Prediction of adverse pregnancy outcome in monochorionic- diamniotic twin pregnancies complicated by selective fetal growth restriction

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Short title: selective fetal growth restriction in monochorionic twins

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ABSTRACT

Objective: To identify key factors implicated in adverse perinatal outcome in monochorionic twin pregnancies complicated by selective fetal growth restriction.

Methods: This is a retrospective cohort study conducted in a single tertiary referral centre included all monochorionic diamniotic (MCDA) twin pregnancies complicated by selective fetal growth restriction (sFGR). The presence of co-existing twin to twin transfusion syndrome (TTTS) was noted. Fetal biometry and Doppler indices, including the umbilical artery (UA) and ductus venosus (DV), were recorded at the time of diagnosis. The type of sFGR was diagnosed according to the pattern of end-diastolic flow (EDF) in the UA of the smaller twin. DV pulsatility indices were converted to z-scores and estimated fetal weight (EFW) values to centiles, to correct for gestational age (GA). Cox proportional hazards model was used to examine for independent predictors of adverse perinatal outcome.

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Adverse perinatal outcome was defined according to survival and included both intra-uterine fetal demise and neonatal death of the FGR twin.

Results:
We analysed 104 pregnancies complicated by sFGR. Sixty-six (63.5%) were diagnosed with type I and 38 (36.5%) with type II at initial presentation. Pregnancies complicated by type II sFGR were diagnosed (median GA 19.6 weeks' vs 21.5 weeks, p=0.012) and delivered (median GA 30.4 weeks' vs 32.57 weeks; p=0.055) earlier and are associated with increased risk of adverse perinatal outcomes (intrauterine demise of the smaller twin 19.7% vs 10.6%, p=0.001), when compared to type I sFGR. Twin pregnancies complicated by sFGR, whether type I or II, resulting in intrauterine demise have a significantly earlier onset of diagnosis (p<0.001), earlier GA at delivery (p<0.05), higher DV pulsatility index (p<0.05), and lower birth weight (BW) centile of the smaller twin (p<0.01) when compared to pregnancies resulting in livebirth. Co-existing TTTS had no significant impact on the perinatal outcome of pregnancies diagnosed with either type I or type II sFGR (p>0.05 for both). Earlier GA at diagnosis (HR 0.70, 95% CI 0.56-0.88; p=0.002), type II sFGR (HR 3.53, 95% CI 1.37-9.07; p=0.008) and higher DV PI z scores (HR 1.36, 95% CI 1.12-1.65; p=0.001) were significantly associated with increased risk of adverse perinatal outcome of the smaller twin.

Conclusion:
Pregnancies complicated by type II sFGR are diagnosed significantly earlier and are associated with increased risk of adverse perinatal outcomes when compared to type I. Co-existing TTTS has no significant impact on the perinatal outcome of pregnancies diagnosed with either type I or type II sFGR. Earlier GA at diagnosis, type II sFGR and higher DV PI z scores are significantly associated with increased risk of adverse perinatal outcome for the smaller twin.

INTRODUCTION

Monochorionic twin pregnancies can be complicated by several unique complications, including sFGR, TTTS, twin reversed arterial perfusion sequence and twin anaemia-polycythaemia sequence.[1,2] As a consequence of this, when compared to dichorionic gestations, they are at increased risk of adverse perinatal outcome.[3,4]

Inconsistences with regards to the definition of sFGR make the prevalence of this condition difficult to determine however, sFGR is observed in approximately 10-15% of monochorionic twin pregnancies.[5] It is conventionally defined as a condition in which the estimated fetal weight (EFW) of one fetus is less than the 10th centile and the inter-twin EFW discordance is greater than 25%.[6] The condition can be further classified into types I, II and III according to the end diastolic flow (EDF) in the UA of the smaller fetus.[7] The EDF is positive in type I, absent or reversed (AREDF) in type II or intermittent AREDF in type III. Pregnancies complicated by sFGR type I (sFGR-I) are typically associated with a favourable outcome.[8] However, a small proportion will progress to type II or III, both of which are associated with significantly higher perinatal morbidity and mortality.[9]

An additional complication of monochorionic twin pregnancies, which arises as a consequence of imbalanced placental blood flow is TTTS. This affects approximately 10% of monochorionic[10] pregnancies and is defined by a marked discordance in amniotic fluid volume with the deepest vertical pool of ≤2 cm in one sac and ≥8 cm before 20 weeks and >10 cm after 20 weeks in the other sac.[11,12] The severity of TTTS is classified according to Quintero staging[12] and endoscopic laser coagulation of the inter-twin communicating placental vessels is the established treatment of choice.[13,14] In 2015, Van Winden *et al* concluded that sFGR, present in up to two thirds of pregnancies complicated by TTTS, was a risk factor for decreased donor survival.[15]

The objectives of this study were to examine MCDA twin pregnancies complicated by sFGR to determine factors implicated in adverse perinatal outcome. A secondary objective was to investigate the impact of co-existing TTTS on perinatal outcome and to determine which ultrasound parameters are valuable predictors of fetal survival.

