Chapter 10

Single fetal demise in monochorionic pregnancies: Incidence and patterns of cerebral injury

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Ultrasound in Obstetrics & Gynecology 2015:45:294-300

Abstract

Objective
To evaluate the incidence, type and severity of cerebral injury in the surviving monochorionic (MC) co-twin after single fetal demise.

Methods
All MC pregnancies with single fetal demise that were evaluated at the Leiden University Medical Center between 2002 and 2013 were included. Perinatal characteristics, neonatal outcome and the presence of cerebral injury, observed on neuroimaging, were recorded for all co-twin survivors.

Results
A total of 49 MC pregnancies with single fetal demise, including one MC pair from a dichorionic triplet, were included in the study ($n = 50$ co-twins). The median gestational age at the occurrence of single fetal demise was 25 weeks and the median interval between single fetal demise and live birth was 61 days, with a median gestational age at birth of 36 weeks. Severe cerebral injury was diagnosed in 13 (26%) of the 50 co-twins and was detected antenatally in 4/50 (8%) and postnatally in 9/50 (18%) cases. Cerebral injury was mostly due to hypoxic-ischemic injury resulting in cystic periventricular leukomalacia, middle cerebral artery infarction or injury to basal ganglia, thalamus and/or cortex. Risk factors associated with severe cerebral injury were advanced gestational age at the occurrence of single fetal demise (odds ratio (OR), 1.14 for each week of gestation; 95% CI, 1.01-1.29; $P = 0.03$), twin–twin transfusion syndrome, developing prior to single fetal demise, (OR, 5.0; 95% CI, 1.30-19.13; $P = 0.02$) and a lower gestational age at birth (OR, 0.83 for each week of gestation; 95% CI, 0.69-0.99; $P = 0.04$).

Conclusions
Single fetal demise in MC pregnancies is associated with severe cerebral injury occurring in 1 in 4 surviving co-twins. Routine antenatal and postnatal neuroimaging, followed by standardized long-term follow-up, is mandatory.

Introduction

Monochorionic (MC) pregnancies are at an increased risk for complications, including twin–twin transfusion syndrome (TTTS), twin anemia–polycythemia sequence and selective intrauterine growth restriction (sIUGR). In the case of single fetal demise in a MC pregnancy, severe complications may arise. Several reports have shown that the co-twin is at an increased risk of fetal demise or severe morbidity due to injury to the brain, gastrointestinal tract or kidneys.[1] These complications are thought to be caused by acute fetal exsanguination into the low-pressure circulation of the demised fetus through the placental vascular anastomoses. Acute hypovolemia, hypotension and anemia may subsequently result in hypoxic-ischemic multi-organ damage, particularly to the brain, and even double fetal death.[2] In a meta-analysis, Hillman *et al.* reported a rate of abnormal postnatal cranial imaging and neurodevelopmental impairment after single fetal demise of 34% and 26%, respectively.[3] However, this meta-analysis was based on a few small series and case reports, which may have introduced selection or publication bias, hampering accurate estimation of the incidence. In addition, little is known on the type, severity and risk factors of cerebral injury after single fetal demise. The aim of this study was to determine the incidence and characteristics of severe cerebral lesions in the surviving co-twin of a large case series of MC pregnancies after single fetal demise.

Methods

In this retrospective analysis of collected data, we included all consecutive MC pregnancies with single fetal demise diagnosed at or referred to the Leiden University Medical Center (LUMC), between June 2002 and November 2013. The LUMC is the national referral center in The Netherlands for fetal therapy. Ethical approval from the parents is not required for this type of retrospective study with anonymized data in The Netherlands. We excluded MC pregnancies with fetal demise occurring after laser treatment for TTTS, selective feticide, cases with double fetal demise occurring on the same day, and cases with single fetal demise occurring during the first trimester. Dichorionic (DC) triplets were included if the fetal demise occurred in one of the MC twins. In such cases, the outcomes of the MC co-twin were analyzed only.

