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Ultrasound Obstet Gynecol 2022; **59**: 756–762
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.24896

Prediction of fetal death in monochorionic twin pregnancies complicated by Type-III selective fetal growth restriction

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KEYWORDS: fetal growth restriction; fetal monitoring; fetal wellbeing; multiple pregnancy; prediction; twins

CONTRIBUTION

What are the novel findings of this work?
Fetal death in Type-III selective fetal growth restriction can be partially predicted. Oligohydramnios, larger intertwin weight discordance and, most prominently, early gestational age at diagnosis and deterioration in umbilical artery Doppler flow are associated with a higher risk of fetal death. High-risk, intermediate-risk and low-risk groups can be identified using clinical parameters.

What are the clinical implications of this work?
Our findings can help counsel patients regarding the individualized risk of fetal death for their pregnancy. The study demonstrates that it is possible to identify pregnancies at high or intermediate risk of fetal death, which could be monitored more closely and which could benefit from fetal intervention.

ABSTRACT

Objective *Monochorionic diamniotic twin pregnancies complicated by Type-III selective fetal growth restriction (sFGR) are at high risk of fetal death. The aim of this study was to identify predictors of fetal death in these pregnancies.*

Methods *This was an international multicenter retrospective cohort study. Type-III sFGR was defined as fetal estimated fetal weight (EFW) of one twin below the 10th percentile and intertwin EFW discordance of ≥ 25% in combination with intermittent absent or reversed end-diastolic flow in the umbilical artery of the smaller fetus. Predictors of fetal death were recorded longitudinally throughout gestation and assessed in univariable and multivariable logistic regression models. The classification and regression trees (CART) method was used to construct a prediction model of fetal death using significant predictors derived from the univariable analysis.*

Results *A total of 308 twin pregnancies (616 fetuses) were included in the analysis. In 273 (88.6%) pregnancies, both twins were liveborn, whereas 35 pregnancies had single (*n *= 19 (6.2%)) or double (*n *= 16 (5.2%)) fetal death. On univariable analysis, earlier gestational age at diagnosis of Type-III sFGR, oligohydramnios in the smaller twin and deterioration in umbilical artery Doppler flow were associated with an increased risk of fetal death, as was larger fetal EFW discordance, particularly between 24 and 32 weeks' gestation. None of the parameters identified on univariable analysis maintained statistical significance on multivariable analysis. The CART model allowed us to identify three risk groups: a low-risk group (6.8% risk of fetal death), in which umbilical artery Doppler did not deteriorate; an intermediate-risk group (16.3% risk of fetal death), in which umbilical artery Doppler deteriorated but the diagnosis of sFGR was made at*

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Accepted: 15 February 2022

or after 16 + 5 weeks' gestation; and a high-risk group (58.3% risk of fetal death), in which umbilical artery Doppler deteriorated and gestational age at diagnosis was < 16 + 5 weeks' gestation.

Conclusions *Type-III sFGR is associated with a high risk of fetal death. A prediction algorithm can help to identify the highest-risk group, which is characterized by Doppler deterioration and early referral. Further studies should investigate the potential benefit of fetal surveillance and intervention in this cohort. © 2022 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Selective fetal growth restriction (sFGR) complicates about 10% of monochorionic twin pregnancies and is subdivided into three types based on the umbilical-artery flow pattern in the smaller fetus[1]. Type-III sFGR, which is characterized by intermittent absent or reversed end-diastolic flow (A/REDF), makes up about a fifth of all sFGR monochorionic twin pregnancies[2]. At the placental level, Type-III sFGR is characterized by unequal placental sharing with a large bidirectional artery-to-artery intertwin anastomosis[3], allowing for acute hemodynamic shift from one fetus to the other[4]. This configuration represents a highly unstable hemodynamic state that facilitates the occurrence of acute fetofetal transfusion[5], which may cause sudden death of the smaller fetus and severe hypovolemic events resulting in brain damage in the larger fetus[6]. Given the underlying pathophysiology, the current belief is that such acute events are mostly unpredictable[7,8] and can happen within days or hours after a normal wellbeing assessment[9]. However, strong research supporting this is lacking. As a result, there is no uniformity in the surveillance and management of affected pregnancies[10]. Many centers use expert-opinion based triggers for intervention (either fetoscopic laser ablation of placental anastomoses or selective fetal reduction prior to viability or delivery after viability), when the risk of fetal death is considered to be increased[11]. These triggers can include a combination of oligohydramnios, lack of fetal growth, increasing growth discordance, abnormal ductus venosus Doppler or fetal heart rate changes.

