Outcome of twin-to-twin transfusion syndrome in monochorionic monoamniotic twin pregnancies: a systematic review and meta-analysis

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CONTRIBUTION

What are the novel findings of this work?

There are no consistent data on the outcome of TTTS in monochorionic monoamniotic twin pregnancies. Moreover, it is not clear whether treatments may be preferable in term of perinatal survival, when managing TTTS in monoamniotic twins.

What are the clinical implications of this work?

The aim of this study was to explore the outcome of monochorionic monoamniotic twin pregnancies affected by TTTS and to evaluate the optimal management in these rare pregnancies.

ABSTRACT

Objectives: To explore the outcome of monochorionic monoamniotic (MCMA) twin pregnancies affected by twin-to-twin transfusion syndrome (TTTS).

Methods: Medline and Embase databases were searched. The primary outcome was intra-uterine death (IUD); secondary outcomes were: miscarriage, single IUD, double IUD, neonatal death (NND), perinatal death (PND), presence of at least one or both survivors and preterm birth (PTB) <32 weeks of gestation. All these outcomes were assessed in MCMA twins affected by TTTS not undergoing intervention and in those treated with amniodrainage, laser therapy and cord occlusion. Sub-group analysis including cases diagnosed <24 weeks of gestation was also performed. Random-effect meta-analyses of proportions were used to analyze the data.

Results: Seventeen retrospective cohort studies (890 MCMA twin pregnancies, 46 affected by TTTS) were included in the review while there was no randomised trial comparing the different management options in MCMA twin pregnancies complicated by TTTS. *In cases not undergoing intervention*, miscarriage occurred in 10.7% of fetuses, while the incidence of IUD, NND and PND was 24.3%, 13.5% and 32.4% respectively. PTB complicated 54.0% of these pregnancies. *In cases treated by laser surgery*, the incidence of miscarriage, IUD, NND and PND was 19.6%, 27.4%, 7.4% and 35.9% respectively. The incidence of PTB <32 weeks of gestation was 64.9%. *In cases treated with amniodrainage*, the incidence of IUD, NND and PND was 30.3%, 19.1% and 35.9% respectively. PTB complicated 78.1% of cases. Analysis of *cases undergoing cord occlusion* was affected by the very small number of included cases. Miscarriage occurred in 19.2%, while there was no IUD or NND of the surviving twin. PTB <32 weeks occurred in 50.0% of cases.

Conclusion: MCMA twin pregnancies complicated by TTTS are at high risk of perinatal mortality and PTB. Further studies are needed in order to elucidate the optimal type of prenatal treatment in these pregnancies.

INTRODUCTION

Twin to twin transfusion syndrome (TTTS) is one of the most severe complications of monochorionic twin pregnancies, with an estimated incidence of 9-15%[1]. Although the pathophysiology of TTTS has not been fully elucidated yet, the anatomical prerequisite for its occurrence is the presence of inter-twin vascular anastomoses within the placenta which are virtually present in every MC gestation[2]. TTTS is associated with a high risk of perinatal mortality and morbidity if not treated. The introduction of laser therapy of placental anastomoses in clinical practice has led to a significant reduction in perinatal mortality of the multiple pregnancies complicated by TTTS, especially in monochorionic diamniotic (MCDA) twin pregnancies.

Monochorionic monoamniotic (MCMA) twin pregnancies are at higher risk of perinatal mortality and morbidity compared to MCDA gestations. The overall incidence of fetal loss in MCA twin pregnancies is approximately 6%, with the large majority of losses them occurring before 30 weeks of gestation[2]. TTTS can also occur in MCMA twin pregnancies; although its incidence has been reported to be 2.4 to 2.7 times lower than in MCDA twin gestations[2]. The lower incidence of TTTS in MCMA pregnancies likely reflects the different anastomotic pattern observed in MA gestations, with a higher prevalence of arterio-arterial anastomoses which are protective against the occurrence of this pathology[3-5]. Despite its importance, there is no consistent data on the outcome of TTTS in MCMA twin pregnancies. Furthermore, the role of laser therapy in MCMA pregnancies affected by TTTS has not been fully established. Moreover, it is not clear whether other treatments (i.e. cord occlusion) may be preferable in terms of perinatal survival, when managing TTTS in MCMA twins. Therefore, the aim of this study was to explore the outcome of MCMA twin pregnancies affected by TTTS.

