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Long-term follow-up of complicated monochorionic twin pregnancies: Focus on neurodevelopment

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A B S T R A C T

Monochorionic twin pregnancies have an increased risk of morbidity and mortality. Due to the advancements in screening and treatment strategies, mortality rates have decreased. Improving survival rates demands a shift in scope toward long-term outcomes. In this review, we focus on neurodevelopmental outcome in survivors from complicated monochorionic twin pregnancies, including twin–twin transfusion syndrome (TTTS), twin anemia-polycythemia sequence (TAPS), acute peripartum TTTS, acute perimortem TTTS, selective fetal growth restriction (sFGR) and monoamnionicity. Our aim is to provide an overview of the current knowledge on the long-term outcome in survivors, including psychomotor development and quality of life, and provide recommendations for future research and follow-up programs.

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Abbreviations: MC, monochorionic; TTTS, twin-twin transfusion syndrome; TAPS, twin anemia-polycythemia sequence; sFGR, selective fetal growth restriction; CP, cerebral palsy; NDI, neurodevelopmental impairment.

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Introduction

Monochorionic (MC) diamniotic twins are identical twins that share one placenta. All MC twin placentas have vascular anastomoses connecting the circulation of the two fetuses, which leads to intertwin blood transfusion. In most cases, blood transfusion between the two fetuses is in balance, resulting in an uncomplicated MC twin pregnancy. However, in the case of unbalanced feto-fetal transfusion, severe complications may occur such as twin-to-twin transfusion syndrome (TTTS) or twin anemia polycythemia sequence (TAPS). Another complication in MC twin pregnancies occurs in the case of unequal sharing of the placenta, which can lead to selective fetal growth restriction (sFGR) [1]. In rare cases, identical twins share not only one placenta but also a single amniotic sac (monoamniotic), which can result in umbilical cord entanglement.

Early detection and improved treatment strategies for these conditions have led to a decrease in mortality. The increase in perinatal survival demands a shift in focus from survival to quality of life and the long-term outcome. The aim of this review is to give a summary of the current knowledge on the long-term outcome in complicated MC pregnancies, to report risk factors, and to provide recommendations for future research and follow-up protocols.

Long-term neurodevelopmental outcome in twin–twin transfusion syndrome (TTTS) fetoscopic laser surgery

TTTS occurs in approximately 10% of all MC twin pregnancies [1]. Untreated, TTTS has a very poor survival rate. Until the late 1990s, serial amnioreduction was the standard of care, reducing the pressure on the placenta and the cervix, thereby restoring to some extent blood flow and preventing immature delivery [2]. Amnioreduction decreased mortality to 50%, yet long-term follow-up studies report cerebral palsy (CP) ranging from 5% to 23%, with a mean of 14% [3]. The long-term neurodevelopmental impairment (NDI), including cognitive, motor, and/or sensorineural disabilities, ranges from 14% to 26%, with a mean of 20%. These numbers must, however, be viewed with caution as methodology and especially definitions of NDI differ widely between studies. Fetoscopic laser surgery has been shown to be the best first-line treatment, a causative treatment aimed at dichorionizing the placenta and arrest the intertwin transfusion [4]. Since the introduction of laser surgery in the early 1990s, survival rates following laser surgery have increased from 55% to 74% [5,6].

Fetoscopic centers around the world initiated long-term follow-up programs and studies to evaluate the neurodevelopmental outcome of TTTS survivors at different time points using various outcome measures and definitions of NDI. Table 1 summarizes 26 follow-up studies published between 1999 and 2021.

In total, 39% (10/26) studies used a composite outcome measure termed NDI including CP, severe motor and/or cognitive developmental delay (scores below 2 SD), and bilateral blindness or deafness requiring amplification with hearing aids. In addition to a neurologic examination, cognitive development was assessed with Ages and Stages Questionnaire (ASQ) or Bayley scales in 54% (14/26) studies. In other studies, multiple methods of follow-up and definitions of NDI were used. CP was diagnosed using the Gross Motor Functioning Classification Scale in 20% (5/24) studies [7]. Two studies did not report CP.

