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

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KEYWORDS: monochorionic monoamniotic; TTTS; twin pregnancies

CONTRIBUTION

What are the novel findings of this work?
There are no consistent data on the outcome of twin-to-twin transfusion syndrome (TTTS) in monochorionic monoamniotic twin pregnancies. Moreover, it is not clear which treatment may be preferable in terms of perinatal survival when managing these pregnancies.

What are the clinical implications of this work?
Monochorionic monoamniotic twin pregnancies affected by TTTS are at very high risk of perinatal mortality. Further studies are needed to elucidate the optimal therapeutic approach for these 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 for studies reporting the outcome of MCMA twin pregnancies complicated by TTTS. The primary outcome was intrauterine death (IUD); secondary outcomes were miscarriage, single IUD, double IUD, neonatal death (NND), perinatal death (PND), survival of at least one twin, survival of both twins and preterm birth (PTB) before 32 weeks' gestation. Outcomes were assessed in MCMA twins affected by TTTS not undergoing intervention and in those treated with amniodrainage, laser therapy or cord occlusion. Subgroup analysis was performed including cases diagnosed before 24 weeks. Random-effects meta-analysis of proportions was used to analyze the data.*

Results *Fifteen cohort studies, including 888 MCMA twin pregnancies, of which 44 were affected by TTTS, were included in the review. There was no randomized trial comparing the different management options in MCMA twin pregnancies complicated by TTTS. In cases not undergoing intervention, miscarriage occurred in 11.0%*

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of fetuses, while the incidence of IUD, NND and PND was 25.2%, 12.2% and 31.2%, respectively. PTB complicated 50.5% 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, and the incidence of PTB before 32 weeks' gestation was 64.9%. In cases treated with amniodrainage, the incidence of IUD, NND and PND was 31.3%, 13.5% and 45.7% respectively, and PTB complicated 76.2% of these pregnancies. 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 case of IUD or NND of the surviving twin. PTB before 32 weeks occurred in 50.0% of these cases.

Conclusions *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 pregnancy, with an estimated incidence of 9–15%[1]. Although the pathophysiology of TTTS has not yet been fully elucidated, the anatomical prerequisite for its occurrence is the presence of intertwin vascular anastomoses within the placenta, which are present in virtually every monochorionic 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 the rate of perinatal mortality in multiple pregnancies complicated by TTTS, especially in monochorionic diamniotic (MCDA) twin pregnancies.

Monochorionic monoamniotic (MCMA) twin pregnancies are at a higher risk of perinatal mortality and morbidity than are MCDA gestations. The overall incidence of fetal loss in MCMA twin pregnancies is approximately 6%, the large majority of which occur before 30 weeks' 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 probably reflects the different anastomotic pattern observed in monoamniotic gestations, in which there is a higher prevalence of arterioarterial anastomoses, which are protective against the occurrence of this pathology[3–5]. Despite its importance, there are 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, and it is not clear whether other treatments (e.g. cord occlusion) may be preferable in terms of perinatal survival when managing these pregnancies. 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 recommended for systematic reviews and meta-analyses[6]. MEDLINE and EMBASE databases were searched electronically on 10 January 2019 for studies reporting the outcome of MCMA twin pregnancies complicated by TTTS, utilizing combinations of the relevant medical subject heading (MeSH) terms, keywords and word variants for 'twin-to-twin transfusion syndrome', 'monoamniotic pregnancy', 'ultrasound' and 'outcome'. The search and selection criteria were restricted to the English language. Reference lists of relevant articles and reviews were searched manually for additional reports. PRISMA guidelines were followed[7]. The study was registered with the PROSPERO database (registration number: CRD42016043062).

