical Systems, Bothell, WA, USA) ultrasound system. All recordings were performed during periods of absent fetal breathing and movements, and during voluntary maternal apnea. According to the local management protocol for fetuses with ARED in the umbilical artery, Doppler velocimetry and CTG were performed daily until delivery. Redistribution of fetal blood flow was defined as fetal middle cerebral artery pulsatility index (PI) > 2 SD below the gestational age-related mean[9]. Abnormal ductus venosus flow was defined as absent or reverse flow during the a-wave. Flow in the umbilical vein was considered abnormal if there were pulsations in the free loop of umbilical cord and/or in the intra-abdominal part of the umbilical vein. Flow velocity waveforms in the uterine arteries were assessed using the uterine artery score[10]. A score of 0 indicates bilateral absence of early diastolic notch and PI within normal limits, i.e. below 1.2[11], and a score of 4 describes cases with bilateral notches and PI ≥ 1.2 bilaterally.

Indications for delivery were deterioration of fetal circulation (ARED in the umbilical artery and/or absent or reversed a-wave flow in the ductus venosus) and/or abnormal FHR tracing (low variability and/or late decelerations). In three cases there was an additional maternal indication, severe pre-eclampsia, defined as diastolic blood pressure (BP) > 110 mmHg on two or more occasions and proteinuria > 300 mg/L. All fetuses of the index group were delivered by an elective Cesarean section, in all cases after at least one 12-mg dose of betamethasone administered intramuscularly to the mother for acceleration of fetal lung maturation.

Control groups

To enable evaluation of outcome variables, two control groups were identified. The first control group (Group A)

consisted of all other very preterm infants born in Lund before 30 gestational weeks during the corresponding time period (1998–2004, $n = 399$). Of these infants, 24 were stillborn and four died in the delivery room, and so 371 infants were admitted to the neonatal intensive care unit. In these infants, with very few exceptions, no data on fetoplacental blood flow were available. The second control group (Group B) was a subgroup of Group A and consisted of paired controls matched with the index group for gender, gestational age at birth and year of birth. All infants in Group B had a birth weight appropriate-for-gestational age (AGA). Twins formed a matched pair if one twin was SGA with ARED, the AGA twin was of same gender, had normal blood flow in the umbilical artery and twin-to-twin transfusion had been excluded. Ten infants in the ARED Group were twins and, among these, seven had the AGA cotwin as a matched control. The distribution of twins and singleton pregnancies according to gestational age at delivery within the ARED Group and Control Group A is presented in Figure 1.

Maternal and obstetric variables of the three groups are shown in Table 1. Mothers of the ARED Group were of comparable age, parity and had the same rate of twin pregnancies as the control groups. Frequency of antenatal steroid treatment did not differ between the ARED Group and Control Group B. Pre-eclampsia was more common in the ARED Group than in the control groups. Pre-eclampsia was defined as diastolic BP > 90 mmHg on two or more consecutive occasions > 4 h apart, arising after 20 weeks of gestation, and proteinuria > 300 mg/L in two random clean-catch midstream urine specimens collected ≥ 4 h apart. Preterm premature rupture of membranes and chorioamnionitis occurred more frequently in the control groups. The Cesarean section rates were 67% and 62% in Control Groups A and B, respectively.

