Placental characteristics in monochorionic twins with selective intrauterine growth restriction in relation to the umbilical artery Doppler classification

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Abstract

Introduction: The objective of this study was to evaluate the placental characteristics of monochorionic twin pregnancies with selective intrauterine growth restriction (sIUGR) classified according to the Gratacós classification based on umbilical artery Doppler measurements.

Methods: All consecutive placentas from monochorionic twin pregnancies with sIUGR, (defined as a birthweight discordance > 25% and/or an estimated fetal weight in one twin <10^{th} centile) examined at our center between May 2002 and February 2018 were included in the study. Each placenta was injected with colored dye to study the angioarchitecture. Primary outcomes were placental share discordance and diameter of the arterio-arterial anastomoses in relation to the umbilical artery Doppler types of sIUGR (Gratacós classification).

Results: Of the 83 sIUGR twins included, 27 were classified as Gratacós type I, 24 as type II and 32 as type III. The median gestational age at delivery was 34.3 weeks for type I, compared to 31.2 weeks and 31.6 weeks for type II and type III respectively. A trend towards a higher placental share discordance in type III sIUGR was observed. The median arterio-arterial diameter was 1.7 mm (0.8-2.6) in type I, 1.7 mm (0.8-2.6) in type II and 2.8 (2.0-3.5) mm in type III (p<0.01).

Conclusions: Type III sIUGR placentas appear to be characterized by a larger diameter of the arterio-arterial anastomoses in type III and a larger placental share discordance compared to type I and II sIUGR. The insights in the placental architecture of sIUGR placentas may offer new views on the pathophysiology of the disease.

Keywords: selective intra-uterine growth restriction, monochorionic twin placentas, umbilical artery Doppler, birth weight discordance

Introduction

Monochorionic (MC) twin pregnancies are at increased risk of adverse perinatal outcome when compared to dichorionic twin pregnancies [1]. This increased risk is mainly caused by the vascular anastomoses on the surface of the shared placenta, allowing inter-twin blood transfusion between the two fetuses, which can lead to complications such as twin-twin transfusion syndrome (TTS), twin anemia polycythemia sequence (TAPS) or selective intra-uterine growth restriction (sIUGR) [2, 3]. sIUGR occurs in 10-15% of MC twin pregnancies and results from both inter-twin blood flow and unequal placental sharing leading to severe growth restriction in the twin with the small placenta share.

In 2007, Gratacós et al proposed a classification system for sIUGR [4] based on the umbilical artery (UA) Doppler flow in the smaller twin. Type I is characterized by positive UA Doppler flow, and is considered to have a benign prognosis. Type II is defined as a persistently absent/reversed UA end-diastolic flow (AREDF) and is associated with the highest perinatal mortality and morbidity. Lastly, type III is characterized by intermittent absent/reversed end-diastolic flow (iAREDF) and has an atypical clinical evolution with an increased risk of unexpected fetal demise of the smaller twin and an increased risk of cerebral injury in the larger twin [4-6].

Several studies previously described the placental angioarchitecture in MC twins with sIUGR [2, 3, 7, 8]. However, no other studies, aside from Gratacós et al. in 2007, evaluated the association between placental characteristics and umbilical artery Doppler classification. The aim of the study is to evaluate the placental characteristics in MC twins with sIUGR according to the Gratacós classification.

Methods

All placentas from MC pregnancies with a birthweight discordance > 25% and/or an estimated fetal weight in one twin <10th centile consecutively examined at our specialized center between May 2002 and February 2018 were eligible for the study We excluded MC pregnancies with co-existing TTS or TAPS, cases where the umbilical artery Doppler classification was not recorded, cases with incomplete placental data (either due to placental damage or loss of the placenta) and cases in which placental measurements on the digital picture could not be performed. Cases with single or double intra-uterine fetal demise

(IUFD), defined as fetal death before 24 weeks of gestational age, were excluded when severe placental maceration made measurements impossible.

