lewi liesbeth (Orcid ID: 0000-0002-9884-5778)
Yinon Yoav (Orcid ID: 0000-0003-0702-370X)
Raio Luigi (Orcid ID: 0000-0003-3957-3810)
Baud David (Orcid ID: 0000-0001-9914-6496)
Melamed Nir (Orcid ID: 0000-0002-2704-1385)
Sun Luming (Orcid ID: 0000-0001-8467-0383)
Shinar Shiri (Orcid ID: 0000-0001-6352-4846)
Couck Isabel (Orcid ID: 0000-0003-3002-7151)
Groene Sophie G. (Orcid ID: 0000-0002-8832-045X)
Van Mieghem Tim (Orcid ID: 0000-0002-3034-6905)

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

T. Van Mieghem[1]*, L. Lewi[2], F. Slaghekke[3], E. Lopriore[4], Y. Yinon[5], L. Raio[6], D. Baud[7], P. DeKoninck[8], N. Melamed[9], E. Huszti[10], L. Sun[11], S. Shinar[1], Collaborators#

[1]Ontario Fetal Centre, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynaecology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada

[2]Department of Obstetrics and Gynecology, Obstetrics, University Hospitals Leuven, Leuven, Belgium

[3]Department of Gynecology, Leiden University Medical center, Leiden, Netherlands

[4]Division of Neonatology, Department of Pediatrics, Leiden University Medical center, Leiden, Netherlands

[5]Department of Obstetrics and Gynecology, Chaim Sheba Medical Center, Tel Hashomer, Tel Aviv University, Tel Aviv, Israel

[6]Department of Obstetrics and Gynecology, Inselspital, University of Bern, Bern, Switzerland

[7]Department Woman-Mother-Child, Lausanne University Hospital, Lausanne, Switzerland

[8]Department of Obstetrics and Gynaecology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

[9]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

[10]Biostatistics Research Unit, University Health Network, Toronto, ON, Canada

[11]Fetal Medicine unit &Prenatal Diagnosis Center, Shanghai 1st Maternity and Infant Hospital of Tongji University, Shanghai, China

***Corresponding author**

T. Van Mieghem

Ontario Fetal Center, Department of Obstetrics and Gynaecology, Mount Sinai Hospital

700 University Avenue, M5G 1Z5 Toronto, ON, Canada.

Email: tim.vanmieghem@sinaihealth.ca

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Short title: Prediction of fetal death in Type III sFGR

Contribution

Novel findings of this work:

- Fetal death in type III selective fetal growth restriction can be partially predicted.
- Oligohydramnios, early gestational age at diagnosis and deterioration of the umbilical artery Doppler flow are associated with higher risks of fetal death.
- A high-risk, intermediate-risk and low-risk group can be identified using clinical parameters

Clinical implications of this work:

- Our findings can help counsel patients regarding individualized risk of fetal death for their pregnancy.
- This study demonstrates that we can identify pregnancies at high or intermediate risk of fetal death, which should be monitored more closely or may benefit from fetal interventions.

Abstract

Objective: Monochorionic diamniotic (MCDA) twin complicated by type III selective fetal growth restriction (sFGR) are at high risk of fetal death. Our aim was to identify predictors of fetal death.

Methods: We performed an international multicenter retrospective cohort study. Type III sFGR was defined as fetal growth of one twin below the 10th percentile and intertwin growth difference of 25% or more, in combination with intermittent absent or reversed end-diastolic flow in the umbilical artery of the smaller fetus. Predictors of fetal death were longitudinally recorded throughout gestation and assessed in uni- and multivariable using 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: Three-hundred and eight twin pregnancies (616 fetuses) were included in the analysis. In 273 pregnancies (88.6%) both twins were liveborn, whereas in 35 pregnancies there was either a single (n=19; 6.2%) or a double fetal death (n=16; 5.2%). Earlier gestational age at diagnosis of type III sFGR, oligohydramnios of the smaller twin and deterioration of umbilical artery Doppler flow were associated with an increased risk of fetal death. Neither parameter identified in the univariable analysis maintained statistical significance in multivariable analysis. The CART model allowed to identify three risk groups: a low risk group (risk of fetal death 6.8%) where the umbilical artery Doppler did not deteriorate, an intermediate risk group (risk of fetal death 16.3%) where the umbilical artery Doppler deteriorated but the diagnosis of sIUGR was first made after 16+5 weeks' gestation and a high-risk group (risk of fetal death 79%) where the umbilical artery Doppler deteriorated and gestational age at diagnosis was less than 16+5 weeks' gestation.