We have documented previously the outcome and fetal growth patterns of a large international cohort of pregnancies complicated by Type-III sFGR[10,12]. The aim of the present study was to assess comprehensively the factors associated with spontaneous fetal death in the same cohort and to evaluate how these factors could be integrated into a prenatal management protocol.

METHODS

We reviewed the charts of all monochorionic diamniotic twin pregnancies complicated by Type-III sFGR that were managed longitudinally between 1 January 2008 and 1 July 2019 at nine fetal medicine centers; the study protocol was approved by all involved research ethics boards. Type-III sFGR was defined as estimated fetal weight (EFW) of one twin $< 10^{th}$ percentile and intertwin EFW difference of $\geq 25\%$ in combination with intermittent A/REDV in the umbilical artery of the smaller fetus on at least one occasion[13]. The intertwin growth difference (%) was calculated using the following formula: (EFW of the larger fetus – EFW of the smaller fetus)/EFW of the larger fetus $\times$ 100. Higher-order multiple pregnancies, pregnancies complicated by major fetal structural or genetic anomaly and those undergoing selective fetal reduction or fetoscopic laser ablation of placental anastomoses for sFGR were not included in the analysis. Additionally, pregnancies complicated by other monochorionic complications, such as twin–twin transfusion syndrome (TTTS), twin anemia–polycythemia sequence or twin reversed arterial perfusion sequence at presentation were excluded.

All pregnancies underwent EFW measurement on ultrasound, amniotic fluid assessment and fetal Doppler evaluation at least once every 2 weeks. The baseline characteristics, fetal growth pattern, management protocol and outcome of these pregnancies have been published previously[10,12].

To identify predictors of fetal death, pregnancies with Type-III sFGR complicated by spontaneous single or double fetal death (cases) were compared with pregnancies with Type-III sFGR and survival of both twins (controls). One set of ultrasound measurements was retrieved for each twin pair at five gestational-age timepoints: 16–20 weeks, 21–24 weeks, 25–28 weeks, 29–32 weeks and > 32 weeks' gestation, if available, for longitudinal analysis. At each timepoint, we assessed EFW[14], umbilical artery Doppler flow pattern, ductus venosus flow pattern, presence of oligohydramnios (defined as a maximal vertical pocket < 2 cm) or polyhydramnios (defined as a maximal vertical pocket > 6 cm before 16 weeks, > 8 cm before 20 weeks or > 10 cm after 20 weeks) at any point during pregnancy, or development of TTTS. For umbilical artery Doppler assessment, evolution from intermittent A/REDF to persistently positive flow was defined as 'Doppler normalization', while development of persistently A/REDF was defined as 'Doppler deterioration'. Ductus venosus flow was defined as either normal (positive a-wave) or abnormal (absent or reversed a-wave).

Statistical analysis

Descriptive statistics are presented as mean ± SD for normally distributed variables and median (interquartile range) for non-Gaussian data. The association between risk of fetal death and potential predictor variables was evaluated using a logistic regression model. For time-varying predictors, the generalized estimating equation (GEE) method with autoregressive (AR-1) correlation structure was used to estimate the parameters of the logistic models. The association between fetal death and multiple predictor variables was also examined

using multivariable logistic regression using GEE. Thresholds of the latest available smaller twin weight *Z*-score for predicting fetal death were assessed using receiver-operating-characteristics (ROC)-curve analysis. The classification and regression trees (CART) method was used to construct a prediction model of fetal death using significant predictors identified in the previous univariable analysis. The decision-tree model was constructed using training data generated by sampling randomly 80% of the available data and then validated on the remaining 20% of the data. The performance of the CART model was evaluated by assessing misclassification rates, and presented as a ROC curves.

RESULTS

A total of 308 twin pregnancies (616 fetuses) were included in the analysis. In 273 pregnancies (88.6%), both twins were liveborn, whereas 35 pregnancies had single ($n = 19$ (6.2%)) or double ($n = 16$ (5.2%)) fetal death. Figure 1 shows the distribution of gestational age at the time of fetal death. Of note, 20 (6.5%) pregnancies were complicated by fetal death at or beyond 24 weeks' gestation and 10 (3.2%) after 28 weeks. Mean gestational age at delivery for the entire cohort was 31.8 ± 3.6 weeks, and 93% of pregnancies with two surviving fetuses were delivered by Cesarean section.

