Sileo Filomena Giulia (Orcid ID: 0000-0001-7380-0576)
Curado Joana Pascoal (Orcid ID: 0000-0003-2477-5479)
D'Antonio Francesco (Orcid ID: 0000-0002-7546-8025)
Khalil Asma (Orcid ID: 0000-0003-2802-7670)

Incidence and outcome of prenatal brain abnormalities in twin-to-twin transfusion syndrome: systematic review and meta-analysis

F. G. Sileo[1,2], J. Curado[3], F. D'Antonio[4], C. Benlioglu[5], A. Khalil[6,7,8]

1. Department of Biomedical, Metabolic and Neural Sciences, International Doctorate School in Clinical and Experimental Medicine, University of Modena and Reggio Emilia, Modena, Italy

2. Unit of Obstetrics and Gynecology, Azienda Unità Sanitaria Locale - IRCCS, Reggio Emilia, Italy

3. Gynaecology and Obstetrics Department. Hospital Garcia de Orta. Almada. Portugal.

4. Prenatal Medicine Unit, Obstetrics and Gynecology Unit, University "G. d'Annunzio" of Chieti, Chieti, Italy

5. Department of Obstetrics and Gynecology, Ankara University Faculty of Medicine, Ankara, Turkey

6. Fetal Medicine Unit, St George's Hospital, St George's University of London, London, UK

7. Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK

8. Twins Trust Centre for Research and Clinical Excellence, St George's Hospital, London, UK

Corresponding Author:
Professor Asma Khalil MBBCh, MD MRCOG, MSc (Epi), DFSRH, Dip (GUM)
Fetal Medicine Unit
Department of Obstetrics and Gynaecology
St. George's University Hospitals NHS Foundation Trust
Blackshaw Road, London, SW17 0QT, UK.
E-mail: akhalil@sgul.ac.uk

Key words: twin, fetus, brain, TTTS, twin to twin transfusion syndrome, bleeding, haemorrhage, prenatal diagnosis, ultrasound, MRI

Short title: Prenatal brain abnormalities in TTTS syndrome

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.24895

Contribution

What are the novel findings of this work?

In twin pregnancies complicated by TTTS and treated with laser the overall incidence of antenatally diagnosed fetal brain abnormalities is around 2% and these lesions are mainly ischemic (30.4%) in nature. In more than half of the cases, parents opted for termination of the pregnancy; fetal and neonatal death occurred in 13% and 15% respectively.

What are the clinical implications of this work?

Brain injury remains one of the most feared complication of twin pregnancies complicated by TTTS especially for the risk of neurodevelopmental impairment in these babies. However, neonatal morbidity data, such as cerebral palsy and neurodevelopmental delay, is rarely reported highlighting the urgent need for long term follow up in these children.

ABSTRACT

Objectives: to ascertain the incidence of antenatally diagnosed brain injuries in twin pregnancies complicated by twin to twin transfusion syndrome (TTTS) and to quantify the perinatal mortality, morbidity and long-term neurodevelopmental outcomes of these fetuses.

Methods: Medline, Embase, Clinicaltrials.gov and Cochrane Library databases were searched. Inclusion criteria were studies reporting on brain abnormalities diagnosed antenatally in twin pregnancies complicated by TTTS. The primary outcome was the incidence of prenatal brain abnormalities. The secondary outcomes were intrauterine demise (IUD), neonatal death, termination of pregnancy (TOP) and long-term morbidity. All these outcomes were explored in the overall population of fetuses with antenatal diagnosis of brain abnormalities. Sub-group analysis according to: type of treatment, gestational age and Quintero stage at diagnosis and/or treatment, co-twin death was planned. Meta-analyses of proportions were used to combine data and reported pooled proportion and their 95% confidence intervals (CI).

Results: Thirteen studies including 1573 cases of TTTS and 88 fetuses with an antenatal diagnosis of brain abnormalities were included in the systematic review. The meta-analysis included only studies reporting on brain abnormalities in twin pregnancies complicated by TTTS cases and treated with laser. Overall, brain injuries occurred in 2.2% of fetuses (eight studies (52/2410 fetuses)). These brain abnormalities were reported in 1.03% and 0.82% of recipients or donors, respectively. These abnormalities were mainly ischemic lesions (30.4%, 95%CI 19.1-43), followed by destructive lesions (23.9%, 95%CI 13.7-35.9), ventriculomegaly (19.9%, 95% CI 10.6-31.3) and hemorrhagic (15.3%, 95%CI 7.1-25.8). Spontaneous IUD occurred in 13.4% (95%CI 5.1-24.8) of fetuses, while TOP was chosen by parents in 53.5% (95%CI 38.9-67.8) cases. Neonatal death was reported only by three studies with an incidence of 15.4% (95%CI 2.8-35.4). Finally, only two studies reported on composite morbidity with 20.4% of morbidity reported overall (95%CI 2.5-49.4) which occurred in 29.7% and 20.4% of the recipient and donor fetuses, respectively. Due to the small numbers, only composite morbidity was analyzed and no information on neonatal intensive care unit admission, respiratory distress syndrome or other long-term outcomes such as neurodevelopmental delay or cerebral palsy could be reliably retrieved.

Conclusions: The overall incidence of antenatally diagnosed fetal brain abnormalities in fetuses from twin pregnancies complicated by TTTS treated with laser is around 2%, mainly ischemic (30.4%) in nature. TOP was chosen by parents in almost half of the cases (53.5%). No information could be retrieved on morbidity outcomes, highlighting the urgent need for long-term follow up studies of these children.

