Long-term neurodevelopmental outcome after fetal therapy

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Chapter 5

Cerebral injury and neurodevelopmental impairment after amnioreduction versus laser surgery in twin-twin transfusion syndrome: A systematic review and meta-analysis

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Fetal Diagnosis and Therapy 2013:33:81-89

Abstract

Objective
To estimate the odds of severe cerebral injury and long-term neurodevelopmental impairment in monochorionic twins treated with amnioreduction versus laser surgery for twin-twin transfusion syndrome.

Methods
A systematic review and meta-analysis of studies on cerebral injury and long-term impairment after amnioreduction versus laser surgery were conducted. Odds ratios with their 95% confidence interval were computed.

Results
Electronic and manual search identified 63 references. Five studies were included for analysis. We found an ample seven-fold higher risk of severe cerebral injury in live-born children treated with amnioreduction compared to laser (OR 7.69, 95% CI 2.78-20.0, P = .00). In children surviving the neonatal period, the odds were three-times higher following amnioreduction (OR 3.23, 95% CI 1.45-7.14, P = .00). Although not significant, monochorionic twins treated with amnioreduction had higher odds of periventricular leukomalacia and intraventricular hemorrhage (OR 2.08, 95% CI .86-5.00, P = .10 and OR 3.56, 95% CI .82-14.29, P = .09). Unfortunately, there were insufficient long-term outcome data available to assess the odds of neurodevelopmental impairment.

Conclusion
Amnioreduction is associated with an increased risk of severe cerebral injury compared to laser surgery in twin-twin transfusion syndrome. Our study highlights a crucial lack of studies focusing on long-term neurodevelopmental outcome. Follow-up into childhood is indispensible to determine outcome in terms of cerebral palsy, cognitive and socio-emotional development.

Introduction

Twin-twin transfusion syndrome (TTTS) is a severe complication of monochorionic (MC) twin pregnancies resulting from shunting of blood from one twin (the donor) to the other twin (the recipient) through placental vascular anastomoses. The donor twin becomes hypovolemic and anuric with oligohydramnios. The recipient twin becomes hypervolemic and polyuric with polyhydramnios. TTTS severity can be staged I to V according to Quintero's classification system[1]. Serial amnioreduction of excessive amniotic fluid (AR) and fetoscopic laser coagulation of the placental vascular anastomoses (laser) are the two main treatment options in TTTS. There is extensive evidence that serial AR is associated with increased perinatal mortality when compared to laser surgery[2]. Reliable information on long-term impairment in survivors after both interventions is lacking[3].

The objective of the current systematic review and analysis was to estimate the odds of severe cerebral injury and long-term neurodevelopmental impairment in MC twins treated with serial AR compared to laser surgery for TTTS.

Methods

This systematic review was performed using PRISMA statement: preferred reporting items for systematic reviews and meta-analyses[4]. Inclusion criteria were formulated according to our pre-defined Patient-Intervention-Comparison-Outcome (PICO) question. The patients are live-born MC diamniotic twins with TTTS diagnosed using standard prenatal ultrasound criteria[5]. The intervention refers to serial AR and the comparison is fetoscopic laser coagulation of placental vascular anastomoses. The primary outcome entails severe cerebral injury and long-term neurodevelopmental impairment (NDI) with a follow-up period from pregnancy outcome to childhood:

1. Severe cerebral injury was defined as intraventricular hemorrhage (IVH) ≥ grade III[6], cystic periventricular leukomalacia (cPVL) ≥ grade II[7], ventricular dilatation ≥ 97th percentile[8], porencephalic cysts, arterial or venous infarction detected on cerebral imaging i.e., cranial ultrasound, Computed Tomography scan or Magnetic Resonance Imaging.
2. Neurodevelopmental impairment (NDI) was defined as cerebral palsy, bilateral blindness, bilateral deafness or cognitive developmental delay > 2 standard deviations (SD) below the population mean, diagnosed using standardized tests.

Due to an anticipated lack of randomized controlled trials, we included both randomized and non-randomized studies. Studies that did not match our PICO question were excluded. English language restrictions were applied.

Data Sources

An electronic literature search was performed with PubMed, MEDLINE and ISI Web of Science (WoS) up to March 2012. Table 1 presents the search strategies for PubMed that were subsequently adapted for use in MEDLINE and ISI WoS. To identify articles not captured by the electronic searches, we hand-searched reference lists of relevant studies.

