Perinatal mortality and morbidity in triplet pregnancies according to chorionicity: a systematic review and meta-analysis

Joana Curado[1], Francesco D'Antonio[2,3], Aris Papageorghiou[1], Amar Bhide[1], Basky Thilaganathan[1,4], Asma Khalil[1,4]

1. Fetal Medicine Unit, St. George's University Hospitals NHS Foundation Trust, London, UK

2. Women´s Health and Perinatology Research Group, Department of Clinical Medicine, Faculty of Health Sciences, UiT-The Arctic University of Norway, Tromsø, Norway

3. Department of Obstetrics and Gynaecology, University Hospital of Northern Norway, Tromsø, Norway

4. Molecular & Clinical Sciences Research Institute, St. George's University of London, London, UK

CORRESPONDENCE

Professor Asma Khalil

Fetal Medicine Unit,

St George's University of London,

London SW17 0RE

E-mail: akhalil@sgul.ac.uk; asmakhalil79@googlemail.com

Short title: Mortality and morbidity in triplet pregnancies

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.20209

Keywords: Perinatal mortality, morbidity, triplet, chorionicity, systematic review, meta-analysis

ABSTRACT

Background: Triplet pregnancies have a high risk of perinatal mortality and morbidity. The incidence of perinatal mortality and morbidity according to chorionicity is yet to be established.

Objectives: To quantify perinatal mortality and morbidity in trichorionic-triamniotic (TCTA), dichorionic-triamniotic (DCTA) and monochorionic-triamniotic (MCTA) triplets..

Search strategy: Medline, Embase and Cinahl databases were searched in December 2017.

Selection criteria: Published literature in English describing outcomes of DCTA, TCTA and/or MCTA triplet pregnancies was eligible.

Data collection and analysis: Data regarding outcomes was extracted. Random effects meta-analyses were used to estimate the risk of mortality and morbidity and to compute the difference in the gestational age (GA) at birth in TCTA and DCTA triplets pregnancies respectively.

Main results: Nine studies (1387 triplet pregnancies of which 1062 TCTA, 275 DCTA and 50 MCTA) were included. The risk of perinatal death (PND) was higher in DCTA compared to TCTA triplet pregnancies (OR 3.3, 95% CI 1.3-8.0), mainly due to the higher risk of intrauterine death (IUD) in DCTA triplet pregnancies (OR 4.6, 95% CI 1.8-

11.7). There was no difference in the GA at birth between TCTA and DCTA triplets (MD: 1.12 weeks, 95% CI -0.29 – 2.52, I^2: 85%; p= 0.12). Neurological morbidity occurred in 2.0% (95% CI 1.1-3.3) of TCTA and in 11.6% (95% CI 1.1-40.0) of DCTA triplets. Respiratory and infectious morbidity affected 28.3% (95% CI 20.7-36.8) and 4.2% (95% CI 2.8-5.9) of TCTA and 34.0% (95% CI 21.5-47.7) and 7.1% (95% CI 2.7-13.3) of DCTA triplets, respectively. Finally, the incidence of composite morbidity in TCTA and DCTA triplets was 29.6% (95% CI 21.1-38.9) and 34.0% (95% CI 21.5-47.7), respectively. When translating these figures into a risk analysis, the risk of neurological morbidity (OR 5.4, 95% CI 1.6-18.3) was significantly higher in DCTA compared to TCTA triplets, while there was no significant difference in the other morbidities explored. Only one study reported on MCTA outcomes, hence no formal comparison with the other groups was performed.

Conclusion: DCTA are at higher risk of perinatal mortality and morbidity compared to TCTA triplet pregnancies.

INTRODUCTION

The increase in the incidence of higher order multiple gestations over the last two decades, due to assisted reproductive techniques[1], is declining. This is mainly a result of transfer of fewer embryos and an increase in the fetal reduction procedures[2,3]. Nevertheless, triplet and higher-order births accounted for 103.6 per 100,000 births in the United States in 2015[4], and such pregnancies provide a higher contribution in terms of perinatal mortality and morbidity compared with twins and singletons[5]. A higher frequency of fetal anomalies, growth restriction and premature birth with its sequelae are likely to represent the main determinant of adverse outcome in triplets, which translates into increased healthcare costs[5]. In the US, the all-cause healthcare cost for a singleton delivery has been estimated to be $21,458 as compared to $407,199 for a triplet or higher order multiple gestation delivery[6].

Another determinant of outcome is likely to be chorionicity. In twins, monochorionicity adversely affects perinatal outcome. The shared circulation and presence of inter-twin placental vascular anastomoses in such twins[7,8] are responsible for the occurrence of twin to twin transfusion syndrome (TTTS), selective intrauterine growth restriction (sIUGR), and acute feto-fetal hemorrhage[7]. Furthermore, the presence of these vascular connections represents the pathophysiological basis for the higher risk of death and severe neurological damage in the surviving twin in case of single fetal demise[9].

