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ORIGINAL RESEARCH ARTICLE

Outcome of early-onset fetal growth restriction with or without abnormal umbilical artery Doppler flow

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ABSTRACT

Introduction: Early-onset fetal growth restriction is a pregnancy complication often coinciding with abnormal Doppler flow in the umbilical artery. Absent or reversed end-diastolic flow in the umbilical artery is associated with adverse perinatal outcome. As the optimal management of this condition is unclear, the objective of this study was to analyze the time interval from admission to delivery of pregnancies with early-onset fetal growth restriction, while pursuing a policy of postponing delivery unless active management of labor would be required because of fetal distress or maternal condition. We also assessed short- and long-term perinatal outcome.

Material and methods: In this historical cohort study, all pregnant women with singleton pregnancies, admitted during 2004–2015 with early-onset fetal growth restriction were included. Pregnancies with absent or reversed end-diastolic flow (AREDF) were compared with pregnancies with a positive end-diastolic Doppler flow (PEDF). Time until delivery was determined and perinatal outcome was assessed for both groups.

Results: In our study, 111 women were allocated to the PEDF group and 109 to the AREDF group. In the AREDF group, fetal distress was more often an indication for delivery, in comparison with the PEDF group (p = .004). Median time until delivery in patients admitted between 26 and 28 weeks' gestation was 6+5 weeks in the PEDF group and 1+4 weeks in the AREDF group (p = .001). No statistically significant difference was found between the Doppler groups in the composite adverse neonatal outcome, which includes at least one of the following outcomes: infant respiratory distress syndrome, sepsis, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage >grade 2, periventricular leukomalacia and perinatal death (p = .63).

Conclusions: In this study, comprising pregnancies with early-onset fetal growth restriction, fetal distress was observed more frequently in the AREDF group with the consequence of delivery at an earlier stage of gestation, compared with the PEDF

Abbreviations: AEDF, absent end-diastolic flow; AREDF, absent or reversed end-diastolic flow; BSID III, Bayley Scales of Infant and Toddler Development, third edition; EFW, estimated fetal weight; FGR, fetal growth restriction; IRDS, infant respiratory distress syndrome; PEDF, positive end-diastolic Doppler flow; PVL, periventricular leukomalacia.

group. AREDF was not associated with increased perinatal morbidity and mortality compared with PEDF.

KEYWORDS
fetal growth restriction, preterm, umbilical artery Doppler

1 | INTRODUCTION

Fetal growth restriction (FGR) is a common but multifactorial and complex complication during pregnancy, defined by a fetus that has not reached its genetic growth potential. It is also a major cause of perinatal morbidity and mortality.[1] In the Netherlands, the definition of FGR is an estimated fetal weight (EFW) below the 10th percentile, an abdominal circumference below the 10th percentile and a deflecting growth of at least 20 percentiles.[2,3] The prevalence of FGR is between 3% and 10%.[2] If FGR is observed before 32 weeks' gestation, it is defined as early-onset FGR.[4,5] Of all cases of FGR, the incidence of early-onset FGR is approximately 20%–30%.[4] It is more often associated with hypertensive disorders and differs from late-onset FGR in its clinical presentation. FGR can be caused by maternal, fetal or placental factors,[4,6] but placental insufficiency, resulting from suboptimal uteroplacental perfusion and placental infarction, is by far the most common cause.[1] In a growth-restricted fetus, absent or reversed end-diastolic Doppler flow (AREDF) in the umbilical artery can be observed as a result of the destruction of small arteries in the tertiary stem villi of the placenta. AREDF, therefore, represents severe placental dysfunction, possibly resulting in early-onset FGR and/or oligohydramnios.[4] Consequently, adverse perinatal outcome has been associated with this condition.[4,7-10] If early-onset FGR is diagnosed, the timing of the decision to initiate delivery becomes crucial. An iatrogenic, early delivery to prevent fetal hypoxia could lead to perinatal death, but delay of delivery in order to let the fetus gain maturity may lead to stillbirth.[11] Obstetricians in the Netherlands manage early-onset FGR differently from other countries, as they prefer to postpone labor despite AREDF until this is no longer feasible because of fetal distress or maternal indication.[2] As there is still no consensus about the management of early-onset FGR, it was our aim to determine the natural course of a pregnancy, complicated by early-onset FGR, while pursuing a policy of postponing delivery until signs of fetal distress or maternal indications would arise and active intervention in terms of a cesarean section would be required. Also, our goal was to assess whether an abnormal umbilical Doppler was associated with increased adverse perinatal outcome.

