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Evolution of Stage 1 Twin-to-Twin Transfusion Syndrome (TTTS): Systematic Review and Meta-Analysis

Asma Khalil, Emily Cooper, Rosemary Townsend, and Basky Thilaganathan
Fetal Medicine Unit, St. George's University of London, London, UK

Objectives: The natural history of stage 1 Twin-to-twin transfusion syndrome (TTTS) remains unclear and its optimal management is yet to be established. The main aims of this meta-analysis were to quantify the incidence of progression in stage 1 TTTS and to ascertain survival in these pregnancies.
Methods: MEDLINE, EMBASE, and The Cochrane Library were searched. Reference lists within each article were hand-searched for additional reports. The outcomes included incidence of progression and survival in stage 1 TTTS. Randomized controlled trials, cohort and case-control studies were included. Case reports, studies including three or fewer cases of stage 1 TTTS, and editorials were excluded. Proportion meta-analysis was used for analysis (Registration number: CRD42016036190).
Results: The search yielded 3,085 citations; 18 studies were included in the review (172 pregnancies to assess progression and 433 pregnancies to assess the survival). The pooled incidence of progression in stage 1 TTTS was 27% [95% CI 16–39%]. The pooled overall survival, double survival and at least one survival in the pregnancies managed expectantly were 79% [95% CI 62–92%], 70% [95% CI 54–84%] and 87% [95% CI 69–98%], respectively. In those undergoing amnioreduction, the corresponding figures were 77% [95% CI 68–85%], 67% [95% CI 57–76%] and 86% [95% CI 76–94%], respectively. The survival rates were 68% [95% CI 54–81%], 54% [95% CI 36–72%], and 81% [95% CI 69–90%], when laser surgery was performed.
Conclusions: The optimal initial management of stage 1 TTTS remains in equipoise. The ongoing randomized trial comparing immediate laser surgery versus conservative management should provide a definitive answer.

■ **Keywords:** twin-to-twin transfusion syndrome, TTTS, stage 1, progression, survival, laser, amniodrainage, conservative

TTTS affects 10–15% of monochorionic twin pregnancies and is associated with increased perinatal mortality and morbidity (Berghella & Kaufmann, 2001). If untreated, it leads to fetal demise in up to 90% of cases, with morbidity rates in survivors of over 50% (Roberts et al., 2008; 2014). Early diagnosis, however, may allow intervention with fetoscopic laser ablation, which significantly improves the prognosis. Laser treatment in these pregnancies results in 60–70% double survival and 80–90% of women being able to take home at least one baby (Baschat et al., 2013; Roberts et al., 2014).

While the exchange of blood between the twins through placental vascular anastomoses is quite common in these pregnancies, it is the imbalance in the degree of transfusion that leads to the development of TTTS. TTTS is currently classified using the Quintero staging system (Quintero et al., 1999; 2003). It has been questioned whether stage I TTTS truly represents the first in a chronological series of stages of deterioration, and suggested that it might not predict survival well after treatment. While incorporation of additional cardiovascular parameters stratifies additional disease features independent of the Quintero staging, these do not improve prediction of outcome following treatment. Nevertheless, the Quintero staging system remains the most commonly used for the classification of twin pregnancies complicated by TTTS.

Despite the fact that the Eurofetus trial has demonstrated clear superiority of fetoscopic laser ablation over amnioreduction in the treatment of severe TTTS, only 11

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ADDRESS FOR CORRESPONDENCE: Dr Asma Khalil, Fetal Medicine Unit, St George's University of London, Cranmer Terrace, London SW17 0RE, UK. E-mail: asmakhalil79@googlemail.com

pregnancies were stage 1 TTTS, hindering any meaningful statistical subanalyses (Senat et al., 2004). Furthermore, the natural history of stage 1 TTTS is unclear. Studies have reported controversial rates of progression in stage 1 TTTS, from as low as 10% (Bebbington et al., 2010) to as high as 45–50% (Dickinson & Evans, 2004; Duryea et al., 2016). For these reasons, the optimal treatment of stage 1 TTTS is yet to be established. Many centers manage Quintero stage I conservatively. Older studies have advocated the use of amnioreduction as an acceptable treatment in these cases (Bebbington et al., 2010; Dickinson & Evans, 2004; Taylor et al., 2000), and more recent studies have used laser, either in progressive cases or as a first-line treatment (Chmait et al., 2011; Huber et al., 2006; Quintero et al., 2003; Wagner et al., 2009).

In a systematic review of the management of stage 1 TTTS, the overall survival appeared to be similar for laser therapy and conservative management (85% and 86% respectively), but somewhat lower for amnioreduction (77%; Rossi & D'Addario, 2013). Of note, this review included seven articles, searched the literature between 1999 and 2011, and assessed the progression even in those pregnancies undergoing intervention, that is, amnioreduction or laser, and did not perform meta-analysis or assessment of the quality of the included studies (Rossi & D'Addario, 2013). The main aims of this meta-analysis were to quantify the incidence of progression in stage 1 TTTS and to ascertain survival in these pregnancies.

