RESEARCH PAPER

Outcome of Very Low Birth Weight Infants with Abnormal Antenatal Doppler Flow Patterns: *A Prospective Cohort Study*

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Background: Fetal growth restriction and abnormal Doppler flow studies are commonly associated. Neonatal outcomes are not well known particularly in developing countries, where the burden of the disease is the highest.

Objective: To determine outcomes of preterm infants with history of absent/reversed end-diastolic umbilical artery Doppler flow (AREDF) *vs.* infants with forward end-diastolic flow (FEDF).

Design: Cohort study.

Setting: Tertiary care perinatal center in India.

Participants: 103 AREDF very low birth weight (<1500 gm) (VLBW) infants and 117 FEDF VLBW infants were prospectively enrolled.

Results: At 40 weeks adjusted post-menstrual age, AREDF *vs*. FEDF group had a higher risk for death in the NICU (12% *vs*. 1%), respiratory distress syndrome (33% *vs.* 19%), and cystic periventricular leukomalacia (12% vs. 1%). At 12-18 months corrected age, AREDF vs. FEDF group had a trend towards increased risk for cerebral palsy (7% *vs*. 1%, *P*=0.06). After logistic regression analysis, adjusting for confounders, AREDF was independently associated only with mortality in the NICU.

Conclusion: AREDF is an independent predictor of adverse outcomes in preterm infants in a developing country setting.

Keywords: *India, Intrauterine growth restriction, Outcome, Prognosis, Pre-eclampsia.*

Intrauterine growth restriction can be caused by a number of conditions but pregnancy induced hypertension and vascular disorders of the placenta are among the most common etiologies responsible for about 25-30% of IUGR [1]. Although the incidence of IUGR is about 8% in the Western world [2], the prevalence in the developing world is much higher at ~35% [3].

Although a number of different modalities are used for fetal surveillance of IUGR, umbilical Doppler flow pattern is one of the most widely used tests [4]. A number of observational studies have reported outcomes in IUGR infants with abnormal antenatal Doppler flow pattern [5-10]. However, there are few studies [11,12] from the developing world, where the global burden of the fetal growth restriction and preeclampsia is the highest [3,13]. This information is essential to devise strategies for reducing the rates of still-births/prematurity globally [14]. We hypothesized that an absent or reversed end diastolic flow in umbilical artery (AREDF) would be an independent predictor of adverse short-term and long-term infant outcomes. We report the comparison of AREDF *vs.* forward end-diastolic flow (FEDF) on comprehensive short-term outcomes and long-term neurosensory and growth outcomes in preterm infants.

METHODS

Parents of 238 very low birth weight (VLBW) infants (<1500 gm birth weight) and gestation <35 weeks born consecutively between the periods January 2007 to December 2008 at our referral perinatal center were prospectively approached for informed consent for enrolment at admission into the NICU. Infants with major congenital malformations were excluded. Gestational age was determined by a first trimester ultrasound scan, or by the mother's last menstrual period. Antenatal umbilical artery Doppler flows (Voluson, Philips and Logic Q machines) were measured in pregnant women less than 35 weeks of gestation and reported as forward, absent or reversal of flow during diastole. The indications for Doppler studies were (*a*) evidence of growth restriction on serial scans (based on Mediscan charts, Chennai [15]), (*b*) pregnancy induced hypertension, and (*c*) history of intrauterine death in a previous pregnancy. The umbilical artery Doppler velocimetries reported in the study were

those obtained closest to delivery. The study population was divided into two cohorts *viz*., AREDF group comprising VLBW infants with absent or reversed end-diastolic flow velocities in the umbilical artery; and FEDF group with VLBW infants with forward Doppler flow velocity in umbilical artery and those in whom antenatal Doppler studies were not indicated.

The primary outcomes included: Composite outcome of death or major neuro-morbidity at 12-18 months of corrected age, defined as presence of cerebral palsy or visual or hearing impairment. The secondary outcomes included morbidities common in preterm infants. The diagnosis of cerebral palsy was made by clinical examination by experienced physicians blinded to the antenatal Doppler studies. Hearing impairment was defined as any degree of hearing loss requiring the need for hearing aids.

