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RESEARCH ARTICLE

Risk factors associated with stillbirth and adverse perinatal outcomes in dichorionic twin pregnancies complicated by selective fetal growth restriction: a cohort study

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Abstract

Objective: The main aim of this study was to investigate the perinatal outcomes of dichorionic twin pregnancies complicated by selective fetal growth restriction (sFGR).

Design: Retrospective cohort study.

Setting: Tertiary reference centre.

Population: Dichorionic twin pregnancies complicated by sFGR between 2000 and 2019 in St George's University Hospital.

Methods: Regression analyses were performed using generalised linear models and mixed-effects generalised linear models where appropriate to account for pregnancy level dependency in variables. Time to event analyses were performed with mixed-effects Cox regression models.

Main outcome measures: Stillbirth, neonatal death or neonatal unit admission with morbidity in one or both twins.

Results: A total of 102 (of 2431 dichorionic twin pregnancies) pregnancies complicated by sFGR were included in the study. The Cochrane–Armitage test revealed a significant trend for increased adverse perinatal outcome rates with more severe forms of umbilical artery flow impedance, i.e. reversed, absent, positive with resistant flow and positive flow without resistance. A multivariable model including maternal and conception characteristics had poor predictive accuracy for stillbirth (area under the curve: 0.68, 95% confidence interval [CI] 0.55–0.81) and composite adverse perinatal outcomes (area under the curve: 0.58, 95% CI 0.47–0.70). When umbilical artery Doppler parameters were added to the models, the area under the curve values improved to 0.95 (95% CI 0.89–0.99) and 0.83 (95% CI 0.73–0.92) for stillbirth and composite adverse perinatal outcomes, respectively.

Conclusion: In dichorionic twin pregnancies complicated by sFGR, the umbilical artery *Z*-scores were associated with both intrauterine death and adverse perinatal outcomes.

KEYWORDS
adverse perinatal outcome, discordance, fetal death, fetal growth restriction, intrauterine demise, middle cerebral artery, multifetal gestation, multiple pregnancy, neonatal, stillbirth, twin, umbilical artery

1 | INTRODUCTION

Twin pregnancies constitute less than 3% of total births yet contribute significantly and disproportionately to perinatal mortality and morbidity.[1] Recent studies have demonstrated that twins may benefit from specialised care (twin-specific growth charts, follow-up protocols, care packages, etc.) and that evidence obtained from singleton pregnancies may not necessarily be applicable to the management of twin pregnancies.[2,3] Monochorionic twin research is more common than that in dichorionic twins because of conditions specific to monochorionic placentation, such as twin-to-twin transfusion syndrome. They are also more susceptible to complications due to sharing placentas compared with dichorionic twins. However, preterm twins have similar neonatal morbidity and mortality regardless of chorionicity. Therefore, more research on dichorionic twin pregnancies is needed.[4]

Selective fetal growth restriction (sFGR) is a twin-specific condition where one fetus is suspected to be growth-restricted whereas the other fetus is presumed to be appropriately grown. It is a common cause of iatrogenic preterm birth in twin pregnancies. The diagnosis is made and management is usually done using criteria similar to growth restriction in singleton pregnancies.[5] The rationale for this approach is the assumption that the dichorionic twin growth pattern is similar to that of singletons. However, it is well established that dichorionic twin growth trajectories differ from those in singletons, and these pregnancies may benefit from twin-specific reference growth standards.[6] Moreover, dichorionic twins with sFGR have conflicting interests, as the smaller twin benefits from earlier delivery while prolongation of pregnancy benefits the larger twin. Management protocols tailored for singletons are often inadequate to cover the complex decision-making process of dichorionic twins with sFGR. Unfortunately, evidence on the antenatal and neonatal outcome of dichorionic twins with sFGR is lacking, including the optimal time to deliver and the value of fetal Doppler in their management.

The main aim of this study was to investigate the perinatal outcomes of dichorionic twin pregnancies complicated by sFGR diagnosed according to the recent Delphi consensus criteria.[7] The secondary objective was to establish the factors associated with adverse perinatal outcomes in these pregnancies.

2 | METHODS

This was a retrospective cohort study in a single tertiary level Fetal Medicine Unit at St George's University Hospitals NHS Foundation Trust, London. All dichorionic twin pregnancies with a diagnosis of sFGR in keeping with the Delphi consensus diagnostic criteria who had undergone ultrasound assessment between 2000 and 2019 were included in our cohort.[7] In brief, pregnancies with one fetus below the third centile for estimated fetal weight (EFW) or below the 10th centile with at least one adjunct finding (estimated fetal weight discordance ≥25% or abnormal umbilical artery [UA] Doppler) were diagnosed with sFGR. Patients were identified through a retrospective search of our ultrasound database (VIEWPOINT version 5.6.26.148; ViewPoint Bildverarbeitung GMBH). Chorionicity was determined at 11–14 weeks' gestation using the presence of the lambda sign at the insertion of the intertwin membrane.[8] Gestation was calculated using the crown–rump length (CRL) of the larger twin in spontaneously conceived twin pregnancies, and the date of oocyte retrieval or embryonic age from fertilisation in those conceived through in vitro fertilisation (IVF).[9] Routine scans prior to the diagnosis of sFGR were carried out 4-weekly after the anomaly scan, and 2-weekly or weekly following diagnosis of sFGR, depending on Doppler indices.[10]

