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Intermittent absent and reversed umbilical artery flows in appropriately grown monochorionic diamniotic twins in relation to proximate cord insertion: A harmful combination?

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Abstract

Objective: To compare the prevalence of intermittent absent or reversed end-diastolic flow (iAREDF) in the umbilical artery in appropriately grown monochorionic diamniotic (MCDA) pregnancies with and without proximate cord insertion (PCI), and to evaluate pregnancy outcome.

Methods: The prevalence of iAREDF in MCDA pregnancies with PCI (n = 11) was compared with a control group without PCI (n = 33). PCI was defined as a distance between the cord insertions below the fifth percentile. Placental sharing, number, and diameter of anastomoses were assessed by placental examination. Pregnancy outcome was evaluated.

Results: iAREDF was present in 7/11 PCI pregnancies, compared with 0/33 in the control group ($P \leq .01$). All PCI pregnancies and 94% of controls had arterioarterial (AA)-anastomoses ($P = .56$), the diameter was larger in the PCI group, respectively 3.3 vs 2.1 mm ($P = .03$). Three cases with iAREDF had adverse outcome, two resulted in fetal death of which one with brain damage in the co-twin, another underwent early premature emergency section for fetal distress.

Conclusion: iAREDF occurs in a large proportion of MCDA pregnancies with PCI and is related to the diameter of the AA anastomosis. We hypothesize that iAREDF in appropriately grown MCDA twin pregnancies reflects an unstable hemodynamic balance with an increased risk for fetal deterioration. Whether outcome in these pregnancies can be improved by altered management requires further investigation.

1 | INTRODUCTION

Monochorionic diamniotic (MCDA) twins carry a high risk for specific pregnancy complications due to their shared placental circulation.[1] Type, number, and size of the vascular anastomoses on the placental surface influence the risk for twin-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence (TAPS), and when combined with an unequally shared placenta, selective fetal growth restriction (sFGR). A combination of a central and velamentous insertion is known to increase the risk for complications as well, especially in sFGR pregnancies.[2,3]

The assessment of Doppler waveforms in the umbilical artery is used to estimate the risk of adverse outcome in complicated monochorionic twins. A specific flow pattern, first described in 1994, is intermittent absent or reversed end-diastolic flow (iAREDF) in the

smaller twin of sFGR .[4] This is attributed to a large arterioarterial (AA) anastomosis that facilitates transmission of the systolic waveforms of one twin into the umbilical cord of the co-twin.[5] The iAREDF reflects an unstable hemodynamic balance between the two fetuses,[6,7] and the presence of iAREDF is associated with unexpected fetal death in cases with sFGR.[7,8] If single fetal death occurs in monochorionic twin pregnancies, this can result in severe cerebral injury or even fetal death in the co-twin.[9-11]

We observed several cases with iAREDF in MCDA twins in absence of TTTS, TAPS of sFGR. In these pregnancies, cord insertions lied very close to each other on the placental surface, which is known as "proximate cord insertion" (PCI). PCI occurs in 3% of monochorionic diamniotic (MCDA) pregnancies and a large AA anastomosis is always present.[9,12] Currently, it is unknown whether this specific subgroup is at increased risk of adverse pregnancy outcome such as known in sFGR. The aim of our study was to assess the presence of iAREDF in appropriately grown MCDA pregnancies with and without PCI, in absence of TTTS, TAPS, or sFGR and evaluate a possible relation to pregnancy outcome.

What's already known about this topic?

iAREDF is observed in monochorionic pregnancies with selective growth restriction. iAREDF is attributed to a large AA-anastomosis, and associated with sudden fetal demise. We observed iAREDF in appropriately grown MCDA twins with proximate cord insertion (PCI). No studies on iAREDF in these cases are currently available.

What does this study add?

We compared the prevalence of iAREDF in MCDA pregnancies with and without PCI, and evaluated placental characteristics and pregnancy outcome in all cases.

