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Growth patterns of monochorionic twin pregnancies complicated by type-3 selective fetal growth restriction

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Contribution

What are the novel findings of this work?

In type 3 sFGR, abnormal fetal growth of the smaller twin is evident from very early in pregnancy while the larger twin's weight remains normal throughout pregnancy.
Intertwin growth discordance remains stable across gestation.
Normalization of umbilical artery Dopplers results in improved growth of the smaller, but not the larger, twin.

What are the clinical implications of this work?

Type 3 sFGR is a diagnosis made early in the second trimester, since the smaller twin is abnormally small already at 16 weeks of gestation.
Because the dynamic flow pattern in the umbilical artery in these pregnancies directly impacts fetal growth, longitudinal umbilical artery Doppler monitoring is essential for risk stratification.

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Abstract

Objective Little is known regarding fetal growth patterns of monochorionic twins complicated by type 3 selective fetal growth restriction (sFGR). We aimed to assess fetal growth and Doppler patterns in type 3 sFGR across gestation and evaluate the effect of changing Doppler flow patterns on growth and intertwin weight discordance.

Methods We retrospectively reviewed all type 3 sFGR pregnancies managed at nine fetal centers over a 12-year time period. Higher-order multiples, major fetal anomalies, or other monochorionicity-related complications at initial presentation were excluded. Estimated fetal weights (EFW) for each twin pair in each of five gestational age blocks (16-20, 21-24, 25-28, 29-32 and above 32 weeks' gestation) were reviewed and compared to singleton growth as well as uncomplicated monochorionic twin growth. EFW and intertwin growth discordance were compared between pregnancies with normalization of umbilical artery Dopplers of the smaller twin and those with persistently abnormal Dopplers .

Results 328 pregnancies (656 fetuses) met the study criteria. In type 3 sFGR, the smaller twin was smaller than the average singleton fetus (z-score ranging from -1.52 at 16 weeks to -2.7 at 36 weeks) and the average monochorionic twin (z-score ranging from -1.73 at 16 weeks to -1.49 at 36 weeks), throughout the entire pregnancy, while the larger twin was larger than an average singleton fetus until 22 weeks' gestation and similar in weight to an average monochorionic twin throughout gestation. As pregnancy advanced, both twin's growth velocities decreased with the larger twin remaining appropriately grown and the smaller twin becoming more growth restricted. Intertwin growth discordance remained stable throughout gestation. In multivariable longitudinal modelling, normalization of fetal Dopplers was associated with better growth of the smaller twin (p=0.002) but not the larger twin (p=0.1), without affecting the intertwin growth discordance (p=0.08).

Conclusion Abnormal fetal growth of the smaller twin in type 3 sFGR was evident from early in pregnancy, while the larger twin's growth remained normal throughout gestation. Normalization of Dopplers resulted in improved fetal growth of the smaller twin.

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Introduction

Approximately 7-14% of all monochorionic twin pregnancies [1,2] are complicated by selective fetal growth restriction (sFGR), defined as an intertwin estimated fetal weight (EFW) discordance exceeding 25% and one twin having an EFW below the 10th percentile. One-fifth of all sFGR cases is categorized as type 3 [3], which is characterized by intermittent absent or reversed end-diastolic flow (iA/REDF) in the umbilical artery of the smaller fetus and unequal placental sharing with large intertwin artery-to-artery anastomoses (AAA) [4]. Although the outcome of type 3 sFGR is considered intermediate when compared with type I (normal umbilical artery Doppler) and type II sIUGR (persistently abnormal umbilical artery Doppler), these pregnancies are at risk of unpredictable fetal death, primarily of the growth restricted fetus but often with subsequent demise of the normal-grown co-twin. In case of survival, the co-twin is at risk of severe brain injury after acute exsanguination [5,6].

We have previously shown that the risk of fetal death is associated with earlier onset of sFGR, but not with the severity of weight discordance between the twins at the time of diagnosis [7]. Little however, is known regarding the growth pattern in monochorionic twins with type 3 sFGR. Some of these pregnancies have shown umbilical artery Doppler normalization later in pregnancy [8,9], and the prognostic implications of this finding are unknown. Therefore, this study aims to assess growth and Doppler patterns in monochorionic twin pregnancies complicated by type 3 sFGR across gestation and evaluate the effect of Doppler flow changes on growth and weight discordance between these twins.

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Methods

This retrospective cohort study includes a consecutive series of monochorionic diamniotic twin pregnancies complicated by type 3 sFGR and managed longitudinally between January 1st, 2008, and July 1st, 2019 at nine fetal medicine centers. All cases, irrespective of gestational age at referral or diagnosis of type 3 sFGR, were included in this analysis. Type 3 sFGR was defined as an intertwin fetal growth difference of 25% or more and fetal growth of one twin below the 10th percentile in combination with iA/REDV of the smaller fetus during at least one ultrasound assessment [4]. Higher-order multiples, pregnancies complicated by major fetal structural or genetic anomalies and pregnancies with missing neonatal data were excluded from the analysis. Additionally, pregnancies complicated by twin-twin transfusion syndrome, and twin anemia-polycythemia sequence at first presentation were excluded.

