Brain matters in twin-twin transfusion syndrome
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Chapter 3

Fetal and neonatal neuroimaging in twin-twin transfusion syndrome

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Abstract

Objectives

To describe the types of brain injury and subsequent neurodevelopmental outcome in fetuses and neonates from pregnancies with twin-twin transfusion syndrome (TTTS). Additionally, to determine risk factors for brain injury and to review the use of neuroimaging modalities in these cases.

Methods

This was a retrospective cohort study of consecutive TTTS pregnancies treated with laser surgery in a single fetal therapy center between January 2010 and January 2020. The primary outcome was the incidence of brain injury, classified into predefined groups. Secondary outcomes included adverse outcome (perinatal mortality or neurodevelopmental impairment (NDI)), risk factors for brain injury and the number of magnetic resonance imaging (MRI) scans.

Results

Cranial ultrasound was performed in all 466 TTTS pregnancies and 685/749 (91%) liveborn neonates. MRI was performed in 3% of pregnancies and 4% of neonates. Brain injury was diagnosed in 16/935 (2%) fetuses and 37/685 (5%) neonates and all predefined injury groups were represented. Four fetal and four neonatal cases of cerebellar hemorrhage were detected. Among those with brain injury, perinatal mortality occurred in 11/16 (69%) fetuses and 8/37 (22%) neonates. Follow-up was available for 29/34 (85%) long-term survivors with brain injury and the mean age at follow-up was 46 months. NDI was present in 9/29 (31%) survivors with brain injury. Adverse outcome occurred in 28/53 (53%) TTTS individuals with brain injury. The risk of brain injury was increased after recurrent TTTS/post-laser twin anemia polycythemia sequence (TAPS) (odds ratio (OR), 3.095, 95% CI 1.581 to 6.059, $p = 0.001$) and lower gestational age at birth (OR per 1-week decrease in gestational age, 1.381, 95% CI 1.238 to 1.541, $p < 0.001$).

Conclusions

Based on dedicated neurosonography and limited use of MRI, brain injury was diagnosed in 2% of fetuses and 5% of neonates with TTTS. Adverse outcome was seen in over half of cases with brain injury. Brain injury was related to recurrent TTTS/post-laser TAPS and a lower gestational age at birth.

Introduction

Twin-twin transfusion syndrome (TTTS) is a condition that results from intertwin transfusion through placental anastomoses in monochorionic twin pregnancy and puts both donor and recipient twins at risk for brain injury.(1, 2) Fetoscopic laser coagulation of placental anastomoses (FLC) is the first-line treatment for TTTS and reduces the risk of brain injury to 3- 16%.(3) Various pathophysiologic explanations for the occurrence of brain injury in TTTS have been suggested and include fetal hemodynamic instability, thromboembolism and anemia or polycythemia with vascular sludging.(4-7) Thromboembolism, due to TTTS itself or following fetal intervention, has been identified as an important pathway leading to focal brain injury, whereas symmetrical, diffuse injury is thought to result from hypoperfusion with or without fetal anemia.(6) In addition, preterm delivery is common after TTTS and exposes survivors to the risk of prematurity-related brain injury.(8)

While many previous studies have used cranial ultrasonography (cUS) to detect brain injury, recent work using prenatal and postnatal brain magnetic resonance imaging (MRI) have demonstrated the additional value of MRI over cUS alone.(9-17) The incidence of brain injury reported by these studies ranges widely and correlation of brain abnormalities on MRI with long-term outcome is lacking. The majority of recent studies report only on the outcomes of TTTS after treatment with laser surgery, as this is now the treatment of choice. However, it is important to realize that laser surgery is not always feasible and that TTTS fetuses not treated with FLC are at increased risk of adverse neonatal outcome, including brain injury.(3, 18)

Improving our understanding of the mechanisms that lead to brain injury in TTTS and their long-term consequences is important for counseling of future parents and may aid in the development of preventive measures based on pathophysiology. The aim of this study was to describe the types of fetal and neonatal brain injury and the long-term outcomes associated with these injuries in a large consecutive TTTS cohort. We also aimed to identify risk factors for brain injury and to review the use of neuroimaging modalities in TTTS cases in our center.

Methods

Study population

This was a retrospective cohort study of fetuses and neonates from consecutive twin and triplet pregnancies with TTTS treated with FLC at the Leiden University Medical Center (LUMC) between January 2010 and January 2020. The LUMC is the Dutch national referral center for fetal therapy. Triplets could be monochorionic or dichorionic, but only fetuses with TTTS were included in the study. After confirmation of TTTS using standard sonographic criteria, FLC was offered for Quintero stage 2 and higher.(19) Between 2011 and 2018, some patients with Quintero stage 1 TTTS were enrolled in a trial and were randomized to receive expectant management or FLC. For stage-1 patients outside the trial, therapy was individualized.(20) For this retrospective study, no formal ethical approval was required. The LUMC ethical review board waived the need for informed consent.

Neuroimaging

Standard prenatal ultrasonography included screening for fetal brain injury and was performed before laser surgery, 1 day and 1 week after laser surgery, and then continued at least once per fortnight. Fetal brain MRI was not part of standard care but was available at the discretion of the fetal therapy team. The fetal MRI protocol included T2-weighted sequences in the coronal, sagittal and transverse planes as well as susceptibility-weighted imaging (SWI), with the possibility of adding diffusion-weighted imaging (DWI). Postnatal cUS was recommended within 24 hours after birth for all TTTS neonates. Additional neonatal cUS scans were performed according to our previously described protocol.(21) Standard cUS images were made using the anterior and mastoid fontanelles.(22) Postnatal brain MRI images were retrieved from our neonatal intensive care unit (NICU) and that of four other Dutch centers. Indication for brain MRI was determined per individual case in our and three other centers, but MRI around term-equivalent age (TEA) was standard for all infants born at < 28 weeks in one center. MRI protocols differed between centers, but all included at least standard T1- and T2-weighted images as well as SWI.

Cerebral injury

Images from all fetal and neonatal MRI scans and all available cUS images were reviewed. Brain injury was categorized as either diffuse or focal injury and divided further into subgroups, as presented in **table 1**.