Methods

Protocol, Eligibility Criteria, Information Sources, and Search

This review was performed according to a protocol designed *a priori* and recommended for systematic reviews and meta-analysis (Henderson et al., 2010; NHS Centre, 2009; Stroup et al., 2000). MEDLINE (1946–January 2016), EMBASE (1947–January 2016) and The Cochrane Library (since inception) including The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and The Cochrane Central Register of Controlled Trials (CENTRAL) were searched electronically on January 27, 2016, utilizing combinations of the relevant MeSH terms, key words, and word variants for 'TTTS', 'progression', 'stage', 'survival', 'fetal loss' (Supplementary Table 1). The search was restricted to the English language. Reference lists of relevant articles and reviews were hand searched for additional reports. The MOOSE guidelines were followed (Stroup, 2000). The study was registered with the PROSPERO database (Registration number: CRD CRD42016036190, http://www.crd.york.ac.uk/PROSPERO).

Study Selection, Data Collection, and Data Items

Studies were assessed according to the following criteria: population, outcome, study design, and prenatal intervention. Studies reporting the incidence of progression or the survival rate in twin pregnancies complicated by Quintero stage 1 TTTS were included. The diagnosis of TTTS relied on the standard criteria of oligohydramnios in the donor's sac (maximal vertical pocket $\leq$2 cm) and polyhydramnios in the recipient's sac (maximal vertical pocket $\geq$8 cm). The Quintero staging system was proposed to assess the severity of TTTS using the following criteria: stage I: visualization of donor's bladder; stage II: bladder not visualized in the donor twin; stage III: abnormal Doppler of the umbilical artery and/or ductus venosus in one or both twins; stage IV: hydrops in one or both twins; stage V: intrauterine demise of one or both twins (Quintero et al., 1999). Cases were excluded if they were treated with selective feticide or the survival rates were not stratified by TTTS stages.

All abstracts were reviewed independently by two authors. Agreement about potential relevance was reached by consensus, and full text copies of those papers were obtained. The same two reviewers independently extracted data regarding study characteristics and outcomes. Inconsistencies were discussed by the reviewers and consensus reached. 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. 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.

The outcomes observed in this systematic review were the incidence of progression and the survival. Progression was defined as an increase in stage (from stage 1 to stage 2 or higher) or progressing polyhydramnios with a shortening cervix, and was assessed in the pregnancies that were managed expectantly. The survival included the overall survival, double survival (both twins survived) and at least one survival (at least one twin survived). Randomized controlled trials, prospective and retrospective cohort, case-control studies and case series with more than three twin pregnancies complicated by Quintero stage 1 TTTS were included. Case reports, conference abstracts, and editorials were excluded.

Risk of Bias, Summary Measures, and Synthesis of the Results

Quality of the included studies was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology statement criteria (Stroup, 2000). We used random-effect meta-analyses of proportions to combine data (Hunter et al., 2014; Manzoli et al., 2011). The survival was analyzed according to the intervention received, including conservative management, amnioreduction, and endoscopic laser photocoagulation. Between-study heterogeneity was assessed using the I^2 statistic (Higgins et al., 2003). Publication bias was explored using funnel plots and was assessed statistically using the Egger test

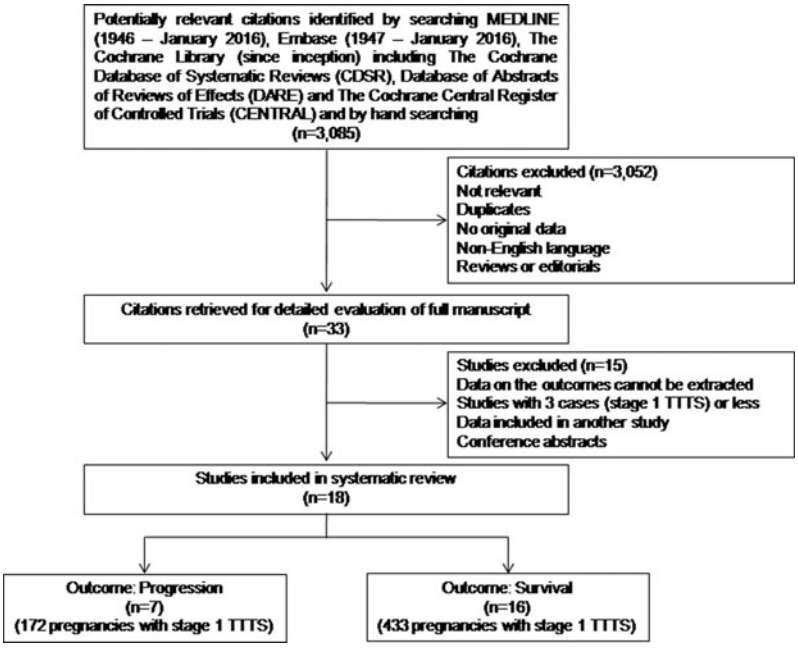

FIGURE 1

Flow of study identification.
Note: TTTS = Twin-to-twin transfusion syndrome.