The effect of chorionicity on the prevalence of perinatal mortality and morbidity in triplet pregnancies is still to be ascertained. This is mainly due to the relatively small sample size of previously published studies, their retrospective design, inclusion of cases affected by anomalies and a lack of stratification of the analysis according to chorionicity. It is also possible that the prevalence of adverse outcome in triplets "mask" the contribution of chorionicity.

Therefore, the aim of this systematic review was to quantify the risk of perinatal mortality and morbidity in triplet pregnancies, including the effect of chorionicity.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to a priori designed protocol recommended for systematic reviews and meta-analysis[10,11,12]. Medline, Embase and Cinahl databases were searched electronically on the 14th December 2017 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "triplet pregnancies" and "outcome" (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[13,14,15]. The study was registered with the PROSPERO database (Registration number: CRD42018088265).

Study selection, data collection and data items

The primary outcomes explored in the present systematic review were:

- Intrauterine death (IUD)
- Neonatal death (NND)
- Perinatal death (PND)
- Gestational age (GA) at birth

IUD was defined as the death of at least one twin from 20 weeks of gestation onwards, while NND as the death of at least one of the newborns up to 28 days of life. PND was defined as the sum of IUD or NND.

The secondary outcomes were:

- Respiratory morbidity (defined as respiratory distress syndrome, transient tachypnea of the newborn, continuous positive airway pressure for at least 24 hours, mechanical ventilation, need for supplemental oxygen, pulmonary hypertension or bronchopulmonary dysplasia).
- Neurological morbidity (defined as seizures, intraventricular hemorrhage and periventricular leukomalacia of any grade detected on ultrasound scan).
- Infectious morbidity (defined as pneumonia, meningitis, culture-proven sepsis)

Furthermore, a composite score of neonatal morbidity, defined as the occurrence of at least one of the morbidities, was ascertained. In cases where the authors did not define a composite morbidity, the composite morbidity was defined as the morbidity with the highest prevalence. All the observed outcomes were reported for trichorionic triamniotic (TCTA), dichorionic triamniotic (DCTA) and monochorionic triamniotic (MCTA) triplets.

Studies reporting the incidence of mortality and morbidity of TCTA, DCTA and/or MCTA triplets were included. Only studies from which the raw numbers to calculate the risk of every explored outcome could be extrapolated were considered suitable for the inclusion. Studies that did not define the chorionicity were not considered suitable for inclusion. Studies with sets of triplets that had embryo reduction were excluded. Studies including cases with fetal anomalies were excluded in view of the higher risk of mortality in twins affected by structural or chromosomal anomalies. Furthermore, studies only reporting on TTTS affected cases were excluded due to the higher risk of

mortality in these sets of triplets. Only full text articles were considered eligible for the inclusion. Case reports, conference abstracts and case series with fewer than 3 cases were excluded to avoid publication bias. Furthermore, studies published before 2000 were not included as advances in management of multiple pregnancies make them less relevant.

Two authors (JC, FD) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus. Full text copies of those papers were obtained and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author. If more than one study was published on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for case-control 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[16]. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts 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[16].

Statistical analysis

We performed meta-analysis of proportions to estimate the pooled incidence of mortality and morbidity in TCTA and DCTA triplets. Proportion meta-analyses were not meaningful when only one study could be included and were performed using a random-effect model to account for the inter-study heterogeneity. For MCTA triplets, due to the fact that we only included one paper in this review, the data was provided as presented in the original paper. We used the random-effect model to compute the summary mean difference (MD) in the gestational age at birth in TCTA compared to DCTA pregnancies. Finally, a random-effect model was used to estimate the pooled odds ratios (OR) for each observed outcome.

The potential publication bias was assessed either graphically, displaying the odds ratios of individual studies vs the logarithm of their standard errors (funnel plots), and formally, using Egger's regression asymmetry test[17]. Tests for publication bias were not performed as the overall number of included studies was less than ten as the power of such formal testing is too low to achieve statistical significance[18].

All analyses were carried out using StatsDirect statistical software (http://www.statsdirect.com. England: StatsDirect Ltd. 2013).

RESULTS

General characteristics

717 articles were identified, 71 were assessed with respect to their eligibility for inclusion (Table 2) and 9 studies[7,8,19,20,21,22.23,24,25] were included in the systematic review (Table 1, Figure 1). These 9 studies included 1387 triplet pregnancies (1062 TCTA, 275 DCTA and 50 MCTA). The results of quality assessment of the included studies using Newcastle-Ottawa Scale (NOS) are presented in Table 2. Most of the included studies showed an overall good score regarding the selection and comparability of the study groups, and for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size and heterogeneity in prenatal management of triplet pregnancies among the included studies.