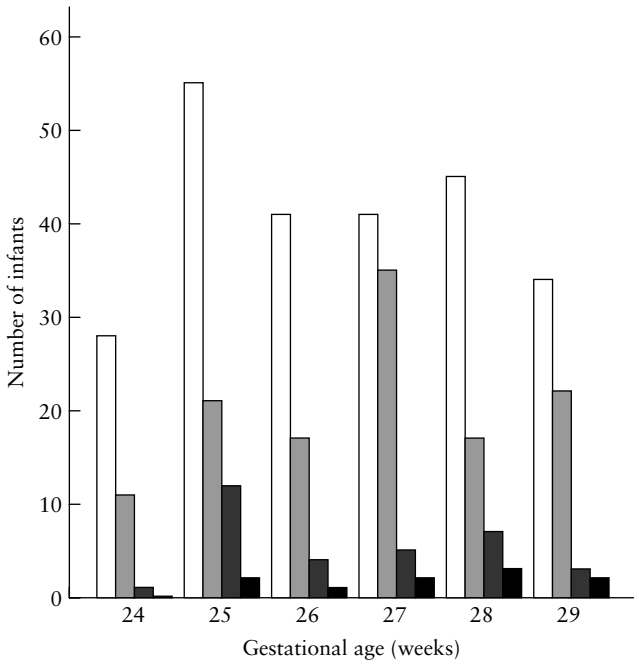

Figure 1 Distribution of liveborn singletons and twins in the ARED Group (absent or reversed end-diastolic flow in the umbilical artery) and in Control Group A, according to gestational age at delivery. □, Control singletons ($n = 244$); ▒, control twins ($n = 127$); ■, ARED singletons ($n = 32$); ■, ARED twins ($n = 10$).

Outcome variables

The perinatal outcome was assessed by perinatal mortality, birth weight, birth weight deviation as a percentage from the expected weight according to the Swedish standard[8], Apgar score at 5 min, umbilical cord arterial pH and base excess. Parameters of the respiratory and circulatory status during the first 12 h of postnatal life, such as oxygen requirement, blood gases and blood pressure, were recorded. Pulmonary morbidity included the following variables: surfactant treatment, duration of mechanical ventilation and continuous positive airway pressure, occurrence of chronic lung disease and of persistent ductus arteriosus. Chronic lung disease was defined as requirement for supplemental oxygen at 36 gestational weeks. Neonatal morbidity was further represented by the occurrence of necrotizing enterocolitis, severe brain damage as detected by cranial ultrasound imaging (intraventricular hemorrhage Grades III–IV and/or periventricular leukomalacia), retinopathy of prematurity (Stages 3–5), and, for survivors, by time until discharge home from the hospital. Finally, survival and prevalence of cerebral palsy at 24 months of age were registered. A separate subanalysis of twin pairs was performed with regard to variables of neonatal morbidity, prevalence of cerebral palsy and survival at 2 years of age.

Data collection and analysis

All data from pregnancies and from neonatal intensive care were collected from the obstetric and pediatric patient records, from the database for perinatal data in the Southern Swedish Health Care Region (Perinatal Revision South Database) and the Regional Registry of Cerebral Palsy. The study was approved by the Regional Research Ethics Committee in Lund.

Statistical analysis was performed using SPSS statistical software, version 13.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared between groups by using Chi-square test or Fisher's exact test as appropriate. Group differences in continuous variables were assessed with the Mann–Whitney *U*-test. $P < 0.05$ was considered statistically significant. Confounders were explored using multivariable logistic regression or linear regression analysis as appropriate.

Post-hoc power calculation ($\alpha = 0.05$, $\beta = 0.20$) indicated that the present material allowed detection of at least the following odds ratios for the main outcome variables: 2.42 for infant mortality, 1.60 for chronic lung disease, and 2.51 for brain damage and retinopathy of prematurity.

RESULTS

In the ARED Group, 29 fetuses (69%) had absent and 13 (31%) had reversed end-diastolic flow in the umbilical artery before delivery. In 32 cases (76%), delivery by

Table 1 Maternal and obstetric characteristics of cases with liveborn infants

Characteristic	*ARED Group* (n = *42*)	*Control Group A* (n = *371*)	*Control Group B* (n = *42*)	P
Maternal age (years)	31 (20–42)	31 (16–43)	31 (17–43)	NS
Primiparous	19 (45)	216 (58)	22 (52)	NS
Twin fetuses	10 (24)	127 (34)	10 (24)	NS
Cesarean section	42 (100)	249 (67)	26 (62)	< 0.001*, < 0.001†
Antenatal steroids	40 (95)	NA	36 (86)	NS
Pre-eclampsia	16 (38)	44 (12)	3 (7)	< 0.001*, < 0.001†
Chorioamnionitis	0 (0)	NA	8 (19)	< 0.01*
Preterm premature rupture of membranes	0 (0)	133 (36)	13 (31)	< 0.001*, < 0.001†

Data expressed as median (range) or *n* (%). ARED Group, index group with absent or reversed end-diastolic umbilical artery blood flow; Control Group A, all other infants born at < 30 gestational weeks during 1998–2004; Control Group B, appropriate-for-gestational age infants matched for gestational age, gender and year of birth. *ARED Group vs. Control Group A; †ARED Group vs. Control Group B. NA, data not available; NS, not significant.