Estimated fetal weight (EFW) discordance was calculated using the difference in EFW divided by EFW of the larger twin multiplied by 100. Twin growth charts were utilised to evaluate growth, and the EFW prior to 20 weeks was calculated using the formula derived by Warsof et al.,[12] and Hadlock's[11] formula thereafter. Twin chorionicity-specific reference standards reported by Ananth et al.[13] were used to calculate birthweight percentiles. EFW percentiles were calculated according to STORK chorionicity-specific EFW standards.[6] Doppler parameter centiles were calculated using the reference ranges published by the Fetal Medicine Foundation.[14]

Investigations such as detailed fetal anatomy and Doppler assessments, congenital infection screening and invasive testing to diagnose chromosomal or genetic abnormalities were offered as appropriate. Pregnancies where either twin was affected by a major structural or genetic anomaly or aneuploidy were excluded from the study. Doppler assessment including UA pulsatility index (PI) and end-diastolic flow (EDF), middle-cerebral artery (MCA) PI, ductus venosus (DV) PI and a-wave were recorded at the time of diagnosis and at the last scan prior to delivery. Progression of sFGR was defined as an increase in the UA PI, progression to absent or reversed UA EDF, increase in the DV PI or progression to absent or reversed a-wave in the DV. Conservative management was carried out prior to 30 weeks' gestation, abnormal DV Doppler velocimetry prompted elective delivery following this gestation, those with reversed UA EDF were delivered after 31–32 weeks, and absent UA EDF at 32–33 weeks. Raised UA PI >95th centile prompted delivery after 34 weeks, and reduced MCA PI <5th centile after 36 weeks. All elective deliveries prior to 37 weeks were preceded by a course of antenatal corticosteroids, and those with normal Dopplers were delivered at or after 37 weeks. In general, women with planned births prior to 34 weeks were delivered via caesarean section, and those thereafter were offered vaginal birth if there were no contraindications.

Birth and neonatal outcomes were collected using maternity and neonatal databases. Stillbirth was defined as death in utero after 24 weeks, and neonatal death (NND) as death within 28 days of birth. Neonatal morbidity included requirement of ventilatory support, respiratory distress

syndrome (RDS), necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH) and neonatal sepsis. Composite adverse perinatal outcome was defined as stillbirth, NND or neonatal unit (NNU) admission with morbidity in one or both twins. Those who were lost to follow-up were also excluded from our cohort.

2.1 | Statistical analysis

Wilcoxon rank sum or *t*-test was used to compare continuous variables. Categorical variables were compared using a chi-square test. Trend significance was tested with the Cochrane–Armitage test. Regression analyses were performed with generalised linear models and mixed-effects generalised linear models where appropriate to account for pregnancy level dependency in variables. Parameter selection was guided by Akaike information criterion (AIC), clinical information and the most parsimonious model minimising AIC was chosen as the best model. Model performance was assessed with area under the curve (AUC) values and predictive accuracy indices at Youden index cut-off points. Optimism-adjusted AUC values were obtained with *k*-fold cross validation ($k=5$). Superiority of mixed-effects regression models were performed with log-likelihood tests. Time to event analyses were performed with mixed-effects Cox regression models. Model calibration was assessed with calibration curves. All analyses were performed using R for statistical computing software (version 4.0.2).

3 | RESULTS

3.1 | Study population

A total of 102 (of 2431 dichorionic twin pregnancies) pregnancies complicated by sFGR were included in the study (Figure 1). Forty-two pregnancies were below 28 weeks' gestation at the time of diagnosis. In this early diagnosis group, there were three smaller fetuses with reversed UA EDF, nine smaller fetuses with absent UA EDF and 30 smaller fetuses with positive UA EDF. All smaller fetuses with reversed EDF died in utero when the diagnosis of sFGR was made prior to 28 weeks' gestation. All of the larger twins in these pregnancies (diagnosis prior to 28 weeks and reversed EDF) survived until delivery, but 67% had adverse perinatal outcomes. An absent UA EDF in the smaller fetus less than 28 weeks' gestation was associated with a 67% intrauterine fetal death (IUFD) rate and 100% adverse perinatal outcome rate for the surviving smaller twins. The larger twins in this group had an adverse perinatal outcome rate of 44% with no IUFD. Smaller twins with a UA PI above the 95th percentile