METHODS

Protocol, information sources and literature search

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis[6]. Medline and Embase databases were searched electronically on the 10th January 2019 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "twin to twin transfusion syndrome", "monoamniotic pregnancies", "ultrasound" and "outcome". The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. Prisma guidelines were followed[7]. The study was registered with the PROSPERO database (Registration number: CRD42016043062).

Outcomes' measures, study selection and data collection

The primary outcome was intra-uterine death (IUD) defined as the death of either twin ≥20 weeks of gestation.

Secondary outcomes were:

- Miscarriage, defined as the loss of either twin prior to 20 weeks of gestation
- Single IUD, defined as the loss of a twin ≥ 20 weeks of gestation
- Double IUD, defined as the loss of both twins ≥ 20 weeks of gestation
- Neonatal death (NND), defined as the death of either twin up to 28 days after birth
- Perinatal death (PND), defined as the sum of IUD and NND
- Rate of survivors, defined as the percentage of twins not affected by PND or miscarriage
- Presence of at least one survivor
- Presence of both survivors
- Preterm birth (PTB) <32 weeks of gestation

All the explored outcomes were reported for MCMA twins not undergoing intervention, for those treated with laser therapy, amniodrainage and cord occlusion respectively. For the purpose of the analysis, single and double IUD, NND, PND and survivors, were not computed in the group of twins undergoing cord occlusion. Since the hydramnios-oligohydramnios sequence cannot be detected in monoamniotic pregnancies, diagnosis of twin–twin transfusion syndrome was based on the identification of other clinical manifestations of the syndrome, such as polyhydramnios (deepest vertical pocket 8 or more cm before 20 weeks of gestation or 10 or more cm after 20 weeks of gestation), discordance in bladder size (absent bladder in the donor and dilated bladder in the

recipient), and abnormal Doppler flow patterns in either twin. Furthermore, we planned a sub-group analysis considering only cases affected by TTTS diagnosed ≤ 24 weeks of gestation.

Only studies reporting the outcome of MCMA twin pregnancies affected by TTTS were considered suitable for the inclusion in the current systematic review. Studies including higher order multiple gestations, those including cases of iatrogenic MCMA twin pregnancies, structural or chromosomal anomalies and those from which data on amnionicity could not be extrapolated were excluded. Studies published before 2000 were also excluded, as we considered that advances in prenatal imaging techniques, improvements in the diagnosis and treatment of TTTS make them less relevant. Only full text articles were considered eligible for the inclusion; case reports and conference abstracts were also excluded in order to avoid publication bias.

Two authors (DM, DB) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus. Full text copies of those papers were obtained, and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted.

Quality assessment, risk of bias and statistical analysis

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for 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 the outcome of interest[8]. 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 start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts on the basis of 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, length and adequacy of follow-up[7]. 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.

Random-effect meta-analyses of proportions were used to combine data. For the purpose of the analysis, the denominator was represented by the number of twins per each group for the computation of IUD, NND, PND and rate of survivors, while the number of pregnancies for the assessment of PTB, presence of at least one and two survivors. Funnel plots displaying the outcome rate from individual studies versus their precision (1/standard error) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than ten. In this case, the power of the tests is too low to distinguish chance from real asymmetry[9-10].

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 no observed heterogeneity, whereas I^2 values of $\geq$50% indicate a substantial level of heterogeneity. All analyses were performed using StatsDirect Statistical Software (StatsDirect Ltd Cambridge, United Kingdom).

RESULTS

Study selection and characteristics

505 articles were identified, 153 were assessed with respect to their eligibility for inclusion (Supplementary Table 1) and 17 studies were included in the systematic review (Table 1, Figure 1). These 17 studies included 890 MCMA twin pregnancies; out of these 48 (96 fetuses) were affected by TTTS[11-27]. There was no randomized controlled trial comparing different management options (expectant vs laser vs cord occlusion) in MCMA twin pregnancies complicated by TTTS.

Gestational age at diagnosis of TTTS was reported only by eight studies (22 pregnancies); TTTS occurred in 9.1% of cases before 16 weeks, in 18.2% between 16 and 20 weeks, in 45.5% between 21 and 24 weeks, in 18.2% between 25 and 28 weeks and in 9.1% after 28 weeks of gestation.

The results of the quality assessment of the included studies using the Newcastle-Ottawa Scale (NOS) are presented in Table 2. Most of the included studies showed an overall good score regarding the selection and comparability of the study groups, and for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size, heterogeneity of outcomes observed and different protocols for antenatal management of the pregnancies complicated by TTTS.