Conclusions:

Type III sFGR is associated with a high risk of fetal death. A prediction algorithm can help identifying the highest risk group (Doppler deterioration and early presentation). Further studies should investigate the potential benefit of fetal surveillance and intervention in this cohort.

Introduction

Selective fetal growth restriction (sFGR) complicates about 10% of monochorionic twin pregnancies and is subdivided in three types based on the umbilical artery flow pattern in the smaller fetus[1]. Type III sFGR, in which intermittent absent and reversed flow (iA/REDF) are seen, makes up about a fifth of all sFGR cases in monochorionic twins[2]. At the placental level, this condition is characterized by unequal placental sharing with a large bidirectional artery-to-artery (AA) intertwin anastomosis[3], allowing for acute hemodynamic shifts from one fetus to the other[4]. This configuration represents a highly unstable hemodynamic situation that facilitates the occurrence of acute feto-fetal transfusion[5], which may cause sudden fetal death of the smaller fetus and severe hypovolemic events resulting in fetal 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 these twins[12]. 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 felt to be increased[13]. These triggers can include a combination of oligohydramnios, lack of interval growth, increasing growth discordance, abnormal ductus venosus Doppler or fetal heart rate changes.

We have previously documented the outcomes and fetal growth patterns of a large international cohort of pregnancies complicated by type III sFGR[12, 14]. The aim of the present study was to comprehensively assess factors associated with spontaneous fetal death in this same cohort and to evaluate how these factors could be integrated in a prenatal management protocol.

Methods

After approval of the study protocol by all research ethics boards, we retrospectively reviewed the charts of all monochorionic diamniotic (MCDA) twin pregnancies complicated by type III sFGR that were managed longitudinally between January 1st, 2008, and July 1st, 2019 at nine fetal medicine centers. We defined type III sFGR as fetal growth of one twin <10th percentile *and* intertwin growth difference of 25% or more in combination with iA/REDV in the umbilical artery of the smaller fetus on at least one occasion[15]. The intertwin growth difference was calculated as (weight of larger fetus – weight of smaller fetus) / weight of the larger fetus. Higher order multiples, pregnancies complicated by major fetal structural or genetic anomalies and those undergoing selective fetal reduction or fetoscopic laser of placental anastomoses for sFGR were not included in this analysis. Additionally, pregnancies complicated by other monochorionic complications, such as twin-twin transfusion syndrome, twin anemia-polycythemia sequence or twin reversed arterial perfusion sequence at first presentation were excluded.

All pregnancies underwent ultrasound assessment of fetal weight, fluid and fetal Dopplers at least once every two weeks. The baseline characteristics, fetal growth patterns, management protocols and outcomes of these pregnancies have been published previously[12, 14].

To identify predictors of fetal death, we compared pregnancies with type III sFGR complicated by spontaneous single or double fetal death (cases) with pregnancies with type III sFGR and survival of both twins (controls). We retrieved one set of ultrasound measurements for each twin pair in each of five gestational age blocks: 16-20 weeks', 21-24 weeks', 25-28 weeks', 29-32 weeks' gestation and above 32 weeks' gestation, if available, to allow for longitudinal analysis. At each timepoint, we assessed estimated fetal weight (EFW)[16], umbilical artery Doppler flow pattern, ductus venosus flow pattern, presence of oligohydramnios (defined as a maximal vertical pocket of less than two cm) or polyhydramnios (defined as a maximal vertical pocket of above six cm before 16 weeks, above eight cm before 20 weeks, or above ten cm after 20 weeks) at any point during pregnancy, or evolution to twin-twin transfusion syndrome (TTTS). For the umbilical artery Dopplers, evolution from intermittent absent or intermittent reversed flow to persistently positive flow was defined as "normalization" of Dopplers, whereas development of persistently absent or persistently reversed flow was defined as "deterioration" of Dopplers. For ductus venosus flow, we differentiated between normal (positive a-wave) and abnormal (absent or reversed a-wave).

