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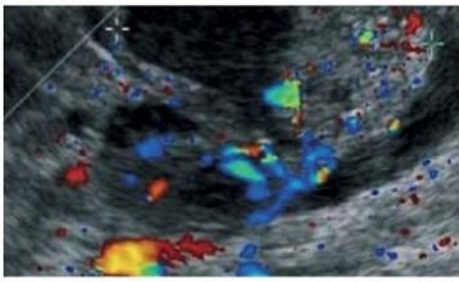

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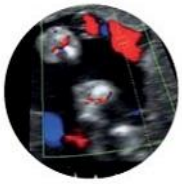

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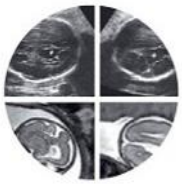

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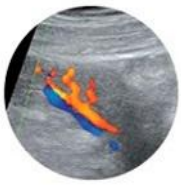

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Outcome of selective intrauterine growth restriction in monochorionic twin pregnancies at 16, 20 or 30 weeks according to the new consensus definition

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Short title: sIUGR in monochorionic twins

KEYWORDS: Monochorionic twin pregnancy, growth restriction, discordance, definition, outcome

CONTRIBUTION

What are the novel findings of this work?

Several definitions are used to define selective intrauterine growth restriction (sIUGR) in monochorionic twin pregnancies. Recently, a new consensus definition has been proposed to define sIUGR using a Delphi procedure. Although sIUGR has a better outcome than twin-twin transfusion syndrome (TTTS), the use of different definitions and reporting on tertiary referral cases make it difficult to estimate the true outcome.

What are the clinical implications of this work?

In an unselected cohort of monochorionic twin pregnancies followed from the first trimester, the survival rate of isolated sIUGR is more than 90%. The subsequent development of TTTS, absent or reversed end-diastolic flow in the umbilical artery of the smaller twin and the presence of a major anomaly adversely affect survival in sIUGR.

ABSTRACT:

OBJECTIVES: Recently, new criteria have been proposed to define selective intrauterine growth restriction (sIUGR) in monochorionic pregnancies based on the Delphi procedure. We report the outcome of sIUGR diagnosed according to this new consensus definition: either an estimated fetal weight (EFW) of 1 twin <3rd centile or 2 of the following: EFW or abdominal circumference of 1 twin <10th centile, EFW discordance ≥25% or umbilical artery pulsatility index of the smaller twin > 95th centile.

METHODS: We performed a retrospective analysis of the outcome of sIUGR diagnosed at 16, 20 or 30 weeks in a cohort of monochorionic diamniotic twin pregnancies followed from the first trimester. sIUGR was defined using the Delphi consensus definition. We used uni- and multivariate generalized estimated equation modelling to identify predictors of survival.

RESULTS: We analysed 675 pregnancies, of which 177 (26%) were diagnosed with sIUGR at 16, 20 or 30 weeks. The overall survival rate was 313/354 (88%) with in 146/177 (82%) survival of both twins, 21/177 (12%) survival of 1 and 10/177 (6%) loss of both twins. Subsequent TAPS developed in 6/177 (3%) and TTTS in 17/177 (10%). All TAPS fetuses survived. Survival in TTTS was 22/34 (65%) compared with 279/308 (91%) in isolated sIUGR (without TAPS or TTTS) ($p < 0.001$). Most sIUGR cases were type I (110/177; 62%) with a survival rate of 212/220 (96%) as compared with 12/22 (55%) in type II ($p < 0.001$) and 55/66 (83%) in type III ($p = 0.006$). The majority of sIUGR pregnancies (130/177; 73%) was first diagnosed at 16 and/or 20 weeks (early-onset) with survival of 221/260 (82%) as compared to 92/94 (98%) of sIUGR first diagnosed at 30 weeks (late-onset) ($p < 0.001$). A major anomaly in at least one twin was present in 28/177 (16%) sIUGR cases. For these pregnancies, survival was 39/56 (70%), compared to 274/298 (92%) for those without anomalies ($p < 0.001$). Subsequent TTTS (OR 0.18; 95% CI [0.06-0.52]), sIUGR type II (OR 0.06; 95% CI [0.02-0.24]) and type III (OR 0.21; 95% CI [0.07-0.60]) and a major anomaly

in one twin (OR 0.12; 95% CI [0.04-0.34]) independently determined survival, but not the time at first diagnosis.

CONCLUSIONS: Isolated sIUGR is associated with a 90% survival rate. The subsequent development of TTTS, absent or reversed end-diastolic flow in the umbilical artery of the smaller twin and the presence of a major anomaly adversely affect survival in sIUGR.

INTRODUCTION

Monochorionic twins are expected to be the same size, as they have the same genetic growth potential. However, external factors may affect their growth differently. As such, the placenta may be unequally divided or the net intertwin transfusion may be unidirectional, resulting in a weight difference between the twins.[1-3] For clinicians, it is crucial to know when this difference becomes clinically important. Whereas most studies use an estimated fetal weight (EFW) discordance of more than 20% or 25%[4-6], some define sIUGR as the growth of at least one twin below the 10th centile[7,8] and yet others use a combination of discordance and growth below the 10th centile.[9] This use of different definitions hampers comparison of data.

Recently, uniform criteria have been proposed to define sIUGR using the Delphi consensus process. According to this new definition, a monochorionic twin pregnancy is classified as having sIUGR if one of the twins has an EFW <3rd centile or if at least 2 out of the following 4 parameters are present: EFW of one twin <10th centile, abdominal circumference of one twin <10th centile, EFW discordance ≥25% and umbilical artery pulsatility index of the smaller twin >95th centile.[10]

This new Delphi consensus definition has not been validated in clinical practice yet. Therefore, we aim to report the outcome of sIUGR diagnosed at 16, 20 or 30 weeks in a cohort of unselected monochorionic twin pregnancies followed in our institution from the first trimester. We applied the new consensus definition for the diagnosis of sIUGR and determined any predictors of survival. We further aimed to document the prospective survival of sIUGR diagnosed at 16, 20 and 30 weeks. We also compared the accuracy and agreement of this new definition with that of using an EFW discordance of 20% or more to predict overall survival and birthweight discordance.