We recorded the presence and characteristics of fetal and/or neonatal cerebral injury detected on antenatal and/or postnatal neuroimaging examination. Neuroimaging was performed using either fetal or neonatal ultrasound or magnetic resonance imaging (MRI). The fetal MRI was performed using a 1.5-T MRI system (Philips Medical Systems,

Best, The Netherlands) and included T_2 turbo spin echo sequences in three directions and T_2* fast field echo. The neonatal MRI was performed using a 3-T MRI system (Achieva 3T; Philips Medical Systems, Best, The Netherlands) and included a 3D T_1 turbo field-echo, T_2 turbo spin echo, T_2* fast field echo, and diffusion weighted sequences. We recorded the neuroimaging data obtained within the first year of life. Cerebral injury was categorized as follows: intraventricular hemorrhage (IVH), parenchymal hemorrhage, cystic periventricular leukomalacia (cPVL), porencephalic cyst, ventricular dilation, arterial or venous infarction, and hypoxic-ischemic injury of basal ganglia, thalamus and/or cortex. Severe cerebral injury was defined as at least one of the following: IVH ≥ Grade III[4], cPVL ≥ Grade II,[5] ventricular dilatation ≥ 97th percentile,[6] porencephalic cyst, arterial or venous infarction, basal ganglia, thalamic and/or cortical injury, or other severe cerebral lesions associated with an adverse neurological outcome.[7]

The following obstetric parameters were recorded: amnionicity, sIUGR (defined as an estimated fetal weight of the growth-restricted fetus < 10th centile), TTTS (including Quintero stage and management),[8] congenital anomalies, gestational age at detection of fetal demise, cause of fetal demise, fetal middle cerebral arterial (MCA) peak systolic velocity (PSV) Doppler measurement, presence of fetal cerebral injury and gestational age at detection, time between fetal demise and delivery, and mode of delivery. In the surviving co-twins that were treated with intrauterine blood transfusion (IUT) for anemia, we recorded the hemoglobin level prior to the transfusion.

The following neonatal parameters were recorded: gestational age at birth, birth weight, gender, occurrence of perinatal asphyxia, neonatal death, presence of respiratory distress syndrome, patent ductus arteriosus, hemoglobin level at birth and need for a blood transfusion, and need for inotropic support. Perinatal asphyxia was defined as the presence of three or more of the following five criteria: non-reassuring cardiotocogram patterns, umbilical cord arterial pH < 7.10 and base excess ≥ 16mmol/L or lactate > 10mmol/L, an Apgar score < 5 at 5 minutes after birth, failure of spontaneous breathing at 5 minutes after birth, and onset of multiple organ failure.

Statistical data were analyzed using SPSS version 20.0 (IBM, Armonk, NY, USA) and reported as *n* (%), mean ± SD or median (interquartile range (IQR)). Statistical analysis was performed using the *t*-test and Mann–Whitney *U*-test for continuous variables. The chi-squared test and Fisher's exact test were used for categorical variables. Risk factors possibly contributing to severe cerebral injury were studied in a univariable regression model. The multivariable model included all variables that showed a significant association in the univariable analysis. Results are expressed as odds ratio (OR) with 95% confidence interval (CI). A *P*-value < 0.05 was considered as statistically significant.

Results

A total of 49 MC pregnancies, including one MC triplet and two DC pregnancies with a MC component, fulfilled our inclusion criteria and were included in the study ($n = 50$ fetuses). The median gestational age at the diagnosis of single fetal demise was 25 (20–29.3) weeks' gestation. In 35/49 (71%) pregnancies, a likely cause of single fetal demise could be identified: monoamnionicity (5/49, 10%), sIUGR (13/49, 27%) or TTTS (17/49, 35%). In all monoamniotic twin pregnancies, umbilical cord entanglement was present. In one monoamniotic pregnancy, fetal co-twin demise was detected at 42 days after single fetal demise. In the sIUGR pregnancies, single fetal demise occurred most often in the growth-restricted fetus (11/13, 85%). In the TTTS pregnancies, single fetal demise occurred mostly in the donors (14/17, 82%). Two pregnancies with sIUGR were also complicated by congenital anomalies in the demised twin (Potter syndrome, transposition of the great arteries and esophageal atresia). MCA-PSV Doppler measurements were performed in 47/50 (94%) cases after single fetal demise. In three cases, MCA-PSV measurements were not performed due to imminent delivery of the surviving co-twin. Treatment with IUT due to signs of severe acute anemia shortly after the demise of the co-twin was performed in 6/50 (12%) cases. The median interval between fetal demise and delivery was 58 (9.5–106) days. Figure 1 presents a flow chart showing the derivation of the study population. Details of the antenatal characteristics of the study group are reported in Table 1.