2 | METHODS

The Leiden University Medical Center is the national referral center for complicated monochorionic twin pregnancies. Data on prenatal ultrasound, placental characteristics, and neonatal outcome of all monochorionic twins born in our unit are prospectively entered in fetal and neonatal databases after given informed consent. Because of the retrospective character of this study, no specific approval of the Ethics Committee was required. Placentas of all monochorionic twins are routinely injected with colored dye. Pictures of the placenta are taken with a measuring tape to allow measurements on the digital picture.[13] To assess the relationship between PCI and iAREDF in MCDA pregnancies, we extracted all PCI cases based on placental examination after birth. We selected all pregnancies that received prenatal care, including ultrasonographic follow-up, in our unit, born between January 2004 and June 2017. PCI was defined as a distance between the cord insertions below the fifth percentile, ranging from 3.3 to 4.0 cm across gestation.[12] We excluded cases with TTTS, TAPS, and sFGR, as the aim of this study was to assess the prevalence of iAREDF in appropriately grown, uncomplicated monochorionic twin pregnancies. TTTS was defined using the Eurofoetus criteria and the Quintero staging system.[14,15] sFGR was defined as an estimated fetal weight below the 10th percentile in one twin and an inter-twin difference of estimated fetal weight at ultrasound of >25%.[7] When manifestation of sFGR took place weeks after the initial finding of iAREDF, the case remained in the study in order to evaluate pregnancy outcome in cases with iAREDF in appropriately grown fetuses at time of examination. As control cases, we included all consecutive uncomplicated MCDA pregnancies between January 2013 and June 2017 without PCI. The size of AA anastomosis and placental share discordance were measured on the placenta pictures.[16] For measurement of AA diameters in this study, the intraobserver and interobserver differences were calculated. Placental share discordance was calculated as (larger placental area - smaller placental area)/(larger placental area) × 100%.

All monochorionic pregnancies attending our clinic receive ultrasonographic examinations biweekly from 14 weeks gestational age onward. In uncomplicated monochorionic twins, labor is induced at 36 weeks of gestation. We reviewed all ultrasound examinations of PCI cases and controls, including biometry, flow velocity waveforms of the umbilical artery, and the flow over the ductus venosus in both twins. iAREDF in the umbilical artery was defined as the clear observation of absent and reversed end diastolic flow, alternating with positive diastolic flow over a short period of time, in the absence of fetal and maternal breathing.[7] Ductus venosus flow was defined as normal when a positive a-wave was present, and abnormal when absent or reversed a-wave in the ductus venosus was seen. We assessed fetal survival, gestational age of delivery and birthweight (BW) discordance, the latter was calculated as (BW larger twin - BW smaller twin)/(BW larger twin) × 100%.

Statistical analysis was performed with IBM SPSS 25.0 statistical package. Categorical variables were analyzed using a chi-square test, and the independent-samples *t*-test was performed to analyze continuous variables. A *P*-value of <.05 was considered statistically significant.

3 | RESULTS

We extracted 23 cases with an MCDA placenta with PCI in our placenta database. Twelve were excluded because of TTTS or sFGR, thus 11 cases remained eligible for analysis. Thirty-three consecutive uncomplicated MCDA pregnancies without PCI were included as controls (see Figure 1).

In 64% (7/11) of PCI cases iAREDF was present, in the 33 control cases iAREDF was never encountered ($P < .01$). Ductus venosus flows were normal in all cases. As shown in Table 1, the presence of AA anastomoses was comparable in both groups ($P = .56$), but the

diameter of the AA anastomosis in the PCI group was significantly larger than in controls (P = .03). The majority of placentas showed only one AA-anastomosis. In the control group, three placentas were found with two AA-anastomoses, while two placentas showed no AA-anastomosis. There were no other differences in placental characteristics between both groups.

