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ORIGINAL RESEARCH ARTICLE

Single fetal demise in monochorionic twins: How to predict cerebral injury in the survivor co-twin?

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Abstract

Introduction: The aims of the study were to evaluate perinatal outcome in monochorionic (MC) twins complicated with single intrauterine fetal death, spontaneously versus after fetal therapy, and to assess antenatal events that increase the risk of cerebral injury.

Material and methods: Historical cohort study of MC pregnancies with single intrauterine fetal death diagnosed or referred to a tertiary referral hospital (2012–2020). Adverse perinatal outcome included termination of pregnancy, perinatal death, abnormal fetal or neonatal neuroimaging and abnormal neurological development.

Results: A total of 68 MC pregnancies with single intrauterine fetal death after 14 weeks of gestation were included. Sixty-five (95.6%) occurred in complicated MC pregnancies (twin to twin transfusion syndrome: 35/68 [51.5%]; discordant malformation: 13/68 [19.1%], selective intrauterine growth restriction: 10/68 [14.7%], twin reversed arterial perfusion sequence: 5/68 [7.3%] and cord entanglement in monoamniotic twins: 2/68 [2.94%]). In 52 cases (76.5%) single intrauterine fetal demise occurred after fetal therapy and in 16 (23.5%) occurred spontaneously. Cerebral damage included 14/68 cases (20.6%): 6/68 cases (8.82%) were prenatal lesions and 8/68 cases (11.8%) were postnatal. Risk of cerebral damage tended to be higher in the spontaneous death group (6/16, 37.5%) compared to the therapy-group (8/52, 15.38%) ($p=0.07$). The risk increased with gestational age at intrauterine death (OR 1.21, 95% CI: 1.04–1.41, $p=0.014$) and was higher in those surviving co-twins who developed anemia (OR 9.27, 95% CI: 1.50–57.12, $p=0.016$). Pregnancies complicated with selective intrauterine growth restriction tended to be at higher risk for neurological damage (OR 2.85, 95% CI: 0.68–11.85, $p=0.15$). Preterm birth rate (<37 weeks of pregnancy) was 61.7% (37/60). Seven of eight postnatal cerebral lesions (87.5%) were

Abbreviations: FPL, fetoscopic placental laser; GA, gestational age; IQR, interquartile range; MA, monoamniotic; MC, monochorionic; MCA-PSV, middle cerebral artery-peak systolic velocity; MRI, magnetic resonance imaging; s-IUFD, single intrauterine fetal death; s-IUGR, selective intrauterine growth restriction; TRAP, twin reversed arterial perfusion; TTTS, twin to twin transfusion syndrome; UCO, umbilical cord occlusion; US, ultrasound scan.

related to extreme prematurity. Overall perinatal survival rate was 88.3% (57/68) and 7% (4/57) of children had an abnormal neurological outcome.

Conclusions: Risk of cerebral damage in single intrauterine fetal death is especially high when it occurs spontaneously. Gestational age at single intrauterine fetal death, selective intrauterine growth restriction and anemia of the surviving co-twin are the main predictors for prenatal lesions and might be useful in parent counseling. Abnormal postnatal neurological outcome is closely related to extreme prematurity.

KEYWORDS
cerebral injury, fetal therapy, monochorionic twins, neuroimaging, single intrauterine fetal death

1 | INTRODUCTION

Intrauterine and perinatal morbimortality are increased in monochorionic (MC) twins compared to dichorionic and single pregnancies due to the presence of a shared placenta that predisposes these fetuses to unique complications, such as twin to twin transfusion syndrome (TTTS), selective intrauterine growth restriction (s-IUGR), twin anemia-polycythemia sequence (TAPS), twin reversed arterial perfusion (TRAP) sequence and single intrauterine fetal death (s-IUFD).[1,2] Single fetal demise exposes the co-twin survivor to exsanguination in the empty placental territory through vascular anastomoses with subsequent hypovolemia and hypotension, which is responsible for severe multiorgan injury, especially at cerebral level, or death.

The incidence of abnormal postnatal neuroimaging and neurodevelopment impairment in MC twins is higher than in dichorionic twins: about 34% and 16% of abnormal postnatal neuroimaging and 26% compared to 2% of neurodevelopmental impairment, respectively.[3] It is well known that fetoscopic selective laser ablation of placental vascular anastomoses (FPL) as treatment for TTTS and umbilical cord occlusion (UCO) of the twin at high risk of death (severe cases of s-IUGR or discordant congenital defect) have a protective role in terms of co-twin survival and cerebral injury in the survivor co-twin.[4] However, these procedures do not ensure definitively the absence of these complications.[5]

Parent counseling and clinical management are challenging in MC twins with s-IUFD, and there is great controversy relating to the follow-up they need (frequency of ultrasound scans [US], neuroimaging including neurosonography and/or magnetic resonance imaging [MRI]). Prematurity is also a main condition that puts the newborn at risk of cerebral damage, and it is well known that s-IUFD in MC twins have a high incidence of both iatrogenic and spontaneous preterm delivery.