The Research Ethics Board at each participating center approved the study protocol. All participating centers have extensive experience with the sonographic assessment and management of monochorionic twins and their associated complications.

All pregnancies underwent ultrasounds for fetal growth at least every two weeks. Additional surveillance strategies of type 3 sFGR varied between centers. This cohort's pregnancy outcomes and details of center-specific antenatal surveillance have been published previously [7].

For this study, we retrieved one set of ultrasound EFW for each twin pair in each of 5 gestational age blocks: 16-20 weeks', 21-24 weeks', 25-28 weeks', 29-32 weeks' gestation and above 32 weeks' gestation, if available. In spontaneous conceptions, the gestational age was determined in the first trimester based on the crown-rump length of the larger twins, whereas embryonic age was used for dating pregnancies after *in vitro* fertilization. EFW was calculated using the fetal head circumference, biparietal diameter, abdominal circumference, and femur length using the Hadlock formula [10]. The intertwin growth difference was calculated as (weight of larger fetus – weight of smaller fetus) / weight of the larger fetus. Fetal growth in our cohort was compared to singleton growth according to Hadlock growth curves [10]. At the same gestational age time points, we reviewed the umbilical artery Doppler patterns. Umbilical artery Dopplers that evolved from being

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intermittently absent or reversed to persistently positive between diagnosis and delivery were categorized as “normalization”. Additional antenatal variables thought to impact fetal growth were collected, including maternal age at delivery, parity, and mode of conception (spontaneous versus assisted reproduction) and maternal comorbidities, defined as any chronic medical condition.

Statistical analysis

The median and interquartile ranges of the EFW by gestational age blocks were calculated, and compared to those of a singleton's EFW [10] and to uncomplicated monochorionic twins' EFW [16], and z-scores were calculated accordingly.

The effect of umbilical artery Dopplers on fetal growth was assessed by comparing the EFW across gestation between pregnancies with Doppler normalization and those in which they remained persistently abnormal.

Linear regression models fitted using generalized estimating equation (GEE) were used to assess the effect of Dopplers on the smaller and larger twin's weight while accounting for the correlations from twin pairs and repeated measures. The association between intertwin weight discordance and Dopplers was evaluated using similar linear regression GEE approach, whose correlation structure was due to the longitudinal measurements of weight discordance. Multivariable models controlled for the potential confounding effects of gestational age (centralized by subtracting the mean from the original gestational age data), maternal age, parity, and mode of conception (spontaneous versus assisted reproduction). The final models included the Dopplers' effect and only those potential confounders with a significant association with the outcome. In order to account for multi-venter variability we also conducted a GEE model step using linear mixed multi-level models, in which level I was the repeated time measurement for each individual and Level II was the center effect. Both levels' effects were modeled using random intercepts. Both analyses excluded data from twins at time points after the occurrence intrauterine fetal death. All analyses were performed using R version 3.6 [11].

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Results

A total of 328 monochorionic diamniotic twin pregnancies (656 fetuses) met the study criteria [7]. Mean maternal age at delivery was 30.2±4.9 years, and median parity was 0 (interquartile range 0,1). Maternal medical comorbidities existed in 38 pregnancies (11.6%), and pregnancies were conceived by assisted reproductive techniques in 32 (9.6%). Mean gestational age at diagnosis of type 3 sFGR and inclusion in the study was 22.0±4.6 weeks gestation (range 14.7-32.7 weeks). Thirty-five pregnancies (10.7% of the entire cohort; 11.3% after exclusion of pregnancies that underwent selective reduction) were complicated by fetal death. Death of one fetus, always the smaller twin, occurred in 19 (5.8%) pregnancies, while 16 (4.9%) pregnancies were complicated by a double death. Mean gestational age at delivery was 31.8 ± 3.6 weeks. Mean birthweight discordance between the twins was 31.2% ± 11.3%.

The EFW of the smaller and the larger twin at each gestational week, their comparison to singleton weights and the growth velocity across gestation are presented in Table 1 and Figure 1, respectively. As can be seen, at as early as 16 weeks, the weight of smaller twin (z-score -1.52 (-2.42, -0.85)) was markedly smaller than that of a singleton at the same gestational age. The larger twin's weight, in contrast, was slightly larger (z-score 0.92 (0.11-1.67) than the singleton at 16 weeks, but started to fall below the average singleton at 23 weeks (Z-score -0.03 (-0.64-0.68), albeit remaining above the 10th centile. Overall, z-scores of both twins decreased gradually between 16 and 30 weeks' gestation, suggesting a slower growth velocity in twins compared to singletons. As such, the z-score of the smaller fetus evolved from -1.52 at 16 weeks (roughly equivalent to an EFW on the seventh percentile on singleton growth charts) to -2.95 at 30 weeks' gestation (equivalent to an EFW below the first centile). Z-scores in the larger fetus evolved from 0.92 at 16 weeks (~90th percentile) to -0.67 at 30 weeks (~30th percentile). Although the intertwin weight discordance increased mildly from 25%±7.54 at 16 weeks to 32%±10.9 at 30 weeks, this increase was not statistically significant (p=0.24).