Table 2 summarizes the seven cases with iAREDF. In four cases the finding of iAREDF was transient and resolved in the third trimester. These cases resulted in a live birth of both twins after 34 weeks of gestation. In three of the seven cases with iAREDF, fetal deterioration occurred in the twin showing iAREDF. In the first case, unexpected fetal demise of this twin occurred at 20 weeks of gestation, despite absence of any sign of TTTS or sFGR. Severe cerebral damage of the co-twin was found on follow-up scans, which was confirmed by fetal MRI. The parents chose to terminate the pregnancy at 23 weeks of gestation. Figure 2 shows the iAREDF in the umbilical artery at 18 weeks of gestation in this case, Figure 3 shows the placenta with proximate cord insertion. The second case was referred for iAREDF in MCDA twins with concordant growth at 20 weeks of gestation. Follow-up in the following weeks showed deteriorating fetal condition with frequent episodes of bradycardia. The estimated fetal weight of the iAREDF twin dropped from 30th percentile to below the 10th percentile within 3 weeks. Selective reduction of the iAREDF twin was chosen by the parents at 23 weeks gestation. The surviving twin was born healthy at 37 weeks of gestation. In this case, placental color dye injection could not be performed due to maceration of the placental share of the demised twin. The third case was referred to our center at 27 weeks with iAREDF of gestation of twin A, but concordant growth of the twins. The patient was admitted for fetal monitoring. After 5 days, caesarean section was performed because of nonreassuring fetal tracings, resulting in two live born twins of 1070 and 910 g, respectively. Postnatal placental examination showed a large AA anastomosis between the umbilical cord insertions.

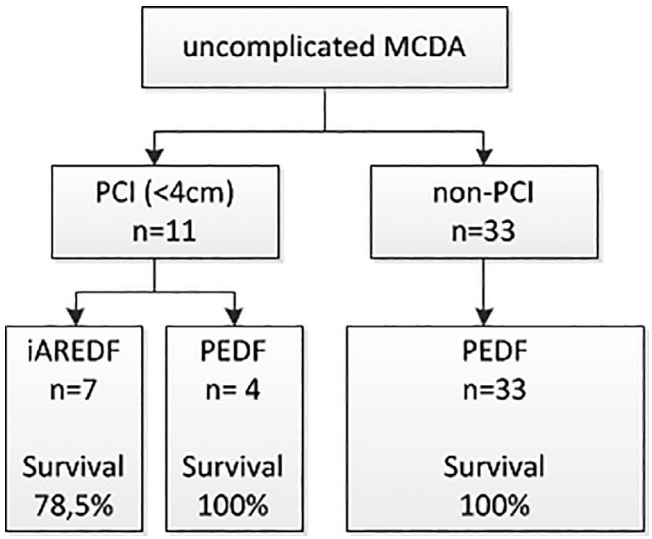

FIGURE 1 Overview of umbilical artery flow in MCDA pregnancies with PCI. iAREDF, intermittent absent or reversed end-diastolic flow in the umbilical artery; MCDA, monochorionic diamniotic; PCI, proximate cord insertion; PEDF, positive end diastolic flow in the umbilical artery; TTTS, twin to twin transfusion syndrome

4 | COMMENTS

The flow pattern of iAREDF in monochorionic twins is best known from the classification system described by Gratacos et al for selective sFGR .[7] iAREDF is caused by a large AA anastomosis and represents instable blood flow between both fetuses, with increased risk for sudden fetal demise in the smaller twin and subsequent brain damage in the larger twin.

This study shows that iAREDF can also been found in MCDA pregnancies with appropriately grown fetuses. Only a few cases have been described in literature so far. We found five cases with favorable

TABLE 1 Clinical and placental characteristics in MCDA pregnancies with and without PCI

	PCI (n = 11)	Controls (n = 33)	*P*-value
iAREDF in the umbilical artery of one twin, n (%)	7 (64)	0 (0)	<.01
Gestational age at delivery in weeks^{+days}, median (IQR)	36^{+2} (34^{+2}-36^{+6})	36^{+0} (35^{+4}-36^{+3})	.35
Fetal demise, n (%)	2 (18)	0 (0)	.06
Birth-weight discordance in %, median (IQR)	7.4 (5.5-13.1)	10.7 (8.6-15.1)	.28
Placental characteristics			
Placental-share discordance in %, median (IQR)	17.7 (0-17.7)	29.5 (12.8-40.8)	.56
Total number of anastomoses, median (IQR)	6 (4-11))	11 (7–19)	.20
Presence of AA anastomoses, n (%)[†]	11 (100)	31 (93.4)	.56
Diameter of AA anastomoses in mm, median (IQR)	3.3 (2.9-5.9)	2.1 (1.1-2.8)	.03

Abbreviations: PCI, proximate cord insertion; iAREDF, intermittent absent and reversed diastolic flow; AA anastomosis, arterioarterial anastomosis; IQR, interquartile range; [†] In this small study, median interobserver difference was 0.1 mm (IQR 0.0-0.1) and median intraobserver difference was 0.1 mm (IQR 0.0-0.125).