(which uses the actual values of the effect sizes and their precision, rather than ranks; Sterne & Egger, 2001). The assessment of the potential publication bias was problematic because of the low number of individual studies, which strongly limits the reliability of formal tests. 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 10. In this case, the power of the tests is too low to distinguish chance from real asymmetry (Higgins & Green, 2009).

Statistical analyses were performed using Stats Direct (Version 2.7.8, Stats Direct Ltd, 9 Bonville Chase, Altrincham, Cheshire WA14 4QA, UK) statistical software.

Results

The search yielded 3,085 citations; of these, 3,052 were excluded by review of the title or abstract, as they did not meet the selection criteria, contain original data, were not relevant, contained data on three cases or less, or had data which were included in another study (Figure 1). Full manuscripts were retrieved for the remaining 33, and a total of 18 studies were included in the review. Seven studies reported data on progression (172 pregnancies with stage 1 TTTS), while data on survival were reported in 16 studies (433 pregnancies with stage 1 TTTS; Figure 1). Table 1 shows the characteristics of the studies included in this systematic review.

Progression in Twin Pregnancies Complicated by Quintero Stage 1 TTTS

Seven studies reported the incidence of progression in stage 1 TTTS managed expectantly (Bebbington et al., 2010; Dickinson & Evans, 2004; Duryea et al., 2016; Meriki et al., 2010; O'Donoghue et al., 2007; Taylor et al., 2002; Wagner et al., 2009). The pooled incidence of progression in these pregnancies was 27% [95% CI 16–39%] (Figure 2). The reported rate of progression in the included studies varied from as low as 10% to as high as 50%. The number of pregnancies with stage 1 TTTS reported in these studies ranged between 9 and 46.

Survival in Twin Pregnancies Complicated by Quintero Stage 1 TTTS Managed Expectantly

Four studies (73 pregnancies) reported the survival rates in pregnancies with stage 1 TTTS that were managed expectantly (Bebbington et al., 2010; Luks et al., 2009; Meriki et al., 2010; Wagner et al., 2009). The pooled overall survival, double survival, and at least one survival were 79% [95% CI 62–92%], 70% [95% CI 54–84%] and 87% [95% CI 69–98%], respectively (Figure 3).The highest survival rate was reported in the study by Meriki et al. (2010), which had only 9 pregnancies, while the lowest survival rate was reported in the study by Luks et al. (2009) which had 14 pregnancies.

Survival in Twin Pregnancies Complicated by Quintero Stage 1 TTTS Managed by Amnioreduction

Eight studies (147 pregnancies) reported the survival rates in pregnancies with stage 1 TTTS that were managed by

TABLE 1

Summary of the 18 Studies Included Which Reported Progression or Survival in Twin Pregnancies Complicated by Quintero Stage 1 Twin-To-Twin Transfusion Syndrome (TTTS)

Author, year	Country	Study design	Data collection	Pregnancies with stage 1 TTTS (*n*)	Inclusion criteria	Intervention
Quintero et al., 1999	USA	Cohort	Prospective	6	TTTS	Expectant (stage I), serial amnioreduction (stage I), laser
Taylor et al., 2002	USA	Cohort	Prospective	13	TTTS	Serial amnioreduction, septostomy, selective reduction
Blaicher et al., 2002	Austria	Cohort	Prospective	13	TTTS	Amnioreduction
Quintero et al., 2003	USA/Australia	Cohort	Prospective	32	TTTS	Serial amnioreduction, laser
Tan et al., 2004	UK	Cohort	Prospective	35	TTTS	Serial amnioreduction, septostomy, or bipolar cord occlusion when one twin is preterminal
Dickinson et al., 2004	Australia	Cohort	Prospective	22	TTTS	Amnioreduction
Huber et al., 2006	Germany	Cohort	Prospective	29	TTTS	Fetoscopic laser ablation
O'Donoghue et al., 2007	UK	Cohort	Retrospective	46	TTTS stage I	Conservative, amnioreduction
Luks et al., 2009	USA	cohort	Prospective	14	TTTS	Expectant or laser
Wagner et al., 2009	Netherlands	Cohort	Retrospective	50	TTTS stage I	Conservative, laser
Bebbington et al., 2010	USA	Cohort	Retrospective	42	TTTS stage I	Conservative, amnioreduction, laser if progressed
Fichera et al., 2010	Italy	Cohort	Retrospective	19	TTTS	Amnioreduction
Meriki et al., 2010	Australia	Cohort	Retrospective	9	TTTS undergoing laser therapy	Laser
Chmait et al., 2011	USA	Cohort	Prospective	114	TTTS undergoing laser therapy	Laser
Sundberg et al., 2012	Denmark	Cohort	Retrospective	12	TTTS	Laser or cord occlusion
Has et al., 2014	Turkey	Cohort	Retrospective	12	TTTS	Fetoscopic laser ablation
Müller et al., 2015	Ireland	Audit	Retrospective	9	TTTS undergoing laser therapy	Fetoscopic laser ablation
Duryea et al., 2016	USA	Cohort	Retrospective	18	TTTS	Conservative, amnioreduction, or laser ablation

amnioreduction (Bebbington et al., 2010; Blaicher et al., 2002; Dickinson & Evans, 2004; Fichera et al., 2010; Quintero et al., 1999; Tan et al., 2004; Taylor et al., 2002). The pooled overall survival, double survival, and at least one survival were 77% [95% CI 68–85%], 67% [95% CI 57–76%] and 86% [95% CI 76–94%], respectively (Figure 4).The highest survival rate was reported in the studies by Blaicher et al. (2002) and Quintero et al. (2003), which had 13 and 11 pregnancies, respectively. The lowest survival rates were reported by the older study by Quintero et al. (1999) and Taylor et al. (2002), which had 10 and 13 pregnancies, respectively.

