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MacKie, Fiona; Rigby, Ashlee; Morris, R. Katie; Kilby, Mark

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Prognosis of the co-twin following spontaneous single intrauterine fetal death in twin pregnancies: a systematic review and meta-analysis

Fiona L MACKIE.

[1]Centre for Women's & Children Health, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, B15 2TT, UK.

Ashlee RIGBY.

[2]Flinders Medical Centre, Adelaide, South Australia, Australia.

R. Katie MORRIS.

[1]Centre for Women's & Children Health, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, B15 2TT, UK.

[3]West Midlands Fetal Medicine Centre, Birmingham Women's and Children's NHS Foundation Trust, Mindelsohn Way, Edgbaston, B15 2TG, UK.

Mark D. KILBY.

[1]Centre for Women's & Children Health, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, B15 2TT, UK.

[3]West Midlands Fetal Medicine Centre, Birmingham Women's and Children's NHS Foundation Trust, Mindelsohn Way, Edgbaston, B15 2TG, UK.

Corresponding author: Fiona L MACKIE, Centre for Women's & Children Health, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, B15 2TT, UK. +447759158255 fionamackie@doctors.org.uk

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Short version of title: Prognosis of co-twin in single intrauterine fetal death

Abstract

Background: Single intrauterine fetal death affects approximately 6% of twin pregnancies and can have serious sequelae for the surviving co-twin.

Objectives: Determine the prognosis of the surviving co-twin following spontaneous single intrauterine fetal death~~IUFD~~s to aid counselling patients and highlight ~~areas of~~ future research areas.

Search strategy: Medline, Embase, Web of Science, and Cochrane Library, from 1980 and June 2017.

Selection criteria: Studies of ≥5 cases of spontaneous single intrauterine fetal death after 14 weeks gestation, in diamniotic twin pregnancies.

Data collection and analysis: Summary event rates were calculated and stratified by chorionicity. Monochorionic and dichorionic twins, and sub-groups, were compared by odds ratios.

Main results: In monochorionic twins, when single intrauterine fetal death occurred at <28 weeks gestation, this significantly increased the rate of co-twin intrauterine fetal death (OR 2.31[95%CI 1.02, 5.25],I^2=0.0%,12 studies,184 pregnancies) and neonatal death (OR 2.84[95%CI1.18,6.77],I^2=0.0%,10 studies,117 pregnancies) compared to when the single intrauterine fetal death~~IUFD~~s occurred >28 weeks. Neonatal death in monochorionic twins was significantly higher if the pregnancy was

complicated by fetalintrauterine growth restriction (OR 4.83[95%CI1.14,20.47],I^2=0.0%,6 studies,60 pregnancies) or preterm birth (OR 4.95[95%CI 1.71,14.30],I^2=0.0%,11 studies,124 pregnancies). Abnormal antenatal brain imaging was reported in 20.0% ([95%CI12.8,31.1]I^2=21.9%,6 studies,116 pregnancies) of surviving monochorionic co-twins. The studies included in this meta-analysis demonstrated small study effects and possible selection bias.

Conclusions: Preterm birth was the commonest adverse outcome affecting 58.5% and 53.7% of monochorionic and dichorionic twin pregnancies and was associated with increased neonatal death risk. The studies included in this meta-analysis demonstrated small study effects and possible selection bias. Outcomes regarding brain imaging and neurodevelopmental comorbidity are an important area for future research but meta-analysis was limited due to different methods of assessment.

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Keywords: co-twin death, fetal brain imaging, fetalintrauterine growth restriction, neonatal death, neurodevelopmental comorbidity, preterm birth, prognosis, single intrauterine fetal death, twin pregnancy, twin-twin transfusion syndrome

Tweetable abstract: Preterm birth highest risk in single #twin death. Abnormal antenatal brain imaging in 1/5 surviving MC twins.