The aims of this study were to (1) evaluate perinatal outcome in MC twins with s-IUFD in a large series of MC twin survivors, focusing on cerebral damage, comparing spontaneous versus fetal death after therapeutic procedures (FPL or UCO) and (2) assess antenatal events that increase the risk of cerebral injury and might be useful in predicting abnormal neurological outcome for prenatal counseling.

Key Message

When single intrauterine fetal demise occurs in monochorionic twins, prediction of neurological damage in the co-twin is challenging. Spontaneous death, especially in the selective intrauterine growth restriction scenario, higher gestational age at the event and fetal anemia in the survivor are the main prenatal predictor factors.

2 | MATERIAL AND METHODS

2.1 | Study population

A historical cohort study was conducted, including all MC pregnancies with s-IUFD after 14 weeks diagnosed or referred to the Fetal Medicine Unit at La Paz University Hospital (Madrid, Spain) between 2012 and 2020. Monochorionicity was confirmed by US at 11–13.6 weeks of gestation (presence of the T sign).[6] Cases with fetal demise of the co-twin within the subsequent 48 h were excluded. Pregnancies complicated by TTTS, s-IUGR, TRAP sequence or discordant malformation treated by FPL or UCO were included, as well as MC monoamniotic (MA) twins. These pregnancies were followed-up in our center, at least after the diagnosis of s-IUFD. All intrauterine procedures were performed in our center.

Data on maternal and pregnancy characteristics (maternal age, parity, conception method), presence and type of complications and gestational age (GA) at fetal therapy if indicated and GA at diagnosis of s-IUFD were recorded. Data on pregnancy complications (anemia and/or cerebral damage in the survivor co-twin, termination of pregnancy [TOP], premature rupture of membranes, preterm delivery)

and neonatal outcome (GA at birth, type of delivery, birthweight, umbilical artery pH and Apgar score) were also registered.

2.2 | Protocol study and follow-up

TTTS was defined by oligo-polyhydramnios sequence according to the EUROFETUS criteria for maximum vertical pocket of amniotic fluid (AF-MVP) in the recipient and donor (≥8 cm before 20 weeks of GA and ≥10 cm after 20 weeks GA in the recipient and <2 cm in the donor);[7] s-IUGR was defined by the presence of one twin with estimated fetal weight <10th percentile and intertwin estimated fetal weight discordance >25% and classified according to the pattern of end-diastolic velocity blood flow in the umbilical artery,[6] and TRAP sequence was diagnosed by the presence of an acardiac mass retrogradely perfused by an apparently anatomical normal (pump) twin.

Follow-up assessment of survivors included Doppler measurement of middle cerebral artery-peak systolic velocity (MCA-PSV) and detailed neurosonography as soon as the event was detected to rule out fetal anemia and to evaluate signs of ischemic/hemorrhagic cerebral lesions, respectively.[8] MCA-PSV greater than 1.5 multiples of the median (MoM) was used as screening test to identify anemic fetus and severity was classified in mild, moderate and severe based on estimated hemoglobin (Hb) values expressed as MoM for GA (0.84 MoM for mild anemia, 0.65 MoM for moderate and <0.55 MoM for severe).[9] Pros and cons of intrauterine fetal transfusion were discussed with parents.

Voluson E6, E8 or E10 equipped with a 4D convex and transvaginal multifrequency transducers were used (GE Healthcare Technologies). Ultrasound was repeated every 2 weeks for the first month after the diagnosis of s-IUFD and then monthly accordingly to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)[6] and the Spanish Society of Gynecology and Obstetrics (SEGO) guidelines.[10]

Fetal MRI study was offered in all cases at least 3 weeks after s-IUFD or before if there was suspected brain damage on US. MRI was performed using a 1.5-T scanner (Magnetom Avanto, Siemens) according to the following protocol: T2-weighted HASTE sequences (repetition time [RT] = 1000 milliseconds [ms] and echo time [ET] = 140 ms, field of view [FoV] = 300–200 millimeters [mm], matrix 256 × 256) with 4-mm thick slices, at an acquisition time of 18 s.

Cerebral damage included abnormal neuroimaging on US and/or MRI both prenatal and/or postnatal. Severe cerebral injury was defined as at least one of the following: intraventricular hemorrhage ≥grade III, cystic periventricular leukomalacia ≥ grade II, porencephalic cyst, arterial or venous infarction, basal ganglia, thalamic and/or cortical hypoxic–ischemic lesions.[11] When a prenatal abnormal finding was detected, parents were counseled by a pediatric neurologist who evaluated the risk for affectation of motor autonomy, language, and visual and global development before making any decision (to continue pregnancy or to opt for TOP).