The reported CP rate ranges from 2% to 18% [8–33] with a mean of 5% (126/2405). NDI ranges from 4% to 18%, with a mean rate of 9% (225/2443). Eight studies reported mild NDI, including scores <1 SD on a developmental test or neurological deficiencies with the prospect of normalization or with no significant impact on quality of life, in 0–34% [14,17,18,20,26,27,30,33]. Although the timing of follow-up assessment of TTTS survivors ranges from 6 months to 6 years of age, the majority of studies (11/26, 42%) report neurodevelopmental outcome at 2 years of age. Longitudinal studies with follow-up at school age are missing. A recent study from our center evaluated 73 TTTS survivors born premature and/or small for gestational age (<1500 g and < P 10) at both 2 and 5 years [33]. We observed an increase in NDI rate compared to their 2-year assessment. The rate of mild-to-moderate NDI increased from 25% to 34% and the rate of severe NDI increased from 9% to 12%. These results emphasize the importance of follow-up beyond 2 years. Twins treated with fetoscopic laser surgery for TTTS seem at

Table 1
Long-term outcome in twin–twin transfusion syndrome treated with fetoscopic laser surgery.

Author, year	Outcome measure	Age	CP % (n/N)	NDI % (n/N)	Lost to FUP	Comments
1. De Lia, 1999 [8]	Neurologic exam	14 months (±10)	4 (3/93)	NA	0%	NDI not reported, no developmental test, FUP at young age, no controls
2. Sutcliffe, 2001 [9]	Neurologic exam, Griffiths Scale	Mean 24 (17–32) months	9 (6/66)	9 (6/66)	19%	47% information only from GP, 54% incomplete developmental test, no controls
3. Banek, 2003 [10]	Neurologic exam, Griffiths Scale, Snijders-Oomen Intelligence Test	Median 22 months	11 (10/89)	11 (10/89)	0%	Severe developmental delay not included as a criterion for NDI, 11% minor neurologic deficiencies, no controls
4. Graef, 2006 [11]	Neurologic exam, Griffiths Scale, Snijders-Oomen Intelligence tests	Median 3 years 2 months	6 (10/167)	8 (13/167)	2%	98% inclusion, incomplete developmental tests, no controls
5. Lenclen, 2009 [12]	Neurologic exam, ASQ	Mean 23 months	10 (9/88)	11 (10/88)	13%	Gestation matched DC controls
6. Lopriore, 2009 [13]	Neurologic exam, Bayley scales	Mean 24 months	6 (17/278)	18 (50/278)	6%	Large multi-center study, no controls
7. Salomon, 2010 [14]	Neurologic exam, Amiel-Tison, ASQ, Wechsler scales	Mean 6–72 months	13 (9/69)	13 (9/69)	25% (at 6 years)	FUP to 6 years, no controls
8. Gray, 2011 (15)	Neurologic exam, Griffiths and Bayley scales	Mean 25 (21–46) months	4 (5/113)	12 (14/113)	3%	Mixed developmental tests, e.g. Griffiths and two versions of Bayley scales, no controls
9. Chang, 2012 [16]	Neurologic exam, Bayley scales, MRI	1 year (corrected age)	5 (3/59)	7 (4/59)	3%	FUP at young age, no controls
10. Graeve, 2012 [17]	Neurologic exam, K-ABC, national screening, questionnaires	Median 77 (59–124) months	NA	9 (17/190)	25%	CP not reported, 53% no neurologic exam, 57% no developmental test
11. Kowitt, 2012 [18]	Clinical exam, evaluation of hearing and vision questionnaire	Median 52 (24–120)	3 (1/38)	8 (3/38)	28%	No developmental test, small sample size
12. Swiatkowska-Freund, 2012 [19]	Clinical exam	Mean 6 months	7 (7/100)	NA	7%	Only CP reported, no developmental test, FUP at young age, no controls
13. McIntosh, 2014 [20]	GHQ, Bayley scales and Wechsler scales	Mean 48 (30–69) months	2 (1/50)	4 (2/50)	16%	No neurologic exam, small sample size, no controls
14. Tosello, 2014 [21]	ASQ, clinical exam	Median 37 (4–60) months	6 (2/35)	NA	20%	Small sample size, NDI not reported, 31% (11/35) at least one ASQ score < −2 SD
15. Vanderbilt, 2014 [22]	Amiel Tison exam, BDI	Mean 24 months	3 (3/100)	4 (4/100)	51%	Lost to FUP 51% with majority Quintero stage IV, no controls
16. Müllers, 2015 [23]	Patient correspondence and pediatric evaluation	Median age 4 years (6 months–7 years)	4 (4/106)	14 (15/106)	10%	No developmental test, NDI based on 'neurodevelopmental concerns' from patient correspondence and pediatric evaluation, no controls
17. Campos, 2016 [24]	Clinical exam, Bayley screening test	5.5 (±1.4) and 9.8 (±1.9) months	18 (6/33)	NA	0%	NDI not reported, 'inadequate' Bayley screen: 18% cognitive domain, 9% receptive and 21% expressive communication, 24% fine and 24%