Table 1. Search Strategies PubMed

Strategy	Mesh and entry terms
#1	("Fetofetal Transfusion"[Mesh] OR "Fetofetal Transfusion"[All Fields] OR "Twin Transfusion Syndrome"[All Fields] OR "Twin Transfusion Syndromes"[All Fields] OR "Twin Transfusion"[All Fields] OR "Twin Transfusions"[All Fields])
#2	("Amniocentesis"[Mesh] OR "Amniocentesis"[All Fields] OR "Amniocenteses"[All Fields] OR "Amnioreduction"[All Fields] OR "Amniodrainage"[All Fields])
#3	("Fetoscopy"[Mesh] OR "Fetoscopy"[All Fields] OR "Fetoscopic Surgeries"[All Fields] OR "Fetoscopic Surgical Procedures"[All Fields] OR "Intrauterine Laser Treatment"[All Fields] OR "Fetoscopic Laser Surgery"[All Fields] OR "In Utero Laser Ablation Therapy"[All Fields] OR "Laser Photocoagulation"[All Fields] OR "Laser Surgery"[All Fields] OR "Endoscopic Laser Surgery"[All Fields] OR "Laser Therapy"[All Fields])
#4	("Infant"[Mesh] OR "Infant"[All Fields] OR "Infant Development"[All Fields] OR "Child"[All Fields] OR "Child development"[All Fields] OR "Neurologic Injury"[All Fields] OR "Cerebral Damage"[All Fields] OR "Neurodevelopmental Outcome"[All Fields] OR "Neurodevelopment"[All Fields] OR "Developmental Follow-Up"[All Fields])
#5	#1 AND #2 AND #3 AND #4 Results: 25

= number.

Study Selection

Eligibility and methodological quality of the studies were assessed independently by the corresponding (JK) and last author (EL). The following data were extracted and tabulated: first author, year of publication, study design, country of origin, selection and allocation of patients, data collection, comparability of patients and controls, potential confounders, operationalization of primary outcome and outcome measurement, efforts to minimize bias, the incidence of severe cerebral injury and NDI in patients and controls (2x2 tables) and the length and completeness of follow-up. In case of overlap or duplications in patients between studies, the study with the best overall study quality was included for review. A randomized controlled trial was, a priori, considered the best study design. Disagreements regarding eligibility, methodological quality and data extraction were resolved by discussion and consensus between authors.

Statistical Analysis

To summarize the results of the selected studies, an Excel spreadsheet was used. We performed statistical analysis using Stata (StataCorp LP, College Station, Texas). Categorical or dichotomous data were meta-analyzed with odds ratios (ORs) and their 95% confidence intervals (CI), using 2x2 tables. We used the recommended method to add 0.5 where 2x2 tables contained cells with zero events, allowing continuity correction. Studies were a priori analyzed into two groups that is, studies including and studies excluding neonatal deaths in their outcome analysis. Heterogeneity between studies was examined with the inconsistency square (I^2) statistics, with between-study heterogeneity at $I^2 \geq 50\%$ and $P \geq .05$ [9]. In case of heterogeneity, a random effects model was used[10]. Otherwise, or in case of limited studies to reliably estimate between study variability, a fixed effect model was used. We performed meta-analyses and constructed forest plots to examine the effect of AR compared to laser surgery on severe cerebral injury with separate analyses for cPVL ≥ grade II and IVH ≥ grade III, and NDI with separate analyses for cerebral palsy, bilateral blindness, deafness and cognitive developmental delay. Publication bias was examined with the construction of a funnel plot and tested for asymmetry with the Egger test[11].

Results

Study identification

Combination of the 4 search strategies revealed 25 references in PubMed, 18 references in MEDLINE and 43 references in ISI WoS. A manual search revealed one additional study for consideration[12]. In total, after removal of duplicates, 63 references were screened. Figure 1 provides a flow diagram with the number of studies screened, assessed for eligibility and included for review according to our PICO question.