On univariable analysis (Tables 1 and 2) there was no difference in maternal age at delivery, parity or mode of conception (spontaneous *vs* assisted reproduction) between women with fetal death *vs* those with two liveborn neonates. Compared to pregnancies with double survival, pregnancies complicated by fetal death were referred to expert fetal centers earlier in pregnancy (18.6 ± 3.2 *vs* 21 ± 4.8 weeks; $P < 0.001$) (Table 2). Earlier gestational age at diagnosis of Type-III sFGR,

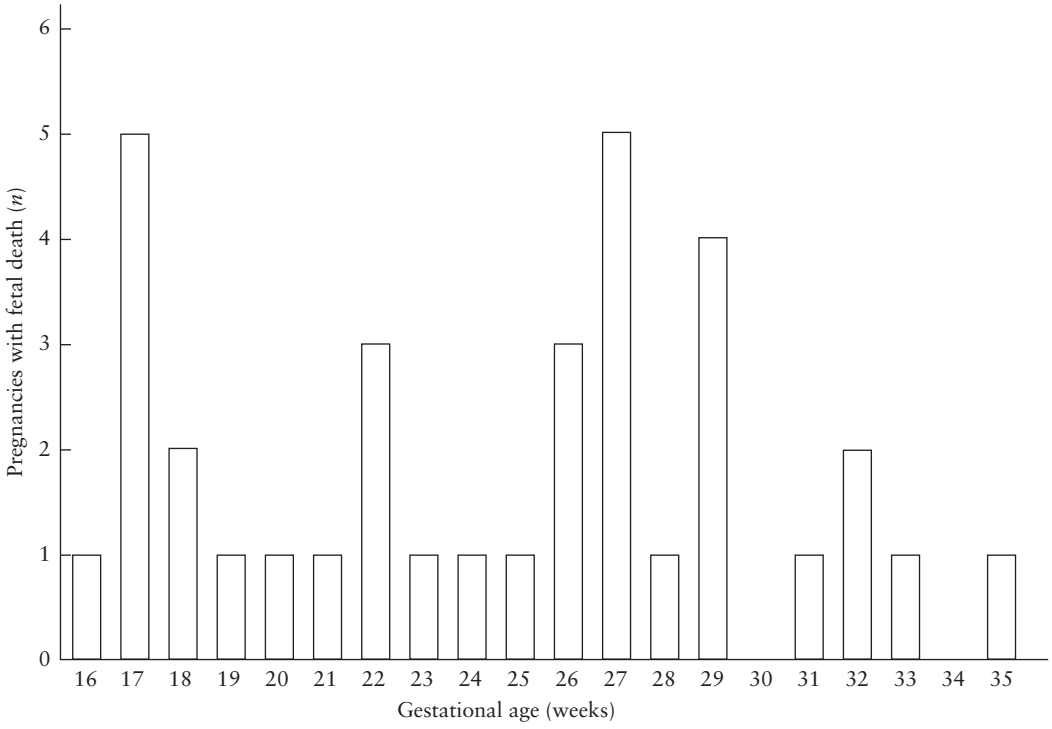

Figure 1 Distribution of gestational age at the time of fetal death in 35 monochorionic diamniotic twin pregnancies complicated by Type-III selective fetal growth restriction.

Table 1 Baseline characteristics of monochorionic diamniotic twin pregnancies complicated by Type-III selective fetal growth restriction, according to fetal outcome

Characteristic	*Total* (n = *308*)	*Double survival* (n = *273*)	*Single/double death* (n = *35*)	*Odds ratio (95% CI)*	P
Maternal age at delivery (years)	30.2 ± 4.95	30.1 ± 5.03	30.7 ± 4.29	1.02 (0.95–1.1)	0.48
Method of conception					0.25
Assisted reproduction	30 (9.7)	25 (9.2)	5 (14.3)	1	
Spontaneous	267 (86.7)	241 (88.3)	26 (74.3)	0.54 (0.20–1.7)	
Data missing	11 (3.6)	7 (2.6)	4 (11.4)		
Parity					0.91
Nulliparous	187 (60.7)	166 (60.8)	21 (60.0)	1	
Parous	120 (39.0)	106 (38.8)	14 (40.0)	1.04 (0.50–2.13)	
Data missing	1 (0.3)	1 (0.4)	0 (0)		

Data are given as mean ± SD or *n* (%), unless indicated otherwise.