Synthesis of the results

No intervention

Thirteen studies (48 fetuses-24 pregnancies) reported the outcome of MCMA twin pregnancies complicated by TTTS and managed expectantly (no intervention). Overall, miscarriage occurred in 10.7% (95% CI 3.8-19.9; 4/48) of fetuses, while IUD in 24.3.4% (95% CI 13.3-37.5; 11/48). When assessing the risk of single and double IUD separately, single fetal loss complicated 11.0% (95% CI 4.2-20.6; 3/48), while double IUD occurred in 11.8% (95% CI 4.7-21.6; 4/48) (Figure 2). The incidence of NND and PND was 13.5% (95% CI 5.8-23.8; 5/48) and 32.4% (95% CI 18.5-48.0; 16/48), respectively. 59.9% (95% CI 45.7-71.5; 28/48) of affected cases were alive at 28 days of life (Figure 2). In 68.4% (95% CI 51.1-83.4;17/24) of cases, at least one twin survived to the neonatal period while in 46.5% (95% CI 27.1-66.5; 11/24) both twins survived. Finally, 54.0% (95% CI 24.8-81.8; 9/16) of these pregnancies delivered before 32 weeks of gestation.

Laser treatment

Three studies (12 fetuses-6 pregnancies) reported the outcome of TTTS following laser treatment. Miscarriage complicated 19.6% (95 CI 3.5-44.5; 2/12), while single and double IUD occurred in

7.4% (95% CI 0.01-27.6; 1/12) and 12.5% (95% CI 0.8-35.0; 1/12), respectively. NND and PND occurred in 7.4% (95% CI 0.01-27.6; 1/12) and 35.9.7% (95% CI 13.1-62.8; 4/12) of cases, respectively. 48.2% of fetuses (95% CI 22.6-74.3; 6/12) survived to the neonatal period. (Table 3, Figure 2). The incidence of PTB <32 weeks of gestation was 64.9% (95% CI 28.7-93.2; 4/6).

Amniodrainage

Three studies (12cfetuses-6 pregnancies) reported the outcome of TTTS following laser treatment. Overall IUD, NND and PND occurred in 30.3% (95% CI 9.7-56.4; 4/12), 19.1% (95% CI 3.4-43.3; 2/12) and 46.5% (95% CI 2.5-90.8; 6/12) of cases, respectively. 29.4% of fetuses (95% CI 2.1-70.9; 6/14) survived to the neonatal period. 53.5% (95% CI 27.7-78.4; 6/12) of twins survived to neonatal period. The incidence of PTB <32 weeks of gestation was 78.1% (95% CI 44.1.3-98.4; 5/6) (Table 3, Figure 2).

Cord occlusion

Finally, only three studies (6 fetuses-3 pregnancies) explored the outcome of non-anomalous MCMA pregnancies complicated by TTTS treated by cord occlusion of one twin. In view of the very small number of included cases and even smaller number of events, the results reported in this review are affected by the low power of the analysis and may not reflect the actual incidence of the explored outcomes in pregnancies undergoing cord occlusion. Furthermore, it was not specified whether all cases had cord transection after occlusion. Miscarriage occurred in 19.2% (95% CI 0.9-52.6); 1/6), while there was no IUD or NND of the surviving twin. Overall, 80.8% (95% CI 47.4-99.1; 5/6) of fetuses survived to the neonatal period, while the incidence of PTB <32 weeks was 50.0% (95% CI 17.2-82.8; 3/6) (Table 3, Figure 2).

Sub-group analysis: TTTS diagnosed ≤24 weeks of gestation

The results of the sub-group analysis of cases complicated by TTTS diagnosed at or before 24 weeks of gestation are shown in Supplementary Table 2. In cases not undergoing intervention, the incidence of IUD was 39.5% (95% CI 9.1-75.5; 6/16). There was no single fetal loss, while the incidence of double IUD was 21.2% (95% CI 6.3-41.8; 3/16). Finally, PND occurred in 50.8% (95% CI 16.9-84.3; 8/16). Two studies (6 fetuses) explored the outcome of TTTS occurring < 24 weeks of gestation treated with laser therapy. IUD occurred in 50.0% (95% CI 16.3-83.7; 3/6). Single and double IUD occurred in 20.4% (95% CI 0.3-51.5; 1/6) and 21.4% (95% CI 11.8-56.4; 1/6), respectively. The incidence of NND and PND was 17.3% (95% CI 0.3-51.5; 1/6) and 68.8% (95% CI 24.6-98.2; 4/6), respectively. It was not possible to compute a pooled data synthesis for

