Perinatal outcomes of pregnancies complicated by twin anemia–polycythemia sequence: a systematic review and meta-analysis

V. Giorgione[1,2,3], F. D'Antonio[4], A. Manji[2], K. Reed[5], A. Khalil[1,2,3]

1. Twin Trust Centre for Research and Clinical Excellence, St George's University Hospitals NHS Foundation Trust, Blackshaw Road, London SW17 0RE, UK
2. Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, Cranmer Terrace, London SW17 0RE, UK.
3. Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust, Blackshaw Road, London SW17 0RE, UK.
4. Center for Fetal Care and High-risk Pregnancy, University of Chieti, Italy
5. Twins Trust

Corresponding author:
Professor Asma Khalil
Fetal Medicine Unit,
St George's University of London,
London SW17 0RE
E-mail: akhalil@sgul.ac.uk; asmakhalil79@googlemail.com

Keywords: Twin anemia polycythemia sequence, TAPS, Twins, Ultrasound
Short title: Outcomes in Twin Anemia Polycythemia Sequence

What are the novel findings of this work?
Spontaneous TAPS may have a better prognosis than post-Laser TAPS. A more favorable outcome in terms of mortality and morbidity was observed in the group of TAPS treated by laser

What are the clinical implications of this work?
The present meta-analysis provides pooled estimates of perinatal mortality, morbidity, and preterm birth in twin pregnancies complicated by TAPS, stratified by the type of TAPS and according to different management options

ABSTRACT

Objective: To report the perinatal outcome in monochorionic diamniotic (MC) twin pregnancies complicated by twin anemia polycythemia sequence (TAPS).

Methods: Medline, Embase and Cochrane Library databases were searched. Inclusion criteria were non-anomalous MCDA twin pregnancies with a diagnosis of TAPS.
The primary outcome was mortality; the secondary outcomes were morbidity and preterm birth (PTB). All these outcomes were stratified according to the type of TAPS (spontaneous or following laser treatment) and management option adopted (expectant, laser, intra-uterine transfusion [IUT] and selective reduction [SR]). Random effect meta-analyses of proportions were used to analyze the data.

Results:

Spontaneous and post-laser TAPS (506 pregnancies): IUD occurred in 5.32 (95% CI, 3.6–7.1) of spontaneous and in 10.2% (95% CI, 7.4-13.3) of post-laser TAPS, while the corresponding figures for NND were 4.0% (95% CI, 2.6-5.7) and 9.2% (95% CI, 6.6-12.3). Severe neonatal morbidity occurred in 29.3% (95% CI, 25.6-33.1) of twins after spontaneous and 33.3% (95% CI, 17.4-51.8) after post-laser TAPS, while the corresponding figures for severe neurological morbidity were 4.0% (95% CI, 3.5-5.7) and 11.1% (95% CI, 6.2-17.2) respectively. PTB complicated 86.3% (95% CI, 77.2- 93.3) of pregnancies with spontaneous and all cases with post-laser TAPS (95% CI, 84.3-100). Iatrogenic PTB was more frequent than the spontaneous PTB in both groups.

Outcome according to different management options (418 pregnancies): IUD occurred in 9.8% (95% CI, 4.3-17.1) of pregnancies managed expectantly and in 13.1% (95% CI, 9.2-17.6), 12.1% (95% CI, 7.7-17.3) and 7.6% (95% CI, 1.3-18.5) of those treated with laser, IUT and SR, respectively. Severe neonatal morbidity affected 27.3% (95% CI, 13.6-43.6) twins in the expectant management group, 28.7% (95% CI, 22.7-35.1) in the laser surgery group, 38.2% (95% CI 18.3-60.5) in the IUT group and 23.3% (95% CI 10.5-39.2) in the SR group. PTB complicated 80.4% (95% CI, 59.8-94.8), 73.4% (95% CI, 48.1- 92.3), 100% (95% CI, 76.5- 100) and 100% (95% CI, 39.8-100) of pregnancies after expectant management, laser, IUT and SR, respectively.

Conclusions: The present meta-analysis provides pooled estimates of perinatal mortality, morbidity and preterm birth in twin pregnancies complicated by TAPS, stratified by the type of TAPS and according to different management options. Although a direct comparison could not be performed, the results from this systematic review suggest that spontaneous TAPS may have a better prognosis than post-Laser TAPS. No differences in terms of mortality and morbidity were observed comparing different management options for TAPS although these findings should be interpreted with caution in view of the limitations of the original studies. An individualized prenatal management, taking into account the severity of TAPS and gestational age, is currently the recommended strategy.

INTRODUCTION

Monochorionic diamniotic (MCDA) twin pregnancies are at higher risk of perinatal mortality and morbidity compared to dichorionic ones, mainly as the consequence of twin to twin transfusion syndrome (TTTS), selective FGR and Twin anemia polycythemia sequence (TAPS). TAPS is a complication of monochorionic twin pregnancies and occurs when small placental anastomoses (<1 mm) lead to a chronic and slow inter-twin transfusion without a volume disparity of amniotic fluid between the donor and the recipient[1]. While significantly discordant hemoglobin levels and reticulocyte counts between the twins are the postnatal diagnostic criteria of TAPS, prenatal diagnosis of TAPS is based on Doppler ultrasound abnormalities without signs of polyhydramnios in the recipient and oligohydramnios in the donor. The fetal middle cerebral artery peak systolic velocity (MCA-PSV) increases in the donor twin (>1.5 Multiples of the Median [MoM]) suggesting fetal anemia, and it decreases (<1.0 MoM) in the recipient twin consistent with polycythemia[2]. The antenatal staging system of TAPS, which can be useful to guide intervention, includes different degrees of fetal hemodynamic impairment assessed by Doppler studies until the demise of one or both fetuses[2, 3].

TAPS may occur spontaneously in 3-5% of monochorionic twin pregnancies and in 2-16% after twin-to twin transfusion syndrome (TTTS) due to residual anastomoses[4-6]. Indeed, the equatorial dichorionization that is performed during Solomon technique showed a 5-fold reduction of post-Laser TAPS compared to the selective technique[7, 8]. The knowledge of TAPS pathogenesis has improved through the use of color dye injection of the placenta[9]. Conversely, there is scarce evidence about its natural history or perinatal outcomes. Furthermore, the best antenatal management, whether expectant, intrauterine fetal Laser therapy, intrauterine transfusion (IUT), selective reduction (SR) or early delivery is currently unknown[10]. The perinatal outcomes may range from an isolated but significant difference in hemoglobin levels at birth to intrauterine demise, neonatal death or severe neonatal morbidity[11, 12]. Moreover, TAPS has been associated with cerebral injury and neurodevelopment impairment[13-16]. However, it is also possible that the resulting perinatal mortality and morbidity are related to prematurity.

The aim of this systematic review was to report the outcome of MCDA twin pregnancies complicated by TAPS according to the type of the disease and management option adopted.

METHODS

Eligibility criteria, information sources and search strategy

This review was performed according to a priori designed protocol recommended for systematic reviews and meta-analysis[17]. Medline, Embase and Cochrane Library databases were searched electronically in May 2020, utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "twin pregnancies" and "anemia polycythemia sequence" (Supplementary Table 1). The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA and MOOSE guidelines were followed[18-20]. The study was registered with the PROSPERO database (Registration number: CRD42019157820).

Study selection

Inclusion criteria were non-anomalous MCDA twin pregnancies with a prenatal diagnosis of TAPS, defined as a MCA-PSV >1.5 MoM in one twin and <1 MoM in the second twin with normal amniotic fluid volumes, or a postnatal diagnosis of TAPS, defined as the presence of inter-twin hemoglobin difference ≥8.0g/dL and at least one of the following: small residual anastomoses at the placental surface after color dye injection and/or reticulocyte count ratio (reticulocyte donor/reticulocyte recipient) ≥1.7[2]. Exclusion criteria were studies with incomplete on type of TAPS or on their management and those including co-existence of TAPS and TTTS.

The primary outcome was mortality, including intra-uterine death (IUD) of either twin, single IUD, double IUD, neonatal death (NND) defined as the death of either twin up to 28 days of life, perinatal death (PND), defined as IUD and NND, live-birth and survival of at least one twin (up to 28 days).

The secondary outcomes were:

- Severe neurological morbidity, including intraventricular hemorrhage ≥ stage 3, ventricular dilatation including post-hemorrhagic ventricular dilatation, cystic periventricular leukomalacia ≥ grade 2, porencephalic or parenchymal cysts, arterial infarction or other severe cerebral lesions associated with adverse outcome.
- Respiratory morbidity, including respiratory distress syndrome (RDS) requiring mechanical ventilation and surfactant, pulmonary hypertension or bronchopulmonary dysplasia
- Necrotizing enterocolitis (NEC)
- Retinopathy of prematurity (ROP)
- Patent ductus arteriosus (PDA)
- Severe neonatal morbidity including at least one of the following: RDS requiring mechanical ventilation and surfactant, PDA requiring treatment, NEC ≥ stage 2, ROP ≥ stage 3, amniotic band syndrome, ischemic limb injury or severe neurological morbidity.
- Intact survival, defined as survival free from severe neurological complications
- Preterm birth (PTB) <37, <34, <32 and <28 weeks of gestation. We also performed a sub-group analysis considering spontaneous and iatrogenic PTB separately

All these outcomes were stratified according to the type of TAPS (spontaneous or following Laser treatment) and according to the management option adopted (expectant, Laser, IUT and SR) only when TAPS was diagnosed prenatally.

Data extraction

Two authors (VG, AM) 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. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author (FD). If more than one study was published on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. Studies reported TAPS cases from the same centers included in the TAPS registry were excluded in order to avoid including overlapping data[21]. 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.

Assessment of risk of bias

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 outcome of interest. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at the start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up. According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability[22].

For case reports and case series, quality assessment of the included studies was assessed using the methodological quality and synthesis of case series and case reports described by Murad et al.[23]. According to this tool, each study is judged on four broad perspectives: the selection of the study groups, the ascertainment and the causality of the outcome observed and the reporting of the case.

Data Analysis

Random-effect meta-analyses of proportions were used to analyze the data. 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 heterogeneity is observed while values >50% are associated with substantial heterogeneity. A random effects model was ultimately used for all meta-analyses because of heterogeneity identified between studies. Potential publication bias was assessed using Egger's test and the creation of funnel plots for visual inspection and were carried out on exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than ten, as the tests then lack power to detect real asymmetry. StatsDirect 3.0.171 (StatsDirect Ltd, Altrincham) and RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) statistical software was used to analyse the data.

RESULTS

General characteristics

265 articles were identified, 89 were assessed with respect to their eligibility for inclusion and 40 studies were included in the systematic review [6, 14, 21, 24-60](Table 1, Figure 1). 38 studies included 506 pregnancies affected by 308 (60.9%) spontaneous and 198 (39.1%) post-Laser TAPS and 21 studies reported outcomes according to the management in 418 TAPS diagnosed prenatally. In the latter group, 178 (42.6%) TAPS were managed expectantly, 120 (28.7%) TAPS were treated by Laser, 86 (20.6%) TAPS by IUT and 34 (8.1%) cases by SR. The proportions of spontaneous and post-Laser TAP were 58% and 42% in the expectant management group, 76 and 24% in the laser group and 34% and 66% in the IUT group.