Outcome measures, study selection and data collection

The primary outcome was intrauterine death (IUD), defined as the death of either twin at or after 20 weeks' gestation. Secondary outcomes were: miscarriage, defined as the loss of either twin prior to 20 weeks; single IUD, defined as the loss of a twin at or after 20 weeks; double IUD, defined as the loss of both twins at or after 20 weeks; 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 survival, defined as the percentage of twins not affected by PND or miscarriage; survival of at least one twin; survival of both twins; and preterm birth (PTB) before 32 weeks' gestation.

The explored outcomes were reported for MCMA twins not undergoing intervention and for those treated with laser therapy, amniodrainage and cord occlusion. For the purpose of the analysis, single and double IUD, NND, PND and survival were not computed in the group of twins undergoing cord occlusion. Since the polyhydramnios–oligohydramnios sequence cannot be detected in monoamniotic pregnancies, the diagnosis of TTTS was based on the identification of other clinical manifestations of the syndrome, such as polyhydramnios (deepest vertical pocket ≥ 8 cm before 20 weeks or ≥ 10 cm after 20 weeks), discordance in bladder size (absent bladder in the donor and dilated bladder in the recipient) and abnormal Doppler flow pattern in either twin. Furthermore, we planned a subgroup analysis considering only cases affected by TTTS diagnosed at or before 24 weeks' gestation.

Only studies reporting the outcome of MCMA twin pregnancies affected by TTTS were considered suitable for inclusion in the current systematic review. Studies including higher-order multiple gestations, those including cases of iatrogenic MCMA twin pregnancies or 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 and improvements in the diagnosis and treatment of TTTS make them less relevant. Only full text articles were considered eligible for inclusion; case reports and conference abstracts were also excluded in order to avoid publication bias.

Two authors (D.M., D.B.) 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 outcomes. Consensus on inconsistencies was reached by discussion between the two reviewers or with a third author. If more than one study had been published on 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 the NOS, each study is judged on three broad perspectives: selection of the study groups; comparability of the groups; and ascertainment of the outcome of interest[8]. Assessment of the selection of the study groups includes evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of the exposure and demonstration that the outcome of interest was not present at the start of the study. Assessment of the comparability of the study includes evaluation of the comparability of the cohorts on the basis of the design or analysis. Finally, ascertainment of the outcome of interest includes evaluation of the type of assessment of the outcome of interest and length and adequacy of follow-up[7]. According to the NOS, a study can be awarded a maximum of one star for each numbered item within the selection and outcome categories, while a maximum of two stars can be given for comparability.

Random-effects meta-analysis of proportions was used to combine data. For the purpose of the analysis, the number of twins in each group was used as the denominator for the computation of rates of IUD, NND, PND and survival, while the number of pregnancies was used for the assessment of PTB, survival of at least one twin and survival of both twins. Funnel plots displaying the outcome rate from individual studies *vs* their precision (1/standard error) were produced 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 10, as the power of the tests would be too low to distinguish chance from true 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. Analysis was performed using StatsDirect Statistical Software (StatsDirect Ltd, Cambridge, UK).

RESULTS

Study selection and characteristics

The search identified 505 articles, of which 152 were assessed with respect to their eligibility for inclusion (Table S1) and 15 were included in the systematic review (Figure 1, Table 1). These 15 studies included 888 MCMA twin pregnancies, of which 44 (88 fetuses) were affected by TTTS[11–25]. There was no randomized controlled trial comparing different management options (expectant *vs* laser *vs* cord occlusion *vs* amniodrainage) in MCMA twin pregnancies complicated by TTTS.

Gestational age at diagnosis of TTTS was reported in only six studies (20 pregnancies); TTTS occurred in 10.0% (2/20) of cases before 16 weeks, in 15.0% (3/20) between 16 and 20 weeks, in 45.0% (9/20) between 21 and 24 weeks, in 20% (4/20) between 25 and 28 weeks and in 10.0% (2/20) after 28 weeks.