Synthesis of the results

There were nine studies[7,8,19,20,21,22.23,24,25] including 3168 fetuses which explored the prevalence of mortality in TCTA triplet pregnancies. In TCTA triplets, IUD occurred in 2.12% (95% CI 1.0-37) of cases, while the corresponding figures for NND and PND were 3.74% (95% CI 1.8-6.3) and 5.20% (95% CI 3.2-7.7) (Table 3, Figure 2). In DCTA triplets[7,8,19,21], the incidence of IUD, NND and PND was 5.2% (95% CI 2.7-8.5), 11.5% (95% CI 1.0-30.8) and 17.6% (95% CI 4.1-37.8), respectively. When assessing those studies reporting a direct comparison, the risk of PND was higher in DCTA compared

to TCTA triplet pregnancies (OR 3.3, 95% CI 1.3-8.0) and was mainly due to the higher risk of IUD in DCTA triplet pregnancies (OR 4.6, 95% CI 1.8-11.7), while there was no difference in the incidence of NND between the two groups. In the only study included in this review that reported outcomes for MCTA triplets[7] the incidence of PND was 5.33%, including 4/150 cases of IUD and 4/150 cases of NND.

A comparison of the GA at birth between TCTA and DCTA triplets was reported by five studies[7,8,19,21,24]. Overall, there was no difference in the GA at birth between TCTA and DCTA triplets (MD: 1.12 weeks, 95% CI -0.29 – 2.52, I^2: 85%; p= 0.12). These results were mainly due to the lack of difference reported by the largest study included[7]. However, when this study was excluded from the analysis, DCTA triplets were delivered at a significantly earlier GA compared to TCTA pregnancies (MD: 1.74 weeks, 95% CI 1.02-2.45, I^2: 0%; p<0.001).

Seven (n=2574)[7,8,19,20,21.23,24] and four (n=783)[7,8,19,21] studies reported the incidence of morbidity in TCTA and DCTA triplets, respectively. Neurological morbidity occurred in 2.04% (95% CI 1.1-3.3) of TCTA and in 11.6% (95% CI 1.1-40.0) of DCTA triplets. The respective values in TCTA versus DCTA for respiratory morbidity were 28.33% (95% CI 20.7-36.8) and 34.0% (95% CI 21.5-47.7); and for infectious morbidity they were 4.22% (95% CI 2.8-5.9) and 7.1% (95% CI 2.7-13.3). Finally, the prevalence of composite morbidity was 29.61% (95% CI 21.1-38.9) and 34.0% (95% CI 21.5-47.7), respectively (Figure 3). When translating these figures into a risk analysis, the risk of neurological morbidity (OR: 5.4, 95% CI 1.6-18.3) was higher in DCTA compared to TCTA triplets, while there was no significant difference in the other morbidities explored

(Table 3, Figure 4 and 5). The occurrence of TTTS in DC triplets varied between 5% and 28% amongst the studies. The overall incidence of TTTS was 12.6% (33/261 DCTA triplets). Of these, 3 sets of triplets[19] (9% of the DCTA population) underwent a fetoscopic laser ablation. Two sets of triplets underwent an amniotic septostomy[8] and 15 had serial amnioreduction[8,21]. In 10 sets of triplets no intervention was offered either because it was not a management option in that specific setting[7] or patients presented in frank labour[21]. The only study included that reports on perinatal morbidity of MCTA triplets[7] showed a prevalence of 2,67% of neurological morbidity, 25,33% of respiratory morbidity, 3,33% of infectious morbidity and 25,33% of composite morbidity.

DISCUSSION

Main findings

The findings from this systematic review confirm the relatively high risk of adverse perinatal outcome in triplet pregnancies. We also showed that chorionicity has an effect, with DCTA triplets having worse outcomes compared to TCTA triplets. The risk of PND was higher in DCTA when compared with TCTA pregnancies, mainly due to a higher rate of IUD in triplets with monochorionic (MC) placentation. Although this group had poorer results for every outcome explored, the neurological morbidity showed the most significant discrepancy, with DCTA triplets exhibiting five-fold higher odds of neurological morbidity. Respiratory morbidity was common in both groups due to the high rate of preterm birth. Of note, the rate of NND doubled the rate of IUD, for both groups. The only study reporting on MCTA outcomes showed poor outcomes but no formal comparison was performed due to the fact that only one study was included.

Strengths and limitations

The small number of studies included, their retrospective non-randomized design, heterogeneity in prenatal management, outcomes explored, and postnatal assessment represent limitations of this review. Assessment of the potential publication bias was also problematic because of the scarce number of individual studies. Not all of the included studies were case-control series reporting matched populations and it might be possible that the presence and degree of association between some of the

observed outcomes and the study populations might have been affected by several co-factors which were not balanced between TCTA and DCTA triplets. Also, it was not possible to analyse separately the outcomes of TTTS affected and non-TTTS affected DCTA. The only authors reporting on these outcomes separately[21] showed poorer results for the TTTS-affected group. Finally, we could not meta-analyze data on the outcomes of MCTA triplets since only one paper was suitable for inclusion. The composite morbidity might include a wide variety of morbidities with different impact in the outcome of these neonates. Some of the neonates experience more than one neonatal complication and it is difficult to accurately ascertain this data from the studies. Nevertheless, our meta-analysis represents the most comprehensive published estimate of the explored outcomes in triplet pregnancies according to chorionicity.