At least two cranial US scans were performed during the first week of life in those cases of preterm delivery or when neurological lesion was suspected in utero, according to our institutional protocol; postnatal damage was diagnosed when abnormal findings appeared ≥48 h after birth. In selected cases, neonatal brain MRI was also performed. Severe postnatal US/MRI lesions were defined by using the same imaging criteria than in prenatal neuroimaging. Postnatal neurodevelopment was subjectively assessed by a pediatric neurologist (follow-up ranged from 1 to 9 years [median, 3.83 years]) and was classified into three groups: (1) normal physical and neurological examination, (2) minor impairment (neurological deficiencies with prospect to normalization), and (3) major neurological impairment (cerebral palsy [CP], deafness and/or blindness).[12]

2.3 | Statistical analyses

Statistical data were analyzed using IBM SPSS version 26.0 for windows 21 (IBM Corporation) and reported as *n* (%), mean ± standard deviation or median interquartile range as appropriate. Statistical analysis was performed using the Student's *t*-test and Mann–Whitney U test for continuous variables, while the chi-squared test and Fisher's exact test were used for categorical variables. Univariate and multiple regression model were conducted to analyze possible predictor factors for severe cerebral damage. *p*-values < 0.05 were considered statistically significant for all variables.

2.4 | Ethics statement

Ethical approval in La Paz University Hospital was obtained from the Investigation Ethics Committee (internal code, PI-5512) on December 22, 2022.

3 | RESULTS

A total of 68 MC pregnancies with s-IUFD accomplished the inclusion criteria and were included in the study.

In 52 cases (76.5%) s-IUFD occurred after fetal therapy. Mean GA at intrauterine treatment was 18.9 (±2.4) weeks (range 14.1–24.3). When pregnancy was complicated by TTTS the main indication was FLP (25/35 cases; 71.4%) while in s-IUGR complication and discordant malformation was UCO (6/10; 60% and 12/13; 92.3%, respectively); interstitial laser was performed in four cases of TRAP sequence (4/5; 80%). In 16 cases (23.5%) s-IUFD occurred spontaneously: there was six TTTS (6/35; 17.1%), one discordant malformation (1/13; 7.7%), four s-IUGR (4/10;40%), two cord entanglement in monochorionic monoamniotic (MCMA) twins and three otherwise uneventful pregnancies.

GA at s-IUFD diagnosis was 20.9 ± 3.9 weeks; in 20 (29.4%) cases, fetal death was detected after 22 weeks, seven of them (10.3%) after 28.0 weeks of gestation. GA at diagnosis was significantly higher in spontaneously s-IUFD compared to the therapy group (22.9 ± 4.09

TABLE 1 Antenatal characteristics of 68 monochorionic (MC) pregnancies complicated with single fetal demise.

Characteristics	MC pregnancies ($n=68$)
Maternal age (years)	34.6 (±4.6)
Conception method	
Spontaneous	51 (75%)
AI	1 (1.5%)
IVF (own eggs)	12 (17.6%)
IVF (donor eggs)	4 (5.9%)
Type of pregnancy	
Twins	62 (91.2%)
MCBA	60 (88.2%)
MCMA	2 (2.9%)
Triplets (BCTA)	6 (8.8%)
Complicated pregnancies before s-IUFD	
Complicated MC pregnancies	65 (92.64%)
TTTS	35 (51.5%)
Discordant malformation	13 (19.1%)
s-IUGR	10 (14.7%)
TRAP sequence	5 (7.3%)
Cord entanglement	2 (2.9%)
Uncomplicated pregnancies	3 (4.4%)
Type of fetal demise	
Spontaneous	16 (23.5%)
After intrauterine therapy	52 (76.5%)
FPL	26 (38.2%)
UCO	22 (32.4%)
IL	4 (5.9%)
GA at intrauterine therapy (weeks)	18.9 (±2.4)
Time interval (in days) between intrauterine therapy and fetal demise	9.23 (0−−98)
GA at single fetal demise (weeks)	20.9 (±3.9)
≤20.0	36 (52.9%)
20−−24	20 (29.4%)
24−−28	6 (8.8%)
≥28	6 (8.8%)

Note: Values are expressed as *n* (%), mean (±SD) or median and interquartile range in brackets.

Abbreviations: AI, artificial insemination; FPL, fetoscopic selective laser ablation of placental vascular anastomoses; GA, gestational age; IL, interstitial laser; IVF, in vitro fertilization; s-IUFD, single uterine fetal death; s-IUGR, selective intrauterine growth restriction; MCBA, monochorionic biamniotic; MCMA, monochorionic monoamniotic; TRAP, twin reversed arterial perfusion; TTTS, twin-twin transfusion syndrome; UCO, umbilical cord occlusion.

vs. 20.13 ± 3.6 weeks, $p=0.009$). Details of the antenatal characteristics of the study group are shown in Table 1.

Cerebral damage included 14 cases (14/68; 20.6%), six cases (6/68; 8.82%) of prenatal lesions (fetal US and/or MRI) and eight cases (8/68; 11.8%) of postnatal lesions with previous normal intrauterine neuroimaging. When TOP were excluded, the rate of neonatal cerebral damage was 16.7% (10/60; Table 2).