Introduction

Twin pregnancies are associated with increased perinatal morbidity and mortality compared to singletons. Single intrauterine fetal death (sIUFD) occurs in approximately 6% of twin pregnancies, making it a common adverse event (1). Monochorionic (MC) twins with placental inter-twin anastomoses conjoining the fetal circulations are associated with an increased risk of sIUFD and consequential fetal morbidity (2, 3). Many are first trimester fetal losses, but sIUFD after 14 weeks gestation is associated with greatest adverse effect on the surviving fetus (4). Morbid events associated with sIUFD in twin pregnancy include: co-twin IUFD, preterm birth (spontaneous or iatrogenic), and long term comorbidity; most commonly ante- or postnatal brain injury. A critical appraisal and interpretation of the literature is complicated by significant heterogeneity in the incidence and management in reported studies (5). In 2011, our group completed a systematic review and meta-analysis of co-twin prognosis following sIUFD, with outcomes stratified by chorionicity. In the 22 included manuscripts there were 343 cases of sIUFD reported in 6225 twin pregnancies (6). A meta-analysis of event rates was not undertaken as there was a high risk of heterogeneity and low number of events within each study. A summary point estimate was produced with a simple binomial confidence interval, thus not allowing for the non-independence of the different studies. This manuscript demonstrated an increased odds ratio of co-twin death and neurodevelopmental morbidity after sIUFD in MC compared to dichorionic (DC) twin pregnancies. The management of multiple pregnancies in general, particularly~~and~~ MC pregnancies ~~in particular~~, has received considerable attention since 2011 with national and international guidelines being published by ~~international~~ professional bodies (7-12).

Importantly the 2011 review included twin pregnancies that had undergone intervention for twin-twin transfusion syndrome (TTTS) and fetal growth restriction (FGR) ~~IUGR~~, thus confounding factors such as surgeon experience may have ~~will~~ affected the reported prognosis (13). This review will focus on spontaneous sIUFD only and will not include pregnancies that have undergone treatment for TTTS~~FLA~~ or ~~IUGR~~FGR.

The objective of the study wa~~i~~s to determine the prognosis of the surviving co-twin following spontaneous sIUFD. The outcomes explored w~~w~~ere~~ill be~~: co-twin IUFD, ~~preterm birth~~PTB, abnormal postnatal brain imaging and neurodevelopmental comorbidity as analysed in our previous systematic review and meta-analysis, and the additional outcomes of abnormal antenatal brain imaging and neonatal death w~~were~~ill also ~~be~~ examined. This review has~~will allow~~ allowed inclusion of the recent literature informing clinical practice to aid counselling patients and highlight areas of future research.

Methods

The systematic review was performed according to an *a priori* protocol and complied with recommended guidance including the 'Meta-analyses and systematic reviews Of Observational Studies' (MOOSE) and 'Preferred Reporting Items for Systematic reviews and Meta-Analyses' (PRISMA) guidelines (14, 15). Ethical approval was not required. FLM is funded by the Richard and Jack Wiseman Trust but they had no involvement in study

Eligibility criteria

Studies must have included at least 5 cases of sIUFD in twin pregnancies, and the gestation of the initial sIUFD must have been after 14 weeks. Twin chorionicity had to be defined but studies did not have to include both MC and DC twin pregnancies in the same study. Studies were excluded if the following conditions could not be abstracted for analysis~~removed for analysis i.e. if the following cases were not identifiable in analysis~~: selective termination, higher order multiple pregnancies, twin reversed arterial perfusion (TRAP) sequence, structural or chromosomal anomalies, conjoined twins, monoamniotic twins, or first-trimester miscarriages associated with twins. As the aim of the study was to assess spontaneous IUFD, IUFDs which occurred following an intervention for TTTS or s~~IUGR~~FGR, including fetoscopic laser ablation (FLA) or bilateral cord occlusion (BCO), were not included in the analysis as there are confounding factors that may affect the outcome of the pregnancy, including surgeon experience, which make this group heterogeneous (13). ~~As FLA dichorionises the placenta and this was considered to have more of an effect on outcome, whereas a~~Amniodrainage was not considered an intervention that~~which~~ affects ~~would affect~~ co-twin~~the~~ prognosis ~~in the co-twin~~, as the main reason for IUFD following amniodrainage is likely due to TTTS itself, rather than a complication of the amniodrainage~~procedure~~, thus these pregnancies remained in the analysis.