The following baseline characteristics were collected from our database: maternal age, gravidity, parity, gender, gestational age at diagnosis, gestational age at birth, mode of delivery, birth weight, birth weight discordance, intertwin hemoglobin (Hb) difference, perinatal survival and severe cerebral injury, defined as periventricular leukomalacia (PVL) ≥ grade 2, intraventricular hemorrhage (IVH) ≥ grade 3, ventricular dilatation, arterial or venous infarct or other severe cerebral injury. Birth weight discordance was calculated as follows: (birth weight larger twin – birth weight smaller twin)/birth weight larger twin x 100%. The Gratacós classification was established based on routine UA Doppler evaluations, with type I defined as a positive end-diastolic flow (PEDF), type II as AREDF and type III as iAREDF. iAREDF was identified within the same acquisition of UA Doppler and checked within a short interval in the same exam. The cord was assessed at the insertion site of the placenta. In case this was not possible, a free loop close to the insertion of the placenta was assessed. When the classification changed over time, the most prevalent type was chosen with help of an ultrasound operator.

Each of the MC placentas was routinely injected with colored dye to examine the pattern of placental anastomoses. Specific colors correlated with specific vessels, allowing for careful observation of different types of anastomoses. The cords of the twins were marked differently at birth: one clamp for the first born and two clamps for the second born twin. The fetal territories were demarcated by the margins of the twin-specific colored dyes and expressed by a percentage of the total placental surface. After the colored dye injection, the placentas were photographed and the images digitally saved for computer analysis. The placental measurements were conducted retrospectively and unblinded by the primary investigator using Image J version 1.57.

We measured the diameter of each arterio-arterial (AA) anastomosis and venovenous (VV) anastomosis and we recorded the proportion of cases with an AA anastomosis > 2mm in diameter. This specific cut-off was solely chosen in analogy with Gratacós et al. [4] to compare our results. The total AA or VV diameter was calculated in case the placenta possessed multiple AA or VV anastomoses by adding the subsequent diameters together.

The umbilical cord insertion ratio was determined by dividing the total distance of the placenta by the distance between the two cord insertions. The umbilical cord insertions were divided into velamentous, marginal and (para)central [9]. The fetal weight ratio was calculated using the following formula: fetal weight larger twin/fetal weight smaller twin. Similarly, placental territory ratio was calculated by dividing the placental territory of the larger twin by the placental territory of the smaller twin.

Primary outcomes were the placental share discordance and the diameter of the AA anastomoses. The primary outcomes were compared according to the Gratacós classification system.

Data are presented as median (range). Data were analyzed using a Chi-square test for categorical variables, a Kruskal Wallis test for numerical variables and a GEE-analysis for survival data. A p-value < 0.05 was considered statistically significant. Statistical data was analyzed using IBM statistics v23.0 (SPSS, Inc., an IBM company, Chicago, IL, USA).

Results

A total of 109 placentas were eligible for the study based on the aforementioned inclusion criteria. Fifteen cases were excluded because a Gratacós classification was not recorded and eleven cases were excluded because measurements could not be performed due to damage of the placenta, leaving 83 placentas to be included in the study (Figure 1).

Of the 83 pregnancies and placentas included, 28 were classified as type I, 24 as type II and 31 as type III. Table 1 summarizes the baseline characteristics of the pregnancies according to the Gratacós classification. Type II and type III had a significantly lower gestational age at birth than type I. Gestational age at birth for type I was 34.3 (32.7-35.9) weeks compared to 31.2 (28.4-34.0) and 31.4 (28.8-34.1) weeks for type II and type III respectively ($p<0.01$). Type II sIUGR cases demonstrated the highest birth weight discordance, namely 38.2% (31.7-44.7) as opposed to 32.8 % (27.8-37.8) in type I and 31.9% (26.4-37.4) in type III ($p=0.035$).

Table 2 summarizes the placental characteristics according to the Gratacós classification. At least one AA anastomosis was detected in all sIUGR placentas. In a few placentas (6.0%, 5/83), more than one AA anastomosis were present.

The diameter of the AA anastomoses was significantly higher in type III compared to type I and II, namely 2.8 mm (2.0-3.5) in type III versus 1.7 (0.8-2.6) in type I and 1.7 (0.8-2.6) in type II ($p<0.01$). Moreover, type III demonstrated the highest proportion of AA anastomoses with a diameter larger than 2 mm, namely 77.4% as opposed to 42.9% in type I and 29.2% in type II ($p<0.01$). The median fetal weight ratio was 1.5 (1.4-1.6) in type I, 1.6 (1.4-1.8) in type II and 1.5 (1.3-1.6) in type III ($p=0.027$). The median placental territory ratio differed between the groups with 2.4 (1.7-2.9) in type I, 2.2 (1.5-2.9) in type II and 2.8 (2.2-3.5) in type III ($p=0.044$). When dividing these (fetal weight ratio/placental territory ratio), type III sIUGR cases had a significantly lower ratio ($p=0.025$), meaning that type III sIUGR cases have a lower fetal weight discordance than expected for the amount of placental territory discordance.