Risk of neurological damage increased with GA at s-IUFD (OR 1.21, 95% CI: 1.04–1.41, $p=0.014$), with no cases of brain injury (pre-/postnatal) when s-IUFD was diagnosed before 17.5 weeks of pregnancy, 11.42% (4/35) when it occurred before 20 weeks, 25% (5/20) between 20 and 24 weeks and 38.46% (5/13) after 24 weeks of gestation (Figure 1).

Risk of cerebral injury was significantly higher in s-IUFD occurring in complicated MC pregnancies (14/65; 21.5%) than in uneventful MC twins (0/3; 0%); this risk reached 22.9% (8/35) in TTTS and 40% (4/10) in s-IUGR ($p=0.047$). Pregnancies complicated with s-IUGR showed a trend to be at higher risk for neurological damage (OR 2.85, 95% CI: 0.68–11.85, $p=0.15$).

Cerebral damage, prenatal or postnatal, were detected in 8/52 (15.38%) in the therapy-group compared to 6/16 (37.5%) in the spontaneous s-IUFD group ($p=0.078$). When intended s-IUFD, that is UCO ($n=22$) and interstitial laser ($n=2$), were separately analyzed, the risk of severe brain lesions was 7.7% (2/26). Univariate analysis showed a lower risk of cerebral damage when s-IUFD occurred after fetal therapy (OR 0.244, 95% CI: 0.66–0.901, $p=0.034$). The main findings in both groups, spontaneous s-IUFD versus after intrauterine therapy, are shown in Table 3.

Fetal anemia was suspected by MCA-PSV >1.5 MoM in six cases (6/68; 8.82%): one TTTS stage II (16.6%), three s-IUGR (50%), one discordant malformation (16.6%) and one cord entanglement in MCMA (16.6%). Intrauterine transfusion was performed in four of six cases of fetal anemia (two moderate and two severe anemia); two of them (50%) resulted in alive children with normal neurological development and two showed severe cerebral lesions (1 late TOP and 1 infant with CP). The risk of fetal anemia was significantly higher in the spontaneous s-IUFD group versus after intrauterine therapy (4/16 [25%] vs. 2/52 [3.8%], $p=0.02$). Moreover, 4/6 (66.7%) fetuses with fetal anemia presented with pre- or postnatal cerebral damage compared to 2/6 (33.3%) fetuses without anemia, $p=0.024$. Fetal anemia in the surviving co-twin was a significant predictor factor of neurological damage (OR 9.27, 95% CI: 1.50–57.12, $p=0.016$).

When prenatal predictor factors of cerebral damage were combined, the best model was achieved including GA at s-IUFD, death after intrauterine therapy and anemia in the surviving co-twin (ROC = 0.79, 95% CI: 0.67–0.91; Figure 2).

Sixty live newborns were obtained from the 68 MC pregnancies with s-IUFD (88.2%). The perinatal outcomes of surviving co-twins are summarized as a flow chart (Figure 3) and shown in Table 4. Abnormal postnatal neuroimaging was detected in eight newborns with previous normal prenatal US and/or MRI (8/60; 13.3%). In 7/8 cases (87.5%), these findings were related to extreme prematurity and three of them died before 30 days of life (Table 4). GA at delivery was the main predictor factor of postnatal cerebral damage, with lower risk when advancing GA at delivery (OR 0.72, CI: 95% 0.58–0.89, $p=0.003$). Multivariate regression model showed no improvement when other prenatal predictor variables were included.

Neonatal death within the first 28 days of life occurred in three newborns, due to extreme prematurity, with an overall perinatal survival of 83.8% (57/68): 44/52 (84.6%) in the s-IUFD after therapy

TABLE 2 Prenatal and postnatal cases of cerebral damage.

	Type of complication	Therapy	GA at therapy (weeks)	GA at IUFD (weeks)	GA at birth (weeks)	Prenatal US/MR	Postnatal US	Outcome
Prenatal cases of cerebral damage								
1	s-IUGR type II	No	—	19+0	—	Destructive lesions. Microcephaly	—	TOP
2	s-IUGR type III	No	—	30+0	30+2	IVH severe anemia	PVL	Cerebral palsy
3	s-IUGR type II	UCO	21	21+0	36+6	IVH severe VMG	IVH Severe VMG	Carrier of ventriculo-peritoneal shunt
4	Discordant malformation	UCO	18	18+0	—	Severe anemia. Bilateral parieto-occipital malacia. IVH	—	TOP
5	TTTS stage I	FLP	23	23+0[a]	—	Severe anemia. Cortical lesions. PVL	—	TOP
6	TTTS stage III	FLP	17	31+0[a]	—	bilateral cortical hyperechogenity Encephalomalacia	—	TOP
Postnatal cases of cerebral damage								
1	s-IUGR type III	No	—	24+6	29	US normal	Severe PV hyperecogenicity	Normal neurological development
2	TTTS stage V	No	—	24+5[b]	27+1	US and MRI Normal	PVL White matter lesion	Deceased (10 days)
3	TTTS stage V	No	—	19+5[b]	33+5	US and MRI Normal	PVL	Global developmental delay
4	Cord entanglement MCMA twin	No	—	24+0	28+1	US and MRI Normal	Several PV hyperecogenicity	Normal neurological development
5	TTTS stage II	FPL	22+0	22+6[b]	26+4	US and MRI Normal	IVH grade III	Language delayed
6	TTTS stage III	FPL	20+0	20+0[b]	24+0	US normal	Several PV hyperecogenicity	Deceased (30 days)
7	TTTS stage III	FPL	24+3	25+2[b]	26+4	US normal	Several PV hyperecogenicity	Deceased (36 days)
8	TTTS stage III	FPL	22+5	24+0[b]	27+5	US normal	IVH grade III	Follow-up at Prematurity Unit