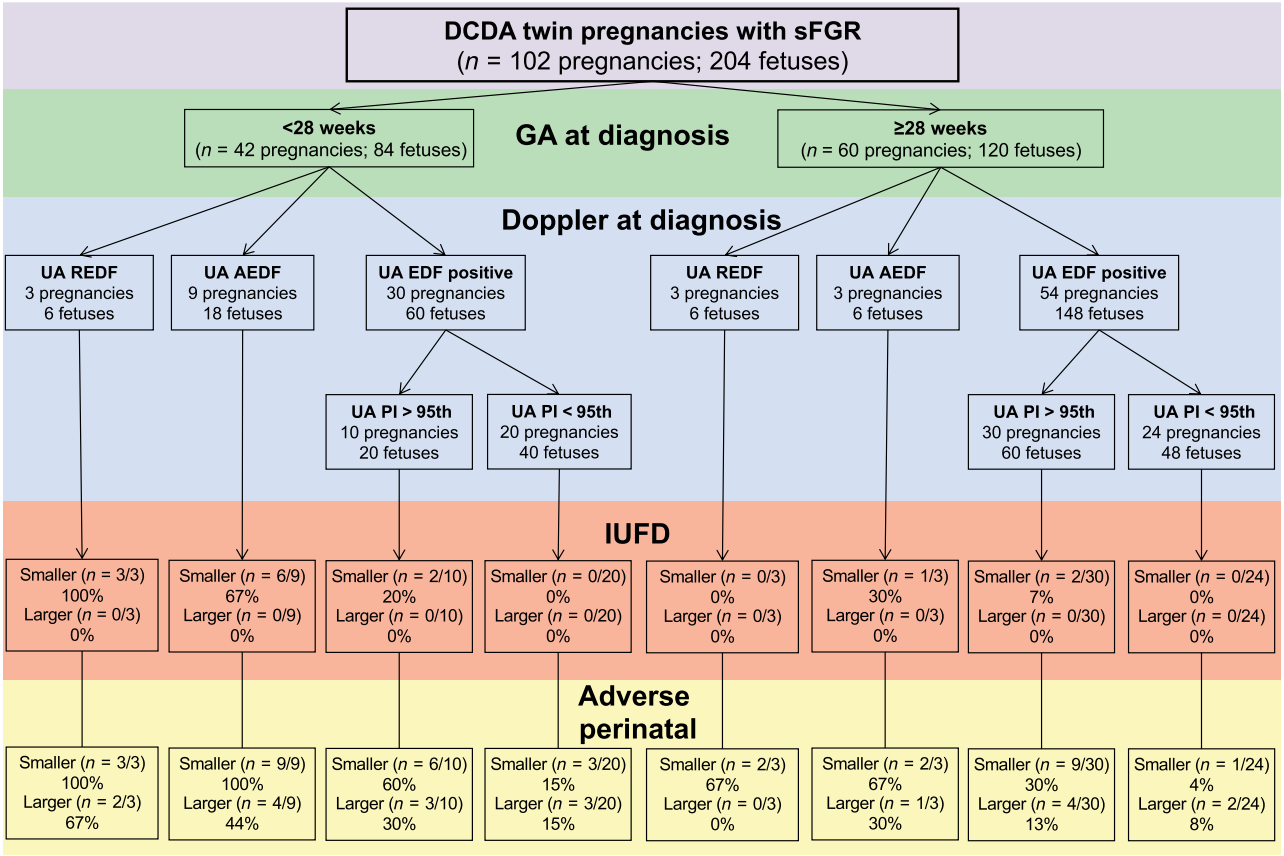

FIGURE 1 Study flowchart outlining the outcomes of twin pregnancies diagnosed with selective fetal growth restriction according to Doppler status.

with positive EDF had higher IUFD rates (20% versus 0%; $P=0.038$) and adverse perinatal outcomes (60% versus 15%; $P=0.011$) compared with those with UA PI <95th percentile. The Cochrane-Armitage test revealed a significant trend for increased adverse perinatal outcome rates with more severe forms of UA flow impedance, i.e. reversed, absent, positive with resistant flow (PI >95th centile) and positive flow without increased resistance, for both the smaller fetus ($P<0.001$) and the larger fetus ($P=0.012$) (Figure 1).

The diagnosis of sFGR was made at ≥28 weeks' gestation in 60 pregnancies; in this group only three (5%) smaller babies died in utero, while none of the larger babies died (Figure 1). Two of the smaller babies that died in utero had a UA PI above the 95th percentile and one had absent EDF. Again, there was a significant trend for increased adverse perinatal outcome rate in the smaller twin with more severe forms of UA flow impedance according to the Cochrane–Armitage test ($P<0.001$). Other baseline maternal characteristics and birth outcomes are provided in Table 1.

3.2 | Predictors of intrauterine fetal death and composite adverse perinatal outcome

Gestational age at diagnosis ($P=0.002$), EFW *Z*-scores ($P=0.003$), UA PI *Z*-scores ($P<0.001$) were associated with IUFD. MCA PI was not associated with IUFD ($P=0.801$). Gestational age at diagnosis of sFGR ($P=0.006$), EFW *Z*-scores ($P<0.001$), UA PI *Z*-scores ($P<0.001$) were associated with composite adverse perinatal outcomes, whereas MCA PI *Z*-scores were not ($P=0.515$) (Table 2). Gestational age at delivery ($P<0.001$) and birthweight *Z*-scores ($P<0.001$) were also significantly associated with composite adverse perinatal outcomes. Adjusted analyses according to maternal age, self-reported ethnicity and conception method revealed similar results and UA PI *Z*-score remained independently associated with composite adverse perinatal outcomes (odds ratio [OR] 8.68, 95% confidence interval [95% CI] 3.00–35.00, $P<0.001$).

Multivariable modelling including maternal and conception characteristics had poor predictive accuracy for IUFD (optimism-adjusted AUC: 0.68, 95% CI 0.55–0.81) and composite adverse perinatal outcomes (optimism-adjusted AUC 0.58, 95% CI 0.47–0.70). The addition of UA PI *Z*-score significantly improved the predictive accuracy of both models ($P<0.001$ for both). The optimism-adjusted AUC values were high for IUFD (0.95, 95% CI 0.89–0.99) and composite adverse perinatal outcome (0.83, 95% CI 0.73–0.92) (Figure 2). A predicted probability over 70% for IUFD using the model yielded an accuracy rate of 90.2% (95% CI 82.7–95.2) with 57.1% sensitivity and 95.4% specificity.