Statistical analysis

Descriptive statistics are presented as mean and standard deviation for normally distributed variables and median and interquartile ranges for non-Gaussian data. Associations between risk of fetal death and potential predictor variables were evaluated using logistic regression models. For time-varying predictors, generalized estimating equation (GEE) method with autoregressive (AR-1) correlation structure was used

to estimate the parameters of the logistic models. Associations between fetal death and multiple predictor variables were also examined using multivariable logistic regression with GEE. Thresholds of the latest available smaller twin weight z-score for predicting fetal death were assessed using receiver operating characteristic (ROC) curve. 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 randomly sampling 80% of the available data, and then validated on the remaining 20%. CART model performance was evaluated by assessing misclassification rates and presented as a ROC curve.

Results

A total of 308 twin pregnancies (616 fetuses) were included in the analysis. In 273 pregnancies (88.6%) both twins were liveborn, whereas in 35 pregnancies there was either a single (n=19; 6.2%) or a double fetal death (n=16; 5.2%). Figure 1 represents the gestational age at fetal death. Of note, 20 pregnancies (7.3%) were complicated by fetal death at or beyond 24 weeks gestation and 10 (3.6%) after 28 weeks gestation. Mean gestational age at delivery for the entire cohort was 31.8 ± 3.6 weeks gestation and 93% of pregnancies with two surviving fetuses were delivered by cesarean delivery.

In univariable analysis (Table 1 & 2), there was no difference in maternal age at delivery, parity or mode of conception (spontaneous versus assisted reproduction) between women with a fetal death versus 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 weeks gestation versus 21 ± 4.8 weeks, respectively; $p<0.001$, Table 1).

Earlier gestational age at diagnosis of type III sFGR, oligohydramnios of the smaller twin, either at presentation or later during pregnancy, and deterioration of umbilical artery Doppler flow with appearance of persistently absent or reversed end-diastolic flow were associated with an increased risk of fetal death (Table 2), as was a larger intertwin growth discordance, especially between 24 and 32 weeks gestation (Figure 2). Maternal age, mode of conception, absolute weight of either fetus (Figure 3a and 3b), polyhydramnios or abnormal ductus venosus blood flow did not predict fetal death. Normalization of the umbilical Doppler was associated with a lower risk of fetal death. Of note, no deaths occurred in the cohort of 44 pregnancies with umbilical Doppler normalization. A multivariable analysis, including all parameters identified in the univariable analysis, demonstrated that neither parameter maintained statistical significance.

A prediction model using the CART methodology is presented in Figure 4. The main variables retained by the algorithm were deterioration of umbilical artery Dopplers and early gestational age at first presentation. Using this model, three groups were identified: a low risk group (risk of fetal death 6.8%) where the umbilical artery Doppler did not deteriorate, an intermediate risk group (risk of fetal death 16.3%) where the umbilical artery Doppler deteriorated but the diagnosis of sIUGR was first made after 16+5 weeks' gestation and a high risk group (risk of fetal death 79%) where the umbilical artery Doppler deteriorated and gestational age at diagnosis was less than 16+5 weeks' gestation. Of all patients presenting with type III sFGR, 77.6% fell in the low-risk group, 17.6% in the intermediate risk group and only 4.9% in the high-risk group. Performance of this decision tree, was suboptimal with an AUC of 0.61 on the training set, but only 0.55 on the validation set (Figure 5).