MATERIALS AND METHODS

This retrospective cohort study was conducted in the Fetal Medicine Unit at St George's Hospital, London, a tertiary referral centre for complicated multiple pregnancies. All cases including external referrals were identified by performing an electronic database search (Viewpoint 5.6.8.428, Wessling, Germany) over a 15-year period between March 2000 and May 2015. The inclusion criteria consisted of any MCDA twin pregnancy diagnosed with sFGR between 16 weeks' gestation and birth. Pregnancies complicated by fetal abnormality, aneuploidy, genetic syndromes or those with missing pregnancy outcome data were excluded from the analysis.

Monochorionicity was determined on the first trimester ultrasound in all cases based on a single placental mass with a T-sign and absent λ-sign.[16] The gestational age was determined according to the crown-rump length (CRL) measurement of the larger twin on the first trimester ultrasound assessment.[17] Pregnancies were dated according to the head circumference measurement when the first ultrasound examination was performed after 14 weeks' gestation.[18] Pregnancies in which in vitro fertilization techniques were employed were dated according to the embryonic age on the date of embryo transfer.

All cases underwent an ultrasound assessment conducted by qualified and experienced operators using a 4-8MHz convex probe on a Voluson GE ultrasound machine (GE Medical Systems, Zipf, Austria). Fetal biometry, Doppler assessment and evaluation of the deepest vertical pool (DVP) of the amniotic fluid was performed for each fetus during the ultrasound examination. The EFW for gestations <20 and >20 weeks was calculated using the formulae by Warsof *et al* and Hadlock *et al,* respectively.[19,20]

Selective fetal growth restriction was diagnosed according to the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) clinical guideline when the EFW of one fetus was less than the 10th centile and the inter-twin EFW discordance was greater than 25%.[6] The inter-twin EFW discordance was calculated as (A − B) × 100/A, where A represented the EFW of the larger fetus and B the EFW of the smaller twin.

Doppler assessment of the umbilical arteries of both fetuses was conducted in all cases and the EDF in the smaller twin was classified as positive, absent or reversed. The UA Doppler waveform was produced by sampling free loops of the umbilical cord using colour Doppler during a period of fetal quiescence. The UA Doppler pattern was classified as type I when the EDF was persistently positive, type II when the flow was persistently absent or reversed and type III in cases where the EDF was intermittently absent or reversed. Classification of the type of sFGR was assigned at initial presentation and all subsequent ultrasound assessments. Doppler evaluation of the fetal DV was performed on both fetuses and the a-wave was categorised as positive, negative or reversed.[21] The DV was identified as the vessel connecting the intra-abdominal portion of the umbilical vein with the inferior vena cava using colour Doppler ultrasonography during a period of fetal quiescence. The pulsatility index (PI) of the DV was calculated according to standard formula[22] for each twin and these values were converted to z scores to correct for GA.[22]

Progression of type I sFGR was defined as the evolution of present EDF in the UA Doppler to absent or reversed (type II) or intermittent or cycling flow (type III) during any subsequent ultrasound assessments. Progression of type II sFGR was defined if absent EDF in UA Doppler at the time of diagnosis proceeded to reversed or intermittent flow. Pregnancies complicated by isolated type I sFGR were managed conservatively. Indications for proceeding with laser coagulation therapy in sFGR cases included progression to type II at

gestations less than 26 weeks where the prognosis was particularly guarded and the presence of co-existing TTTS. Twin-to-twin transfusion syndrome was diagnosed and staged according to the Quintero classification.[12] Pregnancies complicated by stage I TTTS were managed conservatively in keeping with existing evidence. Any pregnancy complicated by or that progressed to stage II TTTS were routinely offered fetoscopic laser intervention. This was performed in keeping with standard techniques described in the literature.[23]. The option of cord occlusion or selective feticide in cases undergoing fetoscopic laser therapy for TTTS complicated by severe sFGR was discussed pre-operatively. Amniodrainage was performed routinely at the end of fetoscopic surgery and in isolation as a therapeutic intervention in one case of atypical late-onset TTTS.

The indications for and mode of delivery were at the discretion of the attending physician. Maternal characteristics including maternal age, ethnicity (Asian, Black, Caucasian, Mixed and Other), body mass index (BMI) and method of conception were recorded for comparison. Data on pregnancy outcome was collected from hospital obstetric and neonatal records. This included pregnancy outcome of both twins (livebirth/stillbirth/neonatal death less than or greater than one week from delivery and termination of pregnancy), GA at delivery, birth weight (BW) and admission to the neonatal intensive care unit. Perinatal mortality included stillbirth and neonatal death within the first 28 days following delivery. A stillbirth was defined as fetal demise after 24 completed weeks of pregnancy. EFW and BW values were converted to centiles to correct for GA.[24,25]

Statistical Analysis

Continuous variables were presented as median with interquartile ranges (IQR), and categorical variables were presented as a fraction of the total with percentages. Distribution assumptions of variables were tested with Shapiro-Wilk test. Comparisons of groups with continuous variables were made with t-test and Wilcoxon rank sum test. Comparison of categorical variables was made with the Fisher's exact test. Cox proportional hazards models were used to assess the importance of antenatal and ultrasound variables on the survival time of the smaller twin. P values below 0.05 were considered statistically significant. The statistical analysis was performed using RStudio (Version 1.0.136, RStudio, Inc.) statistical software.