Mortality rate and the incidence of cerebral injury was low and similar in the three groups (table 1). One twin pair (type I) had missing data concerning the perinatal mortality. In all cases, the cerebral injury affected the larger twin. The first case (type II) experienced an arterial infarction on the first day after birth. In the second case (type III), cerebral injury was caused by post-hemorrhagic ventricle dilatation one week after birth due to intraventricular hemorrhage grade 3. The last case (type III) suffered from a periventricular leukomalacia grade III which was not present antenatally but developed several weeks after birth.

Discussion

This study shows that the placental characteristics vary according to the type of sIUGR, in particular the diameter of the AA anastomoses. We found that the AA diameter in type III pregnancies was significantly larger (almost double the size) compared to type I and II. In addition, we found a trend towards a higher placental share discordance in type III sIUGR. Our data thus confirms that placentas in type III sIUGR cases have larger AA anastomoses and a higher degree of sharing discordance.

The placental characteristics in type I and II placentas appear to be largely similar, with almost identical placental territory ratios (2.4 and 2.2, respectively) and equal size of the AA

anastomoses (diameter of 1.7 mm in both types). Moreover, seven (24.1%) of the type I placentas and six (25.0%) of the type II placentas demonstrated VV anastomoses. Lastly, the umbilical cord insertions were farther apart in both groups compared to type III, as observed in the umbilical cord ratios of 61.5 in type I, 64.5 in type II and 59.6 in type III.
Due to the similarities of the placental characteristics between type I and type II sIUGR, it is difficult to distinguish a type I sIUGR from a type II based solely on observation of the placentas. So far, it is unclear why the UA Doppler of type II is abnormal.

In contrast, type III placentas reveal a different architecture as opposed to type I and II placentas, with a significantly larger mean diameter of the AA anastomoses (2.8 mm) and a trend towards a higher placental share discrepancy, with a placental territory ratio of 2.8. Additionally, the umbilical cord ratio was smaller compared to type I and II.

When interpreting the size of the AA anastomoses, one should take into account the significantly lower gestational age at birth in type II and III sIUGR. Placental vessels grow with advancing gestational age [10] , which could bias the comparison of the AA diameter, as type I twins have a higher gestational age allowing for a longer period of growth. This might lead to an underestimation of the discrepancy in diameter of type I AA anastomoses versus type II and III. However, more extensive research is required in order to confirm the correlation between gestational age and chorionic vessel diameter with more certainty.

Our results are largely similar to the results of Gratacós et al. [4]. The diameter of AA anastomoses in their study was larger than 2 mm, predominantly in type III sIUGR compared to type I and II, namely 98% of the AA anastomoses in type III and 70% and 18% in type I and II respectively ($p<0.01$). This correlates with our findings that type III sIUGR has the largest AA diameter and in our study 77.4% of AA anastomoses also had a diameter > 2mm. However, exact measurement of the AA anastomoses were not reported in the study from Gratacós et al. limiting the comparisons between our studies.
Gratacós et al. also found that the placental territory ratio increased significantly from type I to type III, namely from 1.8 in type I, 2.6 in type II and 4.4 in type III, which is not in agreement with our study results. They also concluded that the ratio between fetal and

placental discordance followed a similar pattern. This is complementary to our results, even though the differences are not as broad.

The reasons for the differences between the studies are not entirely clear. Heterogeneity in study populations may have contributed to the discrepancies between our results, however the true reasons remain elusive.