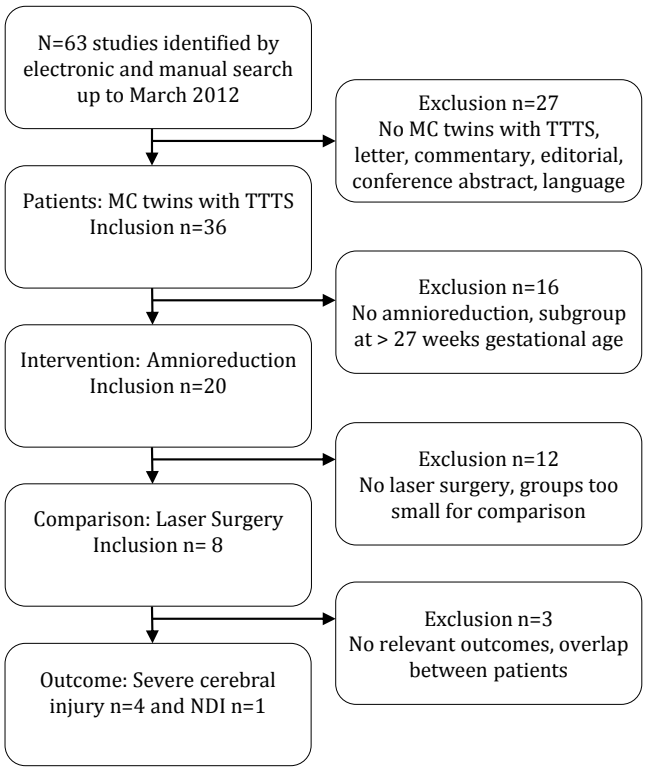

Figure 1. Flow diagram with the number of studies screened, assessed for eligibility and included for review with exclusion criteria according to our Patient- Intervention- Comparison- Outcome-question.

We found two other systematic reviews on AR versus laser surgery[2;13]. Roberts and colleagues (2008) analyzed one randomized controlled trial to compare AR with laser surgery on short-term perinatal outcome in their Cochrane meta-analysis[2]. We also accepted case-series for inclusion to obtain the full range of research to date. Rossi and D'Addario reported on mortality and cerebral anomalies representing the sum of a wide variety of cerebral injuries of varying degrees of severity, regardless of subsequent perinatal deaths or overlap in patients between studies, hence susceptible for bias[13-15]. We selected five studies, directly comparing AR with laser surgery on severe cerebral injury and NDI; three comparative studies plus two follow-up studies from the Eurofetus Trial[15;16]. Although well-designed and highly valuable, the two comparative studies published by Lenclen and colleagues were excluded from analysis, due to a considerable overlap in patients with the two Eurofetus RCT follow-up studies[14;17].

Risk of bias and quality assessment using PRISMA statement

Since no randomization took place in the three comparative studies, performance- or selection bias could not be ruled out[18-20]. However, treatment allocation was unlikely correlated with TTTS severity in these studies since allocation to either AR or laser surgery was based on geographical location and treatment availability; consecutive patients were grouped according to treatment center and year of introduction of laser surgery in a center[18]. The RCT performed prospective power analysis and used computer generated central randomization sequences to maintain adequate allocation concealment[15;16]. Four studies employed a prospective design; of which one staged their AR group retrospectively[15;16;19;20]. All but one were multi-center studies[20]. All studies described techniques for both interventions in detail. Completeness of follow-up ranged from 92 to 100%. Outcome assessment, including timing and frequency of postnatal brain imaging, was fully described in two of five studies and blinded in two[15;16]. Four studies accounted for TTTS stage in their comparison of AR to laser of which one stratified stage on outcome[19]. Two studies reported worse outcomes with increased TTTS stage in both groups; one study found increased TTS stage associated with poorer outcome in the AR group only[19].

Results of individual studies

Summary data for each intervention group are displayed in Table 2. Median gestational age at intervention was 20 to 22 weeks for both intervention groups and comparable in all but one study; 21.6 weeks at first AR versus 20.7 weeks at laser surgery[19]. This study reported an increased incidence of severe cerebral injury following AR which was related to increased TTTS stage. This effect was not observed in their laser group. All but one study staged TTTS, according to Quintero's classification system[1;18]. TTTS stage at intervention was comparable between groups, with limited stage I cases in all studies. Gray and colleagues excluded stage I cases[20]. AR resulted in lower overall survival rates when compared to laser ranging from 39-59% compared to 54-77%, respectively. Treatment with AR resulted in higher neonatal mortality rates ranging from 14-55% compared to 6-15% when treated with laser. Median gestational age at birth was lower with AR, ranging from 28-31 weeks versus 32-34 weeks with laser. Accordingly, birth weight of donor and recipient twins was lower in the AR group ranging from 940-1612 grams versus 1750-2000 grams with laser.

Table 2. Characteristics of the Studies included for Review on Cerebral Injury and Neurodevelopmental Impairment after Amnioreduction versus Laser Surgery.