3.3 | Survival without developing composite adverse perinatal outcomes

Fetuses with increased UA flow impendence as measured using PI *Z*-scores (hazard ratio [HR] 1.34, 95% CI 1.13–1.60,

TABLE 1 Description of maternal demographics, pregnancy characteristics and ultrasound variables of the study cohort.

	Dichorionic twin pregnancies with selective fetal growth restriction ($n=102$)[a]
Maternal and pregnancy characteristics	
Maternal age in years	35.0 (30.0–38.0)
Self-reported ethnicity mother	
White	77 (75.4)
Black	9 (8.8)
Asian	16 (15.7)
Ultrasound variables (at diagnosis), smaller twin	
Estimated fetal weight percentile	2.2 (0.3–4.8)
Umbilical artery pulsatility index (PI) percentile	98.2 (79.8–99.9)
Umbilical artery PI >95th centile	58 (56.8)
Umbilical artery end diastolic flow (EDF)	
Positive	84 (82.3)
Absent	12 (11.8)
Reversed	6 (5.9)
Middle cerebral artery PI percentile	31.6 (5.0–75.7)
Middle cerebral artery PI <5th centile	26 (25.5)
Ultrasound variables (at diagnosis), larger twin	
Estimated fetal weight percentile	44.4 (23.1–61.6)
Umbilical artery PI percentile	65.0 (26.1–90.5)
Umbilical artery PI >95th centile	19 (18.6)
Umbilical artery EDF	
Positive	101 (99.0)
Absent	0
Reversed	1 (1.0)
Middle cerebral artery PI percentile	51.1 (19.6–80.8)
Middle cerebral artery PI <5th centile	7 (6.9)
Delivery characteristics	
Gestational age at birth, weeks	34.2 (32.3–35.5)
Preterm birth <32 weeks	43 (42.1)
Preterm birth <28 weeks	5 (4.9)
Birthweight of the smaller twin, percentile	3.5 (0.1–4.1)
Birthweight of the larger twin, percentile	27.8 (21.6–45.9)
Intrauterine fetal death (IUFD) of the smaller twin	14 (13.7)
IUFD of the larger twin	0
Neonatal unit admission of the smaller twin	78 (88.6)
Neonatal unit admission of the larger twin	72 (70.6)

Note: Continuous variables are presented as median and interquartile range in parentheses, whereas categorical variables are presented as number and percentage of total in parentheses.

[a]Diagnosed according to Delphi consensus criteria.

TABLE 2 The association of maternal and pregnancy characteristics, ultrasound variables and delivery characteristics with stillbirth or composite adverse perinatal outcomes.

	Outcome: Composite adverse perinatal[a]				Outcome: Intrauterine fetal death[b]			
Variables	**OR (95% CI)**	***P*[c]**	**aOR (95% CI)[d]**	***P*[c]**	**OR (95% CI)**	***P*[e]**	**aOR (95% CI)[d]**	***P*[e]**
Maternal characteristics								
Maternal age in years	0.85 (0.37–1.80)	0.655	–	–	1.00 (0.57–1.81)	0.996	–	–
Self-reported ethnicity								
White	Reference		–	–	Reference		–	–
Black-Caribbean	32.1 (2.09–2786.0)	0.029	–	–	7.50 (0.78–169.7)	0.107	–	–
Asian	4.57 (0.69–47.3)	0.130	–	–	2.24 (0.38–42.6)	0.458	–	–
Conception								
Assisted reproduction	0.97 (0.18–4.70)	0.971	–	–	0.45 (0.10–1.58)	0.251	–	–
Ultrasound variables[f]								
Gestational age at diagnosis	0.34 (0.12–0.65)	0.006	0.37 (0.14–0.70)	0.009	0.33 (0.16–0.60)	<0.001	0.36 (0.17–0.67)	0.002
Estimated weight, *Z*-score	0.15 (0.06–0.34)	<0.001	0.17 (0.06–0.44)	<0.001	0.48 (0.27–0.81)	0.007	0.42 (0.22–0.74)	0.003
UA PI, *Z*-score	37.7 (9.68–124.0)	<0.001	8.68 (3.00–35.0)	<0.001	2.27 (1.62–3.58)	<0.001	2.78 (1.80–5.33)	<0.001
UA PI >95th centile	40.9 (6.4–770.9)	0.004	36.8 (6.37–2141.1)	0.012	NE	NE	NE	NE
MCA PI, *Z*-score	0.89 (0.61–1.26)	0.515	0.86 (0.59–1.22)	0.406	1.01 (0.74–1.40)	0.941	0.96 (0.68–1.35)	0.801
MCA PI <5th centile	1.71 (0.43–13.8)	0.464	1.86 (0.47–9.22)	0.389	1.76 (0.16–2.73)	0.708	0.98 (0.20–3.86)	0.983
Delivery characteristics								
Gestational age at delivery	0.24 (0.09–0.42)	<0.001	0.59 (0.42–0.72)	<0.001	NA	NA	NA	NA
Birthweight, *Z* score	0.15 (0.05–0.39)	<0.001	0.15 (0.05–0.38)	<0.001	NA	NA	NA	NA

Note: All continuous variables were scaled using sample mean and variance. Odds ratios correspond to one standard deviation increase in the respective variables.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; MCA, middle cerebral artery; NA, not applicable; NE, not estimable; OR, odds ratio; PI, pulsatility index; UA, umbilical artery.