Table 2 Association of risk factors with fetal death and their predictive performance in monochorionic diamniotic twin pregnancies complicated by Type-III selective fetal growth restriction

Variable	*Double survival (n = 273)*	*Single/double death (n = 35)*	*Odds ratio (95% CI)*	P	*Sensitivity (%)**	*Specificity (%)**	*LR+**	*LR−**
Gestational age at referral (weeks)	21 ± 4.8	18.6 ± 3.2	0.98 (0.97–0.99)	< 0.001	NA	NA	NA	NA
Gestational age at diagnosis (weeks)	23.6 ± 4.9	19.3 ± 3.3	0.967 (0.94–0.99)	< 0.001	NA	NA	NA	NA
Oligohydramnios in smaller twin	51 (18.7)	13 (37.1)	2.68 (1.23–5.64)	0.01	37.1	81.3	1.99	0.77
Polyhydramnios in larger twin	65 (23.8)	8 (22.9)	0.98 (0.40–2.18)	0.96	22.9	76.2	0.96	1.01
UA Doppler deterioration†	53 (19.4)	19 (54.3)	5.45 (2.59–11.8)	< 0.001	54.3	80.6	2.80	0.57
UA Doppler normalization‡	44 (16.1)	0 (0)	NA	0.007	0.00	83.9	0.00	1.19
Abnormal ductus venosus flow	28 (10.3)	7 (20.0)	2.18 (0.82–5.21)	0.95	20.0	89.7	1.95	0.89
Evolution to TTTS	13 (4.8)	4 (11.4)	2.62 (0.70–7.92)	0.11	11.4	95.2	2.40	0.93

Data are given as mean ± SD or *n* (%), unless indicated otherwise. *Sensitivity, specificity and negative (LR−) and positive (LR+) likelihood ratios were calculated assuming cases with missing data did not present the finding. †Progression to persistent absent or reversed end-diastolic flow in the umbilical artery (UA). ‡Evolution to normal UA flow pattern. NA, not applicable; TTTS, twin–twin transfusion syndrome.

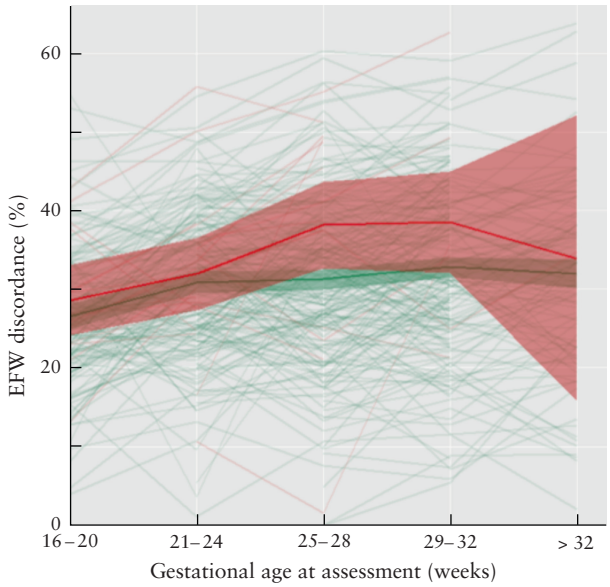

Figure 2 Intertwin estimated fetal weight (EFW) discordance across gestation in monochorionic diamniotic pregnancies complicated by Type-III selective fetal growth restriction, according to whether they had double fetal survival (green) or single/double fetal death (red). Solid thick lines indicate mean EFW discordance, shaded areas are ± 2 SD and thin lines indicate measurements in individual pregnancies.