Discussion

In this manuscript, we explored risk factors for spontaneous fetal death in a large cohort of monochorionic twin pregnancies complicated by type III sFGR. We demonstrate that deaths are in large part unpredictable and occur more frequently in pregnancies complicated by oligohydramnios, deteriorating Dopplers and a larger difference in estimated fetal weight between the fetuses. On the other hand, normalization of Dopplers, which occurred in 16% 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 previously been described[8]. In type II sFGR, fetal mortality can be predicted using Doppler surveillance[17, 18], similar to what is done in singleton FGR. For type III sFGR on the other hand, fetal deaths are felt to be unpredictable as Doppler surveillance is severely hampered by the fluctuating pattern caused by the large placental artery-to-artery anastomosis. Experts nevertheless 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[12, 19]. Our findings support the unpredictability of fetal death in type III sFGR in many cases, but we also show that some factors can be used to quantify the risk of fetal mortality. Indeed, we identified oligohydramnios, larger weight discordances in mid-gestation and deteriorating Dopplers as being associated with a higher risk of fetal death in univariable analysis, thereby supporting current expert management. Abnormal ductus venosus Doppler does not seem to predict death. On the other hand, normalization of umbilical artery Doppler seemed protective. The exact pathophysiology of this umbilical Doppler normalization is not known, but it probably reflects proportionally less intertwin shunting through the large artery-to-artery anastomosis.

Given the lack of statistical significance of the predictors identified here in multivariable analysis, they are interrelated and therefore difficult to use in combination in a clinical setting.

We propose a decision tree analysis leveraging the strongest factors. The highest odds ratio for fetal death (5.45) was seen with progression of the umbilical artery Doppler pattern to persistent absent and reversed flow. It is therefore not surprising that this parameter was selected as the first step in the decision tree and can differentiate low risk of fetal death from intermediate or high risk. Unfortunately, its specificity is weak, as Doppler progression was also seen in 19% of cases with double survival. Further integration of gestational age at diagnosis of FGR allows to improve specificity slightly, but the ultimate decision tree still underperforms for reliable clinical use as evidenced by the low AUC in the validation set. Practically, for 100 type III sFGR pregnancies, 77 would qualify as ‘low-risk’ according to our algorithm, and five

deaths would occur in this cohort; 18 would be intermediate risk (with three deaths) and five would be high-risk (with three deaths).

Such poor predictability makes it hard to improve the outcomes for these pregnancies, but a few strategies could be considered. First and foremost, the data presented here can help in parental counselling and allow to provide patients with realistic and individualized risk estimates for their pregnancy. Additionally, one may consider closer surveillance and earlier delivery in the intermediate risk group, although one needs 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 deteriorating Dopplers, large (>30%) intertwin growth discordance and oligohydramnios, and a strategy of elective delivery at ~33 weeks gestation, similar to what is done in monoamniotic twins should be tested in future prospective studies. Finally, for the high-risk group, selective fetal reduction can be considered as this may result in a higher number of at least one survivor. Indeed, the survival rate of one twin after radiofrequency ablation or cord-occlusion is over 80% with an average gestational age at delivery of 34-35 weeks gestation[20]. Fetoscopic laser of the placental anastomoses could be considered, but is often technically difficult, still results in a high rate of death of the smaller twin and in a lower gestational age at delivery than selective reduction[13].
Further prospective studies or comparisons of large institutional databases with different management patterns may allow 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 reliably analyze a number of parameters which vary throughout pregnancy, such as fetal weight and weight discordance, Dopplers and amniotic fluid levels. Moreover, the pregnancies included here were all followed at centers with extensive experience in the management of monochorionic multiples. Finally, we used robust statistical methods to allow for longitudinal data assessment.

The main weakness of this study is its retrospective character. Even though this was an observational study, all pregnancies were monitored closely in high-risk centers and physicians were not blinded to ultrasound results. As such, interventions (such as delivery or closer surveillance) will likely have taken place based on ultrasound findings, including the findings we here describe as being risk factors for fetal death. Moreover, pregnancies in the poorest prognosis group may have undergone selective reduction and were therefore not included in this study. Our study may therefore underestimate the risk of fetal death in a truly

expectantly managed cohort and may underestimate the predictive power of some of the parameters identified here.

Conclusion

In conclusion, type III sFGR is associated with a high risk of fetal death. A prediction algorithm can help identifying the highest risk group (Doppler deterioration and early presentation), but performs suboptimally. Further studies should investigate the potential benefit of fetal surveillance and intervention in this cohort. Our algorithm also allows to identify a lower risk group (stable or improving Dopplers) in whom counselling can be more reassuring.