The results of the quality assessment of the included studies using Newcastle-Ottawa Scale (NOS) are presented in Table 2. Most of the included studies showed an overall acceptable score regarding selection and comparability of the study groups, as well as for ascertainment of the outcome of interest. The main weaknesses of the studies were their retrospective design, small sample size and heterogeneity in timing of diagnosis and in prenatal management of TAPS.

Synthesis of results

Mortality

Spontaneous and post-Laser TAPS

IUD occurred in 5.2% (28/612, 95% CI, 3.6–7.1) of spontaneous and in 10.2% (37/392, 95% CI, 7.4-13.3) of post-Laser TAPS, while the corresponding figures for NND were 4.0% (19/610, 95% CI, 2.6-5.7) and 9.2% (35/392, 95% CI, 6.6-12.3). Cumulative PND rate was 8.3% (47/612, 95% CI, 6.3-10.6) among pregnancies with spontaneous and 19.0% (35/392, 95% CI, 11.7-27.6) among those with post-Laser TAPS (Table 3, Figure 1).

In the sub-group of twin pregnancies affected by spontaneous TAPS, the livebirth rate was 90.1% (554/612, 95% CI, 83.5-94.1) with a survival of at least one twin of 52.0% (95% CI, 43.2-60.5) and of both twins of 49.2 (95% CI, 40.6-57.7), while the corresponding figures for pregnancies affected by post-Laser TAPS were 83.7% (330/392, 95% CI, 80.0-87.2) , 45.6% (29/64, 95% CI, 34.2-57.2) and 37.2% (23/64, 95% CI, 23.6-48.7) respectively.

Mortality according to different management options

IUD occurred in 9.8% (28/354, 95% CI, 4.3-17.1) of pregnancies managed expectantly and in 13.1% (30/240, 95% CI, 9.2-17.6), 12.1% (19/172, 95% CI, 7.7-17.3) and 7.6% (2/34, 95% CI, 1.3-18.5) of those treated with Laser, IUT and SR respectively (Table 4, Figure 4). There was no case of double IUDs in the group of pregnancies treated with Laser surgery or IUT, while 8.5% (2/42, 95% CI, 2.3-17.9) of pregnancies managed expectantly experienced a double IUD.

The livebirth rate was 92.2% (328/354, 95% CI, 89.1- 94.9), 86.9% (210/240, 95% CI, 82.4-90.8), 87.9% (153/172, 95% CI, 82.7-92.3) and 92.4% (95% CI, 81.5- 98.1) in expectant management, Laser surgery, IUT and SR group, respectively.

Morbidity

Spontaneous versus post-Laser TAPS

Severe neonatal morbidity occurred in 29.3% (162/546, 95% CI, 25.6-33.1) of twins after spontaneous and 33.3% (117/309, 95% CI, 17.4-51.8) after post-Laser TAPS (Table 5, Figure 2). Severe neurological morbidity affected 4.0% (17/546, 95% CI, 3.5-5.7) of twins with spontaneous compared to 11.1% (33/309, 95% CI, 6.2-17.2) with post-Laser TAPS, while respiratory morbidity 24.8% (136/546, 95% CI, 21.3-28.5) of twins with spontaneous and 23.8%, (95% CI, 9.1-42.8) with post-Laser TAPS. Similar figures in terms of NEC, PDA and ROP were reported in the two types of TAPS.

Finally, survival free from neurological impairment was observed in 96.0% (529/546, 95% CI, 94.3-97.5) of twins with spontaneous and in 80.2% (273/309, 95% CI, 64.5-92.2) of those with post-Laser TAPS.

Morbidity according to different management options

Severe neonatal morbidity affected 27.3% (71/296, 95% CI, 13.6-43.6) twins in the expectant management group, 28.7% (57/198, 95% CI, 22.7-35.1) in the Laser surgery group, 38.2% (64/151, 95% CI 18.3-60.5) in the IUT group and 23.3% (7/31, 95% CI 10.5-39.2) in the SR group (Table 6, Figure 5).

Severe neurological morbidity was observed in 7.8% (22/296, 95% CI, 5.1-11.1) twin managed expectantly, 4.0% (6/168, 95% CI, 1.7-7.1) after Laser treatment and 9.8% (14/151, 95% CI, 5.7-15.0) receiving IUT. 92.2% (274/296, 95% CI 88.9-94.9) twins managed expectantly survived free from neurological complications while the corresponding figures for those treated with Laser, IUT and SR were 95.5% (190/198, 95% CI 92.3-97.9), 81.7%, (134/151, 95% CI 60.9-95.7) and 100% (31/31, 95% CI 91.1-100.0) respectively.

Preterm birth

Spontaneous versus post-Laser TAPS

The overall occurrence of PTB in pregnancies complicated by spontaneous TAPS was 86.8% (51/57, 95% CI, 77.2- 93.3) with 59.8% (28/46, 95% CI, 47.0-72.0) delivered <34, 30.2% (12/46, 95% CI, 18.0-44.0) <32 and no case <28 weeks of gestation respectively (Table 7, Figure 3). All cases of post-Laser TAPS delivered preterm, with 79.5% (27/33, 95% CI, 65.6-90.5) <34, 58.8% (20/33, 95% CI, 39.9-76.4) <32, and 21.8% (6/33, 95% CI, 10.4-35.9) <28 weeks of gestation. Iatrogenic PTB was more frequent than the spontaneous PTB (spontaneous TAPS: 61.2%, 95% CI, 42.1-78.08 vs 32.3%, 95% CI, 17.1-49.8; post-Laser TAPS: 79.4%, 95% CI, 58.9-94.1 vs 20.6%, 95% CI, 5.9-41.1).

PTB according to different management options

Overall PTB complicated 80.4% (16/20, 95% CI, 59.8-94.8), 73.4% (8/10, 95% CI, 48.1-92.3), 100% (16/16, 95% CI, 76.5- 100) and 100% (4/4, 95% CI, 39.0-100) of pregnancies after expectant management, Laser, IUT and SR, respectively (Table 8, Figure 6). PTB <34 was 68.3% (14/20, 95% CI, 49.0-84.9) in expectant management group, 50.9% (5/10, 95% CI, 25.8-75.8) in Laser group, 81.1% (14/16, 95% CI, 61.5-94.8) in IUT group and 75.0% (3/4, 95% CI, 19.4-99.4) in SR group. The pooled proportions of PTB <32 and <28 weeks in IUT group were 76.2% (13/16, 95% CI, 55.7-91.8) and 19.9% (2/16, 95% CI, 3.7-44.7), respectively, and they were higher than those in the expectant management and Laser groups. Whereas iatrogenic PTB was more frequent than spontaneous PTB in expectant management (82.5%, 95% CI, 61.8-96.2 vs 17.5%, 95% CI, 3.8-38.2) and IUT groups (100%, 95% CI, 58.1-100 vs 27.3%, 95% CI, 18.0-37.6), an opposite trend was showed in the Laser group (30.3%, 95% CI, 8.4-59.3 vs 56.0%, 95% CI, 47.0-64.9).

DISCUSSION

Summary of the main findings

The findings from this systematic review suggest that the risk of perinatal mortality and severe neurological morbidity is relatively higher in pregnancies complicated by post-Laser compared to spontaneous TAPS, although a direct comparison could not be performed in view of the original study design. PND occurred in 8.3% after spontaneous and in 19.0% after post-Laser TAPS respectively. Likewise, severe neurological morbidity was higher in post-Laser (11.1%) compared to spontaneous TAPS (4.0%).
Conversely, the small number of included cases when considering the different management option did not allow us to extrapolate an objective evidence on the optimal type of management when facing with TAPS.

Comparison with existing literature, strengths and limitations

This is to date the largest meta-analysis reporting perinatal mortality and morbidity of pregnancies complicated by TAPS according to the type of the disease and management option adopted. Nevertheless, the small size of the studies, their retrospective design and the heterogeneity in management are the main limitations of this review. In particular, it was not possible to stratify the results in each group of management option according to the type of TAPS.
While the overall neonatal mortality is similar to uncomplicated monochorionic twin pregnancies[61], differences in perinatal mortality between post-Laser and spontaneous TAPS have yet to be established[21, 24, 25, 36, 40, 49, 62]. In a previous review of Rossi et al., the overall survival was 86% in 17 pregnancies with isolated TAPS, and 79% in 11 cases with TAPS after Laser for TTTS without reaching a statistical significance. However, the latter group was treated in utero more often and required postnatal procedures less frequently than the spontaneous group[63]. Small size of the included studies, their retrospective non-randomized design and dissimilarity in gestational age at presentation and prenatal management of pregnancies complicated by TAPS represent the major limitations of the present review. Furthermore, it was not possible to stratify the analysis according to ultrasound staging of the disease and data on long -term outcomes were reported only in a small minority of included cases, thus not allowing a comprehensive estimation on the long-term sequelae of this disease. The recent results of a large international registry showed high rates of perinatal mortality and severe neonatal morbidity in spontaneous TAPS, post-Laser TAPS and in each management group (expectant management, Laser surgery, IUT, delivery and SR) highlighting a substantial heterogeneity of the condition and of its management undertaken by 17 fetal therapy centers[21, 24, 25].

Approximately 10% of neonates born after post-Laser TAPS experience severe adverse neurological outcome[25, 36, 42, 64]. Slaghekke and colleagues have reported that in those babies, long-term neurodevelopment impairment (NDI) is frequent (9%), which was similar in the donors and recipients; however, it was not higher than the survivors who do not develop TAPS after Laser[16]. Twins born after a diagnosis of spontaneous TAPS can suffer as well from severe neurological pathology, but apparently less frequently than post-Laser TAPS[13, 14, 24, 40, 65]. Tollenaar et al. have evaluated the long-term NDI in spontaneous TAPS survivors and reported its incidence to be 31% and more frequent in the donor than in the recipient. Similarly, only donors showed bilateral deafness in 15% of cases. They have identified gestational age at birth and severe anemia as risk factors for neurodevelopment impairment. As the small sample size and variety of tests used for neurodevelopment evaluation limit the interpretation of these data, larger studies are necessary to investigate the long-term neurodevelopment of twins after TAPS[15].

The results of the present study demonstrated that both types of TAPS presented an increased risk of iatrogenic preterm delivery, in particular pregnancies affected by post-Laser TAPS exhibited a more severe prematurity. This might be caused by a more frequent prenatal diagnosis of TAPS, and therefore, a more frequent surveillance and intervention in monochorionic twin pregnancies undergoing Laser for TTTS. Conversely, it is likely that cases with spontaneous TAPS that were diagnosed postnatally were prenatally treated as "uncomplicated" MCDA and, therefore, induced later in pregnancy. Moreover, it is well-known that the Laser surgery itself increases prematurity in monochorionic twin pregnancies[66, 67].

A recent systematic review on 105 cases of TAPS underwent different intrauterine interventions showed no mortality and morbidity differences among expectant management, Laser and IUT[10]. However, these authors showed that adverse perinatal outcomes were significantly less in Laser-treated and IUT managed TAPS cases when compared to expectantly managed TAPS. Similarly, comparable results in terms of severe neonatal morbidity were found among different management options by a large international study. However, the authors showed that the prevalence of postnatal TAPS and the need for hematological treatment were significantly lower in the Laser group than in the other management group and, thus, they speculated a key role of the Laser procedure in the treatment of TAPS[21]. Although these findings should be interpreted with caution in view of the limitations of the original studies, our findings did not demonstrate marked differences in terms of mortality and morbidity of TAPS managed by different approaches.