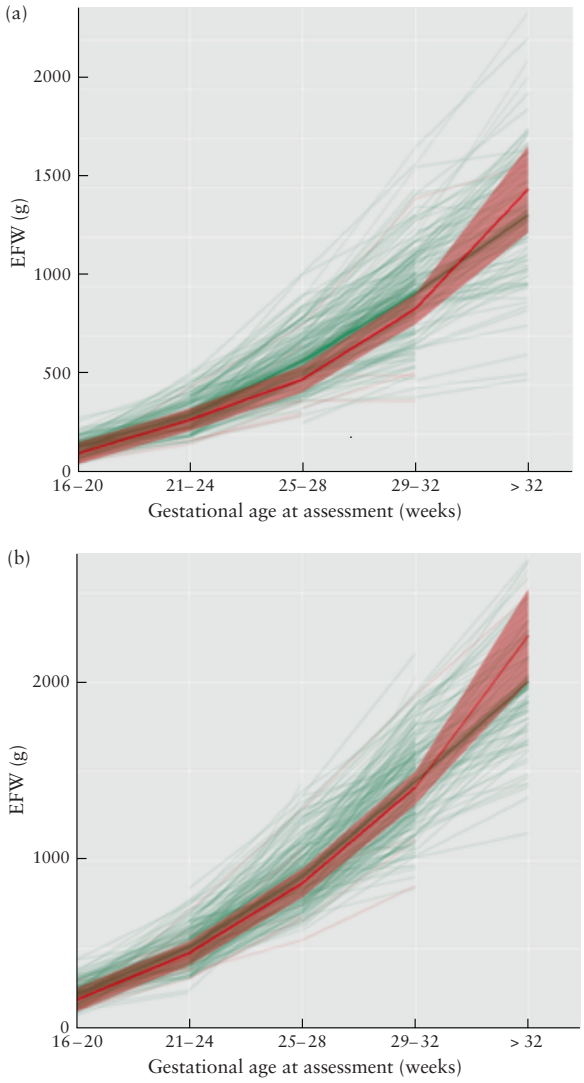

Figure 3 Estimated fetal weight (EFW) of smaller (a) and larger (b) twins across gestation, in monochorionic diamniotic pregnancies complicated by Type-III selective fetal growth restriction, according to whether the fetus survived (green) or died (red). Solid thick lines indicate mean EFW, shaded areas are ±2 SD and thin lines indicate measurements in individual fetuses.

oligohydramnios in the smaller twin, either at presentation or later during pregnancy, and deterioration in umbilical artery Doppler flow with the appearance of persistently A/REDF were associated with an increased risk of fetal death (Table 2), as was larger intertwin EFW discordance, especially between 24 and 32 weeks (Figure 2). Maternal age, mode of conception, EFW of either twin (Figure 3), polyhydramnios and abnormal ductus venosus blood flow were not predictive of fetal death. Normalization of umbilical artery Doppler was associated with a lower risk of fetal death. There were no deaths in the cohort of 44 pregnancies with umbilical artery Doppler normalization. Multivariable analysis, including all parameters identified

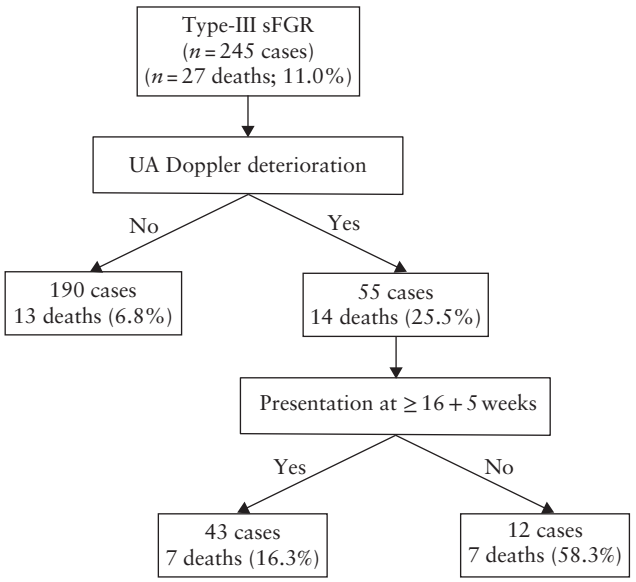

Figure 4 Decision-tree model for prediction of fetal death in monochorionic diamniotic pregnancies complicated by Type-III selective fetal growth restriction (sFGR), applied to the training set. UA, umbilical artery.