Outcomes

There is no core outcome set for multiple pregnancy, particularly sIUFD co-twin survivors, and patients were not involved in the development of the research, thus the outcomes assessed were the outcomes in the previous review, with the addition

of antenatal brain imaging and neonatal death. The outcomes were defined *a priori* as:

- Co-twin intrauterine fetal death, >14 weeks gestation but prior to delivery.
- Preterm birth (PTB), defined as a live birth of the surviving co-twin, irrespective of whether the birth was spontaneous or iatrogenic which will be explored as a sub-group analysis, between 24^{+0}-34^{+0} weeks gestation as some monochorionic diamniotic ~~MCDA~~ twins are routinely delivered at <36 weeks, and with little long-term consequence.
- Abnormal antenatal brain imaging. There was no limit on timing of imaging post-IUFD or type of imaging due to no consensus guidance existing at the time of this review.
- Abnormal postnatal brain imaging. There was no limit on imaging modality. ~~.~~
- Neurodevelopmental comorbidity, defined as per study, as there is no standard test to assess this in sIUFD.
- Neonatal death (NND), defined as death within 28 days of live birth.

Information sources

The search was performed according to previously published methods (6). In brief, Medline, Embase, Web of Science, Cochrane Library and British Nursing Index were searched. Due to including the new outcomes of abnormal antenatal brain imaging,

and neonatal death, the ~~information~~ searches were run from 1980 due to the introduction of ultrasound into clinical practice, to 9th June 2017.

Search strategy

Keywords and variants of “intrauterine” “death” and “twin” were used (see Appendix S1 for search strategy). Bibliographies were manually checked and there was no restriction on language.

Study selection and data extraction

FLM, AR and RKM independently extracted the data needed to assess the quality of the studies and form a 2x2 contingency table, using piloted data collection forms. Data from the previous systematic review by Hillman (6) was re-extracted by FLM and RKM. Any discrepancies were resolved by MDK. If clarification was required authors were contacted.

Quality assessment of included studies

The quality of the studies was assessed according to the ‘Strengthening the Reporting of Observational studies in Epidemiology’ (STROBE) checklist (16).

Assessment of heterogeneity

Heterogeneity between the studies was assessed visually using forest plots and statistically using the I^2 statistic. An I^2 statistic ≥50% indicated a high-risk of heterogeneity. Heterogeneity was investigated via sub-group and sensitivity analysis.

Assessment of reporting bias

If >10 studies were included in a meta-analysis, a funnel plot was generated~~using the *metafunnel* command (17)~~ in Stata (Stata, 2015 Release 13.1, StataCorp. Texas, USA) and Egger's test was performed ~~using the *metabias* command (18),~~ with p<0.05 considered a significant risk of small-study effects publication bias.

Data synthesis

With the additional 20 studies, we have produced a summary event rate statistic which has allowed for the non-independence of different studies when the data is pooled, as is appropriate in a meta-analysis. ~~This was calculated using the *metan* command (1).~~Odds ratios (ORs) with random effects were calculated to compare the risk in MC twin pregnancies with DC twin pregnancies ~~using the *metan* command~~. 0.5 was added to 0 cells in all analyses to allow inclusion of more studies ~~(20).~~(17). If a study only included MC twin pregnancies, the study was used to calculate the summary event rate for MC twins only, and was not included in the DC summary event rate or OR calculation of MC vs. DC twins, and vice versa if a study only included DC twin pregnancies. Sub-group analysis, in analyses of ≥3 studies, was planned to evaluate the effect of factors identified as potential causes of heterogeneity prior to commencing analysis: gestational age of sIUFD <28 weeks, TTTS (managed conservatively meaning no intervention but continued surveillance),