The results of the quality assessment of the included studies using the NOS are presented in Table 2. Most of the included studies showed an overall good score regarding selection and comparability of the study

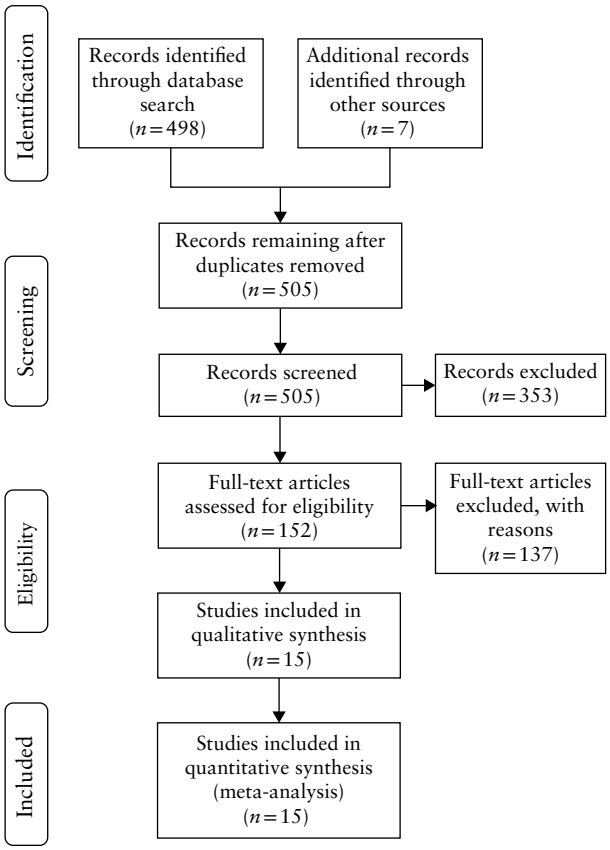

Figure 1 Flowchart summarizing inclusion in systematic review of studies on outcome of monochorionic monoamniotic twin pregnancies complicated by twin-to-twin transfusion syndrome.

Table 1 Characteristics of included studies on outcome of monochorionic monoamniotic twin pregnancies complicated by twin-to-twin transfusion syndrome (TTTS)

Study	*Country*	*Study design*	*Period analyzed*	*GA at diagnosis of TTTS*	*Total pregnancies (n)*	*TTTS pregnancies (n)*
Glinianaia (2019)[11]	UK	Retrospective	2000–2013	18.8 ± 2.8 weeks	85	3
Madsen (2019)[12]	Denmark	Prospective	2004–2013	22 + 0 weeks	61	1
Anselem (2015)[13]	France	Retrospective	1993–2014	29.0 ± 5.0 weeks	38	3
Van Mieghem (2014)[14]	Canada, Belgium, The Netherlands, Austria, Switzerland, USA	Retrospective	2003–2012	NS	193	5
Peeters (2014)[15]	The Netherlands, Belgium, USA	Retrospective	2000–2012	21.9 ± 2.9 weeks	50	9
Murata (2013)[16]	Japan	Retrospective	2001–2011	NS	38	1
Suzuki (2013)[17]	Japan	Retrospective	NS	NS	18	2
Morikawa (2012)[18]	Japan	Retrospective	2002–2009	NS	101	4
Baxi (2010)[19]	USA	Retrospective	2001–2009	NS	25	1
Hack (2009)[20]	The Netherlands	Retrospective	2000–2007	NS	98	6
Cordero (2006)[21]	USA	Retrospective	1990–2005	26 ± 5.3 weeks	36	3
DeFalco (2006)[22]	USA	Retrospective	1991–2001	NS	23	1
Heyborne (2005)[23]	USA	Retrospective	1993–2003	NS	96	3
Demaria (2004)[24]	France	Retrospective	1993–2001	NS	19	1
Sau (2003)[25]	Singapore	Retrospective	1994–2000	14 weeks	7	1

Only first author's name is given. GA, gestational age given as mean ± SD when more than one case of TTTS; NS, not specified.