Reference Design FUP	Selection Allocation Inclusion Data collection	Patient Year Location	Baseline characteristics	Comparison Year Location	Baseline characteristics	Operationalization Outcome measure Blinding	Outcome	Comments
1. Hecher et al 1999[18] Comparative Multicenter Pregnancy outcome	Consecutive, geographical location GA < 25, single MC placenta on ultrasound, oliguria, small-empty bladder, polyuria, distended bladder Prospective FUP	N=86 AR '92-96 Bonn, DE	GA AR 20.4 TTTS < 25 Stage NR IUFD 41% (35/86) NND 14% (7/51) Survival 51% (44/86) GA birth 30.7* BW D 1145* BW R 1560	N=146 FSL '95-97 Hamburg, DE	GA FSL 20.7 TTTS < 25 Stage NR IUFD 35% (51/146) NND 6% (6/95) Survival 61% (89/146) GA birth 33.7* BW D 1750* BW R 2000	IVH III-IV, PVL, parenchyma defects, microcephaly Ultrasound Timing unclear Blinding NR	Cerebral injury AR 18% (8/44) > FSL 6% (5/89)* (ex IUFD, ex NND): **AR** **FSL** + 8 5 - 36 84	Groups different at FUP Survival R > D FSL group* Regimen ultrasound NR Individual observations NNDs cerebral injury NR Adjustment interdependency in overall survival analysis.
2. Quintero et al 2003[19] Comparative Multicenter 18 months	Consecutive, geographical location GA < 27, single placenta, oligohydramnios, polyhydramnios, similar genitalia Retrospective FUP	N=156 AR '90-00 Tampa, FL Perth & Brisbane, AUS	GA AR 21.6* TTTS < 27 Stage I-IV IUFD 17% (26/156) NND 31% (40/130)* Survival 58% (90/156) GA birth 29* BW D 1219* BW R 1612*	N=190 FSL '97-00 Tampa, FL	GA FSL 20.7* TTTS < 27 Stage I-IV IUFD 28% (54/190) NND 10% (14/136)* Survival 64% (122/190) GA birth 32* BW D 1781* BW R 1940*	IVH III-IV, PVL, ventriculomegaly, microcephaly, CP Outcome measure NR Timing NR No blinding	Cerebral injury AR 18% (23/130) > FSL 3% (4/136)* (ex IUFD, inc NND): **AR** **FSL** + 23 4 - 107 132	Groups different at FUP Outcome measure NR Lost to FUP: n=1 AR NNDs with cerebral injury NR Multivariate analyses inc GA intervention, group and TTTS stage.
3. Senat et al 2004[15] RCT Multicenter 6 months	Consecutive 6 countries Computer generated randomization sequence GA 15-26, oliguric oligohydramnios, polyuric polyhydramnios, distended bladder Prospective FUP	N= 140 AR '99-02 17 centers: FR, BE, NL, CH, USA, IT	M GA AR 21 TTTS < 26 Stage I-IV IUFD 16% (29/140) GA birth <24 11% (16/140) NND 43% (41/95)* Survival 39% (54/140)* GA birth 29* BW D & R 1359*	N=144 FSL '99-02 3 centers: NR	M GA FSL 21 TTTS < 26 Stage I-IV IUFD 19% (27/144) GA birth <24 17% (24/144) NND 13% (12/93)* Survival 56% (81/144)* GA birth 33* BW D & R 1757*	IVH III-IV, cystic PVL, blind/deaf, motor disability Ultrasound twice in first 2 weeks, MRI on indication Blinded outcome assessor	IVH AR 8.4% (8/95) = FSL 2.2% (2/93) (ex IUFD, inc NND) PVL AR 15% (14/95) = FSL 9% (8/93) (ex IUFD, inc NND) PVL AR 10% (6/58) = FSL 5% (4/88) (ex IUFD, ex NND) Cerebral injury at 6 mo AR 19% (10/54) > FSL 7% (6/81)* (ex IUFD, ex NND): **AR** **FSL** + 10 6 - 44 75	Groups different at FUP Overrepresentation stage II-III in both groups All children with IVH AR group died One child with IVH FSL survived Adjustment for twin clustering Subgroup analysis IUFD co-twin.