METHODS

Study population

We performed a retrospective cohort study of ongoing monochorionic diamniotic twin pregnancies diagnosed in the first trimester (11.0-14.0 weeks) between January 2002 and September 2018 at the University Hospitals Leuven. Monochorionic twin pregnancies are routinely referred to our center for a detailed ultrasound examination at 11-14, 16, 20, and 26-30 weeks of pregnancy. In addition to these 4 examinations, patients have a sonographic assessment at least every 2 weeks, either at our center or at the referring institution, detect twin-twin transfusion syndrome (TTTS) or twin-anemia polycythemia sequence (TAPS) in time, as per recommendation.[11] Patients explicitly referred in the first trimester for invasive testing or because of an anomaly, were not included. Part of this cohort was included in earlier publications.[1,4,5,11-15] The follow-up protocol used throughout the study period[15] remained unchanged, except that from 2008 onward, we changed the timing of the last evaluation from 26 weeks to 28-30 weeks to detect possible cases of spontaneous TAPS and from 2016 onward, we also measured umbilical venous diameters and flow. This study was approved by the ethics committee of our institution (S62017).

TTTS was defined as oligohydramnios in 1 twin (deepest vertical pool (DVP) <2 cm) and polyhydramnios in the other (DVP >8 cm before 20 weeks' gestation and DVP >10 cm from 20 weeks onwards). Patients with TTTS were offered fetoscopic laser coagulation of the placental anastomoses as first-line treatment.[16] Selective reduction by umbilical cord coagulation or by intrafetal radiofrequency ablation (RFA) was offered as an alternative, especially if one twin had an anomaly, was deemed to have a poor prognosis or as a back-up if laser coagulation of the entire equator was not feasible. Patients could also opt for termination of pregnancy if TTTS presented before viability.

TAPS was defined as a peak systolic velocity in the middle cerebral artery of >1.5 MoM in the anaemic donor and <1.0 MoM in the polycythemic recipient in the absence of TTTS or if the haemoglobin difference at birth was >8 g/dL with no or only minuscule anastomoses on placental injection studies.[17] Patients with TAPS and fetal decompensation were offered fetal therapy with the aim of postponing delivery until after 32 weeks.

Isolated sIUGR in our centre has traditionally been defined as ≥20% difference in EFW or ≥25% difference in birth weight in the absence of TTTS or TAPS.[1] Isolated sIUGR cases were classified according to the umbilical artery Doppler pattern in the smaller twin's cord at the last evaluation prior to intervention, demise or birth into type I, II or III.[18] Patients with continuous or intermittent absent end-diastolic flow in the smaller twin were offered weekly sonographic follow-up, irrespective of the discordance. In the pre-viable period, these patients were counselled about the option of selective reduction if there were signs of imminent demise of the smaller twin, such as a persistent reversed a-wave in the ductus venosus, severe oligohydramnios (deepest vertical pool (DVP) <2 cm) with oliguria[19] , hydrops or arrested fetal growth. When parents opted against selective reduction but wanted to protect the larger twin, laser coagulation of placental anastomoses was offered as an alternative if technically feasible. At 28 weeks, patients with continuous or intermittent absent end-diastolic flow in the smaller twin were eligible for in-patient monitoring with a non-stress test 3 times daily and biweekly ultrasound evaluation. Corticosteroids to improve lung maturity were administered on admission. Elective delivery was scheduled between 32 and 33 weeks after a repeat course of lung maturation.[20,21]

If one of the twins was diagnosed with a major anomaly, parents were offered the option of selective reduction. Also, if PPROM occurred before viability, patients had the choice between conservative management and termination of pregnancy.

Data collection

In spontaneous conceptions, gestational age (GA) was determined by the crown-rump length of the larger twin at the 11-14 weeks scan. In pregnancies resulting from in vitro fertilization, GA was defined using the date of conception in fresh cycles or embryonic age in frozen-thawed cycles. Maternal age, parity and mode of conception were recorded at the time of the first trimester scan. Ultrasound data were collected of the 16, 20, and 30 weeks' scan (range 14+0 to 18+6 weeks, 19+0 to 23+6 weeks and 26+0 to 31+6 weeks, respectively). Experienced sonographers performed the ultrasound scans on Voluson E10/E8/E6/730 (GE Healthcare, Chicago (IL), USA). Ultrasound reports were made using the Astraia software (Astraia software gmbh, Munich, Germany).

Biparietal diameter, head circumference, abdominal circumference and femur length were recorded at each visit. Estimated fetal weight (EFW) was calculated according to the Hadlock IV formula whenever possible.[22] In twin pairs where either head circumference or femur length was missing, the Warsof formula was used.[23] The EFW was then compared to the 3rd and 10th centile for GA[24] and the abdominal circumference was compared to the 10th centile for GA[25] according to Hadlock. Growth discordance was calculated using the following formula: $(EFW_{larger\ twin}–EFW_{smaller\ twin})/EFW_{larger\ twin}$. Also, we measured the umbilical artery Doppler pattern in all twins at each visit near the placental cord insertion. The pulsatility index of the umbilical artery of the smaller twin was compared to the 95th centile for GA[26], according to Acharya.