Interpretation of study findings and comparison with existing literature

In this review, DCTA triplets were generally at higher risk of mortality and morbidity compared to TCTA gestations. Complications unique to monochorionicity such as TTTS and sIUGR are likely to be responsible for the different survival rates. In our study the incidence of TTTS in DC triplets was 12.6%. The fetal and perinatal survival rates are lower in triplets than those reported in twin pregnancies[26]. Although the survival of the unaffected triplet is not usually compromised by the hemodynamic imbalance occurring in the MC pair, the entire pregnancy may be at risk of miscarriage or early preterm labour. Furthermore, fetoscopic laser treatment for TTTS - the recommended treatment modality in twins[27] - could be more challenging in triplet

pregnancies. The timing of IUD was reported in two of the studies included (Table 4). These studies reported low IUD rates for TCTA triplets after 24 weeks gestation. In contrast, DCTA triplets seem to be at higher risk of IUD after 24 weeks, which provides a rationale for closer monitoring and surveillance.

In this review, the risk of neurological morbidity was higher in DCTA compared to TCTA triplets. This might be due to the peculiar vascular arrangement of the MC pair predisposing to TTTS, sIUGR and brain damage in case of single fetal loss. Acute transfusional events may occur in uncomplicated MC pregnancies, potentially leading to sudden fetal ischemia and neurological compromise. The incidence of abnormal neurological outcome in DCTA triplet pregnancies affected by TTTS has been reported to be around 6% in a recent systematic review[28]. Finally, in common clinical practice, DCTA triplets are usually delivered earlier than TCTA which could partially explain the higher incidence of neurological morbidity although in our study there was no significant difference in the GA at birth.

Clinical and research implications

Accurate prenatal counseling of parents with triplet pregnancies is challenging. Lack of high quality epidemiological data on the pregnancy outcome according to chorionicity does not allow us to extrapolate robust evidence on the actual incidence of mortality and morbidity in TCTA and DCTA triplet pregnancies.

Counselling should include the higher risk of perinatal mortality, morbidity and preterm birth compared to singleton and twin pregnancies. Selective reduction from three to two fetuses has been reported to lower the risk of severe preterm delivery, but also to increase the risk of miscarriage in DCTA and TCTA pregnancies[2,3]. In DCTA triplets, reduction to two fetuses by reducing one of the MC pair is not possible using the injection techniques because of the presence of vascular connections, while there is still limited evidence on the use of vascular-occlusive techniques in early uncomplicated DCTA triplets[29]. Another option is to reduce the fetus with a separate placenta resulting in a MC twin pair. However, this option has been reported to be associated with the highest risk of complications. A third option is reduction from three to one fetus by reducing the MC pair, which might not be acceptable for the parents[2,30].

Respiratory morbidity was the commonest observed in all groups (TCTA, DCTA and MCTA), most likely secondary to preterm delivery. Besides, despite the policy of elective preterm delivery for triplet pregnancies, the likelihood of having an NND doubled that of having an IUD for DCTA and TCTA triplets. This raises doubts about what should be the optimal GA to deliver these patients. Women with dichorionic twin pregnancies should be delivered at 37 weeks' gestation to minimize the risk of perinatal deaths near term[31]. Moreover, there is insufficient evidence to recommend routine delivery before 36 weeks' gestation in monochorionic twins[31]. Given the relative rarity of triplet pregnancies and the resulting challenges in even multicenter trials, estimates of NND versus IUD according to GA may help define the optimal timing of planned birth.

Conclusions

DCTA are at higher risk of perinatal mortality and morbidity compared to TCTA triplet pregnancies.

Details of ethics approval

No ethics approval was needed for this article.

Acknowledgements

We would like to thank Ms Karen John-Pierre, NHS liaison librarian at St George's University of London, for her help with the literature search.

REFERENCES

1. Simmons R, Doyle P, Maconochie N. Dramatic reduction in triplet and higher order births in England and Wales. BJOG 2004;111:856–8.
2. Morlando M, Ferrara L, D'Antonio F, Lawin-O'Brien A, Sankaran S, Pasupathy D, Khalil A, Papageorghiou A, Kyle P, Lees C, Thilaganathan B, Bhide A. Dichorionic triplet pregnancies: risk of miscarriage and severe preterm delivery with fetal reduction versus expectant management. Outcomes of a cohort study and systematic review. BJOG 2015; 122:1053-1060.
3. Papageorghiou AT, Avgidou K, Bakoulas V, Sebire NJ, Nicolaides KH. Risks of miscarriage and early preterm birth in trichorionic triplet pregnancies with embryo reduction versus expectant management: new data and systematic review. Hum Reprod. 2006 Jul;21(7):1912-7.
4. Martin JA, Hamilton BE, Osterman MJK. Births in the United States, 2016. NCHS Data Brief. 2017 Sep;(287):1-8.
5. Stone J, Kohari K. Higher-order multiples. Clin Obstet Gynecol 2015; 58, 668–675
6. Lemos EV, Zhang D, Van Voorhis BJ, Hu XH. Healthcare expenses associated with multiple vs singleton pregnancies in the United States. Am J Obstet Gynecol. 2013;209:586.e1–586.e11.
7. Kawaguchi H, Ishii K, Yamamoto R, Hayashi S, Mitsuda N, Perinatal Research Network Group in Japan. Perinatal death of triplet pregnancies by chorionicity. Am J Obstet Gynecol 2013;209:36.e1-7.