Survival in Twin Pregnancies Complicated by Quintero Stage 1 TTTS Managed by Endoscopic Laser Photocoagulation

Four studies (51 pregnancies) reported the survival rates in pregnancies with stage 1 TTTS that were managed by laser (Has et al., 2014; Müllers et al., 2015; Sundberg et al., 2012; Wagner et al., 2009). The pooled overall survival, double survival, and at least one survival were 68% [95% CI 54–81%], 54% [95% CI 36–72%) and 81% [95% CI 69–90%], respectively (Figure 5). The lowest survival rate was reported by the study by Has et al. (2014), which included 12 pregnancies with stage 1 TTTS. The largest study, by Wagner et al. (2009), included 20 pregnancies and reported a double survival rate of 65%.

Survival in Twin Pregnancies Complicated By Quintero Stage 1 TTTS Managed By Endoscopic Laser Photocoagulation as the First-Line Treatment

Three studies (162 pregnancies) reported the survival rates in pregnancies with stage 1 TTTS that were managed by laser as the first-line treatment (Chmait et al., 2011; Huber et al., 2006; Quintero et al., 2003). The pooled overall survival, double survival, and at least one survival were 84% [95% CI 79–88%], 77% [95% CI 71–83%] and 91% [95% CI 86–95%], respectively (Figure 6). The lowest survival rate was reported by the oldest of the four studies (Quintero et al., 2003), which included the smallest number of pregnancies (21 pregnancies with stage 1 TTTS) and reported a double survival rate of 67%. The largest study, by Chmait et al.

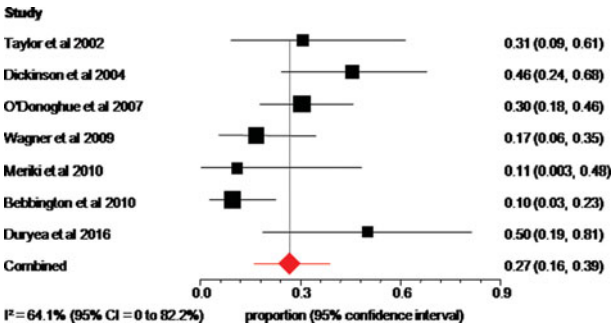

FIGURE 2

(Colour online) Pooled incidence (forest plot) of progression in twin pregnancies complicated by Quintero stage 1 twin-to-twin transfusion syndrome (TTTS). Each study is represented by a line. The box in the middle of the line represents the point effect estimate of this particular study. The midpoint of the box represents the point effect estimate, that is, the mean effect estimate for each study. The area of the box represents the weight given to the study. The diamond below the studies represents the overall estimate. The width of the line shows the confidence interval (CI) of the effect estimate of individual studies. The width of the diamond shows the CI for the overall effect estimate.
Note: *N* = total number in group, while *n* = number in group with the outcome. Heterogeneity (I^2) = diversity between studies.

(2011), included 112 pregnancies with stage 1 TTTS and reported a double survival rate of 80%.

Quality Assessment of the Included Studies

The quality of the studies is summarized in Figure 7. Among the studies included in this review, the title, abstract, study design, eligibility, data variables, data sources, assessment methods, explanation of the quantitative variables, and their analysis, summary of the key findings and the interpretation of the studies were appropriately described in 100%. On the other hand, explanation of study size (sample size calculation) was reported in none, and flow diagrams to describe the study population were rarely used. However, the background, objectives, study setting, recruitment period, and reporting number of outcome events were described in more than 90% of these studies. The statistical methods were adequately described in more than 80% of the studies. Efforts to address bias and acknowledging the limitations of the study were reported in approximately 50% of the studies (Figure 7).