TABLE 2 Pregnancy outcome for PCI pregnancies with iAREDF

	iAREDF (GA in weeks)	Follow-up	GA delivery (weeks^{+days})	Birth weights twin1/twin2 (g)	Birthweight discordance (%)
1	18	Fetal demise 20 weeks, TOP 23 weeks[b]	23^{+5}		
2	20	UCC for fetal deterioration at 23 weeks[c]	37^{+3}	2950	
3	27[a]	Caesarean section at 28 weeks[d]	27^{+5}	1070/910	15.0
4	16	iAREDF resolved after 31 weeks	36^{+3}	2670/2160	18.8
5	16	iAREDF resolved after 24 weeks	36^{+1}	2350/2220	5.5
6	18	iAREDF resolved after 26 weeks	36^{+2}	2645/2350	11.2
7	22	iAREDF resolved after 26 weeks	34^{+2}	1810/1765	2.5

Abbreviations: EFWD, estimated fetal weight discordance; GA, gestational age; MCDA, monochorionic diamniotic; TOP, termination of pregnancy; UCC, umbilical cord coagulation.
[a]No ultrasound data before 27 weeks.
[b]Intracerebral injury following fetal demise of co-twin (case 1).
[c]Selective reduction because of hemodynamic deterioration of fetus with iAREDF (case 2);
[d]Caesarean section because non-reassuring cardiotocography of fetus with iAREDF (case 3).