Table 1. Brain injury categories and groups

Category	Group	Injury
Diffuse	1	Cystic periventricular leukomalacia
	2	Multicystic or generalized encephalomalacia
	3	Migration or gyration disorders
	4	Ventriculomegaly and/or severe volume loss
Focal	5	Infarction
	6	Intraventricular hemorrhage (with or without post-hemorrhagic ventricular dilatation)
	7	Intraventricular hemorrhage with periventricular hemorrhagic infarction
	8	Cerebellar or cerebral parenchymal hemorrhage

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Periventricular leukomalacia (PVL) was included in case of cystic white matter lesions (PVL ≥ grade 2).(23) Ventriculomegaly (VM) was defined as an atrial diameter ≥ 10 mm on fetal US as well as fetal and postnatal MRI, or a ventricular index above the 97th percentile according to Levene on neonatal cUS.(24) VM was termed post-hemorrhagic ventricular dilatation (PHVD) if preceded by intraventricular hemorrhage (IVH) ≥ grade 2, according to Volpe.(25-27) Infarction was diagnosed when cUS showed an area of increased echogenicity within an arterial territory, or MRI/DWI showed typical signal abnormalities in the acute stage, each with subsequent cyst formation. Periventricular hemorrhagic infarction (PVHI) was described according to Volpe.(27) Cerebellar hemorrhage (CBH) detected on postnatal cUS or MRI was subdivided as punctate, limited, or massive.(28) For all postnatal MRI scans performed at a postmenstrual age of between 36 and 46 weeks, the TEA scoring system developed by Kidokoro et al. was applied and included corrections for postmenstrual age for the measures of biparietal width, deep gray matter area and transcerebellar diameter.(25) The Kidokoro global brain abnormality score is the sum of several subscores and is classified as normal (0-3), mild (4-7), moderate (8-11) or severe (≥12). Severe volume loss (group 4) was diagnosed when the Kidokoro score was >3 based on reduced volume as represented by the subscores and without evidence of focal injury. Brain injury that was detected antenatally and confirmed postnatally was reported as fetal brain injury.

Follow-up

Standardized long-term follow-up was part of routine care and included visits at the ages of 2, 5 and 8 years. All follow-up visits consisted of a physical examination by a neonatologist and physiotherapist for the assessment of general health and neurological deficits, including cerebral palsy (CP). CP was classified according to the Gross Motor Function Classification System (GMFCS).(29) In addition, standardized tests were performed by trained professionals for the assessment of motor and cognitive development. At the 2-year visit, the Bayley Scales of Infant and Toddler Development were used. At the 5- and 8-year visits, cognitive functioning was assessed with the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and Wechsler Intelligence Scale for Children (WISC), respectively, whereas motor assessment was performed using the Movement Assessment Battery for Children (M-ABC). In specific cases, the Snijders-Oomen Nonverbal Intelligence Test (SON) was used for the assessment of cognitive functioning. For the purpose of this study, follow-up data from the latest known follow-up visit were retrieved for survivors with brain injury.

Outcome measures

The primary outcome was the incidence of fetal and neonatal brain injury, divided into predefined injury groups. Secondary outcomes were perinatal mortality, neurodevelopmental impairment (NDI), a composite called adverse outcome, risk factors associated with brain injury, Kidokoro scores for TEA MRI scans and the number of fetal and neonatal brain MRI scans. Adverse outcome was defined as perinatal mortality or NDI. Perinatal mortality was defined as fetal death or neonatal death within 28 days after birth. NDI was defined as CP, bilateral blindness or deafness, or cognitive or motor score on a standardized test more than 2 SD below the mean determined at the age of at least 2 years, corrected for prematurity. The following potential risk factors were studied: donor or recipient, TTTS stage, gestational age at FLC, recurrent TTTS after laser or post-laser twin anemia polycythemia sequence (TAPS)) and gestational age at birth.

Statistical analysis

Analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA). Data are reported as n (%), mean $\pm$ SD or median (interquartile range (IQR)), as appropriate. Statistical significance was defined as $p < 0.05$. Potential risk factors for brain injury were studied in a logistic regression analysis using Generalized Estimating Equations (GEE), since results within twin pairs are not independent. Results of the logistic regression are reported as odds ratios (OR) with 95% CI.

Results

We included 935 fetuses from 466 consecutive TTTS pregnancies managed at the LUMC during the study period. Characteristics of the included pregnancies are summarized in **table 2**. Mean ± SD gestational age at laser surgery was 20.0 ± 3.3 weeks. Mean ± SD gestational age at birth was 32.5 ± 3.4 weeks. There were 749/935 (80%) liveborn neonates and neonatal death occurred in 35/749 (5%); thus, the overall rate of perinatal survival was 76% (714/935 fetuses).

Table 2. Characteristics of 466 TTTS pregnancies (935 fetuses)

Twin pregnancies	456
Dichorionic triplet pregnancies*	7
Monochorionic triplet pregnancies*	3
Gestational age at laser surgery (weeks)	20.0 ± 3.3
Fetal death	109/935 (12)
Birth before viability	63/935 (7)
Selective fetal reduction/termination	14/935 (1)
Liveborn neonates	749/935 (80)
Neonatal death	35/749 (5)
Perinatal mortality†	221/935 (24)
Overall survival	714/935 (76)
Quintero stage	2 (1-4)
Stage 1	70/466 (15)
Stage 2	170/466 (36)
Stage 3	210/466 (45)
Stage 4	16/466 (3)
Gestational age at birth (weeks)	32.5 ± 3.4
Birth weight (g)	1736 ± 680
Delivery in LUMC	248/466 (53)

Data are given as n, mean ± SD, n/N (%) or median (range).
* For triplet pregnancy, only fetuses with TTTS were included
† Any cause of fetal death or neonatal death.
LUMC, Leiden University Medical Center.