RESULTS

We identified 123 MCDA twin pregnancies that were diagnosed with sFGR during the defined study period. We excluded 16 (13%) pregnancies that were complicated by fetal structural abnormalities, aneuploidy or that were lost to follow up. A final cohort of 107 pregnancies (214 fetuses) was available for analysis. Of the 107 pregnancies, 66 (61.7%) were diagnosed with type I, 38 (35.5%) type II and 3 (2.8%) type III sFGR at the initial presentation. Seventy-five (70.1%) pregnancies resulted in survival of both twins. Twenty-three (21.5%) pregnancies were complicated by demise of either the smaller or larger twin, thus resulting in one survivor. Two thirds of these cases of a single survivor were secondary to the demise of the smaller twin. Nine (8.4%) pregnancies were complicated by double fetal demise. Given the small number of cases of type III sFGR, the analysis focused primarily on type I and type II sFGR.

The antenatal, ultrasound variables and pregnancy outcome data for the twin pregnancies complicated by type I versus type II sFGR are presented in Table 1. Throughout pregnancy, 13 cases of type I (19.7%) and 13 cases of type II (34.2%) progressed to a more advanced stage. When compared to type I sFGR, pregnancies complicated by type II at initial presentation were diagnosed significantly earlier with a median GA at diagnosis of 19.6 weeks (IQR 17.3-23.9) vs 21.5 weeks (IQR 18.9-26.5), respectively (p=0.012). They were also delivered earlier with a median GA of delivery for type II and type I of 30.4 weeks (IQR 28.0-34.0) vs 32.6 weeks (IQR 30.7-34.8), respectively (p=0.055) with a trend toward statistical significance. With regards to ultrasound variables, the smaller twin in pregnancies complicated by type II sFGR had significantly higher DV PI Z scores (p<0.001). When comparing pregnancy outcomes, pregnancies complicated by type I sFGR had significantly lower rates of demise of the smaller twin (p=0.001) and higher rates of survival of both fetuses (p=0.002). In addition, outcome data of pregnancies with Type-I and Type-II sFGR excluding cases with TTTS (isolated sFGR) are provided in Table S1.

The maternal and gestational characteristics of the pregnancies resulting in livebirth versus those complicated by intrauterine demise (IUD) and subgroup analysis for type I and type II sFGR are presented in Table 2, 2A and 2B, respectively. Pregnancies diagnosed with type I sFGR resulting in IUD were both diagnosed and delivered significantly earlier than those resulting in livebirth (Table 2A). The diagnosis delivery interval was similar between the two groups (median: 10.71 vs. 9.57 weeks, IUD and livebirth respectively, p=0.688) due to earlier diagnosis and delivery time in the IUD group. A comparison of ultrasound characteristics revealed that pregnancies complicated by IUD had higher DV PI Z scores in the smaller (p=0.206) and larger fetus (p<0.001), albeit the difference for the smaller twin did not reach statistical significance. A significant proportion of the pregnancies resulting in IUD underwent fetoscopic laser procedures (64.2% vs. 15.1%, p<0.001) and the BW centile of the smaller fetus was significantly lower (0.00, IQR 0.00-0.16 vs. 1.18, IQR 0.04-6.44; p=0.005). Similar significant findings including the earlier onset of diagnosis (p=0.002), higher DV PI z score of the smaller twin (p=0.003) and lower BW centile of the smaller twin (p=0.004) were replicated when the pregnancies diagnosed with type II sFGR complicated by IUD were examined (Table 2B). With regards to the pregnancy outcome, a significantly higher number of pregnancies diagnosed with type II sFGR complicated by IUD resulted in neonatal death of the surviving twin (15.8 vs. 0%, p=0.033).

Further analysis of sFGR pregnancies complicated with TTTS versus those without is illustrated in Table 3. There was no significant impact on the pregnancy outcomes of either type I or type II sFGR with co-existing TTTS (p>0.05 for both). Type II sFGR pregnancies with co-existing TTTS had significantly increased rates of admission to the neonatal intensive care unit compared to those with sFGR alone (87.5 vs. 45.5%, p<0.001).

Treatment modalities included 36 laser coagulation therapies, one cord occlusion and two amniodrainage procedures. Of the 36 cases treated with endoscopic laser therapy, 28 had co-existing TTTS. There were 8 cases of isolated sFGR who underwent laser treatment. Five cases were type II at initial presentation and 7 progressed to type II by the end of pregnancy. Perinatal outcomes of the 36 cases treated with laser therapy included 6 double losses, 15 pregnancies resulting in 1 survivor and 15 cases of double livebirths.