Table 2 Quality assessment of included studies according to Newcastle–Ottawa Scale for cohort studies

Author	*Selection*	*Comparability*	*Outcome*
Glinianaia (2019)[11]	★★	★	★★
Madsen (2019)[12]	★★	★	★★
Anselem (2015)[13]	★★	★	★
Van Mieghem (2014)[14]	★★	★	★★
Peeters (2014)[15]	★★	★	★★
Murata (2013)[16]	★★	★	★★
Suzuki (2013)[17]	★★	★	★
Morikawa (2012)[18]	★★	★★	★★
Baxi (2010)[19]	★★	★	★★
Hack (2009)[20]	★★	★	★★
Cordero (2006)[21]	★★	★	★★
DeFalco (2006)[22]	★★	★	★★
Heyborne (2005)[23]	★★	★	★★
Demaria (2004)[24]	★★	★	★
Sau (2003)[25]	★★	★	★★

Only first author's name is given. A study can be awarded a maximum of one star for each numbered item within selection and outcome categories. A maximum of two stars can be given for comparability.

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 assessed and different protocols for antenatal management of the pregnancies complicated by TTTS.

Synthesis of results

No intervention

Twelve studies (46 fetuses, 23 pregnancies) reported the outcome of MCMA twin pregnancies complicated by TTTS managed expectantly (no intervention) (Table 3, Figure 2). Overall, miscarriage occurred in 11.0% (95% CI, 3.4–22.2%; 4/46) of fetuses, while IUD occurred in 25.2% (95% CI, 13.4–39.3%; 11/46). When assessing the risk of single and double IUD separately, single fetal loss complicated 11.1% (95% CI, 4.1–21.0%; 3/46), while double IUD occurred in 11.9% (95% CI, 4.6–22.0%; 4/46). The incidence of NND and PND was 12.2% (95% CI, 4.8–22.4%; 4/46) and 31.2% (95% CI, 16.8–47.8%; 15/46), respectively. Of the fetuses, 60.6% (95% CI, 40.1–79.2%; 27/46) were alive at 28 days postpartum. In 72.1% (95% CI, 54.2–86.9%; 17/23) of pregnancies, at least one twin survived the neonatal period, while in 46.1% (95% CI, 25.6–67.3%; 10/23), both twins survived. Finally, 50.5% (95% CI, 19.9–80.9%; 8/15) of these pregnancies delivered before 32 weeks' gestation.

Laser treatment

Two studies (12 fetuses, six pregnancies) reported the outcome of TTTS following laser treatment (Table 3, Figure 2). Miscarriage occurred in 19.6% (95% CI, 3.5–44.5%; 2/12) of fetuses, 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% (95% CI, 13.1–62.8%; 4/12) of fetuses, respectively. Of the fetuses, 48.2% (95% CI, 22.6–74.3%; 6/12) survived the neonatal period. The incidence of PTB before 32 weeks was 64.9% (95% CI, 28.7–93.2%; 4/6).

Amniodrainage

Two studies (10 fetuses, five pregnancies) reported the outcome of TTTS following amniodrainage (Table 3,

Table 3 Pooled proportions for pregnancy outcomes in monochorionic monoamniotic twin pregnancies complicated by twin-to-twin transfusion syndrome (TTTS), according to intervention