						gross motor, small sample size, 22 term singleton controls
18. Sananès, 2016 [25]	ASQ	2–5 years	NA	13 (17/126)	44%	CP not reported, no neurologic exam, 44% lost to FUP with majority Quintero I, 13% (17/126) at least one ASQ score < − 2 SD, no controls
19. Van Klink, 2016 [26]	Neurologic exam, Bayley scales, GMFCS	Mean 24 months	3 (6/216)	4 (9/216)	6%	FUP in two of the five participating trial centers, large multicenter study, 94% inclusion rate, no controls
20. Korsakissok, 2018 [27]	ASQ, parental questionnaire, information attending physician	Mean 59.3 (24–96) months	5 (3/58)	12 (7/58)	45%	No neurologic exam, 30% moderate neurological abnormalities, no controls
21. Sommer, 2018 [28]	GMFCS, evaluation of hearing and vision	18 months corrected GA	15 (2/13)	NA	61%	NDI not reported, no developmental test, small sample size, preterm (<29 weeks GA) TTTS survivors vs. preterm DC twins
22. Schou, 2019 [29]	ASQ, telephone interview parents	25 months (±11)	6 (5/86)	11 (9/86)	18%	Mixed methods for follow-up, TTTS survivors increased risk of NDI compared to uncomplicated MC twins
23. Spruijt, 2019 [30]	Bayley scales, neurologic exam, GFMCS	2 years	2 (4/258)	3 (7/241)	15%	Large sample size with standardized neurologic and developmental tests, no controls
24. Matsushima, 2020 [31]	Tsumori's Mental Development Test and Kyoto Scale of Psychological Development 2001, MRI	3 years, 6 months	3 (6/188)	9 (16/188)	5%	Mixed methods for FUP, no controls
25. Rüegg, 2020 [32]	Parental questionnaires, Bayley scales, neurologic exam	50 (7–111) months	5 (2/42)	7 (3/42)	38%	Bayley scales only in TTTS survivors born premature or SGA, no difference with DC controls
26. Knijnenburg, 2021 [33]	Bayley scales, Wechsler scales, neurologic exam, M-ABC, GMFCS	5 years	3 (2/73)	12 (9/73)	32% (at 5 years)	Only TTTS survivors born premature or SGA age were included in 5-year FUP, no controls
Total			**5.2% (126/2405)**	**9.2% (225/2443)**		
Range			**2–18%**	**4–18%**		

CP, cerebral palsy; NDI, neurodevelopmental impairment; NA, not assessed; TTTS, twin–twin transfusion syndrome; NND, neonatal death; FUP, follow-up; ASQ, Ages Stages Questionnaire; GP, general practitioner; GA, gestational age; DC, dichorionic; SD, standard deviation; K-ABC, Kaufman Assessment Battery for children; GHQ, General Health Questionnaire; BDI, Battelle Developmental Inventory.
Of note: Two studies [70,71] are not included in this table, because the included children are more fully described in these studies [13,26].

risk of long-term neurodevelopmental 'lagging behind', which means that the children do not deteriorate but struggle to achieve the age-appropriate milestones, thereby 'growing into their deficits'.