Cox proportional hazard regression models (Table 4) revealed that the GA at diagnosis (HR 0.70, 95% CI 0.56-0.88; p=0.002), type II sFGR (HR 3.53, 95% CI 1.37-9.07; p=0.008) and DV PI Z scores (HR 1.36, 95% CI 1.12-1.65; p=0.001) were significantly associated with increased risk of adverse perinatal outcome of the smaller twin in all twin pregnancies complicated by sFGR. With regards to pregnancies complicated by type I sFGR, the GA at diagnosis (HR 0.48, 95% CI 0.27-0.84; p=0.010) remained a significant predictor. The DV PI Z scores (HR 1.24, 95% CI 1.00-1.55; p=0.043) was significantly associated with adverse outcome for the smaller fetus in the pregnancies complicated by sFGR type II.

DISCUSSION

Summary of study findings

The findings of this study demonstrate that twin pregnancies complicated by type II sFGR are diagnosed significantly earlier and are associated with increased risk of adverse perinatal outcome when compared to type I. Pregnancies complicated by sFGR and IUD have a significantly earlier onset of diagnosis, earlier GA at delivery, higher DV PI z-scores and lower BW centile of the smaller twin when compared to those resulting in livebirth. Co-existing TTTS had no significant impact on the perinatal outcome of type I or type II sFGR pregnancies. Earlier GA at diagnosis, type II sFGR and higher DV PI z-scores are significantly associated with increased risk of adverse perinatal outcome of the smaller twin.

Interpretation of study findings and comparison with existing literature

The increased risk of adverse perinatal outcome associated with type II sFGR compared to type I has been reported by several research groups.[8,9,26] In 2015, Peeva *et al* examined type II sFGR pregnancies with and without co-existing TTTS treated with endoscopic placental laser coagulation. In keeping with the findings of our study, they determined that survival was not related to the presence or absence of co-existing TTTS.[11] In contrast to our study however, cases complicated by type II sFGR only were included. This group also determined that significant predictors of survival included the DV Doppler findings in the small twin, GA at laser and cervical length. The findings of our study following regression analysis are in keeping with these conclusions.

The overall rate of IUD for all pregnancies included in our study was 31%, which seemed slightly higher than expected. In order to examine this further we performed a comparison of IUD rates reported in the literature (Supplementary Table S2). To the best of our knowledge our study appears to be the first to date to include cases of both sFGR type I and II with co-existing TTTS. The higher IUD rate (50%) amongst pregnancies complicated by type II sFGR may be a consequence of the large number of referred cases to the unit. Referred pregnancies tend to be more complicated cases leading to bias towards poorer perinatal outcomes amongst the results.

Clinical and research implications

Two of the main difficulties of sFGR involve making the diagnosis and determining subsequent management. The diagnostic criteria used in the literature varies significantly between research groups making it difficult to form solid conclusions. In an attempt to standardize the diagnostic features of sFGR in twin pregnancy, a Delphi procedure has been undertaken to reach a consensus.[27]Once the diagnosis has been made there is a distinct lack of robust data with which to counsel patients with regards to the outcomes of these pregnancies. The findings of our study confirm that the GA at diagnosis, the type of sFGR and DV PI should be used in order to identify those pregnancies at increased risk of adverse outcome which may benefit from increased surveillance and a discussion with regards to treatment options.

The optimal management of sFGR remains to be one of the key questions still to be addressed. Pregnancies complicated by sFGR with co-existing TTTS, laser coagulation therapy has been proven to be the optimal choice of treatment through randomized controlled trials (RCTs). In cases of isolated sFGR, observational studies to date and our data would suggest that sFGR type I pregnancies have a favourable outcome and current practice of conservative management seems reasonable. Approximately 20% of our cohort progressed to type II or III throughout pregnancy and this highlights the importance of

regular ultrasound surveillance. In cases of expectant management parents should be adequately counselled regarding the risks of IUD (20% in our cohort) and its consequences for the co-twin. Guidance on the adequate timing of delivery of type I sFGR pregnancies remains to be determined.

Type II sFGR pregnancies have a much poorer prognosis and are typically characterized by progressive deterioration. The evaluation of prognostic factors may assist in triaging these pregnancies to determine those at increased risk of demise who would possibly benefit from therapeutic intervention. As well as conservative management and early delivery, treatment modalities include placental laser coagulation, selective reduction via cord occlusion or termination of pregnancy. We performed laser treatment in 8 cases of isolated sFGR. Due to small numbers, it is difficult to draw conclusions however the survival rate was much lower than pregnancies complicated with co-existing TTTS. To guide future clinical practice, we advocate the promotion of prospective multi-centre observational studies and the formation of a registry to delineate accurate criteria for predicting outcome in sFGR on which a subsequent RCT can be based.