The EFW of the smaller and the larger twin at each gestational week and their comparison to uncomplicated monochorionic twin weights is presented in Table 2. This comparison demonstrates that, similar to singletons, here also the weight of smaller twin is significantly smaller than that of

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an uncomplicated monochorionic twin at the same gestational age (z-score -1.73 at 16 weeks increasing to -2.60 at 28 weeks). Although the growth restricted fetus remained significantly smaller than the uncomplicated monochorionic twin, in the third trimester this difference was less pronounced that that observed for singletons (z-score of -1.94 versus z-score of -2.89, respectively, at 34 weeks). As for the larger twin, its growth did not differ significantly when compared to uncomplicated monochorionic twins. Similarly to singletons, the larger twin's weight was slightly larger (z-score 0.55) than the uncomplicated monochorionic twin at 16 weeks (z-score of 0.55) but started to fall below the median after 16 weeks (z-score -0.32), albeit remaining well above the 10^{th} centile across all gestational ages.

In 45 pregnancies (13.7 %), the umbilical artery Doppler flow in the smaller fetus normalized at a mean gestational age of 26.7 ± 4.2 weeks. This was more likely to occur in pregnancies which presented with abnormal Dopplers at an earlier gestational age (18.8±4.0 weeks versus 21.0±4.8 weeks, respectively, p=0.003). In those pregnancies, EFW of both the smaller and the larger fetuses were significantly higher later in gestation than in pregnancies with persistent iA/REDF (Figure 2a and 2b). In multivariable longitudinal modelling, this effect on EFW remained statistically significant for the smaller twin (p=0.002) but not for the larger twin (p=0.1). Although the growth discordance was somewhat larger in twin pairs with persistent iA/REDV compared to those with Doppler normalization, this was not statistically significant (p=0.09; Figure 3). The additional analysis utilizing a multi-level model to account for inter-center variability yielded very similar results (data not shown).

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Discussion

In this cohort of monochorionic twins complicated by type 3 sFGR, we found that the smaller twin was persistently and markedly smaller than a singleton fetus from as early as 16 weeks, while the larger twin was slightly larger than a singleton until approximately 22 weeks. Beyond 22 weeks, the mean weight of the larger twin fell below the singleton's, but remained appropriate for gestation, being above the singleton's tenth centile. Similar findings were found when comparing the growth velocities of the twins complicated by type 3 sFGR to uncomplicated monochorinic twins, with the exception that although the smaller twin was substantially smaller, this difference was less pronounced in the third trimester when compared to the singleton, and the weight of the larger twin was only slightly below the median of the uncomplicated monochorionic twin. Although the growth velocities of both twins decreased across gestation, the intertwin growth discordance was stable. Normalization of fetal Dopplers was associated with significantly improved growth of the smaller twin but did not affect the intertwin growth discordance.

Previous retrospective studies have confirmed that the intrauterine growth of uncomplicated twin fetuses is reduced in comparison to singletons starting from 26-32 weeks [12-16]. This reduction is more evident in monochorionic than dichorionic twins and with advancing gestational age [13]. In our cohort of type 3 sFGR, the growth velocity of the larger twin deviated from singleton growth earlier in gestation, at roughly 23 weeks. This discordance pattern has been previously shown to be associated with high risk of adverse perinatal outcomes [17]. Although twin specific growth curves may be beneficial [18], we compared twin growth to singleton growth curves instead, since these represent the optimal conditions for fetal growth. Additionally, before the third trimester the differences in singleton and twin growth are not statistically significant, and their clinical significance remains to be shown [15,18].

The finding that the intertwin growth discordance remained stable across gestation is not surprising. Indeed, the smaller fetus in this condition has a small but otherwise healthy placenta. Therefore, this twin's growth is not expected to start lagging further with ongoing pregnancy such as what is seen in singletons or twins with true placental insufficiency and vascular malperfusion. Similarly, the size of the large AAA, which helps sustain the smaller fetus's growth, develops in line with overall placental development [5,19].