Reference Design FUP	Selection Allocation Inclusion Data collection	Patient Year Location	Baseline characteristics	Comparison Year Location	Baseline characteristics	Operationalization Outcome measure Blinding	Outcome	Comments
4. Gray et al 2006[20] Comparative Single center Perinatal outcome	Consecutive AR <2002> FSL TTTS stage ≥ II, oligohydramnios, polyhydramnios, thin dividing membrane sacs on ultrasound Retrospective AR Prospective FSL	N=54 AR '94-02 Brisbane, AUS	GA AR 20 TTTS < 28 Stage ≥ II IUFD 24% (13/54) NND 22% (9/41)* Survival 59% (32/54)* GA birth 28* BW D 940* BW R 1312	N=62 FSL '02-03 Brisbane, AUS	GA FSL 21 TTTS < 28 Stage ≥ II IUFD 18% (11/62) NND 6% (3/51)* Survival 77% (48/62)* GA birth 34* BW D 1780* BW R 1870	PVH III-IV, cystic PVL, cerebral atrophy, ischemic brain injury Ultrasound first week of life and after on indication Blinding NR	No PVH III-IV PVH AR 7% (3/41) > FSL 0% (0/51* (ex IUFD, inc NND) Cerebral injury FSL 0% (0/51) < AR 12% (5/41)* (ex IUFD, inc NND): **AR** **FSL** + 5 0 - 36 51	Groups different at FUP One center Survival R > D FSL* No stage I TTTS NNDs with cerebral injury NR Two pregnancies FSL group intention-to-treat basis
5. Salomon et al 2010[14] RCT Multicenter 1-6 years	Subgroup Eurofetus RCT delivered in FR Prospective FUP	N=120 AR '99-02 Paris, FR	GA diagnosis 21 TTTS < 26 Stage I-IV IUFD 39% (47/120) NND 55% (26/73)* Survival 39% (47/120)* GA birth NR BW NR	N=136 FSL '99-02 Paris, FR	GA diagnosis 21 TTTS < 26 Stage I-IV IUFD 37% (50/136) NND 15% (13/86)* Survival 54% (73/136)* GA birth NR BW NR	NDI: CP, blind, deaf 1-2 yr: questionnaire neurodevelopment 1-2-4-5 yr: ASQ 5 yr: neurologic exam 6 yr: WISC Blinded outcome assessor	M ASQ 2 yr: AR 192 (±76) = FSL 203 (±80) M ASQ 4 yr: AR 227 (±81) = FSL 241 (±58) M ASQ 5 yr: AR 229 (±80) < FSL 261 (±54)* M WISC 6 yr: AR 91 (±33) = FSL 91 (±20) Developmental delay: AR 14% (4/28) = FSL 5.5% (3/55) CP, blind, deaf 5-6 yr: AR 15% (6/41) = FSL 13% (9/69): **AR** **FSL** + 6 9 - 35 60	Subgroup Eurofetus RCT Groups different at FUP: NND AR > FSL* FUP 5 yr: n=10 exam GP Lost to FUP 6 yr: 8% (10/120) (n=4 FSL, n=6 AR) Large SDs ASQ and WISC AR group NDI as a composite outcome NR Cumulative incidence death or impairment with Kaplan-Meier curves.

FUP = follow-up; N = the number of children; GA = median gestational age in weeks; MC = monochorionic; AR = amnioreduction; DE = Germany; TTTS = twin-twin transfusion syndrome; NR = not reported; IUFD = intrauterine fetal death; NND = neonatal death; BW = median birth weight in grams; D = donor; R = recipient; FSL = fetoscopic laser coagulation; IVH III-IV = intraventricular hemorrhage grade III or IV; PVL = periventricular leukomalacia; ex = excluding; FL = Florida; AUS = Australia; CP = cerebral palsy; inc = including; RCT = randomized controlled trial; FR = France; BE = Belgium; NL = the Netherlands; CH = Switzerland; USA = United States America; IT = Italy; M = mean; MRI = magnetic resonance imaging; PVH = periventricular hemorrhage; NDI = neurodevelopmental impairment; ASQ = Ages and Stages Questionnaire; WISC = Wechsler Intelligence Scale for Children; GP = general practitioner; SDs = standard deviations; values are medians unless stated otherwise; * indicates a significant difference at P<.05.

Synthesis of results

A fixed effect model was used throughout because of the small number of included studies to reliably assess between study variability. To assess the odds of severe cerebral injury in children treated with either AR or laser, data were derived from four studies with 269 children in the AR group versus 357 children in the laser group[15;18-20]. The odds of severe cerebral injury in live-born children treated with AR were seven- to eight-times higher when compared to children treated with laser (OR 7.69, 95% CI 2.78-20.0, *P* = .00; fig. 2). With subsequent neonatal deaths excluded from outcome analysis, the odds were three-times higher in the AR group compared to the laser group (OR 3.23, 95% CI 1.45-7.14, *P* = .00; fig. 2).

To assess the odds of cPVL ≥ II in live-born children, data were derived from two studies, one RCT and one comparative study, with 136 children in the AR and 144 children in the laser group [15;20]. The OR demonstrated no significant difference in cPVL ≥ II in live-born children treated with either AR or laser (OR 2.08, 95% CI .86-5.00, *P* = .10; fig. 3).

