OBSTETRICS

Magnetic resonance neuroimaging after laser for twin-twin transfusion syndrome with single fetal demise

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BACKGROUND: Neurologic injury in the surviving twin is a risk after single fetal demise in a monochorionic pregnancy.

OBJECTIVE: This study aimed to describe fetal magnetic resonance neuroimaging findings in pregnancies complicated by single fetal demise after laser photocoagulation for twin-twin transfusion syndrome.

STUDY DESIGN: This was a single-center retrospective analysis of a cohort of prospectively collected patients in a monochorionic twin registry who had fetoscopic laser photocoagulation for twin-twin transfusion syndrome with single fetal demise at follow-up. Magnetic resonance neuroimaging was offered 3 to 4 weeks after the demise to assess for potential neurologic sequelae. Magnetic resonance images were interpreted by 2 board-certified neuroradiologists and classified as normal, mildly abnormal, or severely abnormal. The groups were compared on the basis of recipient vs donor demise using the Fisher exact test and Mann-Whitney *U* test. Multivariate logistic regression was performed to determine risk factors for abnormal magnetic resonance neuroimaging.

RESULTS: In 378 laser photocoagulation procedures, 64 cases (16.9%) of single demise were identified (36 in the donor group and 28 in the recipient group). Of note, 6 patients had rupture of membranes with nonviable delivery (3 from each group). Moreover, 40 patients (69%) underwent magnetic resonance imaging. Of those patients, 12 (30%) had abnormal findings: 10 (83%) were associated with mild changes, and 2 (17%) were associated with severe findings. Abnormal magnetic resonance neuroimaging was seen in 3 of 22 patients (14%) after donor demise and 9 of 18 patients (50%) after recipient demise (P=.02). Logistic regression revealed that recipient vs donor demise was an independent risk factor for abnormal magnetic resonance imaging. In addition, 2 pregnancies with severe magnetic resonance imaging findings had complicated courses.

CONCLUSION: Mildly abnormal magnetic resonance neuroimaging findings were common after laser photocoagulation for twin-twin transfusion syndrome complicated by single fetal demise and were more common in cases of recipient demise than donor demise. Severe magnetic resonance neuroimaging findings in this series were limited to patients with complicated peri- or postoperative courses.

Key words: fetal magnetic resonance imaging, fetal neuroimaging, laser, monochorionic twins, twin-twin transfusion syndrome

Introduction

Fetal neurologic injury in the co-twin survivor is a known risk after single fetal demise in a monochorionic pregnancy.[1–3] Exsanguination of the survivor into the placental territory of the demised fetus is thought to cause a hypotensive episode that can lead to multiorgan failure, neurologic damage, and/or death.[4] In those that survive the acute episode, the risk of neurologic impairment is approximately 20%.[2,5,6] Monochorionic pregnancies complicated by twin-twin transfusion syndrome (TTTS) are at increased risk of single fetal demise with or without fetal therapy.

Fetoscopic laser photocoagulation of the vessels on the surface of the placenta is the optimal treatment of advanced-stage TTTS.[7] The procedure functionally dichorionizes the placenta by occluding the vascular connections so that each fetus has its placental share. In most cases, both fetuses survive after the procedure, and the TTTS gradually resolves. In some cases, fetal death of 1 twin occurs after laser photocoagulation. Given the functional dichorionization of the placenta, the risk of neurologic damage in the surviving twin is lower than if co-twin demise occurred without laser photocoagulation, but residual risk exists.[5,6] Many centers adhere to a management protocol that includes weekly fetal ultrasound assessment with fetal magnetic resonance (MR) neuroimaging at 2 to 4 weeks after the diagnosis of single demise.[8,9] MR serves as an adjunct to ultrasound and improves diagnostic accuracy, particularly in detecting hemorrhagic insults because of the ability to perform echo-planar imaging (EPI) sequences.[10,11] In addition, MR may detect abnormalities earlier than is possible with ultrasound.

Prior literature has focused on severe cerebral sequelae after laser photocoagulation complicated by single fetal demise.[6,9] With technologic advances in fetal MR, milder cerebral findings may now be appreciated. This study aimed to report fetal MR neuroimaging findings in pregnancies complicated by single fetal demise after laser photocoagulation for TTTS.

Materials and Methods

After institutional review board approval, we conducted a single-center retrospective review of a cohort of prospectively collected patients in a monochorionic twin registry who had laser photocoagulation for TTTS with single fetal demise at follow-up between 2009

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AJOG at a Glance

Why was this study conducted?