Abbreviations: FLP, laser coagulation of anastomosis; GA, gestational age; IVH, intraventricular hemorrhage; MCMA, monochorionic monoamniotic; MRI, magnetic resonance imaging; PVL, periventricular leukomalacia; S-IUGR, selective intrauterine growth restriction; TOP, termination of pregnancy; TTTS, twin-to-twin transfusion syndrome; US, ultrasound; UCO, umbilical cord occlusion; VMG, ventriculomegaly.

[a]Recipient.

[b]Donor.

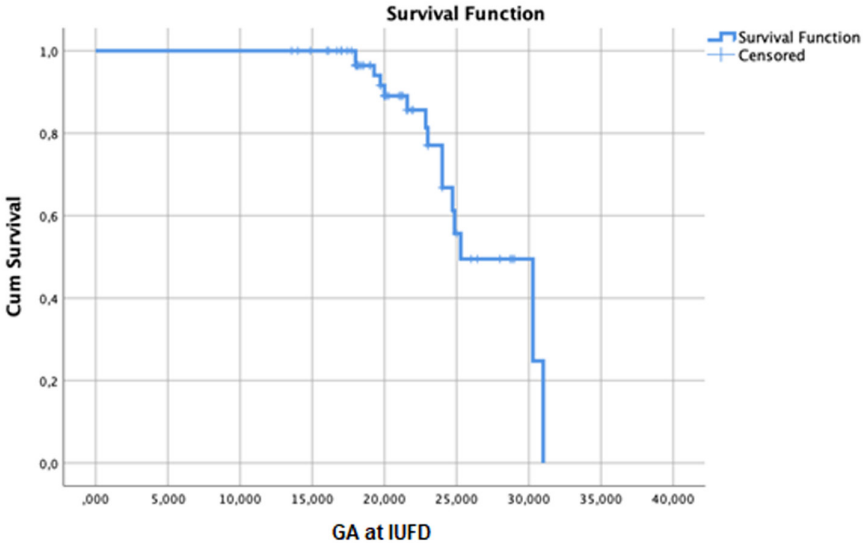

FIGURE 1 Kaplan–Meier survival curve analysis for gestational age (GA) at single intrauterine fetal demise (IUFD).

TABLE 3 Gestational complications in spontaneous single intrauterine fetal demise versus after intrauterine therapy.

	Spontaneous	After intrauterine therapy
Total	16 (23.5)	52 (76.5)
GA at intrauterine therapy (weeks)	—	18.9 (±2.4)
GA at single fetal demise (weeks)	22.99 (±4.1)	20.13 (±3.6)
Co-twin death	0	1 (1/52 = 1.92)
TOP	2 (12.5)	5 (9.61)
GA at delivery (weeks)	32.62 (±3.2)	34.61 (±3.8)
>37 weeks	1/13 (7.69)	19/44 (43.18)
Late preterm (32–37 weeks)	7/13 (53.84)	13/44 (29.54)
Very preterm (28–32 weeks)	4/13 (30.76)	8/44 (18.18)
Extreme preterm (<28 weeks)	1/13 (7.69)	4/44 (9.09)
Prenatal cerebral damage	2/16 (12.5)	4/52 (7.69)
Postnatal cerebral damage	4/16 (25)	4/52 (7.69)
Neonatal mortality	1/16 (6.25)	2/52 (3.84)
Neurological morbidity	2/16 (12.5)	1/52 (1.92)

Note: Values are expressed as mean (±SD) or *n* (%).

group versus 13/16 (81.2%) in the spontaneous s-IUFD group. Abnormal neurological outcome was detected in four infants (4/60; 6.7%), all of them with cerebral lesions on neuroimaging.

4 | DISCUSSION

Risk of severe cerebral neuroimaging lesions in the surviving MC co-twin is high, around 20%. This risk is related to GA at s-IUFD and severe fetal anemia in the survivor. Previous therapy and higher GA at delivery are protective factors for cerebral damage. A prenatal multivariate model including GA at IUFD, previous fetal therapy and anemia in the survivor, improves the prediction of cerebral lesions.