Collaborators: Yidi Jiang[1], Wei Xing[2], Chen Jianping[2], Isabel Couck[3], Sophie Groene[4], Linoy Batsry[5] Sofia Amylidi-Mohr[6], Fannie Kneuss[7], Joske Moscou[8], Jon Barrett[9], Vagisha Pruthi[10], Greg Ryan[10].

[1]Biostatistics Research Unit, University Health Network, Toronto, ON, Canada

[2]Fetal Medicine unit &Prenatal Diagnosis Center, Shanghai 1st Maternity and Infant Hospital of Tongji University, Shanghai, China

[3]Department of Obstetrics and Gynecology, Obstetrics, University Hospitals Leuven, Leuven, Belgium

[4]Division of Neonatology, Department of Pediatrics, Leiden University Medical center, Leiden, Netherlands

[5]Department of Obstetrics and Gynecology, Chaim Sheba Medical Center, Tel Hashomer, Tel Aviv University, Tel Aviv, Israel

[6]Department of Obstetrics and Gynecology, Inselspital, University of Bern, Bern, Switzerland

[7]Department Woman-Mother-Child, Lausanne University Hospital, Lausanne, Switzerland

[8]Department of Obstetrics and Gynaecology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

[9]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

[10]Ontario Fetal Centre, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynaecology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada

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Figures

Figure 1. Gestational age distribution of fetal deaths.

Figure 2. Evolution of growth discordance across gestation stratified by outcome. Pregnancies with double fetal survival are represented in green. Those complicated by single or double fetal death are represented in red. Mean discordance is marked in solid lines with two standard deviations above and below the mean denoted by shaded areas. Individual thin lines mark each pregnancy separately.

Figure 3. Fetal weights across gestation stratified by outcome for (a) smaller twins and (b) larger twins. Surviving fetuses are represented in green and those that died in red. Mean estimated fetal weight is marked in solid lines with two standard deviations above and below the mean denoted by shaded areas. Individual thin lines mark each twin separately.

Figure 4. Prediction of fetal death in MCDA pregnancies complicated by type III sFGR.

Figure 5. Receiver Operator Curves (ROC) for the decision tree in the training set (A) and validation set (B).

Tables

Table 1. Maternal and pregnancy characteristics in type III sFGR

	Total (N = 308)	**Both alive (N = 273)**	**One or both dead (N = 35)**	**P-value**	**Odds ratio (95%CI)**
Maternal age (years)	30.2 (4.95)	30.1 (5.03)	30.7 (4.29)	0.48	1.02 (0.95 - 1.1)
Conception					
Assisted reproduction	30 (9.7%)	25 (83.3%)	5 (16.6%)	0.25	1
Spontaneous	267 (86.7%)	241 (90.3%)	26 (9.7%)		0.54 (0.20 - 1.7)
Missing	11 (3.6%)	7	4		
Parity					
Primigravid (n,%)	187 (60.7%)	166 (88.7%)	21 (11.2%)		1
Multiparous (n,%)	120 (39.0%)	106 (88.3%)	14 (11.6%)	0.91	1.04 (0.50 - 2.13)
Missing (n,%)	1 (0.3%)	1 (100%)	0 (0%)		
Gestational age at referral (weeks ± SD)	20.7 ± 4.8	21 ± 4.8	18.6 ± 3.2	<0.001	0.98 (0.97- 0.99)

Table 2. Risk factors for spontaneous fetal death in type III sFGR

Total (n=308)	**Both alive (N = 273)**	**One or both dead (N = 35)**	**P-value**	**Odds ratio (95%CI)**	**Sensitivity**	**Specificity**	**LR+**	**LR-**
Gestational age at diagnosis (weeks, SD)	23.6 (4.9)	19.3 (3.3)	<0.001	0.967 (0.94 - 0.99)	NA	NA	NA	NA
Oligohydramnios in smaller twin (N,%)	51 (18.7%)	13 (37.1%)	0.01	2.68 (1.23 - 5.64)	37.1%	81.3%	1.99	0.77
Polyhydramnios in larger twin (N,%)	65 (23.8%)	8 (22.9%)	0.96	0.98 (0.40 - 2.18)	22.9%	76.2%	0.96	1.01
Deterioration of umbilical artery Dopplers (N,%)*	53 (19.4%)	19 (54.3%)	<0.001	5.45 (2.59 - 11.8)	54.3%	80.6%	2.80	0.57
Improvement of umbilical artery Dopplers (N,%)**	44 (16.1%)	0 (0%)	0.007	NA	0%	83.9%	0	1.19
Abnormal ductus venosus flow (N,%)	28 (10.3%)	7 (20.0%)	0.95	2.18 (0.82 - 5.21)	20%	89.7%	1.95	0.89
Evolution to TTTS (N,%)	13 (4.8%)	4 (11.4%)	0.11	2.62 (0.70 - 7.92)	11.4%	95.2%	2.4	0.93