8. Bajoria R, Ward S, Adegbite A. Comparative study of perinatal outcome of dichorionic and trichorionic iatrogenic triplets. Am J Obstet Gynecol (2006);194: 415–24.
9. Ong S, Zamora J, Khan K, Kilby M. Prognosis for the co-twin following single-twin death: a systematic review. BJOG 2006;113:992-998.
10. Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC. How to write a Cochrane systematic review. Nephrology (Carlton) 2010;15:617-624.
11. NHS Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. University of York: York (UK), 2009. Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Retrieved December 3, 2016.
12. Welch V, Petticrew M, Petkovic J, Moher D, Waters E, White H, Tuqwell P. Extending the PRISMA statement to equity-focused systematic reviews (PRISMA-E 2012): explanation and elaboration. J Clin Epidemiol 2016;70:68-89.
13. Moher D, Liberati A, Tetzlaff J, Altman DG, and the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Ann Intern Med* 2009;151:264–269.
14. Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, Moher D, Vohra S; PRISMA harms group. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ 2016;352: i157.
15. 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.

16. Newcastle-Ottawa Scale for assessing the quality of nonrandomised studies in metaanalyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
17. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629-634.
18. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2009. at www.cochrane-handbook.org. Accessed 3 December 2016].
19. Simões T, Queiros A, Gonçalves MR, Periquito I, Silva P and Blickstein I. Perinatal outcome of dichorionic-triamniotic as compared to trichorionic triplets. J. Perinat. Med. 2016 Oct 1;44(8):875-879.
20. Combs CA, Garite T, Maurel K, Das A, Porto M, Obstetrix Collaborative Research Network. Failure of 17-hydroxyprogesterone to reduce neonatal morbidity or prolong triplet pregnancy: a doubleblind, randomized clinical trial. Am J Obstet Gynecol 2010;203:248.e1-9.
21. Adegbite AL, Ward SB, Bajoria R. Perinatal outcome of spontaneously conceived triplet pregnancies in relation to chorionicity. Am J Obstet Gynecol 2005;193,1463-1471.
22. Antsaklis A, Souka A. P., Daskalakis G., Papantoniou N., Koutra P., Kavalakis Y., Mesogitis S. Embryo reduction versus expectant management in triplet pregnancies. J Matern Fetal Neonatal Med 2004; 16:219–222.
23. Downing M, Sulo S, Parilla BV. Perinatal and Neonatal Outcomes of Triplet Gestations Based on Chorionicity. Am J Perinatol Rep 2017;7:e59–e63.

24. Spencer JV, Ingardia CJ, Nold CJ, Borgida AF, Herson VC, Egan JFX. Perinatal and Neonatal Outcomes of Triplet Gestations Based on Placental Chorionicity. Am J Perinatol 2009; 26(8):587-90.
25. Geipel A, Berg C, Katalinic A, Plath H, Hansmann M, Germer U, Gembruch U. Prenatal diagnosis and obstetric outcomes in triplet pregnancies in relation to chorionicity. BJOG 2005,112:554–558.
26. D'Antonio F, Thilaganathan B, Toms J, Manzoli L, Bhide A, Papageorghiou A, Khalil A. Perinatal outcome after fetoscopic laser surgery for twin-to-twin transfusion syndrome in triplet pregnancies. BJOG. 2016 Feb;123(3):328-36.
27. Senat, MV, Jan Deprest, Boulvain M, Paupe A, Winer N, Ville Y, Endoscopic Laser Surgery versus Serial Amnioreduction for Severe Twin-to-Twin Transfusion Syndrome. N Engl J Med 2004;351:136-44.
28. Miralles-Gutiérrez A, Narbona-Arias I, González-Mesa E. Neurological complications after therapy for fetal-fetal transfusion syndrome. J. Perinat. Med. 2017; aop.
29. Bhide A, Sankaran S, Sairam S, Papageorghiou AT, Thilaganathan B. Relationship of intertwin crown-rump length discrepancy to chorionicity, fetal demise and birth-weight discordance. Ultrasound Obstet Gynecol. 2009 Aug;34(2):131-5.
30. Papageorghiou AT. Ethical considerations in embryo-reduction. Current Obstetrics & Gynaecology. Volume 16, Issue 3, June 2006, 181-184.
31. Cheong-See F, Schuit E, Arroyo-Manzano D, Khalil A, Barrett J, Joseph K S, Asztalos E, Hack K, Lewi L, Lim A, Liem S, Norman J, Morrison J, Combs CA, Garite TJ, Maurel K, Serra V, Perales A, Rode L, Worda K, Nassar A, Aboulghar

M, Rouse D, Thom E, Breathnach F, Nakayama S, Russo FM, Robinson JN, Dodd JM, Newman RB, Bhattacharya S, Tang S, Mol B W J, Zamora J, Thilaganathan B, Thangaratinam S, A Global Obstetrics Network (GONet) Collaboration. Prospective risk of stillbirth and neonatal complications in twin pregnancies: systematic review and meta-analysis. BMJ 2016;354:i4353.