cases undergoing amniodrainage because we could extract the data for the outcomes observed in the present systematic review only from one study[21]. Finally, three studies explored the outcome of MCMA pregnancies affected by TTTS undergoing cord occlusion. The rate of miscarriage was 26.2% (95% CI 0.03-7.9; 1/6), while there were no cases of IUD and NND, although only 6 pregnancies were included in the analysis. Inter-group comparison among the three management options could not be reliably computed in view of the very small number of studies reporting the three management options, which precluded a comprehensive assessment of the strength of association between a given management and the observed outcomes.

DISCUSSION

Main findings

The findings from this systematic review show that, in MCMA twin pregnancies complicated by TTTS, IUD occurred in 24.3% of cases with no fetal treatment and in 27.4% and 30.3% of those undergoing laser and amniodrainage, while there was no loss of the surviving twin in cases undergoing cord occlusion. The large majority of fetal losses were double IUD. Finally, in view of the very small number of included studies and lack of direct comparison, it was not possible to extrapolate objective evidence on the optimal type of prenatal treatment in these complex pregnancies.

Strengths and limitations

Thorough literature search aimed at identifying all the possible relevant studies, multitude of outcomes explored and stratification of the analysis according to the type of prenatal management are the main strengths of the present systematic review. The small number of cases in some of the included studies, their retrospective non-randomized design, lack of standardized criteria for the antenatal management and surveillance of MCMA twin pregnancies complicated by TTTS represent the major limitations of this systematic review. Furthermore, the large majority of the included studies did not report the comparison between the different management options, thus making the different populations potentially unbalanced for the main determinants of outcome in TTTS, such as gestational age at occurrence or severity of the disease. Other major limitations of the present systematic review were the lack of stratification of the results according to the ultrasound staging of the disease and the type of fetal monitoring (in- vs outpatient) [28-30].

Interpretation of findings and comparison with other published evidence.

The findings from this review confirm the high rate of perinatal mortality observed in MCMA pregnancies affected by TTTS. Prenatal diagnosis of TTTS in MCMA gestations is challenging since the polyhydramnios-oligohydramnios sequence cannot be detected and diagnosis should be based on other signs, including polyhydramnios, discordance in bladder size, cardiomegaly and abnormal Doppler flow patterns in either twin[15]. Conversely, the peculiar anastomotic pattern of MCMA twin placentas, with larger placental anastomoses compared to MCDA pregnancies, may predispose to acute TTTS leading to sudden fetal death, thus explaining the high rate of perinatal mortality observed in the present systematic review. This may explain the relatively large number of cases not undergoing intervention included in the present review. In view of the lack of direct comparison between the different types of interventions (laser treatment vs cord occlusion) in the

original publications and the very small number of included cases, it was not possible to extrapolate an objective evidence on the optimal type of management of MCMA twins affected by TTTS. Therefore, perinatal management of these pregnancies should be individualized according to gestational age at occurrence, severity of the disease, legal regulations and parents' wishes.

Clinical and research implications

The optimal type of monitoring of MCMA twin pregnancies is yet to be ascertained[31]. There are no randomized controlled trials comparing the different management protocols in MCMA twin pregnancies. There is also wide variation in practice with regards to the type and frequency of fetal monitoring and timing at initiation of fetal surveillance among the recently published studies[2]. Fortnightly ultrasound assessment and prompt referral of cases affected by TTTS to centers with high expertise in fetal surgery has led to a significant reduction in perinatal mortality in MCDA twin pregnancies[32,33]. Laser coagulation of placental anastomoses is the gold standard for managing MCDA twin pregnancies affected by TTTS before third trimester. In the present review, the survival rate of MCMA twins undergoing laser was lower compared to what reported for MCDA pregnancies (30% vs 38%). The relatively higher risk of IUD in pregnancies undergoing laser therapy might be partially explained by the fact that TTTS in MCMA twins occurs more acutely compared to MCDA pregnancies. Furthermore, although often performed with technical success, laser treatment in MCMA pregnancies can be technically challenging. High incidence of proximate cord insertions and the large-diameter of artero-arterial anastomoses can make photocoagulation difficult and this may represent an additional source of bias among the included cases. Finally, it is also likely that the high incidence of perinatal mortality of MCMA pregnancies treated with laser observed in the present review might have been the result of inclusion of mainly cases with advanced cardiovascular compromise, considering the fact that TTTS can be difficult to diagnose in MCMA pregnancies.