[a]Intrauterine fetal death, early neonatal death within 7 days of delivery or neonatal care unit admission with neonatal morbidity. Neonatal morbidity was defined as any one of the following; ventilation support, respiratory distress, necrotising enterocolitis, intraventricular haemorrhage or neonatal sepsis.

[b]Intrauterine fetal death after 24 weeks' gestation.

[c]Binomial mixed-effects regression analysis with random intercepts for individual pregnancies.

[d]Adjusted for maternal age, self-reported ethnicity and conception method.

[e]Binomial regression analysis.

[f]Reported odds ratio for intrauterine fetal death belong to smaller twin where applicable (i.e. ultrasound variables, birthweight).

$P < 0.001$) or UA PI >95th centile (HR 3.62, 95% CI 2.66–7.91, $P = 0.001$) had higher composite adverse perinatal outcome hazard (Table 3). Analyses adjusted for maternal age, ethnicity and conception method revealed similar results ($P < 0.001$ for both). The UA PI >95th centile categorisation allowed for better differentiation of survival hazard compared with UA EDF type in pregnancies complicated by sFGR ($P < 0.001$, Figure 3A,B). In a subgroup analysis including smaller fetuses only, the UA PI >95th centile categorisation also allowed for better differentiation survival hazard compared with UA EDF ($P < 0.001$, Figure 4). Moreover, smaller fetuses with normal UA flow (PI <95th centile) reached peak adverse outcome incidence around 32 weeks' gestation, whereas fetuses with positive UA EDF but increased impedance (PI >95th centile) had an increasing adverse perinatal outcome, even after 32 weeks (Figure 4A,B).

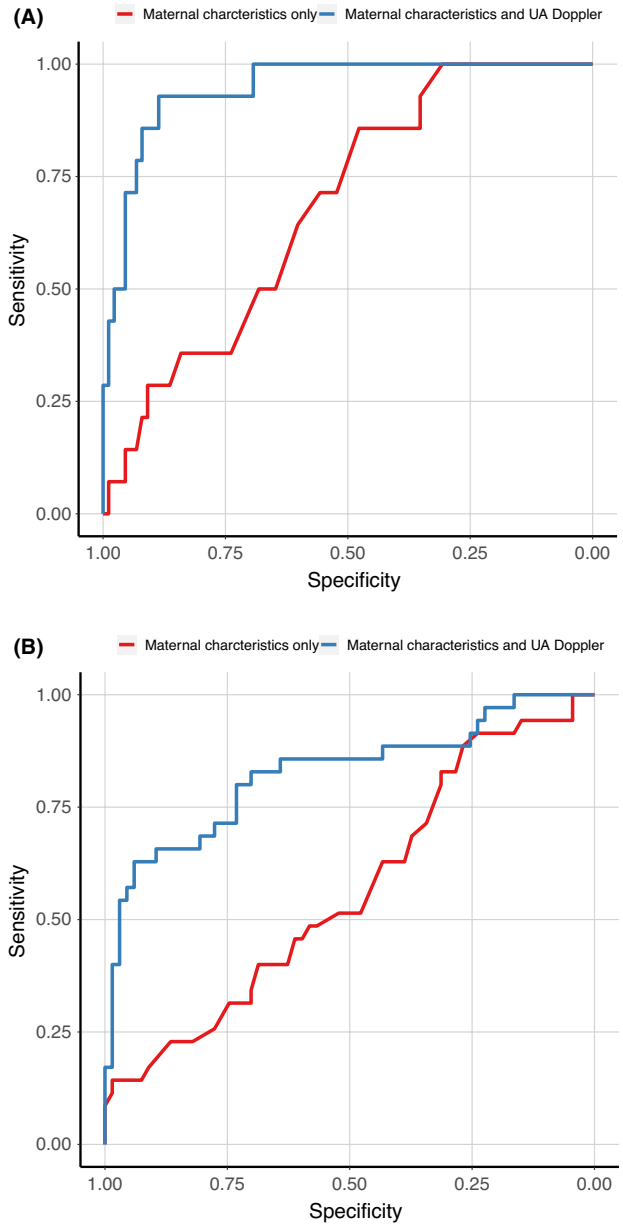

FIGURE 2 Receiver operating characteristics curves for twin pregnancies diagnosed with selective fetal growth restriction and complicated by (A) intrauterine fetal death (either twin) and (B) composite adverse perinatal outcome (either twin). Baseline models including maternal characteristics had poor predictive accuracy with optimism area under the curve values of 0.68 (0.55–0.81) and 0.58 (95% CI 0.47–0.70) for intrauterine fetal death and composite adverse perinatal outcome, respectively. The addition of umbilical artery pulsatility index *Z*-score significantly increased predictive accuracy for both outcomes with area under the optimism-adjusted curve values of 0.95 (95% CI 0.89–0.99) and 0.83 (95% CI 0.73–0.92), respectively ($P < 0.001$ for both).