BACKGROUND

Twin-to-twin transfusion syndrome (TTTS) occurs in around 10-15% of monochorionic diamniotic (MCDA) pregnancies as the result of a chronic unbalance in intertwin blood volume exchange through the anastomoses present in their placenta.[1-3] When left untreated, fetal demise rates can reach 90% with over 50% morbidity rates in survivors.[1] At present, fetoscopic laser photocoagulation of placental anastomoses is considered the first line treatment in pregnancies complicated by TTTS in view of its superiority in reducing both perinatal mortality and neurological morbidity.[4-7] When treated with fetoscopic laser photocoagulation, the overall survival rate is 50-70% and the risk of abnormal neurodevelopmental outcome is between 4% and 18%. [1, 6-7] Moreover, when stratifying MCDA twin pregnancies according to Quintero staging, the overall survival is higher at earlier Quintero stages (I-II), but the perinatal survival rates are reasonable even at stage III and IV when treated with laser therapy. [8-9]

Despite these improvements in mortality and morbidity compared to alternative management options, [4] after laser treatment for TTTS, mild neurodevelopmental delay (NDI) occurred in up to 23% of surviving children.[10] These figures are derived from studies with long-term follow-up studies usually until two years of age.[11] Several studies have reported that severe brain lesions are diagnosed in 3-16% of the survivors after laser.[8, 12-13] The interdependency of two fetal circulations that characterizes monochorionic placentas is likely to play a causative role in the development of cerebral lesions in these pregnancies for which several theories have been proposed, [14-16] hemodynamic instability and brain prematurity are both likely to play a role.

Despite its importance, however, the true incidence of prenatal brain injuries in twin pregnancies complicated by TTTS and robust estimates of perinatal mortality and morbidity of these fetuses are yet to be established. The aim of this systematic review and meta-analysis was to firstly ascertain the incidence of antenatally diagnosed brain injuries in twin pregnancies complicated by TTTS and to secondly quantify the perinatal mortality and morbidity, as well as the long-term neurodevelopmental outcomes of these fetuses.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to an a-priori designed protocol for systematic reviews and meta-analysis. Medline, Embase, Clinicaltrials.gov and Cochrane Library databases were searched electronically in June 2020 and updated in July 2021, utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "twin-to-twin transfusion syndrome" and "brain abnormalities" and "fetus and newborn" (Supplementary Table 1). The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA[17] and MOOSE[18] guidelines were followed. Reference lists of relevant articles and reviews were hand searched for additional reports. The study was registered with the PROSPERO database (Registration Number: CRD42021200149).

Inclusion criteria, primary and secondary outcomes

The inclusion criteria were studies reporting on brain abnormalities diagnosed antenatally in twin pregnancies complicated by TTTS. The primary outcome was the estimation of the incidence of prenatal brain abnormalities.

The secondary outcomes were:

- Intrauterine demise (IUD), defined as fetal loss after 20 weeks' gestation
- Neonatal death (NND), defined as the death of the newborn up to 28 days of life
- Survival of at least one twin (up to 28 days)
- Termination of pregnancy (TOP)
- Long-term morbidity, defined as the presence of any degree of neurodevelopmental delay (defined according to the specific psychometric tests used by each author to evaluate the included children) or cerebral palsy (defined according to the European Cerebral Palsy Network and classified as diplegia, hemiplegia, quadriplegia, dyskinetic, or mixed).

All these outcomes were explored in the overall population of fetuses with antenatal diagnosis of brain abnormalities. Furthermore, we planned to perform sub-group analysis according to:

- Type of treatment, i.e. Fetoscopic laser ablation of anastomoses, amnioreduction, selective termination
- Gestational age at diagnosis and/or treatment
- Quintero stage at diagnosis and/or treatment
- Whether the pregnancy was complicated by single intrauterine demise

Study selection, data collection and quality assessment

Only studies reporting the incidence of antenatally diagnosed brain abnormalities in fetuses from twin pregnancies complicated by TTTS were considered eligible for inclusion. Cases associated with other major structural anomalies on ultrasound were not included, because the presence of other abnormalities made the brain abnormalities unlikely to be related to the phenomenon of TTTS. We excluded triplet pregnancies complicated by TTTS, studies where the brain assessment was not systematically conduced or pediatric studies only including surviving children after TTTS and not reporting on prenatal assessment as these studies could have introduced a selection bias. We also excluded studies with less than three cases and studies published before 2000, as we considered that advances in prenatal imaging techniques, improvements in the diagnosis and definition of brain anomalies make these less relevant. Finally, studies not providing a clear classification of the anomaly were not considered suitable for the inclusion in the current review.

Three authors (FGS, CB, JC) independently reviewed each potentially relevant record based on the title and abstract. Agreement regarding potential relevance was reached by consensus. Full texts were retrieved for each potentially relevant citation. Two authors (FGS, JC) independently reviewed the full text of each selected study to assess eligibility for inclusion and, using a standardised extraction form, independently extracted relevant data regarding study characteristics and pregnancy outcomes. Discrepancies between the authors were resolved by discussion with a fourth author (AK).

If more than one study was published on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Quality assessment of the included studies

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for case-control or cohort studies. According to NOS, each study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups and the ascertainment of outcome of interest. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at the start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, its length and the adequacy of

follow up. According to NOS, a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. [19]

Case series were evaluated with a modified version of NOS, which is based on 8 questions in the domains of selection, ascertainment, causality and reporting (Supplementary Table 2). Although a formal score could be assigned giving a binary response to each question, the numeric representation of methodological quality was not considered appropriate as recommended, the overall final judgment was made based on questions 1, 2, 3, 7 and 8, which were deemed most critical in this specific clinical scenario. [20]

Statistical analysis

We used meta-analyses of proportions to combine data and reported pooled proportions and their 95% confidence intervals (CI). Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates that no heterogeneity was observed, whereas values >50% are associated with substantial heterogeneity. Due to the clinical heterogeneity among studies, a random effects model was used for all meta-analyses. [21] Egger's test was used to assess potential publication bias and funnel plots were created for visual inspection.[22] Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than 10, as the tests lack power to detect real asymmetry in this scenario. [23] The analysis was performed using Statsdirect 3.0.171 (Stats Direct Ltd) and Revman 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) statistical software.