Flowcharts summarizing the use of neuroimaging modalities in fetuses and neonates are presented in **figures 1a and 1b**, respectively. In all cases, both fetuses had normal intracranial ultrasound findings prior to laser surgery. For 64/749 (9%) liveborn neonates, of whom all were born in other hospitals, no postnatal neuroimaging results or reports could be identified. Consequently, neonatal neuroimaging results were available for 685/749 (91%) neonates. All 37 neonates with postnatally diagnosed brain injury had their first postnatal cUS scan within 24 hours after birth. This early scan showed brain injury in 12/37 (32%) neonates.

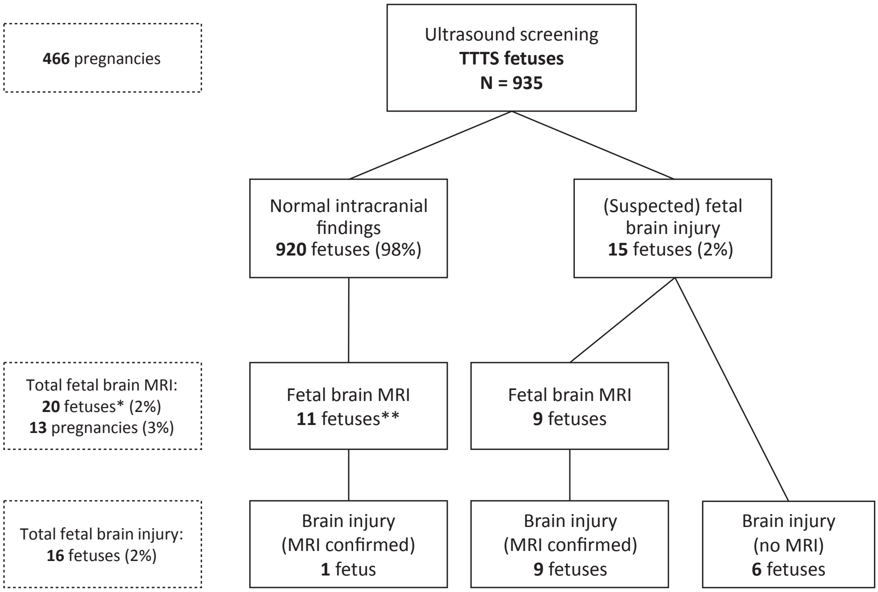

Figure 1a. Flowchart summarizing neuroimaging in fetuses from TTTS pregnancies.

† Reasons for fetal MRI: suspected skull anomaly (n=1; not confirmed on MRI); co-twin of fetus with indication for fetal MRI (n=6); incomplete laser surgery as reported by fetal surgeon (n=4).

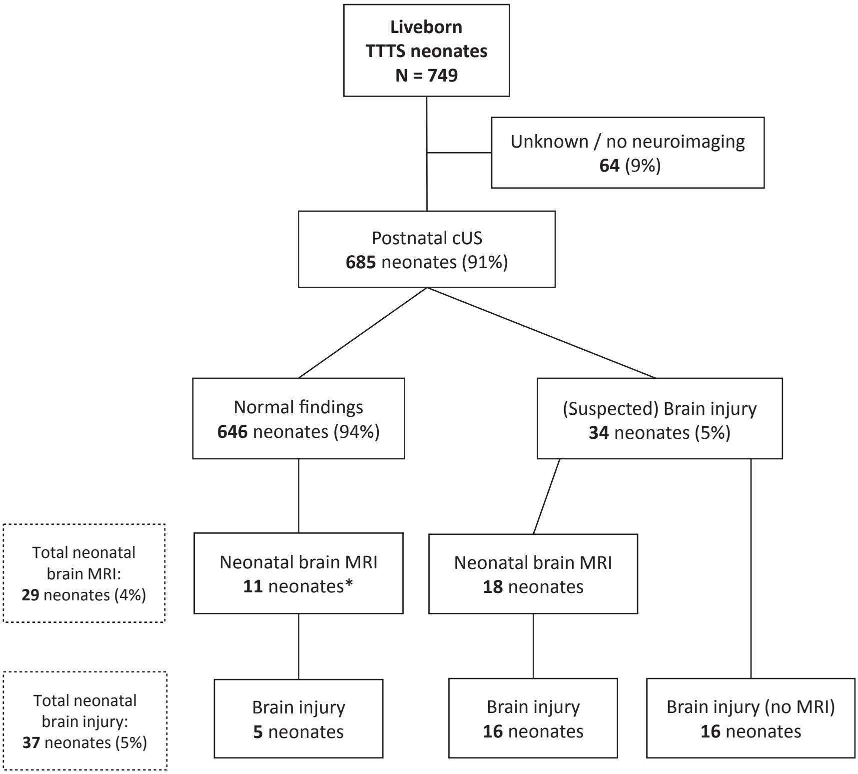

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Figure 1b. Flowchart summarizing neuroimaging in neonates from TTTS pregnancies.

‡ Reasons for MRI at term-equivalent age: (extremely) preterm infant (n=10), incomplete laser surgery as reported by fetal surgeon (n=1). cUS, cranial ultrasound.

Primary outcome

Brain injury was diagnosed prenatally in 16/935 (2%) fetuses and postnatally in 37/685 (5%) neonates. The incidence of each predefined group of brain injury is presented in **table 3**. Injuries were diffuse (groups 1-4) in 9/16 (56%) fetal cases and 12/37 (32%) neonatal cases. The most common type of diffuse brain injury was VM or severe volume loss (group 4), occurring in 9/53 (17%) cases. Brain injury was focal (groups 5-8) in 7/16 (44%) fetal cases and 25/37 (68%) neonatal cases. The most common type of focal brain injury was IVH (groups 6 and 7), occurring in 18/53 (34%) cases.

Brain injury was confirmed after birth in 4/5 (80%) survivors diagnosed with fetal brain injury. In one case with a fetal diagnosis of grade 1 IVH, the postnatal cUS scan, performed 14 weeks after IVH was first seen, was normal. Details of the 16 fetuses in which cerebral injury was diagnosed prenatally are provided in **table 4**, arranged according to injury group. Details of the 37 neonates who were diagnosed with a brain injury postnatally are presented in **table 5**. Different brain injury groups visualized pre- and postnatally using different imaging modalities are depicted in **figure 2**.