~~IUGR~~FGR (managed conservatively), year of publication pre-and post-2011. Twenty-eight weeks was chosen as a cut-off to distinguish between trimesters as there is no research to determine an evidence-based cut-off. PTB as an outcome was also divided by iatrogenic and spontaneous where possible. Antenatal and postnatal brain imaging were divided by imaging modality, and the postnatal outcomes were also divided by PTB where possible, the latter irrespective of whether the PTB was iatrogenic or spontaneous. The sub-group summary event rate was reported as the rate of the outcome (e.g. co-twin IUFD) in women with or without that factor (e.g. sIUFD at <28 weeks, TTTS, ~~IUGR~~FGR) to enable maximum clinical utility for counselling women in each scenario. ORs were calculated to compare the summary event rate for each factor in MC and DC twin pregnancies.

Results

Study selection and characteristics

The search revealed 2966 citations potentially eligible for inclusion, of which 2629 were excluded on the title or abstract, 337 complete manuscripts~~full papers~~ were assessed, and 42 full papers were eligible for inclusion (2, 3, 18-57) (Figure S1). The characteristics of the included studies are described in Supplementary File Table S1 which summarises the study design, study population, and details of abnormal brain imaging and neurodevelopmental comorbidity. The previous review included 22 studies (2, 19, 20, 22, 26, 28, 30, 32, 34, 35, 37, 41-43, 47, 49, 50, 52, 54, 55, 57, 58). Of the 42 studies, 39 were included in the meta-analysis (for details of excluded studies and Appendix S2). The additional outcomes of antenatal brain imaging and

neonatal death were reported by 6 studies, and 19 studies respectively. The imaging modalities used were ultrasound and fetal magnetic resonance imaging (fMRI) antenatally, and CT scan was also used postnatally.

Risk of bias of included studies

The quality of the included studies is displayed in Figure 1. All the studies reported study design and the number of outcome events. None of the studies explained how their sample size was determined. The number of participants at each stage of the study was reported in 20/42 (47.6%) studies which may be that selective reporting occurred in some studies. Only 15/42 (35.7%) studies reported which data were missing, and 19/42 (45.2%) adequately reported the limitations of their study. When there were >10 studies and Egger's test was performed, the results were reported below with each outcome as some analyses did suggest small-study effects ~~publication bias~~.

Figure 1 about here please

Synthesis of results

Summary event rates

Table 1 about here please

The co-twin survivor in MC twin pregnancies was at significantly higher risk of co-twin IUFD (Table 1, Figure 2. Additional forest plots and extracted 2x2 data are shown in Appendix S3.

) and abnormal postnatal brain imaging than co-twin survivors in DC twin pregnancies. No significant difference was found between MC and DC twin pregnancies in the rate of PTB, neurodevelopmental comorbidity or NND, although the latter outcome was borderline significant. The rate of abnormal antenatal brain imaging in MC twin pregnancies was 20%, but as no studies were found reporting this outcome in DC twin pregnancies, the OR was not calculated. The abnormal brain imaging findings included: intraventricular haemorrhage, periventricular haemorrhage, focal infarction, extensive encephalomalacia, poor sulcation and abnormal cortex consistent with extensive reparative polymicrogyria.

~~Additional forest plots and extracted 2x2 data are shown in Appendix S3.~~

Figure 2 about here please

Sub-group

Sub-group analysis demonstrated that in MC twin pregnancies, those with an~~the~~ sIUFD <28 weeks were significantly more likely to have a co-twin IUFD than those with an~~the~~ sIUFD ≥28 weeks. The pathologies of TTTS and ~~IUGR~~FGR were not associated with an increased risk of co-twin IUFD (Table 2). Pregnancies