The obstetric and neonatal outcome data were collected after birth. The presence of major congenital anomalies was recorded according to the EUROCAT criteria. A major congenital anomaly was defined as incompatible with life, requiring major surgery for correction or producing significant dysfunction.[27]

Analyses of primary and secondary outcomes

As a primary outcome, we documented the overall survival rate (up to day 28 of life) and risk of loss of one or both twins of pregnancies diagnosed with sIUGR according to the Delphi consensus definition at 16, 20 or 30 weeks. Loss of one or both twins was defined as fetal or neonatal demise (up to day 28 of life). We also determined the prospective survival of sIUGR at each respective time point (16, 20 and 30 weeks) separately, in order to evaluate survival with advancing gestational age. We excluded cases diagnosed with single or double demise, TTTS or TAPS prior to or at these specific time points, because the diagnosis of isolated sIUGR implies an ongoing twin pregnancy and the absence of TTTS or TAPS.[14] More specifically, a pregnancy with sIUGR complicated by TTTS at 19 weeks was included in the 16 weeks analysis but no longer in the 20 weeks analysis as this pregnancy would no longer be diagnosed with isolated sIUGR. Likewise, twin pairs diagnosed with a lethal condition (such as bilateral renal agenesis) were also excluded from the time of diagnosis onward.

We further determined possible predictors of overall survival including maternal characteristics (age (years), parity (nulliparous *versus* multiparous) and mode of conception (spontaneous *versus* assisted)), subsequent TTTS *versus* no TTTS, type II or III *versus* type I sIUGR at the last ultrasound prior to intervention, demise or birth, time of first diagnosis (early-onset ≤20 weeks *versus* late-onset at 30 weeks) and the presence of a major anomaly. Predictors that were significant in univariate analysis ($p < 0.05$) were then further included in a multivariate analysis.

As secondary outcomes, we documented the need for fetal intervention and the birth characteristics of sIUGR diagnosed at each time point. We also compared the accuracy of the Delphi consensus definition with that of using an EFW discordance of ≥20% to predict loss of one or both twins and to predict a birth weight discordance of ≥25%. Birth weight discordance was calculated in cases with double survival or double loss only. Finally, we

determined the agreement between the Delphi consensus definition and EFW discordance of ≥20%

For the analyses on a fetal level (survival), we used uni- and multivariate generalized estimated equation modelling to account for the clustering of twins in a twin pregnancy. For the analysis on a pregnancy level (loss one or both, survival of one and both, gestational age, discordance, birthweight larger and smaller twin), we compared categorical outcomes using the Chi-square or Fisher's Exact test, as appropriate. For continuous outcomes, we calculated medians and interquartile ranges and conducted the Kruskal-Wallis test with pairwise comparisons using Dunn's procedure to detect differences between groups.

Diagnostic accuracy was assessed by constructing receiver operating characteristics (ROC) curves. We further compared the areas under the curve (AUC) using the test of equality of ROC areas. We documented the agreement between both definitions using Cohen's kappa.

All analyses were performed using STATA 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). A 2-sided P-value of $P < .05$ was considered statistically significant.

RESULTS

678 monochorionic diamniotic twins were eligible for inclusion. Outcome data were not available for 3 patients who were lost to follow-up. The demographic details and pregnancy outcomes of the remaining 675 patients are specified in Table 1. The patient flow is illustrated in Figure 1. Mean GA at the time of 16 weeks' scan was 16.5 ± 0.8 weeks, 20.6 ± 0.9 weeks at the 20 weeks' scan and 29.4 ± 1.5 weeks at the 30 weeks' scan. The Hadlock formula was used to calculate EFW in nearly all cases, except for 19 twin pairs at 16 weeks (3%) and 10 twin pairs at 20 weeks (2%), where the Warsof formula was used. Hadlock was used in all cases at 30 weeks.

Of the 675 pregnancies included in this study, 177 (26%) were diagnosed with sIUGR at some time in pregnancy according to the Delphi consensus definition and overall survival was 313/354 (88%) with in 146/177 (82%) survival of both twins, 21/177 (12%) survival of 1 and 10/177 (6%) loss of both twins. (Table 2). Loss of one or both twins was present in 31/177 (18%) of sIUGR cases. TAPS occurred in 6/177 (3%), whereas 17 out of 177 (10%) developed subsequent TTTS. All TAPS twins survived and were born after 32 weeks. Survival of sIUGR cases that subsequently developed TTTS was 22/34 (65%), while survival for those who did not develop TAPS or TTTS (isolated sIUGR) was 279/308 (91%) ($p < 0.001$).

The majority of sIUGR cases were type I (110/177; 62%) and these had the highest survival rate. In 44 of 177 sIUGR pregnancies (25%) the smaller twin had continuous or intermittent absent or reversed end-diastolic umbilical artery flow, which was classified as sIUGR type II in 11 and type III in 33 cases with survival rates of 55% (12/22) and 83% (55/66), respectively ($p = 0.006$). Loss of one or both occurred in 7/11 (64%) Type II cases and 9/33 (27%) Type III cases ($p = 0.067$)

An intervention was performed in the majority of cases with subsequent TTTS (82%) and with sIUGR type II (55%), while it was performed in 21% of cases with type III sIUGR and rarely in type I (2%) ($p < 0.001$). All isolated sIUGR cases that underwent intervention (15/154; 10%) were either complicated by co-existing anomalies (9 out of 15) or showed signs of imminent demise of the growth-restricted twin (6 out of 15) (Supplementary Table S1).

The characteristics of pregnancies with early- and late-onset sIUGR are shown in Table 3. The majority of sIUGR pregnancies (130/177; 73%) were first diagnosed at 16 and/or 20 weeks (early-onset) with survival of 221/260 (82%). When sIUGR was first diagnosed at 30 weeks (late-onset), the survival rate was 92/94 (98%). Of the 130 cases with early-onset sIUGR, 38 (29%) were type II or III at first diagnosis. In contrast, only 2 out of 47 late-onset cases (4%) presented as type III and none were type II ($p = 0.001$). In 6/38 (16%) early-onset cases with abnormal umbilical artery Doppler in the smaller twin, the type III Doppler pattern normalized, and the pregnancies continued as type I. All cases that were diagnosed as type II remained so. In contrast, 13/92 early-onset cases (14%) were classified as type I at first diagnosis but progressed to type II (4 cases) or III (9 cases) later on. Of the 45 late-onset cases with type I, only 1 (2%) progressed to type III.