Table 1 Antenatal characteristics of the 49 monochorionic (MC) pregnancies after single fetal demise

Characteristic	MC pregnancies
Female fetus	25 (50)
Twin–twin transfusion syndrome	17 (35)
Amnioreduction	4/17 (24)
Selective IUGR	13 (27)
Monoamniotic twin	5 (10)
GA at single fetal demise (weeks)	25 (20–29.3)
Interval between fetal demise and delivery (days)	58 (9.5–106)
IUT after single fetal demise	6 (12)
Hb level at transfusion (g/dL)	5 (3–5.9)
Cerebral injury	4 (8)
GA at detection (weeks)	26.5 (22.3–30.8)

Data are given as *n* (%), *n*/*N* (%) or median (interquartile range).
GA, gestational age; Hb, hemoglobin; IUGR, intrauterine growth restriction; IUT, intrauterine transfusion.

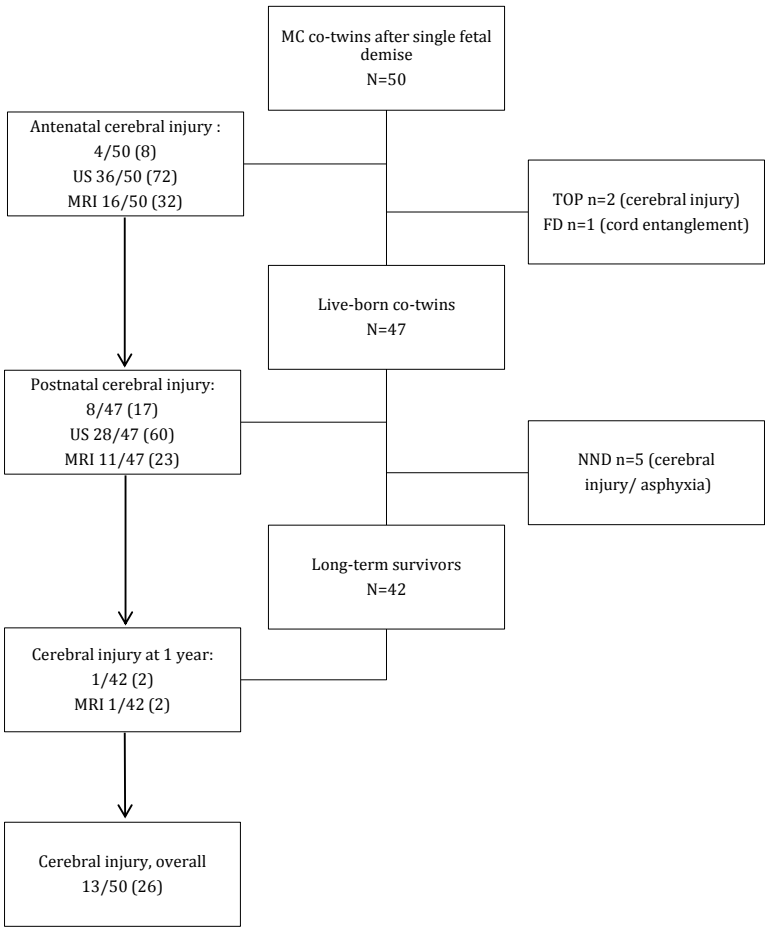

Figure 1 Derivation of the study population.
MC, monochorionic; *US,* ultrasound; *MRI*, magnetic resonance imaging; *TOP*, termination of pregnancy; *FD,* fetal demise; *NND*, neonatal death.