Figure legends

Figure1. Systematic review flowchart

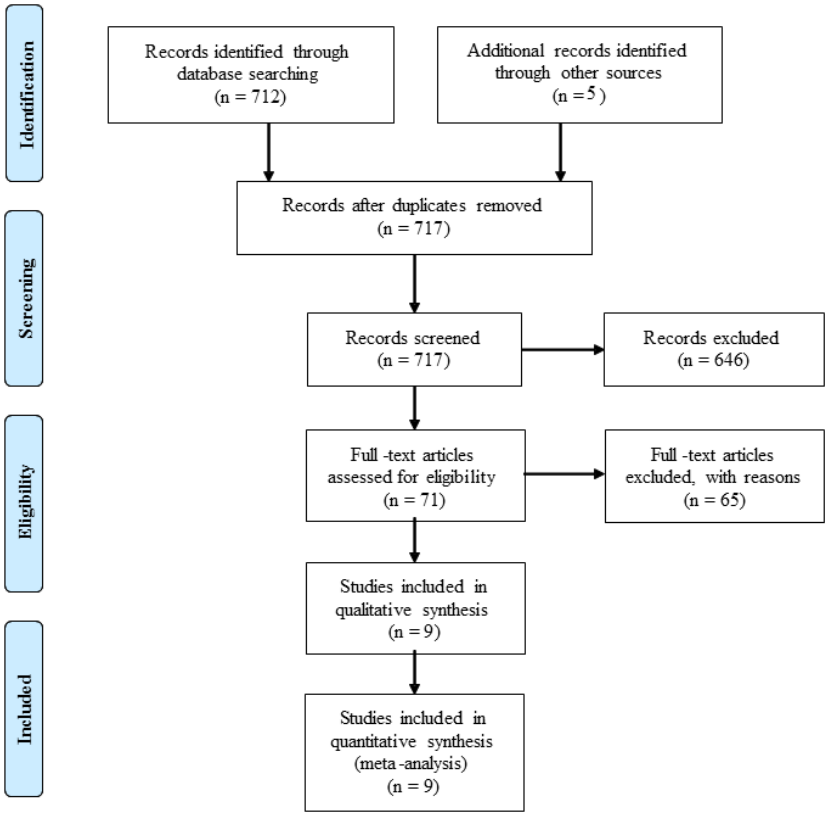
Figure 2. Pooled proportions of the perinatal death in trichorionic-triamniotic (TCTA) and dichorionic-triamniotic (DCTA) triplet pregnancies

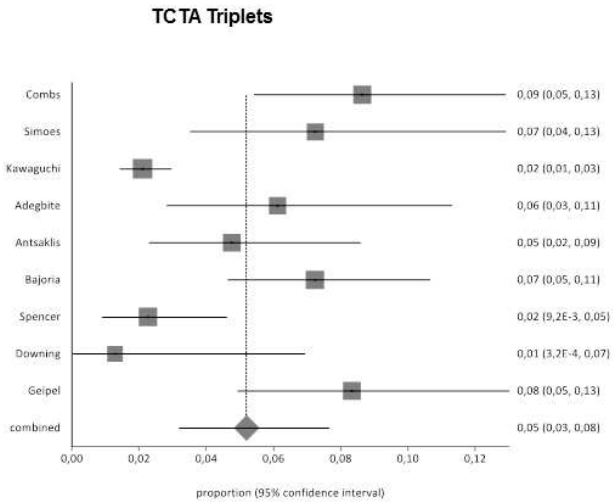
Figure 3. Pooled odds ratios (OR) of the perinatal death in trichorionic-triamniotic (TCTA) and dichorionic-triamniotic (DCTA) triplet pregnancies

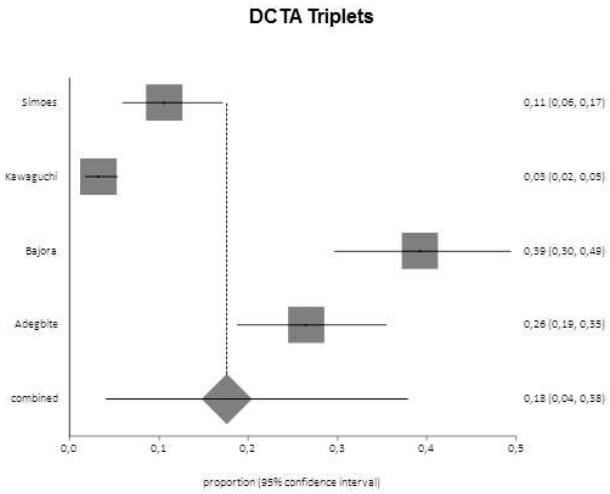
Figure 4. Pooled proportions of composite neonatal morbidity in trichorionic-triamniotic (TCTA) and dichorionic-triamniotic (DCTA) triplet pregnancies