Outcome	*Studies* (n)	*Cases* (n/N)*	*Raw proportions (95% CI)*	I^2 *(%)*	*Pooled proportions (95% CI)*
No intervention†					
Miscarriage	12	4/46	8.70 (2.4–20.8)	17.9	11.00 (3.4–22.2)
IUD (overall)	12	11/46	23.91 (12.6–38.8)	16.3	25.23 (13.4–39.3)
Single IUD	12	3/46	6.52 (1.4–17.9)	0.0	11.12 (4.1–21.0)
Double IUD	12	4/46	8.70 (2.4–20.8)	0.0	11.91 (4.6–22.0)
NND	12	4/46	8.70 (2.4–20.8)	0.0	12.20 (4.8–22.4)
PND	12	15/46	32.61 (19.5–48.0)	32.5	31.23 (16.8–47.8)
Survivors	12	27/46	58.70 (43.2–73.0)	53.4	60.56 (40.1–79.2)
At least one survivor‡	12	17/23	73.91 (51.6–89.8)	4.2	72.11 (54.2–86.9)
Two survivors‡	12	10/23	43.48 (23.2–65.5)	26.1	46.06 (25.6–67.3)
PTB < 32 weeks‡	8	8/15	53.33 (26.6–78.7)	52.3	50.53 (19.9–80.9)
Laser therapy					
Miscarriage	2	2/12	16.67 (2.1–48.4)	0.0	19.63 (3.5–44.5)
IUD (overall)	2	3/12	25.00 (5.5–57.2)	0.0	27.39 (7.6–53.7)
Single IUD	2	1/12	8.33 (0.2–38.5)	69.0	7.36 (0.01–27.6)
Double IUD	2	1/12	8.33 (0.2–38.5)	0.0	12.46 (0.8–35.0)
NND	2	1/12	8.33 (0.2–38.5)	69.0	7.36 (0.01–27.6)
PND	2	4/12	33.33 (9.9–65.1)	79.0	35.93 (13.1–62.8)
Survivors	2	6/12	50.00 (21.1–78.9)	61.8	48.23 (22.6–74.3)
At least one survivor‡	2	3/6	50.00 (11.8–88.2)	7.0	47.30 (12.5–83.7)
Two survivors‡	2	3/6	50.00 (11.8–88.2)	7.0	47.30 (12.5–83.7)
PTB < 32 weeks‡	2	4/6	66.67 (22.3–95.7)	0.0	64.86 (28.7–93.2)
Amniodrainage					
Miscarriage	2	0/10	0.00 (0–27.8)	0.0	0.00 (0–23.4)
IUD (overall)	2	4/10	40.00 (12.2–73.8)	80.8	31.33 (0.8–91.8)
Single IUD	2	0/10	0.00 (0–27.8)	0.0	0.00 (0–23.4)
Double IUD	2	2/10	20.00 (2.5–55.6)	43.2	19.42 (0.4–56.7)
NND	2	1/10	10.00 (0.3–44.5)	0.0	13.48 (0.6–38.7)
PND	2	5/10	50.00 (18.7–81.3)	87.4	45.66 (29.4–99.7)
Survivors	2	5/10	50.00 (18.7–81.3)	87.4	54.34 (25.9–81.4)
At least one survivor‡	2	3/5	60.00 (14.7–94.7)	53.7	64.78 (11.2–99.8)
Two survivors‡	2	2/5	40.00 (5.3–85.3)	82.9	46.28 (5.3–97.5)
PTB < 32 weeks‡	2	4/5	80.00 (28.4–99.5)	0.0	76.17 (37.7–98.8)
Cord occlusion¶					
Miscarriage	3	1/6	16.67 (0.4–64.1)	50.7	19.18 (0.9–52.6)
IUD (overall)	3	0/6	0.00 (0–39.0)	0.0	0.00 (0–37.0)
NND	3	0/6	0.00 (0–39.0)	0.0	0.00 (0–37.0)
PND	3	0/6	0.00 (0–39.0)	0.0	0.00 (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	50.00 (14.7–94.7)	0.0	50.00 (17.2–82.8)

*Number of fetuses, unless stated otherwise. †Includes cases managed expectantly or those in which *in-utero* therapy could not be performed. ‡Number of pregnancies used for calculation of outcome. ¶Fetuses undergoing cord occlusion were not considered for calculation of observed outcomes. IUD, intrauterine death; NND, neonatal death; PND, perinatal death; PTB, preterm birth.