The antenatal details of study infants were collected retrospectively from a computerized database and patient medical records. All enrolled infants were followed up weekly/biweekly till they were 40 weeks of corrected postmenstrual age, and then at 3,6,9,12 and 18 months of corrected age for growth and neurological assessment in the high-risk neurodevelopmental follow-up clinic. At 40 weeks of corrected postmenstrual age, each infant had a cranial ultrasound and a brain stem evoked response audiometry. Growth was evaluated by measuring the weight, head circumference and length by a trained nurse and plotted on the Indian Academy of Pediatrics growth charts. Neurological assessment was done by experienced physicians using the Amiel-Tison method [16]. All measurements were performed by investigators blinded to antenatal studies.

Statistical analysis: Outcome variables were compared between the study and the control groups. Statistical analyses were performed by using SPSS (Version 16.0 for Windows, SPSS Inc., Chicago, IL) followed by the R package (Version 13.2.1). Fisher's exact test was used for categorical variables and for continuous variables the student t-tests (normally distributed data) or Mann-Whitney U tests (data not distributed normally) were used. Significance was accepted at $P<0.05$. For multivariate analyses, initial exploration of associations were performed using classification tree and random forest methodology (not reported). Based on the initial exploratory analysis, several responses were modeled as predictors of outcome of interest. The odds ratio of a predictor adjusted for the presence of the other predictors along with 95% confidence interval is reported.

We estimated that a sample size of 88 patients in each group would provide 80% power at 95% confidence level to detect a 4-fold difference in risk of the primary outcome (death or major neuromorbidity) between the groups.

RESULTS

238 VLBW infants fulfilled the eligibility criteria. Of these, 220 infants were analyzed for short-term outcomes. Long-term outcomes were evaluated in 181 infants for growth and neurological outcomes (***Fig.* 1**). Compared to the AREDF group, more infants in the FEDF group were lost to follow up (3.3% *vs* 18.6%, $P=0.001$).

Although the degree of prematurity did not differ, the infants in the AREDF group were smaller compared with FEDF group. Expectedly, more infants in the AREDF group were growth restricted at birth. Delivery by Caesarean section, and oligohydramnios was significantly higher in the AREDF group compared with the FEDF group. (***Table* I)**.

Short-term outcomes: More infants had hospital deaths in the AREDF group compared to the FEDF group (***Table* II).** Need for resuscitation at birth was similar between