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A few small cohort studies have demonstrated previously that the umbilical artery flow pattern in the smaller fetus can change throughout pregnancy in type 3 sFGR [8,20] and that, in a minority of cases, the flow pattern can revert to normal in more advanced gestation [5]. Concordant with this finding, in 13.7% of our cohort's pregnancies the Dopplers changed from iA/REDF to positive umbilical artery flow . Normalization of Doppler flows was associated with improved growth of the smaller but not of the larger twin. We hypothesize that normalization of the iA/REDF represents milder disease, where the placenta is less unequally shared. In these placentas, the AAA may relatively decrease in size with progressive placental growth, explaining why the iA/REDF observed in the early second trimester disappears later on. In very unequally shared placentas, the smaller twin depends entirely on the blood exchange with the larger co-twin for its survival and angiogenetic factors may promote the growth of the AAA and persistence of the iA/REDF pattern. This observation needs to be confirmed in postnatal placental studies. Another possible explanation for alternating Dopplers may be improved vascular development in the placental portion supplying the smaller twin with subsequent reduction in the placental resistance to blood flow as well as spontaneous regression or thrombosis of AAA. Lastly, it is possible that type 1 sFGR was misclassified as type 3 sFGR, since in early gestation iAEDF may be a normal finding. This hypothesis would also support the finding that in fetuses with an earlier diagnosis of type 3 sFGR the Dopplers were more likely to normalize. Because the dynamic flow pattern in the umbilical artery in type 3 sFGR directly impacts fetal growth, longitudinal umbilical artery Doppler monitoring is essential for risk stratification in monochorionic pregnancies with sFGR.

Strengths and limitations

This study documents the collaborative experience of nine expert centers across North America, Europe and Asia and provides longitudinal data on almost twice as many type 3 sFGR pregnancies than what has been published in the collective literature to date, thereby strengthening the validity of the findings. The longitudinal documentation of growth and Doppler evolution across gestation enabled us to draw conclusions regarding their association that have not been described previously. Lastly, our robust statistical methodology with correction for important confounders is noteworthy, particularly in the setting of fetal growth in twins, which is affected by independent maternal characteristics [13].

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The study, nevertheless, has some weaknesses. Indeed, we were limited by a retrospective design and only included pregnancies from the second trimester of pregnancy onwards as umbilical artery Dopplers are not assessed in the first trimester of pregnancy. Those pregnancies that resulted in early fetal death were excluded by study design, leading to a potential selection bias. Moreover, exclusion of pregnancies that underwent selective reduction (often those with more severe growth restriction and a greater growth discordance) may have resulted in an overestimation of fetal growth. Lastly, our study lacks placental injection studies and histological analysis. The collection of these data would have given more insight into the pathophysiology of Doppler normalization.

Conclusions

We showed that in type 3 sFGR, the smaller twin is small from a very early gestational age, while the larger twin is larger than the average singleton. As pregnancy advances, both twins' growth velocities decrease with the larger twin remaining appropriately grown and the smaller becoming more growth restricted. Although the degree of growth discordance remains relatively stable across gestation, Dopplers may normalize, resulting in improved growth of the smaller twin.

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Figure legend

Figure 1

Comparison of estimated fetal weights across gestation to singleton weights in type 3 sFGR

Figure 2

Evolution of estimated fetal weights across gestation by Dopplers A) Smaller twin B) Larger twin

Figure 3

Evolution of growth discordance across gestation by umbilical artery Doppler pattern

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Tables

Table 1. Weekly estimated fetal weights and Z-scores of the estimated weights compared to singleton estimated weights across gestation