Strengths and Limitations

The main limitations of this study include the number of pregnancies involved in the analysis, as well as its retrospective design, and therefore the risk of bias. To ensure adequate numbers for comparison, we performed the search over a 15-year period. This may be a limitation as clinical practice and protocols are subject to change over this time period. An example of this is the small number of pregnancies diagnosed with type III sFGR. The main reasons for this may be the lack of classification of sFGR prior to 2007 or the sampling methods used to interrogate the umbilical artery. The finding of significant relationships despite these numbers indicates the strength of the associations and the potential utility in a clinical setting. Cases that subsequently developed TTTS after an initial diagnosis of sFGR were included in order to give true representation of the clinical outcomes associated with pregnancies complicated by sFGR. Our study therefore provides information for comprehensive counselling of all growth restricted monochorionic twin pregnancies. When performing statistical analysis, we adjusted for confounding variables such as GA to ensure accurate analysis and interpretation of the data.

Conclusions

Pregnancies complicated by type II sFGR are diagnosed significantly earlier and are associated with increased risk of adverse perinatal outcomes when compared to type I. Co-existing TTTS has no significant impact on the perinatal outcome of the twin pregnancies diagnosed with either type I or type II sFGR. Earlier GA at diagnosis, type II sFGR and higher DV PI z scores are significantly and independently associated with increased risk of adverse perinatal outcome of the smaller twin.

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Table 1. Comparison of the maternal and pregnancy characteristics between twin pregnancies diagnosed with selective fetal growth restriction type I and type II

	Type I selective fetal growth restriction at diagnosis (n=66)	**Type II selective fetal growth restriction at diagnosis (n=38)**	**P value**
Antenatal variables			
Maternal age in years, median and IQR	32.50 (28.00-36.00)	31.00 (26.00-34.00)	0.137
Body-mass index in kg/m^2, median and IQR	24.40 (21.78-28.00)	22.40 (21.20-28.00)	0.313
Ethnicity			0.813
Caucasian, n (%)	46 (69.7)	26 (68.4)	
Asian, n (%)	7 (10.6)	7 (18.4)	
Black, n (%)	6 (9.1)	3 (7.9)	
Mixed, n (%)	3 (4.5)	1 (2.6)	
Not reported, n (%)	4 (6.1)	1 (2.6)	
Gestational age at diagnosis in weeks, median and IQR	21.50 (18.89-26.46)	19.64 (17.29-23.93)	0.012

Gestational age at delivery in weeks, median and IQR			
All twins	32.57 (30.68-34.79)	30.43 (28.00-34.00)	0.055
Both twins IUD	22.57 (22.21-23.29)	23.07 (22.32-26.82)	0.604
One twin IUD	31.14 (30.07-32.75)	34.21 (30.64-36.57)	0.306
Both twins liveborn	33.14 (31.86-35.14)	30.43 (29.00-32.86)	0.014
Conception, n (%)			0.390
Spontaneous conception	60 (90.9)	37 (97.4)	
Assisted reproduction	6 (9.1)	1 (2.6)	
Ultrasound and Doppler variables			
Estimated fetal weight centile (small twin) at diagnosis, median and IQR			
All twins	0.84 (0.16-4.49)	1.61 (0.05-6.27)	0.784
Both twins IUD	0.17 (0.14-0.49)	1.59 (0.03-7.10)	0.999
One twin IUD	0.31 (0.01-0.50)	1.72 (0.63-13.96)	0.144
Both twins liveborn	1.23 (0.24-4.67)	1.51 (0.04-3.59)	0.574
Estimated fetal weight centile (large twin) at diagnosis, median and IQR			
All twins	74.57 (54.79-93.18)	94.05 (73.24-99.74)	0.022
Both twins IUD	66.04 (65.34-78.17)	84.49 (33.59-98.84)	0.714
One twin IUD	56.67 (30.65-89.02)	92.75 (73.41-99.79)	0.144
Both twins liveborn	75.95 (57.15-93.75)	95.75(77.67-98.00)	0.102
Estimated fetal weight discordance in % at diagnosis, median and IQR	30.22(26.92-35.00)	32.93 (28.35-36.70)	0.103
Birthweight centile (small twin), median and IQR			
All twins	0.57 (0.02-5.99)	0.04 (0.00-2.45)	0.070