The larger diameter of the AA anastomoses and higher degree of sharing discordance in type III sIUGR found in these two studies may explain the high rate of adverse outcome. This in turn leads to more detrimental clinical consequences, such as cerebral injury [5, 6] or neurodevelopmental impairment [11, 12]. Our study results elicit a possible pathophysiology of sIUGR. Due to the AA anastomoses, there is a compensatory flow of the large twin to the smaller twin. This flow can serve as a rescue transfusion for the smaller twin, since its placental share is temporarily perfused by the flow of the larger twin through the AA anastomosis after the systole [4]. These flow patterns can be recognized in umbilical artery Doppler measurements. As the diameter of the AA anastomoses increases, there is more fetofetal transfusion, resulting in an increased compensatory flow. However, larger AA anastomoses might also result in acute fetofetal transfusion which leads to intrauterine fetal demise (IUFD) or neurological damage in either of the twins [6, 13]. Therefore, the larger diameter of AA anastomoses in type III is the most likely cause of the unpredictable clinical outcomes.

The lower gestational age at birth of type III sIUGR twins is probably the direct consequence of the atypical clinical course, which leads to earlier iatrogenic delivery as compared to type I and type II as was observed in our results.

Furthermore, our results show that there is a larger discrepancy between fetal weight and placental share discordance in type III, suggesting that the placental anastomoses have less effect on the fetal weight than expected. A possible explanation for this is the rescue transfusion of the larger twin to the smaller twin. Since the AA anastomoses in type III have a significantly larger diameter, there is a larger net transfusion which compensates for the amount of placental share discordance and allows for growth of the smaller twin.

According to a study performed by Rustico et al. [14] , the umbilical artery Doppler classification is not static, but rather dynamic and may change over time into another type.

This presents difficulty in determining the Gratacós type. The dynamic character of the flows could also have consequences for the outcomes and management and should be taken into account when assessing the individual risk per pregnancy. It stresses the importance of frequent and consistent monitoring of the umbilical artery flow, in order to document changes in flow patterns.

When interpreting our data, there are certain limitations that should be taken into account. Firstly, the retrospective character of the data collection and the relatively small sample size could introduce bias into our results. Since our institution is a specialized center, referral bias could interfere with our results as well. Generally, only the complicated cases of sIUGR are referred to our center for further diagnosis and therapy. Nevertheless, the number of cases with type I, II and III was evenly distributed in our study without an overrepresentation of the more severe cases. Additional studies with a prospective character and a larger study population of MC twin pregnancies with sIUGR might present more evidence on the placental characteristics in relation to the umbilical artery Doppler classification with superior quality.

In conclusion, this study shows that the types of the Gratacós classification are associated with specific placental features, with type I and II having a relatively similar architecture as opposed to type III. These placental features can in turn determine the level of severity of the sIUGR and perinatal outcomes. Type III sIUGR has a larger AA anastomosis diameter and a larger placental share discordance and therefore has the most unpredictable clinical outcome due to the risk of acute fetofetal transfusion, leading to IUFD or neurological damage. More research may lead to a better understanding of how the placental architecture contributes to the pathophysiology and clinical outcomes in MC twins with sIUGR according to the umbilical artery Doppler measurements. In the future, early antenatal visualization of the AA anastomoses identifying the Gratacós classification with its associated risks might lead to timely and appropriate management.

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Table 1. Baseline characteristics according to umbilical artery Doppler classification.

	Gratacós type I (n=28)	Gratacós type II (n=24)	Gratacós type III (n=31)	p-value
Age mother – yrs	32.5 (29.0-36.0)	32.0 (27.0-37.0)	31.0 (29.0-33.0)	0.610
Gravidity - n	1.5 (1.0-2.0)	1.5 (0.5-2.5)	2.0 (1.0-3.0)	0.512
Parity - n	0.0 (-0.5-0.5)	0.0 (-0.5-0.5)	0.0 (-0.5-0.5)	0.800
Gestational age at diagnosis – wks	17.0 (13.7-20.4)	17.9 (13.1-22.8)	18.7 (16.9-20.6)	0.805
Gestational age at birth – wks	34.3 (32.7-35.9)	31.2 (28.4-34.0)	31.4 (28.8-34.1)	0.001
Caesarian section – n (%)	16 (57.1)	18 (75.0)	24 (77.4)	0.273
Female gender – n (%)	12 (42.9)	8 (33.3)	18 (58.1)	0.226
Birth weight – g				
Larger twin	2356 (1966-2746)	1635 (1270-2001)	1540 (1015-2065)	0.000
Smaller twin	1474 (1117-1830)	941 (571-1311)	968 (671-1266)	0.000
Birth weight discordance - %	32.8 (27.8-37.8)	38.2 (31.7-44.7)	31.9 (26.4-37.4)	0.035
Intertwin Hb difference at birth – mmol/L	0.9 (0.0-1.8)	1.5 (0.5-2.5)	0.5 (-0.1-1.1)	0.194
Perinatal survival rate – n/N (%)	49/54 (90.7)	40/48 (83.3)	53/62 (85.5)	0.577
Severe cerebral injury – n/N %	0/39 (0.0)	1/41 (2.4)	2/47 (4.3)	0.433