Serial fetal cranial ultrasound after single fetal demise was performed in 36/50 (72%) fetuses, of which, 16/36 (44%) also underwent fetal MRI. In 4/36 (11%) fetuses, severe cerebral injury was detected at a median gestational age of 26.5 (22.3–30.8) weeks. Among these were two pregnancies complicated with TTTS, of which, single fetal demise of the donor twin occurred at 19 and 23 weeks' gestation. Fetal MRI at 21 and 26 weeks, respectively, revealed infarction of the MCA in the recipient co-twin. In both cases, the parents opted for termination of the pregnancy after extensive counseling. In the third case of severe cerebral injury, occurring in a DC triplet pregnancy, single fetal demise of the growth-restricted MC co-twin was detected at 25 weeks' gestation. Fetal MRI performed at 27 weeks displayed multicystic encephalopathy in the surviving MC co-twin. In the fourth case, in a TTTS-complicated pregnancy, single fetal demise

of the donor twin was detected at 28 weeks' gestation and fetal MRI at 32 weeks showed cerebral atrophy, diffuse white matter loss and abnormalities of the thalamus and internal capsula in the recipient co-twin. Postnatal MRI confirmed the cerebral abnormalities detected with a fetal MRI in both the surviving co-twins.

The median interval between the occurrence of single fetal demise and delivery of the 47 live-born co-twins was 61 (9–114) days, with a median gestational age at live-birth of 36 (33–38) weeks. Perinatal asphyxia was detected in 6/47 (13%) neonates and three (3/47; 6%) neonates were diagnosed with persistent pulmonary hypertension, of which, one required extracorporeal membrane oxygenation. This child was diagnosed with severe renal failure and died at 2 years of age after a renal transplant[9]. Eight (8/47; 17%) neonates were treated with blood transfusion, of which five also required inotropic medication at birth. These children were born shortly after the demise of their co-twin (range, 0–2 days). One (2%) child presented with an unexpected limb reduction at birth. Neonatal death occurred in 5/47 (11%) co-twins, due to asphyxia and/or severe cerebral injury. Detailed information on neonatal outcome is presented in Table 2.

Table 2 Neonatal outcome of live-born co-twins after single fetal demise

Outcome	Co-twins (*n* = 47)
GA at birth (weeks)	36 (33–38)
Birth weight (g)	2622.5 (1816.3–2985)
Perinatal asphyxia	6 (13)
Respiratory distress syndrome	10 (21)
Patent ductus arteriosus	4 (9)
Renal failure	1 (2)
Hb level at birth (g/dL)*	15 (9.4–18.1)
Blood transfusion at birth	8 (17)
Neonatal death	5 (11)
Age at death (days)	6 (3.5–19)

Data are given as *n* (%) or median (interquartile range). *$n = 23$. GA, gestational age; Hb, hemoglobin.

Postnatal ultrasound was performed, within the first days of life, in 28/47 (60%) neonates, of which, 11/28 (39%) also underwent MRI. Severe cerebral injury was detected on postnatal imaging in 8/28 (29%). Overall, antenatal or postnatal neuroimaging at birth was performed in all but one case (49/50, 98%). This child was born at 37 weeks gestational age in another hospital where cranial ultrasound was not part of standard procedure. However, the child presented with severe developmental delay at almost 1 year of age and subsequent MRI showed severe cerebral injury. In total, severe cerebral injury was detected in 13/50 (26%) co-twins after single fetal

demise. Of these 13 co-twins, eight (62%) were diagnosed with TTTS prior to single fetal demise. The median gestational age at single fetal demise was 27 (24–33) weeks, compared to 23.5 (19–28.75) weeks in co-twins without severe cerebral injury ($P = 0.03$). The median gestational age at live birth was 35 (28–37) and 37 (34–38) weeks, respectively ($P = 0.04$). Details on characteristics and outcome of the 13 co-twins with severe cerebral injury after single fetal demise are presented in Table 3. Figure 2 shows T2-weighted MRI scans of four children with different types of severe cerebral injury.