4 | DISCUSSION

4.1 | Summary of the main study findings

In dichorionic twin pregnancies complicated by sFGR, UA PI *Z*-scores were associated with both IUFD and adverse perinatal outcomes. A model for estimating the risk of IUFD was developed and showed high accuracy (>90%) and good model fit. Fetuses with higher UA flow impedance had increased survival hazard (i.e. without composite adverse outcomes). The addition of UA flow categorisation using percentiles (PI below or above 95th centile) to the type of EDF was better at predicting adverse perinatal outcomes than the established classification of reversed, absent or positive EDF alone. Our findings suggest that the smaller twins with increased UA flow impedance may benefit from planned delivery after 32 weeks' gestation rather than 34 weeks, which is the current established practice derived from the management of singletons.

4.2 | Interpretation of study findings and comparison with published evidence

We developed a prediction model for IUFD of any or both twins. Some studies reported on factors associated with IUFD in monochorionic twins, but they did not present a prediction model for clinical use. Stillbirth prediction models derived from unselected populations for singleton pregnancies have shown limited utility. Recent research has demonstrated that twin pregnancies benefit from twin-specific standards for more accurate prediction of stillbirth, hypertensive disorders of pregnancy, and preterm birth.[15–18] Predictive factors for adverse outcomes in monochorionic twins have been published and management algorithms are available.[19] However, it is unclear whether these principles apply to dichorionic twins or whether the management of dichorionic twins with sFGR using the same criteria as for singletons with FGR is appropriate. A study by Vanlieferinghen et al.[20] comparing the outcome of SGA singleton and twin neonates has suggested that the prognostic value of Dopplers may differ between singletons and twins. Our findings corroborate this point, as we found smaller twins with abnormal UA Doppler had increasing adverse outcomes from 32 weeks onwards.

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TABLE 3 The association of maternal and pregnancy characteristics, ultrasound variables and delivery characteristics with survival without the development of composite adverse perinatal outcomes.

	Outcome: Composite adverse perinatal[a]			
Variables	**HR (95% CI)**	***P*-value[b]**	**aHR (95% CI)[c]**	***P*-value[b]**
Maternal characteristics				
Maternal age in years	0.98 (0.50–1.94)	0.970	–	–
Self-reported ethnicity				
White	Reference			
Black	15.1 (1.72–132.3)	0.014	–	–
Asian	1.15 (0.18–7.46)	0.890	–	–
Conception				
Assisted reproduction	1.36 (0.21–8.66)	0.751	–	–
Ultrasound variables				
Estimated fetal weight percentile	0.75 (0.60–0.94)	0.012	0.75 (0.60–0.94)	0.013
UA PI, *Z*-score	1.34 (1.13–1.60)	<0.001	1.35 (1.14–1.58)	<0.001
UA PI >95th centile	3.62 (1.66–7.91)	0.001	3.75 (1.76–7.97)	<0.001
UA end diastolic flow				
Positive	Reference		Reference	
Absent or reversed	NE	NE	5.62 (1.98–15.9)	0.001
MCA PI, *Z*-score	0.92 (0.73–1.15)	0.465	0.86 (0.72–1.15)	0.430
MCA PI <5th centile	1.42 (0.52–3.92)	0.498	1.42 (0.54–3.73)	0.472

Note: All continuous variables were scaled using sample mean and variance. Hazard ratios correspond to one standard deviation increase in the respective variables.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery.

[a]Stillbirth, early neonatal death within 7 days of delivery or neonatal care unit admission with neonatal morbidity. Neonatal morbidity was defined as any one of the following; ventilation support, respiratory distress, necrotising enterocolitis, intraventricular haemorrhage or neonatal sepsis.

[b]Mixed-effects Cox regression analysis with random intercepts for individual pregnancies.

[c]Adjusted for maternal age, self-reported ethnicity and conception method.

Our findings suggest that the UA should be the primary prognostic tool for dichorionic pregnancies with sFGR and the brain-sparing effect has no impact on outcomes. The UA resistance/flow is the primary method for managing singletons with FGR. Dichorionic twins with UA PI above the 95th centile had an increased rate of adverse events. Moreover, the rate of adverse events steadily increased starting from 32 weeks' gestation, whereas the event rate was flat for smaller twins with normal flow impedance (UA PI <95th centile). Data from singleton pregnancies usually support expectant management of fetuses with FGR until 34 weeks as long as the UA EDF is present. These data differ from our findings in twins with sFGR that delivery may be considered between 32 and 34 weeks' gestation when EDF is positive but there is increased flow impedance. Finally, factoring the UA PI into categorisation yielded a better model for predicting time to adverse outcomes. The potential impact of an earlier planned delivery on the normally grown co-twin is uncertain, and a clinical trial would be necessary to establish the balance of benefits and harms.

4.3 | Clinical and research implications

Our study adhered strictly to twin-specific standards by using charts and diagnostic criteria tailored to twin pregnancies. Although several studies demonstrate that twin-specific charts are superior to singleton standards for many adverse outcomes, future studies should try to replicate these findings using other reference standards.[15–18] It may be speculated that using singleton standards would increase the number of pregnancies diagnosed with sFGR and reduce the association we observed in this study. We used optimism-adjusted AUC values for internal validation and also reported the model fit. However, external validation is critical for any prediction model, and our findings should be tested in other populations. Finally, the results imply that twins may be mismanaged using evidence derived from singleton pregnancies. There are no randomised trials to guide the management of twins with sFGR. Intervention bias is always an issue in observational studies and unobserved confounders can influence findings. The optimal timing of delivery for twins with sFGR should be investigated in a randomised setting to develop robust clinical management algorithms.