Several risk factors for long-term NDI have been reported, including advanced GA at fetoscopic laser, cerebral injury, low gestational age at birth, and low birth weight, in particular fetal growth restriction [34]. Whether neuroimaging technologies (cerebral ultrasound and/or magnetic resonance imaging, MRI) are useful or not in predicting the long-term neurodevelopment remains a subject of debate. Two studies used (neonatal) cranial imaging in combination with the long-term neurodevelopmental assessment. Chang et al. (2012) reported two TTTS survivors with a severe cerebral injury on MRI, but normal neurologic examinations at a corrected age of 1 year, and one survivor with a normal MRI but severe neurologic impairment [16]. Spruijt et al. (2019) reported normal neonatal cranial ultrasound examinations in the majority of children diagnosed with NDI at 2 years of age (10/17) [30]. However, the severe cerebral injury was associated with decreased Bayley motor scores ($p = 0.012$). Large prospective outcome studies are required to determine the predictive value of neuroimaging in MC twins.

Long-term neurodevelopmental outcome in post-laser and spontaneous twin anemia polycythemia sequence (TAPS)

TAPS develops either spontaneously in 3–5% of MC pregnancies or after laser therapy for TTTS in 2–16% [35]. To date, no consensus has been reached on the optimal treatment in TAPS. Whether fetal surgery (fetoscopic laser coagulation of vascular anastomoses, selective reduction, and intrauterine transfusions), obstetrical interventions (elective preterm birth), or expectant management may or may not improve the outcome remains to be determined. Data on the long-term outcome is scarce and limited to a few small studies. A research group from Japan studied the long-term outcome of three twin pairs who developed TAPS after laser surgery and detected bilateral deafness and cognitive delay in a 9-year-old donor and spastic paralysis and cognitive delay in a 2-year-old recipient [36]. The largest post-laser TAPS follow-up study thus far was performed by our research group and included 47 post-laser TAPS cases managed at our center. The rate of severe NDI and mild impairment was 9% and 17%, respectively, which is within the range of NDI reported in case series of TTTS treated with laser. We found no difference in the outcome between donors and recipients after post-laser TAPS [35]. Low gestational age and low birth weight were significant risk factors for lower cognitive scores. In addition, the post-laser TAPS subgroup of eight survivors treated with intrauterine transfusions had significant lower cognitive scores than those who underwent expectant management, laser reintervention, and selective reduction procedures.

For spontaneous TAPS, available literature on the neurodevelopmental outcome is limited to two studies. In a small study, Han et al. evaluated the long-term outcome in 17 spontaneous TAPS survivors from 11 MC pregnancies and found no cases with CP at 2 years of age in survivors [37]. The developmental outcome was not assessed in this study. A larger long-term follow-up study by our research group detected a worse long-term neurodevelopmental outcome in spontaneous TAPS donors compared to recipients [38]. At a median age of 4 years, NDI was present in 18% of spontaneous TAPS donors compared to 3% in TAPS recipients (overall 9%). Mild-to-moderate NDI was present in 20% (15/74) of the donors and in 15% (6/40) of the recipients. Overall, donors showed higher rates of mild (−1 SD) cognitive impairment (35% vs. 18%) and lower rates of disease-free survival (45% vs. 80%) than recipients. Remarkably, a high rate of bilateral deafness was observed in spontaneous TAPS donors, 15% vs. 0% in recipients. In all donors, deafness was based on auditory neuropathy spectrum disorder. The exact cause of the high rate of deafness in donor twins was unclear. This finding was not observed in TTTS donors or children who suffered from chronic fetal anemia based on erythrocyte alloimmunization [39].

Long-term neurodevelopmental outcome in acute peripartum TTTS

Acute peripartum TTTS is a rare condition occurring in approximately 2% of MC twin pregnancies, where acute intertwin transfusion occurs during birth leading to large differences in hemoglobin levels

between the donor and the recipient [40,41]. In contrast to TAPS, there is no reticulocyte discordance as the reticulocyte count in donors did not have time to increase, reflecting the acute occurrence of the disorder. Donors can suffer from the sequelae of acute blood loss and hypovolemic shock, including cerebral injury [42–44]. However, data on short-term outcome in acute peripartum TTTS is limited and mainly based on casuistic reports.

The long-term outcome of survivors is currently unknown. Since this condition is rare, a collaboration in an international registry could be a solution to gather more data on the long-term outcome of survivors of acute peripartum TTTS.