Clinical and research implications

The natural history of TAPS with different onset could be useful in order to offer an accurate prenatal counselling, to define an appropriate monitoring and to guide the optimal individualized management. Firstly, the high perinatal mortality of post-Laser TAPS should be considered carefully during prenatal counselling. Moreover, such high perinatal mortality must be counteracted by a strict ultrasound monitoring of these complicated pregnancies, particularly if TAPS develops after intrauterine Laser surgery for TTTS. This is consistent with the recent update of the National Institute for Health and Care Excellence (NICE) guidance on twin and multiple pregnancy where twin pregnancies complicated by TTTS and treated by Laser surgery should have ultrasound monitoring for the development of TAPS using MCA PSV[68]. While a stable and chronic clinical balance between anemic and polycythemic twins can be managed conservatively, any sudden worsening of fetal hemodynamic or cardiac impairment should trigger an active prenatal fetal intervention. The exact nature of this fetal intervention will vary according to the gestational age, the severity of TAPS and the co-existing of TTTS and/or fetal growth restriction. The proportions of twins with co-existing severe and moderate fetal growth restriction account for 23% and 44%, respectively, in post-Laser TAPS with similar risk in the donors and recipients[25]. In spontaneous TAPS, on the other hand, they are reported to be 29% and 49%, respectively, with a significant predominance of donors[24]. This might be due to the fact that spontaneous TAPS might be a chronic and enduring condition where the role of donor and recipient do not change between twins throughout the pregnancy. Instead, in post-Laser onset, it is less likely that TAPS donors become growth restricted because they are often former TTTS recipients, who are usually larger than TTTS donors[6].

The reluctance of adoption of routine antenatal monitoring for TAPS, as evidence in the American College of Obstetricians and Gynecologists (ACOG) and NICE guidelines[68, 69], could be explained by the scarce data on the natural history, validation of the antenatal diagnostic criteria, perinatal outcomes and best management strategy. Over the last few years, researchers have been trying to address some of these uncertainties, including a Delphi consensus on the antenatal diagnostic criteria[70], validation study of these criteria[71] and a multicenter international registry reporting on the perinatal outcomes of twin pregnancies complicated by TAPS according to the onset, severity and management options[21, 24, 25].

Conclusions

Perinatal mortality and morbidity are relatively higher in post-Laser compared to spontaneous TAPS, although a direct comparison between these two entities could not be performed. The findings from systematic review highlight the need of appropriately designed and powered randomized controlled trials aimed at evaluating the impact of the different management options on perinatal mortality and morbidity of twin pregnancies complicated by TAPS.

Acknowledgement

Veronica Giorgione has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 765274.

REFERENCES

1. Lopriore E, Sueters M, Middeldorp JM, Klumper F, Oepkes D, Vandenbussche FP. Twin pregnancies with two separate placental masses can still be monochorionic and have vascular anastomoses. *Am J Obstet Gynecol* 2006; **194**: 804-808.
2. Tollenaar LS, Slaghekke F, Middeldorp JM, Klumper FJ, Haak MC, Oepkes D, Lopriore E. Twin Anemia Polycythemia Sequence: Current Views on Pathogenesis, Diagnostic Criteria, Perinatal Management, and Outcome. *Twin Res Hum Genet* 2016; **19**: 222-233.
3. Slaghekke F, Kist WJ, Oepkes D, Pasman SA, Middeldorp JM, Klumper FJ, Walther FJ, Vandenbussche FP, Lopriore E. Twin anemia-polycythemia sequence: diagnostic criteria, classification, perinatal management and outcome. *Fetal Diagn Ther* 2010; **27**: 181-190.
4. Lewi L, Jani J, Blickstein I, Huber A, Gucciardo L, Van Mieghem T, Done E, Boes AS, Hecher K, Gratacos E, Lewi P, Deprest J. The outcome of monochorionic diamniotic twin gestations in the era of invasive fetal therapy: a prospective cohort study. *Am J Obstet Gynecol* 2008; **199**: 514 e511-518.
5. Lopriore E, Slaghekke F, Middeldorp JM, Klumper FJ, Oepkes D, Vandenbussche FP. Residual anastomoses in twin-to-twin transfusion syndrome treated with selective fetoscopic laser surgery: localization, size, and consequences. *Am J Obstet Gynecol* 2009; **201**: 66 e61-64.
6. Robyr R, Lewi L, Salomon LJ, Yamamoto M, Bernard JP, Deprest J, Ville Y. Prevalence and management of late fetal complications following successful selective laser coagulation of chorionic plate anastomoses in twin-to-twin transfusion syndrome. *Am J Obstet Gynecol* 2006; **194**: 796-803.
7. Baschat AA, Barber J, Pedersen N, Turan OM, Harman CR. Outcome after fetoscopic selective laser ablation of placental anastomoses vs equatorial laser dichorionization for the treatment of twin-to-twin transfusion syndrome. *Am J Obstet Gynecol* 2013; **209**: 234 e231-238.
8. Slaghekke F, Lopriore E, Lewi L, Middeldorp JM, van Zwet EW, Weingertner AS, Klumper FJ, DeKoninck P, Devlieger R, Kilby MD, Rustico MA, Deprest J, Favre R, Oepkes D. Fetoscopic laser coagulation of the vascular equator versus selective coagulation for twin-to-twin transfusion syndrome: an open-label randomised controlled trial. *Lancet* 2014; **383**: 2144-2151.
9. Lewi L, Deprest J, Hecher K. The vascular anastomoses in monochorionic twin pregnancies and their clinical consequences. *Am J Obstet Gynecol* 2013; **208**: 19-30.
10. Hill KM, Masoudian P, Fung-Kee-Fung K, El Demellawy D. Intrauterine Interventions for the Treatment of Twin Anemia-Polycythemia Sequence: A Systematic Review. *J Obstet Gynaecol Can* 2019; **41**: 981-991.
11. Genova L, Slaghekke F, Klumper FJ, Middeldorp JM, Steggerda SJ, Oepkes D, Lopriore E. Management of twin anemia-polycythemia sequence using intrauterine blood transfusion for the donor and partial exchange transfusion for the recipient. *Fetal Diagn Ther* 2013; **34**: 121-126.
12. Lopriore E, Hecher K, Vandenbussche FP, van den Wijngaard JP, Klumper FJ, Oepkes D. Fetoscopic laser treatment of twin-to-twin transfusion syndrome followed by severe twin anemia-polycythemia sequence with spontaneous resolution. *Am J Obstet Gynecol* 2008; **198**: e4-7.
13. Lopriore E, Slaghekke F, Kersbergen KJ, de Vries LS, Drogtrop AP, Middeldorp JM, Oepkes D, Benders MJ. Severe cerebral injury in a recipient with twin anemia-polycythemia sequence. *Ultrasound Obstet Gynecol* 2013; **41**: 702-706.

14. Luminoso D, Figueira CO, Marins M, Peralta CF. Fetal brain lesion associated with spontaneous twin anemia-polycythemia sequence. *Ultrasound Obstet Gynecol* 2013; **42**: 721-722.
15. Tollenaar LSA, Lopriore E, Slaghekke F, Oepkes D, Middeldorp JM, Haak MC, Klumper F, Tan R, Rijken M, Van Klink JMM. High risk of long-term impairment in donor twins with spontaneous twin anemia polycythemia sequence. *Ultrasound Obstet Gynecol* 2019. DOI: 10.1002/uog.20846.
16. Slaghekke F, van Klink JMM, Koopman HM, Middeldorp JM, Oepkes D, Lopriore E. Neurodevelopmental outcome in twin anemia-polycythemia sequence after laser surgery for twin-twin transfusion syndrome. *Ultrasound Obst Gyn* 2014; **44**: 316-321.
17. Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC. How to write a Cochrane systematic review. *Nephrology (Carlton)* 2010; **15**: 617-624.
18. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339**: b2535.
19. Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, Moher D, Vohra S, Group PR. PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ* 2016; **352**: i157.
20. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008-2012.
21. Tollenaar LSA, Slaghekke F, Lewi L, Ville Y, Lanna M, Weingertner A, Ryan G, Arevalo S, Khalil A, Brock CO, Klaritsch P, Hecher K, Gardener G, Bevilacqua E, Kostyukov KV, Bahtiyar MO, Kilby MD, Tiblad E, Oepkes D, Lopriore E, collaborators. Treatment and outcome in 370 cases with spontaneous or post-laser twin anemia polycythemia sequence managed in 17 different fetal therapy centers. *Ultrasound Obstet Gynecol* 2020. DOI: 10.1002/uog.22042.
22. Newcastle–Ottawa Scale for assessing the quality of nonrandomised studies in metaanalyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/ oxford.asp. [Accessed 30/11/2019.].
23. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med* 2018; **23**: 60-63.
24. Tollenaar LSA, Slaghekke F, Lewi L, Colmant C, Lanna M, Weingertner AS, Ryan G, Arevalo S, Klaritsch P, De Sousa MT, Khalil A, Papanna R, Gardener GJ, Bevilacqua E, Kostyukov KV, Bahtiyar MO, Kilby MD, Tiblad E, Oepkes D, Lopriore E. Spontaneous Twin Anemia Polycythemia Sequence: Diagnosis, Management and Outcome in an International Cohort of 249 Cases. *Am J Obstet Gynecol* 2020. DOI: 10.1016/j.ajog.2020.07.041.
25. Tollenaar LSA, Lopriore E, Faiola S, Lanna M, Stirnemann J, Ville Y, Lewi L, Devlieger R, Weingertner AS, Favre R, Hobson SR, Ryan G, Rodo C, Arevalo S, Klaritsch P, Greimel P, Hecher K, de Sousa MT, Khalil A, Thilaganathan B, Bergh EP, Papanna R, Gardener GJ, Carlin A, Bevilacqua E, Sakalo VA, Kostyukov KV, Bahtiyar MO, Wilpers A, Kilby MD, Tiblad E, Oepkes D, Middeldorp JM, Haak MC, Klumper F, Akkermans J, Slaghekke F. Post-Laser Twin Anemia Polycythemia Sequence: Diagnosis, Management, and Outcome in an International Cohort of 164 Cases. *J Clin Med* 2020; **9**.
26. Murata S, Nakata M, Sugino N. Prevalence of right ventricular outflow tract abnormalities among recipients in twin-twin transfusion syndrome after fetoscopic laser surgery in 90 consecutive cases. *J Med Ultrason (2001)* 2020; **47**: 117-121.