Results

General characteristics of the study

A total of 658 articles were identified, 92 were assessed with respect to their eligibility for inclusion; 13 studies (Table 1) were included in the systematic review (Table 1; Figure 1). These 13 studies[15, 24-35] included 1573 cases of TTTS and 88 fetuses with an antenatal diagnosis of brain injury (Table 1). No randomized controlled trials were available for inclusion; data for this review were only derived from observational cohort studies or case-series. A list of the excluded studies and the reason for their exclusion is outlined in Supplementary Table 3.

These studies included all TTTS cases treated with Laser surgery in five studies,[24, 26, 28, 32, 35] more than one management in two studies[15,29] and selective termination in one study.[34] Only cases of single IUD post TTTS and laser were included in one study,[25] sIUD post TTTS treated with laser and amnioreduction in another study[30] or without any specified management in one study.[31] Finally, the brain imaging was performed before any procedure in one study (33) and no treatment was specified in one study. [27]

The imaging modality was MRI in seven studies,[26-29, 33-35] ultrasound together with MRI in five studies[15, 25, 30-32] and only ultrasound in one study[24] where although laser was the recommended management, the diagnosis of brain abnormality was made before the treatment. No information on gestational age at imaging was reported (Table 1) in eight studies.

Quality assessment of the included studies

Table 2 presents the results of the quality assessment of the included studies using NOS or its modified version. The cohort studies showed an overall good score regarding the three domains evaluated, i.e. selection and comparability of the study groups, and for ascertainment of the outcome of interest; the case series, instead, were mainly judged to be of low quality. The main weaknesses of these studies were their retrospective design, small sample size, heterogeneity of outcomes observed and lack of postnatal follow-up.

Synthesis of the results

Incidence and types of brain abnormalities

For the meta-analysis we decided to include only studies reporting on brain abnormalities in TTTS cases treated with Laser as this is more likely to reflect current best practice and because the studies focusing on other management options were too few and with small sample sizes. We excluded from

the meta-analysis studies not reporting on the management or where the imaging was performed at diagnosis before any active fetal intervention of a therapeutic procedure.

Eight studies[15, 25-26, 28-30, 32, 35] including 2410 fetuses reported on the overall incidence of brain anomalies in twin pregnancies complicated by TTTS. Overall, brain abnormalities occurred in 2.2% (95%CI 1.6-2.8) with a very high heterogeneity among studies as reported in Table 3. Five studies[15, 29-30, 32, 35] reported on brain injuries according to the status (donor versus recipient twin) with similar distribution, i.e. 1.03% and 0.82% of abnormalities occurring in the recipient and donor twin, respectively. Regarding the nature of brain abnormalities, which were reported in seven studies,[15, 25-26, 28-29, 32, 35] they were mainly ischemic lesions (30.4%, 95%CI 19.1-43) followed by destructive lesions (23.9%, 95%CI 13.7-35.9) and ventriculomegaly (19.9%, 95% CI 10.6-31.3). The nature of the lesions was hemorrhagic in 15.3% (95%CI 7.1-25.8) of the fetuses with brain abnormalities.

Pregnancy and neonatal outcomes in fetuses with brain abnormalities secondary to TTTS

Overall, spontaneous IUD occurred in 13.4% (95%CI 5.1-24.8) of fetuses with brain abnormalities after TTTS with low heterogeneity among studies. Six studies[25-26, 28-29, 32, 35] reported on the incidence of TOP after the diagnosis of brain lesions and this option was chosen by parents in 53.5% (95%CI 38.9-67.8), but only three studies with 16 fetuses with brain injuries reported also if TOP was chosen for recipient or donor (see Table 3). Very few studies (n=3) reported on NND, which occurred in 15.4% (95%CI 2.8-35.4) of neonates born alive with brain abnormalities after TTTS. Since most studies did not report on neonatal outcomes, data on perinatal death were available for only two studies reporting on 12 fetuses with a diagnosis of brain abnormalities after TTTS.

Only four studies[25,28-29,32] reported data on survival in fetuses with brain abnormalities. Overall, 76.3% (95%CI 61.6-88.2) of fetuses with brain abnormalities survived after birth but only two studies reported on the survival in recipient versus donor as shown in Table 3. Only three studies[25, 28-29] with a total of 14 pregnancies complicated by brain abnormalities of the fetuses reported also on gestational age at birth: 28.5% (95%CI 9.6-52.7) of these babies were born prematurely (i.e. before 32 weeks).

Finally, only two studies[28,29] reported on neonatal composite morbidity. Overall composite morbidity was reported in 20.4% of neonates (95%CI 2.5-49.4), which occurred in 29.7% and 20.4% of the recipient and donor fetuses, respectively. Due to the small numbers, only composite morbidity was analyzed and no information on neonatal intensive care unit (NICU) admission, respiratory distress syndrome (RDS) or other long-term outcomes such as neurodevelopmental delay or cerebral palsy could be reliably retrieved.

Discussion

Main findings

Overall, the incidence of antenatally diagnosed fetal brain abnormalities in fetuses from twin pregnancies complicated by TTTS treated with laser is around 2% and is similar in donor and recipient twins. Lesions are mainly ischemic (30.4%) in nature. Notably, among studies reporting on mortality and TOP, this option was chosen by parents in more than half of the cases (53.5%). Spontaneous IUD occurred in less than 15% of the cases.