Legend: TTTS: twin-twin transfusion syndrome.*: progression to persistent absent or reversed end diastolic flow. **evolution to normal umbilical flow pattern. LR+: Likelihood ratio of a positive test. LR-: Likelihood ratio of a negative test.

Figures

Figure 1. Gestational age distribution of fetal deaths.

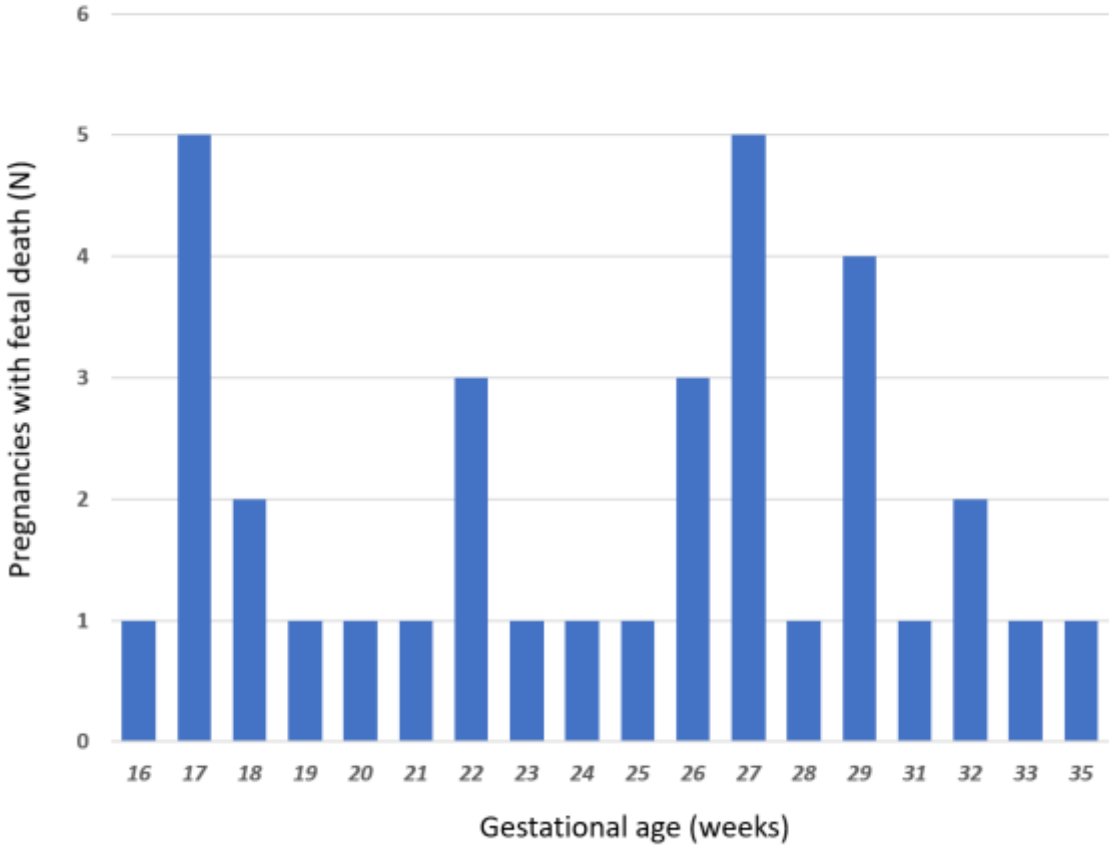
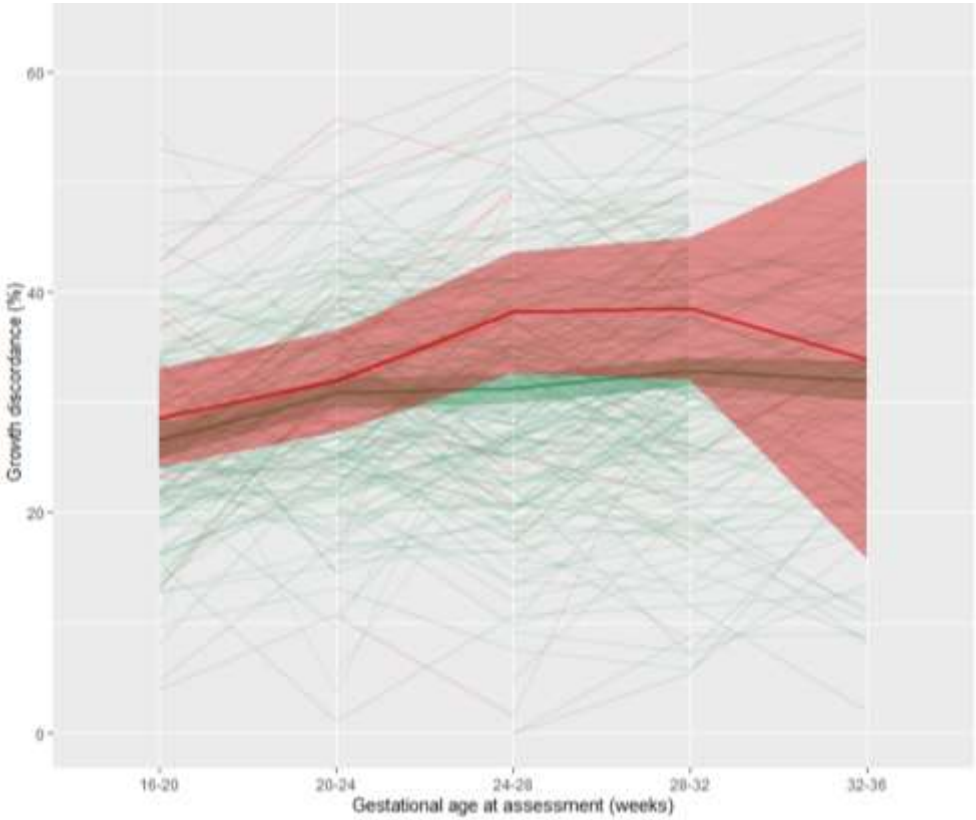
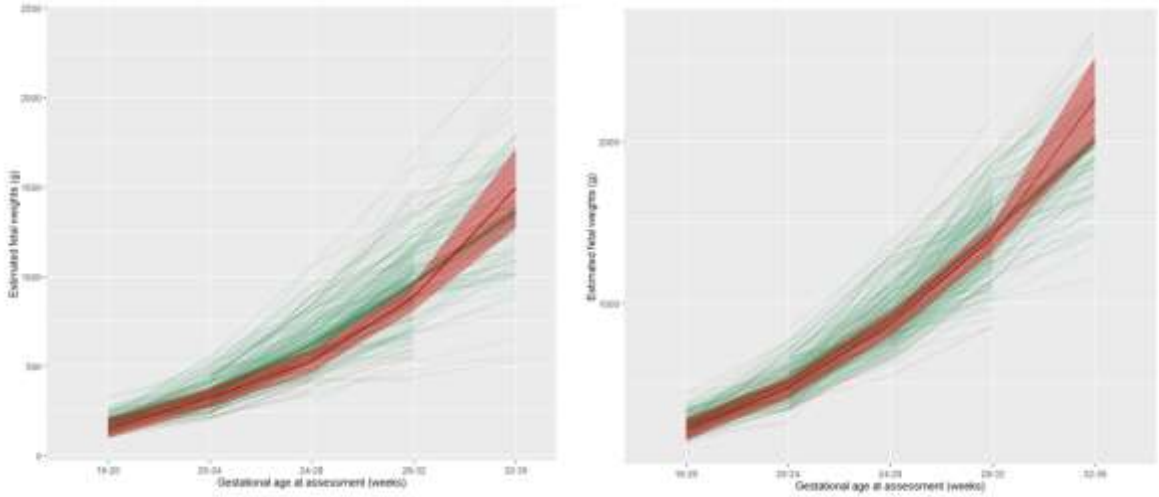


Figure 2. Evolution of growth discordance across gestation stratified by outcome. Pregnancies with double fetal survival are represented in green. Those complicated by single or double fetal death are represented in red.