Data are median (IQR), n/N(%) or n (%); severe cerebral injury defined as periventricular leukomalacia (PVL) ≥ grade 2, intraventricular hemorrhage (IVH) ≥ grade 3, ventricular dilatation, arterial or venous infarct or other severe cerebral injury

Table 2. Placental features and anastomoses according to umbilical artery Doppler classification.

	Gratacós type I (n=28)	Gratacós type II (n=24)	Gratacós type III (n=31)	p-value
Placental share – %				
Larger twin	70.9 (64.4-77.3)	69.4 (62.7-76.2)	73.9 (69.6-78.3)	0.091
Smaller twin	29.1 (22.7-35.6)	30.6 (23.8-37.3)	26.1 (22.0-30.6)	0.091
Placental territory ratio	2.4 (1.7-2.9)	2.2 (1.5-2.9)	2.8 (2.2-3.5)	0.044
Fetal weight ratio	1.5 (1.4-1.6)	1.6 (1.4-1.8)	1.5 (1.3-1.6)	0.027
Fetal weight ratio/placental territory ratio	0.6 (0.4-0.8)	0.7 (0.4-0.9)	0.5 (0.4-1.6)	0.025
Arterioarterial anastomoses				
1 AA anastomoses - n (%)	27 (96.4)	23 (95.8)	28 (90.3)	0.730
>1 AA anastomoses - n (%)	1 (3.6)	1 (4.2)	3 (9.7)	
Total AA diameter - mm	1.7 (0.8-2.6)	1.7 (1.2-2.2)	2.8 (2.0-3.5)	0.002
AA anastomoses > 2 mm – n (%)	12 (42.9)	7 (29.2)	24 (77.4)	0.001
Venovenous anastomoses				
0 VV anastomoses – n (%)	22 (75.9)	18 (75.0)	24 (77.4)	0.764
1 VV anastomoses - n (%)	6 (20.7)	5 (20.8)	5 (16.1)	
>1 VV anastomoses - n (%)	1 (3.4)	1 (4.2)	2 (6.4)	
Total VV diameter - mm	2.2 (1.3-3.2)	2.7 (1.9-3.6)	3.0 (1.5-4.4)	0.884
Cord insertion – n (%)				
Larger twin				
Velamentous or marginal	4 (7.1)	2 (4.2)	1 (1.6)	0.293
Smaller twin				
Velamentous or marginal	20 (35.7)	22 (45.8)	26 (41.9)	0.117
Umbilical cord insertion ratio	61.5 (46.5-86.5)	64.5 (56.0-73.0)	59.6 (43.6-75.6)	0.741

Data are median (IQR), n/N(%) or n (%)

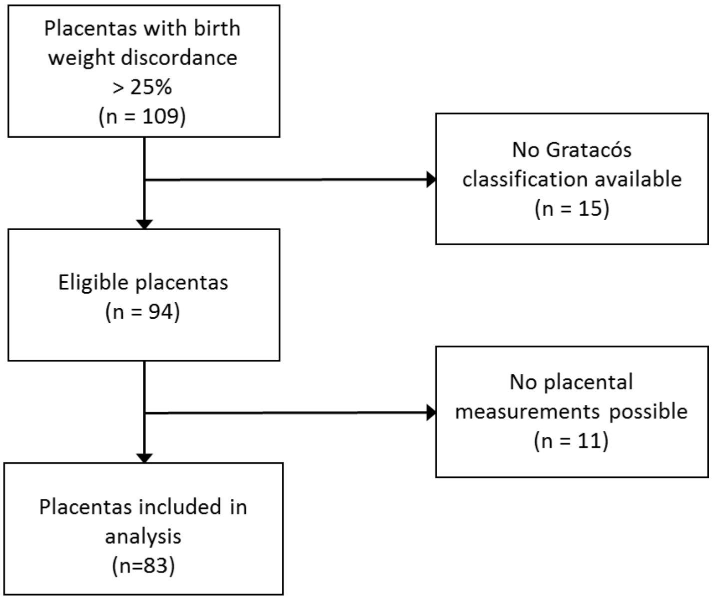

Figure 1. Flowchart of placenta inclusion.