Data on contemporary magnetic resonance (MR) neuroimaging findings of survivors after laser photocoagulation for twin-twin transfusion syndrome (TTTS) complicated by single fetal demise is lacking. This study aimed to describe the findings and evaluate the risk factors for abnormal neuroimaging.

Key findings

Abnormal MR neuroimaging occurred in 30% of survivors after laser photocoagulation for TTTS complicated by co-twin demise. Abnormal MR neuroimaging was more common after recipient demise than donor demise. Most abnormal findings were mild with severe abnormalities in this series being limited to patients with complicated peri- and postoperative courses.

What does this add to what is known?

Our findings revealed a higher incidence of abnormal MR neuroimaging than previously reported. We identified recipient loss as a risk factor for abnormal neuroimaging by MR in the survivor.

and 2021. Selective fetoscopic laser photocoagulation was performed in the standard fashion ablating all donor-recipient anastomoses on the surface of the placenta. In our center, laser photocoagulation is offered in cases of Quintero stage II to IV TTTS and in select cases with stage I TTTS at increased risk of pregnancy loss (massive polyhydramnios, elevated Children's Hospital of Philadelphia cardiovascular score, or short cervix).[12,13] We routinely performed ultrasounds on postoperative day (POD) 1 and POD 7 after the procedure. Patients were generally followed up locally after that time with weekly ultrasound assessments. In complicated cases, we performed additional ultrasound examinations postoperatively. Single (or dual) demise may be identified at any of these follow-up visits or during local follow-up.

After single demise was diagnosed, the patients were continued to be followed up weekly with ultrasound and are offered MR neuroimaging at least 3 weeks after the demise to assess for potential neurologic sequelae in the surviving twin. Fetal MR was performed using a 1.5T or 3.0T system (Siemens Healthcare) without maternal or fetal sedation. Brain images were obtained in multiple axial, sagittal, and coronal planes, with a section thickness of no more than 3 mm using single-shot fast spin-echo T2, EPI, and diffusion-weighted imaging. Respecting our institutional protocol, the MR studies were interpreted by 2 board-certified neuroradiologists with expertise in interpreting fetal neuroimaging. Here, the results were classified as normal, mildly abnormal, or severely abnormal. Mild MR changes included isolated choroid plexus or grade I to II germinal matrix (GM) hemorrhages or mild ventriculomegaly. Severe MR changes included grade III to IV GM hemorrhages, severe ventriculomegaly, and/or parenchymal abnormalities. Furthermore, most patients had an ultrasound performed on the day of the MR, but a few were undergoing local ultrasound surveillance and only returned to our center for MR.

Pregnancy characteristics were obtained from the prospective registry, which included information from electronic medical records and review of delivery records from the hospital of birth. Continuous variables were reported as median and interquartile range, whereas categorical variables were reported as frequency and percentage. Comparison between pregnancies with and without abnormal neuroimaging findings was done using the Fisher exact test and Mann-Whitney *U* test. Multivariate logistic regression was performed to determine risk factors for abnormal MR neuroimaging (Stata version 11; StataCorp, College Station, TX).

Although there was no formal pediatric neurodevelopmental follow-up program, follow-up information was sought for pregnancies with abnormal MR neuroimaging. Some children had follow-up at our center, and available registry records were reviewed. For those without available records, parental follow-up was performed by telephone when possible.

Results

Of 378 patients who underwent laser photocoagulation during the study period, 305 (80.7%) had dual survival, 36 (9.5%) had donor demise, 28 (7.4%) had recipient demise, and 9 (2.4%) had dual demise. In the 64 cases (16.9%) of single demise, 6 patients had rupture of membranes with nonviable delivery within 1 week of the laser photocoagulation procedure (3 from each group: recipient vs donor demise).

Of the 58 ongoing pregnancies, 40 patients (69%) underwent fetal MR neuroimaging 3 to 4 weeks after the single demise, including 22 pregnancies after donor demise and 18 pregnancies after recipient demise. Of note, 18 patients (31%) did not have MR, including 3 patients who delivered before the scheduled MR appointment and 15 patients that declined to return to our center because of logistic reasons. Of those who had MR, abnormal neuroimaging was seen in 12 pregnancies (30%), including 9 of 18 pregnancies (50%) after recipient demise and 3 of 22 pregnancies (14%) after donor demise ($P=.02$) (Table 1). There was no difference in prelaser TTTS stage ($P=.48$), postoperative interval at the time of diagnosis of demise ($P=.13$), or rate of twin-anemia polycythemia sequence (TAPS) between groups ($P=.24$). Logistic regression revealed that recipient vs donor demise was an independent risk factor for abnormal MR neuroimaging (Table 2).