A major anomaly in at least one twin was present in 28 out of 177 (16%) sIUGR cases *versus* 34/498 (7%) of pregnancies without sIUGR ($p < 0.001$). For fetuses from pregnancies with sIUGR and a major anomaly in at least one twin, the survival rate was 39/56 (70%), compared with 274/298 (92%) for those without major anomalies ($p < 0.001$). All major anomalies occurred in pregnancies with early-onset sIUGR, except for a critical pulmonary artery stenosis in a larger twin that occurred in a pregnancy with late-onset sIUGR. Therefore, 27/130 (21%) twin pairs with early-onset sIUGR also had a major anomaly. In all instances, only one was affected, except for one pregnancy where both had symptomatic

cytomegalovirus infection. The smaller twin was affected in 21 out of the 26 remaining cases (81%).

Univariate analysis revealed that maternal characteristics such as age, parity and mode of conception were not associated with survival, in contrast to subsequent TTTS, Type II and III sIUGR, early-onset sIUGR and the presence of a major congenital anomaly. In multivariate analysis, subsequent TTTS, type II and III sIUGR, and the presence of a major anomaly remained significantly associated with decreased survival (Table 4).

The prospective outcomes per time point are illustrated in Supplementary Tables S2 to S4. At 16, 20 and 30 weeks, 89, 83 and 102 cases were diagnosed with sIUGR using the Delphi consensus definition and the prospective survival rate was 80%, 92% and 98%, respectively. At 20 weeks, the survival for type II-III sIUGR was 51/56 (91%) as compared with 41/62 (66%) at 16 weeks. The proportion of cases with subsequent TTTS decreased from 16% to 7% and 1% at 16, 20 and 30 weeks, respectively.

Of the 675 included pregnancies, 106 (16%) were complicated by the loss of one or both twins. A birth weight discordance of ≥25% was observed in 71 out of 600 (12%) twin pairs where both were either live born or stillborn. Both the Delphi consensus definition and a ≥20% discordance cut-off were significantly associated with loss of one or both twins and birth weight discordance of ≥25% at 16, 20 and 30 weeks (Table 5). The AUC between both definitions did not differ and was poor (AUC between 0.52-0.64) to predict loss of one or both twins and fair (AUC between 0.70-0.82) to predict a birth weight discordance of ≥25% (Table 6). Only at 30 weeks, the ≥20% cut-off had a higher AUC (0.816) than the Delphi consensus definition (0.753, $p = 0.025$) to predict birthweight discordance of ≥25% (Figure 2). The agreement between both definitions was moderate to good (kappa's coefficient between 0.58-0.64) at all time points.

DISCUSSION

Our series is the first to report on the outcome of sIUGR according to the new Delphi consensus definition in an unselected cohort of monochorionic twins. Isolated sIUGR is associated with a more than 90% survival rate. Subsequent TTTS, absent or reversed end-diastolic flow in the umbilical artery of the smaller twin and the presence of a major anomaly adversely affect survival in sIUGR, but not the timing of onset. Nevertheless, as pregnancy progresses, the survival improves from 80% at 16 weeks to 98% at 30 weeks.

The development of TTTS significantly decreased survival. This is in contrast with the study by Monaghan et al. where there was no significant difference in survival between isolated sIUGR (86%) and sIUGR complicated by TTTS (70%).[28] However, they report on a referral population, which likely introduces a bias towards more severe cases. They observed 86% double survival in sIUGR type I, compared to our 95%, which is more in line with other studies.[18,29] It is counterintuitive to assume that subsequent TTTS will not worsen the outcome. There is consensus that TTTS requires an intrauterine intervention and is the main cause of mortality in monochorionic twins[15], whereas isolated sIUGR is mostly managed expectantly and has a more "benign" course. In our study, 10% of sIUGR pregnancies developed TTTS. Unfortunately, we cannot identify the sIUGR pregnancy that will ultimately progress to TTTS.[30-33] Therefore, it is important to caution parents that the outcome of sIUGR is expected to be good, provided no TTTS develops.

Umbilical artery Doppler in the smaller twin also affects survival: from 96% in type I sIUGR, over 83% in type III to 55% in type II. Type II and type III Doppler are independent predictors of survival. As known, expectant management of type II-III sIUGR is associated with a survival rate of 50-85%.[7,19] In cases treated with laser therapy, overall survival is 53-64%[7,34], while this is around 47% for pregnancies undergoing cord occlusion.[6] In our study, 70% of sIUGR type II-III cases were managed expectantly.

Major congenital anomalies were more frequent in the sIUGR group and were associated with lower survival. About a third (9/28) underwent a fetal intervention, mostly selective reduction. One in 5 pregnancies with early-onset sIUGR had a major anomaly in at least one twin, while this was rarely the case in late-onset sIUGR. Therefore, the diagnosis of early-onset sIUGR should prompt a detailed anatomic examination of the smaller twin.

Timing of onset of sIUGR was not independently associated with survival, but analysis of prospective survival at 16, 20 and 30 weeks showed improving survival rates. This is probably related to loss of the most severe cases. Previous studies focused on the outcome of sIUGR, irrespective of gestational age.[18,29]

A major strength of our series is that we assessed the Delphi consensus definition in a cohort of unselected monochorionic twin pregnancies. Others have used different definitions of sIUGR and reported outcome of tertiary referral centers, usually from the time of referral, making it difficult to compare series and likely introducing selection bias towards more severe cases.[4-9] We did not exclude cases with subsequent TTTS, since clinicians do not know which sIUGR pregnancies will eventually develop TTTS. This is an important difference compared to other studies that exclude TTTS cases and therefore give more optimistic survival estimates.[35,36] Likewise, we specifically chose to only exclude lethal anomalies, from the time of diagnosis onwards. In clinical practice, not all anomalies are picked up in early pregnancy. Another strength of our study is that we adhered to a uniform follow-up protocol for all monochorionic diamniotic twins with extensive Doppler measurements.