Table 3. Incidence of predefined brain injury categories and groups

Brain injury group		Category	Fetal diagnosis (n=935)	Neonatal diagnosis (n=685)	Total
1	cPVL		3	3	6
2	Encephalomalacia		4	1	5
3	Migration/gyration disorder		0	1	1
4	VM / severe volume loss		2	7	9
		Diffuse	9	12	21 (40)
5	Infarction		1	3	4
6	IVH ± PHVD		2	8	10
7	IVH with PVHI		0	8	8
8	CBH / parenchymal hemorrhage		4	6	10
		Focal	7	25	32 (60)
		Total	16 (30)	37 (70)	53 (100)

Data are given as n or n (%)

Secondary outcomes

Perinatal mortality occurred in 11/16 (69%) fetuses and 8/37 (22%) neonates with brain injury, compared to 175/919 (19%) fetuses and 27/648 (4%) neonates without evidence of brain injury. An end-of-life decision (selective fetal reduction, termination of pregnancy or withdrawal of NICU treatment) was the cause of death in 9/11 (82%) cases of fetal brain injury and 8/8 (100%) cases of neonatal brain injury. Neurodevelopmental follow-up at the age of at least 2 years was available for 29/34 (85%) survivors with prior fetal or neonatal brain injury, and the mean age at follow-up was 46 months. NDI was present in 9/29 (31%) cases. None of the five children who survived after a fetal diagnosis of brain injury had NDI. These children had relatively mild forms of brain injury: two had VM, two had grade 1 IVH and one had a unilateral CBH that did not appear to be massive on fetal or neonatal cUS. The details of their long-term follow-up are shown in **table 4**. All of the nine children with NDI had CP following postnatally diagnosed brain injury, with varying cognitive outcome (**table 5**). Overall, adverse outcome was present in 28/53 (53%) TTTS individuals with brain injury.

Results of the logistic regression analysis of potential risk factors for any brain injury are shown in **table 6**. Recurrent TTTS/post-laser TAPS (OR 3.095, 95% CI 1.581 to 6.059, p = .001) and lower gestational age at birth (OR per 1 week reduction in gestational age, 1.381, 95% CI 1.238 to 1.541, p < .001) were identified as significant risk factors for brain injury. A multivariate analysis could not be performed because gestational age at birth was assessed in a smaller group (only liveborn neonates). Mean ± SD gestational age at birth was 31.0 ± 3.5 weeks in liveborn neonates with recurrent TTTS/post-laser TAPS, compared to 32.7 ± 3.3 weeks in those without.

The Kidokoro score was assessed in 23 MRI scans obtained at a post-menstrual age of between 36 and 46 weeks. The overall median Kidokoro score was 5 (IQR, 2-9), indicating mild injury. Ten TEA MRI scans were made because of extreme prematurity after normal findings on repeated cUS examinations, and the median Kidokoro score in this subset was 3.5 (IQR, 1-5). In 11 infants who underwent MRI around TEA because of brain injury diagnosed on cUS, the median Kidokoro score was 9 (IQR, 5-11), indicating moderate injury.

Prenatal brain MRI was performed in 13/466 (3%) TTTS pregnancies. The indication for fetal MRI was brain abnormality on fetal neurosonography in nine fetuses (nine different pregnancies). The other fetal MRI scans were performed because of incomplete laser surgery (as reported by the fetal surgeon) in three pregnancies (four live fetuses) and a suspected fetal skull abnormality in one fetus. Fetal MRI confirmed sonographic abnormalities in all nine cases and identified new lesions in one fetus. Fetal MRI findings were followed by termination of pregnancy, selective reduction or palliative neonatal care in 5/13 (38%) cases.

Postnatal brain MRI was performed in 29/685 (4%) neonates. Suspected brain injury on cUS was the indication for MRI in 18/29 (62%) neonates. Brain injury was confirmed with MRI in 16/18 (89%) cases. In 10 infants born < 28 weeks' gestation without evidence of brain injury on prior cUS examinations, TEA MRI scans were made as a part of standard care, and five of these MRI scans identified new abnormalities. One revealed a massive unilateral CBH that had been missed on cUS, while the other four had VM and/or volume reduction that had been within the normal limits on earlier cUS examinations.