Gestational Age	Smaller twin EFW	Larger twin EFW	Smaller twin EFW Z-Score*	Larger twin EFW Z-Score*
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
16 Weeks	117 (100, 131)	161 (148, 165)	-1.52 (-2.42, -0.85)	0.92 (0.11, 1.67)
17 Weeks	136.5 (124, 148)	178.5 (165, 191)	-1.37 (-1.97, -0.93)	0.61 (0.11, 1.04)
18 Weeks	158 (148, 178)	225 (207, 240)	-1.83 (-2.33, -1.24)	0.74 (-0.08, 1.53)
19 Weeks	193 (185, 210)	260 (237, 279)	-1.80 (-2.25, -1.22)	0.36 (-0.36, 0.91)
20 Weeks	228 (204, 250)	328.5 (300, 350)	-2.06 (-2.62, -1.57)	0.61 (-0.16, 1.16)
21 Weeks	282 (245, 298)	391 (352, 424)	-2.03 (-2.54, -1.49)	0.40 (-0.38, 1.05)
22 Weeks	318 (280, 353)	460 (426, 509)	-2.18 (-3.00, -1.74)	0.22 (-0.36, 0.92)
23 Weeks	370 (322, 416)	534 (483, 572)	-2.49 (-3.01, -1.82)	-0.03 (-0.64, 0.68)
24 Weeks	409 (365, 470)	619 (568, 669)	-2.66 (-3.27, -1.98)	-0.01 (-0.51, 0.63)
25 Weeks	532 (482, 562)	750 (684, 807)	-2.16 (-2.84, -1.88)	0.21 (-0.62, 0.67)
26 Weeks	574 (530, 640)	840.5 (772, 896)	-2.59 (-3.20, -2.10)	-0.34 (-0.76, 0.30)
27 Weeks	660.5 (572, 750)	964 (897, 1052)	-2.59 (-3.28, -2.07)	-0.27 (-0.74, 0.48)
28 Weeks	723.5 (608, 824)	1088.5 (967, 1222)	-2.95 (-3.76, -2.22)	-0.33 (-1.20, 0.27)
29 Weeks	845 (706, 941)	1268 (1148, 1382)	-2.70 (-3.60, -2.20)	-0.37 (-1.10, 0.51)
30 Weeks	929 (854, 1020)	1381 (1258, 1510)	-2.95 (-3.32, -2.46)	-0.67 (-1.07, 0.09)
31 Weeks	1062 (967, 1185)	1592 (1474, 1707)	-2.84 (-3.27, -2.23)	-0.27 (-0.74, 0.12)
32 Weeks	1155 (1017, 1347)	1766 (1609, 1929)	-3.07 (-3.66, -2.35)	-0.39 (-1.22, 0.15)
33 Weeks	1327.5 (1138, 1464)	1950.5 (1837,2092)	-2.89 (-3.51, -2.32)	-0.52 (-1.06, 0.05)
34 Weeks	1446 (1263, 1612)	2157 (1912,2330)	-2.89 (-3.49, -2.24)	-0.47 (-1.23, 0.09)
35 Weeks	1725.5 (1612, 2006)	2296.5 (2272,2377)	-2.33 (-2.81, -1.54)	-0.56 (-0.71, -0.22)
36 Weeks	1790 (1790, 1790)	2476 (2476,2476)	-2.69 (-2.69, -2.69)	-0.52 (-0.61, -0.43)

EFW estimated fetal weights

*Calculated by comparing to singleton Z-scores of the weight according to Hadlock's growth curves[10]

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Table 2. Weekly estimated fetal weights and Z-scores of the estimated weights compared to uncomplicated monochorionic twin estimated weights across gestation

Gestational Age	Smaller twin EFW	Larger twin EFW	Smaller twin EFW Z-Score*	Larger twin EFW Z-Score*
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
16 Weeks	117 (100, 131)	161 (148, 165)	-1.73 (-2.604, -1.002)	0.55 (-0.12, 0.76)
17 Weeks	136.5 (124, 148)	178.5 (165, 191)	-2.09 (-2.62, -1.616)	-0.32 (-0.88, 0.21)
18 Weeks	158 (148, 178)	225 (207, 240)	-2.43 (-2.79, -1.719)	-0.11 (-0.73, 0.41)
19 Weeks	193 (185, 210)	260 (237, 279)	-2.40 (-2.627, -1.935)	-0.51 (-1.16, 0.03)
20 Weeks	228 (204, 250)	328.5 (300, 350)	-2.50 (-3.052, -1.987)	-0.18 (-0.84, 0.32)
21 Weeks	282 (245, 298)	391 (352, 424)	-2.31 (-3.016, -2.015)	-0.23 (-0.97, 0.41)
22 Weeks	318 (280, 353)	460 (426, 509)	-2.56 (-3.148, -2.004)	-0.32 (-0.84, 0.46)
23 Weeks	370 (322, 416)	534 (483, 572)	-2.59 (-3.217, -1.981)	-0.44 (-1.11, 0.07)
24 Weeks	409 (365, 470)	619 (568, 669)	-2.83 (-3.314, -2.158)	-0.51 (-1.07, 0.05)
25 Weeks	532 (482, 562)	750 (684, 807)	-2.26 (-2.724, -1.978)	-0.22 (-0.84, 0.31)
26 Weeks	574 (530, 640)	840.5 (772, 896)	-2.54 (-2.887, -2.018)	-0.43 (-0.97, 0.02)
27 Weeks	660.5 (572, 750)	964 (897, 1052)	-2.48 (-3.086, -1.872)	-0.41 (-0.87, 0.19)
28 Weeks	723.5 (608, 824)	1088.5 (967, 1222)	-2.6 (-3.278, -2.01)	-0.45 (-1.17, 0.33)
29 Weeks	845 (706, 941)	1268 (1148, 1382)	-2.41 (-3.122, -1.918)	-0.26 (-0.86, 0.33)
30 Weeks	929 (854, 1020)	1381 (1258, 1510)	-2.44 (-2.77, -2.028)	-0.42 (-0.97, 0.16)
31 Weeks	1062 (967, 1185)	1592 (1474, 1707)	-2.27 (-2.639, -1.783)	-0.19 (-0.65, 0.27)
32 Weeks	1155 (1017, 1347)	1766 (1609, 1929)	-2.26 (-2.738, -1.598)	-0.15 (-0.69, 0.42)
33 Weeks	1327.5 (1138, 1464)	1950.5 (1837,2092)	-2 (-2.578, -1.579)	-0.09 (-0.44, 0.34)
34 Weeks	1446 (1263, 1612)	2157 (1912,2330)	-1.92 (-2.411, -1.464)	0.01 (-0.65, 0.48)
35 Weeks	1725.5 (1612, 2006)	2296.5 (2272,2377)	-1.44 (-1.707, -0.761)	-0.06 (-0.12, 0.13)
36 Weeks	1790 (1790, 1790)	2476 (2476,2476)	-1.49 (-1.488, -1.488)	-0.02 (-0.02, -0.02)