Key message

When observing the natural course of pregnancies with early-onset fetal growth restriction, delivery was at an earlier stage of gestation in the AREDF group than in the PEDF group. AREDF does not seem to be associated with increased perinatal morbidity or mortality.

2 | MATERIAL AND METHODS

2.1 | Study setting and participants

This was a historical cohort study, conducted at the Department of Obstetrics of the Erasmus University Medical Center in Rotterdam. From 2004 until 2015, women were eligible when they met the following inclusion criteria: (1) singleton pregnancy with FGR (EFW between 500 and 1250 g and an abdominal circumference below the 10th percentile) and AREDF or singleton pregnancy with FGR and PEDF in combination with additional complications such as hypertension and suboptimal cardiotocography, based on the FIGO classification (Table S1); (2) gestational age (GA) of 24–32 weeks at time of admission to our hospital; (3) intended active obstetric management in case of fetal distress or maternal indication. We set the lower threshold of 24 weeks' gestation, as pregnancies diagnosed with FGR before 24 weeks' gestation are allowed to be terminated because of a detrimental fetal prognosis, as stated by law in the Netherlands. We excluded cases of congenital infections (TORCH infections) and pregnancies with a suspicion of structural or genetic fetal anomalies, as these conditions can independently result in FGR.[4] It was our aim to include cases of growth restriction, solely caused by placental insufficiency.

2.2 | Baseline characteristics

Included maternal baseline characteristics were maternal risk factors (age, nulliparity, smoking, alcohol consumption, drugs use, body mass index and hypertensive disorder) and a completed course of antenatal corticosteroids with two doses of betamethasone 12 mg i.m., 24 hours apart. Hypertensive disorders comprised preexisting hypertension, pregnancy-induced hypertension, preeclampsia and superimposed preeclampsia, as defined in the literature.[12]

2.3 | Measurements and management

Patients were admitted from the outpatient clinic or transferred from hospitals that provided secondary care. Antenatal

corticosteroids were administrated (two repeated doses, 24 hours apart) to facilitate fetal lung maturation. Clinical management and treatment were equal for both groups. Measurement of the end-diastolic flow in the umbilical artery was conducted weekly and fetal biometry every 2 weeks. To calculate the EFW, we used the Hadlock formula.[13] Sonography was performed by trained healthcare providers or professional sonographers. We used cardiotocography to measure fetal heart frequency and uterine contractions daily. Additional tests, such as blood tests, were performed on indication, but at least weekly. Delivery was initiated on signs of fetal distress, maternal indications or both. Fetal distress was defined as spontaneous repeated persistent unprovoked decelerations on the cardiotocogram. The cardiotocogram was then classified as abnormal.[14] Maternal indications for delivery arose when there was a considerable chance of maternal morbidity or mortality. Women were discharged from our hospital to outpatient clinics or hospitals that provided secondary care when they had reached 32 weeks of gestation or an EFW >1250 g, unless there was an indication for prolonged admission. Neonates that required active and intensive care were admitted to our Neonatal Intensive Care Unit, level III. After approximately 24 months, infants underwent multiple tests to determine cognitive and motor scores.

2.4 | Outcomes

The primary outcome was the time to delivery from admission. Secondary short-term outcomes were the incidence of infant respiratory distress syndrome (IRDS), sepsis, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage >grade 2, periventricular leukomalacia and perinatal death (fetal or neonatal death from 24 weeks GA to 7 days, neonatal age). Also, a composite adverse neonatal outcome was defined, which consisted of at least one of the complications mentioned above.[15] Our first long-term outcome was the neurodevelopment at 2 years of age, which was measured using the Bayley Scales of Infant and Toddler Development, third edition (BSID III). The second long-term outcome was death within the first year of life.