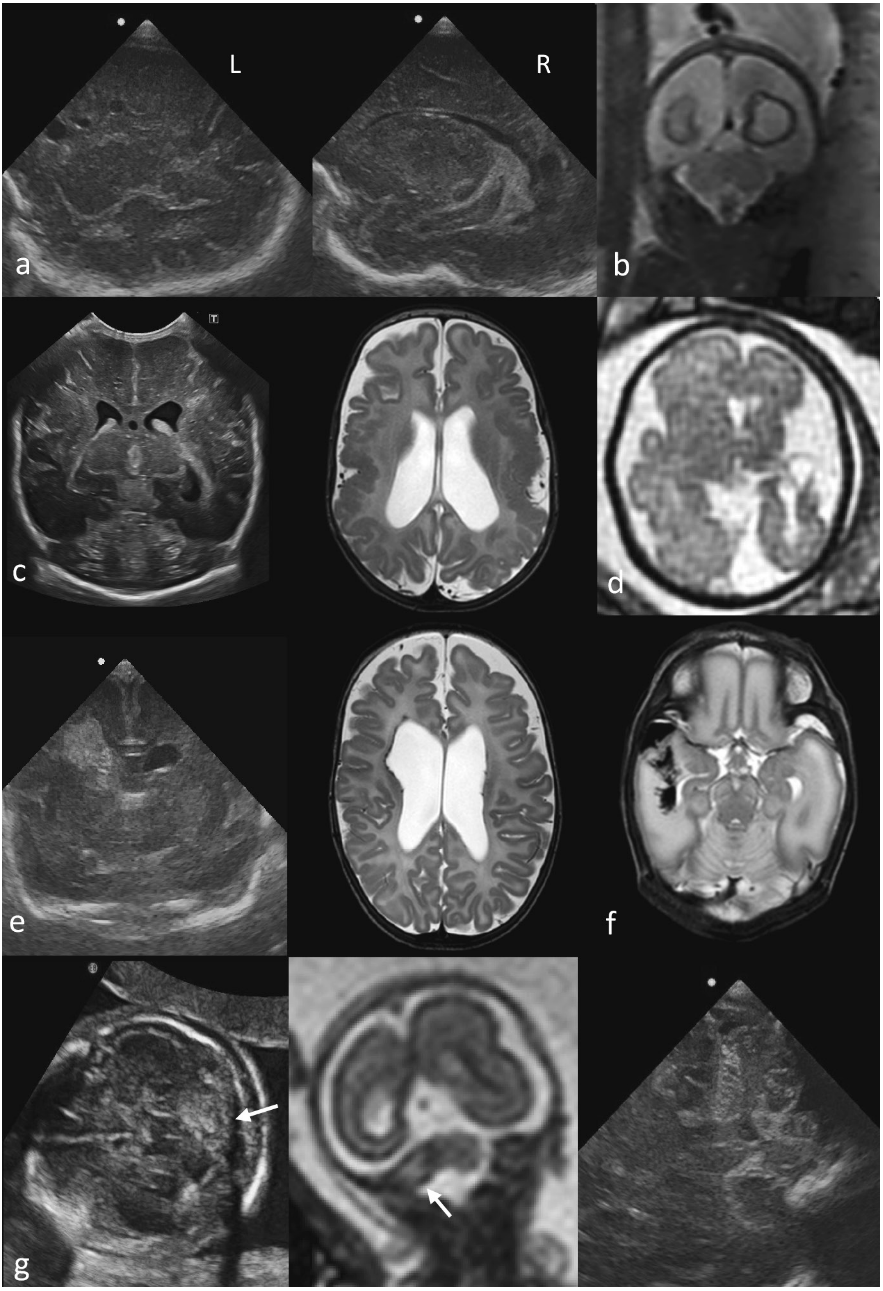

Figure 2. Different types of brain injury encountered in monochorionic twins with TTTS treated with fetoscopic laser coagulation.

a. Group 1 (periventricular leukomalacia): TTTS-recipient and subsequent donor in post-laser TAPS born at 32 weeks gestation. Postnatal cUS on day 1 with images in two parasagittal planes showing left frontal and right parieto-occipital cysts consistent with periventricular leukomalacia grade 3.
b. Group 2 (multicystic or generalized encephalomalacia): TTTS donor, fetal MRI at 26 weeks gestation, T2-weighted image in coronal plane showing near total cerebral atrophy.
c. Group 3 (migration or gyration disorders): TTTS donor, born at 31 weeks gestation. Postnatal cUS at 33 weeks (left) showing ventriculomegaly and bilateral suspected abnormal gyration around the insula. Transverse T2-weighted MR image at 45 weeks postmenstrual age (middle) showing perisylvian polymicrogyria, reduced white matter volume and ventriculomegaly.
d. Group 5 (infarction): TTTS recipient. Fetal T2-weighted MRI at 30 weeks' gestation in transverse plane showing large parenchymal defect in the territory of the left main cerebral artery.
e. Group 7 (intraventricular hemorrhage (IVH) with periventricular hemorrhagic infarction (PVHI)): TTTS donor born at 27 weeks gestation. Postnatal cUS on day 3 (left) showing right-sided IVH grade 3 with fan-shaped periventricular echogenicity, representing PVHI. T2-weighted transverse MRI at 45 weeks postmenstrual age (middle) showing right porencephalic cyst communicating with the lateral ventricle and bilateral posthemorrhagic ventricular dilatation.
f. Group 8 (cerebellar or cerebral parenchymal hemorrhage): TTTS recipient born at 30 weeks gestation. Postnatal transverse T2-weighted MRI at 31 weeks postmenstrual age, showing right temporal intraparenchymal hemorrhage.
g. Group 8 (cerebellar or cerebral parenchymal hemorrhage): TTTS donor. Fetal neurosonography (left) and fetal MRI (middle) around 23 weeks gestation, and postnatal cUS (right) at 33 weeks' gestation. Suspected right-sided fetal cerebellar hemorrhage (arrows), postnatal cUS showing the chronic stage with underdevelopment of right cerebellar hemisphere.

Withdrawal of NICU care occurred in one preterm infant after MRI had confirmed extensive cystic lesions seen on cUS. Care was withdrawn in six (extremely) preterm infants based on severe brain injury diagnosed with cUS alone. One infant underwent MRI because of incomplete laser surgery as reported by the fetal surgeon despite normal cUS findings, and the MRI was normal in this infant. None of the infants with a postnatal MRI report had previously undergone fetal MRI.

Table 4. Details of cases with prenatally diagnosed brain injury, according to injury group (n = 16)

Brain injury group	Donor/ recipient	Imaging	GA at FLC (weeks)	GA at Dx of brain injury (weeks)	Indication for MRI
1	Recipient	US	16	19	-
	Recipient	US	22	2	-
	Recipient	US	21	23	-
2	Donor	US, MRI	18	20	Abnormal fetal US
	Donor	US, MRI	23	25	Abnormal fetal US
	Donor	US, MRI	25	27	Incomplete FLC†, abnormal US
	Donor	US, MRI	16	24	Abnormal fetal US
4	Donor	US, MRI	18	20	Abnormal fetal US
	Donor	US, MRI	16	19	Abnormal fetal US
5	Recipient	US, MRI	23	28	Abnormal fetal US
6	Donor	US, MRI	23	27	Abnormal fetal US
	Donor	US, MRI	16	20	incomplete FLC†, sFD
8	Donor	US, MRI	20	21	Abnormal fetal US
	Donor	US	14	15	-
	Donor	US	19	23	-
	Recipient	US	18	23	-