Discussion

Summary of Findings

The findings of this meta-analysis suggest that the incidence of progression in stage 1 TTTS was 27%. The pooled overall survival was 79%, 77%, 68%, and 84% in stage 1 TTTS managed expectantly, by amnioreduction, laser if there is progression, and laser as first-line treatment, respectively. The

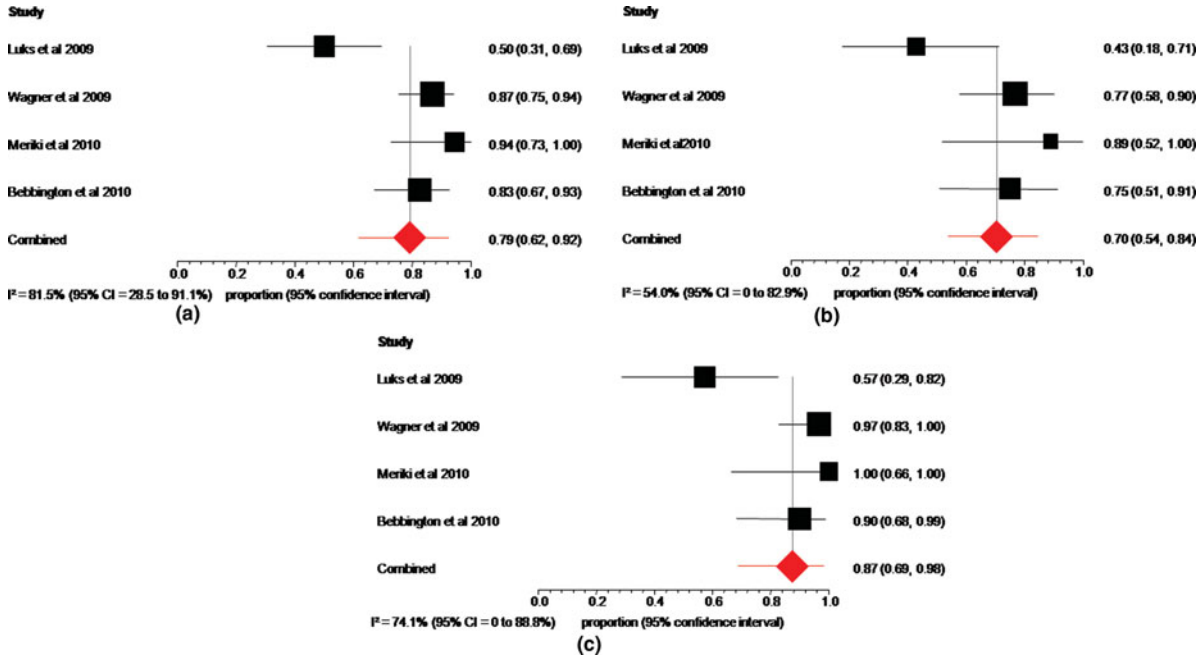

FIGURE 3

(Colour online) Pooled survival (forest plot) of twin pregnancies complicated by Quintero stage 1 twin-to-twin transfusion syndrome (TTTS) managed conservatively. The overall survival (a), double survival, (b) and at least one survival (c) are shown. Each study is represented by a line. The box in the middle of the line represents the point effect estimate of this particular study. The midpoint of the box represents the point effect estimate, that is, the mean effect estimate for each study. The area of the box represents the weight given to the study. The diamond below the studies represents the overall estimate. The width of the line shows the confidence interval (CI) of the effect estimate of individual studies. The width of the diamond shows the CI for the overall effect estimate.
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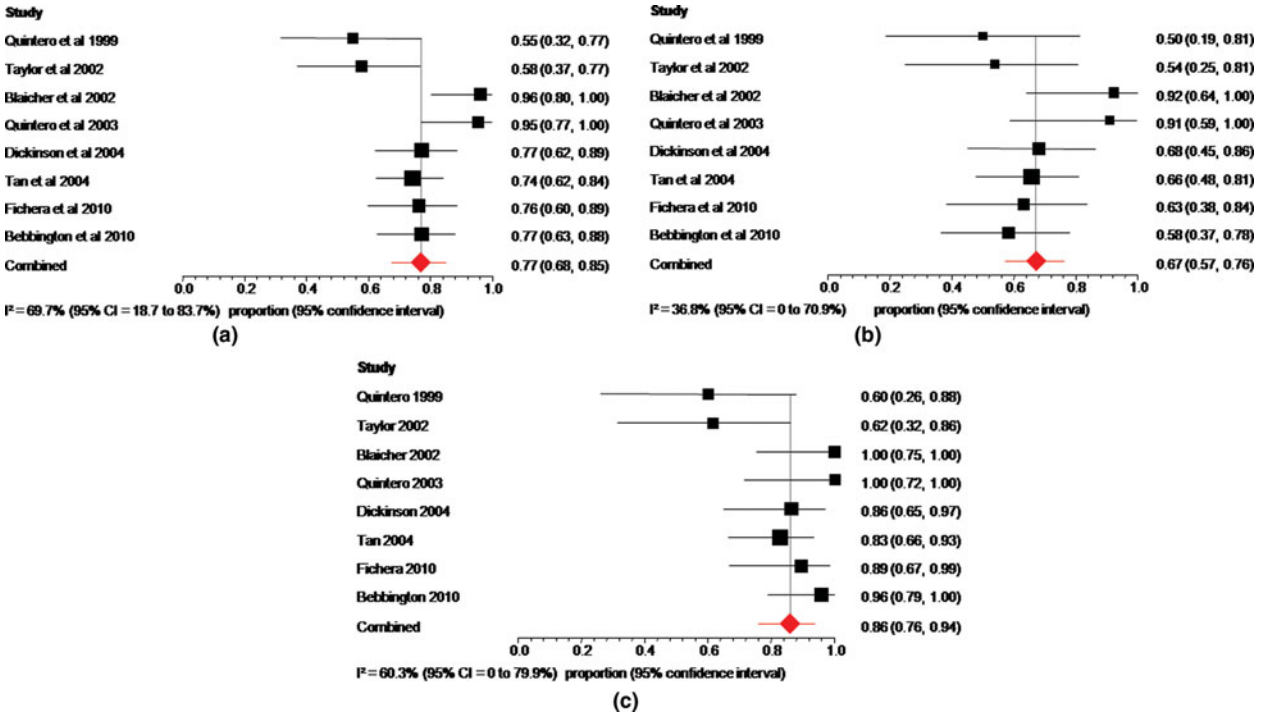