Long-term neurodevelopmental outcome in acute perimortem TTTS

Acute perimortem TTTS occurs when one of the fetuses dies, leading to acute exsanguination and eventually death of the co-twin in up to 41% of cases [45]. When the co-twin survives, the acute exsanguination and hypovolemic shock may lead to severe cerebral injury in 26% of cases [46]. In a recent meta-analysis combining the results of six diffferent studies, brain abnormalities in fetal MRI were reported in 20% of 116 pregnancies. Postnatally, brain imaging was defined as 'abnormal' in 43% of 140 pregnancies reported by 12 studies [45]. Therefore, cranial imaging, including fetal MRI, is important in this subgroup. Two cases of renal failure due to severe renal dysplasia were described in the surviving co-twin [47,48].

The long-term neurodevelopmental outcome is severely impaired in 29% of the survivors [45]. The rate of NDI is significantly higher compared to DC twins (10%) and represents the highest NDI rate compared to other MC complications (Fig. 1) [45].

Long-term neurodevelopmental outcome in selective fetal growth restriction (sFGR)

sFGR occurs in approximately 10–15% of all MC twin pregnancies and is caused by an unequal sharing of the placenta, often accompanied by a marginal or velamentous cord insertion of the smaller twin [49,50]. sFGR is usually defined as an estimated fetal weight below the 10th percentile in the smaller twin and/or a birth weight discordance of more than 20%. The optimal management in MC

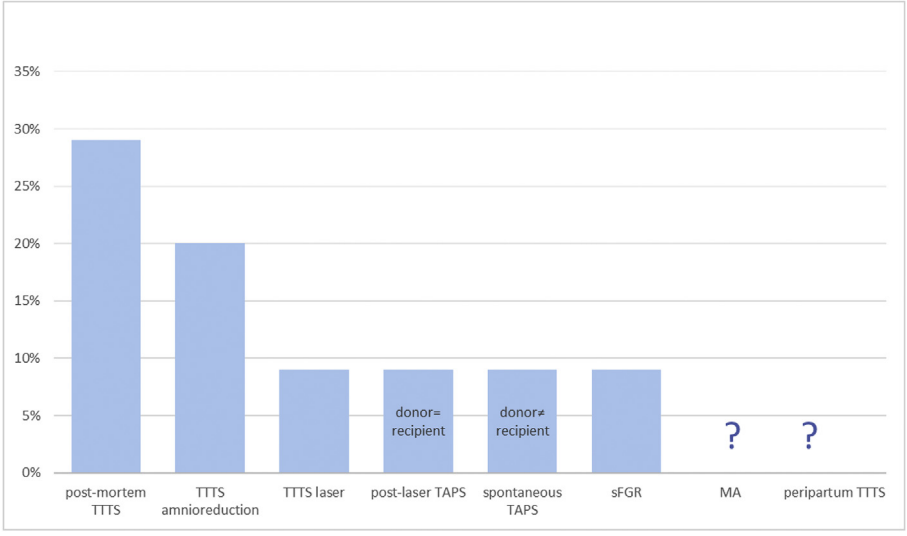

Fig. 1. Risk of neurodevelopmental impairment in complicated MC twin pregnancies.

twins with sFGR is not clear and there is still no international consensus on the best treatment strategy. Whether fetal surgery (fetoscopic laser coagulation of vascular anastomoses, selective reduction) or obstetrical interventions (elective preterm birth) may improve the (long-term) outcome remains to be determined. How to balance the benefit from prolonging the pregnancy in preventing prematurity-related injury against the risk of single fetal demise and concomitant damage to the co-twin is a clinical challenge and warrants further study. A systematic review shows that the incidence of severe cerebral injury in MC twins with sFGR varies greatly from 0% to 33%, with an estimated average of 8% [51–53]. The highest incidence of cerebral injury is reported in the pregnancies complicated by single fetal demise of a co-twin, in pregnancies with abnormal umbilical artery Doppler findings, and in cohorts with a lower gestational age at birth. Table 2 summarizes the eight long-term follow-up studies in twins with sFGR [54–61]. Although the between-study variation in the definition of sFGR and methodology hampers comparability, the overall reported rate of CP ranges between 5% and 19% with a mean of 6% (17/289). NDI ranges from 1% to 42% with a mean of 9% (50/553). The growth-restricted twins tend to show lower cognitive scores and more mild motor/neurological impairments [55,56,58–60]. Insight into the long-term outcomes will lead to improved prognostics, which are essential in parent counseling and crucial in the process of forming a management protocol specifically for twins with sFGR to optimally monitor and support their development.