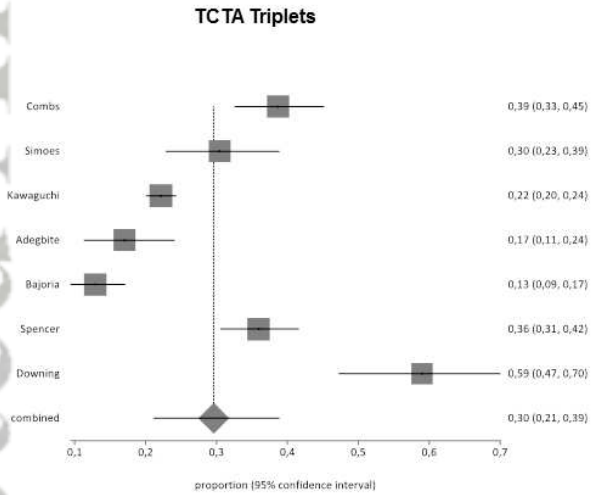
Figure 5. Pooled odds ratios (OR) of composite neonatal morbidity in in trichorionic-triamniotic (TCTA) and dichorionic-triamniotic (DCTA) triplet pregnancies

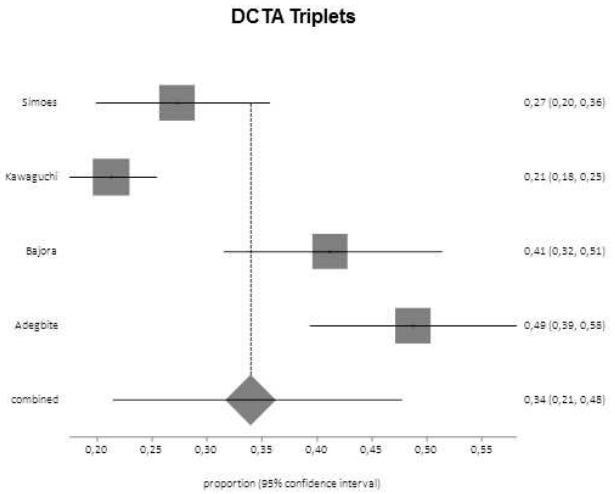
Each study is represented by a line. The box in the middle of the line represents the point effect estimate of this particular study. The midpoint of the box represents the point effect estimate, that is, the mean effect estimates for each study. The area of the box represents the weight given to the 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. N = total number in group, while n = number in group with the outcome. Heterogeneity (I^2) = diversity between studies.

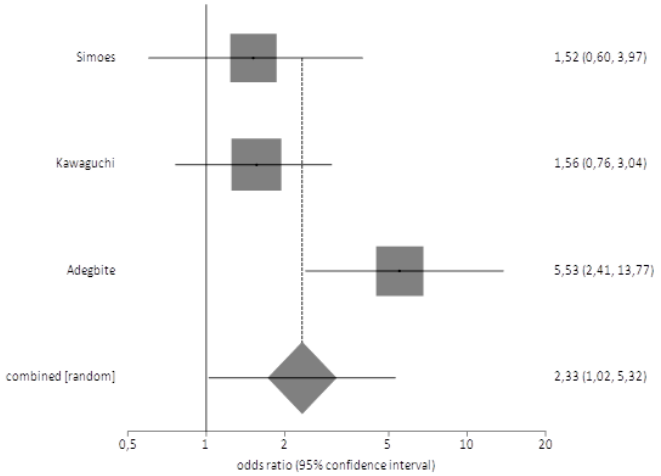


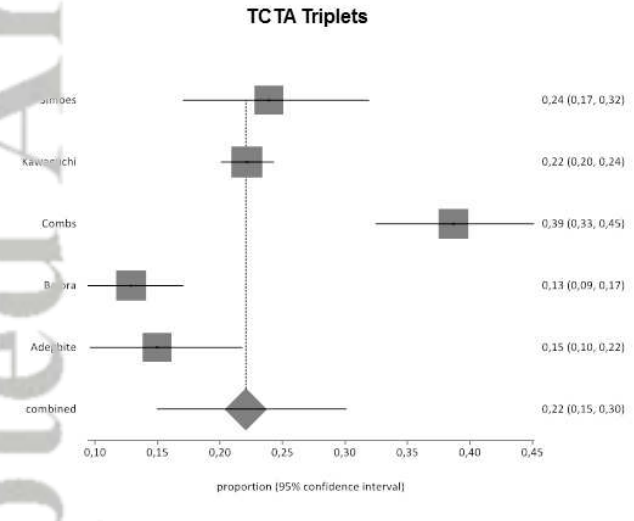












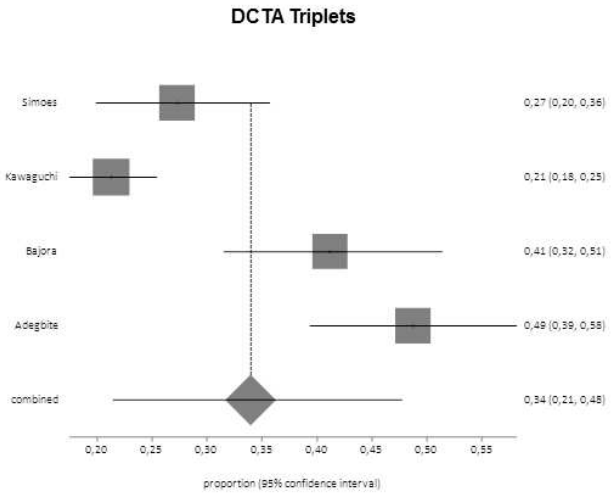


Table 1. General characteristics of the studies included.