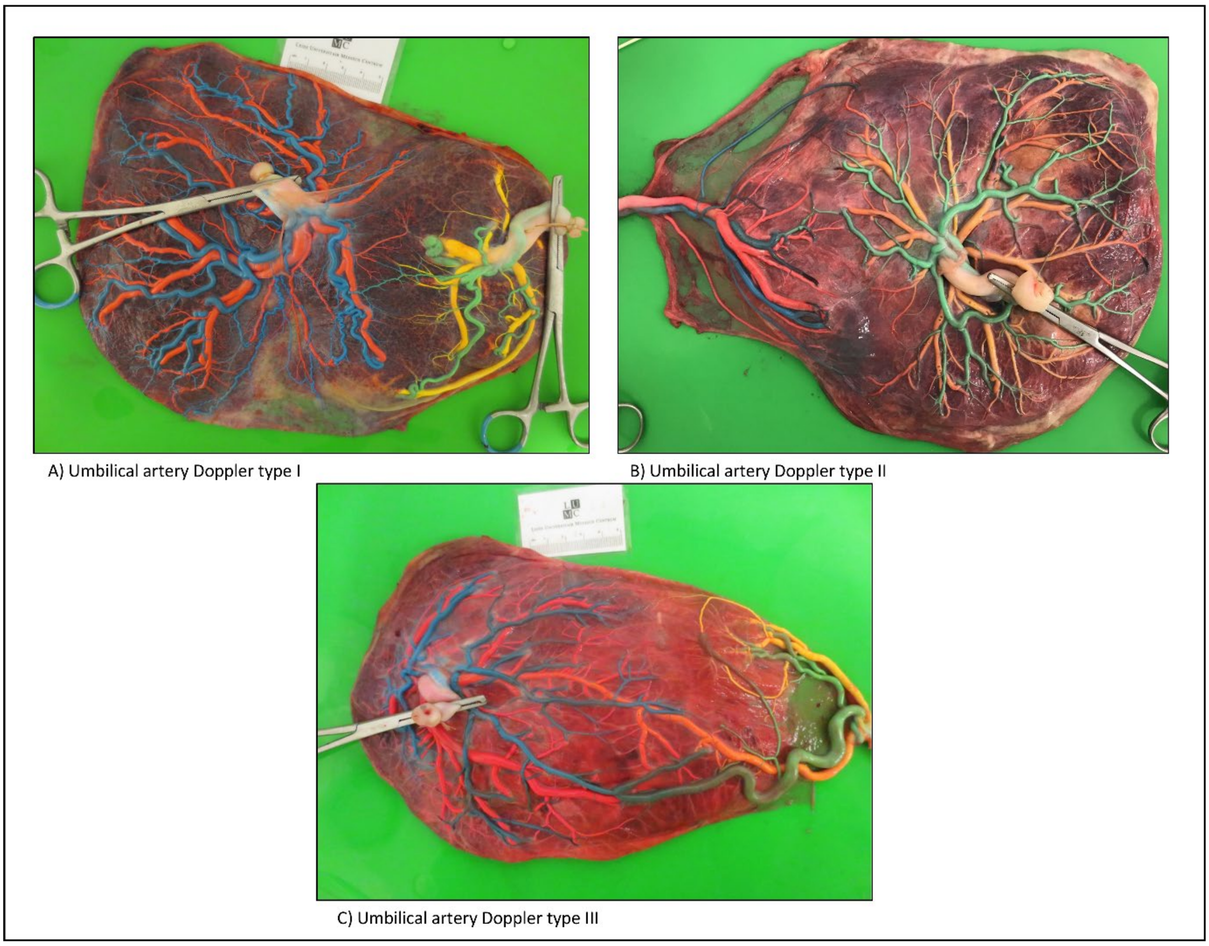

Figure 2. Pictures of injected placentas of pregnancies with sIUGR with umbilical artery Doppler type I (A), type II (B) and type III (C). Type I demonstrates a small AA anastomosis. In type II the diameter of the AA anastomosis is slightly larger. Type III shows the largest diameter.