Long-term neurodevelopmental outcome in monoamniotic (MA) pregnancies

Only in approximately 1% of monozygotic twin pregnancies do both twins share the same amniotic sac [62]. MA twin pregnancies can be challenged with all the aforementioned complications. Unique to spontaneous MA twin pregnancies is the 100% risk of cord entanglement, which is associated with an increased risk of fetal mortality. To prevent fetal demise and peripartum complications, MA pregnancies are usually delivered around 33 weeks of gestation by cesarean section [63]. The preterm delivery is a known risk factor for cerebral injury and long-term neurodevelopmental impairment. Rates of cerebral injury range from 0% to 15% depending on the gestational age [64]. However, data on the long-term neurodevelopmental outcome is not available. A (inter)national database for MA twin pregnancies could facilitate the study of the natural history and possible risk factors for adverse (long-term) outcome including the often elective preterm delivery and following complications accompanying prematurity.

Recommendations for uniform reporting, definitions, and outcome measures of long-term neurodevelopment

The importance of long-term follow-up studies lies in the necessity of evaluating fetal therapy and care of complicated MC twin pregnancies as well as in evidence-based counseling of future parents. In addition, when a center decides to treat fetuses *in utero*, with the knowledge that a significant proportion will develop long-term morbidity, this center also has the responsibility to ensure that survivors will eventually receive the care they need. A long-term follow-up should be an integrated component in the care of complicated MC twin pregnancies. Unfortunately, long-term neurodevelopmental studies are costly and difficult to perform and, consequently, hard to realize. Challenges include, among others, tracking families, organizing follow-up assessments with trained pediatricians and child psychologists, and complete data acquisition and analysis. Structured long-term follow-up programs of MC twins require a dedicated follow-up team including fetal medicine specialists, neonatologists, physiotherapists, child psychologists, and research nurses.

A recurrent issue in the follow-up of complicated MC twins is the lack of a uniform approach. Definitions, methodology, and time points at the follow-up differ between studies and centers. Core outcome sets for the evaluation of care of MC twin pregnancy are essential and could help standardize outcome collection and reporting in follow-up studies. Multicenter efforts are of utmost importance to study the natural history in complicated MC pregnancies and the effect of interventions to determine optimal management (timing and type of intervention).

In most fetal therapy centers with follow-up programs, children are evaluated (with a validated test) for the first time at the age of 2 years. Outcome data later in childhood or puberty is often lacking. It is

Table 2
Long-term outcome in selective fetal growth restriction.

Author, date	Definition of sFGR	Outcome measure and age at FUP	CP % (n/N)	NDI % (n/N)	Large vs. small twin
1. Adegbite, 2004 [54]	Birth weight discordance ≥20% and abdominal circumference ≤5th	Griffiths Scale at 24 months DC-twin controls	19 (5/26)	42 (11/26)	No difference test score small vs. large twin, NDI increased compared to DC controls
2. Hack, 2009 [55]	Birth weight discordance ≥20%	Griffiths Scale at 22 months	0 (0/14)	7 (1/14)	Test scores (trend) lower in small twin
3. Edmonds, 2010 [56]	Continuous variable for birth weight discordance	Wechsler scales at 7–17 years	Excluded	NA ($N = 71$)	Lower Wechsler verbal IQ in small twin
4. Halling, 2016 [57]	Birth weight discordance ≥20%	Bayley scales at 24–42 months	NA	NA ($N = 24$)	No analysis small vs. large MC twin Lower Bayley scores in sFGR MC twins vs. sFGR DC twins
5. Rustico, 2017 [59]	Estimated fetal weight <10th or estimated fetal weight difference ≥20%	No neurodevelopmental test, evaluation at 8 years	5 (9/191)	6 (11/191)	More mild NDI in small twin
6. Vedel, 2017 [58]	Birth weight discordance >75th	ASQ up to 48–60 months	NA	NA ($N = 119$)	ASQ scores lower in small twin ($p = 0.05$)
7. Swamy, 2018 [60]	Birth weight discordance ≥20% (12% (6/51) complicated by TTTS)	British Ability Scales, Strength Difficulties Questionnaire at 6 years	2 (3/58)	Excluded from cognitive analysis	Lower scores in small twin
8. Groene, 2019 [61]	Estimated fetal weight <10th and TTTS	Bayley scales at 2 years, control group TTTS twins without sFGR	NA	9 (27/299)	No difference small vs. large twin, no difference TTS + sFGR compared to TTTS without sFGR
Total **Range**			**5.8% (17/289)** **5–19%**	**9.0% (50/553)** **1–42%**	