2.5 | Statistical analyses

We allocated women with PEDF in the umbilical artery to group 1 (PEDF group) and women with AREDF to group 2 (AREDF group). Participants were also divided into subgroups of GA at admission, arranged in intervals of 2 weeks to compare the time of delivery for each GA at admission subgroup. The time to delivery, fetal outcome and perinatal outcome were compared between the AREDF and PEDF groups using the *t* test, Mann-Whitney *U* test or Pearson's chi-square test, as appropriate. Univariable and multivariable logistic regression analyses was conducted to compare the incidence of adverse perinatal outcome between the Doppler groups. For IRDS, we used Doppler group, EFW at admission, time interval until delivery, antenatal corticosteroids and male fetal gender as independent variables, as described in previous literature.[16,17] We used Doppler group, EFW at admission and time interval until delivery as independent variables for sepsis and death within the first year of life.[18] The independent variables for the composite adverse neonatal outcome included: (1) Doppler group, (2) EFW at admission, (3) time interval until delivery, (4) antenatal corticosteroids, (5) male fetal gender, (6) maternal age, (7) nulliparity and (8) smoking and/or consumption of alcohol or drugs.[15] All multivariable logistic regression analyses were adjusted for the year of diagnosis, and all possible interactions between the variables were tested, as appropriate. Multivariable linear regression analysis was also conducted to predict neurodevelopment at 2 years of age. We used Doppler group, EFW at admission, time interval until delivery and a variable indicating smoking and/or consumption of alcohol or drugs as independent variables. Statistical significance was confirmed when a *p* value <.05 was observed. All statistical analyses were performed using Statistical Package for the Social Sciences version 24 (IBM Corp., New York, NY, USA).

2.6 | Ethical approval

This study was reviewed and approved by the Medical Ethics Committee Erasmus MC, Rotterdam (reference number MEC-2017–271, 22 February 2018). The rules laid down in the Medical Research Involving Human Subjects Act did not apply to our study, as participants were not subject to procedures and were not required to follow rules of behavior.

3 | RESULTS

During the study period, 430 pregnant women with the diagnosis of early-onset FGR were admitted to our tertiary care center (Figure 1). After exclusion, based on the criteria described in the Material and methods section, 217 patients were included and allocated to the PEDF group (*n* = 108) or the AREDF group (*n* = 109). Two patients opted for a non-intervention management and were excluded from the analysis. The AREDF group consisted of 66 (61%) women with an absent end-diastolic flow (AEDF) at or during admission, 25 (23%) women with a reversed end-diastolic flow (REDF) and 18 (17%) women who developed both AEDF and subsequently REDF during admission.

Baseline maternal characteristics are shown in Table 1. There were no statistically significant differences between the AREDF and the PEDF group. With regard to the indications for admission (Table S1), fetal cerebral redistribution (cerebro-placental ratio <1.00) was significantly more often a reason for admission in the AREDF group (*n* = 14, 13%) than in the PEDF group (*n* = 2, 2%) (*p* = .002). In the PEDF group, 20 women (19%) were admitted because of a suboptimal CTG vs 5 (5%) women in the AREDF group (*p* = .001).