In MCDA twins, amnioreduction does not represent the primary treatment for TTTS as laser therapy has been proved to be associated with a better perinatal outcome[5]. However, amnioreduction may be indicated especially in pregnancies presenting with TTTS >26 weeks of gestation with symptoms of to uterine overdistension debilitating symptoms (eg, significant respiratory distress and/or uterine contractions) in order to relieve maternal symptoms. In the present review, amniodrainage was affected by a very high incidence of PTB, without a recognizable improvement in survival compared to other management options.

The very small number of include cases and even smaller number of events did not allow to draw any objective conclusion on the role of cord occlusion in the surgical management of MCMA twins pregnancies affected by TTTS. Cord occlusion may represent an alternative in those pregnancies presenting with signs impending fetal demise of one twin especially when far from viability, but may be not ethically acceptable for some parents. In case cord occlusion is performed, cord transection after occlusion has been reported a feasible technique potentially able to prevent the complications of cord entanglement[34].

CONCLUSION

MCMA twin pregnancies complicated by TTTS are at high risk of perinatal mortality and PTB. In view of the small number of included cases, heterogeneity in gestational age at treatment, disease severity and study populations, the present systematic review could not elucidate the optimal treatment for MCMA twins affected by TTTS. Further large multicenter studies sharing objective protocols for antenatal surveillance, indication for fetal surgery and post-natal follow-up are needed in order to establish the optimal treatment for TTTS in MCMA twin pregnancies.

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Figure legend

Figure 1. Systematic review flowchart.

Figure 2. Forest plots displaying the pooled proportions of the different outcomes observed in the present systematic review.

Table 1. General characteristics of the included studies

Author	Year	Country	Study design	Period analysed	GA at diagnosis (week)*	Pregnancies (n)	Pregnancies complicated by TTTS
Glinianaia[11]	2018	United Kingdom	Retrospective	2000-2013	18.8 (2.8)	85	3
Madsen[12]	2018	Denmark	Prospective	2004-2013	NS	61	1
Anselem[13]	2015	France	Retrospective	1993-2014	NS	38	3
Van Mieghem[14]	2014	Canada, Belgium, The Netherlands, Austria, Switzerland, United States	Retrospective	2003-2012	NS	193	5
Peeters[15]	2014	The Netherlands, Belgium, United States	Retrospective	2000-2012	II-III trimester	50	9
Murata[16]	2013	Japan	Retrospective	2001-2011	NS	38	1
Suzuki[17]	2013	Japan	Retrospective	NS	NS	18	2
Morikawa[18]	2012	Japan	Retrospective	2002-2009	NS	101	4
Baxi[19]	2010	United States	Retrospective	2001-2009	NS	25	1
Hack[20]	2009	Netherlands	Retrospective	2000-2007	NS	98	6
Schaap[21]	2006	Netherlands	Case report	NS	NS	1	1
Cordero[22]	2006	United States	Retrospective	1990-2005	28 (2.8)	36	3
DeFalco[23]	2006	United States	Retrospective	1991-2001	NS	23	1
Gallot[24]	2005	France	Case report	NS	16	1	1
Heyborne[25]	2005	United states	Retrospective	1993-2003	NS	96	3
Demaria[26]	2004	France	Retrospective	1993-2001	NS	19	2
Sau[27]	2003	Singapore	Retrospective	1994-2000	NS	7	1

*: data reported as mean and standard deviations; NS: not specified; TTTS: twin-to-twin transfusion syndrome

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) for cohort studies; 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.