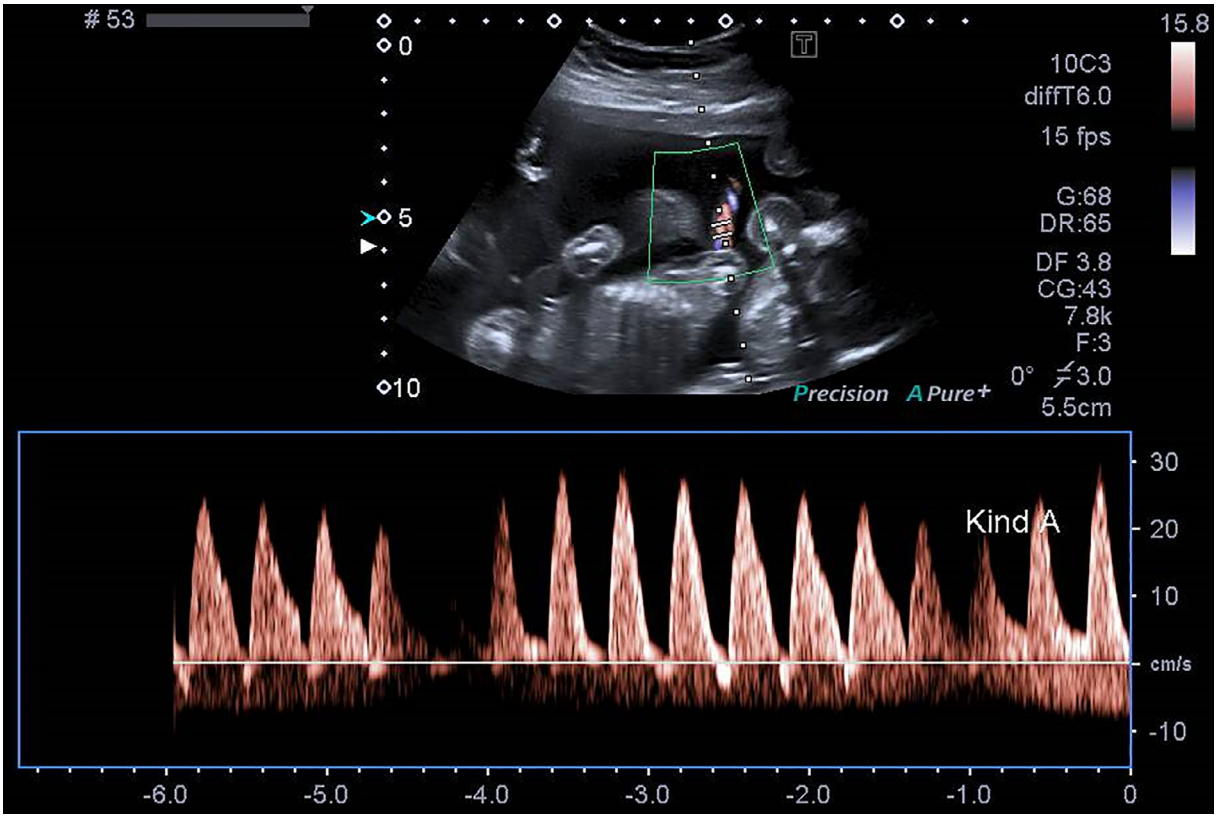

FIGURE 2 iAREDF at 18 weeks of gestation in an equal size MCDA pregnancy [Colour figure can be viewed at wileyonlinelibrary.com]

pregnancy outcome after 34 weeks of gestation in the literature. One is a case report[16] and four were part of a larger cohort. [8] A large AA-anastomosis was found in all these cases, but the distance between the cord insertions was not reported. Another case with iAREDF with appropriately grown fetuses is described in a cohort study on iAREDF in MCDA pregnancies. In this case, delivery took place at 29 weeks of gestation with a birth weight difference of only 2%, but no other details were given.[17]

In our study, iAREDF was only found in cases with PCI, none of the controls showed abnormal flow in the umbilical artery. In the majority of PCI cases, iAREDF was absent or transient and pregnancy outcome was favorable. In case of transient abnormal flows, we hypothesize that the growth of an AA-anastomosis is not proportional with gestational age. The diameter of the AA-anastomoses might increase less compared with the placental volume with gestational