Two studies reported on the incidence of IVH ≥ III in live-born children[15;20]. Data were available from 136 children treated with AR versus 144 children treated with laser[15]. The OR demonstrated no significant difference in IVH ≥ III in live-born children treated with either AR or laser (OR 3.56, 95% CI .82-14.29, *P*=.09; fig. 4). Senat and colleagues identified eight (8/95) cases of IVH ≥ III in live-born children in their AR group versus two live-born children (2/93) in their laser group. Of these ten cases, only one child, treated with laser, was alive at six months of age[15]. According to Gray and colleagues, none of the live-born children developed IVH ≥ III in their first week of life[20].

There were insufficient long-term outcome data to assess the odds of NDI as a composite outcome. In their original article, Salomon and colleagues did not report individual observations of cognitive developmental delay as measured with the Ages and Stages Questionnaire (ASQ) and the Wechsler Intelligence Scale (WISC-IV)[16]. Salomon and colleagues did provide individual observations of CP, blindness or deafness. Data were available from 41 children treated with AR and 69 children treated with laser[16]. At 6-year follow-up, four children presented with CP, one child was blind and one child was deaf in the AR group (15%; 6/41) versus six children with CP, two children with blindness, and one child with deafness in the laser group (13%; 9/69). The absence of differences in long-term outcome was probably due to the significant higher neonatal death rate in the AR group that is, 55% (26/73) versus 15% (13/86) in the laser group. Kaplan-Meier curves showed that the probability of survival without major neurological impairment was lower with AR, adjusted for TTS stage (hazard ratio .61, 95% CI .41-.90, *P* = .01)[16]. Individual results of early brain imaging of these children were not reported.

Since the number of included studies was too small for a reliable assessment, construction and analysis of the funnel plot was precluded.

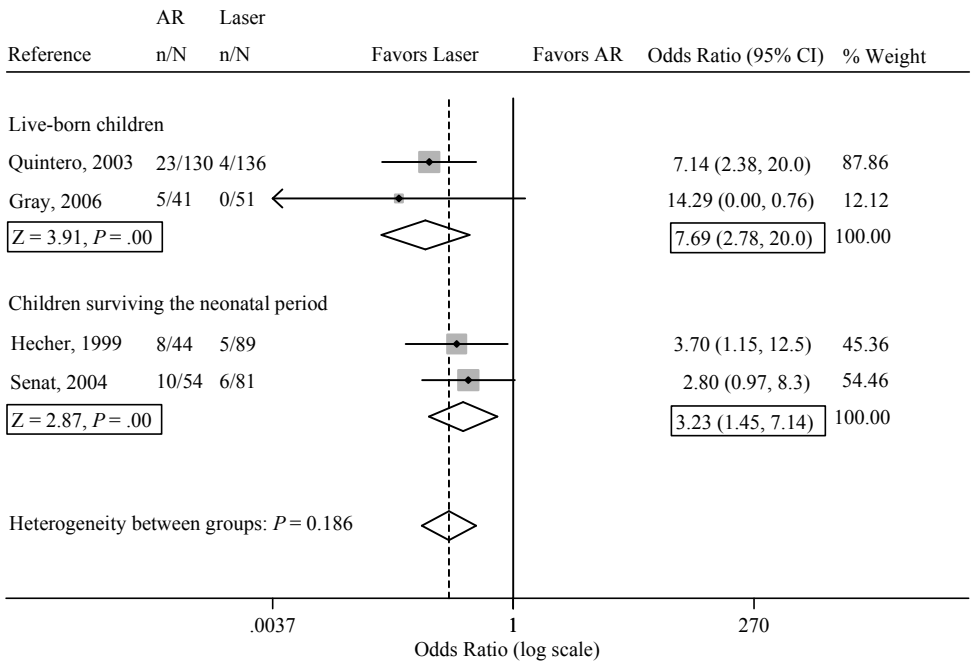

Figure 2. Fixed effect analysis of severe cerebral injury after amnioreduction versus laser surgery.