EFW estimated fetal weights

*Calculated by comparing to monochorionic twin Z-scores of the weight according to monochorionic twins' growth curves[16]

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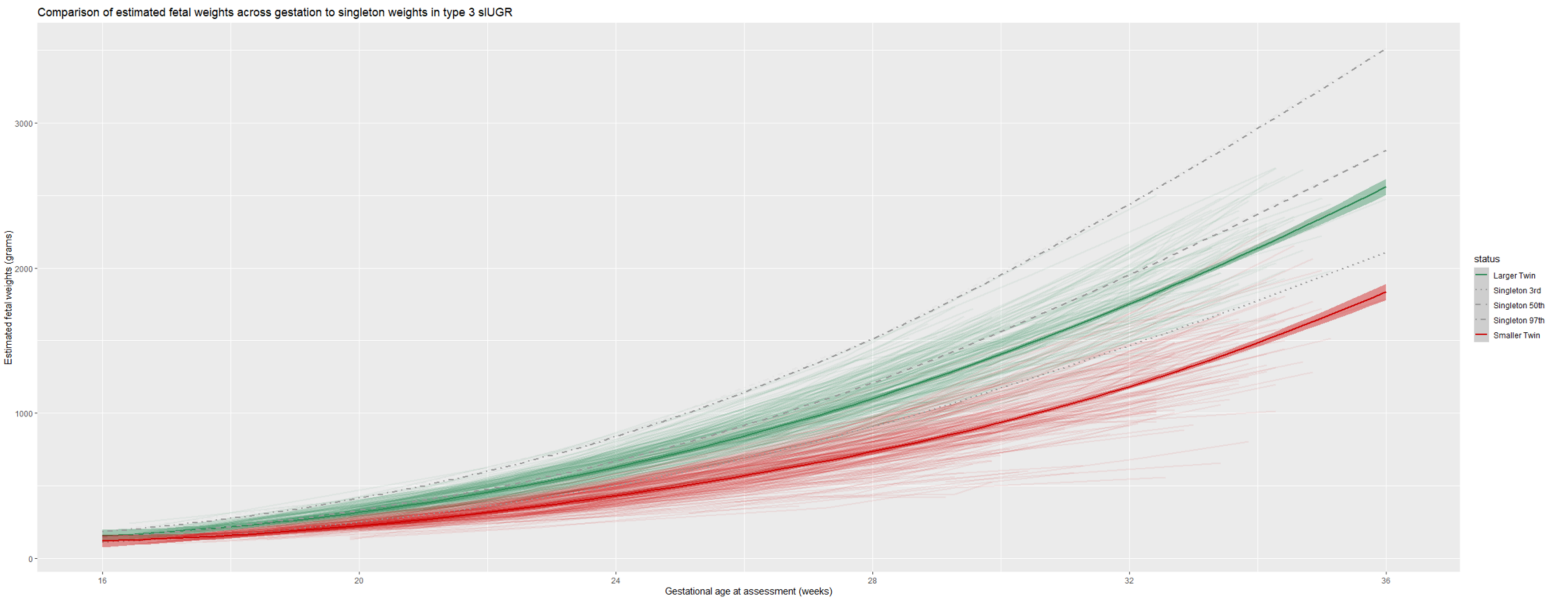

Figure1 Comparison of estimated fetal weights across gestation to singleton weights in type 3 sIUGR.png