complicated by TTTS were significantly more likely to have a PTB than twin pregnancies without TTTS. When preterm birth was divided according to whether it was iatrogenic or spontaneous, in MC twins the summary event rate of iatrogenic PTB was 60.4% ([95%CI 33.5, 109.1] I^2=0.00%, 3 studies, 7 pregnancies) compared to a spontaneous PTB rate of 37.1% % ([95%CI 20.5, 66.9] I^2=24.1%, 3 studies, 4 pregnancies). There were no significant sub-group results for abnormal postnatal brain imaging, or neurodevelopmental comorbidity in MC twins, and it was not possible to perform sub-group analysis for the abnormal antenatal brain imaging, as often this information was not included in the primary full manuscripts. In DC twins the summary event rate of iatrogenic PTB was 32.4% ([95%CI 14.6, 72.1] I^2=32.7%, 3 studies, 6 pregnancies) compared to a spontaneous PTB rate of 70.7% ([95%CI 31.8, 157.4] I^2=0.0%, 3 studies, 6 pregnancies), although the wide 95% CIs should be noted, which may be due to small sample size. Other sub-group analysis in DC twins was limited due to small numbers, but the following analyses were possible, none of which found a significant difference: sIUFD <28 weeks did not affect co-twin IUFD, PTB, abnormal postnatal brain imaging, neurodevelopmental comorbidity or NND; IUGRFGR did not affect co-twin IUFD or PTB, neurodevelopmental comorbidity or NND; PTB did not affect abnormal postnatal brain imaging, neurodevelopmental comorbidity or NND.

Table 2 about here please

All six MC twin pregnancy studies which reported antenatal brain imaging compared fMRI with fetal ultrasound in the same pregnancy (18, 26, 29, 38, 46, 48). Ultrasound "missed" 6/19 (31.5%) lesions detected on fMRI in 3 studies (29, 38, 46) and the other 3 studies demonstrated concordance between the two imaging modalities (18, 26, 48), although this difference was not statistically significant. In abnormal postnatal brain imaging, it was not possible to perform sub-group analysis based on the imaging modalities of MRI or CT scan as 2 studies used ultrasound and MRI (43, 48), 1 study used ultrasound and CT (32), and 2 studies did not state the mode of imaging (31, 44). The rate of NND was higher in MC twin pregnancies where the initial sIUFD occurred <28 weeks gestation, in those with ~~IUGR~~FGR, and those with a PTB. No factors affected the risk of adverse outcome in DC twin survivors. It was not possible to calculate ORs for the year of publication sub-group analysis.

Publication bias

The funnel plots for co-twin IUFD, PTB, abnormal postnatal brain imaging and neurodevelopmental comorbidity appear asymmetrical, and Egger's test suggests small-study effects such as ~~-~~publication bias may exist in MC and the DC twins (funnel plots available from authors on request).

Discussion

Main findings

Abnormal antenatal brain imaging following sIUFD has not previously been meta-analysed; we report a rate of 1 in 5 surviving MC co-twins demonstrating abnormal

316 brain imaging, which doubled on postnatal brain imaging. NND was another novel
317 outcome in our review; ~~we report a rate of~~ almost 3 in 10 liveborn ~~surviving~~ MC co-
318 twins die in the neonatal period~~resulting in a NND~~, and 2 in 10 DC co-twins. In MC
319 twins, if the initial sIUFD occurred at <28 weeks gestation, this significantly increased
320 the rate of co-twin IUFD and NND compared to pregnancies in which the initial
321 sIUFD occurred >28 weeks. The presence of TTTS was associated with a significant
322 increase in the rate of PTB, but no other adverse outcome.

323

324 *Strength and limitations*

325 This ~~rigorous and robust~~ systematic review provides clinicians and parents with the
326 most up to date rates of complications in the surviving twin following spontaneous
327 sIUFD as reported by the literature. It also allows more tailored counselling, for
328 example, depending on the gestation of the initial sIUFD. According to international
329 guidance (7-12), MC twins should be scanned at a minimum frequency of every 2
330 weeks, and DC twins every 4 weeks, therefore it is possible that some cases of co-
331 twin IUFD have been missed by studies as there may appear to be a double IUFD at
332 the subsequent ultrasound scan, although the surviving co-twin may have been alive
333 for a substantial period following the initial sIUFD. Some of the sub-group analysis
334 was limited because these data were not reported by the included studies. For
335 example it was not possible to perform the sub-group analysis based on year of
336 publication, thus the inclusion of older studies with different antenatal care guidance
337 and neonatal care provision may increase the risk of heterogeneity. Ideally for the
338 PTB outcome we would have performed further analysis using cut-offs of 24-28, 28-
339 32 weeks etc. as our definition of <34 weeks was somewhat crude, however there