A weakness of our study is the low number of type II sIUGR cases: only 6% of isolated sIUGR pregnancies and 1.5% of our total population. Gratacos et al. reported that 22% of sIUGR patients had type II Doppler, but they studied patients between 16 and 28 weeks, while sIUGR that was picked up at 30 weeks in our series, was mostly type I and

never type II. Furthermore, they reported on a tertiary referral population, resulting in a low fraction of type I cases (29%).[18] Likewise, Ishii et al. reported a prevalence of type II Doppler of 54% in sIUGR cases referred to tertiary care before 26 weeks.[19] It is reasonable to assume that cases with persistent abnormal Doppler are more easily referred. Also, type III is often misclassified as type II, as the intermittent Doppler anomalies are missed when sampling is not done at the site of placental cord insertion.

Another potential comment is that we did not exclude the 10% of sIUGR cases that underwent a fetal intervention. Some may feel that our analysis is therefore biased, as performing selective reduction automatically reduces survival. However, 9 out of these 15 cases had major anomalies. In the remaining 6, demise was deemed imminent. Parents are usually counselled about the option of intrauterine surgery in these scenarios. Nevertheless, the survival rate of isolated sIUGR in our cohort was still 91%. Finally, our series does not address the neonatal and long-term neurodevelopmental outcome, which is obviously of crucial importance as well.

We showed that there was no difference between the new Delphi consensus definition of sIUGR and a ≥20% discordance in EFW to predict loss of one or both twins and birth weight discordance, except at 30 weeks when the 20% discordance cut-off was more accurate. However, both methods remain poor in predicting loss of one or both twins. This may be because only 17 out of all 82 TTTS cases occurred in sIUGR pregnancies and TTTS is the main cause of loss in monochorionic pregnancies.[15] As the Delphi consensus definition requires reference curves and the assessment of multiple variables, the 20% cut-off may be easier to use in daily clinical practice to select cases for increased surveillance. The Delphi consensus definition could then be reserved for uniform outcome reporting in a research setting.

CONCLUSION

Our study shows that isolated sIUGR, as defined by the new consensus definition, is associated with a more than 90% survival rate. Subsequent TTTS, absent or reversed end-diastolic flow in the umbilical artery of the smaller twin and the presence of a major anomaly, but not the timing of onset, independently determine the survival in sIUGR.

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FIGURE LEGENDS

Figure 1: Flowchart illustrating the patients that were included for the analysis of the overall survival of sIUGR diagnosed at 16, 20 or 30 weeks (bold) and for the analysis of the prospective survival at 16, 20 or 30 weeks (italic)

* Lethal anomalies excluded at 16 weeks were 2 cases with anencephaly, 1 case with caudal regression syndrome, 1 case with bilateral renal agenesis, 1 case with hypoplastic left heart syndrome and 1 case with mosaic triploidy and trisomy 2. All these fetuses had a normal co-twin. At 20 weeks, an additional case with bilateral multicystic kidney dysplasia in 1 twin was identified and excluded.

TTTS = twin-twin transfusion syndrome;

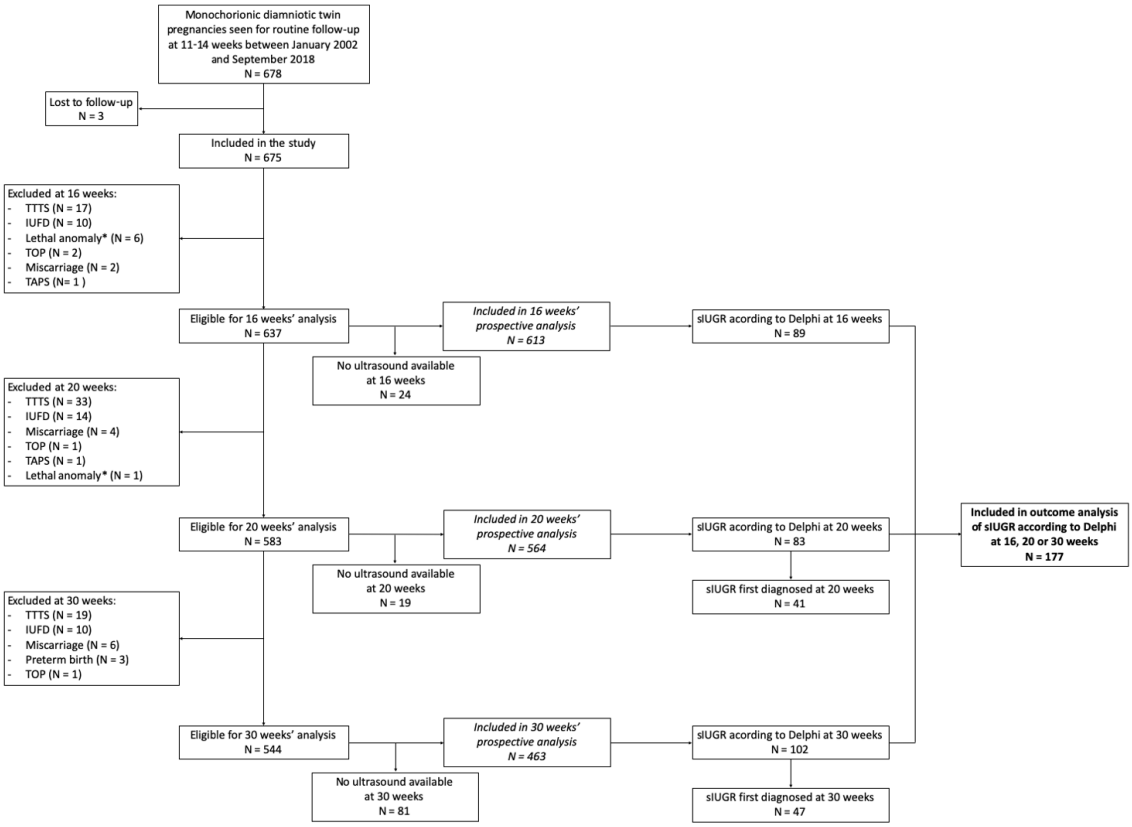
IUFD = intra-uterine fetal demise;