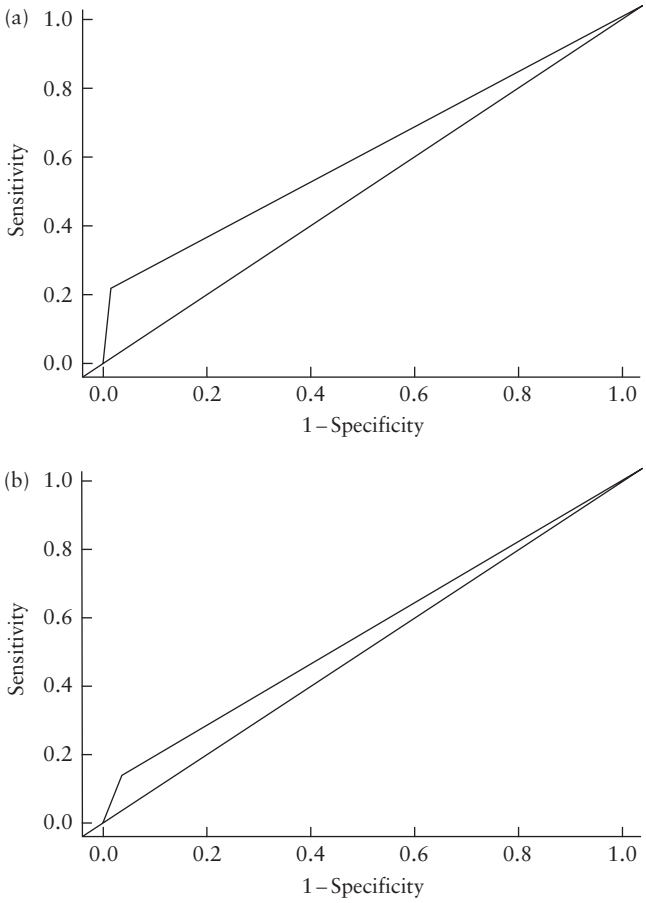

Figure 5 Receiver-operating-characteristics curves for performance of the decision-tree model in predicting fetal death in monochorionic diamniotic pregnancies complicated by Type-III selective fetal growth restriction, in training (a) and validation (b) sets.

on univariable analysis, demonstrated that none of the parameters maintained statistical significance.

A prediction model using the CART methodology is presented in Figure 4. The main variables retained by the algorithm were deterioration in umbilical artery Doppler and early gestational age at referral. Using this model, three groups were identified: a low-risk group (6.8% risk of fetal death), in which umbilical artery Doppler did not deteriorate; an intermediate-risk group (16.3% risk of fetal death), in which umbilical artery Doppler deteriorated, but the diagnosis of sFGR was made at or after 16 + 5 weeks' gestation; and a high-risk group (58.3% risk of fetal death), in which umbilical artery Doppler deteriorated and gestational age at diagnosis was < 16 + 5 weeks. Of all patients presenting with Type-III sFGR, 77.6% were in the low-risk group, 17.6% were in the intermediate-risk group and only 4.9% were in the high-risk group. The performance of the decision tree was suboptimal, with an area under the ROC curve (AUC) of 0.61 in the training set and an AUC of only 0.55 in the validation set (Figure 5).

DISCUSSION

In this study, we explore risk factors for spontaneous fetal death in a large cohort of monochorionic twin pregnancies complicated by Type-III sFGR. We have demonstrated that fetal death is in large part unpredictable and occurs more frequently in pregnancies complicated by oligohydramnios, deterioration in umbilical artery Doppler and larger intertwin EFW discordance. On the other hand, normalization of umbilical artery Doppler, which occurred in 14% of the cohort, is associated with a very low risk of fetal death. However, prediction algorithms for fetal death remain suboptimal.

The high risk of fetal death in Type-II and -III sFGR (12–16%) has been described previously[8]. In Type-II sFGR, fetal mortality can be predicted using Doppler surveillance[15,16], similar to that in singleton FGR. For Type-III sFGR, on the other hand, fetal deaths are considered to be unpredictable, as Doppler surveillance is severely hampered by the fluctuating pattern caused by the large placental artery-to-artery anastomosis. Nevertheless, experts use non-evidence-based parameters such as oligohydramnios, abnormal ductus venosus flow or severe growth discordance to decide on earlier delivery or selective fetal reduction in Type-III sFGR[10,17]. Our findings support the unpredictability of fetal death in Type-III sFGR in many cases but also show that some factors can be used to quantify the risk of fetal mortality. We identified oligohydramnios, larger intertwin EFW discordance in mid-gestation and deterioration in umbilical artery Doppler as being associated with a higher risk of fetal death on univariable analysis, thereby supporting current expert management. Abnormal ductus venosus Doppler does not appear to be predictive of fetal death. On the other hand, normalization of umbilical artery Doppler appears to be protective. The exact pathophysiology of umbilical artery Doppler