Interpretation of the findings and mechanism of brain lesions in TTTS

Injuries described in TTTS used to include both hemorrhagic and ischemic lesions[15] but, due to the increased availability of fetal and neonatal MRI, also white matter injuries, migration disorders, polymicrogyria or even subtle biometric changes in the cerebellum have been described.[27,29,32] Injuries can affect both twins: in the donor, hypovolemia and chronic inter-twin shift of blood are the presumed mechanisms for hypoxic-ischemic insults, while the occurrence of cerebral arterial stroke seems to be a specific risk for the recipient. Additionally, both prematurity and low birthweight increase the risk of cerebral injury postnatally.

High-flow insults are responsible of hemorrhagic lesions such as germinal matrix bleeding, intraventricular and parenchymal hemorrhages while low-flow insults are likely to cause ischemic lesions leading to cerebral atrophy, leukomalacia, migration anomalies, ventriculomegaly and hydranencephaly, etc. Both high-flow and low-flow insults can equally affect the donor and recipient twin and can be the result of a chronic or acute event.[15] Moreover, the location and imaging of fetal lesions are likely to depend upon the maturity of the brain at the time of the injury. Porencephalic cysts without gliosis are more likely to occur in immature brains, while septated cysts develop when the injury occurs during the late second or early third trimester of pregnancy since there is an increasing astrocytic reaction to insults with maturation.[36] Low-flow insults occurring before 28 weeks can alter the neuronal population and consequently neuronal migration with the development of leukoencephalopathy and PVL, hemorrhage in the subependymal germinal matrix extending to the lateral ventricles and cerebral parenchyma. From 36 weeks onward, instead, acute hemodynamic imbalance can cause subcortical leukomalacia, affecting the basal ganglia or cause the development of lenticulostriate vasculopathy.[37-39]

The observed variation in incidence of brain injury could be explained by the different definitions of cerebral injuries, different imaging protocols in terms of frequency or modality and not always routinely performed prenatally and postnatally after laser in all centres. More importantly, the clinical

relevance of these findings has to be linked to the risk of neurodevelopmental impairment. However, this outcome is poorly reported: only two studies of the review reported on morbidity with a total of 9 fetuses with brain abnormalities with available outcomes, including neurodevelopmental delay in 20.4% of these infants. This highlights that in most cases only perinatal data or short-term outcomes are available because of both logistic challenges and the scarcity of funding for organizing long-term follow-up studies.

Strengths and limitations

The main strengths of our systematic review include the detailed and systematic literature search and multitude of outcomes explored. Nevertheless, the small number of included studies, their retrospective non-randomized design, differences among the included populations, management protocols, types of imaging used and high heterogeneity among studies represent the main limitations of this review.

No subgroup analysis could be performed on stage or GA. Despite our systematic literature search, the study by Stirnemann et al[32] accounted for 65% (i.e. 1023 pregnancies) of the included cases. This partly explains both the low incidence of injuries and the high rate of heterogeneity that we found.

Moreover, we focused only on antenatally diagnosed cases to evaluate the true incidence of cerebral injuries, not affected by prematurity, which might be an important contributor in twins, and quantify mortality in these fetuses. This choice precluded the inclusion of several pediatric studies (Supplementary Table 3) which were more comprehensive in terms of neurodevelopmental outcomes but extremely biased in terms of selection of the cohort as shown by the fact that TOP was frequently chosen by parents. Furthermore, the incidence of antenatally diagnosed brain injuries appears to be lower than expected from studies reporting the incidence of brain injuries in the postnatal series. This is likely to be due to the fact that most studies did not perform a systematic assessment of these fetuses and were retrospective in nature. Despite these limitations, however, our review represents the most up-to-date assessment of the totality of the evidence related to this important pathology.

Implications for clinical practice and research

Before the introduction of laser surgery for TTTS, almost 10% of the surviving fetuses were reported to have congenital cerebral malformations and ischemic or hemorrhagic lesions.[27] After the introduction of laser, the incidence of antenatally diagnosed cerebral injuries have decreased to

around 2%. Despite the implementation of antenatal protocols and the increased number of reports on brain injuries, this review shows that, in centres performing laser for TTTS, given the risk of cerebral injury for twin survivors after TTTS, a more standardized antenatal protocol should be offered to systematically look for antenatally acquired lesions. Due to the risk linked to prematurity, postnatal imaging should also be offered. This should enable us to determine the origin, timing and type of brain damage in these twins.

Identification and characterization of brain lesions is of paramount importance to plan the follow up and improve the long-term outcomes of these children. In fact, the goal of fetal therapy should be survival without neurodevelopmental impairment, rather than survival only. There is an urgent need for long-term follow up studies of these children. In fact, experts have proposed that long-term outcomes should be offered at three main timepoints: first, at two years of age when both gross motor function deficits and high risk for cognitive deficits can be detected, at 5 to 7 years of age and when individuals are adolescent or young adults. [40]

Conclusions

The overall incidence of antenatally diagnosed fetal brain abnormalities in twin pregnancies complicated by TTTS treated with laser is around 2% with a similar incidence in donor and recipient twins. The most common type of lesions is ischemic (30.4%) in nature. Among studies reporting on mortality that included TOP, this option was chosen by parents in more than half of the cases (53.5%). No evidence could be extrapolated on both short-term and long-term outcomes such as cerebral palsy and neurodevelopmental delay, highlighting the urgent need for long-term follow up studies of these children. These results should be interpreted with caution due to high heterogeneity among included studies.

Conflict of interests: None

Funding source: None

References

1. Khalil A, Rodgers M, Baschat A, Bhide A, Gratacos E, Hecher K, Kilby MD, Lewi L, Nicolaides KH, Oepkes D, Raine-Fenning N, Reed K, Salomon LJ, Sotiriadis A, Thilaganathan B, Ville Y. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. Ultrasound Obstet Gynecol. 2016;47:247-263.

2. Lewi L, Deprest J, Hecher K. The vascular anastomoses in monochorionic twin pregnancies and their clinical consequences. Am J Obstet Gynecol. 2013;208:19-30.