TOP = termination of pregnancy;

TAPS = twin anemia polycythemia sequence

Figure 2: Receiver operating characteristics curve for the prediction of birth weight discordance ≥ 25%

AUC = area under the curve



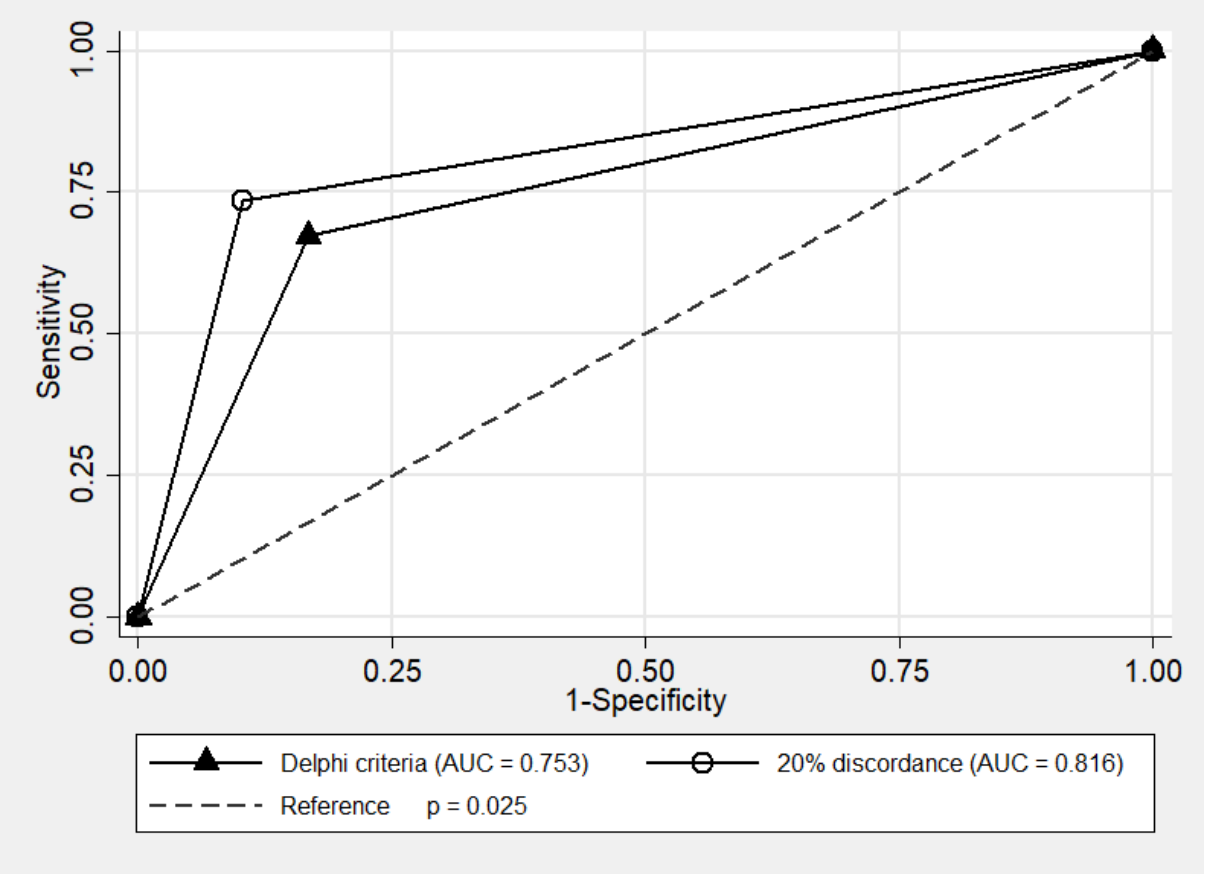


Table 1: Demographic details and pregnancy outcome of the cohort

Demographic details (N = 675 pregnancies)		
	Maternal age (years)	30 ± 0.2 years
	Nulliparous	316/675 (47%)
	Spontaneous conception	573/675 (85%)
	Insemination	2/675 (0%)
	Ovulation induction ± insemination	20/675 (3%)
	IVF or ICSI	80/675 (12%)
Fetal complications (N = 675 pregnancies)		
	IUFD of 1 or both twins	75/675 (11%)
	Twin-twin transfusion syndrome	82/675 (12%)
	Twin anemia-polycythemia sequence	19/675 (3%)
	Loss of one or both twins	106/675 (16%)
Congenital anomalies (N = 675 pregnancies, 1350 fetuses)		
	Pregnancies with major congenital anomalies† in at least 1 twin	62/675 (9%)
	Fetuses with major congenital anomalies [1]	68/1350 (5%)
Gestational age at birth (N = 675 pregnancies, missing data in 1)		
	Termination of pregnancy < 24 weeks	9/674 (1%)
	Miscarriage < 24 weeks	14/674 (2%)
	Double IUFD < 24 weeks	17/674 (3%)
	Delivery 24w – 27w6d	19/674 (3%)
	Delivery 28w – 31w6d	82/674 (12%)
	Delivery 32w – 33w6d	95/674 (14%)
	Delivery 34w – 36w6d	325/674 (48%)
	Delivery ≥ 37w	113/674 (17%)
Mode of delivery after 24 weeks (N = 635 pregnancies, missing data in 9)		
	Vaginal delivery	252/626 (40%)
	Cesarean section	365/626 (58%)
	Cesarean section for second twin	9/626 (1%)
Birth weight of liveborn infants after 24 weeks (N = 1208 neonates, missing data in 10)		
	< 1500g	158/1198 (13%)
	1500-2499g	686/1198 (57%)
	> 2500g	354/1198 (30%)
	Birth weight discordance of ≥ 25% in pregnancies with 2 livebirths (N = 579, missing data in 5)	64/574 (11%)
Neonatal complications in livebirths after 24 weeks (N = 1208 neonates)		
	Neonatal death	14/1208 (1%)
	5-minute Apgar score < 7 (missing values in 43)	44/1165 (4%)
	Endotracheal intubation and ventilation (missing data in 60)	101/1148 (9%)
	Sepsis (missing data in 60)	47/1148 (4%)

Variables are expressed as means ± standard deviation and proportions (%). IVF = in vitro fertilization; ICSI = intra-cytoplasmic sperm injection; IUFD = intra-uterine fetal demise [1] Major congenital anomalies were defined according to the Eurocat criteria (27).