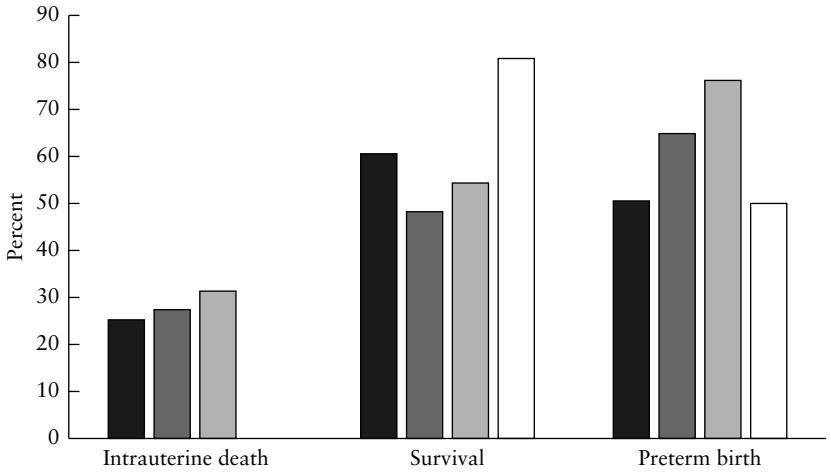

Figure 2 Pooled proportions of intrauterine death, survival and preterm birth before 32 weeks' gestation in monochorionic monoamniotic twin pregnancies complicated by twin-to-twin transfusion syndrome, according to treatment: no intervention (■), laser therapy (■), amniodrainage (■) or cord occlusion (□).

Figure 2). Overall IUD, NND and PND occurred in 31.3% (95% CI, 0.8–91.8%; 4/10), 13.5% (95% CI, 0.6–38.7%; 1/10) and 45.7% (95% CI, 29.4–99.7%; 5/10) of fetuses, respectively. Of the fetuses, 54.4% (95% CI, 25.9–81.4%; 5/10) survived the neonatal period. The incidence of PTB before 32 weeks was 76.2% (95% CI, 37.7–98.8%; 4/5).

Cord occlusion

Finally, three studies (six fetuses, six 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 for this group 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) of the surviving twins, while there was no case of IUD or NND. Overall, 80.8% (95% CI, 47.4–99.1%; 5/6) of fetuses survived the neonatal period, while the incidence of PTB before 32 weeks was 50.0% (95% CI, 17.2–82.8%; 3/6) (Table 3, Figure 2).

Subgroup analysis: TTTS diagnosed at or before 24 weeks' gestation

The results of the subgroup analysis of cases complicated by TTTS diagnosed at or before 24 weeks was affected by the very small number of included studies and even smaller number of events, thus precluding a comprehensive estimation of the different outcomes in this subgroup of pregnancies (Table 4). Five studies (14 fetuses, seven pregnancies) reported the outcome of MCMA pregnancies affected by TTTS at or before 24 weeks not undergoing intervention. In these cases, the incidence of IUD was 46.4% (95% CI, 10.2–85.5%; 6/14). There was no case of single IUD, while the incidence of double IUD was 23.4% (95% CI, 6.8–46.0%; 3/14). PND occurred in 51.3% (95% CI, 12.0–89.6%; 7/14) of fetuses. Two studies (six fetuses; three pregnancies) explored the outcome of TTTS occurring at or before 24 weeks treated with laser therapy. IUD occurred in 50.0% (95% CI, 16.3–83.7%; 3/6) of fetuses. 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) of fetuses, respectively (Table 4). 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. Finally,

Table 4 Pooled proportions for pregnancy outcomes in monochorionic monoamniotic twin pregnancies complicated by twin-to-twin transfusion syndrome (TTTS) diagnosed at or before 24 weeks' gestation, according to intervention