27. Han SJ, Lee SM, Oh S, Hong S, Oh JW, Shin SH, Park CW, Park JS, Jun JK. Short- and long-term outcomes of preterm spontaneous twin anemia-polycythemia sequence. *J Perinat Med* 2020. DOI: 10.1515/jpm-2019-0437.
28. Suzuki T, Kagami K, Mitani Y, Yamazaki R, Ono M, Fujiwara H. Twin anemia-polycythemia sequence with blood chimerism in monochorionic dizygotic opposite-sex twins. *J Obstet Gynaecol Res* 2019; **45**: 1201-1204.
29. Rojas Perez EK-K, M.; Źródłowska, P.; Fiedorowicz-Kaźmierczak, M.; Malinowski, W. Twin anaemia-polycythaemia sequence or twin-to-twin transfusion syndrome? How to distinguish postnatally? A case report. *Pediatr Pol* 2018; **93**: 488-491.
30. Sheales MP, Sheth S, Edwards AG, Carden SM. Discordant retinopathy of prematurity in twin anemia-polycythemia sequence. *J AAPOS* 2017; **21**: 173-174.
31. Robinson A, Teoh M, Edwards A, Fahey M, Goergen S. Fetal brain injury in complicated monochorionic pregnancies: diagnostic yield of prenatal MRI following surveillance ultrasound and influence on prognostic counselling. *Prenat Diagn* 2017; **37**: 611-627.
32. Gosavi A, Vijayakumar PD, Ng BS, Loh MH, Tan LG, Johana N, Tan YW, Sandikin D, Su LL, Wataganara T, Biswas A, Choolani MA, Mattar CN. Rapid initiation of fetal therapy services with a system of learner-centred training under proctorship: the National University Hospital (Singapore) experience. *Singapore Med J* 2017; **58**: 311-320.
33. Brinsmead SK, Walsh CA. TAPS-related fetal cerebellar disruption. *J Matern Fetal Neonatal Med* 2017; **30**: 2354-2355.
34. Takeuchi M, Maruyama H, Oura N, Kanazawa A, Nakata Y, Minami S, Kikkawa K. Erythroblastosis of the Donor Twin of Twin Anemia-Polycythemia Sequence. *Acta Med Okayama* 2016; **70**: 269-272.
35. Suzuki S. Perinatal Outcomes of Monochorionic-Diamniotic Twin Pregnancies Uncomplicated at 28 Weeks of Gestation. *Jpn Clin Med* 2016; **7**: 15-17.
36. Moaddab A, Nassr AA, Espinoza J, Ruano R, Bateni ZH, Shamshirsaz AA, Mandy GT, Welty SE, Erfani H, Popek EJ, Belfort MA, Shamshirsaz AA. Twin anemia polycythemia sequence: a single center experience and literature review. *Eur J Obstet Gynecol Reprod Biol* 2016; **205**: 158-164.
37. Guenot C, Robyr R, Jastrow N, Vial Y, Raio L, Baud D. Fetal Intra-Peritoneal Transfusion for the Management of Very Early Spontaneous Twin Anemia-Polycythemia Sequence in an Obese Patient With a Whole Anterior Placenta. *Twin Res Hum Genet* 2016; **19**: 154-157.
38. Dassios T, ; Ali, K.; Hickey, A.; Greenough, A. Transient iatrogenic heart block following foetal intracardiac transfusion for severe twin anaemia-polycythaemia sequence. *Case Rep Perinat Med* 2016; **5**: 127-129.
39. Bae JY, Oh JJ, Hong SY. Prenatal diagnosis of spontaneous twin anemia-polycythemia sequence and postnatal examination of placental vascular anastomoses. *Obstet Gynecol Sci* 2016; **59**: 539-543.
40. Ashwal E, Yinon Y, Fishel-Bartal M, Tsur A, Chayen B, Weisz B, Lipitz S. Twin Anemia-Polycythemia Sequence: Perinatal Management and Outcome. *Fetal Diagn Ther* 2016; **40**: 28-34.
41. Yokouchi T, Murakoshi T, Mishima T, Yano H, Ohashi M, Suzuki T, Shinno T, Matsushita M, Nakayama S, Torii Y. Incidence of spontaneous twin anemia-polycythemia sequence in monochorionic-diamniotic twin pregnancies: Single-center prospective study. *J Obstet Gynaecol Res* 2015; **41**: 857-860.

42. Taniguchi K, Sumie M, Sugibayashi R, Wada S, Matsuoka K, Sago H. Twin anemia-polycythemia sequence after laser surgery for twin-twin transfusion syndrome and maternal morbidity. *Fetal Diagn Ther* 2015; **37**: 148-153.
43. Abdel-Sattar M, Platt LD, DeVore G, Porto M, Benirschke K, Chmait RH. Treatment of Complicated Spontaneous Twin Anemia-Polycythemia Sequence via Fetoscopic Laser Ablation of the Vascular Communications. *Fetal Diagn Ther* 2015; **38**: 233-237.
44. Yarci E, Alyamac Dizdar E, Oncel MY, Kose Cetinkaya A, Derme T, Canpolat FE, Oguz SS, Dilmen U. Successful management of twin anemia/polycythemia sequence by syngeneic partial exchange transfusion. *Fetal Diagn Ther* 2014; **36**: 251-254.
45. Stritzke A, Thomas S, Somerset D. Placental dichotomy: a hint in twin anemia polycythemia sequence. *J Obstet Gynaecol Can* 2014; **36**: 1097-1100.
46. Soundararajan LP, Howe DT. Starry sky liver in twin anemia-polycythemia sequence. *Ultrasound Obstet Gynecol* 2014; **43**: 597-599.
47. Sainz JA, Romero C, Garcia-Mejido J, Soto F, Turmo E. Analysis of middle cerebral artery peak systolic velocity in monochorionic twin pregnancies as a method for identifying spontaneous twin anaemia-polycythaemia sequence. *J Matern Fetal Neonatal Med* 2014; **27**: 1174-1176.
48. Movva VC, Rijhsinghani A. Discrepancy in placental echogenicity: a sign of twin anemia polycythemia sequence. *Prenat Diagn* 2014; **34**: 809-811.
49. Mabuchi A, Ishii K, Yamamoto R, Taguchi T, Murata M, Hayashi S, Mitsuda N. Clinical characteristics of monochorionic twins with large hemoglobin level discordance at birth. *Ultrasound Obstet Gynecol* 2014; **44**: 311-315.
50. Ishii K, Hayashi S, Mabuchi A, Taguchi T, Yamamoto R, Murata M, Mitsuda N. Therapy by laser equatorial placental dichorionization for early-onset spontaneous twin anemia-polycythemia sequence. *Fetal Diagn Ther* 2014; **35**: 65-68.
51. Casanova J, Paiva C, Carvalho C, Cunha AC. Twin anemia polycythemia sequence: a report of three cases. *J Reprod Med* 2014; **59**: 596-598.
52. Ruano R, Rodo C, Peiro JL, Shamshirsaz AA, Haeri S, Nomura ML, Salustiano EM, de Andrade KK, Sangi-Haghpeykar H, Carreras E, Belfort MA. Fetoscopic laser ablation of placental anastomoses in twin-twin transfusion syndrome using 'Solomon technique'. *Ultrasound Obstet Gynecol* 2013; **42**: 434-439.
53. Groussolles M, Sartor A, Connan L, Vayssiere C. Evolution of middle cerebral artery peak systolic velocity after a successful laser procedure for iatrogenic twin anemia-polycythemia sequence. *Ultrasound Obstet Gynecol* 2012; **39**: 354-356.
54. Fratelli N, Prefumo F, Zambolo C, Zanardini C, Fichera A, Frusca T. Conservative management in a case of iatrogenic twin anemia-polycythemia sequence. *Ultrasound Obstet Gynecol* 2012; **39**: 597-598.
55. Biran V, Bornes M, Aboura A, Masmoudi S, Drunat S, Baumann C, Osimani S, Dalle JH, Sterkers G, Verloes A, Farnoux C, Maury L, Schmitz T, Khung S, Baud O. A long-term competent chimeric immune system in a dizygotic dichorionic twin. *Pediatrics* 2011; **128**: e458-463.
56. Weingertner AS, Kohler A, Kohler M, Bouffet N, Hunsinger MC, Mager C, Hornecker F, Neumann M, Schmerber E, Tanghe M, Viville B, Favre R. Clinical and placental characteristics in four new cases of twin anemia-polycythemia sequence. *Ultrasound Obstet Gynecol* 2010; **35**: 490-494.
57. Chmait RH, Assaf SA, Benirschke K. Residual vascular communications in twin-twin transfusion syndrome treated with sequential laser surgery: frequency and clinical implications. *Placenta* 2010; **31**: 611-614.

58. Herway C, Johnson A, Moise K, Moise KJ, Jr. Fetal intraperitoneal transfusion for iatrogenic twin anemia-polycythemia sequence after laser therapy. *Ultrasound Obstet Gynecol* 2009; **33**: 592-594.
59. de Laat MW, Manten GT, Nikkels PG, Stoutenbeek P. Hydropic placenta as a first manifestation of twin-twin transfusion in a monochorionic diamniotic twin pregnancy. *J Ultrasound Med* 2009; **28**: 375-378.
60. Sunagawa S, Kikuchi A, Kurihara N, Hiroma T, Ono K, Miyachi K, Takagi K, Ogiso Y, Nakamura T. Monochorionic twin fetuses showing a reversal of donor-recipient phenotypes in severe twin-twin transfusion syndrome without oligo-polyhydramnios sequence. *Congenit Anom (Kyoto)* 2008; **48**: 92-96.
61. Lopriore E, Slaghekke F, Oepkes D, Middeldorp JM, Vandenbussche FP, Walther FJ. Clinical outcome in neonates with twin anemia-polycythemia sequence. *Am J Obstet Gynecol* 2010; **203**: 54 e51-55.
62. Sananes N, Veujoz M, Severac F, Barthoulot M, Meyer N, Weingertner AS, Kohler M, Guerra F, Gaudineau A, Nisand I, Favre R. Evaluation of the Utility of in utero Treatment of Twin Anemia-Polycythemia Sequence. *Fetal Diagn Ther* 2015; **38**: 170-178.
63. Rossi AC, Prefumo F. Perinatal outcomes of twin anemia-polycythemia sequence: a systematic review. *J Obstet Gynaecol Can* 2014; **36**: 701-707.
64. Rustico MA, Lanna MM, Faiola S, Schena V, Dell'avanzo M, Mantegazza V, Parazzini C, Lista G, Scelsa B, Consonni D, Ferrazzi E. Fetal and maternal complications after selective fetoscopic laser surgery for twin-to-twin transfusion syndrome: a single-center experience. *Fetal Diagn Ther* 2012; **31**: 170-178.
65. Bahtiyar MO, Ekmekci E, Demirel E, Irani RA, Copel JA. In utero Partial Exchange Transfusion Combined with in utero Blood Transfusion for Prenatal Management of Twin Anemia-Polycythemia Sequence. *Fetal Diagn Ther* 2019; **45**: 28-35.
66. Beck V, Lewi P, Gucciardo L, Devlieger R. Preterm prelabor rupture of membranes and fetal survival after minimally invasive fetal surgery: a systematic review of the literature. *Fetal Diagn Ther* 2012; **31**: 1-9.
67. Malshe A, Snowise S, Mann LK, Boring N, Johnson A, Bebbington MW, Moise KJ, Jr., Papanna R. Preterm delivery after fetoscopic laser surgery for twin-twin transfusion syndrome: etiology and risk factors. *Ultrasound Obstet Gynecol* 2017; **49**: 612-616.
68. National Institute for Health and Care Excellence. Twin and trip-let pregnancy. . https://www.nice.org.uk/guidance/ng137.].
69. Committee on Practice B-O, Society for Maternal-Fetal M. Practice Bulletin No. 169: Multifetal Gestations: Twin, Triplet, and Higher-Order Multifetal Pregnancies. *Obstet Gynecol* 2016; **128**: e131-146.
70. Khalil A, Gordijn S, Ganzevoort W, Thilaganathan B, Johnson A, Baschat AA, Hecher K, Reed K, Lewi L, Deprest J, Oepkes D, Lopriore E. Consensus diagnostic criteria and monitoring of twin anemia-polycythemia sequence: Delphi procedure. *Ultrasound Obstet Gynecol* 2020; **56**: 388-394.
71. Liu B, Kalafat E, Bhide A, Thilaganathan B, Khalil A. Performance of Antenatal Diagnostic Criteria of Twin-Anemia-Polycythemia Sequence. *J Clin Med* 2020; **9**.