Table 2: Overall survival of sIUGR according to the Delphi consensus definition at 16, 20 or 30 weeks.

	N = 177[1]						
	sIUGR type I	**sIUGR type II**		**sIUGR type III**		**Subsequent TTTS**	
	N=110 (62%)	**N=11 (6%)**	**p-value**	**N=33 (19%)**	**p-value**	**N=17 (10%)**	**p-value**
Overall survival[2]	212/220 (96%)	12/22 (55%)	**< 0.001**	55/66 (83%)	0.006	22/34 (65%)	**< 0.001**
Survival larger twin	107/110 (97%)	7/11 (64%)	**0.001**	31/33 (94%)	0.326	13/17 (76%)	0.006
Survival smaller twin	105/110 (95%)	5/11 (45%)	**< 0.001**	24/33 (73%)	**< 0.001**	9/17 (53%)	**< 0.001**
Survival of both	105/110 (95%)	4/11 (36%)	**< 0.001**	24/33 (73%)	**< 0.001**	7/17 (41%)	**< 0.001**
Survival of one	2/110 (2%)	4/11 (36%)	**< 0.001**	7/33 (21%)	**< 0.001**	8/17 (47%)	**< 0.001**
Loss of both	3/110 (3%)	3/11 (27%)	0.010	2/33 (6%)	0.326	2/17 (12%)	0.133
Loss of one or both	5/110 (5%)	7/11 (64%)	**< 0.001**	9/33 (27%)	**< 0.001**	10/17 (59%)	**< 0.001**
Interventions	2/110 (2%) (1 CO, 1 laser)	6/11 (55%) (3 CO, 2 laser, 1 RFA)	**< 0.001**	7/33 (21%) (5 CO, 1 RFA, 1 TOP)	**< 0.001**	14/17 (82%) (9 laser, 4 CO, 1 RFA)	**< 0.001**
Survival expectant management[2]	210/216 (97%)	6/10 (60%)	0.004	49/52 (94%)	0.430	4/6 (67%)	**0.001**
GA at birth (weeks)	34.6 [32.5 –	30.0 [26.5 –	0.012	32.0 [29.4 –	**<**	32.5 [29.6 –	0.061

	36.1]	38.0]		32.4]	**0.001**	36.2]	
Birth before 32 weeks	17/110 (15%)	7/11 (64%)	**0.001**	16/33 (48%)	**< 0.001**	7/17 (41%)	0.019
Discordance at birth (%)[3]	16 [8 – 23]	38 [36 – 41]	**0.001**	27 [20 – 32]	**< 0.001**	9 [4 – 26]	0.260
Birth weight larger twin (gram)[3]	2140 [1875 – 2440]	1200 [1120 – 1355]	**< 0.001**	1643 [1280 – 2000]	**< 0.001**	1800 [1260 – 2100]	0.039
Birth weight smaller twin (gram)[3]	1760 [1500 – 2080]	735 [680 – 888]	**< 0.001**	1175 [1000 – 1345]	**< 0.001**	1540 [1205– 2000]	0.094

Data are expressed as medians [interquartile range] or proportions (%). Analyses are on a pregnancy level unless stated otherwise. To compare the groups, sIUGR type I was set as a reference. Numbers in bold indicate a p-value of ≤ 0.001 and are considered significant after Bonferroni correction for multiple comparisons. TTTS = twin-to-twin transfusion syndrome; sIUGR = selective intra-uterine growth restriction; GA = gestational age; CO = cord occlusion; RFA = radiofrequency ablation; TOP = termination of pregnancy [1] 6/177 patients developed TAPS and were not included. All 12 survived and were born after 32 weeks; [2] Analysis on a fetal level with correction for clustering of twins within mothers; [3] Calculated in live born twin pairs.

Table 3: Characteristics of early- and late-onset sIUGR

	N = 177		
	Early-onset sIUGR (N=130; 73%)	**Late onset sIUGR (N=47; 27%)**	**P-value**
Overall survival[1]	221/260 (82%)	92/94 (98%)	**0.040**
Survival larger twin	118/130 (91%)	46/47 (98%)	0.189
Survival smaller twin	103/130 (79%)	46/47 (98%)	**0.002**
Survival of both	100/130 (77%)	46/47 (98%)	**< 0.001**
Survival of one	21/130 (16%)	0/47 (0%)	**0.001**
Loss of both	9/130 (7%)	1/47 (2%)	0.294
Loss of one or both	30/130 (23%)	1/47 (2%)	**< 0.001**
sIUGR type II-III prior to intervention, demise or birth	41/130 (32%)	3/47 (6%)	**< 0.001**
Subsequent TTTS	17/130 (13%)	0/47 (0%)	**0.007**
Subsequent TAPS	4/130 (3%)	2/47 (4%)	0.657
Interventions	29/130 (22%)	0/47 (0%)	**< 0.001**
Survival expectant management[1]	189/202 (94%)	92/94 (98%)	0.288
GA at birth (weeks)	33.6 [31.2 – 36.0]	34.6 [32.5 – 36.0]	0.055
Birth before 32 weeks	42/130 (32%)	5/47 (11%)	**0.004**
Discordance at birth (%)[2]	22 [12 – 31]	13 [6 – 19]	**< 0.001**
Birth weight larger twin (gram)[2]	2045 [1640 – 2310]	1995 [1680 – 2270]	0.886
Birth weight smaller twin (gram)[2]	1540 [1220 – 2000]	1700 [1495 – 2020]	0.049

Data are expressed as medians [interquartile range] or proportions (%). Analyses are on a pregnancy level, unless stated otherwise. Numbers in bold indicate a p-value of ≤ 0.05 and are considered significant. TTTS = twin-to-twin transfusion syndrome; TAPS = twin anemia polycythemia sequence; GA = gestational age; sIUGR = selective intra-uterine growth restriction classified according to the Delphi consensus criteria. [1] Analysis on a fetal level with correction for clustering twins within mothers; [2] Calculated in live born twin pairs.