normalization is not known, but it probably reflects a relative decrease in intertwin shunting through the large artery-to-artery anastomosis. The lack of statistical significance of the predictors on multivariable analysis indicates that they are interrelated and therefore difficult to use together in a clinical setting.

We propose a decision-tree analysis incorporating the strongest risk factors. The highest odds ratio for fetal death (5.45) was related to progression of the umbilical artery Doppler pattern to persistent absent or reversed flow. It is therefore not surprising that this parameter was selected as the first step in the decision tree and was able to differentiate between low risk and intermediate/high risk of fetal death. Unfortunately, the specificity of this risk factor is suboptimal, as Doppler deterioration was also seen in 19% of cases with double survival. Further integration of gestational age at diagnosis of sFGR allowed us to improve specificity, but the ultimate decision tree still underperformed for reliable clinical use, as evidenced by the low AUC in the validation set. In a population of 100 Type-III sFGR pregnancies, 77 would qualify as low risk according to our algorithm (with five deaths), 18 would have intermediate risk (with three deaths) and five would be high risk (with three deaths).

Poor predictability makes it difficult to improve the outcome of these pregnancies, but a few strategies could be considered. First and foremost, the data presented here could help in parental counseling and allow us to provide patients with realistic and individualized risk estimates for their pregnancy. Additionally, closer surveillance and earlier delivery could be considered in the intermediate-risk group, although it is necessary to remain cautious not to trade rare fetal deaths for an increased risk of postnatal death or long-term prematurity-related morbidity. The potential benefit of fetal-heart-rate monitoring should be explored, particularly in pregnancies with deterioration in umbilical artery Doppler, large (> 30%) intertwin growth discordance and oligohydramnios, and a strategy of elective delivery at ~33 weeks' gestation, similar to that in monoamniotic twins, should be tested in future prospective studies. Finally, for the high-risk group, selective fetal reduction could be considered, as this may result in a higher number of cases with at least one survivor. Indeed, the survival rate of one twin following radiofrequency ablation or cord occlusion is over 80%, with an average gestational age at delivery of 34–35 weeks[18]. Fetoscopic laser ablation of the placental anastomoses could be considered, although it is often technically difficult and results in a high rate of death of the smaller twin and lower gestational age at delivery than does selective reduction[11].

Further prospective studies and analyses of large institutional databases with different management patterns may allow us to better define optimal management protocols.

Strengths and limitations

Our study has multiple strengths. Through international multicenter collaboration, we were able to gather a large, well-defined cohort of fetuses with a rare condition and obtain extensive longitudinal data, allowing us to analyze reliably a number of parameters that vary throughout pregnancy, such as EFW and intertwin EFW discordance, Doppler parameters and amniotic fluid levels. Moreover, the women included in the study were followed at centers with extensive experience in the management of monochorionic multiple pregnancies. Finally, we used robust statistical methods to allow for longitudinal data assessment.

The main weakness of this study is its retrospective design. Even though this was an observational study, all pregnancies were monitored closely in a high-risk center and physicians were not blinded to ultrasound findings. As such, interventions such as delivery or closer surveillance are likely to have taken place based on ultrasound findings, including abnormalities that were considered to be risk factors for fetal death in this study. Moreover, pregnancies in the group with the poorest prognosis may have undergone selective reduction and were therefore not included in the study. Our study may therefore underestimate the risk of fetal death in a truly expectantly managed cohort and underestimate the predictive power of some of the identified parameters.

Conclusions

Type-III sFGR is associated with a high risk of fetal death. In our study, a prediction algorithm helped to identify the highest-risk group, which was characterized by umbilical artery Doppler deterioration and early referral, but performed suboptimally. Further studies should investigate the potential benefit of fetal surveillance and intervention in this cohort. Our algorithm also allowed us to identify a lower-risk group (stable or improving umbilical artery Doppler), in whom counseling can be more reassuring.

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