FIGURE 4

(Colour online) Pooled survival (forest plot) of twin pregnancies complicated by Quintero stage 1 twin-to-twin transfusion syndrome (TTTS) managed by amnioreduction. The overall survival (a), double survival (b), and at least 1 survival (c) are shown. Each study is represented by a line. The box in the middle of the line represents the point effect estimate of this particular study. The midpoint of the box represents the point effect estimate, that is, the mean effect estimate for each study. The area of the box represents the weight given to the study. The diamond below the studies represents the overall estimate. The width of the line shows the confidence interval (CI) of the effect estimate of individual studies. The width of the diamond shows the CI for the overall effect estimate.
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corresponding pooled double survival figures were 70%, 67%, 54%, and 77%, respectively. Lastly, the corresponding pooled at least one survival figures were 87%, 86%, 81%, and 91%, respectively.

Interpretation of the Findings

Stage 1 TTTS progresses to a higher stage or more severe polyhydramnios in approximately one quarter of the pregnancies. There is a considerable variation in the incidence of progression reported in the published studies. One potential explanation could be the variation of the criteria for defining progression across the studies. Most of the included studies defined progression as an increase in stage (from stage 1 to stage 2 or higher), so potentially have underestimated the risk of progression.

The survival rates in the various subgroups, according to the management of stage 1 TTTS, do not show marked variation, but suggest that laser surgery as a first-line treatment might be associated with better survival. However, these results should be interpreted with caution as they are derived from observational data with their inherent risk of bias. The survival rates associated with amnioreduction or laser as the management of cases that had progressed, are likely to be worse than those which did not progress, so were managed expectantly, or in those pregnancies where laser surgery was performed, as a first-line treatment.

It is generally accepted that TTTS diagnosed before 26 weeks of gestation is best treated by laser ablation as the evidence suggests that it leads to better outcomes compared with amnioreduction or septostomy (Roberts et al., 2014). However, where laser ablation expertise is not available, an acceptable alternative in pregnancies diagnosed after 26 weeks of gestation is amnioreduction (Roberts et al., 2014). But there is some evidence that laser ablation is still the best form of treatment for TTTS, even if diagnosed early (before 16 weeks) or late (after 26 weeks' gestation; Baud et al., 2013; Middeldorp et al., 2007).

Clinical and Research Implications of the Review Findings

In view of the risk of progression in approximately one quarter of stage 1 TTTS, these pregnancies require regular weekly monitoring looking for signs of deterioration. This monitoring should include ultrasound assessment of the fetal bladders, Dopplers, severity of polyhydramnios, and cervical length. There is no evidence to date supporting the use any ultrasound or biochemical markers to predict the risk of progression in these pregnancies. Furthermore, in