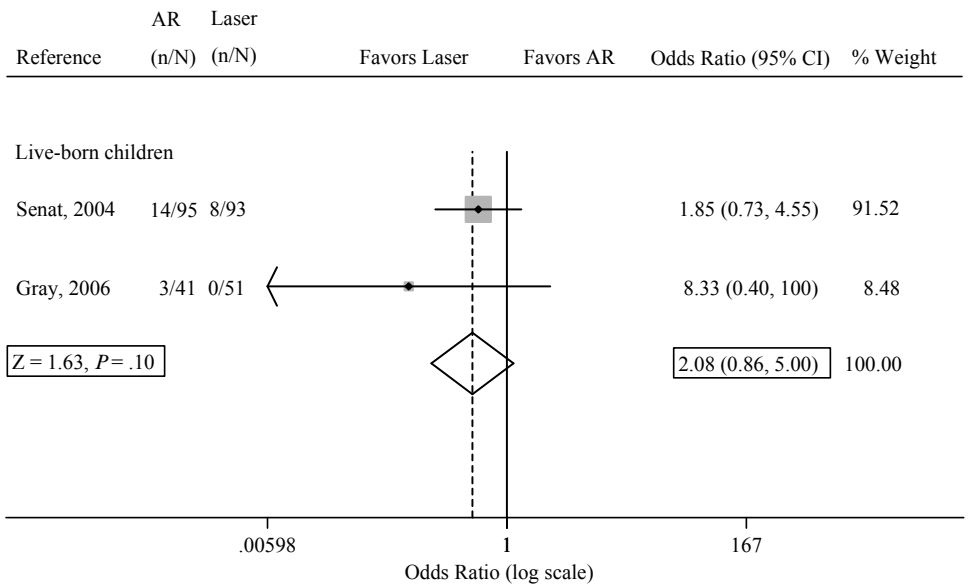

Figure 3. Fixed Effect Analysis of Cystic Periventricular Leukomalacia in Amnioreduction versus Laser Surgery.

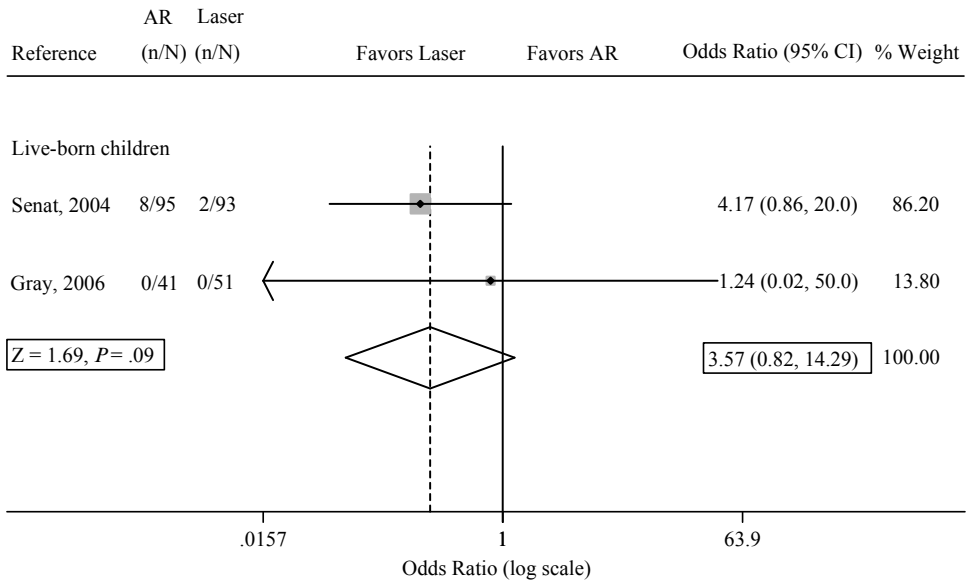

Figure 4. Fixed Effect Analysis of Intraventricular Hemorrhage in Amnioreduction versus Laser Surgery.

Discussion

The objective of our systematic review and meta-analysis was to evaluate severe cerebral injury and long-term impairment in MC twins treated with AR compared to laser for TTTS. We found an ample seven-fold higher risk of severe cerebral injury in live-born children treated with AR compared to laser surgery. In children surviving the neonatal period, the odds were three-times higher following AR versus laser. Detailed analysis per type of severe cerebral injury demonstrated no significant difference between treatments regarding the incidence of cPVL ≥ II and IVH ≥ III. Importantly, there were not enough follow-up data to analyze long-term neurodevelopmental impairment in children treated with AR compared to laser surgery.

Roberts and colleagues showed in their Cochrane review of only one trial that more children were alive without neurological abnormality at six months following laser surgery compared to AR (RR 1.66; 95% CI 1.17 to 2.35 adjusted for clustering, one trial)[2]. They reported no difference in the children alive at six months with neurological abnormality between interventions (RR 0.58; 95% CI 0.18 to 1.86 adjusted for clustering, one trial). The authors suggest that this might be secondary to plasticity of the developing brain or the demise of more severely affected fetuses. No data were available on outcome beyond six months at the time of writing their Cochrane review.

We aimed to present the full range of the research to date and included case-series as well, with a longer follow-up period.