3. Robyr R, Quarello E, Ville Y. Management of fetofetal transfusion syndrome. Prenat Diagn 2005;25:786–95.

4. Roberts D, Neilson JP, Kilby MD, Gates S. Interventions for the treatment of twin–twin transfusion syndrome. Cochrane Database Syst Rev 2014; 1: CD002073.

5. Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. N Engl J Med. 2004;351:136-144

6. Diehl W, Diemert A, Grasso D, Sehner S, Wegscheider K, Hecher K. Fetoscopic laser coagulation in 1020 pregnancies with twin-twin transfusion syndrome demonstrates improvement in double-twin survival rate. Ultrasound Obstet Gynecol. 2017;50:728-735

7. Van Klink J, Koopman H, Rijken M, Middeldorp J, Oepkes D, Lopriore E. Long-term neurodevelopmental outcome in survivors of twin-to-twin transfusion syndrome. Twin Res Hum Genet. 2016;19:255-261.

8. Lopriore E, van Wezel-Meijler G, Middeldorp JM, Sueters M, Vandenbussche FP, Walther FJ. Incidence, origin, and character of cerebral injury in twin-to-twin transfusion syndrome treated with fetoscopic laser surgery. Am J Obstet Gynecol 2006;194:1215–20.

9. Bamberg C, Diehl W, Diemert A, Sehner S, Hecher K. Differentiation between TTTS Stages I vs II and III vs IV does not affect probability of double survival after laser therapy. Ultrasound Obstet Gynecol. 2021 Aug;58(2):201-206.

10. Spruijt MS, Lopriore E, Tan RNGB, Slaghekke F, Klumper FJCM, Middeldorp JM, Haak MC, Oepkes D, Rijken M, van Klink JMM. Long-Term Neurodevelopmental Outcome in Twin-to-Twin Transfusion Syndrome: Is there still Room for Improvement? J Clin Med 2019; 8: 1226.

11. Khalil A, Townsend R, Reed K, Lopriore E. Call to action: long-term neurodevelopment in monochorionic twins. Ultrasound Obstet Gynecol. 2021;58(1):5-10. doi:10.1002/uog.23591

12. Lenclen R, Paupe A, Ciarlo G, Couderc S, Castela F, Ortqvist L, Ville Y. Neonatal outcome in preterm monochorionic twins with twin-to- twin transfusion syndrome after intrauterine treatment with amnioreduction or fetoscopic laser surgery: comparison with dichorionic twins. Am J Obstet Gynecol 2007;196:450.e1–7.

13. Cincotta RB, Gray PH, Gardener G, Soong B, Chan FY. Selective fetoscopic laser ablation in 100 consecutive pregnancies with severe twin-twin transfusion syndrome. Aust N Z J Obstet Gynaecol 2009;49:22–7.
14. Bendon RW, Siddiqi T. Acute twin-to-twin in utero transfu- sion. Ped Pathol 1989;9:591–598.
15. Larroche JC, Droulle P, Delezoide AL, Narcy F, Nessmann C. Brain damage in monozygous twins. Biol Neonat 1990; 57:261–278.
16. Quarello E, Molho M, Ville Y. Incidence, mechanisms, and patterns of fetal cerebral lesions in twin-to-twin transfusion syndrome. J Matern Fetal Neonatal Med. 2007;20(8):589-597. doi:10.1080/14767050701449638
17. Prisma statement. http://www.prisma-statement.org/ [accessed 10 June 2020].
18. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008-12.
19. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Accessed June 10, 2020]
20. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med.2018;23:60-63.
21. Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. J Health Serv Res Policy. 2002;7:51-61.
22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-634.
23. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. J Clin Epidemiol. 2014;67:897-903.
24. Gray PH, Poulsen L, Gilshenan K, Soong B, Cincotta RB, Gardener G. Neurodevelopmental outcome and risk factors for disability for twin-twin transfusion syndrome treated with laser surgery. Am J Obstet Gynecol. 2011;204(2):159.e1-159.e1596. doi:10.1016/j.ajog.2010.08.041
25. Griffiths PD, Sharrack S, Chan KL, Bamfo J, Williams F, Kilby MD. Fetal brain injury in survivors of twin pregnancies complicated by demise of one twin as assessed by in utero MR imaging. Prenat Diagn. 2015;35(6):583-591. doi:10.1002/pd.4577
26. Hoffmann C, Weisz B, Yinon Y, Hogen L, Gindes L, Shrim A, Sivan E, Schiff E, Lipitz S. Diffusion MRI findings in monochorionic twin pregnancies after intrauterine fetal death. AJNR Am J Neuroradiol. 2013;34(1):212-216. doi:10.3174/ajnr.A3279

27. Kline-Fath BM, Calvo-Garcia MA, O'Hara SM, Crombleholme TM, Racadio JM. Twin-twin transfusion syndrome: cerebral ischemia is not the only fetal MR imaging finding. Pediatr Radiol. 2007;37(1):47-56. doi:10.1007/s00247-006-0337-5

28. Merhar SL, Kline-Fath BM, Meinzen-Derr J, Schibler KR, Leach JL. Fetal and postnatal brain MRI in premature infants with twin-twin transfusion syndrome. J Perinatol. 2013;33(2):112-118. doi:10.1038/jp.2012.87

29. Robinson A, Teoh M, Edwards A, Fahey M, Goergen S. Fetal brain injury in complicated monochorionic pregnancies: diagnostic yield of prenatal MRI following surveillance ultrasound and influence on prognostic counselling. Prenat Diagn. 2017;37(6):611-627. doi:10.1002/pd.5059

30. Senat MV, Bernard JP, Loizeau S, Ville Y. Management of single fetal death in twin-to-twin transfusion syndrome: a role for fetal blood sampling. Ultrasound Obstet Gynecol. 2002;20(4):360-363. doi:10.1046/j.1469-0705.2002.00815.x