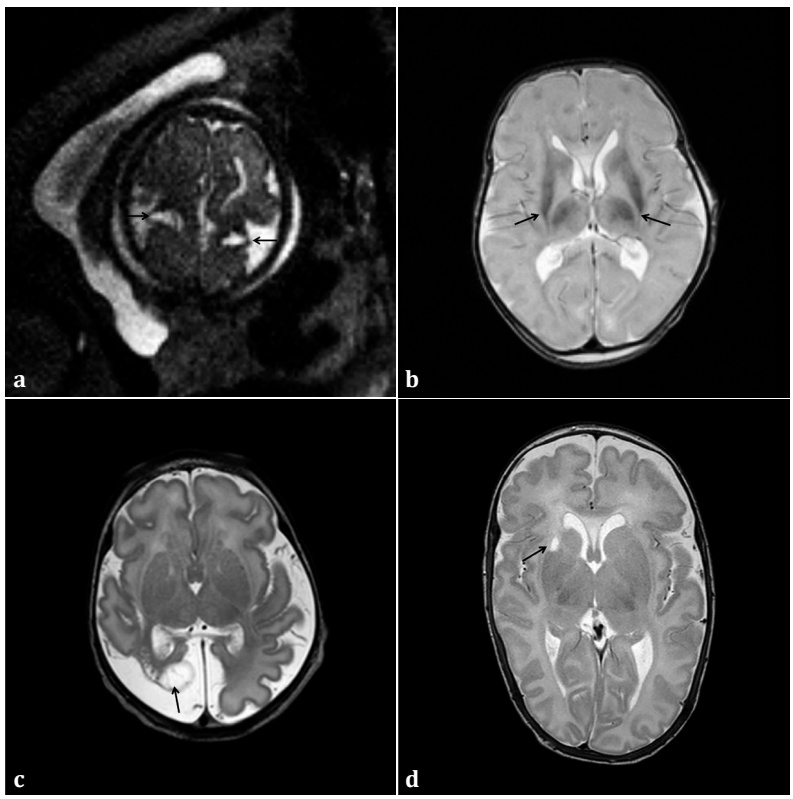

Figure 2 (a) T2-weighted fetal magnetic resonance image (MRI) obtained at 26 weeks' gestation, 3 weeks after single fetal demise in a monochorionic pregnancy, showing bilateral middle cerebral artery infarction (arrows). (b) T2-weighted MRI in a 3-day-old neonate who was born asphyxiated at 36 weeks' gestation, one day after single fetal demise, showing diffuse cortical necrosis, white matter injury and severe basal ganglia/thalamic injury (arrows). (c) T2-weighted postnatal MRI in a 2-day-old neonate who was born at 37 weeks' gestation, 63 days after single fetal demise, showing bilateral severe cerebral atrophy and cystic parenchymal destruction of right posterior cerebral hemisphere (arrow). (d) T2-weighted MRI in a 12-week-old neonate who was born at 28 weeks' gestation, 10 days after single fetal demise, in whom neonatal cranial ultrasound showed Grade II unilateral intraventricular hemorrhage and infarction in the right caudate nucleus (not shown). A cystic lesion in the right caudate nucleus (arrow) can be seen, confirming the ultrasound diagnosis.

Table 3 Characteristics of the 13 co-twins with severe cerebral injury after single fetal demise

Case	Cause of single fetal demise	GA at fetal demise (wks)	GA at birth (wks)	Outcome	Type and age at neuroimaging (wks)	Cerebral injury
1	TTTS donor	19	23	TOP	aMRI (21)	Right MCA infarction
2	TTTS donor	23	34	TOP	aMRI (26)	Bilateral MCAinfarction
3	TTTS and sIUGR small twin	25	37	survival	aMRI (27)	Multicystic encephalopathy
4	TTTS donor	28	37	survival	aMRI (32)	Severe cerebral atrophy, diffuse white matter loss, abnormal thalamus and capsula interna
5	TTTS donor	22	37	survival	pMRI at 1 year	cPVL Grade 3
6	TTTS recipient	26	27	NND	pUS (28)	Bilateral IVH Grade 3 with PVHI, cPVL Grade 3
7	TTTS recipient	27	28	survival	pMRI (40)	Unilateral IVH Grade 2, infarction right nucleus caudatus
8	TTTS donor	29	29	NND	pMRI (30)	Multicystic encephalopathy
9	sIUGR large twin	35	35	survival	pMRI (35)	Diffuse cortical necrosis
10	sIUGR large twin	27	27	NND	pUS (27)	Bilateral IVH Grade 3
11	Unknown	31	31	survival	pMRI (32)	Multicystic encephalopathy
12	Unknown	36	36	NND	pMRI (36)	Diffuse cortical necrosis, white matter injury and severe basal ganglia/thalamic injury
13	Unknown	36	36	NND	pMRI (36)	Cortical necrosis, white matter injury and severe basal ganglia/thalamic injury