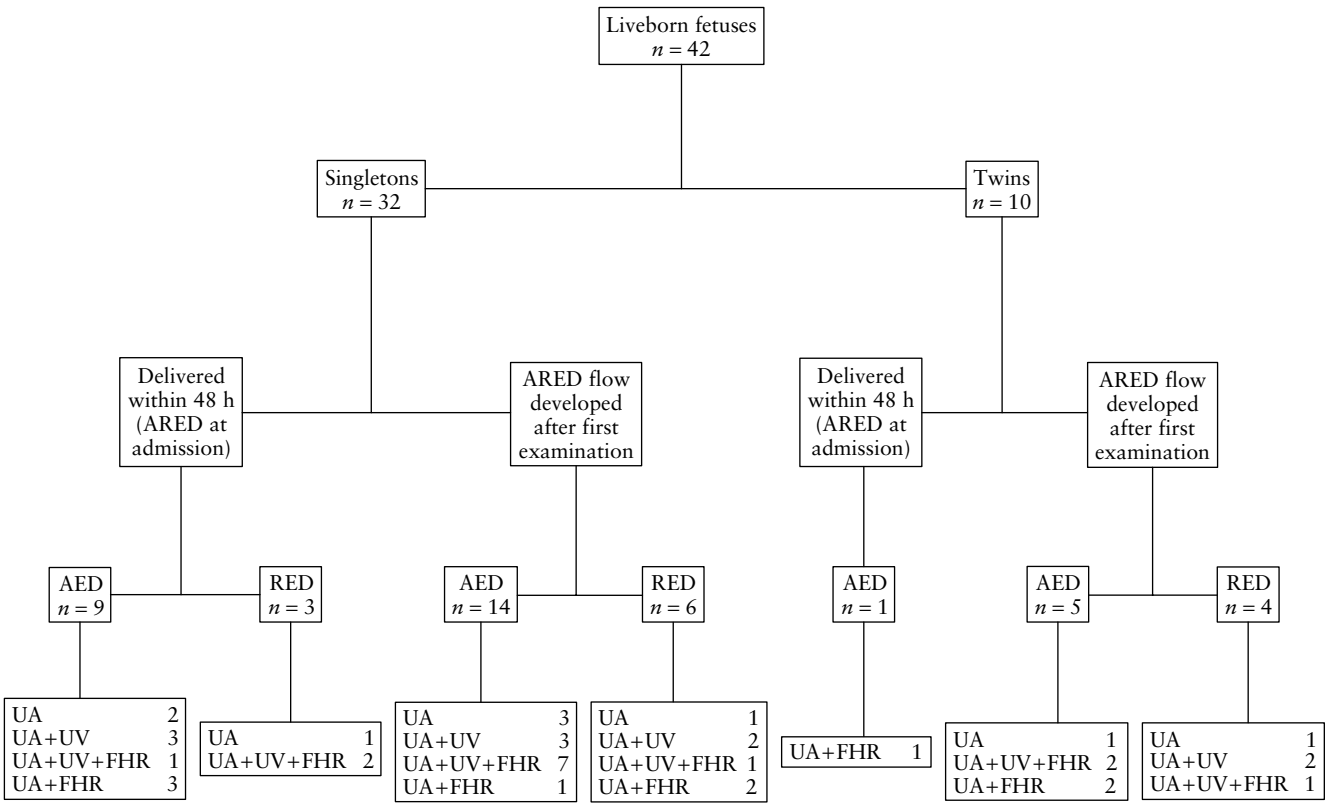

Figure 2 Doppler characteristics and fetal findings, alone or in combination, indicating delivery in the ARED Group (absent or reversed end-diastolic flow in the umbilical artery). AED, absent end-diastolic flow; FHR, abnormal or pathological fetal heart rate tracing and/or decreasing short-term variability; RED, reversed end-diastolic flow; UA, pathological umbilical artery blood flow; UV, flow velocity pulsations in the umbilical vein and/or deteriorating velocities in the ductus venosus.