31. Simonazzi G, Segata M, Ghi T, Sandri F, Ancora G, Bernardi B, Tani G, Rizzo N, Santini D, Bonasoni P, Pilu G. Accurate neurosonographic prediction of brain injury in the surviving fetus after the death of a monochorionic cotwin. Ultrasound Obstet Gynecol. 2006;27(5):517-521. doi:10.1002/uog.2701

32. Stirnemann J, Chalouhi G, Essaoui M, Bahi-Buisson N, Sonigo P, Millischer AE, Lapillonne A, Guigue V, Salomon LJ, Ville Y. Fetal brain imaging following laser surgery in twin-to-twin surgery. BJOG. 2018;125(9):1186-1191. doi:10.1111/1471-0528.14162

33. Tarui T, Khwaja OS, Estroff JA, Robinson JN, Gregas MC, Grant PE. Altered fetal cerebral and cerebellar development in twin-twin transfusion syndrome. AJNR Am J Neuroradiol. 2012;33(6):1121-1126. doi:10.3174/ajnr.A2922

34. Wang HM, Li HY, Wang XT, Wang YY, Li L, Liang B, Wang J, Song J. Radiofrequency ablation for selective reduction in complex monochorionic multiple pregnancies: A case series. Taiwan J Obstet Gynecol. 2017;56(6):740-744. doi:10.1016/j.tjog.2017.10.006 doi: 10.1016/j.tjog.2017.10.006. PMID: 29241912.

35. Weisz B, Hoffmann C, Ben-Baruch S, Yinon Y, Gindes L, Katorza E, Shrim A, Bar Yosef O, Schiff E, Lipitz S. Early detection by diffusion-weighted sequence magnetic resonance imaging of severe brain lesions after fetoscopic laser coagulation for twin-twin transfusion syndrome. Ultrasound Obstet Gynecol. 2014;44(1):44-49. doi:10.1002/uog.13283

36. Barkovich AJ. Brain and spine injuries in infancy and childhood. Congenital malformations of the brain and the skull in pediatric neuroimaging. Chapters IV and V. In: Barkovich AJ, editor. Pediatric neuroimaging. Third ed. Philadelphia: Lippincott, Williams & Wilkins; 2000. pp 157–249

37. Larroche JC, Girard N, Narcy F, Fallet C. Abnormal cortical plate (polymicrogyria), heterotopias and brain damage in monozygous twins. Biol Neonate 1994;65:343–352.

38. Levene MJ, Chervenak FA, Whittle M, Benett MJ, Punt J, editors. Fetal and Neonatal Neurology and Neurosurgery. 3rd ed. Edinburgh, Scotland: Churchill Livingstone; 21:pp 323–404.

39. de Vries LS, Beek FJ, Stoutenbeek P. Lenticulostriate vasculopathy in twin-to-twin transfusion syndrome: Sonographic and CT findings. Pediatr Radiol 1995;25:S41–42.
40. Hecher K, Gardiner HM, Diemert A, Bartmann P. Long-term outcomes for monochorionic twins after laser therapy in twin-to-twin transfusion syndrome. Lancet Child Adolesc Health. 2018 Jul;2(7):525-535. doi: 10.1016/S2352-4642(18)30127-5.

Figure Legends

Figure 1 – Flow chart of the included studies

Table 1. List of the included studies in the systematic review and their characteristics

First Author (publication year)	Country	Type of study (Study period)	Type of management (GA at diagnosis or management, weeks)	TTTS cases (n)	Imaging modality used (GA at imaging)	Cases affected by brain injuries (n)	Type of abnormalities (n)	Outcomes observed
Gray (2011)[24]	Australia	Prospective cohort study (2002-2006)	FLA (21.5 ± 2.7)	75	US (NS)	4	Ventriculomegaly (2), IVH (2) *(diagnosis made before treatment)*	Incidence; Obstetric outcome; mortality; neurodevelopmental delay
Griffiths (2015) [25]	UK	Retrospective observational study (2004-2013)	FLA (19; 15-24): only sIUD post TTTS	27	US + MRI (NS)	4	Ventriculomegaly (1); Complex (Reduction of volume, focal infarction and polymicrogyria) (1); Polymicrogyria (1); Infarction (1)	Incidence; Obstetric outcome; mortality
Hoffmann (2012) [26]	Israel	Prospective cohort study (2007-2010)	FLA (NS)	10	MRI (NS)	3	Temporal lobe infarct (1), Germinal matrix bleeding (2)	Incidence
Kline-Fath (2006) [27]	USA	NS (2003-2005)	NA (20; 18-23)	23	MRI (20; 18-23)	3	IVH (2); cortical malformation (1)	Incidence; mortality
Merhar (2013) [28]	USA	Prospective case series (2009-2011)	FLA (22.5; 17-26)	11	MRI (22; 17-26)	5	Ventriculomegaly (3), hemorragic lesion (2)	Incidence; Obstetric outcome; mortality;

								neurodevelopmental delay
Quarrello (2007) [15]	France	Retrospective cohort study (1999-2004)	FLA, AR, CO, Exp (22; 15-27)	298	US + MRI (NS)	24	IVH II (1), IVH (1), CC necrosis + PVL (2), atrophy (1), hemorrhages (2), clastic lesion (1), V, (4), Vm + IVH III (2), PVL (4), porencephaly (1), necrosis (1), ischemic lesion (2), hydranencephaly (1), frontal necrosis hemorrhage (1)	Incidence
Robinson (2017) [29]	Australia	Retrospective cohort study (2007-2017)	FLA, Exp (NS)	19	MRI (NS)	6	Dural sinus thrombosis (1); cystic lesion in frontal lobe, possible infarct germinal matrix (1); encephalomalacia + Vm (1); encephalomalacia (1); Complex (Vm + abnormal sulcation + atrophy) (1); atrophy (1);	Incidence; Obstetric outcome; mortality; neurodevelopmental delay
Senat (2002) [30]	France	Retrospective case series (NS)	FLA, AR (21; 17-26): only sIUD post TTTS	12	US + MRI (NS)	1	Periventricular leukomalacia (PVL) (1)	Incidence; obstetric outcome; mortality.