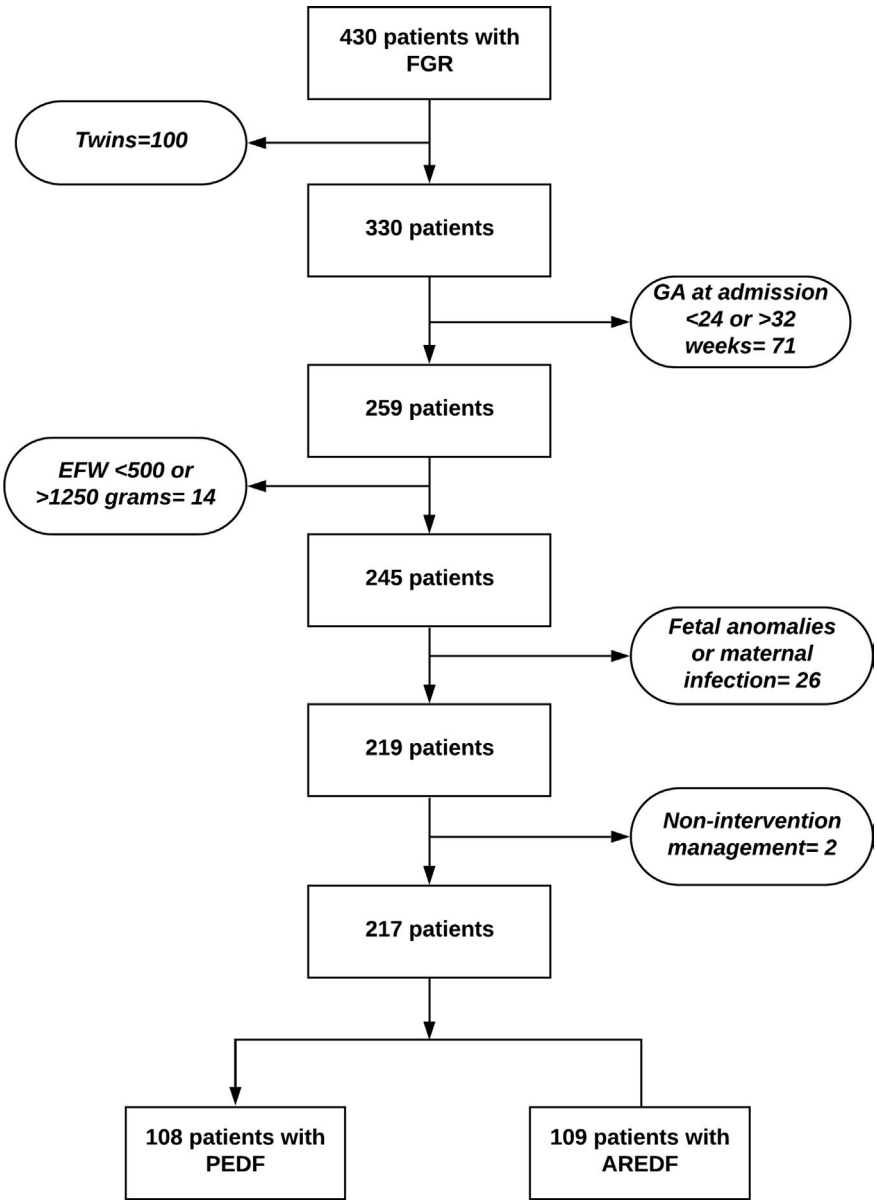

FIGURE 1 Flowchart of included patients. FGR, fetal growth restriction; GA, gestational age; EFW, estimated fetal weight, PEDF, positive end-diastolic flow; AREDF, absent or reversed end-diastolic flow

The first delivery in our study occurred at 25+2 weeks' gestation in the AREDF group and the last one at 41+1 weeks in the PEDF group (Table 2, Figure 2). Delivery occurred at an earlier stage of gestation in the AREDF group than in the PEDF group ($p < .001$). Women admitted between 26 and 28 weeks GA with PEDF delivered after a median time of 6+5 weeks, whereas in women admitted in the same gestational period but with AREDF, delivery occurred after 1+4 weeks after admission ($p = .001$).

During admission, two cases (2%) of stillbirth occurred in the PEDF group and one (1%) in the AREDF group ($p = .56$) (Table 3). In the PEDF group, one case of fetal death occurred at 29+2 weeks GA as a consequence of premature prelabor rupture of membranes and an oligohydramnios from 18 weeks of gestation. The second woman was discharged from the hospital after 3 days of active management, in agreement with the patient. One week later, fetal death was detected at 28+4 weeks GA. In the AREDF group, the case of fetal death was due to placental abruption after the patient had left the hospital against medical advice.