Both twins IUD One twin IUD Both twins liveborn	0.00 (0.00-0.00) 0.00 (0.00-0.22) 1.18 (0.04-6.44)	0.00 (0.00-0.00) 0.00 (0.00-0.00) 0.73 (0.01-2.63)	0.666 0.111 0.186
Birthweight centile (large twin), median and IQR All twins Both twins IUD One twin IUD Both twins liveborn	 49.59(28.75-74.12) 11.45 (11.45-11.45) 60.82 (51.82-84.00) 49.13 (29.36-73.01)	 50.34 (5.28-81.22) 1.34 (1.34-1.34) 63.38 (8.86-81.17) 49.55 (27.34-74.92)	 0.642 0.500 0.268 0.490
Ductus venosus pulsatility index Z score (small twin), median and IQR	0.78 (0.36-1.53)	2.43 (1.10-3.58)	<0.001
Ductus venosus pulsatility index Z (large twin), median and IQR	0.60 (-1.03 – 1.45)	0.77 (0.05-1.63)	0.258
Twin-to-twin transfusion syndrome, n (%)	23 (34.8)	16 (42.1)	0.599
Progression of Doppler findings, n (%)	13 (19.7)	13 (34.2)	0.158
Invasive therapy			
Fetoscopic laser ablation, n (%)	17 (25.8)	19 (50.0)	0.022
Amniodrainage, n (%)	2 (3.0)	0 (0.0)	0.686
Cord occlusion, n (%)	1 (1.5)	0 (0.0)	0.999
Perinatal outcome			
Interval between diagnosis and delivery in weeks, median and IQR	9.71 (5.35-13.85)	9.57 (5.28-13.00)	0.998
Intrauterine fetal death of the smaller twin, n (%)	7 (10.6)	15 (19.7)	0.001

Intrauterine fetal death of the bigger twin, n (%)	6 (9.1)	5 (6.6)	0.750
Survival of both twins, n (%)	53 (40.2)	19 (25.0)	0.002
Neonatal intensive care unit admission, n (%)	46 (34.8)	35 (46.1)	0.147
Neonatal death, n (%)	3 (2.3)	6 (7.9)	0.117

Table 2. Comparison of the maternal and pregnancy characteristics between twin pregnancies with selective fetal growth restriction type I and II according to whether they were complicated by intrauterine demise or not

	Pregnancies complicated by intrauterine death (n=25)	**Pregnancies not complicated by intrauterine death (n=79)**	**P value**
Antenatal variables			
Maternal age in years, median and IQR	28.00 (24.50-33.50)	32.00 (28.00-36.00)	0.045
Body-mass index in kg/m^2, median and IQR	24.55 (21.80-28.15)	23.40 (21.10-28.00)	0.293
Ethnicity			0.850
Caucasian, n (%)	18 (72.0)	54 (68.3)	
Asian, n (%)	3 (12.0)	11 (13.9)	
Black, n (%)	1 (4.0)	8 (10.1)	
Mixed, n (%)	2 (8.0)	2 (2.5)	
Not stated, n (%)	1 (4.0)	4 (5.1)	
Gestational age at diagnosis in weeks, median and IQR	17.43 (16.79-20.79)	21.57 (19.57-27.14)	<0.001

Gestational age at delivery in weeks, median and IQR	30.43 (25.29-34.07)	32.57 (30.57-34.68)	0.023
Conception, n (%)			0.867
Spontaneous conception	24 (96.0)	73 (92.4)	
Assisted reproduction	1 (4.0)	6 (7.6)	
Ultrasound and Doppler variables			
Estimated fetal weight centile (small twin) at diagnosis, median and IQR	0.80(0.14-6.48)	0.94 (0.09-4.03)	0.718
Estimated fetal weight centile (large twin) at diagnosis, median and IQR	91.50 (65.34-99.71)	78.20 (54.82-95.67)	0.236
Estimated fetal weight discordance in % at diagnosis, median and IQR	30.85 (26.55-36.74)	30.43 (27.34-35.47)	0.673
Birthweight centile (small twin), median and IQR	0.00 (0.00-0.22)	0.68 (0.01-3.90)	0.008
Birthweight centile (large twin), median and IQR	78.72 (27.47-91.70)	48.86 (27.02-72.94)	0.133
Ductus venosus pulsatility index Z score (small twin), median and IQR	2.02 (1.64-3.61)	0.85 (0.37-1.66)	0.003
Ductus venosus pulsatility index Z (large twin), median and IQR	1.45 (0.63-2.31)	0.08 (-0.80 – 0.97)	0.001
Twin-to-twin transfusion syndrome, n (%)	10 (40.0)	30 (38.0)	1.000
Progression of Doppler findings, n (%)	17 (68.0)	9 (11.4)	<0.001
Invasive therapy			

Fetoscopic laser ablation, n (%)	16 (64.0)	20 (25.3)	0.003
Amniodrainage, n (%)	0 (0.0)	3 (3.8)	0.761
Cord occlusion, n (%)	1 (4.0)	0 (0.0)	0.541
Perinatal outcome			
Interval between diagnosis and delivery in weeks, median and IQR	10.57 (5.64-15.42)	9.35 (4.25-13.64)	0.189
Neonatal intensive care unit admission, n (%)	7 (14.0)	119 (75.3)	<0.001
Neonatal death, n (%)	1 (2.0)	8 (5.1)	0.588

Table 2A. Comparison of the maternal and pregnancy characteristics between twin pregnancies with selective fetal growth restriction type I according to whether they were complicated by intrauterine demise or not