Table 4: Univariate and multivariate analysis of predictors for fetal survival in pregnancies that were screen positive according to the Delphi criteria at 16, 20 or 30 weeks (N=354)

Predictor	OR in univariate analysis (95% CI)	P-value in univariate analysis	OR in multivariate analysis (95% CI)	P-value in multivariate analysis
Maternal age	0.96 [0.87 – 1.07]	0.482	-	-
Assisted conception	0.48 [0.19 – 1.20]	0.115	-	-
Nulliparity	1.39 [0.64 – 3.05]	0.404	-	-
Early diagnosis	0.12 [0.02 – 0.93]	0.043	0.49 [0.06 – 4.16]	0.514
Subsequent TTTS	0.18 [0.08 – 0.42]	< 0.001	0.18 [0.06 – 0.52]	0.002
UA doppler in the smaller twin prior to birth, intervention or demise				
- **Type I**	1.00	-	1.00	-
- **Type II**	0.07 [0.02 – 0.21]	< 0.001	0.06 [0.02 – 0.24]	< 0.001
- **Type III**	0.23 [0.10 – 0.58]	0.002	0.21 [0.07 – 0.60]	0.003
Major anomaly[1]	0.12 [0.05 – 0.29]	< 0.001	0.12 [0.04 – 0.34]	< 0.001

OR = odds ratio; CI = confidence interval; sIUGR = selective intra-uterine growth restriction; TTTS = twin-twin transfusion syndrome; UA = umbilical artery. The analysis was adjusted for the clustering of twins within mothers**.** [1] Major congenital anomalies are defined according to the Eurocat criteria (27).

Table 5: Prediction of sIUGR according to the Delphi consensus definition and the cut-off of ≥ 20% discordance in estimated fetal weight

		16 weeks	16 weeks RR (95%CI)	20 weeks	20 weeks RR (95%CI)	30 weeks	30 weeks RR (95%CI)
Delphi consensus definition	**Screen positive vs negative**						
	- Incidence	89/612 (15%) versus 523/612 (85%)		83/563 (15%) versus 480/563 (85%)		102/458 (22%) versus 356/458 (78%)	
	- Loss of one or both	27/89 (30%) versus 47/523 (9%)	4.4 (2.56 – 7.59)	10/83 (12%) versus 29/480 (6%)	2.13 (1.00 – 4.56)	3/102 (3%) versus 6/356 (2%)	1.77 (0.43 – 7.20)
	- Birth weight discordance ≥ 25%[1]	31/68 (46%) versus 34/491 (7%)	6.58 (4.35 – 9.97)	37/75 (49%) versus 24/464 (5%)	9.54 (6.07-14.99)	33/100 (33%) versus 17/350 (5%)	6.79 (3.95 – 11.67)
≥ 20% discordance	**Screen positive vs negative**						
	- Incidence	92/612 (15%) versus 520/612 (85%)		81/563 (14%) versus 482/563 (86%)		79/458 (17%) versus 379/458 (83%)	
	- Loss of one or both	29/92 (32%) versus 45/520 (9%)	4.86 (2.84 – 8.30)	11/81 (14%) versus 28/482 (6%)	2.55 (1.21 – 5.35)	2/79 (3%) versus 7/379 (2%)	1.38 (0.28 – 6.77)
	- Birth weight discordance ≥ 25%[1]	36/68 (52%) versus 29/491 (6%)	8.96 (5.90 – 13.62)	33/73 (45%) versus 28/466 (6%)	7.52 (4.85 – 11.67)	36/77 (47%) versus 14/373 (4%)	12.46 (7.07 – 21.95)
Cohen's kappa coefficient for agreement		0.58 (95% CI 0.49-0.67)	-	0.61 (95% CI 0.51-0.70)	-	0.64 (95%CI 0.55-0.73)	-

Variables are expressed as proportions (%) or coefficients (95% confidence interval (CI)). RR = relative risk. [1] Calculated in twin pairs where both were live born or both were stillborn.

Table 6: Area under the curve for receiver operating characteristics curves in the prediction of adverse outcome and ≥ 25% birth weight discordance

Outcome	Gestational age	AUC for the Delphi consensus definition and 95% CI	AUC for 20% discordance	P-value
Loss of one or both	16 weeks	0.625 (0.568 – 0.682)	0.637 (0.580 – 0.695)	0.577
	20 weeks	0.559 (0.488 – 0.623)	0.574 (0.501 – 0.647)	0.653
	30 weeks	0.556 (0.392 – 0.721)	0.525 (0.380 – 0.670)	0.580
Birth weight discordance ≥ 25%[1]	16 weeks	0.709 (0.645 – 0.772)	0.753 (0.691 – 0.816)	0.152
	20 weeks	0.774 (0.710 – 0.837)	0.738 (0.673 – 0.803)	0.229
	30 weeks	0.753 (0.684 – 0.822)	0.816 (0.752 – 0.880)	0.025

Variables are expressed as area under the curve (AUC) (95% confidence interval (CI)). [1] Calculated in twin pairs where both were live born or both were stillborn