Regarding fetal and neonatal outcomes (Table 3, Table S2), fetal distress was the principal indication to initiate labor with 104 (95%) women in the AREDF group and 90 (84%) women in the PEDF group ($p = .004$). Subsequently, more emergency cesarean sections were performed in the AREDF group, 107 (98%), than in the PEDF group, 99 (92%) ($p = .03$). Fetuses in the AREDF group had a decreased EFW (816 g) compared with the PEDF group (876 g) ($p = .03$). No differences in the condition of the fetuses, immediately postpartum, were identified (Table 3). Newborns in the PEDF group had a higher birthweight (1160 vs 940 g; $p < .001$), even after adjustment of gestational age at time of delivery.

In multivariable logistic regression analyses (Table 4), EFW at admission (odds ratio [OR] 0.62, 95% CI 0.51–0.74; $p < .001$), male fetal gender (OR 2.08, 95% CI 1.03–4.19; $p = .04$), and the time interval from admission until delivery in days (OR 0.94, 95%

TABLE 1 Baseline characteristics

	PEDF group (*n* = 108)	AREDF group (*n* = 109)	*p* value
Age, years, median (interquartile range)	29 (24–33)	30 (26–34)	.17
Systolic blood pressure, mm Hg Mean ± SD	126 ± 15	127 ± 15	.49
Diastolic blood pressure, mm Hg Mean ± SD	79 ± 13	80 ± 10	.54
Smoking, *n* (%)	20 (19)	24 (22)	.50
Alcohol consumption, *n* (%)	2 (2)	0 (0)	.15
Drug use, *n* (%)	3 (3)	2 (2)	.64
Ethnic group, Dutch, *n* (%)	68 (63)	69 (63)	.81
Maternal comorbidity, *n* (%)	23 (21)	30 (28)	.29
History of hypertension, *n* (%)	18 (17)	12 (11)	.23
Hypertensive disorder in current pregnancy, *n* (%)	27 (25)	32 (29)	.47
Body mass index, preconceptional, kg/m^2, mean ± SD	26 ± 7	25 ± 5	.14
Nullipara, *n* (%)	58 (54)	65 (60)	.38
Administration of antenatal corticosteroids, full dose, *n* (%)	76 (70)	81 (74)	.52

Abbreviations: AREDF, absent or reversed end-diastolic flow; PEDF, positive end-diastolic flow.

CI 0.93–0.96; $p < .001$) had a statistically significant effect on the occurrence of the composite adverse neonatal outcome (Table 4). The AREDF group was not statistically significantly associated with sepsis ($p = .30$), composite adverse neonatal outcome ($p = .19$) or death within the first year of life ($p = .10$). A significant effect of AREDF on IRDS was found in multivariable analysis (OR 0.33, 95% CI 0.16–0.68; $p = .003$), whereas no statistically significant effect could be detected in univariable analysis (OR 0.82, 95% CI 0.46–1.645; $p = .50$) (Table S5). To investigate the source of this confounding, we added independent variables to the univariable logistic regression analysis one by one. After adding "year of diagnosis" and "EFW", the negative effect of AREDF on IRDS increased (OR 0.68; $p = .21$), and after adding "time interval until delivery", the negative effect of AREDF on IRDS became statistically significant (OR 0.36; $p = .004$), with results similar to the full multivariable model. Table 3 shows a negative association between the variables "EFW" and "AREDF" and the variables "time interval until delivery" and "AREDF" compared with the PEDF group ($p = .03$ and $p = .01$, respectively), which indicates that "EFW" and "time interval until delivery" were likely the most important confounders. No significant interaction effects were detected in the logistic regression models. Because of the small number of cases, we could not perform logistic regression analyses for perinatal complications, other than sepsis and IRDS. No cases of periventricular leukomalacia were reported.

As for the long-term outcomes, 15 cases of death in the first year of life were observed in our study without a significant difference in occurrence rate between the groups, ($p = .76$) (Table S2). EFW was the only significant predictive factor for this outcome (OR 0.40 per 100 g, 95% CI 0.25–0.64; $p < .001$) (Table 4).