	Pregnancies complicated by intrauterine death (n=13)	**Pregnancies not complicated by intrauterine death (n=53)**	**P value**
Antenatal variables			
Maternal age in years, median and IQR	33.00 (25.00-36.00)	32.00 (28.00-36.00)	0.929
Body-mass index in kg/m^2, median and IQR	25.20 (22.25-28.20)	24.10 (21.95-27.40)	0.506
Ethnicity			0.071
Caucasian, n (%)	9 (69.2)	38 (71.7)	
Asian, n (%)	0 (0.0)	7 (13.2)	
Black, n (%)	1 (7.7)	5 (9.4)	
Mixed, n (%)	2 (13.4)	0 (0.0)	
Not stated, n (%)	1 (7.7)	3 (5.7)	
Gestational age at diagnosis in weeks, median and IQR	18.57 (17.00-21.29)	22.43 (19.71-28.14)	0.002

Gestational age at delivery in weeks, median and IQR	30.43 (26.50-31.93)	33.14 (31.86-35.14)	0.007
Conception, n (%)			0.252
Spontaneous conception	11 (84.6)	50 (94.3)	
Assisted reproduction	2 (15.4)	3 (5.7)	
Ultrasound and Doppler variables			
Estimated fetal weight centile (small twin) at diagnosis, median and IQR	0.19 (0.03-0.53)	1.23 (0.24-4.67)	0.028
Estimated fetal weight centile (large twin) at diagnosis, median and IQR	64.64 (41.88-90.31)	75.95 (57.15-93.75)	0.191
Estimated fetal weight discordance in % at diagnosis, median and IQR	33.33 (29.90-35.47)	30.08 (26.95-33.67)	0.478
Birthweight centile (small twin), median and IQR	0.00 (0.00-0.16)	1.18 (0.04-6.44)	0.005
Birthweight centile (large twin), median and IQR	57.82 (43.38-79.94)	49.13 (29.36-73.01)	0.542
Ductus venosus pulsatility index Z score (small twin), median and IQR	1.50 (0.20-1.70)	0.75 (0.36-1.35)	0.206
Ductus venosus pulsatility index Z (large twin), median and IQR	2.01 (1.51-2.89)	0.00 (-1.73 - -0.74)	<0.001
Twin-to-twin transfusion syndrome, n (%)	7 (53.8)	16 (30.2)	0.192
Progression of Doppler findings, n (%)	5 (38.4)	8 (15.1)	0.112
Invasive therapy			

Fetoscopic laser ablation, n (%)	9 (64.2)	8 (15.1)	<0.001
Amniodrainage, n (%)	0 (0.0)	2 (3.8)	0.999
Cord occlusion, n (%)	1 (7.7)	0 (0.0)	0.197
Perinatal outcome			
Interval between diagnosis and delivery in weeks, median and IQR	10.71 (6.28-13.28)	9.57 (4.00-13.85)	0.688
Neonatal intensive care unit admission, n (%)	6 (46.2)	46 (86.8)	<0.001
Neonatal death, n (%)	2 (15.4)	1 (1.8)	0.108

Table 2B. Comparison of the maternal and pregnancy characteristics between twin pregnancies with selective fetal growth restriction type II according to whether they were complicated by intrauterine demise or not

	Pregnancies complicated by intrauterine death (n=19)	**Pregnancies not complicated by intrauterine death (n=19)**	**P value**
Antenatal variables			
Maternal age in years, median and IQR	28.00 (26.00-33.00)	32.00 (27.00-36.00)	0.168
Body-mass index in kg/m^2, median and IQR	23.10 (21.35-27.90)	21.80 (20.60-29.13)	0.564
Ethnicity			0.879
Caucasian, n (%)	13 (68.4)	13 (68.4)	
Asian, n (%)	4 (21.1)	3 (15.8)	
Black, n (%)	2 (10.5)	1 (5.3)	
Mixed, n (%)	0 (0.0)	1 (5.3)	
Not stated, n (%)	0 (0.0)	1 (5.3)	
Gestational age at diagnosis in weeks, median and IQR	17.43 (16.86-20.29)	21.29 (19.43-27.14)	0.002

Gestational age at delivery in weeks, median and IQR	31.00 (25.75-34.75)	30.43 (29.00-32.86)	0.732
Conception, n (%)			1.000
Spontaneous conception	18 (94.7)	19 (100.0)	
Assisted reproduction	1 (5.3)	0 (0.0)	
Ultrasound and Doppler variables			
Estimated fetal weight centile (small twin) at diagnosis, median and IQR	1.72 (0.08-13.96)	1.51 (0.02-3.86)	0.682
Estimated fetal weight centile (large twin) at diagnosis, median and IQR	96.26 (72.72-99.79)	92.75 (77.13-98.16)	1.000
Estimated fetal weight discordance in % at diagnosis, median and IQR	30.85 (26.54-37.37)	35.14 (29.97-36.48)	0.145
Birthweight centile (small twin), median and IQR	0.00(0.00-0.00)	0.73 (0.01-2.98)	0.004
Birthweight centile (large twin), median and IQR	50.34 (1.34-81.22)	49.55 (18.95-82.44)	0.752
Ductus venosus pulsatility index Z score (small twin), median and IQR	3.37 (2.40-4.43)	1.46 (0.79-2.45)	0.003
Ductus venosus pulsatility index Z (large twin), median and IQR	1.06 (0.36-1.84)	0.40 (-0.21 – 1.23)	0.175
Twin-to-twin transfusion syndrome, n (%)	9 (47.4)	7 (36.8)	0.527
Progression of Doppler findings, n (%)	8 (42.1)	5 (26.3)	0.320
Invasive therapy			