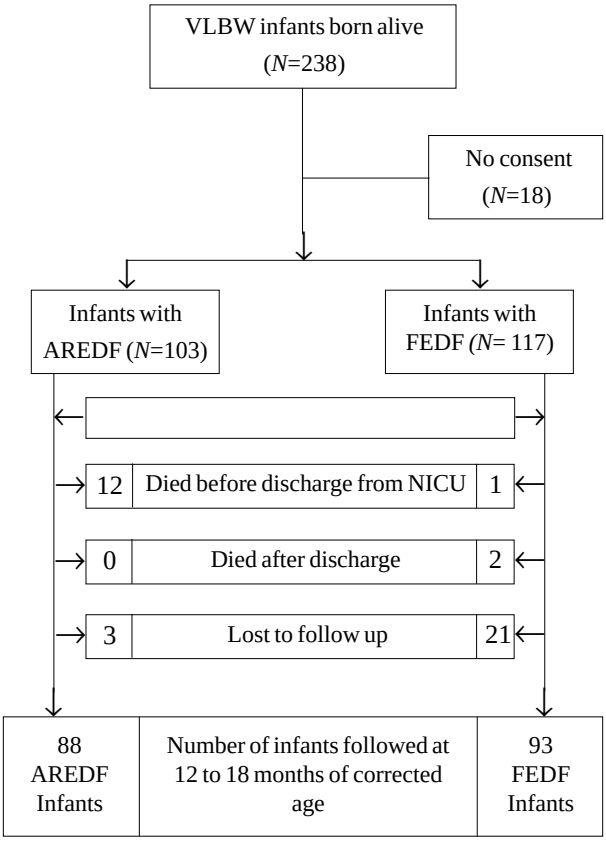

FIG. 1 *Study flow chart.*

the groups, but the incidence of respiratory distress syndrome (RDS) was higher in the AREDF *vs* FEDF group. There was a tendency to need more respiratory support in the AREDF *vs* FEDF group. However both the groups were comparable for morbidities such as patent ductus arteriosus, neonatal jaundice, chronic lung disease, and retinopathy of prematurity.

Of the 17 infants with abnormal cranial ultrasounds in the AREDF group, leucomalacia and the others had grade III-IV intraventricular hemorrhage (***Table* II**).

Long term outcomes: The odds for the combined outcome of death or cerebral palsy (*n*=18,17% *vs n*=4, 3%, OR 5.9, 95% CI 1.9 to 25) was 5.9 times higher in the AREDF group compared to the FEDF**.** Also AREDF infants showed a trend toward higher risk for developing cerebral palsy compared to the FEDF infants (*n*=6,7% *vs n*=1,1%: *P*=0.06). None of the infants in either group were blind or had deafness. There were also no differences between the groups in the incidence of microcephaly, short stature or poor weight gain**.**

On logistic regression analysis for the short-term outcomes after adjusting for ELBW (birth weight<1000g) and IUGR status, AREDF continued to have an independent association with neonatal mortality (OR 9.8, 95% CI 2.1- 46.4) and RDS (OR 2.4, 95% CI,1.1-5.0). For the long-term outcomes, AREDF had an

TABLE I *BASELINE CHARACTERISTICS OF STUDY INFANTS*

Variable	*AREDF group N=103*	*FEDF group N= 117*
*Birth weight[a] (g)	1095 (951-1288)	1260 (1080-1400)
Gestation[a] (wk)	31 (30-33)	31 (30-32)
[†]Birth weight <1000g	32 (31)	20 (17)
Gestation <30 wk	22 (21)	24 (21)
Males	52 (50)	47 (40)
*IUGR	59 (57)	36 (31)
Apgar scores (5min)	8 (7-8)	8 (7-8)
[#]Cesarean delivery	103 (99)	103 (88)
*Singleton pregnancy	98 (95)	79 (68)
Antenatal steroids	95 (92)	102 (87)
Maternal age, mean (SD)	27.2 (4.4)	26.7 (4.7)
PIH	77 (75)	92 (79)
[$]Oligohydramnios	35 (34)	25 (21)
PROM	1 (1)	21 (18)
[#]Preterm labor	2 (2)	17 (15)

*Data shown as [a]median (inter-quartile range), rest as n (%); * P=0.001; [#]P=0.001; [$]P=0.05; [†]P=0.02; P≤0.05; AREDF: absent/ reversed end-diastolic umbilical artery Doppler flow; FEDF=forward end-diastolic flow; IUGR=Intrauterine growth restriction; PIH: Pregnancy induced hypertension; PROM: Preterm rupture of membranes.*

TABLE II SHORT-TERM OUTCOME OF STUDY INFANTS

Outcome	*AREDF (n=103)*	*FEDF (n=117)*	*P value*
Mortality	12 (12)	1 (1)	0.001
Delivery room resuscitation	16 (16)	23 (20)	0.48
Hypoglycaemia	8 (8)	4 (4)	0.23
Respiratory distress syndrome	33 (33)	21 (19)	0.02
Continuous positive airway pressure	32 (32)	23 (20)	0.06
Conventional ventilation	34 (34)	26 (23)	0.09
Necrotizing enterocolitis (≥ Bell stage IIa)	15 (15)	9 (8)	0.13
Culture positive sepsis	24 (24)	15 (13)	0.051
Hemodynamically significant Patent ductus arteriosus	5 (5)	12 (11)	0.20
Chronic lung disease (supplemental O_2 at 28d)	1 (1)	3 (3)	0.62
Retinopathy of prematurity (≥stage II)	15 (15)	11 (9)	0.40
Abnormal cranial ultrasound	17 (17)	13 (11)	0.42
Cystic periventricular leukomalacia	10 (12)	1 (1)	0.004
Time to reach full feeds[a] (d)	8 (6-10)	7 (4-8)	0.001
Duration of hospitalization[a] (d)	20 (14-29)	15 (11-71)	0.03