Cesarean section was carried out within 48 h from the first recording of absent ($n = 25$) or reversed ($n = 7$) end-diastolic flow. The remaining fetuses (five with absent and five with reversed flow) were monitored for a median of 6.5 (range, 3–18) days before delivery. The fetal monitoring variables that were the basis for indication to deliver, alone or in combination, are presented schematically in Figure 2. In three cases (delivered at $25 + 2$, $24 + 4$ and $24 + 6$ weeks), the rapid worsening of severe pre-eclampsia was a contributing indication for delivery.

Among singleton fetuses in the ARED Group ($n = 32$), 12 had ARED in the umbilical artery present at the first examination of fetal circulation. Additional flow characteristics of this group are shown in Table 2. Twenty singleton fetuses developed ARED subsequent to their first examination. In this subgroup, of fetuses with absent end-diastolic flow before delivery, 71% exhibited pulsations in the umbilical vein, 17% showed abnormal flow in the ductus venosus, 50% had a uterine artery score of 4, and 57% had an abnormal or pathological FHR tracing. In fetuses with reversed flow before delivery the

Table 2 Abnormal Doppler findings contributing to the decision to deliver the 42 very preterm growth-restricted fetuses with absent or reversed end-diastolic flow (ARED) in the umbilical artery

			Additional abnormal findings			
Subgroup	n	*Time from admission (start of observation) to delivery (days, median (range))*	*Time from ARED to delivery (days, median (range))*	*Pulsations in umbilical vein* (n)	*Deterioration in ductus venosus waveform* (n)	*Abnormal ductus venosus velocity** (n)	*Uterine artery score = 4*† (n)
Singleton fetuses							
AED present at admission	9	< 2	NA	4	NA	0 of 7	6
RED present at admission	3	< 2	NA	2	NA	1 of 3	2
AED developed after 1st exam	14	4 (2–18)	0.5 (0–14)	10	2 of 12	2 of 12	7
RED developed after 1st exam	6¶	3.5 (3–12)	1 (0–1)	3	1 of 4	0 of 4	3
Total	32	4 (2–18)§	1 (0–14)§	19	—	3 of 26	18
Twin fetuses							
AED	6‡	8 (0–16)	0 (0–1)	2	0 of 4	2 of 4	1
RED	4¶	25.5 (6–34)	3 (0–6)	1	1 of 4	1 of 4	0
Total	10	13 (6–34)	1 (0–6)	3	—	3 of 8	1

*Ductus venosus velocity during atrial contraction close to zero line or reversed (ductus venosus Doppler velocimetry was not performed in all cases). †Bilateral uterine artery notch and pulsatility index > 1.20[10]. §Calculated for 20 fetuses which developed ARED subsequent to first examination. ¶One fetus delivered because of change in reversed end-diastolic flow (RED) only. ‡Two fetuses delivered because of change in absent end-diastolic flow (AED) and one fetus (29 + 6 weeks) with AED at admission delivered within 24 h (no additional abnormal findings). NA, not applicable.

corresponding figures were 50%, 0%, 50% and 17% (Table 2).

Among twin fetuses of the ARED Group, 50% of those with absent end-diastolic flow had an abnormal FHR tracing compared with 25% of those with reversed flow. The flow characteristics of these two subgroups are summarized in Table 2. There was no significant difference in the ARED-to-delivery time between the fetuses with absent and those with reversed end-diastolic flow, either among singletons or among twins (Table 2).

In total, 22 fetuses in the ARED Group (52%) had pulsatile flow in the umbilical vein. In all, 73% of fetuses showed signs of blood flow redistribution with decreased PI in the middle cerebral artery. Of 34 fetuses in whom ductus venosus recordings were available, 18% had abnormal flow during the a-wave. Bilateral uterine artery notches were present in 63% of the pregnancies. In the last FHR recording before delivery, there were decelerations in eight fetuses (19%) and 17 fetuses (40%) had decreased FHR variability.