For the 12 patients with abnormal fetal MR neuroimaging, 8 (67%) had ultrasound on the same day in whom 7 (88%) were normal and 1 (12%) revealed an abnormal-appearing middle cerebral artery waveform. Of the 12 abnormal MR findings, 10 (83.3%) were

classified as mild, whereas 2 (16.7%) were classified as severe. Prelaser donor fetal growth restriction was similar in pregnancies with normal (19/28) vs abnormal (6/12) MR neuroimaging (P=.31). Figures 1 to 4 show examples of mild abnormal findings, whereas Figures 5 and 6 reflect the cases with severe findings. Both pregnancies with severe MR findings had a complicated peri- or postoperative course. The case depicted in Figure 1 was conducted for stage II TTTS and was complicated by severe maternal supraventricular tachycardia with hypotension during laser photocoagulation. After the procedure, the donor developed ventriculomegaly, and donor demise was noted on POD 49. The case depicted in Figure 2 occurred in a pregnancy treated for stage III TTTS that subsequently developed severe TAPS postoperatively.

Although there was no formal pediatric follow-up program, 10 of 12 pregnancies (83%) with abnormal findings had some postnatal clinical information available (Table 3). Of the 10 pregnancies with mild findings prenatally, 5 (50%) had postnatal head ultrasound, and all studies were normal. Clinical information at age ≥3 years was available for 7 children (70%). Of note, 1 child (patient 1) with antenatal right choroid plexus hemorrhage was born at 37 weeks of gestation and diagnosed with autism at 18 months of age requiring special education. Another child (patient 2) born at 36 weeks of gestation received an individualized education program (IEP) for reading support in his second grade classroom. The other 5 children had normal neurodevelopment by standardized testing or at pediatric follow-up visits. Of the severe cases, 1 fetus (patient 8) was prenatally diagnosed with diffuse polymicrogyria bilaterally with primitive sulcation and decreased parenchyma posteriorly. After birth at 33 weeks of gestation, the neonate was diagnosed with "in utero stroke" and had severe developmental delay at age 7 years, including need for tracheostomy and gastrostomy tube support. The severe findings in the other fetus (patient 9) included left frontoparietal malformation of cortical development with polymicrogyria and suspected schizencephaly. After birth at 39 weeks of gestation, the infant was diagnosed with a left perisylvian neuronal migration disorder consisting of polymicrogyria and pachygyria. At 7 years of age, the child had epilepsy, developmental delay, and right hemiparesis.

TABLE 1
Clinical and magnetic resonance imaging findings in pregnancies complicated by single fetal demise after laser photocoagulation for twin-twin transfusion syndrome based on type of demised fetus

Variable	Recipient demise (n=18)	Donor demise (n=22)	*P* value
Prelaser TTTS stage			.48
Stage I	2	3	
Stage II	7	7	
Stage III	7	12	
Stage IV	2	0	
Post-op interval in days to demise, median (IQR)	7 (1–20)	1 (1–7)	.13
Days between demise and MRI, median (IQR)	24 (20–28)	26 (21–29)	.32
TAPS, n (%)	5 (27)	3 (14)	.24
Normal MRI	9	19	
Mild MRI changes in survivor			
CP hemorrhage	2	0	
Grade I hemorrhage	5	2	
Grade II hemorrhage	1	0	
Total	8	2	
Severe MRI changes in survivor	1	1	
Total abnormal MRI, n (%)	9 (50)	3 (14)	.02

MRI changes: mild (choroid plexus or grade I to II GM hemorrhage or mild ventriculomegaly) and severe (grade 3 to 4 GM hemorrhage, severe ventriculomegaly, or parenchymal abnormalities).

CP, choroid plexus; *GM*, germinal matrix; *IQR*, interquartile; *MRI*, magnetic resonance imaging; *TAPS*, twin-anemia polycythemia sequence; *TTTS*, twin-twin transfusion syndrome.

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Comment

Principal findings

Abnormal MR neuroimaging findings were common after laser photocoagulation for TTTS complicated by single fetal demise. Cerebral abnormalities were found in 12 of 40) of pregnancies (30%) in our series with mild findings in 10 of

TABLE 2
Logistic regression of factors associated with abnormal magnetic resonance imaging findings

Variable	Odds ratio (95% CI)	*P* value
Demised fetus (recipient vs donor)	7.75 (1.52–39.54)	.01
TAPS	0.35 (0.05–2.77)	.32
Post-op day of demise	1.02 (0.98–1.06)	.45

CI, confidence interval; *TAPS*, twin-anemia polycythemia sequence.