The risk of brain damage in the survivor after s-IUFD in MC twins raises diagnostic and management challenges for the obstetrician. Although several prenatal predictor factors have been described there is no risk stratification regarding the occurrence of this event.[13] Also, cerebral damage by neuroimaging (US and/or MRI) does not necessarily imply a long-term developmental delay. To identify predictors of neurological sequel is the mainstay for ensuring proper parental counseling.[14]

In our series, 14 of 68 (20.1%) survivors showed severe cerebral damage: six of 68 cases (8.82%) were diagnosed prenatally and eight of 68 (11.8%) were postnatally mainly related to preterm birth. We must highlight the high proportion of s-IUFD after FPL or UCO in our cohort, with more than 75% of s-IUFD after fetal therapy. This makes it difficult to compare results with a previous series in which only spontaneous s-IUFD were considered. In a systematic review, Mackie et al. excluding cases of s-IUFD after fetal therapy, reporting a 20% of abnormal antenatal brain imaging (95% CI: 12.8–31.1, $I^2 = 21.9\%$ six studies, 116 cases),[15] comparable to Lanna et al. in a series of 78 cases of single survivors after spontaneous s-IUFD, with a rate of 18% of cerebral damage in survivor co-twin.[16] In a series of 49 cases, Van Klink et al. reported a slightly higher incidence of cerebral injury, 26%.[17] In all these studies, cases of IUFD after fetal therapy were excluded. In our series, if only spontaneous s-IUFD were considered, rate of cerebral damage was noticeably higher, 37.5% (6/16) versus 15.38% (8/52) in the therapy-group, comparable to the 34% (95% CI: 28.8%–46.1%) reported in the meta-analysis of Hillman et al.[3] We can compare our results to those published by Robinson et al. They analyzed the rate of cerebral injury detected by US and MRI in a group of 33 patients with complicated MC twins, including 10 cases of spontaneous fetal demise and eight cases after FPL and the rate of brain abnormalities was 20% (2/10) by US and 30% (3/10) by prenatal MRI in those with

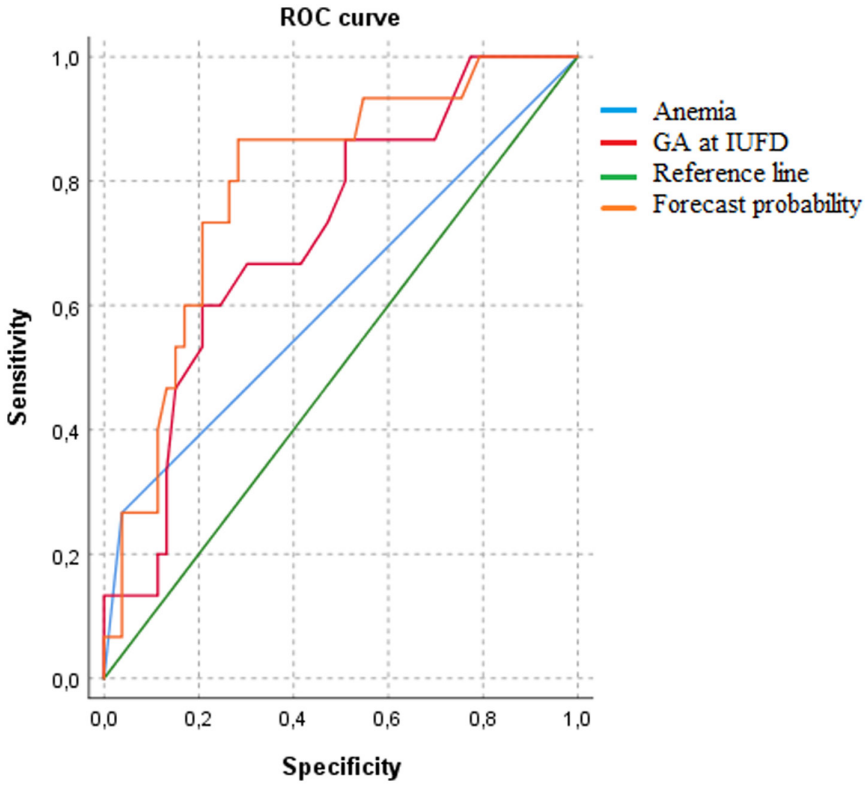

FIGURE 2 Prenatal prediction of cerebral damage in the survivor co-twin. Multivariate regression analysis. The best model includes gestational age (GA) at single intrauterine fetal death (s-IUFD), death after intrauterine therapy and anemia in the surviving co-twin.