Table 3 shows the infant characteristics at birth in the index and control groups. All infants of the index group had birth weight more than 2 SD below the mean of the Swedish reference population[8]. There were no differences in gender distribution or gestational age at birth between the index group and the two control groups. Umbilical cord artery pH and base excess showed no differences, with the exception of base excess in Control Group A, which was lower than the base excess in the ARED Group ($P = 0.048$). All but one infant in the ARED Group had a pH and base excess within normal limits. The frequency of 5-min Apgar score < 7 was lower in the ARED Group than in Control Group A ($P = 0.035$). Birth weight, birth weight deviation from the gestational age-related mean and placental weight differed significantly between the groups ($P < 0.001$).

During the first 12 h of postnatal life, oxygen requirement was lower in the ARED Group than in Control Group A and Control Group B (Table 4). The lowest pH was lower in both control groups than in the ARED Group. Neither the lowest base excess nor the lowest mean arterial BP differed significantly between the ARED Group and the control groups (Table 4).

Variables related to neonatal morbidity are presented in Table 5. The frequency of persistent ductus arteriosus, necrotizing enterocolitis, severe brain damage and severe retinopathy of prematurity did not differ between the groups. Duration of treatment on continuous positive airway pressure and length of hospitalization were greater in the ARED Group than in Control Group A. Chronic lung disease, as determined by requirement for supplemental oxygen at 36 gestational weeks in surviving infants, was significantly higher in the ARED Group than in either control group.

Table 6 summarizes the components of perinatal mortality and the outcome at 24 months of age in the ARED Group and in Control Group A. The four cases of intrauterine death in the ARED Group are described below. Of 42 liveborn infants in the ARED Group, four

Table 3 Infant characteristics at birth

Characteristic	*ARED Group* (n = *42*)	*Control Group A* (n = *371*)	*Control Group B* (n = *42*)	P
Gestational age (weeks)	27 + 1 (24 + 4 to 29 + 5)	27 + 1 (23 + 6 to 29 + 6)	26 + 6 (24 + 3 to 29 + 5)	NS
Male gender	21 (50)	202 (54)	21 (50)	NS
Birth weight (g)	642 (395–1165)	945 (466–2590)	1015 (660–1790)	< 0.001†, < 0.001‡
Birth weight deviation (%)*	−37.5 (−64.4 to −21.4)	−9.6 (−57.5 to 71.8)	−4 (−18.2 to 14.3)	< 0.001†, < 0.001‡
Placental weight (g)	240 (130–830)	380 (150–1045)	390 (200–830)	< 0.001†, < 0.001‡
Umbilical artery pH	7.29 (7.02–7.43)	7.30 (6.76–7.51)	7.34 (6.79–7.51)	NS
Umbilical artery base excess (mmol/L)	−2.9 (−16.0 to 8.7)	−4.2 (−26.8 to 4.0)	−3.7 (−25.4 to 0.0)	0.048†, NS‡
Apgar score at 5 min < 7	7 (17)	124 (33)	9 (21)	0.035†, NS‡

Data expressed as median (range) or *n* (%). ARED Group, index group with absent or reversed end-diastolic umbilical artery blood flow; Control Group A, all other infants born at < 30 gestational weeks during 1998–2004; Control Group B, appropriate-for-gestational age infants matched for gestational age, gender and year of birth. *Calculated as percentage deviation from expected birth weight according to Swedish standard[8] (11% corresponds to 1 SD). †ARED Group vs. Control Group A; ‡ARED Group vs. Control Group B. NS, not significant.