sFGR, selective fetal growth restriction; CP, Cerebral palsy; NDI, neurodevelopmental impairment; DC, dichorionic; NA, not assessed; IQ, intelligence quotient; ASQ, ages and stages questionnaire; TTTS, twin–twin transfusion syndrome.

crucial to continuously assess child development including standardized measures of well-documented quality, with increasing reliability of results with increasing age of surviving MC twins. A proposition of a long-term follow-up schedule would include visits at the age of 5½, 8, 12, and 16 years. We propose the following recommendations for the long-term follow-up of cognitive, neurologic, motor, social–emotional, and behavioral functioning (Table 3).

If feasible, cognition should be tested using standardized psychometric tests, such as Bayley and Wechsler scales, with age-appropriate norms. Results should be interpreted by qualified professionals, e.g. child psychologists. If parents and children have to travel long distances and/or are unable to travel, questionnaires such as Ages and Stages (ASQ) or the Parent Report of Children's Abilities (PARCA) are alternative, reliable screening tools [65]. To be able to compare results between studies, regardless of the definition of developmental impairment, it is crucial to report the number of children included for assessment with a specific test and the number of children scoring below a certain threshold of the test. For example, the number of children scoring below a Wechsler intelligence quotient of 70 (<– 2 SD) and with scores between 70 and 85 (>–2 SD and < – 1 SD).

Neurologic functioning and the presence of CP should be diagnosed by a pediatrician using a standardized system such as Touwen and the gross motor function classification system (GMFCS) for CP [7]. Again, for comparison between studies, it is important to report the number of children within the different levels of functioning.

Various criteria are used to define NDI, a composite outcome including neurological, cognitive, motor, visual, and auditory outcomes. We recommend severe NDI be defined as at least one of the following: CP GFMCS level 3–5, severe motor and/or cognitive developmental delay (–2 SD scores), bilateral blindness, or deafness requiring amplification with hearing aids. Mild-to-moderate NDI be defined as at least one of the following: CP level 1 to 2 on GFMCS, mild–moderate motor and/or cognitive developmental delay (–1 SD scores), mild hearing loss, and/or mild visual impairment. Definitions of mild hearing loss and mild visual impairment should match the criteria as stated by the international classification of diseases (ICD) 11th revision [66].

The use of systematic, homogeneous methods to evaluate development will benefit the comparability of studies. Comparing and combining the available literature will improve counseling of future parents of complicated MC twins and will enhance an early support to children at risk of developmental impairments. The ideal study design to evaluate new interventions in the management of complicated MC twin pregnancies is an adequately powered randomized controlled trial with 'survival without NDI' as the primary outcome. An international registry to record and evaluate the

Table 3
Proposition for systematic follow-up.

Fetus	Newborn	2 years	5–6 years	8 years	12 years	16 years
Brain development: cerebral imaging (cranial ultrasound, MRI)						
Senses: hearing test (ABR in TAPS donors) and screening for (sensorineural) deafness, vision test, and ROP screening						
Physical: General health, growth (catch-up), neurological exam (Touwen, Hempel), gross motor development (AIMS, Bayley scales, M-ABC), cerebral palsy (GMFCS)						
Cognition: Bayley scales, Wechsler scales (IQ), ASQ or PARCA-R						
Neuropsychological: Learning difficulties (reading, mathematics), expressive and receptive language, executive functioning, memory, visual spatial abilities, fine motor development, sensory processing (Sensory Profile)						
Psychosocial and behavioral: Adaptive behavior (ABAS), attachment, internalizing (e.g. anxiety) and externalizing behavior (e.g. aggressive behavior), social skills, quality of life, sleep						
Educational: Pre-academic skills, special needs education, comparison to age-appropriate level						
Developmental disorders: e.g. attention deficit/hyperactivity, autism spectrum, disruptive mood dysregulation						