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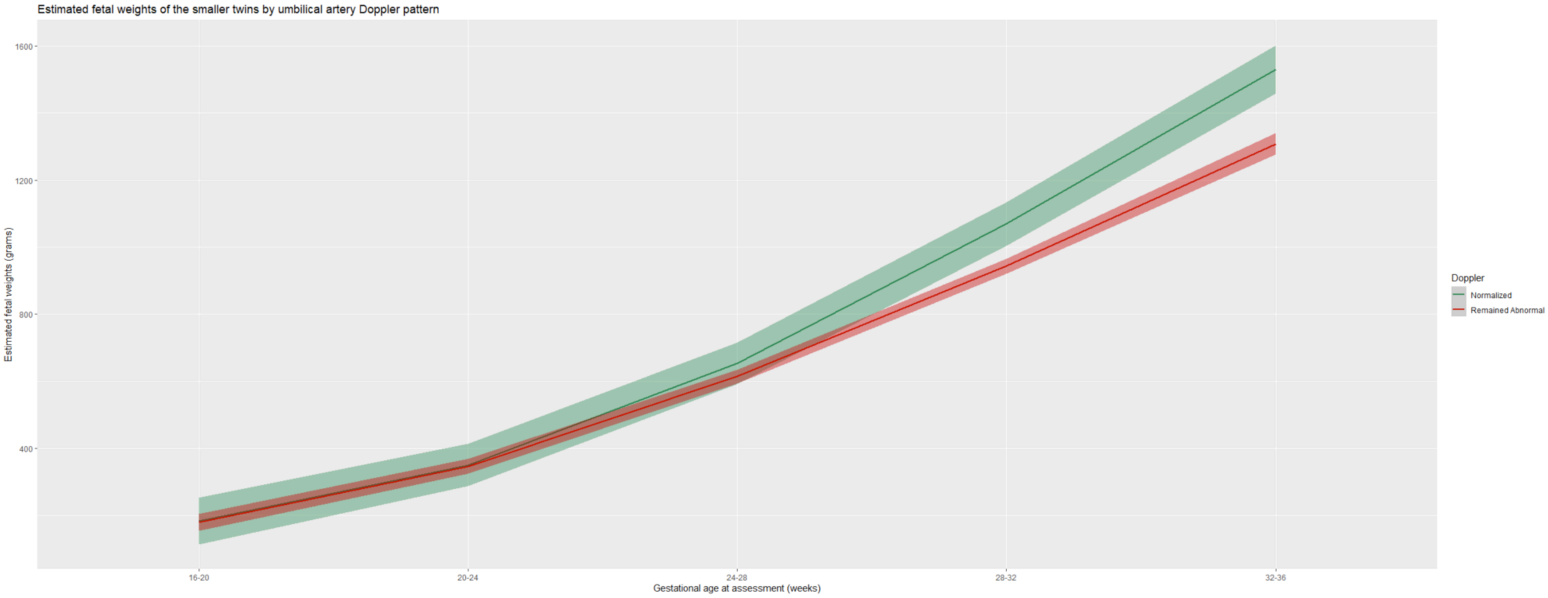

Graph2a Estimated fetal weights of the smaller twins by umbilical artery Doppler pattern.png

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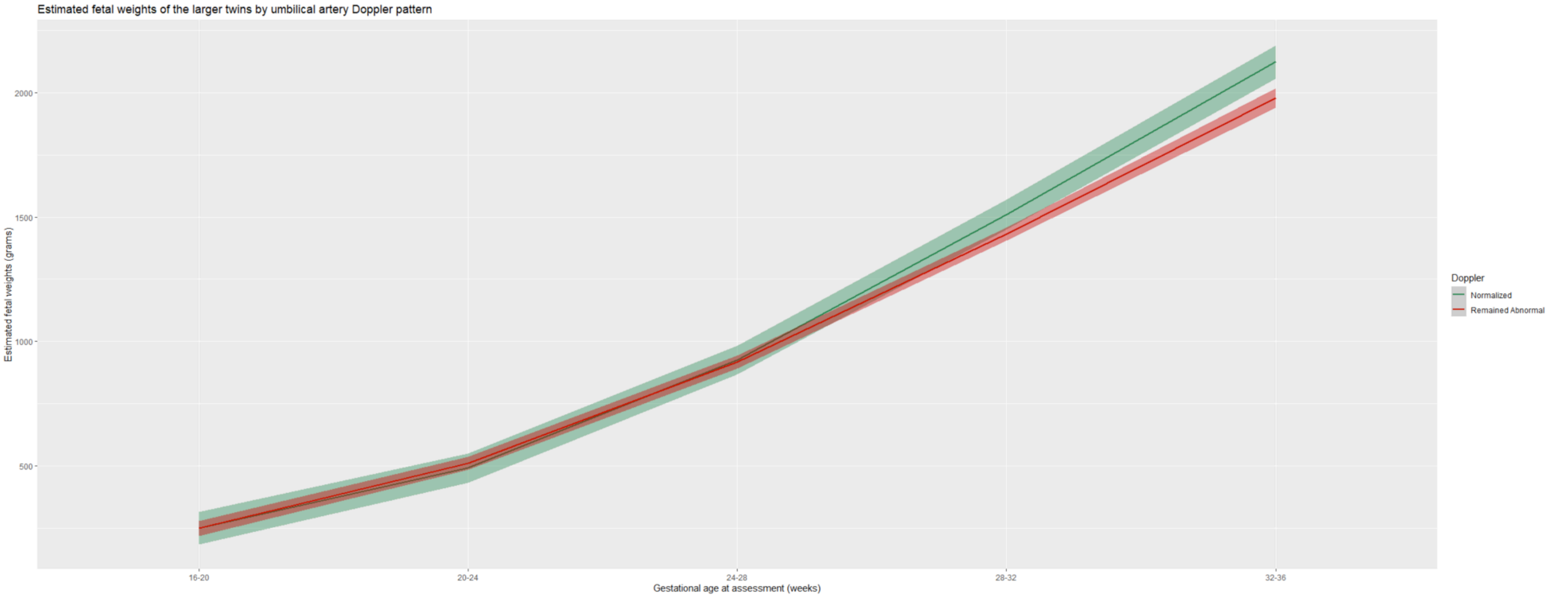