Table 4 Morbidity during first 12 h of postnatal life

Parameter	*ARED Group* (n = *42*)	*Control Group A* (n = *371*)	*Control Group B* (n = *42*)	P
Lowest FiO_2	0.21 (0.21–0.36)	0.21 (0.21–1.0)	0.23 (0.23–1.0)	0.014*, 0.002†
Highest FiO_2	0.40 (0.21–1.00)	0.43 (0.21–1.0)	0.52 (0.21–1.0)	< 0.05*, 0.03†
Lowest pH	7.30 (7.10–7.41)	7.27 (6.60–7.42)	7.26 (7.0–7.38)	< 0.05*, 0.03†
Lowest base excess (mmol/L)	−5.5 (−10.4 to 7.2)	−5.1 (−29.5 to 8.3)	−6.0 (−21.6 to 7.2)	NS
Lowest mean arterial pressure (mmHg)	27.0 (18–39)	26.5 (10–41)	26.5 (18–38)	NS

Data expressed as median (range). ARED Group, index group with absent or reversed end-diastolic umbilical artery blood flow; Control Group A, all other infants born at < 30 gestational weeks during 1998–2004; Control Group B, appropriate-for-gestational age infants matched for gestational age, gender and year of birth. *ARED Group vs. Control Group A; †ARED Group vs. Control Group B. FiO_2, fraction of inspired oxygen; NS, not significant.

died during hospitalization; the cause of death was chronic lung disease in two cases (at 45 and 135 postnatal days), intestinal complications in one case (age 36 days) and suspected septicemia in one case (age 17 days). One of the infants that died from chronic lung disease was found to have trisomy 21 several weeks after birth. Perinatal mortality, and survival at discharge and at 24 months of age did not differ between the groups. All infants survived from the time of home discharge to the age of 24 months. The rate of cerebral palsy at 24 months was similar in survivors of both groups, and did not differ from that of Control Group B (seven of 41 infants; 17%). A separate subanalysis of twins showed no differences compared with singletons in the main outcome variables: asphyxia, severe brain damage, chronic lung disease, cerebral palsy and overall mortality.

Of the four fetuses that died *in utero*, in three cases the parents refused active management. In the first case, a woman, para 2, with poor obstetric history was admitted at 24 + 1 weeks because of pre-eclampsia. At admission there was a pathological FHR trace, oligohydramnios, estimated fetal weight deviation of −29%, umbilical artery PI > mean + 2 SD, decreased fetal middle cerebral artery PI, pulsations in the intra-abdominal part of the umbilical vein and bilateral uterine artery notches. ARED subsequently developed and the fetus died *in utero* at 24 + 5 weeks. In the second case a nulliparous woman was admitted at 24 + 4 gestational weeks following suspected premature rupture of membranes at 18 weeks, with estimated fetal weight deviation of −31%, absent end-diastolic flow in the umbilical artery, decreased fetal middle cerebral artery PI and bilateral uterine artery notching. Intrauterine death occurred at 25 + 4 gestational weeks. In the third case a nulliparous woman with poor obstetric history was admitted at 23 + 3 weeks with severe pre-eclampsia. At admission, oligohydramnios, estimated fetal weight deviation of −60%, absent end-diastolic flow in the umbilical artery, decreased fetal middle cerebral artery PI and bilateral uterine artery notching were observed. Reversal of the umbilical artery diastolic flow and of ductus venosus a-wave flow occurred at 23 + 5 gestational weeks. Owing to the extremely poor prognosis and the wish of the parents, the managing clinician decided to induce labor. Fetal death occurred during labor. The final case was a twin pregnancy in a mother admitted at 22 + 4 weeks because of severe pre-eclampsia and heart failure. At admission, the first twin had absent end-diastolic flow, while the other twin had normal umbilical artery flow. No active management was considered on behalf of the first twin and at 24 + 0 weeks the twin died *in utero*. At that time, the second twin had an elevated umbilical artery

Table 5 Neonatal morbidity

Parameter	*ARED Group* (n = 42)	*Control Group A* (n = 371)*	*Control Group B* (n = 42)	P
Persistent ductus arteriosus	17 (40)	167/355 (47)	17 (40)	NS
Necrotizing enterocolitis	5 (12)	17/348 (5)	2 (5)	NS
Severe brain damage	4 (10)	42/369 (11)	6/36 (17)	NS
Retinopathy of prematurity, Stage 3–5	4 (10)	35/329 (11)	5 (12)	NS
Surfactant treatment	24 (57)	228/371 (61)	26 (62)	NS
Ventilator treatment (days)	4 (0–34)	3 (0–51)	4 (0–24)	NS
Duration of CPAP (days)	26 (1–113)	15 (0–112)	20 (0–72)	0.011†, NS‡
Supplemental oxygen at 36 gestational weeks	26/40 (65)	122/329 (37)	17 (40)	0.001†, 0.03‡
Time to discharge of survivors (days)	104.5 (49–230)	91 (39–258)	93 (41–181)	0.011†, NS‡