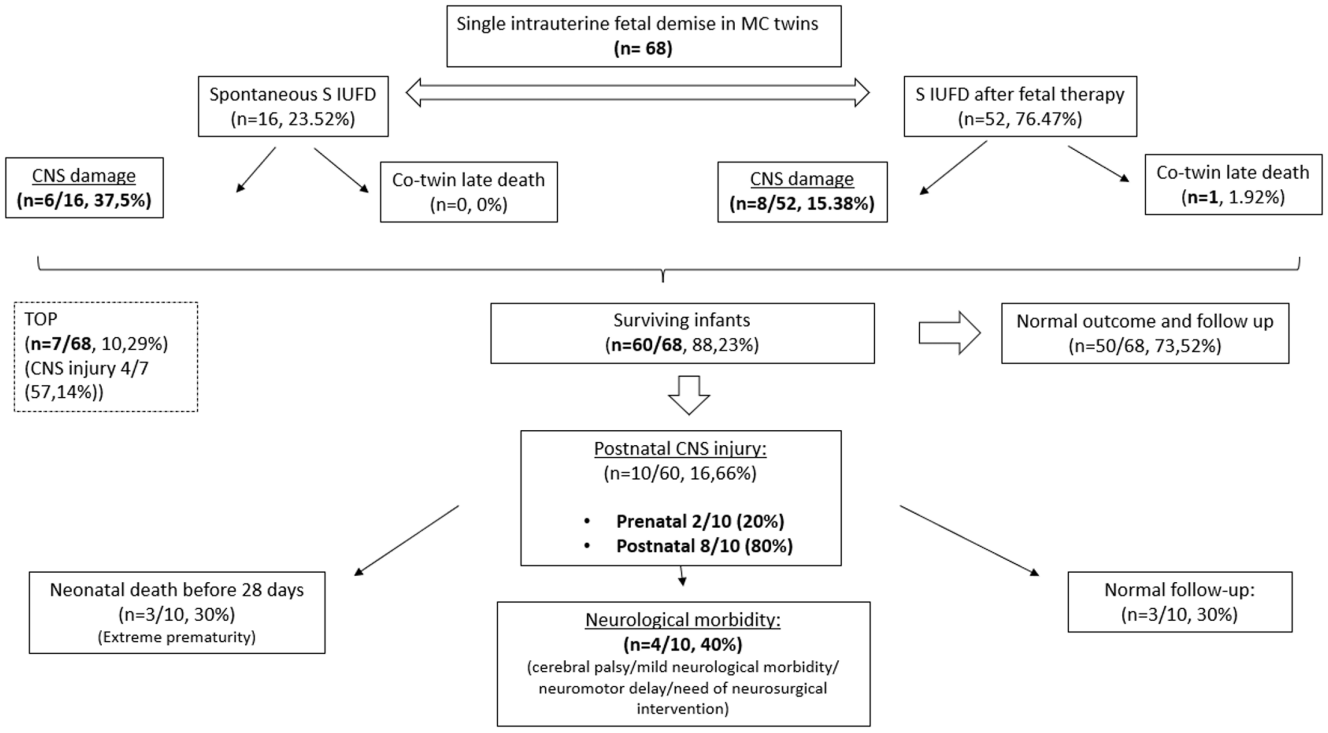

FIGURE 3 Flow chart of study population. CNS, central nervous system; MC, monochorionic; s-IUFD, single intrauterine fetal death; TOP, termination of pregnancy.

spontaneous IUFD and 13% (1/8) by US and 38% (3/8) by prenatal MRI in those after FLP.[18]

We found that the main factors that had an impact on the appearance of brain injury were GA at s-IUFD and the presence of anemia in the surviving co-twin. IUFD in the context of s-IUGR, mainly type III, also seems to influence although with less impact. Previous fetal therapy had a protective effect. GA at birth was a clear predictor factor for cerebral damage (OR 0.72, CI: 0.58–0.89,

TABLE 4 Perinatal outcomes.

Characteristics	MC pregnancies ($n=68$), live births = 60
Prenatal complications of the surviving co-twin:	
CNS prenatal injury	6 (8.8%)
Fetal anemia	6 (8.8%)
Co-twin demise	1 (1.5%)
TOP	7 (10.3%)
Liveborn	60 (88.2%)
GA at delivery (weeks)	33.9 (±3.9)
Preterm delivery rate:	
<37	37/60 (61.7%)
24–28 weeks	5 (8.3%)
28–32 weeks	12 (20%)
32–36 + 6 w	20 (33.3%)
≥37 w	23 (38.3%)
Type of delivery:	
Vaginal	26 (45.6%)
Cesarean section	30 (52.6%)
Birth weight (g)	2191 (±831)
<1000	7 (10.3%)
1000–1499	6 (8.8%)
1500–1999	12 (14.7%)
≥2000	32 (50%)
Postnatal complications of the surviving co-twin:	
Neonatal death (28 days of life)	3 (5%)
CNS postnatal injury	8 (13.3%)
Any cerebral damage (prenatal and postnatal)	10 (16.7%)
Abnormal neurological outcome	4 (6.7%)
Perinatal survival	57/68 (83.8%)
Intact perinatal survival	53/68 (77.9%)

Note: Values are expressed as *n* (%) or mean (±SD).

Abbreviations: CNS, central nervous system; GA, gestational age; MC, monochorionic; TOP, termination of pregnancy.

$p=0.003$), but because of its postnatal nature is not useful in prenatal counseling. However, GA has a great impact on the management: immediate delivery when IUFD occurs far from the term worsens the prognosis of the surviving twin and must be avoided, since immediate delivery does not protect against brain lesions but may contribute to a worse neurological outcome because of the prematurity.