No statistically significant differences between the groups were detected in linear regression for the cognitive and motor BSID III scores ($p = .13$ and $p = .88$, respectively). However, we the percentage of valid BSID III scores was low in both groups (Table S3 and S4). In the PEDF group, 34 (31%) of the cognitive BSID III scores were reported and in the AREDF group, 56 (51%). In the PEDF group, we detected 31 (29%) valid results in motor development vs 47 (43%) in the AREDF group.

4 | DISCUSSION

In this historical cohort study in women with early-onset FGR, detected at 24–32 weeks' gestation and allocated to an AREDF or a PEDF group, delivery occurred significantly earlier in the AREDF group. This is particularly the case in women admitted between 26 and 28 weeks' gestation, where a difference of 5 weeks was observed in the time interval from admission to delivery between the groups. The TRUFFLE study[15] also reported a median time to delivery of 8 days in the group with deteriorated Doppler patterns.

Even though management in both Doppler groups was identical in our study, fetuses in the AREDF group were more likely to experience fetal distress during an earlier period in pregnancy and therefore more cesarean sections were performed in this group. As a possible consequence of remaining significantly longer in utero compared with the AREDF group, fetuses in the PEDF group were born with a higher birthweight. We calculated that, based on our study, every 100 g of extra fetal weight, reduced the chance of composite adverse neonatal outcome by 38% and the chance of death within the first year of life by 60%.

TABLE 2 Time until delivery

	PEDF group, (*n*)	AREDF group, (*n*)	Time until delivery in weeks/days in the PEDF group, median (interquartile ranges)	Time until delivery in weeks/days in the AREDF group, median (interquartile ranges)	*p* value
Admission at 24–26 weeks GA	11	16	4/6 (0/6–12/4)	1/6 (0/0–9/1)	.08
Admission at 26 + 1 to 28 + 0 weeks GA	25	24	6/5 (0/0–13/5)	1/4 (0/0–7/6)	.001
Admission at 28 + 1 to 30 + 0 weeks GA	37	42	0/6 (0/0–10/0)	0/6 (0/0–9/1)	.84
Admission at 30 + 1 to 32 + 0 weeks GA	35	27	2/0 (0/0–10/0)	0/5 (0/0–6/0)	.35

Abbreviations: AREDF, absent or reversed end-diastolic flow; GA, gestational age; PEDF, positive end-diastolic flow.

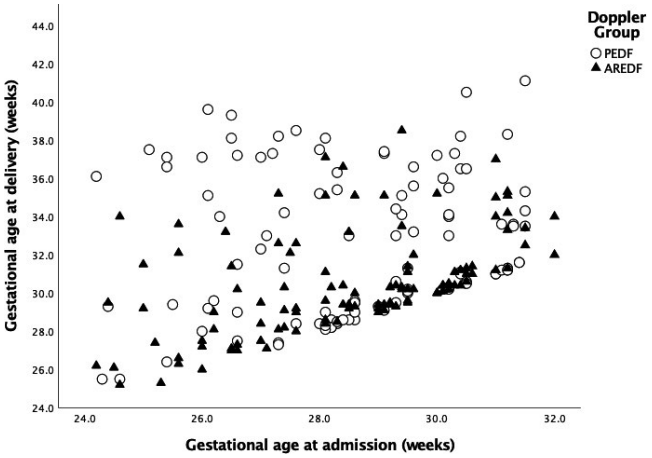

FIGURE 2 Gestational age at delivery, sorted by gestational age at admission in weeks. PEDF, positive end-diastolic flow; AREDF, absent or reversed end-diastolic flow

In our study, there were three cases of stillbirth (1%) and six cases of neonatal death (3%),

A number of earlier studies[11,15] reported an intrauterine fetal demise rate of respectively 1% and 2% and a neonatal death rate of 6%. Therefore, perinatal survival in our study was comparable to that described in the literature. A study by Soothill[19] showed that each day a fetus is not delivered, survival improves by 1–2%.