Rossi and D'Addario showed in their meta-analysis of four studies comparing AR to laser that fetuses treated with AR were less likely to survive when compared to laser (overall survival: OR 2.04; 95% CI 1.52-2.76, $P < .0001$; neonatal death: OR .24, 95% CI .15-.40, $P < .001$)[13]. However, among these four studies, two studies have a considerable overlap in patients since both studies included participants of the Eurofetus RCT recruited and delivered in France[15;21]. Furthermore, their analysis of cerebral injury represented a sum of a wide variety of cerebral anomalies regardless of severity of the injury. Also, perinatal deaths were not taken into consideration in their outcome analysis. We excluded studies to avoid overlap between patients, specified cerebral injury according to type and severity and studies were a priori analyzed into two groups i.e., studies including and studies excluding neonatal deaths in outcome analysis.

We speculate that the increased risk of severe cerebral injury following AR is due to the higher rate of prematurity, which is a well-known risk factor for neonatal morbidity and mortality[3]. In addition, since AR is only a symptomatic intervention, fetuses remain exposed to TTTS for a longer period of time when compared to fetuses treated with laser coagulation of the placental anastomoses. The lack of difference in cPVL ≥ II and IVH ≥ III in live-born children between groups could be due to the small sample size since only two studies reported individual observations of these injuries in live-born children. The only RCT follow-up study concluded that there is no difference in neurodevelopmental impairment between interventions. However, these conclusions are likely biased by the significantly higher neonatal death rate in their AR group[2;16].

The main limitation of the current systematic analysis is the small number of studies available for review and small sample size. Studies directly comparing AR to laser on outcome are scarce. The majority of the studies included in this systematic review employed a comparative design which is highly susceptible for bias. Among the studies, there were no stringent criteria regarding what constitutes severe cerebral injury. Although cranial ultrasound is useful for detecting neurologic morbidity, its sensitivity for subsequent neurodevelopmental impairment is not high[3]. In addition, a normal cranial ultrasound scan without cerebral injury does not necessarily equate with normal neurodevelopmental outcome[20]. This can only be ascertained by long-term follow-up to childhood in order to determine outcome in terms of CP, cognitive and socio-emotional development[3;20].

Our study highlights the crucial lack of studies focusing on cerebral injury and long-term neurodevelopmental outcome in TTTS. Although serial AR and laser surgery have been introduced more than 2 decades ago, most studies in TTTS have focused mainly on immediate perinatal outcome[2]. Knowledge on long-term outcome and quality of life

of survivors is indispensable for determining best practice for clinicians as well as for counseling future parents using evidence-based information. This requires cooperation between obstetricians, pediatricians and other experts in the field of child cognitive and social-emotional development in order to look beyond perinatal survival as well as cooperation between international treatment centers to obtain reliable data with large enough case series with sufficient power. We suggest defining what is considered severe cerebral injury and neurodevelopmental impairment consistently, to provide individual information on all cases including early brain imaging in order to reliably estimate the effect on later development. It is important to continuously assess development of the children including formal psychological testing and standardized measures of well documented psychometric quality, with increasing reliability of results with increasing age. Table 3 represents a proposition for future research.

Conclusion

Setting up a new RCT with long-term follow-up after AR versus laser surgery is not ethical, since higher overall survival rates and better perinatal outcomes have already been established with laser surgery. However, long-term follow-up with emphasis on child cognitive, socio-emotional development and quality of life is indispensible for conducting future RCTs in all fields of fetal medicine, in order to implement new techniques.

Table 3. A proposition for future research: Assessment according to age in years.

Development	Neonate	2 years	4 years	7 years	8 years	10 years	12 years	14 years	16 years
Brain:	Imaging of the brain								
Senses:	Hearing	Vision							
Physical:		Neurologic exam, Cerebral Palsy, Gross Motor Function Classification System							
Cognitive:		BSID, WPPSI		WISC					
Psychosocial:		Achenbach System, Quality of Life							
School:			Special education, number of grades below age appropriate educational level						
Neuropsychological:				Learning, language, executive functioning, attention, visual spatial abilities, memory, fine motor development					
Neuropsychiatric:				Attention Deficit Hyperactivity Disorder, Autism Spectrum Disorder					

BSID = Bayley Scales of Infant and Toddler Development for children 1 month to 3 years of age; WPPSI = Wechsler Preschool and Primary Scale of Intelligence for children 2 years and 6 months to 7 years and 11 months of age; WISC = Wechsler Intelligence Scale for Children 6 to 16 years of age.

Acknowledgements

J.M.M. van Klink was financially supported by a grant from the Willem-Alexander Kinder Fonds (Leiden, The Netherlands).

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