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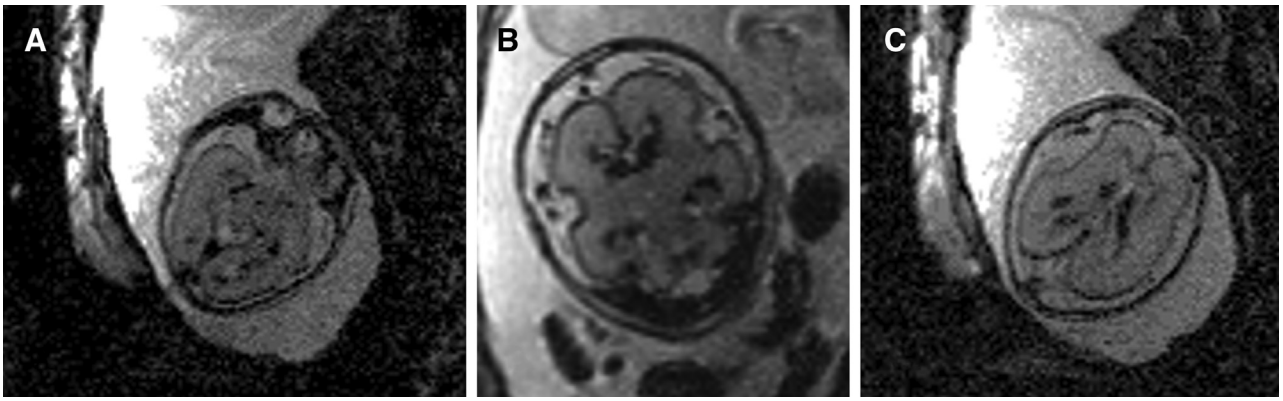
FIGURE 1
Prenatal MR from patient 2 at 23 weeks: bilateral GM hemorrhage



Bilateral GM hemorrhage on axial (**A** and **C**) and coronal EPI (**B**).

EPI, echo-planar imaging; *GM*, germinal matrix; *MR*, magnetic resonance.

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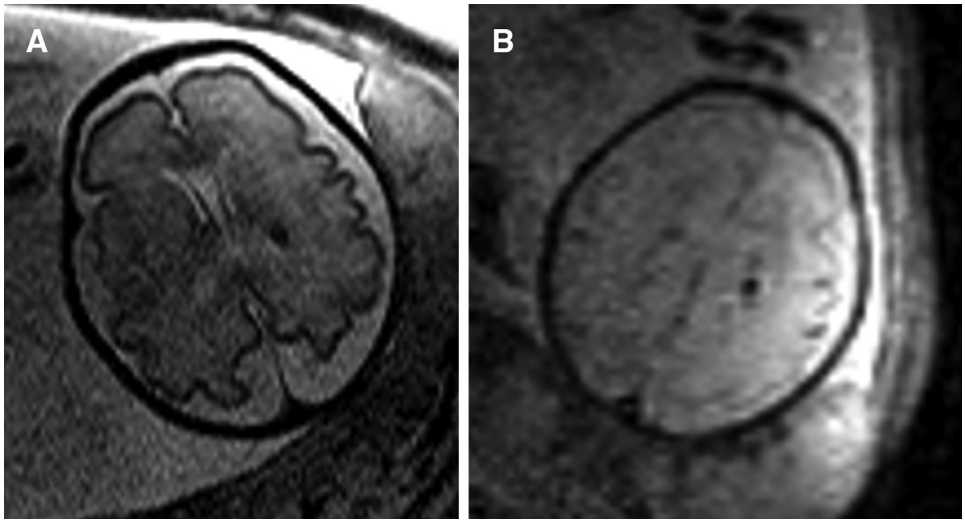
12 pregnancies (83.3%). Many of these mild findings were most likely to resolve, but long-term follow-up was warranted. Of note, 1 child with antenatal right choroid plexus hemorrhage was diagnosed with autism at 18 months of age, and another child with bilateral GM hemorrhage received an IEP for reading support in the second grade. These clinical findings may or may not be related to the antenatal MR images. The 2 patients with severe findings had complicated courses that were most likely the etiology of the substantial neurologic injury that resulted in profound clinical sequelae.