*Results of Bayley test and Wechsler Intelligence Scale for Children (WISC) have mean of 100 and SD of 15: result of <70 is consistent with <-2SD. †As reported by fetal surgeon. GA: gestational age; MRI: magnetic resonance imaging; FLC: fetoscopic laser coagulation; cPVL: cystic periventricular leukomalacia; US: ultrasound; cUS: cranial ultrasound; PV: periventricular; sFD: single fetal demise; TOP: termination of pregnancy; VM: ventriculomegaly; WMI: white-matter injury; SFR: selective fetal reduction; Bayley-III:

Main findings at neuroimaging	Outcome/follow-up*
Bilateral frontal cystic PVL	sFD donor, TOP because of brain injury recipient
Progressive PV inhomogeneous echogenicity & VM	SFR
PV inhomogeneous echogenicity & VM, IVH	SFR
Cystic degeneration of almost complete right hemisphere, left VM	Died after palliative neonatal care (GA at birth 32 wks)
Progressive PV cystic lesions, followed by near total atrophy, brain stem & cerebellum spared	Died after palliative neonatal care (GA at birth26 wks)
Symmetrical, extensive frontoparietal cystic degeneration	Died after palliative neonatal care (GA at birth 30 wks)
Bilateral WMI with severe atrophy, VM	SFR of recipient at 19 weeks for recurrent TTTS, TOP donor after fetal brain MRI
Bilateral VM 13 mm	Birth at 36 wks, stable VM on neonatal cUS; Bayley-III at 2 years: cog 105, mot 92
Bilateral VM 11 mm	Birth at 36 weeks; stable VM on neonatal cUS; hydrocephalus, VP shunt at 2 years; BSID-II at 2 years: MDI 115, PDI unknown
Large parenchymal defect in left MCA territory	SFR
Bilateral grade 1 IVH	Birth at 29 weeks; PVL gr 1, no IVH on neonatal cUS; WISC at 8 years: TIQ 86, M-ABC p5
Unilateral grade 1 IVH	Birth at 34 weeks; normal postnatal cUS; Bayley-III at 2 years: cog 115, mot 89
Right-sided CBH	Birth at 33 weeks; underdeveloped right cerebellar hemisphere on neonatal cUS; Bayley-III at 2 years: cog 125, mot 100, normal v/h
CBH, symmetrical VM	sFD of recipient after FLC; TOP of donor for brain injury
CBH and IVH	Spontaneous sFD at 25 weeks
CBH	Spontaneous birth before viability

Bayley Scales of Infant and Toddler Development, third edition; cog: cognitive composite score of Bayley-III, mot: motor composite score of Bayley-III; VP: ventriculoperitoneal; BSID-II: Bayley Scales of Infant and Toddler Development, second edition; MDI: mental development index, PDI: psychomotor development index; IVH: intraventricular hemorrhage; TIQ: total intelligence quotient; M-ABC: Movement Assessment Battery for Children; CBH: cerebellar hemorrhage; v/h: vision/hearing; p5, 5th percentile.

Table 5. Details of cases with postnatally diagnosed brain injury, according to injury group (n=37)

Brain injury group	Donor/ recipient	Imaging	GA at FLC (weeks)	GA at birth (weeks)	BW (g)	GA at MRI (weeks)	Indication for MRI
1	Donor	cUS	20	29+4	1288	–	–
	Recipient	cUS	24	29+2	1400	–	–
	Recipient/ donor†	cUS	23	32+4	1635	–	–
2	Recipient/ donor†	cUS, MRI	21	27+4	980	28	Abnormal cUS
3	Donor	cUS, MRI	16	31+6	726	45	Abnormal cUS
4	Donor	cUS, MRI	18	30+5	625	33	Abnormal cUS
	Donor	cUS, MRI	21	26+6	865	40	Extreme prematurity
	Donor	cUS, MRI	25	26+6	890	46	Extreme prematurity
	Recipient	cUS, MRI	25	26+6	795	46	Extreme prematurity
	Donor	cUS, MRI	16	31+2	528	36	Abnormal cUS
	Donor	cUS, MRI	19	26+6	889	45	Extreme prematurity
	Donor	cUS, MRI	21	26+4	820	40	Abnormal cUS
5	Recipient	cUS, MRI	18	31+2	2084	38	Abnormal cUS
	Recipient	cUS, MRI	20	33+6	1740	34	Abnormal cUS
	Recipient	cUS, MRI	26	32+4	1263	33	Abnormal cUS
6	Recipient	cUS, MRI	20	25 + 4	625	43	Abnormal cUS
	Recipient	cUS, MRI	21	26+6	1075	40	Abnormal cUS
	Donor	cUS	17	25+4	800	–	–
	Donor	cUS	23	26+0	1070	–	–
	Recipient	cUS	17	25+4	880	–	–
	Donor	cUS	27	27+6	1190	–	–
	Recipient	cUS	16	28+2	1170	–	–
	Donor	cUS	17	26+2	840	–	–

Main findings at neuroimaging	Kidokoro global score	Outcome/follow-up*
Unilateral PVL Grade 2	–	8 years: USCP, GMFCS 1, WISC: TIQ 100
Unilateral PVL Grade 2, IVH Grade 1	–	2 years: USCP, GMFCS unknown, BSID-II: MDI 82
Bilateral PVL Grade 3	–	2 years: BSCP, GMFCS 1, BSID-II: MDI 100
Multiple cysts in basal ganglia and thalamus, extensive PWML, IVH, CBH	N/A	Died after withdrawal of care
Bilateral perisylvian PMG, markedly reduced WM volume with VM	15	2 years: BSCP, GMFCS 2 with general developmental delay, gastrostomy
Generalized cerebral atrophy	N/A	2 years: Bayley-III: cog 77, mot 75
Bilateral VM, reduced WM volume	5	6 years: WPPSI: TIQ 102, normal v/h
Bilateral VM, germinolytic cysts	5	8 years: WISC: TIQ 97, M-ABC p50
Bilateral VM, germinolytic cysts	6	8 years: WISC: TIQ 115, M-ABC p50
VM, severely reduced WM volume, two punctate CBH	11	1 year: motor delay and tubefeeding
Reduced WM volume	4	8 years: WISC: TIQ 97, M-ABC p75
Bilateral VM, unilateral IVH Grade 1	5	2 years: Bayley-III: cog 105, mot 87
Focal infarction thalamus just outside PLIC	3	2 years: Bayley-III: mot 76, cog incomplete
Cystic degeneration in left MCA territory	N/A	2 years: USCP GMFCS II, BSID-II: MDI 95
Bilateral caudate stroke, small IVH	N/A	Lost to follow-up
Unilateral IVH Grade 2, VM	5	2 years: Bayley-III: cog 77, mot 98
Bilateral IVH Grade 2, PHVD	6	6 years: WPPSI: TIQ 105, normal v/h
Bilateral IVH Grade 3, PHVD	–	Died after withdrawal of care
Bilateral IVH Grade 3	–	Died after withdrawal of care
Bilateral IVH Grade 3, PHVD	–	Discharged alive, lost to follow-up
Bilateral IVH Grade 2–3	–	2 years: Bayley-III: cog 105 mot 98
IVH Grade 3, PHVD	–	2 years: no CP, BSID-II: MDI 87
Unilateral IVH Grade 2, bilateral VM	–	Lost to follow-up