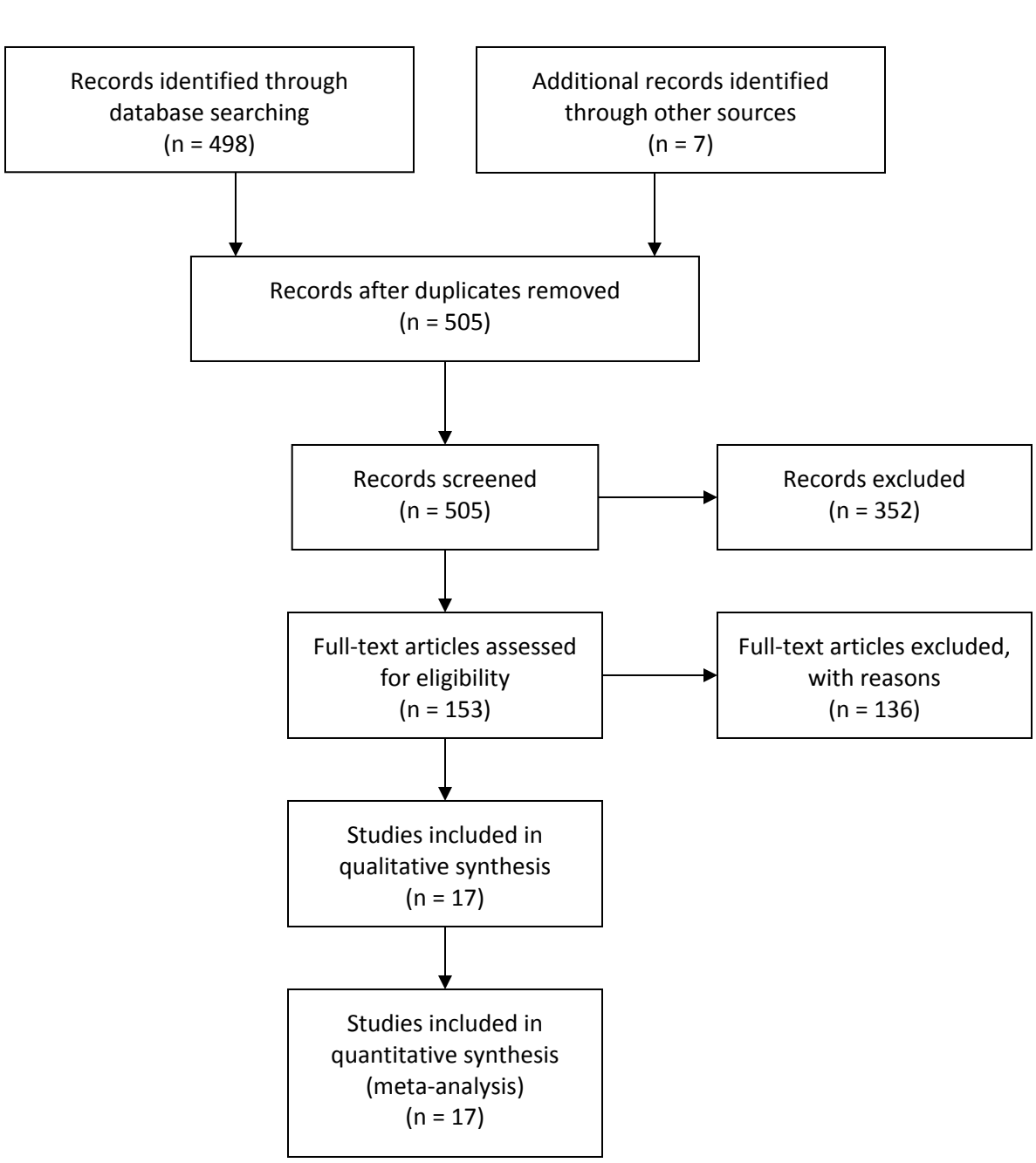
Author	Year	Selection	Comparability	Outcome
Glinianaia[11]	2018	★★	★	★★
Madsen[12]	2018	★★	★	★★
Anselem[13]	2015	★★	★	★
Van Mieghem[14]	2014	★★	★	★★
Peeters[15]	2014	★★	★	★★
Murata[16]	2013	★★	★	★★
Suzuki[17]	2013	★★	★	★
Morikawa[18]	2012	★★	★★	★★
Baxi[19]	2010	★★	★	★★
Hack[20]	2009	★★	★	★★
Schaap[21]	2006	★★	★	★
Cordero[22]	2006	★★	★	★★
DeFalco[23]	2006	★★	★	★★
Gallot[24]	2005	★★	★	★★
Heyborne[25]	2005	★★	★	★★
Demaria[26]	2004	★★	★	★
Sau[27]	2003	★★	★	★★

Table 3. Pooled proportions for the outcomes observed in the present systematic review in monochorionic mono-amniotic (MCMA) twin pregnancies complicated by twin-to-twin transfusion syndrome (TTTS).