Interestingly, our results showed that abnormal neuroimaging is more frequent in pregnancies complicated by postlaser demise of the recipient (50%) than of the donor (14%). We proposed 2

FIGURE 2
Prenatal MR from patient 7 at 30 weeks: left GM hemorrhage



Left GM hemorrhage on axial SSFSE T2 imaging (**A**) and axial EPI (**B**).

EPI, echo-planar imaging; *GM*, germinal matrix; *MR*, magnetic resonance; *SSFSE*, single-shot fast spin-echo.

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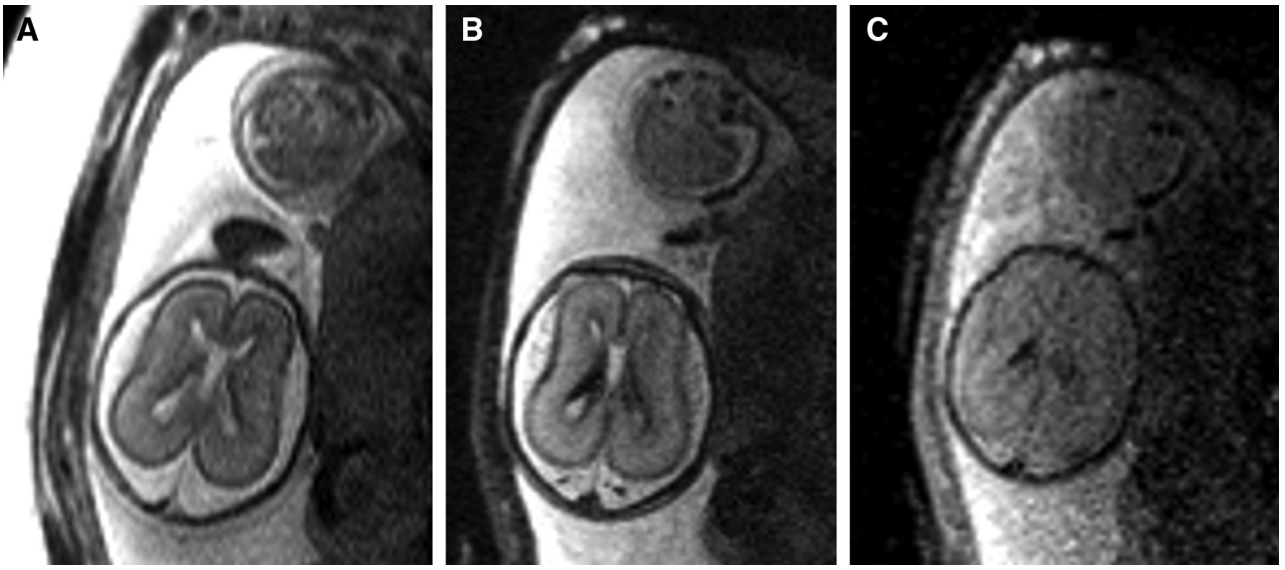
FIGURE 3
Prenatal MR from patient 5 at 24 weeks: right grade I GM hemorrhage



Right grade I GM hemorrhage on axial SSFSE imaging (**A**) and axial EPI (**B** and **C**).

EPI, echo-planar imaging; *GM*, germinal matrix; *MR*, magnetic resonance; *SSFSE*, single-shot fast spin-echo.