Figure legend

Figure 1. Mortality in monochorionic diamniotic twin pregnancies complicated by spontaneous and post-laser TAPS. IUD intrauterine death, NND neonatal death, PND perinatal death

Figure 2. Morbidity in monochorionic diamniotic twin pregnancies complicated by spontaneous and post-laser TAPS.

Figure 3. Preterm birth in monochorionic diamniotic twin pregnancies complicated by spontaneous and post-laser TAPS. PTB preterm birth

Figure 4. Mortality in monochorionic diamniotic twin pregnancies managed by different approaches. PND perinatal death, IUT intra-uterine transfusion, SR selective reduction.

Figure 5. Morbidity in monochorionic diamniotic twin pregnancies managed by different approaches. IUT intra-uterine transfusion, SR selective reduction.

Figure 6. Preterm birth in monochorionic diamniotic twin pregnancies complicated by spontaneous and post-laser TAPS. SPTB spontaneous preterm birth, IPTB iatrogenic preterm birth

Supplementary Information
Supplementary Table 1. Research strategy

Table 1. General characteristic of the studies included in the systematic review

Author	Year	Country	Study design	Period considered	Type of TAPS	Outcomes observed	Pregnancies (n)	TAPS (n)
Tollenaar et al.[21]	2020	Netherlands, Belgium, Spain, Germany, France, Austria, Canada, Italy USA, UK, Australia, Sweden, Russia	Retrospective register-based cohort study	2014-2019	spontaneous, post-Laser	mortality, morbidity	370	370
Tollenaar et al.[24]	2020	Netherlands, Belgium, Spain, Germany, France, Austria, Canada, Italy USA, UK, Australia, Sweden, Russia	Retrospective register-based cohort study	2014-2019	spontaneous	mortality, morbidity	249	249
Tollenaar et al.[25]	2020	Netherlands, Belgium, Spain, Germany, France, Austria, Canada, Italy USA, UK, Australia, Sweden, Russia	Retrospective register-based cohort study	2014-2019	post-Laser	mortality, morbidity	173	173
Murata et al.[26]	2020	Japan	Retrospective cohort study	2010-2015	post-Laser	mortality, morbidity	90	1
Han et al. [27]	2020	Korea	Retrospective cohort study	2003-2006	spontaneous	mortality, morbidity	172	11
Suzuki et al. [28]	2019	Japan	Case report	NR	spontaneous	mortality	1	1
Perez et al. [29]	2018	Poland	Case report	NR	spontaneous	mortality, morbidity	1	1
Sheales et al. [30]	2017	Australia	Case report	NR	spontaneous	mortality, morbidity	1	1
Robinson et al. [31]	2017	Australia	Retrospective cohort study	2007-2016	spontaneous	mortality	33	2
Gosavi et al. [32]	2017	Singapore	Cohort study	2015	post-Laser	mortality, morbidity	8	1

Brinsmead et al. [33]	2017	Australia	Case report	NR	spontaneous	mortality	1	1
Takeuchi et al. [34]	2016	Japan	Case report	NR	spontaneous	mortality, morbidity	1	1
Suzuki [35]	2016	Japan	Retrospective cohort study	2011-2014	spontaneous	mortality	88	2
Moaddab et al. [36]	2016	USA	Case series	NR	spontaneous, post-Laser	mortality, morbidity	2	2
Guenot et al.[37]	2016	Switzerland	Case report	NR	spontaneous	mortality, morbidity	1	1
Dassios et al. [38]	2016	UK	Case report	NR	spontaneous	mortality, morbidity	1	1
Bae et al. [39]	2016	Korea	Case report	NR	spontaneous	mortality, morbidity	1	1
Ashwal et al. [40]	2015	Israel	Retrospective cohort study	2011-2014	spontaneous, post-Laser	mortality, morbidity	179	10
Yokouchi et al.[41]	2015	Japan	Prospective cohort study	2006-2013	spontaneous	mortality	185	3
Taniguchi et al. [42]	2015	Japan	Case series	2003-2012	post-Laser	mortality, morbidity	3	3
Abdel-Sattar et al. [43]	2015	USA	Case series	NR	spontaneous	mortality, morbidity	3	3
Yarci et al. [44]	2014	Turkey	Case report	NR	spontaneous	mortality, morbidity	1	1
Stritzke et al. [45]	2014	Canada	Case report	NR	spontaneous	mortality, morbidity	1	1
Soundararajan et al. [46]	2014	UK	Case series	NR	spontaneous, post-Laser	mortality	2	2

Sainz et al. [47]	2014	Spain	Case report	NR	spontaneous	mortality, morbidity	1	1
Movva et al. [48]	2014	USA	Case series	NR	spontaneous	mortality	2	2
Mabuchi et al. [49]	2014	Japan	Retrospective cohort study	2003-2012	spontaneous, post-Laser	mortality, morbidity	432	7
Ishii et al. [50]	2014	Japan	Case report	NR	spontaneous	mortality, morbidity	1	1
Casanova et al. [51]	2014	Portugal	Case series	NR	spontaneous	mortality	3	3
Ruano et al. [52]	2013	Brazil, Spain, USA	Retrospective cohort study	2010-2012	post-Laser	mortality	102	6
Luminoso et al. [14]	2013	Brazil	Case report	NR	spontaneous	mortality, morbidity	1	1
Groussolles et al. [53]	2012	France	Case report	NR	post-Laser	mortality, morbidity	1	1
Fratelli et al. [54]	2012	Italy	Case report	NR	post-Laser	mortality, morbidity	1	1
Biran et al. [55]	2011	France	Case report	NR	spontaneous	mortality, morbidity	1	1
Weingertner et al. [56]	2010	France	Case series	2006-2008	spontaneous	mortality, morbidity	4	4
Chmait et al. [57]	2010	USA	Prospective cohort study	2006-2009	post-Laser	mortality	105	1
Herway et al. [58]	2009	USA	Case report	NR	post-Laser	mortality, morbidity	1	1

de Laat et al. [59]	2009	Netherlands	Case report	NR	spontaneous	mortality	1	1
Sunagawa et al. [60]	2008	Japan	Case report	NR	spontaneous	mortality, morbidity	1	1
Robyr et al. [6]	2006	France, Belgium	Prospective cohort study	Until 2004	post-Laser	mortality	151	13

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. For case reports on fetal therapy, quality assessment of the included studies was assessed using the methodological quality and synthesis of case series and case reports described by Murad et al. According to this tool, each study is judged on four broad perspectives: the selection of the study groups, the ascertainment and the causality of the outcome observed and the reporting of the case. A study can be awarded a maximum of one star for each numbered item within the Selection and Reporting categories, two stars for Ascertainment and four stars for Causality.

Cohort studies					
Author	**Year**	**Selection**	**Comparability**	**Outcome**	
Tollenaar et al.[21]	2020	****	*	***	
Tollenaar et al.[24]	2020	****	*	***	
Tollenaar et al.[25]	2020	****	*	***	
Murata et al. [26]	2020	***		***	
Han et al. [27]	2020	***	*	**	
Robinson et al.[31]	2017	***	*	***	
Gosavi et al.[32]	2017	****	*	**	
Suzuki[35]	2016	****	*	***	
Ashwal et al.[40]	2015	****	**	***	
Yokouchi et al.[41]	2015	***	*	***	
Mabuchi et al.[49]	2014	****	*	***	
Ruano et al.[52]	2013	****	**	***	
Chmait et al.[57]	2010	****	*	**	
Robyr et al.[6]	2006	****	**	***	
Case reports and case series					
Author	**Year**	**Selection**	**Ascertainment**	**Causality**	**Reporting**
Suzuki et al.[28]	2019	*	**	*	*
Perez et al. [29]	2018	*	**		*
Sheales et al.[30]	2017		**	*	*
Brinsmead et al.[33]	2017	*	**	*	*
Takeuchi et al.[34]	2016	*			
Moaddab et al.[36]	2016	*	*		*
Guenot et al.[37]	2016	*	**	*	*
Dassios et al.[38]	2016	*	**		*

Bae et al.[39]	2016	*	**	*	*
Taniguchi et al.[42]	2015	*	**	*	*
Abdel-Sattar et al.[43]	2015	*	**	*	*
Yarci et al.[44]	2014	*	**	*	*
Stritzke et al.[45]	2014	*	**	*	*
Soundararajan et al.[46]	2014	*	**		*
Sainz et al.[47]	2014	*	**	*	*
Movva et al.[48]	2014	*	**		*
Ishii et al.[50]	2014		**	*	*
Casanova et al.[51]	2014	*	*	*	*
Luminoso et al.[14]	2013	*	**		
Groussolles et al.[53]	2012	*	**	*	*
Fratelli et al.[54]	2012	*	**	*	*
Biran et al.[55]	2011	*	*	*	*
Weingertner et al.[56]	2010	*	**	*	*
Herway et al.[58]	2009		**	*	*
de Laat et al.[59]	2009	*	**		*
Sunagawa et al.[60]	2008	*	**	*	*

Table 3. Pooled proportions of mortality in monochorionic diamniotic twin pregnancies affected by spontaneous or post-Laser TAPS (95% confidence intervals, CI, between parentheses).

Outcome	Studies (n)	Fetuses (n/N)	I^2	Pooled proportions (95% CI)
	Spontaneous TAPS			
Intrauterine demise (overall)	27	28/612	0	5.18 (3.6-7.1)
Single intrauterine demise	26	2/118	0	5.26 (2.2-9.7)
Double intrauterine demise	26	1/118	0	4.45 (1.6-8.6)
Neonatal death (overall)	26	19/610	0	4.00 (2.6-5.7)
Single neonatal death	25	1/116	0	5.09 (2.0-9.5)
Double neonatal death	25	0/116	0	0 (0-8.1)
Perinatal death (overall)	27	47/612	0	8.33 (6.3-10.6)
Single perinatal death	26	3/118	0	6.47 (2.9-11.3)
Double perinatal death	26	1/118	0	4.45 (1.6-8.6)
Livebirths	27	554/612	0	90.12 (87.7-92.3)
Survival of at least one twin	26	61/118	0	52.02 (43.2-60.5)
Survival of both twins	26	58/118	0	49.15 (40.6-57.7)
	Post-Laser TAPS			
Intrauterine demise (overall)	14	37/392	0	10.15 (7.4-13.3)
Single intrauterine demise	13	2/64	0	6.93 (2.2-14.0)
Double intrauterine demise	13	1/64	0	5.15 (1.3-11.5)
[redacted]onatal death (overall)	14	35/392	23.5	9.24 (6.6-12.3)
Single neonatal death	13	2/64	0	7.46 (2.5-14.7)
Double neonatal death	13	3/64	0	7.00 (2.3-14.1)
Perinatal death (overall)	14	35/392	19.7	19.01 (11.7-27.6)
Single perinatal death	13	4/64	0	10.08 (4.2-18.1)
Double perinatal death	13	4/64	0	8.03 (2.9-15.4)
Livebirths	14	330/392	0	83.70 (80.0-87.2)
Survival of at least one twin	13	29/64	0	45.57 (34.2-57.2)
Survival of both twins	13	23/64	0	37.16 (23.6-48.7)

Table 4. Pooled proportions of mortality in monochorionic diamniotic twin pregnancies complicated by spontaneous or post-Laser TAPS according to different management options
(95% confidence intervals, CI, between parentheses)