Despite earlier timing of delivery, AREDF did not lead to an increase in the adverse composite neonatal outcome, compared with the PEDF group. A previously published retrospective study[20] also showed that delivery occurred earlier in the AREDF group and that more cesarean sections were performed in this group, compared with the PEDF group. Also, studies conducted earlier with a comparable study population[15,21,22] reported intraventricular hemorrhage rates of 2–4%, which is similar to our findings. However, a prospective study by Baschat[23] with a study population consisting of 52% AREDF fetuses, showed higher rates of neonatal morbidity (bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis) and mortality. AREDF was not a significant predictor for sepsis, after adjusting for EFW and the time from admission to delivery (Table 4). The factors contributing the most to the incidence of IRDS in our study were in accordance with the literature,[16] except for AREDF, which was a protective factor in the multivariable logistic analysis, leading to a decrease of IRDS with an OR of 0.33 (Table 4). This association was not present in the univariate analysis (Table S5). After additional analyses, there seemed to be a confounding effect of "EFW" and "time interval until delivery" that led to an increase of the negative effect of the Doppler group on IRDS. The variable "year of diagnosis" only became statistically significant, providing a positive effect on the occurrence of IRDS, after adding the variable "time interval until delivery". Also, we observed that there was a negative correlation between the variables "EFW" and "AREDF", and "time interval until delivery" and "AREDF" (Table 3). As there is a negative correlation between "EFW" and "AREDF", and "AREDF" has a negative effect on "IRDS", the indirect effect of "AREDF" on "IRDS" is positive. The same conclusion can be drawn regarding the indirect effect "AREDF" through "time interval until delivery". With regard to the variable "year of diagnosis", there was no statistically significant difference between the Doppler groups ($p = .74$) (Table 3). However, this variable had a positive effect on IRDS in the multivariate logistic analysis after adding "time interval until delivery".

Given these results, it is possible that over the years, obstetricians postponed delivery for a longer period of time, resulting in a decreased chance of IRDS in fetuses with AREDF, compared with fetuses with the same EFW, but without an observed abnormal umbilical Doppler flow.

In terms of long-term outcome, cognitive functions in infants after 2 years of life were relatively normal. However, the low response rate and missing data may have caused a bias in our results and therefore we are not able to make a conclusive statement about this outcome. The exact reason for the missing data is unknown. It was often reported that the appointment in the outpatient clinic was cancelled or that the infant was not willing to cooperate. We hypothesize that the infants that had developed a cognitive or behavioral impairment did not require an appointment because the impairment had already been diagnosed or in the course of being diagnosed, and therefore these infants were in no condition to undergo these tests. On the other hand, it is possible that parents of children who developed normally, did not feel the need to expose their children to these tests.

TABLE 3 Fetal outcome

	PEDF group (*n*= 108)	AREDF group (*n*= 109)	*p* value
Intrauterine death, *n* (%)	2 (2)	1 (1)	.56
Estimated fetal weight (EFW), median (interquartile range)	876 (753–1026)	816 (624–993)	.03
Year of diagnosis median (interquartile range)	2009 (2007–2012)	2009 (2006–2013)	.74
Indication for delivery: fetal distress, *n* (%)	90 (84)	104 (95)	.004
Mode of delivery: elective cesarean section, *n* (%)	6 (6)	1 (1)	.07
Mode of delivery: emergency cesarean section, *n* (%)	99 (92)	107 (98)	.03
Gestational age at delivery, weeks, days, median (interquartile range)	31.4 (29.3–36.1)	30.1 (29.1–32.0)	<.001
Time until delivery (weeks/days), median (interquartile range)	2/5 (0/2-7/1)	1/0 (0/3-3/0)	.01
Fetal gender (male), *n* (%)	50 (46)	55 (51)	.54
Birthweight, g, median (interquartile range)	1160 (925–1622)	940 (722–1123)	<.001
Apgar score after 1 min, median (interquartile range)	8 (6–9)	7 (6–9)	.34
Apgar score after 5 min, median (interquartile range)	9 (8–9)	9 (8–10)	.48
Umbilical arterial pH, median (interquartile range)	7.28 (7.22–7.32)	7.27 (7.23–7.31)	.39

Abbreviations: AREDF, absent or reversed end-diastolic flow; PEDF, positive end-diastolic flow.