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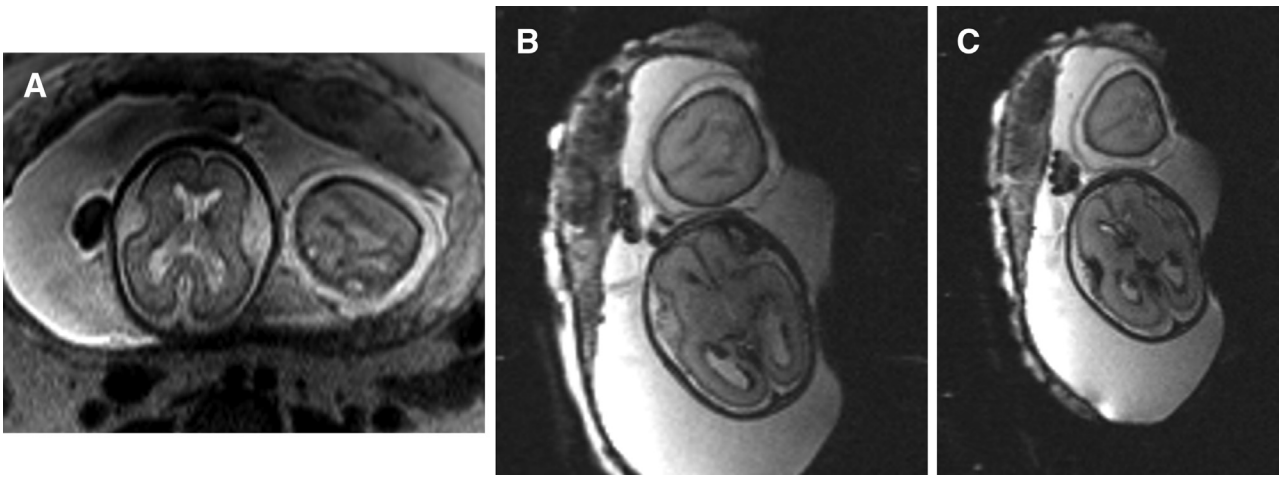
potential mechanisms to explain this finding. The first is that the relatively smaller placental territory of the donor would likely pose less of a risk for exsanguination either via a residual anastomosis postoperatively or before completion of the laser intraoperatively. In addition, recipient hypervolemia because of the TTTS pathophysiology may provide a buffer if the recipient loses blood into the deceased donor circulation. Similarly, the lower placental share and hypovolemia of the donor may lead to an increased risk of cerebral damage if the donor loses blood into the recipient

FIGURE 4
Prenatal MR from patient 3 at 24 weeks: bilateral grade II intraventricular hemorrhage



Bilateral grade II intraventricular hemorrhage and presence of co-twin demise on axial SSFSE T2 imaging (**A**) and axial EPI (**B** and **C**).

EPI, echo-planar imaging; *MR*, magnetic resonance; *SSFSE*, single-shot fast spin-echo.

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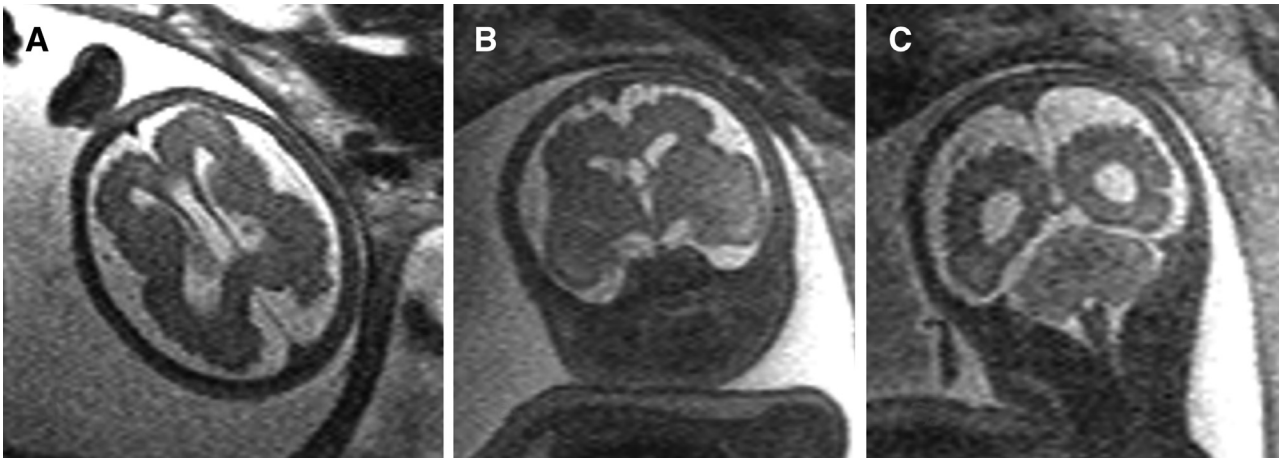
FIGURE 5
Prenatal MR from patient 8 at 32 weeks: diffuse polymicrogyria, abnormal sulcation and decreased parenchyma posteriorly



Diffuse polymicrogyria bilaterally, abnormal sulcation and decreased parenchyma posteriorly on axial (**A**) and coronal (**B** and **C**) SSFSE T2 imaging.

EPI, echo-planar imaging; *MR*, magnetic resonance; *SSFSE*, single-shot fast spin-echo.