Outcome	Studies (n)	Fetuses (n/N)	I^2	Pooled proportions (95% CI)
	Expectant management			
Intrauterine demise (overall)	12	28/354	15.2	9.76 (4.3-17.1)
Single intrauterine demise	11	0/42	0	0 (0-13.0)
Double intrauterine demise	11	2/42	0	8.46 (2.3-17.9)
Neonatal death (overall)	11	27/352	0	8.05 (5.5-11.1)
Single neonatal death	10	1/40	0	7.01 (1.5-16.2)
Double neonatal death	10	1/40	0	7.01 (1.5-16.2)
Perinatal death (overall)	12	55/354	46.5	15.81 (6.2-28.8)
Single perinatal death	11	1/42	0	7.12 (1.6-16.1)
Double perinatal death	11	3/42	0	9.89 (3.1-19.9)
Livebirth	12	328/354	0.4	92.23 (89.1-94.9)
Survival of at least one twin	12	168/354	0	47.46 (42.3-52.6)
Survival of both twins	12	133/354	0	37.74 (32.8-42.8)
	Laser therapy			
Intrauterine demise (overall)	9	30/240	0	13.13 (9.2-17.6)
Single intrauterine demise	8	2/20	0	15.38 (4.1-32.2)
Double intrauterine demise	8	0/20	0	0 (0-21.1)
Neonatal death (overall)	9	10/240	0	4.99 (2.6-8.1)
Single neonatal death	8	0/20	0	0 (0-21.1)
Double neonatal death	8	0/20	0	0 (0-21.1)
Perinatal death (overall)	9	40/240	0	17.22 (12.8-22.2)
Single perinatal death	8	2/20	0	15.38 (4.1-32.2)
Double perinatal death	8	0/20	0	0 (0-21.1)

Livebirth	9	210/240	0	86.87 (82.4-90.8)
Survival of at least one twin	9	109/240	0	45.51 (39.3-51.8)
Survival of both twins	9	86/240	0	36.06 (30.2-42.2)
	Intra-uterine transfusion			
Intrauterine demise (overall)	9	19/172	0	12.08 (7.7-17.3)
Single intrauterine demise	8	1/32	0	8.37 (1.7-19.5)
Double intrauterine demise	8	0/32	0	0 (0-13.5)
Neonatal death (overall)	9	9/172	31.2	7.93 (1.7-18.1)
Single neonatal death	8	0/32	0	0 (0-13.5)
Double neonatal death	8	1/32	0	5.95 (0.7-15.9)
Perinatal death (overall)	9	28/172	16.4	15.51 (7.6-25.6)
Single perinatal death	8	1/32	0	8.37 (1.7-19.5)
Double perinatal death	8	1/32	0	5.95 (0.7-15.9)
Livebirth	9	153/172	0	87.92 (82.7-92.3)
Survival of at least one twin	9	82/172	0	47.63 (40.3-55.0)
Survival of both twins	9	63/172	0	36.89 (29.9-44.1)
	Selective reduction			
Intrauterine demise (overall)	2	2/34	0	7.61 (1.3-18.5)
Single intrauterine demise	1	0/4	-	0 (0-60.2)
Double intrauterine demise	1	0/4	-	0 (0-60.2)
Neonatal death (overall)	2	1/34	0	2.31 (0.1-9.8)
Single neonatal death	1	1/4	-	25.00 (0.6-80.6)
Double neonatal death	1	0/4	-	0 (0-60.2)
Perinatal death (overall)	2	3/34	0	11.63 (1.4-30.0)
Single perinatal death	1	1/4	-	25.00 (0.6-80.6)
Double perinatal death	1	0/4	-	0 (0-60.2)
Livebirths	2	32/34	0	92.39 (81.5-98.1)
Survival of at least one twin	2	31/34	0	88.37 (70.0-98.6)

Table 5. Pooled proportions of morbidity in monochorionic diamniotic twin pregnancies affected by spontaneous or post-Laser TAPS (95% confidence intervals, CI, between parentheses).

Outcome	Studies (n)	Newborns (n/N)	I^2	Pooled proportions (95% CI)
	Spontaneous TAPS			
Severe neonatal morbidity	26	162/546	38.5	29.29(25.6-33.1)
Severe neurological morbidity	26	17/546	0	3.97 (3.5-5.7)
Respiratory morbidity	26	136/546	0	24.80 (21.3-28.5)
NEC	26	17/546	0	4.04 (2.6-5.8)
PDA	25	36/524	0	7.77 (5.7-10.2)
ROP	25	9/524	0	3.83 (2.4-5.6)
Survival free from neurological impairment	26	529/546	0	96.03 (94.3-97.5)
	Post-Laser TAPS			
Severe neonatal morbidity	12	117/309	63.1	33.34 (17.4-51.8)
Severe neurological morbidity	12	33/309	7.4	11.11 (6.2-17.2)
Respiratory morbidity	12	96/309	70.3	23.80 (9.1-42.8)
NEC	12	6/309	0	2.74 (1.2-4.8)
PDA	12	21/309	0	7.41 (4.8-10.6)
ROP	12	9/309	0	3.72 (1.9-6.1)
Survival free from neurological impairment	12	273/309	59.1	80.22 (64.5-92.2)

Table 6. Pooled proportions of morbidity in monochorionic diamniotic twin pregnancies complicated by spontaneous or post-Laser TAPS according to different management options
(95% confidence intervals, CI, between parentheses)

Outcome	Studies (n)	Newborns (n/N)	I^2	Pooled proportions (95% CI)
	Expectant management			
Severe neonatal morbidity	10	71/296	44.6	27.29 (13.6-43.6)
Severe neurological morbidity	10	22/296	0	7.80 (5.1-11.1)
Respiratory morbidity	9	6/32	0	17.43 (6.1-33.0)
NEC	9	0/32	0	0 (0-14.9)
PDA	9	1/32	0	8.56 (1.8-19.6)
ROP	9	0/32	0	0 (0-14.9)
Survival free from neurological impairment	10	274/296	0	92.19 (88.9-94.9)
	Laser therapy			
Severe neonatal morbidity	9	57/198	0	28.68 (22.7-35.1)
Severe neurological morbidity	9	6/198	0	4.00 (1.7-7.1)
Respiratory morbidity	8	0/18	0	0 (0-22.8)
NEC	8	0/18	0	0 (0-22.8)
PDA	8	0/18	0	0 (0-22.8)
ROP	8	0/18	0	0 (0-22.8)
Survival free from neurological impairment	9	190/198	33.5	95.53 (92.3-97.9)
	Intra-uterine transfusion			
Severe neonatal morbidity	8	64/151	62.2	38.21 (18.3-60.5)
Severe neurological morbidity	8	14/151	0	9.82 (5.7-15.0)
Respiratory morbidity	7	5/29	57.9	14.46 (4.7-28.4)
NEC	7	0/29	0	0 (0-13.9)
PDA	7	2/29	0	8.21 (1.3-20.1)
ROP	7	2/29	46.4	12.46 (0.9-34.2)
Survival free from neurological impairment	8	134/151	65.2	81.69 (60.9-95.7)
	Selective reduction			
Severe neonatal morbidity	2	7/31	0	23.29 (10.5-39.2)
Severe neurological morbidity	2	0/31	0	0 (0-7.9)
Respiratory morbidity	1	0/3	-	0 (0-70.8)
NEC	1	0/3	-	0 (0-70.8)
PDA	1	0/3	-	0 (0-70.8)
ROP	1	0/3	-	0 (0-70.8)
Survival free from neurological impairment	2	31/31	0	100 (92.1-100)

Table 7. Pooled proportions of preterm birth in monochorionic diamniotic twin pregnancies complicated by spontaneous or post-Laser TAPS (95% confidence intervals, CI, between parentheses)

Outcome	Studies (n)	Pregnancies (n/N)	I^2	Pooled proportions (95% CI)
	Spontaneous TAPS			
Overall preterm birth	24	51/57	0	86.29 (77.2-93.3)
Spontaneous preterm birth	18	9/34	24.3	32.33 (17.1-49.8)
Iatrogenic preterm birth	18	23/34	34.1	61.27 (42.1-78.8)
Preterm birth <34 weeks	23	28/46	0	59.83 (47.0-72.0)
Preterm birth <32 weeks	23	12/46	0	30.20 (18.0-44.0)
Preterm birth <28 weeks	23	0/46	0	0 (0-16.9)
	Post-Laser TAPS			
Overall preterm birth	14	34/34	0	100 (84.3-100)
Spontaneous preterm birth	10	2/14	0	20.60 (5.9-41.1)
Iatrogenic preterm birth	10	12/14	0	79.40 (58.9-94.1)
Preterm birth <34 weeks	12	27/33	0	79.50 (65.6-90.5)
Preterm birth <32 weeks	12	20/33	0	58.80 (39.9-76.4)
Preterm birth <28 weeks	12	6/33	0	21.75 (10.4-35.9)

Table 8. Pooled proportions of preterm birth in monochorionic diamniotic twin pregnancies complicated by spontaneous or post-Laser TAPS according to different management options
(95% confidence intervals, CI, between parentheses)

Outcome	Studies (n)	Pregnancies (n/N)	I^2	Pooled proportions (95% CI)
	Expectant management			
Overall preterm birth	9	16/20	20	80.43 (59.8-94.8)
Spontaneous preterm birth	7	2/14	28.1	17.51 (3.8-38.2)
Iatrogenic preterm birth	7	12/14	28.1	82.49 (61.8-96.2)
Preterm birth <34 weeks	9	14/20	0	68.33 (49.0-84.9)
Preterm birth <32 weeks	9	6/20	0	35.28 (14.7-59.2)
Preterm birth <28 weeks	9	0/20	0	0 (0-21.4)
	Laser therapy			
Overall preterm birth	8	8/10	0	73.36 (48.1-92.3)
Spontaneous preterm birth	7	64/116	0	56.04 (47.0-64.9)
Iatrogenic preterm birth	6	2/8	0	30.32 (8.4-59.3)
Preterm birth <34 weeks	8	5/10	0	50.93 (25.8-75.8)
Preterm birth <32 weeks	8	4/10	0	42.55 (18.8-68.3)
Preterm birth <28 weeks	8	0/10	0	0 (0-33.9)
	Intra-uterine transfusion			
Overall preterm birth	8	16/16	0	100 (76.5-100)
Spontaneous preterm birth	6	20/75	0	27.28 (18.0-37.6)
Iatrogenic preterm birth	5	6/6	0	100 (58.1-100)
Preterm birth <34 weeks	8	14/16	0	81.06 (61.5-94.8)
Preterm birth <32 weeks	8	13/16	0	76.24 (55.7-91.8)
Preterm birth <28 weeks	8	2/16	0	19.94 (3.7-44.7)
	Selective reduction			
Overall preterm birth	1	4/4	-	100 (39.8-100)
Spontaneous preterm birth	1	24/29	-	82.76 (64.2-94.2)
Iatrogenic preterm birth	0	-	-	-
Preterm birth <34 weeks	1	3/4	-	75.00 (19.4-99.4)
Preterm birth <32 weeks	1	1/4	-	25.00 (0.6-80.6)
Preterm birth <28 weeks	1	1/4	-	25.00 (0.6-80.6)