Simonazzi (2006) [31]	Italy	Retrospective case series (1990-2004)	NS (NS): only sIUD post TTTS	6	US + MRI (NS)	4	Cerebral atrophy + porencephaly (1), encephalomalacia (1), IVH IV (1), cortical hyperecogenicity and microcephaly (1)	Incidence; Obstetric outcome; mortality.
Stirnemann (2016) [32]	France	Retrospective cohort study (2003- 2015)	FLA (20+4; 18+4–22+7)	1023	US + MRI (30-32)	21	Leukomalacia (3); polymicrogyria (2), infarct + atrophy (1), unknown (1), schizencephaly (1), Vm + abnormal gyration (1), infarct (3); atrophy (1); Vm (3); ischemic lesions (4); IVH+Vm (1)	Incidence; mortality.
Tarui (2012) [33]	USA	Retrospective case series (2003- 2009)	Imaging before any procedure (20+2; 15+5-32+1)	33	MRI (20+2; 15+5-32+1)	11	Ventriculomegaly (7), Mild cortical irregularity (3), Dandy-Walker malformation (1)	Incidence.
Wang (2017) [34]	China	Prospective case series (2011-2015)	RFA (24; 18-26)	6	MRI (NS)	0	/	Incidence

Weisz (2014) [35]	Israel	Prospective cohort study (2009-2012)	FLA (23; 17-27)	30	MRI (early + "conventional" at 30-32 weeks)	2	atrophy post infarct (1); atrophy (1)	Incidence; Mortality.

AR: Amnioreduction; CC: Corpus Callosum; CO: Cord occlusion; Exp: Expectant Management; FLA: Fetoscopic Laser Ablation; IVH: Intraventricular Hemorrhage; MRI: Magnetic Resonance Imaging; NS: Not Specified; PVL: Periventricular Leukomalacia RFA: Radio Frequency Ablation; sIUD: single Intra Uterine Death; Vm: Ventriculomegaly;

Table 2. Quality assessment of the included studies according to Newcastle–Ottawa Scale (NOS)* or to modified Newcastle-Ottawa, Pierson and Bradford Hill scales for case series**.

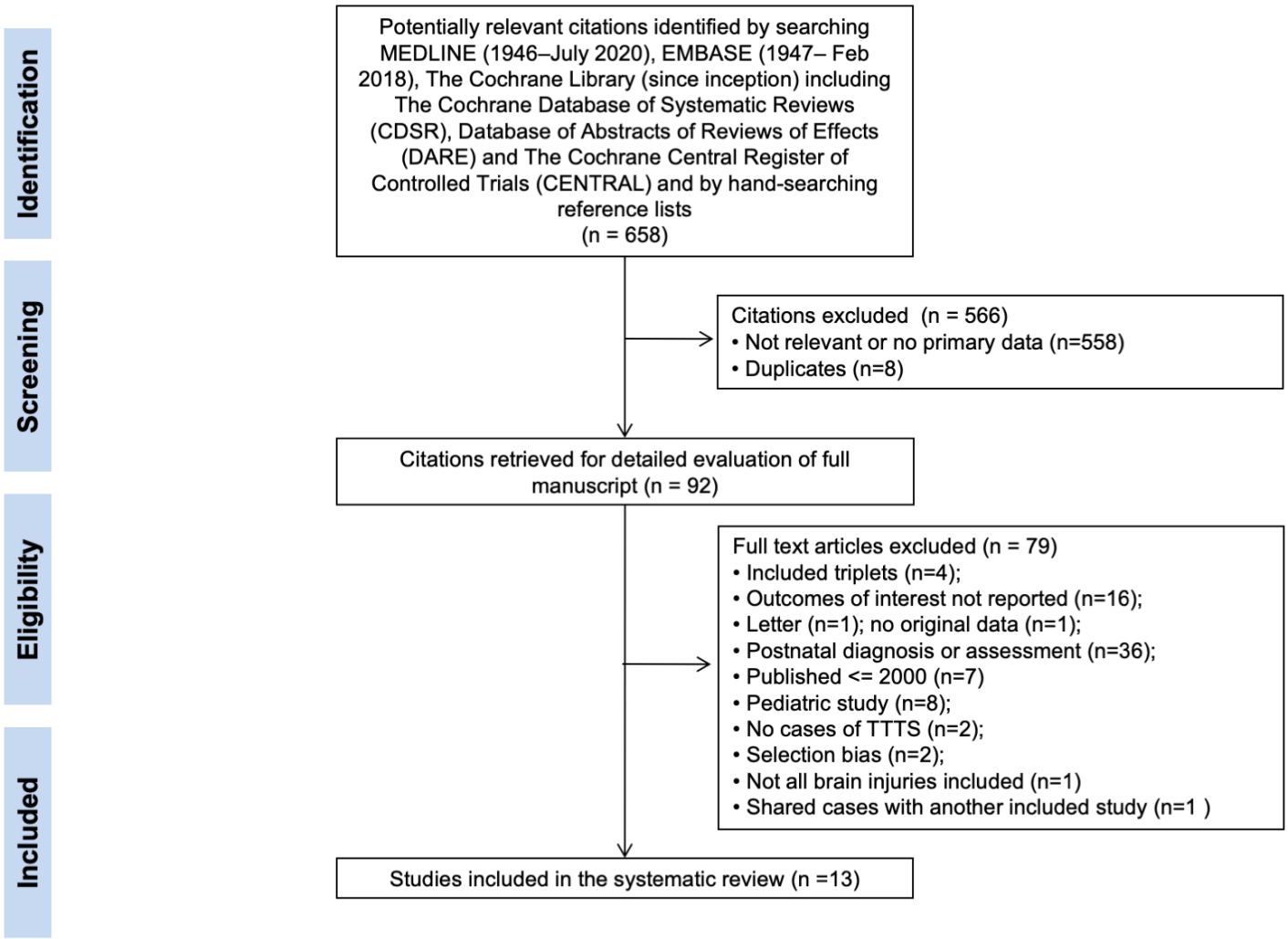
Author	Year	Selection	Comparability	Outcome
Gray[24]	2011	★★★	★	★★
Griffiths[25]	2015	★★	★	★★
Hoffmann[26]	2012	★★★	★	★★
Kline-Fath[27]	2006	★★	★	★
Merhar[28]	2013	Low quality		
Quarrello[15]	2007	★★	★	★★★
Robinson[29]	2017	★★	★	★★★
Senat[30]	2002	Low quality		
Simonazzi[31]	2006	Low quality		
Stirnemann[32]	2016	★★★	★	★★
Tarui[33]	2012	Moderate quality		
Wang[34]	2017	Moderate quality		
Weisz[35]	2014	★★★	★	★★