aMRI, antenatal magnetic resonance imaging; cPVL, cystic periventricular leukomalacia; GA, gestational age; IVH, intraventricular hemorrhage; MCA, middle cerebral artery; NND, neonatal death; pMRI, postnatal magnetic resonance imaging; pUS, postnatal ultrasound; PVHI, periventricular hemorrhagic infarction; sIUGR, selective intrauterine growth restriction; TOP, termination of pregnancy; TTTS, twin–twin transfusion syndrome; wks, weeks.

Univariable and multivariable analysis of the potential risk factors contributing to severe cerebral injury was performed (Table 4). The associated risk factors were advanced gestational age at occurrence of single fetal demise (OR, 1.14 for each week; 95% CI, 1.01-1.29; $P = 0.03$), diagnosis of TTTS prior to single fetal demise (OR, 5.0; 95% CI, 1.30-19.13; $P = 0.02$) and gestational age at live birth (OR, 0.83 for each week; 95% CI, 0.69-0.99; $P = 0.04$).

Table 4 Analysis of potential risk factors for severe cerebral injury in the surviving co-twin after single fetal demise ($n = 50$)

Characteristics	Cerebral injury ($n = 13$)	No cerebral injury ($n = 37$)	*P*	Univariable OR (95% CI)	*P*	Multivariable OR (95% CI)
GA at single fetal demise (weeks)	27 (24–33)	23.5 (19–28.8)	0.03	1.14 (1.01-1.29)	0.01	1.34 (1.06-1.69)
TTTS	8/13 (62)	9/37 (24)	0.02	5.0 (1.30-19.13)	0.02	19.2 (1.65-223.69)
sIUGR	2/13 (15)	11/37 (30)	0.32	0.43 (0.08-2.27)		
Monoamniotic pregnancy	1/13 (8)	4/37 (11)	0.75	0.69 (0.07-6.78)		
GA at birth (weeks)	35 (28–37)	37 (34–38)	0.04	0.83 (0.69-0.99)	0.05	0.77 (0.59-1.00)

Data are presented as median (interquartile range) or n/N (%).
OR, odds ratio; *CI*, confidence interval; *GA*, gestational age; *TTTS*, twin-twin transfusion syndrome; *sIUGR*, selective intrauterine growth restriction.

Discussion

This study shows that the incidence of severe cerebral injury in MC pregnancies after single fetal demise is high (13/50, 26%) and is mostly due to hypoxic-ischemic injury resulting in cystic PVL, MCA infarction, or injury to basal ganglia, thalamus and/or cortex. The exact mechanisms leading to these different types of cerebral injury are still unclear. In the past, co-twin morbidity after single fetal demise was thought to result from transfusion of thromboembolic material from the demised fetus into the circulation of its co-twin. At present, most experts think that co-twin morbidity results from acute exsanguination from the surviving co-twin into the low-pressure circulation of the demised co-twin. Acute exsanguination results in acute hemodynamic changes (hypovolemia and anemia) leading to hypoxic-ischemic injury and multi-organ failure.[2] In a previous study, we showed that perinatal asphyxia in MC twins, in contrast to DC twins, is strongly associated with acute exsanguination and anemia at birth.[10] However, alternative explanations can be considered to explain the observed cerebral injury. In this study, we found that severe cerebral injury in the surviving co-twin was associated