Data shown as [a]median (inter-quartile range); Rest as n(%); AREDF: absent/reversed end-diastolic umbilical artery Doppler flow; FEDF= forward end-diastolic flow.

independent association with the composite outcome of death or cerebral palsy (OR 8.4, 95% CI 2.3- 30.5) but not cerebral palsy or microcephaly alone.

To better capture the contribution of AREDF in neonatal outcomes, we examined all predictors of bad outcome in the NICU. Since there were very few cases of chronic lung disease in this population, bad outcome was defined as death or cystic periventricular leukomalacia, or culture positive sepsis or necrotizing enterocolitis. The only predictors that were significant were birthweight (P=0.01) and Doppler flow status (P=0.05). To better model the relationship between the predictors and bad outcome as a response, a logistic regression curve of the probability of bad outcome as a function of birth weight adjusted for AREDF or FEDF was fitted (***Fig.* 2**). The preterm infants in the AREDF group had a consistently higher probability of a bad outcome compared to the FEDF group with the disadvantage being more pronounced at lower birth weights.

DISCUSSION

In this cohort of moderately preterm infants with a history of fetal growth restriction or exposure to pre-eclampsia, demonstration of antenatal absent or reversed end-diastolic flow in the umbilical artery was shown to increase the risk for neonatal death. This study was specifically designed to prospectively compare outcomes after AREDF *vs* FEDF, the gestational ages between the groups were comparable, and the numbers of infants were relatively large permitting meaningful comparisons. We evaluated both short-term and long-term outcomes comprehensively with follow-up rates in excess of 90%, all infants were enrolled in a 2-year time-span from a single-perinatal center minimizing the confounding of changing or differing management practices on the outcomes, and the groups were relatively homogenous in that the underlying diagnosis was PIH in a great majority. To our knowledge, the present study is the largest and the most comprehensive report on the contribution of abnormal Doppler flow patterns, and IUGR to outcomes in Indian preterm infants.

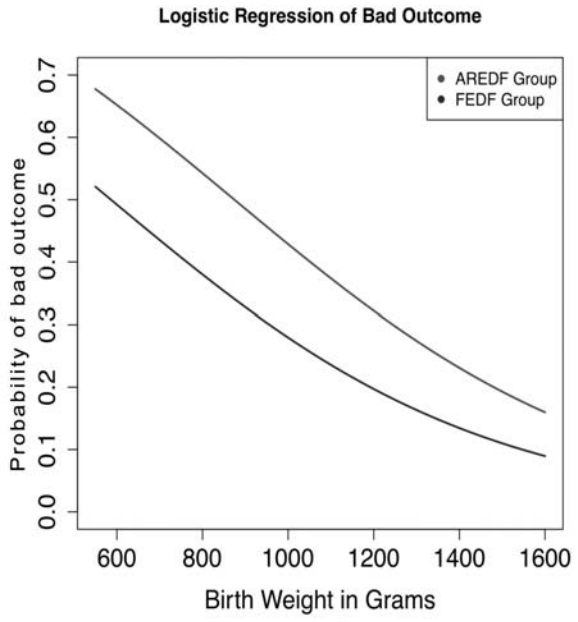

FIG. 2 *Relationship between birth-weight, umbilical Doppler flow patterns and outcome. Bad outcome (defined as death or periventricular leukomalacia, or culture positive sepsis or necrotizing enterocolitis); AREDF: Absent/reversed end-diastolic unbilical artery doppler flow; FEDF: Forward end-diastolic flow.*