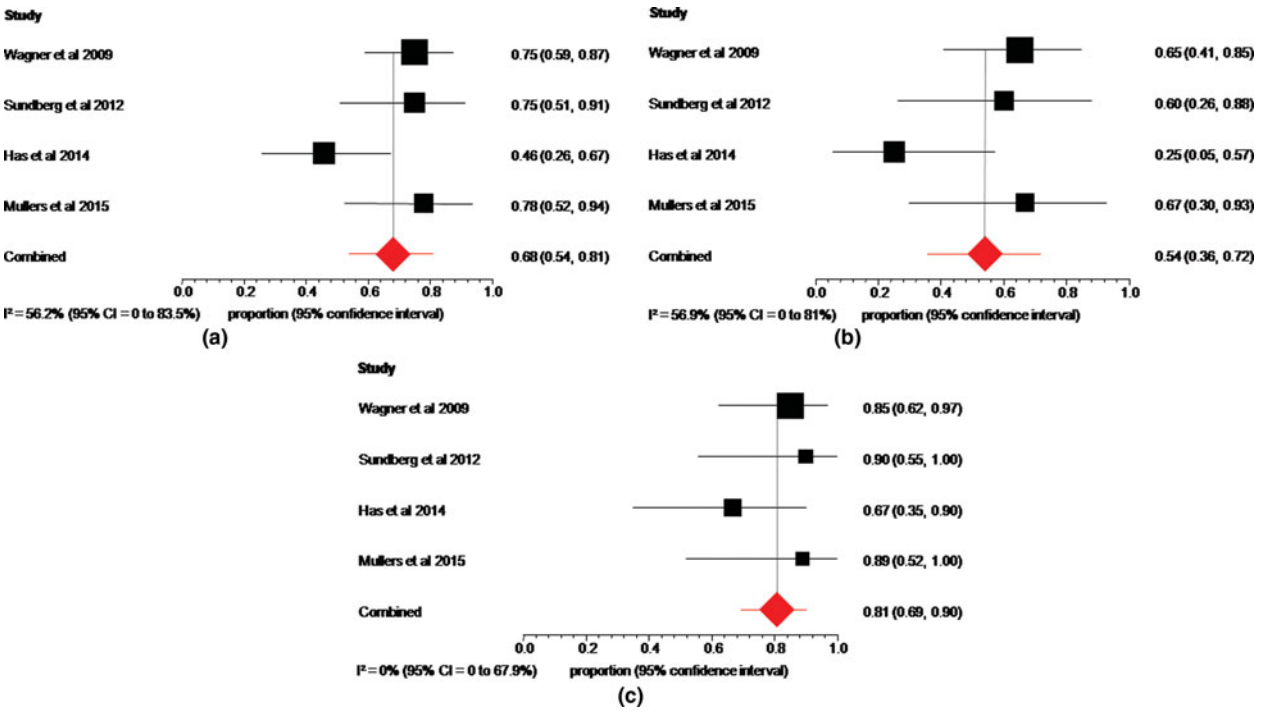

FIGURE 5

(Colour online) Pooled survival (forest plot) of twin pregnancies complicated by Quintero stage 1 twin-to-twin transfusion syndrome (TTTS) managed by endoscopic laser photocoagulation. The overall survival (a), double survival (b), and at least 1 survival (c) are shown. Each study is represented by a line. The box in the middle of the line represents the point effect estimate of this particular study. The midpoint of the box represents the point effect estimate, that is, the mean effect estimate for each study. The area of the box represents the weight given to the study. The diamond below the studies represents the overall estimate. The width of the line shows the confidence interval (CI) of the effect estimate of individual studies. The width of the diamond shows the CI for the overall effect estimate.

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view of the limited predictive ability of the Quintero staging system, management decisions should take into account other known risk factors associated with worse outcome, such as the gestational age at diagnosis and cervical length.

The results of this meta-analysis present evidence that the optimal initial management of stage 1 TTTS remains in equipoise. On one hand, some could argue that three quarters of these cases regress or remain stable, with a survival rate that is far better than that quoted for the untreated cases of severe TTTS (80% overall survival in the group with expectant management vs. 80–90% mortality). On the other hand, it is true that this survival rate might be over-optimistic, as it does not take into account those pregnancies that have progressed and required intervention, or ended in fetal demise, preterm birth and/or neurological impairment. In fact, postponing surgery could arguably increase the rates of spontaneous fetal demise and secondary neurological morbidity, as well as preterm premature rupture of the membranes and very preterm birth. The ongoing international randomized trial comparing the two management strategies, immediate percutaneous laser surgery versus conservative management, in stage 1 TTTS should provide a definitive answer to this question.

Strengths and Limitations of the Meta-Analysis

The strengths of this meta-analysis are the *a priori* designed protocol following the recommended guidelines for systematic reviews and meta-analysis of observational studies, the thorough literature search, the assessment of the quality of the included studies, the quantitative synthesis of evidence, and the relatively large number of included articles and pregnancies with stage 1 TTTS, which occurs in a minority of TTTS cases. The quality of the data available for meta-analysis limits the current study findings. Small retrospective observational studies and selection bias were the main drawbacks. This meta-analysis reported on the survival, rather than intact survival, in stage 1 TTTS. This reflects the limited reported data on intact survival in these pregnancies. When reported, expectant management seems to be associated with worse short- and long-term neurodevelopmental outcomes than those pregnancies treated with laser (Wagner et al., 2009). Moreover, the survival rates in these pregnancies are influenced by a number of risk factors, such as the gestational age at diagnosis as well as at treatment, birthweight discordance, type of inter-twin vascular anastomoses, and placental territory. Unfortunately, these variables are not reported in the majority of the published