Graph2b Estimated fetal weights of the larger twins by umbilical artery Doppler pattern.png

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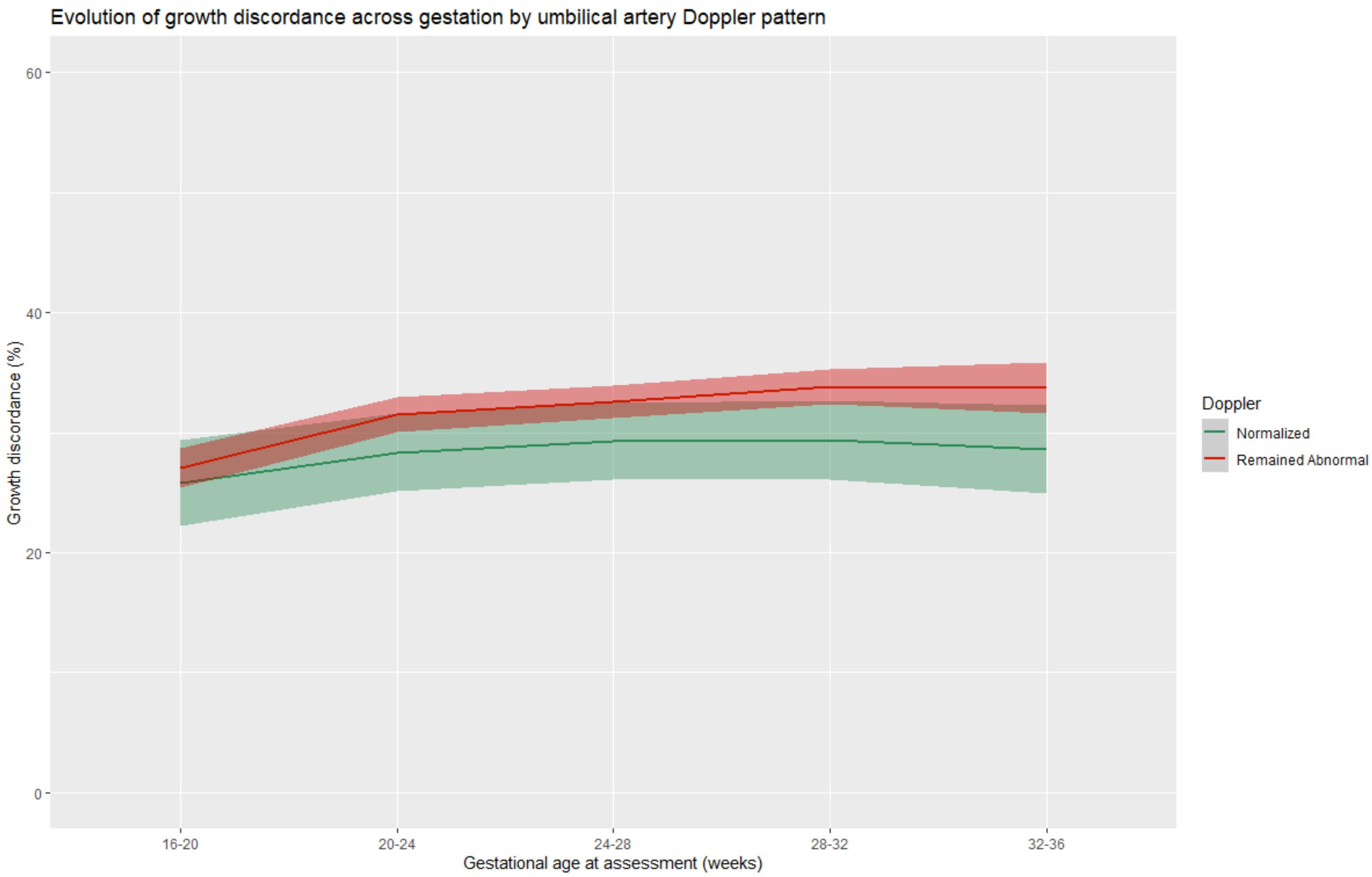

Graph3 Evolution of growth discordance across gestation by umbilical artery Doppler pattern.png

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