Outcome	*Studies* (n)	*Cases* (n/N)*	*Raw proportions (95% CI)*	I^2 *(%)*	*Pooled proportions (95% CI)*
No intervention†					
Miscarriage	5	2/14	14.29 (1.8–42.8)	53.6	18.35 (0.7–51.8)
IUD (overall)	5	6/14	42.86 (17.7–71.1)	66.5	46.44 (10.2–85.1)
Single IUD	5	0/14	0.00 (0–23.2)	0.0	0.00 (0–23.6)
Double IUD	5	3/14	21.43 (4.7–50.8)	0.0	23.36 (6.8–46.0)
NND	5	1/14	7.14 (0.2–33.9)	0.0	12.39 (1.4–32.0)
PND	5	7/14	50.00 (23.0–77.0)	69.5	51.30 (12.0–89.6)
Survivors	5	5/14	35.71 (12.8–64.9)	67.1	31.62 (28.5–73.0)
At least one survivor‡	5	3/7	42.86 (9.9–81.6)	18.7	42.44 (12.1–76.5)
Two survivors‡	5	2/7	28.57 (3.7–71.0)	33.6	30.23 (34.9–68.6)
PTB < 32 weeks‡	5	5/7	71.43 (29.0–96.3)	33.1	66.02 (27.8–94.8)
Laser therapy					
Miscarriage	2	0/6	0.00 (0–45.9)	0.0	0.00 (0–34.6)
IUD (overall)	2	3/6	50.00 (11.8–88.2)	0.0	50.00 (16.3–83.7)
Single IUD	2	1/6	16.67 (0.4–64.1)	49.2	20.39 (0.3–51.5)
Double IUD	2	1/6	16.67 (0.4–64.1)	0.0	21.24 (11.8–56.4)
NND	2	1/6	16.67 (0.4–64.1)	49.2	17.34 (0.3–51.5)
PND	2	4/6	66.67 (22.3–95.7)	31.8	68.76 (24.6–98.2)
Survivors	2	2/6	33.33 (4.3–77.7)	31.8	31.24 (1.8–75.4)
At least one survivor‡	2	0/3	0.00 (0–70.8)	0.0	0.00 (0–54.4)
Two survivors‡	2	0/3	0.00 (0–70.8)	0.0	0.00 (0–54.4)
PTB < 32 weeks‡	2	3/3	100.00 (29.2–100)	0.0	100.00 (45.6–100)
Cord occlusion¶					
Miscarriage	3	1/6	16.67 (0.4–64.1)	50.7	26.20 (0.3–79.0)
IUD (overall)	3	0/6	0.00 (0–39.0)	0.0	0.00 (0–37.0)
NND	3	0/6	0.00 (0–39.0)	0.0	0.00 (0–37.0)
PND	3	0/6	0.00 (0–39.0)	0.0	0.00 (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	50.00 (14.7–94.7)	0.0	50.00 (17.2–82.8)

Pooled analysis could not be performed for pregnancies undergoing amniodrainage because fewer than two studies reported outcome in these cases. *Number of fetuses, unless stated otherwise. †Includes cases managed expectantly or those in which *in-utero* therapy could not be performed. ‡Number of pregnancies used for calculation of outcome. ¶Fetuses undergoing cord occlusion were not considered for calculation of observed outcomes. IUD, intrauterine death; NND, neonatal death; PND, perinatal death; PTB, preterm birth.

three studies (six fetuses, six pregnancies) explored the outcome of MCMA pregnancies affected by TTTS at or before 24 weeks undergoing cord occlusion (Table 4). The rate of miscarriage was 26.2% (95% CI, 0.3–79.0%; 1/6), while there were no cases of IUD or NND, although only six pregnancies were included in the analysis. Intergroup 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 comprehensive assessment of the strength of association between a given management option and the observed outcomes.

DISCUSSION

Main findings

The findings of this systematic review show that, in MCMA twin pregnancies complicated by TTTS, IUD occurred in 25% of fetuses that had no treatment and in 27% and 31% of those undergoing laser therapy and amniodrainage, respectively, while there was no case of loss of the surviving twin in pregnancies 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 of treatment options, it was not possible to extrapolate objective evidence on the optimal type of prenatal treatment in these complex pregnancies.