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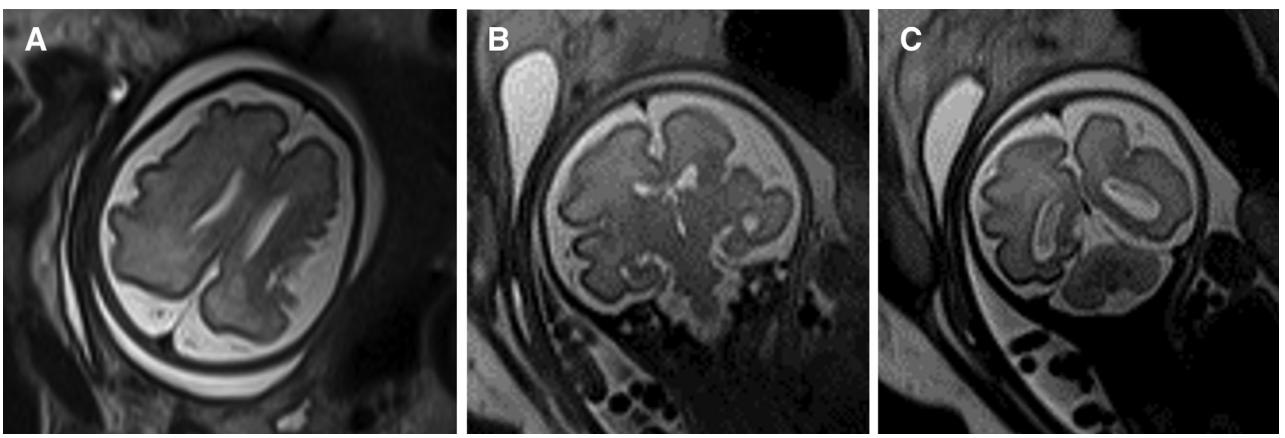
circulation whether during laser photocoagulation or through a residual anastomosis after recipient demise.

Results in the context of what is known

Our study revealed a higher incidence of abnormal neuroimaging than previously reported. Previous literature has focused on severe MR pathology and showed an approximately 2% to 5% risk of cerebral lesions in co-twin survivors after laser photocoagulation complicated by single fetal demise.[5,6] This was similar to the 5% incidence (2/40) of severe cerebral lesions in our series. In addition, we reported mildly abnormal MR findings. Although many of these mild findings may not result in postnatal clinical sequelae, they presented a counseling conundrum and may cause undue parental anxiety that extends beyond the pregnancy. Furthermore, it is currently not known whether formal neurodevelopmental testing of survivors of co-twin demise may reveal an increased risk of particular deficits even

FIGURE 6
Prenatal MR from patient 9 at 26 weeks: left frontoparietal malformation of cortical development



Left frontoparietal malformation of cortical development with polymicrogyria and schizencephaly on axial (**A**) and coronal (**B** and **C**) SSFSE T2 imaging.

EPI, echo-planar imaging; *MR*, magnetic resonance; *SSFSE*, single-shot fast spin-echo.

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TABLE 3
Prenatal and postnatal findings in pregnancies complicated by abnormal magnetic resonance neuroimaging after single fetal demise after laser photocoagulation for twin-twin transfusion syndrome