MRI, magnetic resonance imaging; ABR, auditory brainstem response; TAPS, twin anemia polycythemia sequence; ROP, retinopathy of prematurity; GMFCS, gross motor functioning classification system; ASQ, ages and stages questionnaire; PARCA-R, parent report children's abilities revised; IQ, intelligence quotient; ABAS, adaptive behavior assessment system.

outcome in large groups of MC twins is necessary to improve our knowledge, specifically of subgroups.

Conclusions

Survival rates of complicated MC pregnancies are increasing due to improvement in prenatal care, but survivors are confronted with an increased risk of long-term impairments. Rates of CP in twins with TTTS, TAPS, and/or sFGR are estimated to be around 5% and rates of severe NDI around 9–10%. Importantly, spontaneous TAPS donors are at increased risk of cognitive delay and deafness, highlighting the importance of support and an early (appropriate) hearing test. In sFGR, the smaller twin tends to score lower on cognitive tests, requiring more attention. The highest risk of permanent long-term impairment is reported in the group after acute postmortem TTTS, in which one in three survivors may develop NDI. Little is known about the long-term outcome in acute peripartum TTTS and monoamniotic twins. Evaluation of the risk of NDI in these two subgroups is urgently needed.

To put the results into perspective, in the general population, the rate of CP ranges from 2 to 3.5 per 1000 live births [67]. In children born between 32 and 36 weeks of gestation, the prevalence of CP is estimated to be 7 in 1000 [68]. Moderate-to-severe NDI is described in 2–3% in a healthy control group of 13,689 Danish children in a study of group B streptococcal disease [69]. Comparing these rates with the long-term outcomes in complicated MC twins emphasizes the importance of subsequent dedicated follow-up in this high-risk group of children. To clarify and assess the impact of severe MC pregnancy complications on the long-term neurodevelopmental outcome of survivors, the inclusion of a control group of twins from uncomplicated MC pregnancies is essential.

A uniform follow-up program should be an important goal of every fetal therapy center in the world. An international registry to record and evaluate the outcome in large groups of MC twins is of paramount importance to increase current knowledge and improve management in specific subgroups.

Summary

Improving survival rates in monochorionic (MC) twins demands a shift in scope toward the long-term outcome. Long-term outcome studies are scarce, especially in TAPS, and are often limited to one assessment in early childhood. Outcome data in acute peripartum TTTS and monoamnionicity is lacking. Neurodevelopmental impairment (NDI) rates are approximately 9% in TTTS treated with laser, spontaneous and post-laser TAPS, and sFGR. Almost one in three survivors of postmortem acute TTTS has a long-term NDI. Higher rates of hearing and cognitive impairment are reported in spontaneous TAPS donors. The smaller twin in sFGR is more prone to developmental problems compared to the appropriate grown co-twin. Uniform follow-up studies including control groups of twins from uncomplicated MC twin pregnancies are of utmost importance to improve the care for MC twins from complicated pregnancies.

Practice points

- Monochorionic twins have a higher risk of neurodevelopmental impairments compared to the general population.
- The long-term neurodevelopmental impairment in TTTS survivors treated with laser, spontaneous and post-laser TAPS, and sFGR is reported in ~9%.
- Spontaneous TAPS donors and growth-restricted twins are at increased risk of long-term neurodevelopmental impairment compared to spontaneous TAPS recipient and appropriate grown co-twins.
- Knowledge on the neurodevelopmental outcome in monoamniotic twins and survivors of acute peripartum TTTS is lacking.

Research agenda

- Longitudinal studies on the developmental trajectory of MC twins into school-age and early adolescence.
- Follow-up studies should include MC twins from uncomplicated pregnancies to determine the impact of TTTS, TAPS, and FGR.
- To build an international registry to identify the risk factors for adverse long-term neurodevelopmental outcome, especially in the subgroups of acute peripartum TTTS and monoamniotic twins.
- To determine optimal management and treatment, randomized controlled trials should be powered to detect a difference in survival without NDI'.

Declaration of competing interest

There is no conflict of interest.

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