GA at IUFD is a well-known predictor factor for cerebral damage. According to our data, the higher the GA at s-IUFD, the higher the risk of brain lesions (OR 1.21, 95% CI: 1.04–1.41, $p=0.014$). Six cases of prenatal brain injury were diagnosed: in three of them s-IUFD occurred between 23 and 31 weeks of pregnancy. There is no risk stratification regarding the occurrence of cerebral lesions; however, according to reported data, it seems that the critical period would be from 24 to 34 weeks of gestation, when the impact of cerebral lesions is amplified by the immaturity of the fetal brain.[14]

Complicated MC pregnancies, like TTTS and s-IUGR, are associated with higher risk of antenatal cerebral injury, even in those cases with double survival, thus the combination of both factors (s-IUFD in the context of TTTS or s-IUGR) may increase the risk of brain damage. In our series, IUGR type III was diagnosed in 50% of cases with antenatal cerebral damage (3/6) and in one of eight cases of postnatal damage, and TTTS in two of six cases (33.3%) of antenatal cerebral damage and in six of eight (75%) of postnatal damage.

Type-III s-IUGR is characterized by unequal placental sharing with large bidirectional artery-to-artery (AA) intertwin anastomoses, allowing for acute hemodynamic shift from one fetus to the other.[19] A sudden death of the smaller fetus may result in the exsanguination of the larger twin through a large AA anastomosis: a severe hypovolemic event resulting in brain damage.[20] Regarding TTTS, survivor fetuses have been shown to be at increased risk of abnormal neurodevelopment compared to uncomplicated MC twins: before the introduction of FPL its incidence was reported to be between 17 and 42%[21] but nowadays FPL has decreased the rate to 4%–18%.[22]

Risk of cerebral damage seems higher when sigle fetal demise affects to the recipient twin instead of the donor one. Gebb et al. in a retrospective study including 64 cases of s-IUFD in TTTS treated by FLP, reported an abnormal MRI in 12 co-twin survivors (30%): nine of 18 (50%) after recipient demise and three of 22 (14%) after donor demise ($p=0.02$).[23] Unidirectional exsanguination through arteriovenous anastomoses from the donor to the death recipient might explain this higher risk.

UCO may be indicated to prevent neurological damage associated with s-IUFD (in cases complicated by severe s-IUGR or by TTTS when technical factors make FPL unfeasible or in discordant malformation) by preventing the massive blood transfusion from the surviving fetus to the occluded twin. We prefer not to talk about prevention but about reduction, as it is possible to observe cases of severe cerebral damage in the survivor after a successful UCO.[5] That is why we decided to include these cases even when the pathophysiological mechanism of cerebral injury is different.

Intrauterine procedures decrease the mortality rate and the risk of cerebral damage but increase the risk of premature rupture of membranes and prematurity. In line with this, O'Donoghue et al. reported an abnormal postnatal brain MRI in 3.2% of co-twin survivors after UCO or interstitial laser compared to 22.2% in spontaneous s-IUFD.[24] The protective effect against cerebral damage was also found in our series (OR 0.244, 95% CI: 0.66–0.901, $p=0.034$).

Our data showed that the presence of anemia in the co-twin was the main factor for brain injury (OR 9.27, 95% CI: 1.50–57.12, $p=0.016$). Four of six (66.7%) anemic survivors presented with cerebral damage. Fetal anemia was identified as the main cause of brain damage in survivor MC twins more than 20 years ago.[25] MCA-PSV greater than 1.5 MoM may increase five-fold the relative risk

of cerebral injury,[16] but it is still unclear whether intrauterine fetal transfusion can reduce the risk of neurological damage in anemic fetuses and if this treatment is beneficial for long-term prognosis. Tedjawiria et al. found the same risk of brain injury in the surviving anemic co-twin following intrauterine fetal transfusion than in those who received expectant management, which was around 26%.[26]

MRI was supposed to be superior to US in an early and detailed description of cerebral lesions[27] but in our series we found no differences between both neuroimaging techniques. Superiority of diffusion-weighted imaging (DWI) sequences over conventional MRI has recently been reported, and early detection of discrete acute ischemic injuries may shorten the time to diagnosis.[14] Where there is a very high risk of cerebral damage after s-IUFD, especially when severe fetal anemia is detected in the survivor co-twin, offering DWI sequences appears to be a reasonable option.

Finally, we propose a multivariate model for increasing the prediction of cerebral damage in s-IUFD; combining GA at IUFD, previous fetal therapy and anemia in the co-twin survivor achieves the best performance. GA at birth, although the strongest predictor factor, is not useful for prenatal counseling. Multivariate models may be useful for clinical purposes.

5 | CONCLUSION

A multivariate model for increasing the prediction of cerebral damage in s-IUFD is proposed. A combination of GA at IUFD, previous fetal therapy and anemia in the co-twin survivor achieves the best performance. Multivariate models may be useful for clinical purposes.

AUTHOR CONTRIBUTIONS

All the authors contributed to the design, drafting and revision of the manuscript and approved the final submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors confirm there are no conflicts of interest.

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