Data expressed as *n* (%) or median (range). ARED Group, index group with absent or reversed end-diastolic umbilical artery blood flow; Control Group A, all other infants born at < 30 gestational weeks during 1998–2004; Control Group B, appropriate-for-gestational age infants matched for gestational age, gender and year of birth. *Data determined in surviving infants; information not available in some cases. Severe brain damage comprised intraventricular hemorrhage Grade III–IV and/or periventricular leukomalacia. †ARED Group vs. Control Group A; ‡ARED Group vs. Control Group B. CPAP, continuous positive airway pressure; NS, not significant.

Table 6 Perinatal mortality and outcome at 2 years of age

	ARED Group	*Control Group A*	P
All infants	46	399	
Stillborn	4 (9)	24 (6)	NS
Neonatal death in delivery room	0 (0)	4 (1)	—
Neonatal death (at 0–6 days) of infants admitted to NICU	0 (0)	27 (7)	—
Perinatal mortality	4 (9)	55 (14)	NS
Liveborn infants	42	375	
Survival to home discharge	38 (90)	326 (87)	NS
Survival at 2 years of age	38 (90)	326 (87)	NS
Cerebral palsy*	5/36 (14)	34/321 (11)	NS

Data expressed as *n* (%). ARED Group, index group with absent or reversed end-diastolic umbilical artery blood flow; Control Group A, all other infants born at < 30 gestational weeks during 1998–2004. *Data on cerebral palsy were not available for all infants. NICU, neonatal intensive care unit; NS, not significant.

PI and was subsequently delivered by Cesarean section at 25 + 0 weeks because of the occurrence of absent end-diastolic flow (the latter infant is among survivors of the ARED Group).

DISCUSSION

In the present study, fetuses with ARED in the umbilical artery and growth restriction delivered on fetal indication before 30 gestational weeks did not display an increased perinatal mortality when compared with all other fetuses delivered at the Department of Obstetrics and Gynecology in Lund at a corresponding gestational age during the same time period. The survival rate of liveborn infants up to 2 years of age was 90%, similar to that reported by Schwarze *et al.*[12] for infants with ARED born before 32 weeks (6/53; survival until discharge from the neonatal unit 89%). These survival rates contrast with other data published for growth-restricted fetuses with abnormal umbilical artery blood flow and with gestational age comparable to that in the present study. In the study by Hartung *et al.*[13], 7/11 (64%) infants delivered before 29 weeks survived and, in the large multicenter study by Baschat *et al.*[14], the corresponding figure for 326 infants born before 30 weeks was 69%. Interestingly, the two studies with high survival – the present study and the study by Schwarze *et al.*[12] – also reported low rates of intrauterine death (9% and 11%, respectively), including cases where the parents did not wish intervention, than reported by others[13,15].

Our study certainly has limitations; it is a descriptive study, the number of index cases is small and blood flow data in the matched AGA fetuses were not available. As the study does not have a controlled design, it is not possible to conclude with certainty whether or not the active attitude of obstetricians and early intervention were of importance for the excellent outcome of these preterm growth-restricted fetuses with ARED. Naturally, a crucial prerequisite for good outcome of very preterm fetuses with IUGR is a high standard of neonatal intensive care, as also reflected in the results of the background population, i.e. of Control Group A.

It is possible that the disadvantage of slightly lower gestational age at birth in compromised fetuses that undergo timed preterm delivery could be outweighed by the fact that the infant is in a better condition when delivered than it would have been following expectant management. However, the only published randomized trial, the Growth Restriction Intervention Trial (GRIT), to approach this question did not find any significant differences in the rates of survival and disabilities at 2 years of age between the groups with deferred and intermediate intervention[16]. Regrettably, the GRIT study does not seem to offer the final answer as its external validity was not guaranteed[17].