Author	Year	Country	Study design	Period considered	Triplet pregnancies (n)	TCTA triplets (n)	DCTA triplets (n)	MCTA triplets (n)
Downing	2017	United States	Retrospective	2009-2015	42	26	14†	2†
Simões	2016	Portugal	Prospective	1994-2014	90	46	44	6 *
Kawaguchi	2013	Japan	Retrospective	1999-2009	651	507	144	50
Combs	2010	United States	Prospective	2004-2008	81	81	0	0
Spencer	2009	United States	Retrospective	1995-2007	134	109	23†	0
Bajoria	2006	United Kingdom	Retrospective	1986-2000	140	106	34	0
Adegbite	2005	United Kingdom	Retrospective	1986-2000	88	49	39	0
Geipel	2005	Germany	Retrospective	1998-2003	87	68	NS	NS
Antsaklis	2004	Greece	Retrospective	1982-2001	70	70	0	0

NS – not specified, * not included in the analysis, † not possible to extract data on these triplets

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (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.

Author	Year	Selection	Comparability	Outcome
Downing	2017	★★	★	★★
Simoes	2016	★★	★★	★★
Kawaguchi	2013	★★★	★★	★★
Combs	2010	★★	★	★★
Spencer	2009	★★	★	★★
Bajoria	2006	★★	★	★★
Adegbite	2005	★★	★	★★
Geipel	2005	★★★	★	★
Antsaklis	2004	★★	★	★

Table 3. Pooled proportions (PP) and odd ratios (OR) for the occurrence of the different outcomes explored in this systematic review in trichorionic-triamniotic (TCTA) vs dichorionic-triamniotic (DCTA) triplets.

	TCTA triplets					***DCTA triplets***							
Outcome	**Studies (n)**	**Fetuses**	**PP (95% CI)**	**I^2 (%)**		**Studies (n)**	**Fetuses**	**PP (95% CI)**	**I^2 (%)**		**OR (95% CI)**	**p-value**	**I^2**
Mortality													
IUD	7	44/2781	2.12 (1.0-37)	79.8		4	34/783	5.22 (2.7-8.5)	64.7		4.56 (1.8-11.7)[a]	0.001	49.3
NND	7	78/2781	3.74 (1.8-6.3)	87.0		4	65/783	11.46 (1.0-30.8)	97.5		2.22 (0.8-6.6)[b]	0.149	81.4
PND	9	130/3168	5.20 (3.2-7.7)	84.5		5	99/783	17.61(4.1-37.8)	97.2		3.27 (1.3-8.0)[c]	0.001	84.7
Morbidity													
Neurological	7	42/2754	2.04 (1.1-3.3)	65.6		4	67/783	11.62 (1.1-40.0)	97.5		5.43 (1.6-18.3)[d]	0.006	76.0
Respiratory	7	671/2754	28.33 (20.7-36.8)	94.1		4	227/783	33.97 (21.5-47.7)	92.5		2.28 (0.9-5.8)[e]	0.08	94.0

Infectious	6	94/2676	4.22 (2.8-5.9)	66.0		4	43/783	7.05 (2.7-13.3)	86.5		1.52 (0.9-2.5)[f]	0.208	24.6
Composite	5	696/2754	29.61 (21.1-38.9)	95.1		4	227/783	33.97 (21.5-47.7)	92.5		2.28 (0.9-5.8)[g]	0.08	94.0

a: Computation based on 4 studies (19/2124 TCTA vs 34/783 DCTA triplets)

b: Computation based on 4 studies (55/2124 DCTA vs 65/783 MA pregnancies)

c: Computation based on 4 studies (74/2124 vs 99/783 MA triplets)

d: Computation based on 4 studies (28/2124 TCTA vs 67/783 DCTA triplets)

e: Computation based on 4 studies (433/2124 TCTA vs 227/783 DCTA triplets)

f: Computation based on 4 studies (68/2124 TCTA vs 43/783 DCTA triplets)

g: Computation based on 4 studies (433/2124 TCTA vs 227/783 DCTA triplets)

Table 4. Timing of IUD for DCTA and TCTA triplets.

	<24 weeks	24-28 weeks	>28 weeks
DCTA*	4/34	3/34	3/34
TCTA†	10/176	1/176	0/176

*** data extracted from one study[8]; † data extracted from two studies [8,22]**