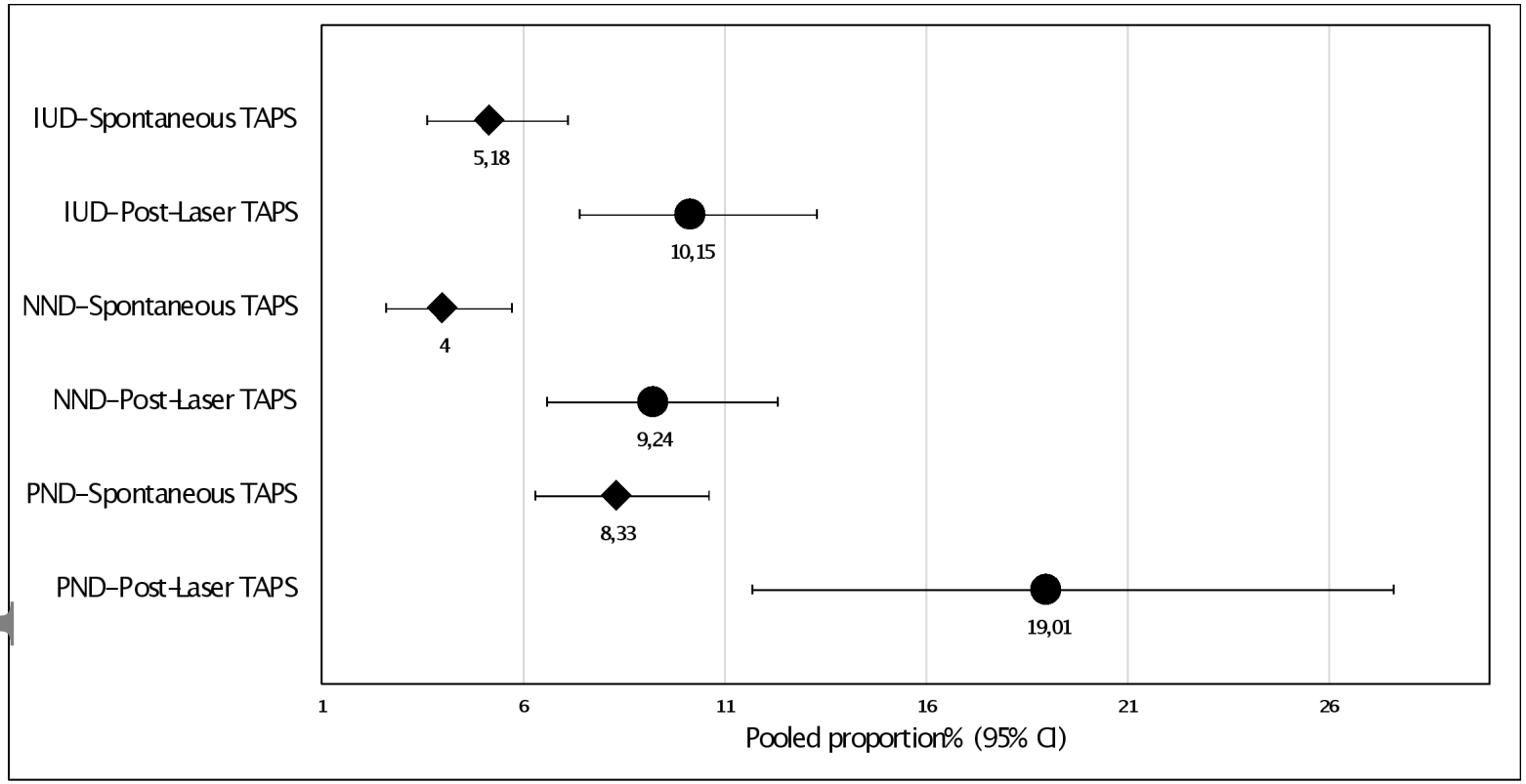

Figure 1

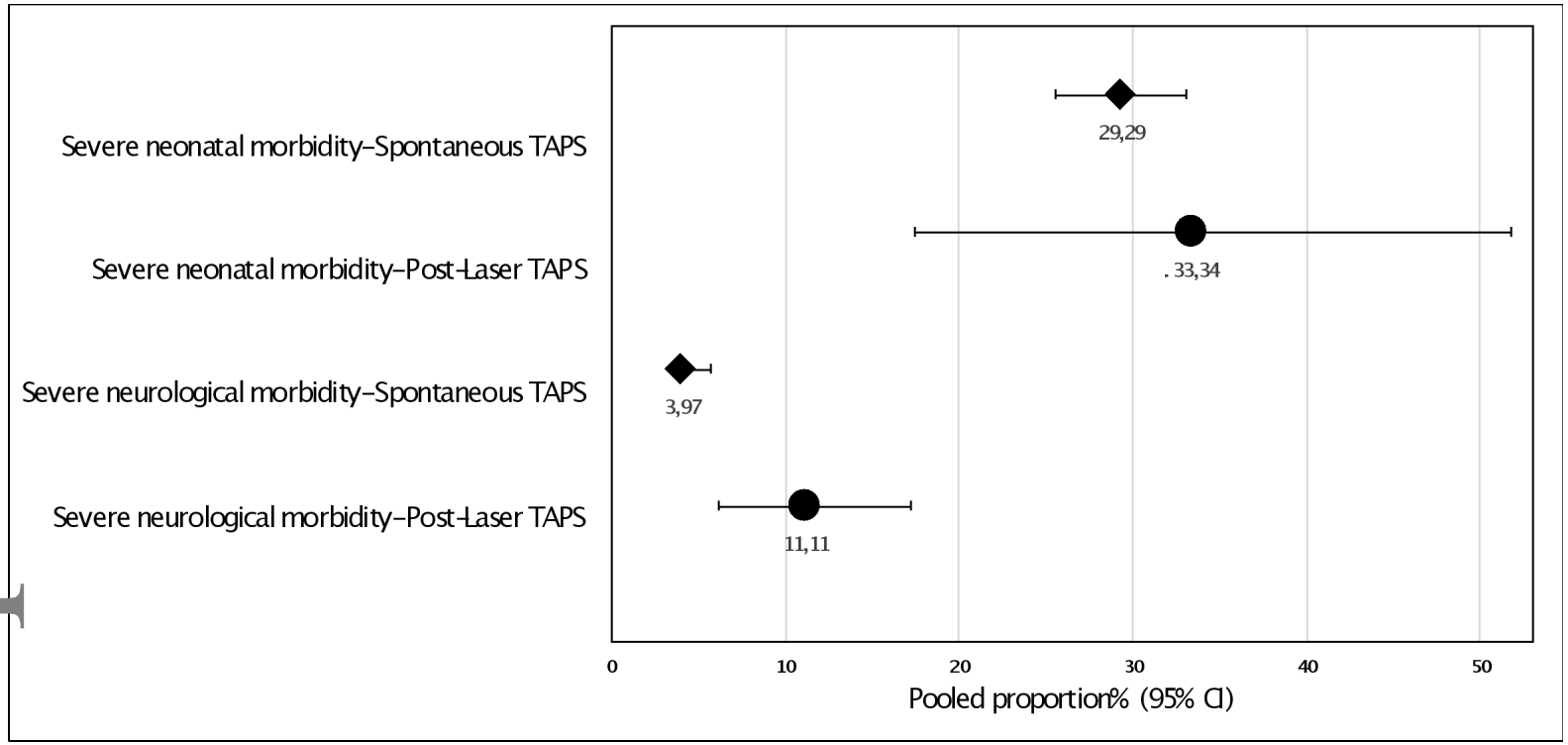

Figure 2

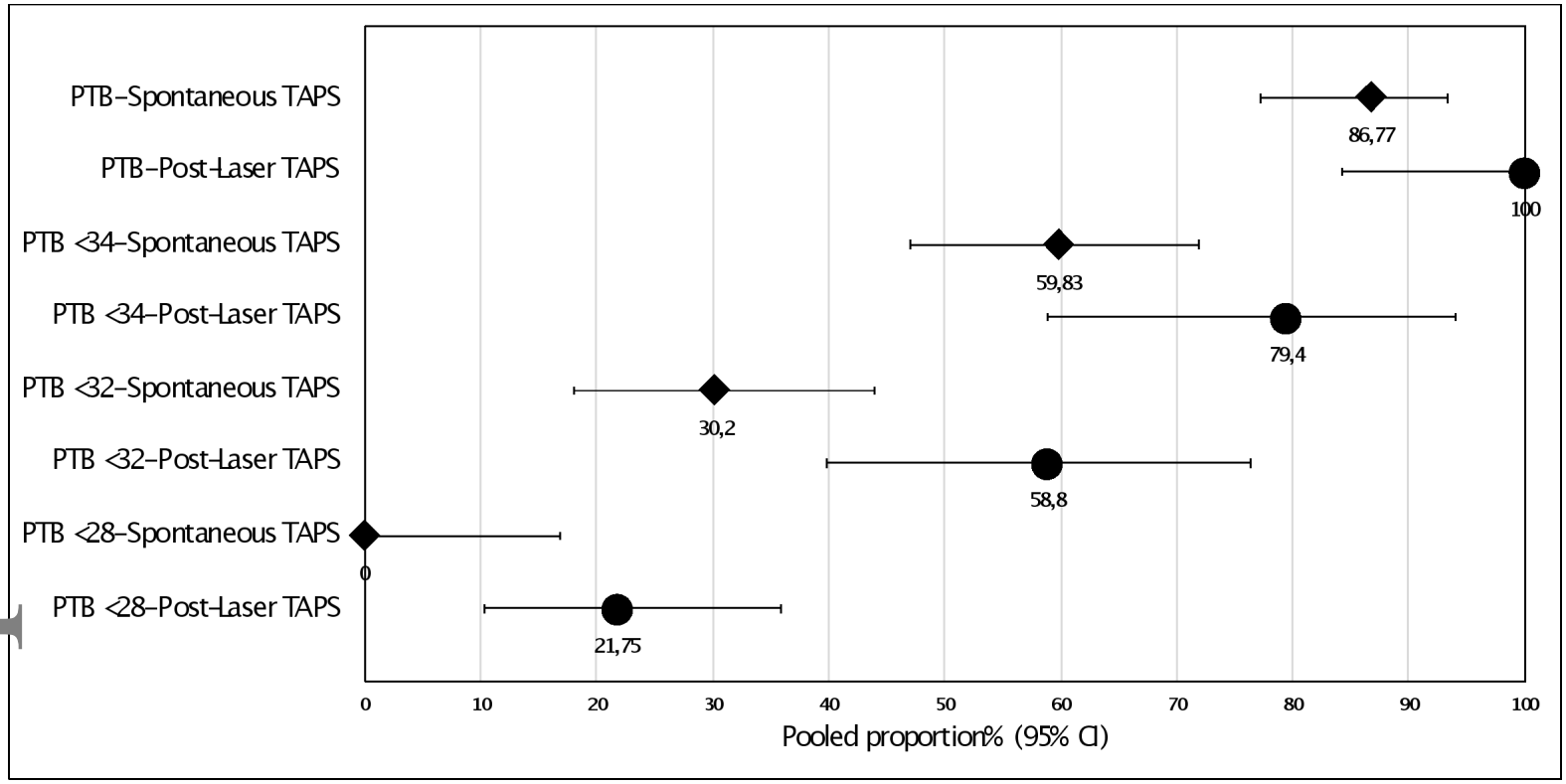

Figure 3