4.4 | Strengths and limitations

The strengths of our study include the relatively large number of twin pregnancies with sFGR managed at a single tertiary care facility. We used twin-specific charts and the

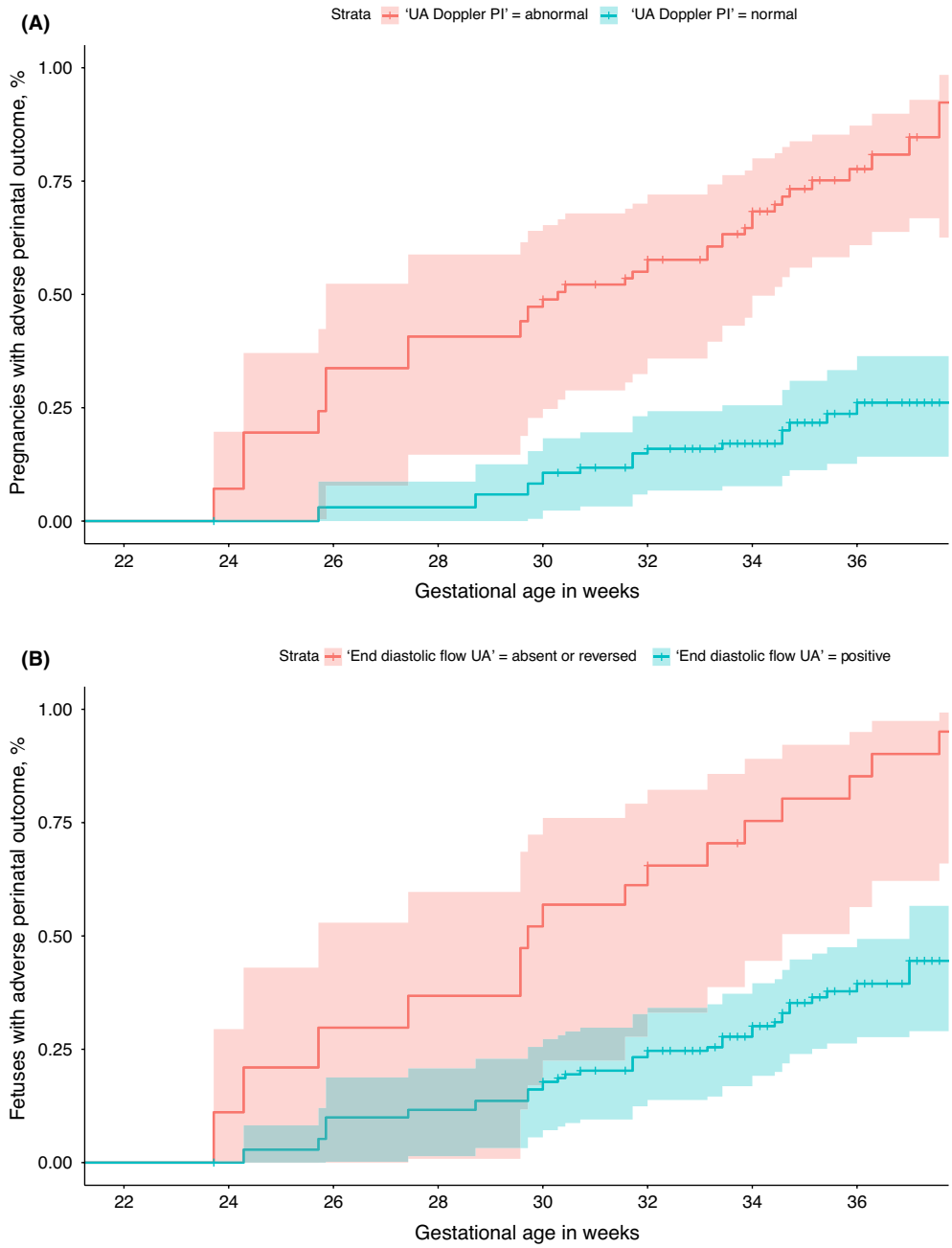

FIGURE 3 Adverse perinatal outcome cumulative incidence curve for all twins stratified according to the umbilical artery Doppler status. When stratified according to umbilical artery pulsatility index above the 95th centile (A) compared with the presence of end diastolic flow (B) cumulative incidence curves showed better divergence ($P < 0.001$).

recently published Delphi consensus diagnostic criteria.[7] The use of twin charts significantly reduces the number of twins diagnosed with sFGR and consolidates a higher risk group in the cohort. We provided risk estimates for both IUFD and adverse perinatal outcomes.

Some limitations apply to our findings. First, we did not validate our findings in an external cohort. The sample size allowed only for testing of association. The sample size was large enough for the estimation of the association. However, the predictive accuracy might have been overestimated due to model overfit. Finally, this was an analysis of retrospective observational data and a management algorithm was already in place. Our study speculates how these patients may have been differently managed for better outcomes. Our findings have limitations inherent in all retrospective observational data, including the effect of intervention bias.