Outcome	Studies	Fetuses	Raw proportions (95% CI)	I^2 (%)	Pooled proportions (95% CI)
No intervention[a]					
Miscarriage (overall)	13	4/48	8.33 (2.3-20.0)	10.4	10.74 (3.8-19.9)
IUD (overall)	13	11/48	22.92 (12.0-37.3)	11.8	24.34 (13.3-37.5)
Single IUD	13	3/48	6.25 (1.3-17.2)	0	11.03 (4.2-20.6)
Double IUD*	13	4/48	8.33 (2.3-20.0)	0	11.78 (4.7-21.6)
NND	13	5/48	10.42 (3.5-22.7)	0	13.52 (5.8-23.8)
PND	13	16/48	33.33 (20.4-48.4)	27.7	32.36 (18.5-48.0)
Survivors	13	28/48	58.33 (43.2-72.4)	49.3	59.85 (45.7-71.5)
At least one survivor[c]	13	17/24	70.83 (48.9-87.4)	0	68.39 (51.1-83.4)
Two survivors[c]	13	11/24	45.83 (25.6-67.2)	20.8	46.54 (27.1-66.5)
PTB < 32 weeks	10	9/16	56.25 (29.9-80.2)	48.6	54.0 (24.8-81.8)
Laser therapy					
Miscarriage (overall)	2	2/12	16.67 (2.1-48.4)	0	19.63 (3.5-44.5)
IUD (overall)	2	3/12	25.00 (5.5-57.2)	0	27.39 (7.6-53.7)
Single IUD	2	1/12	8.33 (0.2-38.5)	69	7.36 (0.01-27.6)
Double IUD*	2	1/12	8.33 (0.2-38.5)	0	12.46 (0.8-35.0)
NND	2	1/12	8.33 (0.2-38.5)	69	7.36 (0.01-27.6)
PND	2	4/12	33.33 (9.9-65.1)	79	35.93 (13.1-62.8)
Survivors	2	6/12	50.0 (21.1-78.9)	61.8	48.23 (22.6-74.3)
At least one survivor[c]	2	3/6	50.0 (11.8-88.2)	7	47.30 (12.5-83.7)
Two survivors[c]	2	3/6	50.0 (11.8-88.2)	7	47.30 (12.5-83.7)
PTB < 32 weeks	2	4/6	66.67 (22.3-95.7)	0	64.86 (28.7-93.2)
Ammniodrainage					
Miscarriage (overall)	3	0/12	0 (0-26.5)	0	0 (0-22.5)
IUD (overall)	3	4/12	33.33 (9.9-65.1)	67.4	30.31 (9.7-56.4)
Single IUD	3	0/12	0 (0-26.5)	0	0 (0-22.5)
Double IUD*	3	2/12	16.67 (2.1-48.4)	0	18.29 (3.0-42.3)
NND	3	2/12	16.67 (2.1-48.4)	0	19.06 (3.4-43.3)
PND	3	6/12	50.0 (21.1-78.9)	74.8	46.46 (2.5-90.8)
Survivors	3	6/12	50.0 (21.1-78.9)	74.8	53.54 (27.7-78.4)
At least one survivor[c]	3	4/6	66.67 (22.3-95.7)	20.3	68.75 (29.2-96.6)
Two survivors[c]	3	2/6	33.33 (4.3-77.7)	68	33.92 (6.8-68.9)
PTB < 32 weeks	3	5/6	83.33 (35.9-99.6)	0	78.14 (44.1-98.4)
Cord occlusion[b]					
Miscarriage (overall)	3	1/6	16.67 (0.4-64.1)	50.7	19.18 (0.9-52.6)
IUD (overall)	3	0/6	0 (0-39.0)	0	0 (0-37.0)
NND	3	0/6	0 (0-39.0)	0	0 (0-37.0)
PND	3	0/6	0 (0-39.0)	0	0 (0-37.0)
Survivors	3	5/6	83.33 (35.9-99.6)	50.7	80.82 (47.4-99.1)
PTB < 32 weeks	3	3/6	60.0 (14.7-94.7)	0	50.00 (17.2-82.8)

a: includes cases managed expectantly or those in which in utero therapy could not be performed.
b: The fetus undergoing cord occlusion was not considered for the computation of the different observed outcomes.
c: Computed upon the number of pregnancies.

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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