were insufficient numbers of pregnancies to do this. It would also be more clinically useful if the gestation of sIUFD could be more specific than before or after 28 weeks, but this would require individual patient data. There was a myriad of differences between studies reporting brain imaging findings, including different referral criteria, different timing of antenatal imaging varying from 0-12 weeks post IUFD, different imaging modalities, antenatal imaging findings were rarely linked to postnatal imaging findings and neurodevelopmental comorbidity, follow-up was poor and no studies were found reporting antenatal brain imag~~in~~ing in DC twins. Different methods of assessing neurodevelopment were used, making interpretation difficult. The results of this meta-analysis are not applicable to women in low-income countries as most studies include populations from developed countries.

Interpretation

When co-twin IUFD is viewed in the context of the summary event rates, the rate appears higher in both MC and DC twins compared to our previous review. We advise caution when interpreting this result as it is possibly an overestimate. This may be because of the existence of small-study effects, such as ~~-~~publication bias in this outcome, and it is likely that there is selecti~~ve~~on bias as authors are more likely to report adverse outcomes than normal outcomes. Nevertheless, these event rates are the most recent data available and 10 additional studies have been published since the previous review. The smaller 95%CI when comparing co-twin IUFD between chorionicities suggests that the most recent results are more realistic, and the increased rate seen in MC twins compared to DC twins is to be expected given the presence of vascular anastomoses in the former. The significant difference may

also be a consequence of an improved ability to determine chorionicity, better knowledge, and changes in monitoring over time. The lack of difference in adverse outcome, including co-twin IUFD, in TTTS pregnancies may be because of excluding TTTS pregnancies undergoing FLA or BCO, thus there was a higher proportion of milder cases of TTTS. This was different to the previous review but as the treatment for TTTS has advanced dramatically, ~~and~~ its use ~~is~~ more widespread since 2011, and there are different confounding factors compared to in spontaneous sIUFD, it was important to include this restriction. TTTS was associated with an increased PTB rate, although it was not possible to determine if they~~in these cases the PTBs~~ were spontaneous or iatrogenic. No difference was found in PTB between MC and DC surviving co-twins, suggesting that the mechanism of PTB in these cases is not inherent to chorionicity or vascular anastomoses, but to factors common to all twin pregnancies. With regards to abnormal antenatal and postnatal brain imaging, these results are difficult to interpret for reasons previously outlined. The higher rate of abnormal postnatal brain imaging in MC twins compared to DC twins was expected as it is believed that when one MC twin dies, acute transfusional events through inter-twin placental anastomoses occur as reviewed by ~~(as reviewed by~~ Mackie et al. ~~62)~~(59) resulting in cerebral injury detectable on postnatal brain imaging in the surviving co-twin. Whereas in DC twins the cause of the cerebral pathology is more likely a result of the pathological condition which killed the other twin, rather than a consequence of the sIUFD. The similarity between chorionicities and sub-group analysis in the neurodevelopmental comorbidity outcome may be due to small study size, or be a reflection of there being no difference in PTB between the chorionicities~~.~~. The borderline-significantly higher rate of NND in MC twins compared to DC twins was to be expected, particularly ~~as~~ if the initial sIUFD was <28 weeks, or

~~IUGR~~FGR or PTB was involved, the rate of NND was significantly higher in MC twins. It would be interesting to explore the relationship between these factors further, but it was not possible.