Table 3. A summary of the pooled estimated of the outcomes included in this meta-analysis.

Outcomes	**Studies (n)**	**Fetuses (n/N)**	**Pooled proportions FE (95% CI)**	**Pooled proportions RE (95% CI)**	**I^2 (%)**
Brain anomalies (overall)	8	52/2410	2.16 (1.6-2.8)	17.04 (1.2-22.6)	89
• Recipient	5	24/2321	1.03 (0.7-1.5)	6.00 (1.2-14.2)	89.9
• Donor	5	19/2321	0.82 (0.5-1.3)	1.92 (0.4-4.3)	58.1
Ischemic lesions	7	16/52	30.38 (19.1-43.0)	27.69 (13.2-45.2)	39
Hemorragic lesions	7	8/52	15.27 (7.1-25.8)	17.46 (5.8-33.7)	42.4
Destructive lesions	7	12/52	23.89 (13.7-35.9)	25.90 (11.1-44.2)	45
Ventriculomegaly	7	10/52	19.91 (10.6-31.3)	20.17 (9.4-33.7)	18.2
Other	7	6/52	12.20 (5.0-22.0)	12.13 (4.9-22.1)	1.4
Miscarriage	4	0/17	0 (0-18.6)	0 (0-18.6)	0
IUD (overall)	6	5/42	13.39 (5.1-24.8)	13.39 (5.1-24.8)	0
• Recipient	4	0/17	0 (0-18.6)	4.8 (0.001-18.6)	0
• Donor	4	0/17	0 (0-18.6)	4.8 (0.001-18.6)	0
Single IUD	6	5/42	13.39 (5.1-24.8)	13.39 (5.1-24.8)	0
Double IUD	6	0/42	0 (0-9.5)	2.79 (0.04-9.5)	0
TOP	6	23/42	53.45 (38.9-67.8)	47.42 (14.6-81.6)	80.6
• Recipient	3	0/16	0 (0-17.9)	4.07 (0.01-17.9)	
• Donor	3	2/16	13.70 (2.1-33.1)	13.30 (1.4-34.7)	15.6
Single TOP	6	23/42	53.45 (38.9-67.8)	47.42 (14.6-81.6)	80.6

Double TOP	6	0/42	0 (0-9.5)	2.79 (0.04-9.5)	0
NND (overall) • Recipient • Donor	3 2 2	2/16 0/12 1/12	15.41 (2.8-35.4) 0 (0-0-20.1) 11.39 (0.5-33.4)	15.41 (2.8-35.4) 3.69 (0.1-20.1) 11.39 (0.5-33.4)	0 0 0
Single NND	3	2/16	15.41 (2.8-35.4)	15.41 (2.8-35.4)	0
Double NND	3	0/16	0 (0-17.9)	4.07 (0.1-17.9)	0
PND (overall) • Recipient • Donor	2 2 2	1/12 0/12 1/12	11.39 (0.5-33.4) 0 (0-0-20.1) 11.39 (0.5-33.4)	11.39 (0.5-33.4) 3.69 (0.1-20.1) 11.39 (0.5-33.4)	0 0 0
Single PND	2	1/12	11.39 (0.5-33.4)	11.39 (0.5-33.4)	0
Double PND	2	0/12	0 (0-20.1)	3.69 (0.1-20.1)	0
Survivor • Recipient • Donor	4 2 2	28/36 6/11 2/11	76.26 (61.6-88.2) 54.31 (26.9-80.3) 30.35 (8.8-58.1)	76.26 (61.6-88.2) 55.19 (17.5-89.6) 30.35 (8.8-58.1)	0 51 0
Both survivors	4	13/36	35.58 (21.3-51.2)	37.77 (13.6-65.8)	60.9
No survivors	4	7/36	20.51 (9.4-34.6)	20.55 (8.7-35.9)	8.4
Composite morbidity (overall) • Recipient • Donor	2 2 2	2/9 1/4 1/5	20.44 (2.5-49.4) 29.66 (18.8-72.1) 20.38 (0.5-58.3)	22.07 (0.6-75.4) 29.66 (18.8-72.1) 36.26 (7.3-99.9)	69.5 0 75.2
PTB<32 weeks*	3	2/14	28.51 (9.6-52.7)	28.14 (6.2-58.1)	33.6

IUD: Intrauterine death; NND: Neonatal Death; PND: Perinatal Death; PTB: Preterm Birth; TOP: Termination of Pregnancy; * expressed per pregnancy



UOG_24895_Fig1_FlowChart.tiff