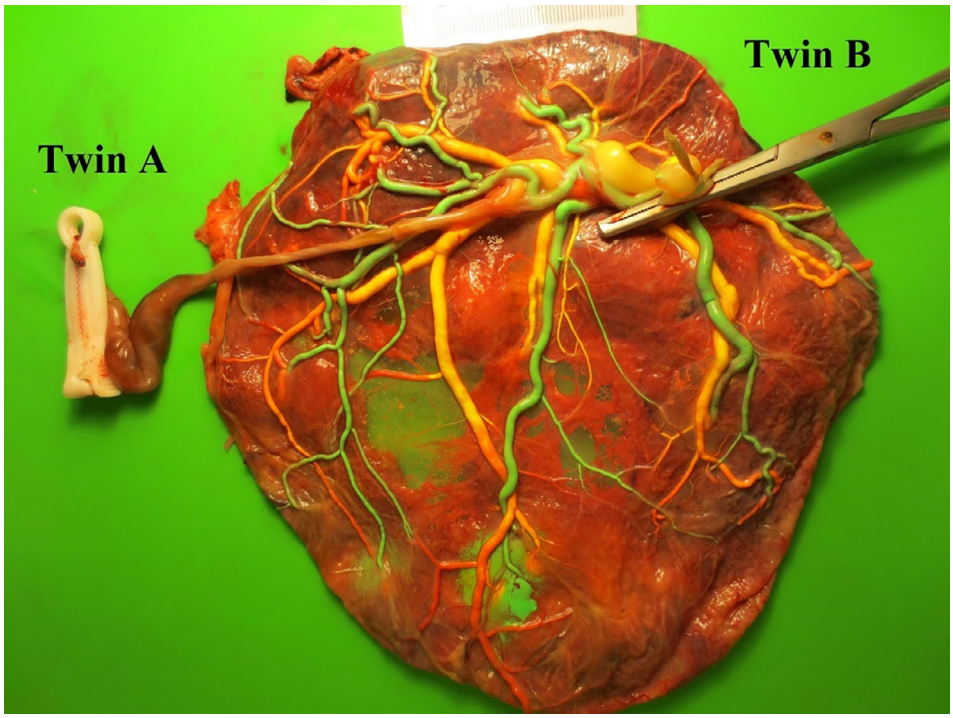

FIGURE 3 Placenta of MCDA-pregnancy with PCI and fetal demise of iAREDF in twin [Colour figure can be viewed at wileyonlinelibrary.com]

age, and the hemodynamic influence on the pregnancy might diminish in time.

Sudden fetal deterioration occurred in three of the seven pregnancies with iAREDF in this study, suggesting a possible correlation between iAREDF, PCI, and fetal deterioration. Although cord insertion patterns such as velamentous insertion are known to increase the risk of complications[2,3] not much is known about the risk of proximate cord insertion. In monochorionic monoamniotic (MCMA) pregnancies, however, PCI is frequently seen.[9] Unexpected fetal demise in one or both twins is a known risk in these pregnancies[18] and is mostly attributed to cord entanglement. However, entanglement is not always found postnatally. Lewi et al[19] hypothesized that other causes such as acute exsanguination across the often present large caliber anastomoses between cord insertions may be an important cofactor in unexpected demise as well. The hypothesis could be in concordance with our findings in MCDA pregnancies. We did not find reports on iAREDF in appropriately grown MCMA twins. In PCI, monoamniotic or diamniotic, diameters of the AA anastomoses are larger and distance to the other twin is shorter compared with monochorionic placenta's without PCI. The vascular resistance in the AA anastomosis is lower when the diameter is larger and the distance between the cord insertions is shorter. Therefore, systolic hemodynamic forces increase when distance between the cord insertions is shorter and the diameter of the vessel is larger. Consequently, these hemodynamic changes are magnified in case of unbalance, and might be responsible for sudden deterioration and may even result in fetal demise. In addition, when demise of the iAREDF twin occurs, the short anastomosis with a large diameter, with therefore a lower resistance, may allow a more rapid and massive exsanguination in reverse direction, which can result in severe cerebral injury in the surviving twin as represented in case 1.

4.1 | Strengths and limitations

Our study evaluates the occurrence of iAREDF in appropriately grown MCDA pregnancies with PCI in a center with a high volume of MCDA pregnancies and a standardized follow-up, including placenta examination. A limitation of this study is the limited sample size, due to the low frequency of PCI in MCDA pregnancies. In addition, selection bias could play a role since our center is the referral center for monochorionic twin pregnancies in our country. MCDA with persistent abnormal flows are referred to our clinic for a second opinion (cases 2 and 3) more often than MCDA pregnancies with normal flows.

4.2 | Recommendations

Regarding management of MCDA pregnancies with PCI and iAREDF, strong conclusions cannot be made based on this small case series. We, however, recommend heightened awareness in the presence of the combination of iAREDF and PCI irrespective of fetal growth. We realize that such an as yet unproven concern may lead to increased anxiety by both parents and doctors, with the risk of (too) early interventions and possibly unnecessary harm of iatrogenic preterm birth. However, it is known that sudden fetal death occurs in up to 3.6% of appropriately grown, uncomplicated MCDA pregnancies after 24 weeks of gestation, and in up to 1.2% after 32 weeks of gestation.[20-22] Some of these cases may be associated with (unrecognized) PCI cases with iAREDF. A large observational multicenter study is needed to evaluate the prevalence and pregnancy outcome of iAREDF in PCI in monochorionic pregnancies, before we can suggest specific management for such cases.

5 | CONCLUSION

MCDA pregnancies with PCI show a higher incidence of iAREDF in the umbilical artery. As in sFGR, iAREDF might be a reflection of an unstable hemodynamic balance, which might result in adverse pregnancy outcome. Prospective studies with a larger sample size should be performed to evaluate this phenomenon.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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