Conclusion

Our results will help clinicians counsel parents with a sIUFD and give information based upon chorionicity. The high rate of adverse outcomes highlights the importance of close antenatal surveillance, particularly in MC surviving co-twins, and those in which the sIUFD has occurred at <28 weeks. PTB was the commonest adverse outcome and clinicians and parents should be aware of the high risk of PTB in these pregnancies, and the potential requirement of neonatal unit admission. Outcomes regarding brain imaging and neurodevelopmental comorbidity are an important area for future research as this outcome is important to parents and will affect the quality of life of not only the surviving twin, but also other family members. The high rate of 20% of co-twins with an abnormal antenatal fMRI highlights that parents should always be offered antenatal brain imaging. In line with our findings, and those of the MERIDIAN study, the imaging modality should be fMRI not ultrasound(60). A study is needed examining antenatal and postnatal brain imaging and neurodevelopmental comorbidity in the same surviving co-twins, in a standardised manner, with adequate follow-up. The studies included in this meta-analysis were small and small study effects were shown to exist, consequently the authors have recognised the need to perform a large population-based study and are in the process of conducting a study using data from the UK Obstetric Surveillance Survey (UKOSS). This will be the largest study of complications in the surviving co-

twin in a population cared for using the same national guidance (for further details see (61)).

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Contribution to authorship: FLM extracted the data, performed the analysis and data interpretation, and drafted the article. AR extracted the data, assisted with data interpretation, and amended the article. RKM assisted extracting the data, contributed to the analysis and data interpretation, and amended the article. MDK conceived, designed, and oversaw the work, made final decisions where there were discrepancies, and amended the article. MDK is the guarantor for the study.

Ethical approval: not required

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Table/figure caption list

Table 1 Summary event rates and odds ratio of adverse outcome in surviving co-twin following single intrauterine fetal death in monochorionic (MC) and dichorionic (DC) twin pregnancies

615

616 Table 2 Significant results for sub-group analysis of adverse outcomes in surviving
617 co-twin following single intrauterine fetal death in monochorionic twin pregnancies.
618 Summary event rates for each sub-group are presented, and the significant odds
619 ratio (OR) comparing the two sub-groups

620 FGR: fetal growth restriction~~fMRI: fetal magnetic resonance imaging~~, GA: gestational
621 age, ~~IUGR: intrauterine growth restriction,~~ NA: not applicable as a sub-group for
622 outcome, ~~NP: not possible to calculate odds ratio,~~ NS: not statistically significant,
623 TTTS: twin-twin transfusion syndrome~~, USS: ultrasound scan~~. p value in the OR
624 column denotes the significance of OR=1. Note TTTS and ~~IUGR~~FGR were
625 conservatively managed.

626

627 Figure 1 Quality assessment of included studies according to 'Strengthening The
628 Reporting of Observational studies in Epidemiology' (STROBE) checklist

629

630 Figure 2 Forest plot comparing the risk of co-twin intrauterine fetal death (co-twin
631 IUFD) following single intrauterine fetal death in monochorionic (MC) and dichorionic
632 (DC) twin pregnancies

633

634 **Supporting information**

635 Figure S1 Study selection from initial search

636 Table S1 Study characteristics of included studies

637 Appendix S1 Search strategy

638 Appendix S2 Studies not included in meta-analysis

639 Appendix S3 Additional forest plots and extracted 2x2 data

~~Appendix S4 MOOSE checklist~~

~~Appendix S5 PRISMA checklist~~

Table 1 Summary event rates and odds ratio of adverse outcome in surviving co-twin following single intrauterine fetal death in monochorionic (MC) and dichorionic (DC) twin pregnancies