The higher neonatal mortality and morbidity in infants with history of AREDF noted in this study is similar to previous studies [17-21]. In comparison with these older studies, we had higher numbers of infants with absent or reversed end-diastolic flow and the gestational ages in both the groups were comparable. Consistent with the reported literature, findings from the present study confirm that birthweight and gestational age are more potent predictors of short-term adverse neonatal outcomes in infants with IUGR, compared to Doppler flow patterns. Interestingly, our data clearly demonstrated that despite birth weight being a potent predictor of poor neonatal outcomes, the diagnosis of AREDF had an independent adverse impact at all birth weights with a more pronounced effect at lower birth weights.

For long-term outcomes, our study showed an independent association of AREDF with the composite outcome of cerebral palsy or death in infancy. This effect was largely due to increased neonatal deaths. Interestingly, although the rate of PVL at term gestation was higher in the AREDF group, this did not translate into an increased risk for adverse neuromorbidity (cerebral palsy tended to be more common in the AREDF group). A factor that may explain the lack of adverse neurological outcomes despite increased rates of PVL is developmental plasticity in the preterm [22]. In this regard, infants in the early delivery arm of a randomized trial evaluating early *vs*. delayed delivery in IUGR infants had an increased risk for adverse neurodevelopmental outcomes at two years that was not sustained at school age [23,24]. Studies of neurodevelopmental outcome in infants with IUGR and abnormal Doppler flows have reported inconsistent outcomes. Studies with smaller numbers of infants have reported adverse neurological outcomes [9,10,25], while others failed to demonstrate neurologic impairments [8,26]. These discrepancies

WHAT IS ALREADY KNOWN?

- Fetal growth restriction and abnormal Doppler flow studies are commonly associated.
- Neonatal outcomes are not well known in developing countries.

WHAT THIS STUDY ADDS?

- Preterm IUGR infants with antenatal abnormal umbilical artery doppler, are at increased risk for immediate mortality and long term neurological disabilities.

largely appear to be due to different patient populations and the degree of prematurity appears to be a predominant determinant of adverse long term neurological outcomes rather than abnormal Doppler flow patterns [5,27,28].

The variables of birthweight, gestation, IUGR and Doppler flow patterns are inevitably interlinked. In this regard a randomized trial (GRIT trial) evaluated trade-offs between immediate *vs.* delayed delivery in the management of preterm infants ~28 weeks gestation with fetal growth restriction [29]. The immediate delivery group had higher neonatal deaths but the stillbirth rate was higher in the delayed group. Adverse neurological outcome at 2 years was more common in the earlier delivery group, but these handicaps did not persist at school age [23,24]. The prevalent practice at our study site is to give maternal glucocorticoids and deliver infants within 48 hours after demonstration of absent/reversed end-diastolic flow, similar to the early delivery arm of the GRIT trial. Despite the immediate delivery, fetuses with AREDF had an increased mortality and morbidity in our study, suggesting that the umbilical Doppler changes may be a late finding in the pathophysiology of fetal compromise in IUGR and pre-eclampsia [27]. Alternatively, the fetuses in our study may have been sicker than previously reported. Regardless, the findings are informative for clinicians managing these high risk pregnancies .

Despite several strengths of our study, some weaknesses were apparent. The study population was entirely from a large referral perinatal center with a higher rate of IUGR and pre-eclampsia than the general population. Lost to follow up was significantly higher in the forward flow group. The study was not randomized. Therefore the findings of the study may not be generalizable. We did not evaluate multiple different ultrasound measurements of fetal well-being, because umbilical artery doppler studies are the most commonly used modality at most perinatal centers dealing with high risk pregnancies.

In a cohort of moderate preterm delivery with IUGR or maternal pre-eclampsia, absent or reversed end diastolic umbilical arterial blood flow independently increased the risk for neonatal mortality, and had a trend towards increased incidence of cerebral palsy at 12-18 months corrected age.

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