TABLE 4 Neonatal outcome

	Sepsis			IRDS			Composite adverse neonatal outcome			Death within the first year of life		
	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
Doppler group, AREDF	1.46	0.72–2.99	.30	0.33	0.16–0.68	.003	0.63	0.32–1.25	.19	0.35	0.10–1.23	.10
EFW, per 100 g	0.68	0.57–0.82	<.001	0.66	0.54–0.79	<.001	0.62	0.51–0.74	<.001	0.40	0.25–0.64	<.001
Year of diagnosis	0.86	0.76–0.96	.01	1.23	1.08–1.39	.001	1.03	0.92–1.15	.65	0.97	0.80–1.18	.77
Time interval from admission to delivery, days	0.95	0.93–0.97	<.001	0.95	0.93–0.97	<.001	0.94	0.93–0.96	<.001	0.99	0.96–1.01	.32
Administration of ACS				0.62	0.27–1.43	.26	0.64	0.28–1.46	.29			
Fetal gender, male				3.17	1.54–6.53	.002	2.08	1.03–4.19	.04			
Maternal age, years							0.99	0.94–1.05	.82			
Nulliparity							0.67	0.33–1.35	.26			
Smoking, alcohol or drug use							0.94	0.40–2.17	.88			

Multivariable logistic regression analyses: incidence of sepsis, IRDS, composite adverse neonatal outcome and death within the first year of life between the Doppler groups (0 = PEDF, 1 = AREDF), adjusted for estimated fetal weight (per 100 g), year of diagnosis (per year), time interval from admission to delivery (in days), administration of a full dose of corticosteroids (0 = incomplete dose, 1 = complete dose), fetal gender (0 = female, 1 = male), maternal age (per year), nulliparity (0 = nullipara, 1 = multipara) and smoking, alcohol or drug use of the mother (0 = no, 1 = yes), as appropriate.

Abbreviations: ACS, antenatal corticosteroids; AREDF, absent or reversed end-diastolic flow; CI, confidence interval; EFW, estimated fetal weight; IRDS, idiopathic respiratory distress syndrome; OR, odds ratio.

The retrospective setting is both a limitation and strength of this study because all women received equivalent management for this reason. Another limitation is that in some cases, AREDF was detected in a referring hospital but could not be confirmed in our center. In those cases, we used the measurements performed in our hospital to avoid bias, as discrepancies in Doppler flow measurements may

be caused by interobserver variability. Because of the chance of discrepancies, we chose not to separate the AREDF group into AEDF and REDF, even though these conditions represent different levels of severity of placental dysfunction. Also, AEDF and REDF are often described as one group in the literature as AREDF. Our study had a long inclusion period of 12 years, but we conducted a correction for the year of diagnosis, which had a statistically significant effect on the incidence of sepsis and IRDS but not on the composite adverse perinatal outcome. Admission indications and guidelines on management of early-onset FGR did not change during the study period. Another possible limitation is that the clinicians were not blinded to the Doppler results but this may be compensated by the large numbers. Another limitation of our study is the lack of additional tests during admission, such as biophysical profiles and non-stress tests. Finally, the missing BSID III scores were a weakness of this study. A major strength of this study is that we included a well-defined population and the results from our study are in accordance with previous important trials on FGR.[11,15] To our knowledge, this is the first study to describe such a large cohort of women with early-onset FGR managed conservatively, irrespective of their umbilical artery Doppler flow patterns.

5 | CONCLUSION

In this historical cohort study, comprising early-onset FGR pregnancies with AREDF or PEDF, delivery was initiated in an earlier stage of pregnancy in the AREDF group, compared with the PEDF group despite intentional conservative management. AREDF was not associated with an increase in the adverse composite perinatal outcome, in comparison with PEDF.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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