Table 5. Continued

Brain injury group	Donor/ recipient	Imaging	GA at FLC (weeks)	GA at birth (weeks)	BW (g)	GA at MRI (weeks)	Indication for MRI
7	Recipient	cUS	23	26+0	1053	–	–
	Donor	cUS	18	30+1	1693	–	–
	Donor	cUS, MRI	20	25+4	730	42	Abnormal cUS
	Donor	cUS, MRI	19	27+3	984	45	Abnormal cUS
	Recipient	cUS, MRI	19	27+3	890	45	Abnormal cUS
	Donor	cUS	21	25+3	910	–	–
	Recipient	cUS, MRI	17	29+2	1450	6 months	Abnormal cUS
	Recipient	cUS	21	26+0	701	–	–
8	Donor	cUS, MRI	16	24+3	630	42	Extreme prematurity
	Recipient	cUS, MRI	20	33+4	2020	38	Abnormal cUS
	Recipient	cUS, MRI	20	30+1	1589	31, 46	Abnormal cUS
	Recipient	cUS	18	25+6	705	–	–
	Recipient	cUS	26	27+2	987	–	–
	Recipient	cUS	21	26+4	880	–	–

*Results of Bayley, Wechsler Intelligence Scale for Children (WISC), Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and Snijders-Oomen Nonverbal Intelligence Test (SON) have mean of 100 and SD of 15: result of <70 is consistent with <-2SD. †Recipient in TTTS, donor in post-laser twin anemia polycythemia sequence and received intrauterine transfusion. GA: gestational age; FLC: fetoscopic laser coagulation; BW: birth weight; cUS: cranial ultrasound; CP: cerebral palsy; BSCP: bilateral spastic cerebral palsy; USCP: unilateral spastic cerebral palsy; GMFCS: Gross Motor Function Classification System; TIQ: total intelligence quotient;

Main findings at neuroimaging	Kidokoro global score	Outcome/follow-up*
Bilateral massive IVH and PVHI	–	Died after withdrawal of care
Bilateral IVH and PVHI, extensive cystic evolution in WM	–	Died after withdrawal of care
Bilateral IVH and PVHI, PHVD, developing porencephalic cyst	9	5 years: VP shunt, USCP, GMFCS 1, mild cognitive delay
Bilateral IVH, unilateral PVHI, PHVD, developing porencephalic cyst	10	5 years: WPPSI: TIQ 103. M-ABC p91, no asymmetry
Bilateral IVH, unilateral PVHI, PHVD, developing porencephalic cyst	10	5 years: USCP, GMFCS 1, WPPSI: TIQ 105
Bilateral IVH, unilateral PVHI developing porencephalic cyst	–	6 years: SON: TIQ 66, USCP, GMFCS I, ASS
Bilateral IVH, PHVD, unilateral PVHI, porencephalic cyst, interrupted PLIC	N/A	2 years: USCP, GMFCS I, BSID-II: MDI 100
Bilateral IVH, unilateral PVHI, contralateral cPVL	–	Died after withdrawal of care
Massive unilateral CBH, small IVH	7	2 years: Bayley-III cog 96, mot 95, normal v/h
Multiple CBH of limited size, small IVH, diffusely high WM signal	8	Discharged home in good condition, lost to follow-up
Right temporal hemorrhagic venous infarction, punctate CBH	12	5 years: WPPSI: TIQ 104 8 years: M-ABC p91
Massive bilateral CBH	–	Died after withdrawal of care
Hemorrhage right thalamus, small IVH	–	2 years: Bayley-III cog 101, mot 104
Bilateral large parenchymal hemorrhage	–	Died after withdrawal of care

BSID-II: Bayley Scales of Infant Development, second edition; MDI: Mental Developmental Index; N/A: not applicable; PMWL: punctate white-matter lesion; CBH: cerebellar hemorrhage; WM: white matter; Bayley-III: Bayley Scales of Infant and Toddler Development, third edition; cog: cognitive composite score of Bayley-III, mot: motor composite score of Bayley-III; M-ABC: Movement Assessment Battery for Children; PLIC: posterior limb of internal capsule; MCA: middle cerebral artery; VP: ventriculoperitoneal; ASS: autism spectrum disorder; v/h: vision/hearing; p50, 50th percentile.

3

Table 6. Potential risk factors for any brain injury

Risk factor	Brain injury (n=53)	No Brain injury (n=818)	Univariate OR (95%-CI)	p value
Donor	27/53 (51)	413/818 (51)	1.029 (0.627 - 1.689)	0.909
TTTS Stage	2 (2-3)	3 (2-3)	1.030 (0.681 - 1.557)	0.890
GA at laser*	20.4 ± 3.3	19.9 ± 3.3	0.956 (0.882 - 1.036)	0.273
Recurrent TTTS/ post-laser TAPS	14/53 (26)	85/818 (10)	3.095 (1.581 - 6.059)	0.001
GA at birth*†	29.1 ± 3.3	32.8 ± 3.2	1.381 (1.238 - 1.541)	<0.001

Data are given as n (%), median (interquartile range) or mean ± SD, unless specified otherwise.
*Per 1 week reduction in gestational age (GA).
†Analyzed only in liveborn neonates with known neuroimaging results (n=685).
OR, odds ratio; TAPS, twin anemia polycythemia sequence.