with the presence of TTTS (diagnosed prior to single fetal demise), higher gestational age at the time of single fetal demise and lower gestational age at birth. In two pregnancies complicated by TTTS, MCA infarction in the recipient twin was detected antenatally. Whether the cerebral lesions in the TTTS cases occurred before or after single fetal demise is not clear. As shown in previous studies, TTTS is known to be associated with the development of antenatal cerebral injury, including arterial infarctions in recipient twins.[11] The combination of TTTS and single fetal demise may increase the risk of cerebral injury. Similarly, a lower gestational age at birth is a well-known risk factor for cerebral injury; prematurity may have accounted for the cases with severe IVH in our series. The explanation for the association between a higher gestational age at single fetal demise and the presence of cerebral injury is not clear. Since the size of placental vascular anastomoses increases with gestational age, we hypothesize that the severity of acute exsanguination may also increase with gestational age, with reduced vascular resistance through the larger vascular anastomoses. However, care should be taken when interpreting these results and speculating on possible explanations due to the relatively small sample size. In order to reliably investigate risk factors contributing to the development of severe cerebral injury in co-twins following single fetal demise, larger studies are needed.

The incidence of severe cerebral injury reported in this study (26%) is slightly lower than the 34% (95% CI, 28.8–46.1%) risk reported in the recent meta-analysis of Hillman *et al*.[3] Methodological differences and heterogeneity between the studies included in this meta-analysis could have led to an overestimation of the true risk. Our study, the largest single-center series to date, with antenatal and postnatal imaging in the majority of cases, still has limited numbers.

In our study, all but one fetus underwent routine antenatal or postnatal cerebral imaging after single fetal demise. In two cases, severe cerebral injury was detected antenatally and had important clinical implications which led to termination of the pregnancy in both cases. In the majority of cases, severe cerebral injury was detected postnatally, and led to either neonatal death or subsequent neurological symptoms related to perinatal asphyxia. In one case, cerebral imaging was not performed at birth but neurological symptoms became apparent several months later. Given the important clinical and prognostic implications, we recommend routine ante- and postnatal imaging in all MC co-twins after single fetal demise, to enable appropriate ante- and postnatal intervention and timely counseling.

The intriguing question remains as to why the majority (37/50; 74%) of surviving co-twins do not suffer from cerebral injury. We speculate that the type and size of the anastomoses may play an important role in the pathogenesis of cerebral injury. Hypothetically, the presence of large arterioarterial or venovenous anastomoses may

allow a more rapid and massive exsanguination due to the low resistance of these anastomoses. However, this relation is not easy to establish, since the interval between fetal demise and birth is often more than 1 week, after which, placental anastomoses cannot be evaluated due to maceration of the placental share of the demised co-twin.

Severe injury on cerebral imaging does not equal long-term developmental delay. Outcome can vary from healthy development to mild impairment on multiple domains to severe developmental delay. The presence of clinically relevant, long-term impairment can only reliably be ascertained by standardized long-term follow-up of these children until at least school age.[11;12] Hillman *et al.* found a rate of long-term neurodevelopmental impairment after single fetal demise in MC co-twins of 26%.[3] Neurodevelopmental impairment was only defined broadly as cerebral palsy or 'minor delay' in motor development and standardized developmental tests were not employed. In addition, the timing of follow-up was often unclear. As such, the true rate of long-term impairment in MC co-twins after single fetal demise is still unknown. We intend to perform long-term follow-up in the surviving MC co-twins after single fetal demise using standardized developmental tests.

Our findings should be interpreted with care due to the retrospective nature of this study and the relatively small number of cases. In addition, the combination of either pre- and/or postnatal imaging is an important limitation. We recommend stringent and precise ante- and postnatal imaging protocols to evaluate accurately the incidence of antenatal cerebral injury and investigate the correlation between antenatal and postnatal imaging findings. Given the extreme rarity of these events, more accurate estimations of the incidence of severe cerebral injury, and other complications such as gastrointestinal or renal lesions, can only be obtained through an international multicenter registry of MC pregnancies with single fetal demise. Nevertheless, this is the largest cohort thus far, showing clearly that single fetal demise in MC pregnancies is associated with an increased risk of severe cerebral injury for the surviving co-twin. We would strongly advocate careful follow-up with antenatal and postnatal neuroimaging investigations as well as long-term neurodevelopmental follow-up in all MC pregnancies with single fetal demise.

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