5 | CONCLUSION

Prediction of IUFD and adverse perinatal outcomes in dichorionic twin pregnancies with sFGR is possible using fetal Doppler, combined with maternal- and pregnancy-related variables. Smaller twins with higher UA PI more frequently

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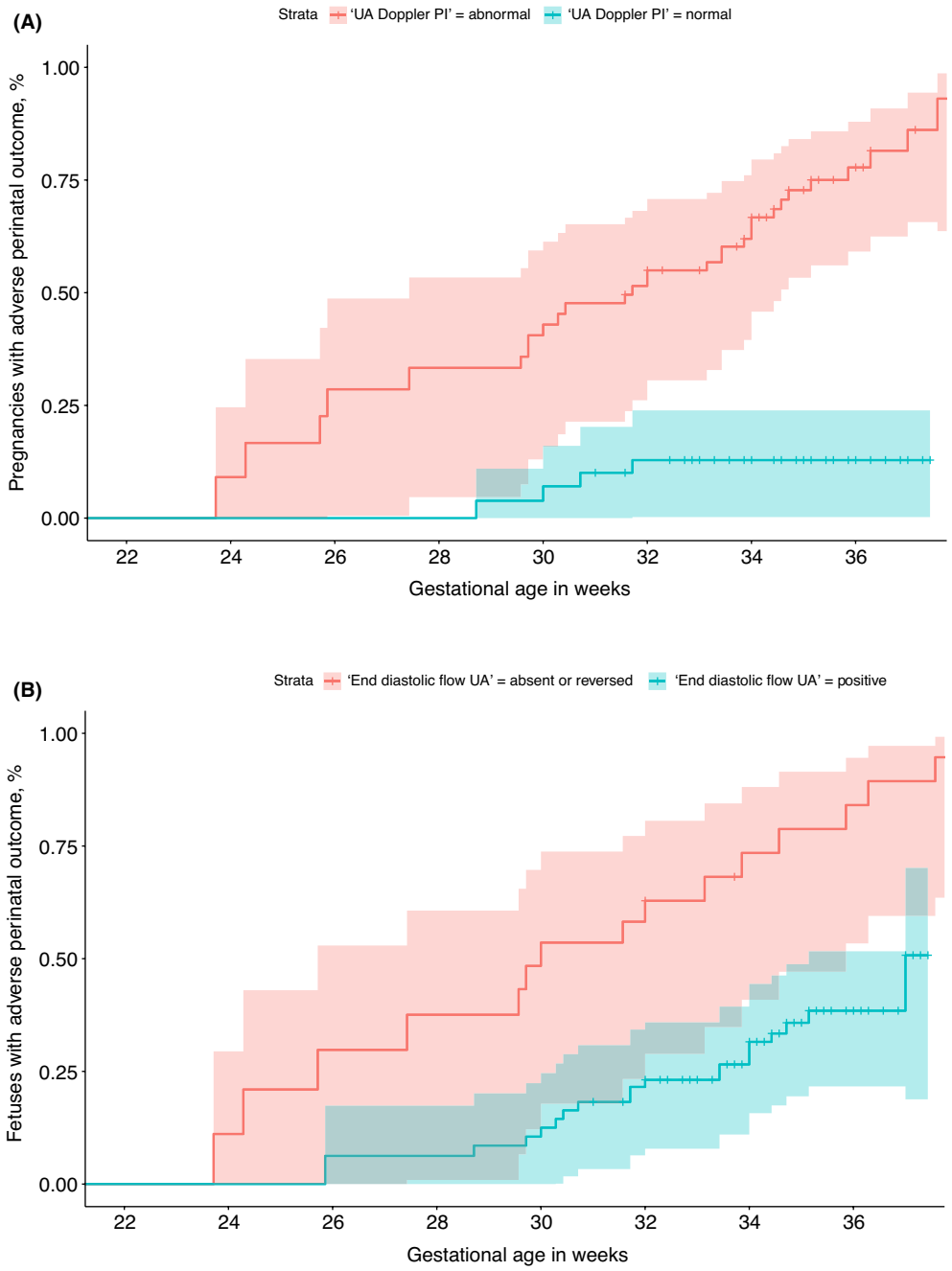

FIGURE 4 Adverse perinatal outcome cumulative incidence curve for the smaller twin stratified according to the umbilical artery Doppler status. When stratified according to the umbilical artery pulsatility index above the 95th centile (A) compared with the presence of end diastolic flow (B) cumulative incidence curves showed better divergence ($P < 0.001$). Smaller fetuses with a normal umbilical artery flow (PI <95th centile) reach peak incidence around 32 weeks' gestation, whereas fetuses with positive end diastolic flow but increased impedance (PI >95th centile) have an increasing adverse perinatal outcome incidence even after 32 weeks.

develop adverse outcomes than do those with normal UA PI. The larger twins from such pregnancies are also at risk of adverse perinatal outcomes when the diagnosis is made before 28 weeks' gestation.

AUTHOR CONTRIBUTIONS

Data collection: BL, IB, RB. Study conception: AK. Analysis plan and execution: AK, EK. Writing of the draft: EK, BL, IB, RB, AP, AK. Critical revision for the intellectual content: AK, EK, AP, BL, IB, RB.

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None.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL

This retrospective study of routinely collected clinical data was collated from ongoing continuous audit and was deemed not to require ethics approval or signed patient consent as per the HRA decision tool.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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