Patient number, demised fetus	GA during laser photocoagulation, POD during demise	Complications	Prenatal ultrasound	Prenatal MRI with severity	GA during delivery (wk)	Postnatal imaging or follow-up
1, recipient	16.6, 42	Stage I TAPS	Normal	Mild: minimal blood products in right CP	37.0	HUS: normal Clinical: diagnosed with speech delay or mild autism at 18 mo of age; requires special education services
2, recipient	18.3, 1	Conversion to general anesthesia. Bleeding from insertion site—limited visualization	Normal	Mild: bilateral GM hemorrhage	36.0	HUS: very questionable tiny left GM hemorrhage (dubious clinical significance) Clinical: receiving early intervention for reading support at age 7 y
3, recipient	21.1, 3	Bleeding from placental vessel—limited visualization	Normal	Mild: bilateral grade II IVH	37.5	HUS: none Clinical: normal development at 4 mo
4, recipient	19.0, 1	None	Normal	Mild: right grade I GM hemorrhage	38.2	HUS: none Clinical: normal development at pediatric visit at age 3 y
5, recipient	17.1, 8	Elevated MCA of recipient POD 1 with normal MCA of donor	Normal	Mild: right grade I GM hemorrhage	38.4	HUS: none Clinical: following balloon dilation for pulmonary valve stenosis; normal developmental assessment at age 5 y (WPPSI-IV: high average)
6, recipient	18.1, 7	None	Not available	Mild: right CP hemorrhage	31.2	HUS: normal Clinical: normal development at pediatric visit at age 7 y
7, donor	26.0, 1	None	Not available	Mild: left GM hemorrhage	30.2	HUS: normal
8, donor	20.0, 49	Maternal SVT and severe hypotension in the operating room	Not available	Severe: diffuse polymicrogyria bilaterally with primitive sulcation and decreased parenchyma posteriorly	33.0	HUS: prominent CSP and high normal lateral vents MRI: "in utero stroke" per patient Clinical: global developmental delay, seizures, G-tube, trach before NICU discharge
9, recipient	18.0, 14	Stage V TAPS	Abnormal left MCA waveform	Severe: left frontoparietal malformation of cortical development with polymicrogyria and schizencephaly	39.5	MRI: perisylvian neuronal migration disorder consisting of polymicrogyria and pachygyria Clinical: epilepsy, developmental delay, and right hemiparesis
10, recipient	22.2, 1	None	Not available	Mild: left grade I GM hemorrhage	29.0	HUS: normal Clinical: normal developmental assessment at (corrected) age 2 y (BSID, III: cognitive [100], language [89], and motor [94])
11, recipient	17.4, 7	None	Normal	Mild: left grade I GM hemorrhage	38.7	Clinical: normal developmental assessment at age 2 y (BSID, III: cognitive [105], language [129], and motor [97])
12, donor	23.3, 1	None	Normal	Mild: bilateral grade I GM hemorrhage	36.7	HUS: none

BSID, Bayley Scales of Infant and Toddler Development; *CP*, choroid plexus; *CSP*, cavum septum pellucidum; *GA*, gestational age; *GM*, germinal matrix; *HUS*, head ultrasound; *IVH*, intraventricular hemorrhage; *MCA*, middle cerebral artery; *MRI*, magnetic resonance, *NICU*, neonatal intensive care unit; *POD*, post-op day; *SVT*, supraventricular tachycardia; *TAPS*, twin-anemia polycythemia sequence; *WPPSI*, Wechsler Preschool and Primary Scale of Intelligence.

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in those who have absent or only mild MR changes.

Clinical implications

Our results highlighted the importance of long-term pediatric neurodevelopmental follow-up of infants from pregnancies complicated by TTTS, particularly in cases of co-twin demise with and without abnormal fetal MR neuroimaging. Improvements in imaging technology without the matching long-term neurodevelopmental follow-up data currently make it difficult to appropriately counsel patients on any positive neuroimaging findings. Although we believe that many mild cerebral lesions on MR resolve without clinical impact, we need long-term data to support this. Furthermore, there is growing evidence that abnormal MR neuroimaging can be seen in pregnancies with TTTS treated with laser photocoagulation even in the absence of co-twin demise.[14] Therefore, we believe that all survivors of TTTS would benefit from formal neurodevelopmental testing with referral to early intervention if specific deficits are seen.

Research implications

The need for research, including the long-term formal neurodevelopmental assessment of co-twin survivors after laser photocoagulation for TTTS with single fetal demise, is clear. Given the already elevated risk of neurodevelopmental impairment of 9% to 11% in pregnancies with TTTS treated with laser photocoagulation, pediatric neurodevelopmental assessment is crucial to delineate if abnormal neuroimaging is associated with a further increased risk of neurologic impairment or not.[15]

Strengths and limitations

The strengths of this study were that it provided contemporary data on fetal MR neuroimaging findings in a relatively large cohort at a specialized fetal center with expert fetal neuroradiology support. Given advancements in technology, we were detecting more mild cerebral differences than have been previously reported. Although the clinical implications of these findings were unknown, it is important information to highlight the need for long-term follow-up to improve counseling.

The limitations of this study included the retrospective design, changes in MR technology over time, lack of placental pathologic analysis, and lack of formal pediatric neurodevelopmental assessment. The latter was the most important limitation, and in particular, we did not have clinical information on the patients in the cohort with normal neuroimaging or those with TTTS and dual survival. This limited the ability to conclude whether neuroimaging findings were associated with increased risk of impairment or not, except in severe cases.

Conclusions

We believe that this study has provided useful information about fetal MR neuroimaging in surviving co-twins after laser photocoagulation for TTTS complicated by single fetal demise. Although the study findings were limited by a lack of standardized pediatric follow-up, we feel that this study has provided a useful framework on which to design a larger, multicenter study with standardized imaging protocols and pediatric neurodevelopmental assessment. ■

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