Fetoscopic laser ablation, n (%)	12 (63.2)	7 (36.8)	0.137
Amniodrainage, n (%)	1 (5.3)	0 (0.0)	1.000
Cord occlusion, n (%)	0 (0.0)	0 (0.0)	NA
Perinatal outcome			
Interval between diagnosis and delivery in weeks, median and IQR	10.24 (5.28-17.35)	8.42 (5.00-10.71)	0.249
Neonatal intensive care unit admission, n (%)	12 (31.6)	30 (78.9)	<0.001
Neonatal death, n (%)	6 (15.8)	0 (0.0)	0.033

Table 3. Comparison of the maternal and pregnancy characteristics between twin pregnancies with selective fetal growth restriction (sFGR) according to the presence of twin-to-twin transfusion syndrome (TTTS)

	sFGR with TTTS (n=39)	**sFGR without TTTS (n=65)**	**P value**
sFGR type I (23 pregnancies with TTTS, 43 without TTTS)			
Interval between diagnosis and delivery in weeks, median and IQR	9.71 (5.35-13.85)	9.57 (5.28-13.85)	0.858
Intrauterine fetal death of the smaller twin, n (%)	2 (8.7)	5 (11.6)	1.000
Intrauterine fetal death of the bigger twin, n (%)	4 (17.4)	2 (4.7)	0.205
Survival of both twins, n (%)	16 (69.6)	37 (86.0)	0.200
Neonatal intensive care unit admission, n (%)	24 (52.2)	50 (58.1)	0.635
Neonatal death, n (%)	2 (4.3)	1 (1.2)	0.577
sFGR type II (16 pregnancies with TTTS, 22 without TTTS)			
Interval between diagnosis and delivery in weeks, median and IQR	9.57 (5.28-13.00)	9.71 (5.07-11.39)	0.828

Intrauterine fetal death of the smaller twin, n (%)	5 (31.2)	10 (45.5)	0.583
Intrauterine fetal death of the bigger twin, n (%)	3 (18.8)	2 (9.1)	0.701
Survival of both twins, n (%)	7 (43.8)	11 (50.0)	0.958
Neonatal intensive care unit admission, n (%)	28 (87.5)	20 (45.5)	<0.001
Neonatal death, n (%)	5 (15.6)	1 (2.3)	0.089

Table 4. Cox proportional hazards models to assess the importance of antenatal and ultrasound variables on the survival time of the smaller twin

Antenatal and ultrasound predictors	Hazard ratio (95% confidence intervals)	P value
All twin pregnancies complicated by selective fetal growth restriction (sFGR) *(n=104)*		
Maternal age in years	0.93 (0.86-1.01)	0.106
Body-mass index in kg/m^2	1.05 (0.94-1.18)	0.336
Conception method	0.94 (0.14-6.05)	0.953
Estimated fetal weight discordance	1.00 (0.93-1.09)	0.854
Twin-to-twin transfusion syndrome	1.27 (0.49-3.25)	0.619
Gestational age at diagnosis	0.70 (0.56-0.88)	0.002
Estimated fetal weight centile of smaller twin	1.01 (0.98-1.04)	0.403
Ductus venosus pulsatility index Z score	1.36 (1.12-1.65)	0.001
Type II sFGR	3.53 (1.37-9.07)	0.008
Type I sFGR (n=66)		
Maternal age in years	0.96 (0.84-1.09)	0.584

Body-mass index in kg/m^2	1.13 (0.97-1.30)	0.102
Conception method	1.44 (0.22-9.32)	0.697
Estimated fetal weight discordance	0.99 (0.86-1.14)	0.957
Twin-to-twin transfusion syndrome	1.09 (0.20-5.79)	0.914
Gestational age at diagnosis	0.48 (0.27-0.84)	0.010
Estimated fetal weight centile of smaller twin	1.02 (0.96-1.07)	0.452
Ductus venosus pulsatility index Z score	2.69 (0.98-7.32)	0.052
Type II sFGR (n=38)		
Maternal age in years	0.95 (0.83-1.10)	0.565
Body-mass index in kg/m^2	1.05 (0.87-1.20)	0.769
Conception method	0.62 (0.13-2.02)	0.995
Estimated fetal weight discordance	0.94 (0.83-1.07)	0.368
Twin-to-twin transfusion syndrome	0.90 (0.28-2.89)	0.863
Gestational age at diagnosis	0.86 (0.70-1.05)	0.153
Estimated fetal weight centile of smaller twin	1.00 (0.96-1.04)	0.872
Ductus venosus pulsatility index Z score	1.24 (1.00-1.55)	0.043