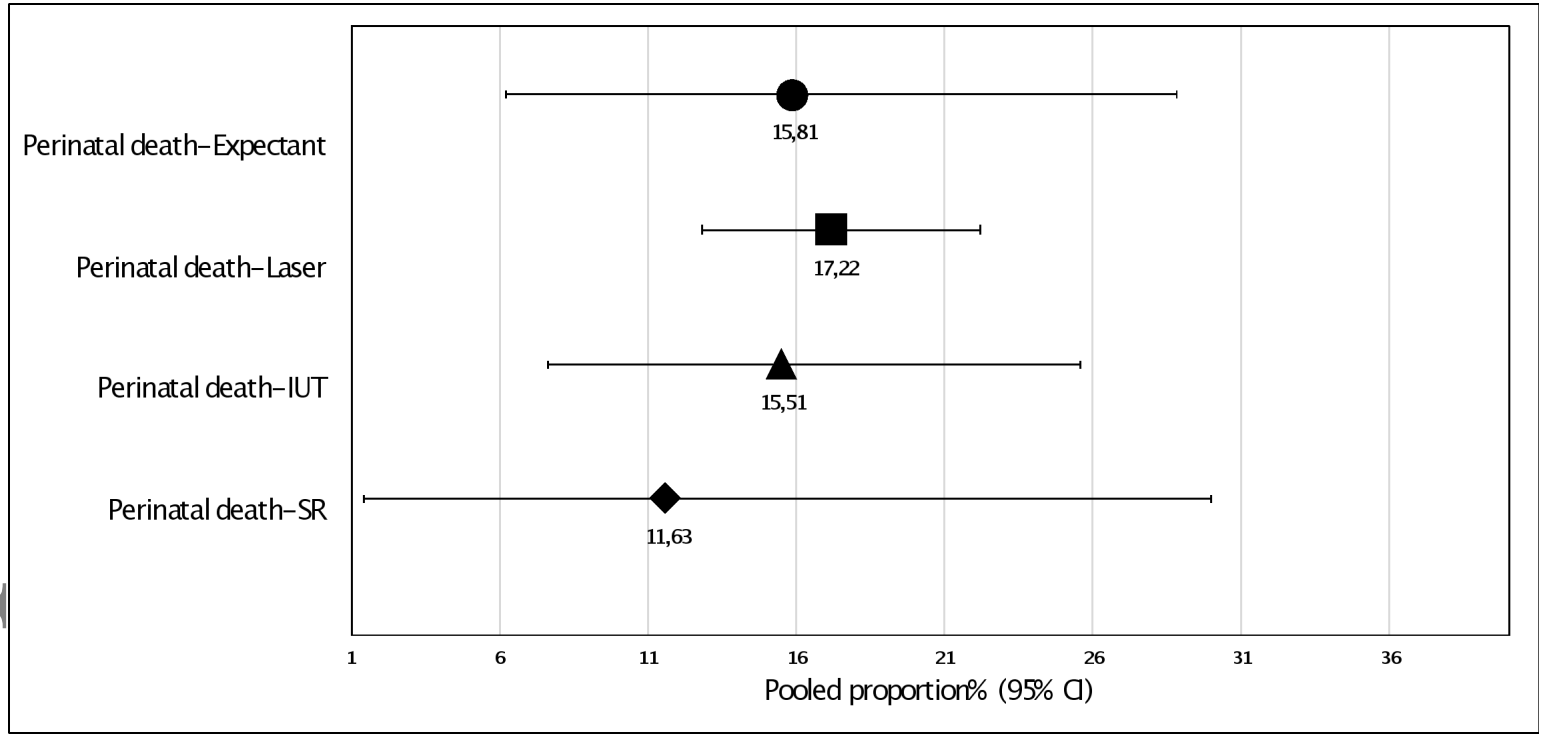

Figure 4

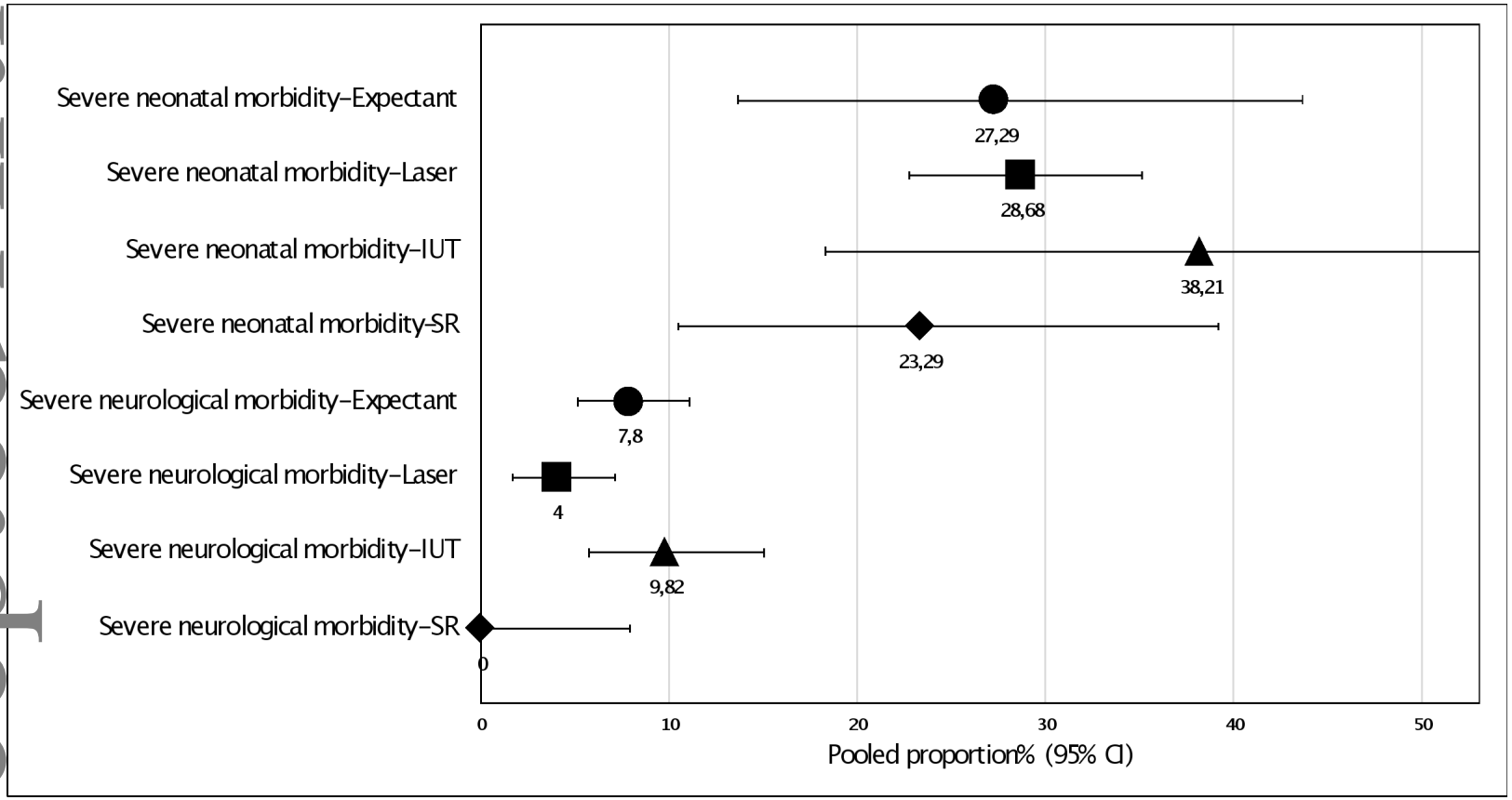

Figure 5

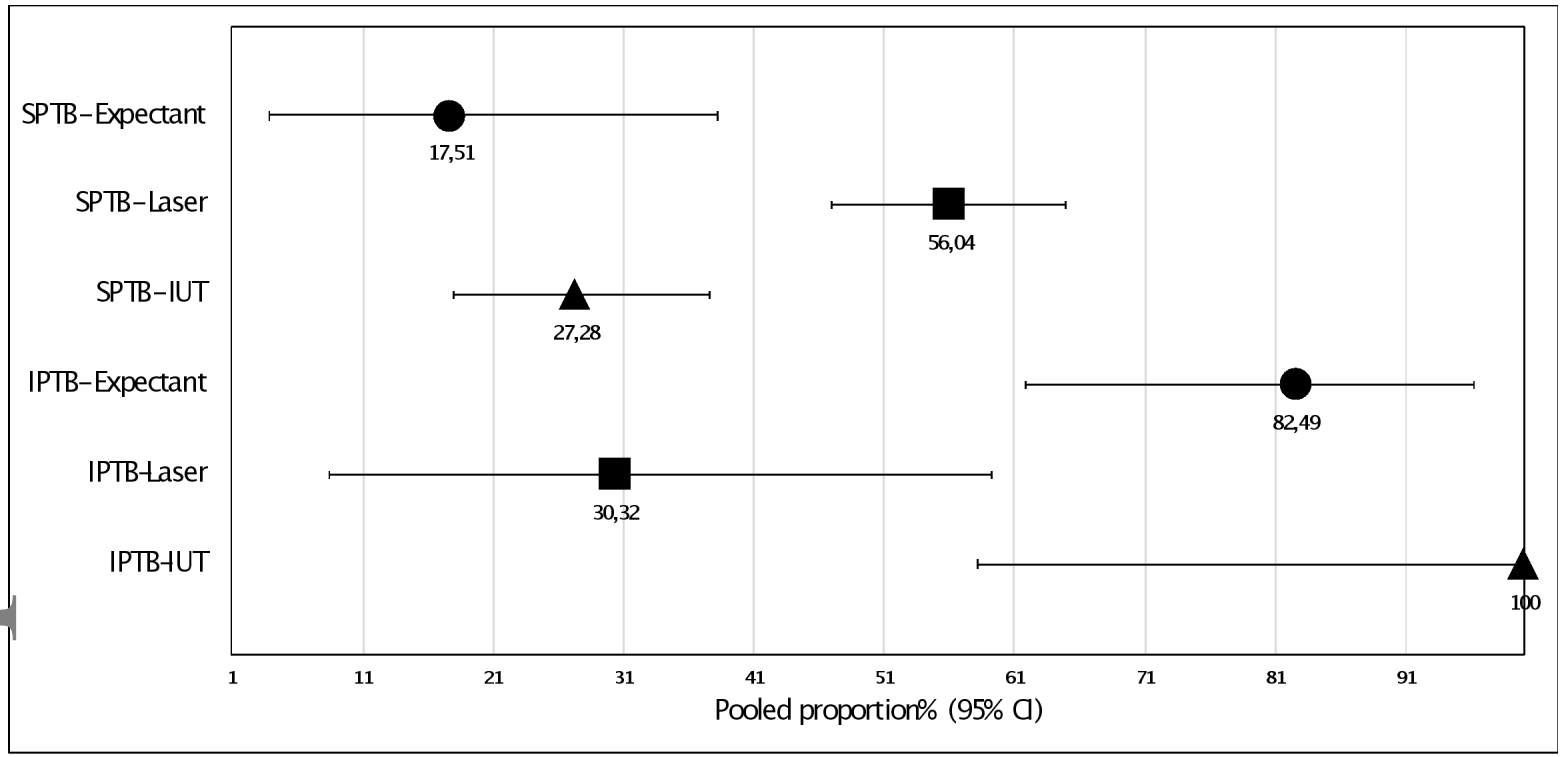

Figure 6