The policy of early intervention, with the intention of preventing deterioration of fetal state *in utero* and in many cases eventual fetal death, is well reflected in the present study: in the majority of fetuses (29 of 42) the final finding in the umbilical artery before delivery was absent end-diastolic flow (Figure 2). Similarly, only 18% of fetuses had an abnormal flow pattern in the ductus venosus, and any impairment of the ductus venosus waveform during observation was noted in a total of 29% of fetuses (Table 2). In several studies, a strong correlation has been shown between abnormal ductus venosus velocity waveform and adverse outcome in early IUGR[6,7,13]. In our clinical protocol, which is empirical, based on those studies and clinical experience over the years, deteriorating ductus venosus waveform, alone or in combination with pulsations in the umbilical vein and/or abnormal FHR tracing, supported the decision to deliver a singleton fetus with absent end-diastolic flow in the umbilical artery. Reversed end-diastolic umbilical artery flow in a singleton fetus after 25 gestational weeks was considered in itself a strong indication for delivery after the administration of steroids. The frequently observed abnormal Doppler findings in the fetal middle cerebral artery and in the maternal uterine arteries did not contribute significantly to clinical decision making.

The decision to deliver on fetal indication in the very preterm period, and especially near the limits of viability, is a very difficult task that needs a team approach. The discussion, which always comprises rather complex ethical considerations, should include recent data from the literature and the relevant information on clinical outcome in the institution concerned. To involve the parents in the discussion is a condition *sine qua non*. The opinion and wishes of the parents-to-be must be considered, provided that they are given adequate and understandable information. In Sweden, the law does not allow any intervention in pregnancy without the agreement of the mother. In the present study, parents did not wish any active management in three cases and the fetuses died *in utero*.

In twin pregnancies the decision can be even more complicated and the ethical problems, if possible, still more pronounced when there is a question of whether to deliver an extremely preterm fetus that shows no signs of distress because of the worsening condition of its cotwin. Generally, multiple very preterm births are reported to have lower survival rates than singleton births[18] and thus the risk of iatrogenic prematurity will be considerable for such a fetus. Often, the prognosis for the distressed twin fetus, either staying *in utero* or being delivered, is very difficult to assess. Besides, the changes of fetoplacental circulation in twin pregnancies are quite often difficult to evaluate as they can develop differently from those in singleton fetuses.

Overall, the ARED Group did not exhibit greater neonatal morbidity than the two control groups, with the exception of chronic lung disease, as also described for very preterm SGA infants in previous studies[19,20]. We hypothesize that there might be a causative relationship between IUGR with abnormal fetal blood flow and the development of chronic lung disease. Previous studies on animal models of induced IUGR have shown a decrease in air wall area in newborn lambs[21] and postnatal respiratory impairment such as reduced lung compliance[22]. Furthermore, decreased lung perfusion in human growth-restricted fetuses was demonstrated using power Doppler ultrasound imaging[23].

Similar to Hartung *et al.*[13], we did not detect differences in the incidence of neurological morbidity between the ARED Group and the control groups. In 74% of fetuses Doppler findings in the middle cerebral artery indicated redistribution of blood flow, supporting the assumption that this mechanism, at least early in intrauterine hypoxia, protects the brain rather than being a sign of brain damage[24]. Moreover, the incidence of cerebral palsy at 2 years of age was also comparable between the groups. Contrary to our findings, Vossbeck *et al.*[25], in a retrospective study on 40 infants with ARED, demonstrated a higher incidence of severe motor impairment in comparison to gestational age-matched controls. In their study, the postnatal mortality rate was as high as 35% and no detailed data on other Doppler parameters or FHR recordings were presented.

We conclude that delivery on fetal indication of very preterm fetuses with ARED and IUGR and active care of the newborns resulted in high survival rate (90%), and rates of neonatal complications and cerebral palsy at 24 months of age that were comparable to those of other very preterm infants born before 30 weeks of gestation in Lund. The only significant difference found was in the occurrence of chronic lung complications, which were more frequent in the ARED Group. Long-term follow-up of further development of these infants is essential and is currently in progress.

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