Discussion

Brain injury was detected in 2% of fetuses and 5% of neonates in this large consecutive TTTS cohort treated with FLC. Antenatally, diffuse types of brain injury were slightly more common, whereas postnatally over two thirds of cases had focal injury. Adverse outcome was present in the majority of cases with brain injury. Recurrent TTTS/post-laser TAPS and lower gestational age at birth were identified as risk factors for brain injury. Fetal and neonatal brain MRI were performed in 3% of pregnancies and 4% of survivors, respectively.

Previous fetal MRI studies in pregnancies with TTTS have reported an incidence of brain injury between 2 and 33%.(9, 14, 15, 17, 30, 31) In a recent systematic review that included MRI and ultrasound results, the incidence of fetal brain injury was 2%.(32) Two small studies performing neonatal brain MRI reported abnormalities in as many as 40% and 68% of TTTS infants.(16, 17) The relatively low incidence of brain injury in our study compared with studies that used MRI exclusively likely reflects the limitations of ultrasound, which may show only overt brain lesions. Since none of the previous MRI studies have reported on neurodevelopmental outcome, the true relevance of abnormalities seen only on MRI remains unknown. In the current study, NDI was present in 31% of TTTS survivors with brain injury, but follow-up data were not retrieved for children without brain injury. However, in a previous study on neurodevelopmental outcome at 2 years of age in TTTS survivors treated between 2011 and 2014, NDI was seen in 3% of all TTTS survivors and brain injury was found to be predictive of NDI.(33) Even though the presence of brain injury increases the risk of NDI, the positive and negative predictive values of prenatal neuroimaging remain limited. In fact, none of the five survivors after fetal brain injury in this study met our criteria for NDI, although all had relatively mild forms of brain injury that may be associated with mild neurodevelopmental sequelae that manifest at a later age.

Long-term neurodevelopmental outcome depends on many different factors. Prematurity remains common after TTTS and is a well-known risk factor for brain injury as well as NDI. Our results confirm the increased risk of postnatal brain injury at a lower gestational age. However, based on our previous findings that early (<24 hours) postnatal cUS abnormalities are more common in TTTS compared with non-TTTS neonates, we assume that a portion of postnatally diagnosed brain injuries actually originated prenatally as the result of TTTS or fetal treatment.(21, 34) Moreover, in at least three cases with "postnatal" brain injury and subsequent CP (one with evidence of arterial infarction, one with cystic PVL and one with polymicrogyria), findings on early postnatal neuroimaging were consistent with injuries that originated during fetal life.

Although the types of brain injury described in this study are mostly comparable to the literature, some discrepancies stand out. A remarkable finding is the relatively frequent occurrence of CBH. One of the fetal CBH cases in this study was described previously in a small case series from our center of three fetuses that had undergone fetal therapy.(35) Besides that report, only Merhar et al. described one case of fetal CBH in TTTS.(17) Aside from fetal therapy, known risk factors for antenatal CBH are various causes of maternal hemodynamic disturbance, as well as fetal factors including coagulopathies and fetal anemia. In the newborn, CBH has been mostly attributed to preterm birth, impaired autoregulation of cerebral blood flow and other risk factors that compromise the cerebral circulation.(36, 37) Interestingly, two studies have reported an association between CBH and multiple gestation.(38, 39) In recent years, there has been an increased focus on the preterm cerebellum. Advances in neuroimaging, including cUS with mastoid fontanelle views, have increased the recognition of CBH.(40) Our data show that special attention should be paid to the posterior fossa when screening for brain injury in TTTS fetuses and neonates. CBH may have a significant impact on neurodevelopment and, therefore, should not be overlooked.(41, 42)

The brain injury groups in this study were adapted from Conte et al., who investigated fetal brain injury in survivors of monochorionic twin pregnancy complicated by single intrauterine death and proposed that focal brain injury was more common in TTTS because of thromboembolic phenomena.(6)

We found diffuse types of injury in 56% of prenatal cases, suggesting that hypoperfusion is at least an equally important mechanism leading to fetal brain injury in TTTS.

Recurrent TTTS/post-laser TAPS and lower gestational age were identified as risk factors for brain injury. We assume that persistence of TTTS poses a direct risk of fetal brain injury due to prolonged hemodynamic instability, whereas post-laser TAPS increases the risk by means of polycythemia or anemia. These results highlight the importance of ultrasonographic follow-up after FLC. Due to small numbers, we could not perform a reliable analysis of potential risk factors for prenatal and postnatal brain injury separately.

Strengths of our study include the detailed description of fetal and neonatal brain injuries found in TTTS cases, the reports of long-term follow-up and the large size of this cohort. Limitations include the retrospective design, the small number of MRI scans and the lack of a standardized protocol that indicates when to perform MRI. Because the majority of TTTS infants were born preterm, our data on postnatal brain injury should be interpreted with care, as prematurity is an important confounding factor.

Future research into brain injury in TTTS should include serial imaging, including fetal ultrasound and MRI and postnatal cUS and (TEA) MRI, with long-term follow-up. MRI studies should preferably use state-of-the-art techniques, including SWI, DWI and quantitative measures of brain volume and maturation, to enable the description of more subtle brain injuries and disturbed growth, supporting the counseling of future parents.(14, 30, 31, 43)

In conclusion, a wide range of brain injuries reflecting different pathophysiological mechanisms were encountered in TTTS fetuses and neonates treated with laser surgery. The incidence of brain injury was likely underestimated due to the limited use of MRI. Adverse outcome was common after brain injury. Recurrent TTTS/post-laser TAPS and a lower gestational age at birth increased the risk of brain injury. The relatively frequent finding of CBH means that attention should be paid to the posterior fossa by clinicians taking care of women and children with TTTS.

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