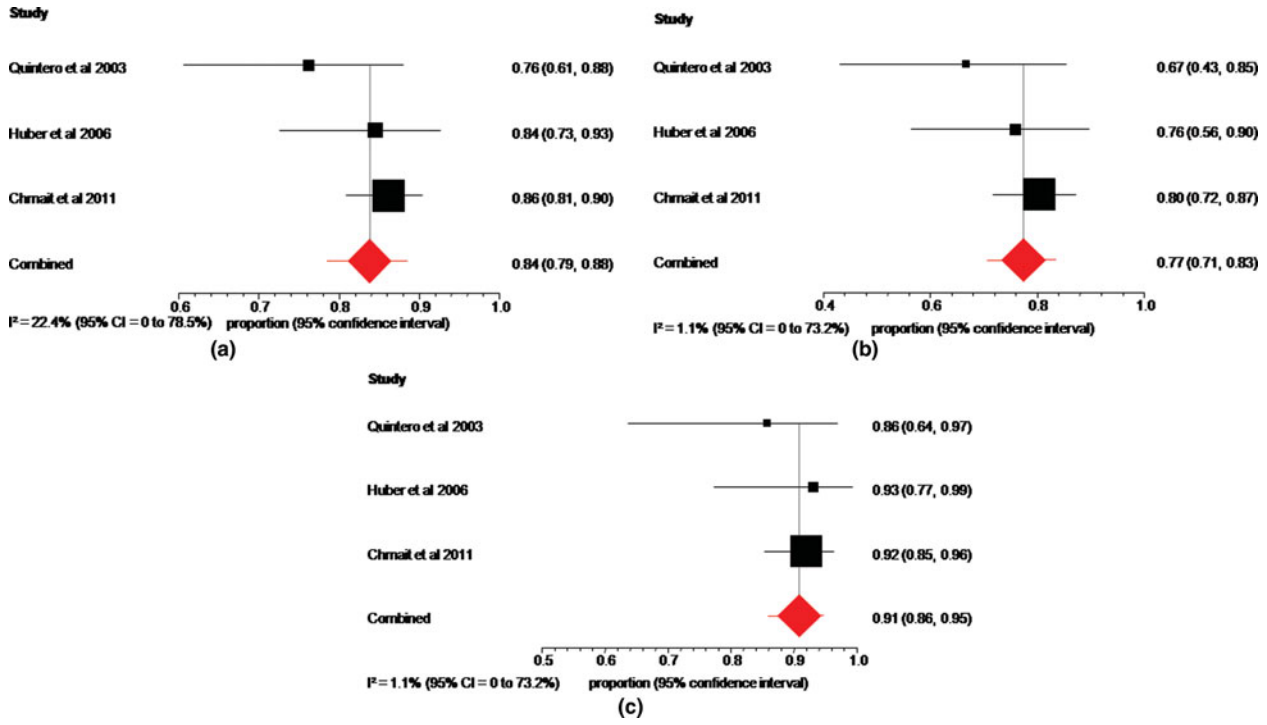

FIGURE 6

(Colour online) Pooled survival (forest plot) of twin pregnancies complicated by Quintero stage 1 twin-to-twin transfusion syndrome (TTTS) managed by endoscopic laser photocoagulation as first line. The overall survival (a), double survival (b), and at least 1 survival (c) are shown. Each study is represented by a line. The box in the middle of the line represents the point effect estimate of this particular study. The midpoint of the box represents the point effect estimate, that is, the mean effect estimate for each study. The area of the box represents the weight given to the study. The diamond below the studies represents the overall estimate. The width of the line shows the confidence interval (CI) of the effect estimate of individual studies. The width of the diamond shows the CI for the overall effect estimate.

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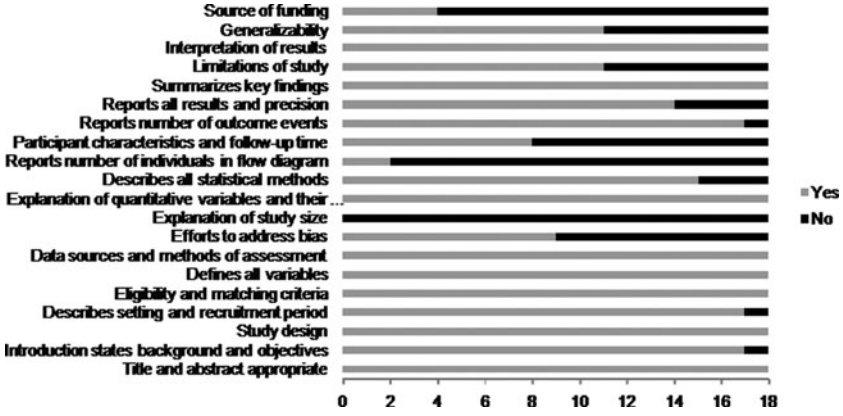

FIGURE 7

Quality criteria of the included articles, as assessed using the Strengthening the Reporting of Observational Studies in Epidemiology checklist.

studies, and furthermore, such analysis would require individual participant data (IPD) instead of aggregate data meta-analysis, in order to adjust for these potential confounders.

Large, multicenter randomized controlled trials are required to improve the robustness of the results, and target intact survival that takes into account the neurodevelopmental outcome of the infants. Prospective national collection of data on twin pregnancies with stage 1 TTTS, their management and outcomes would be a valuable source while waiting for the results of the RCT.

Conclusion

Progression occurred in 27% of pregnancies with stage 1 TTTS. The overall survival was 79%, 77%, 68%, and 84% in stage 1 TTTS managed expectantly, by amnioreduction, laser surgery if there is progression, and laser as first-line treatment, respectively. The optimal initial management of stage 1 TTTS remains in equipoise. The ongoing randomized trial comparing immediate laser surgery versus conservative management in stage 1 TTTS should provide a definitive answer to this question. Meanwhile, prospective national collection of data on these pregnancies, their management and outcomes are needed.

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Supplementary Material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/thg.2016.33.

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