Strengths and limitations

The thorough literature search aimed at identifying all the possible relevant studies, the multitude of outcomes explored and stratification of the analysis according to type of prenatal management are the main strengths of this systematic review. The small number of cases in some of the included studies, their retrospective non-randomized design and the lack of standardized criteria for the antenatal management and surveillance of MCMA twin pregnancies complicated by TTTS represent the major limitations of this review. Furthermore, the large majority of the included studies did not report on a 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 onset or severity of the disease. Other major limitations of the review are the lack of stratification of the results according to the ultrasound staging of the disease and the type of fetal monitoring (in- *vs* outpatient)[26–28].

Interpretation of findings and comparison with other published evidence

The findings of 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, as 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[11]. Conversely, the peculiar anastomotic pattern of MCMA twin placentae, which have larger placental anastomoses compared with MCDA pregnancies, may predispose to acute TTTS leading to sudden fetal death, thus explaining the high rate of perinatal mortality observed in this review. This may explain the relatively large number of included cases that did not undergo intervention. In view of the lack of direct comparison between the different types of intervention (laser treatment *vs* cord occlusion *vs* amniodrainage *vs* no intervention) in the original publications and the very small number of included cases, it was not possible to extrapolate 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 onset, severity of the disease, legal regulations and parents' preferences.

Clinical and research implications

The optimal type of monitoring of MCMA twin pregnancies is yet to be ascertained[29]. There are no randomized controlled trials comparing the different management protocols in MCMA twin pregnancies. There is also wide variation in practice with regard to the type and frequency of fetal monitoring and timing of initiation of fetal surveillance among recently published studies[2]. Fortnightly ultrasound assessment and prompt referral of cases affected by TTTS to centers with high expertise in fetal surgery have led to a significant reduction in the rate of perinatal mortality in MCDA twin pregnancies[29]. Laser coagulation of placental anastomoses is the gold standard for managing MCDA twin pregnancies affected by TTTS before the third trimester[30]. In the present review, the survival rate of at least one twin in MCMA pregnancies undergoing laser therapy was lower than that reported in MCDA pregnancies[31] (47% *vs* 65%). The relatively lower survival rate in MCMA pregnancies undergoing laser therapy might be partially explained by the fact that TTTS in MCMA twins occurs more acutely than in MCDA pregnancies. Furthermore, although often performed with technical success, laser treatment in MCMA pregnancies can be challenging. The high incidence of proximal cord insertion and the large diameter of arterioarterial 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 in MCMA pregnancies treated with laser therapy observed in the present review might have been the result of the inclusion mainly of 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 better perinatal outcome[5]. However, amnioreduction may be indicated, especially in pregnancies presenting with TTTS after 26 weeks'

gestation with debilitating symptoms of uterine overdistension and/or uterine contractions, in order to relieve maternal symptoms. In the present review, pregnancies undergoing amniodrainage were affected by a very high incidence of PTB, without recognizable improvement in survival compared with other management options.

The very small number of included cases and the even smaller number of events did not allow us to draw any objective conclusion on the role of cord occlusion in the surgical management of MCMA twin pregnancies affected by TTTS. Cord occlusion may represent an alternative management option in those pregnancies presenting with signs of the impending fetal demise of one twin, especially when far from viability, but may not be ethically acceptable to some parents. When cord occlusion is performed, cord transection after occlusion has been reported to be a feasible technique that could, potentially, prevent the complications of cord entanglement[32].

Conclusions

MCMA twin pregnancies complicated by TTTS are at high risk of perinatal mortality and PTB. In view of the small number of included cases and 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 postnatal follow-up are needed in order to establish the optimal treatment for TTTS in MCMA twin pregnancies.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Excluded studies and reason for exclusion