Mean discordance is marked in solid lines with two standard deviations above and below the mean denoted by shaded areas. Individual thin lines mark each pregnancy separately.

Figure 3. Fetal weights across gestation stratified by outcome for (a) smaller twins and (b) larger twins. Surviving fetuses are represented in green and those that died in red.



Mean estimated fetal weight is marked in solid lines with two standard deviations above and below the mean denoted by shaded areas. Individual thin lines mark each twin separately.

Figure 4. Prediction of fetal death in MCDA pregnancies complicated by type III sFGR.

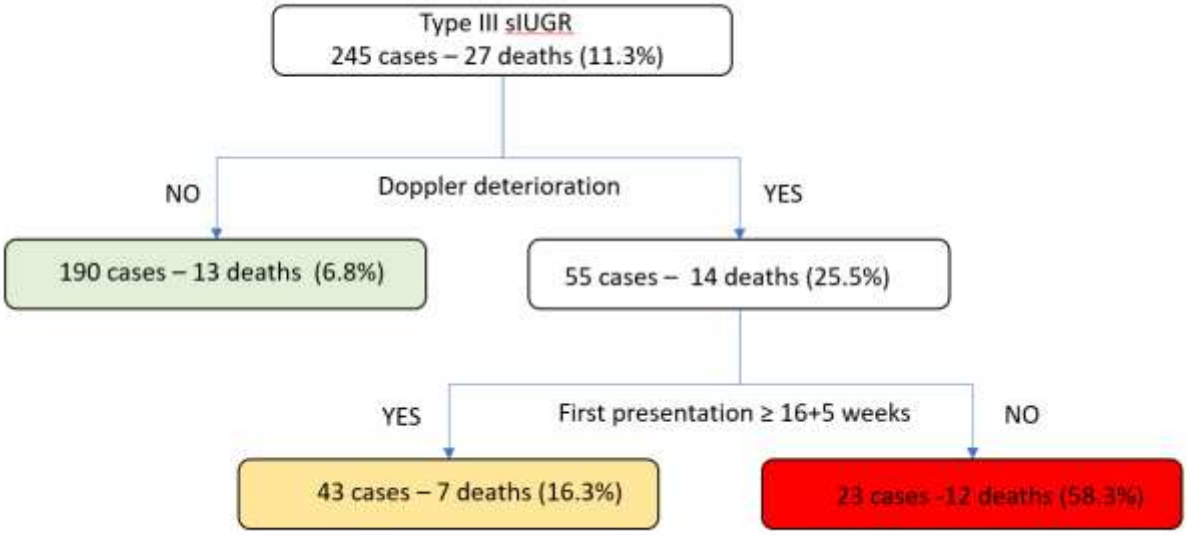
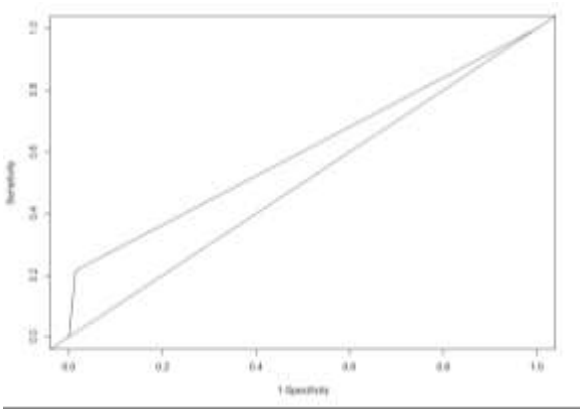


Figure 5. Receiver Operator Curves (ROC) for the decision tree in the training set (A) and validation set (B).

A. Training set



B. **Validation set**