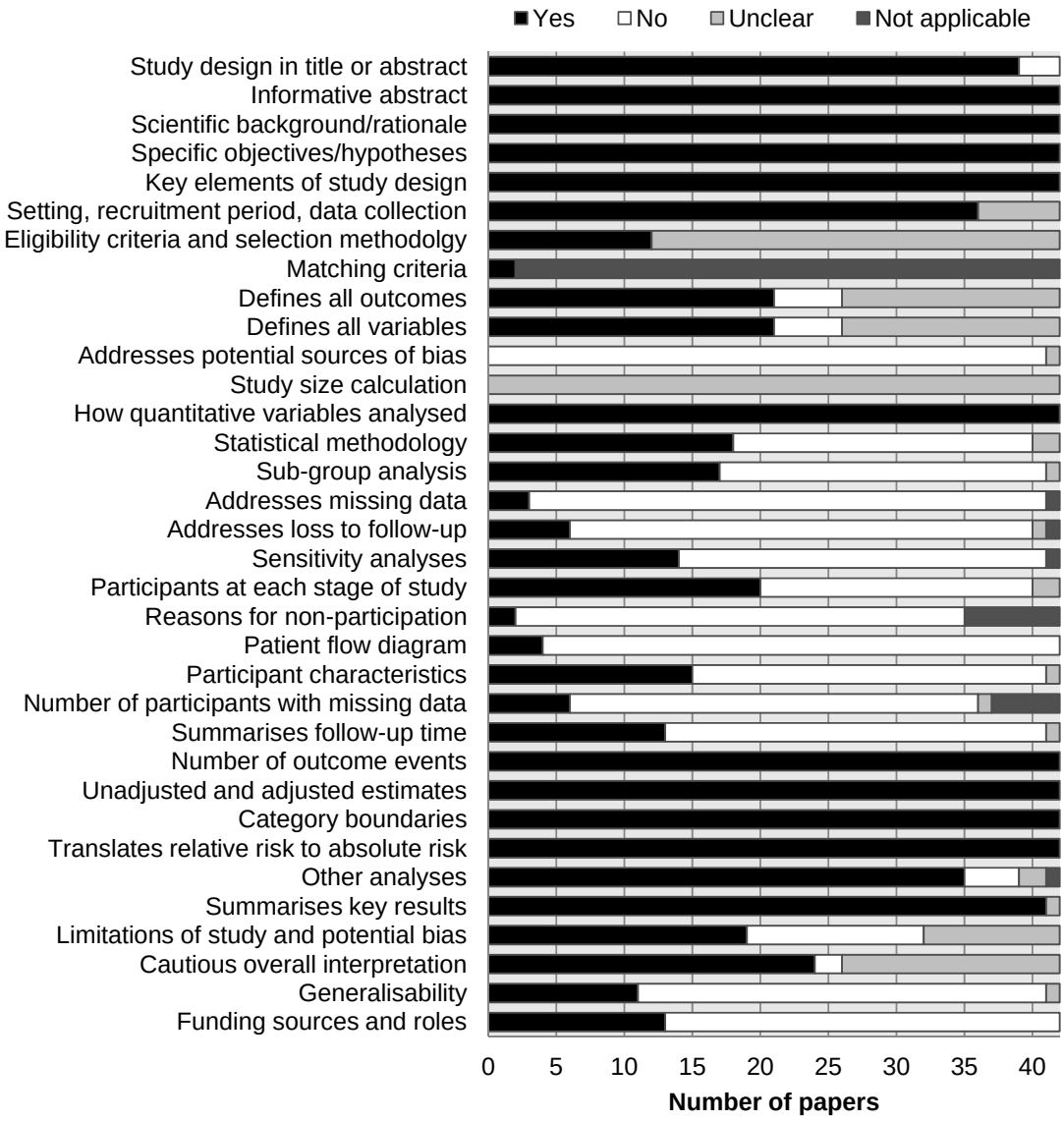
Adverse outcome in co-twin	Monochorionic event rate	Dichorionic event rate	Odds ratio [95%CI] comparing MC v DC
Co-twin intra-uterine fetal death	41.0% [95%CI 33.7, 49.9] I^2=44.2%, 32 studies, 379 pregnancies	22.4% [95%CI 16.2, 30.9] I^2=21.7%, 20 studies, 255 pregnancies	**2.06 [95%CI 1.14, 3.71] p=0.016, I^2=0.0%, 19 studies, 441 pregnancies**
Preterm birth	58.5% [95%CI 48.2, 70.9] I2=11.7%, 20 studies, 202 pregnancies	53.7% [95%CI 40.8, 70.6] I^2=0.0%, 12 studies, 107 pregnancies	1.42 [95%CI 0.67, 2.99] p=0.356, I^2=1.5%, 10 studies, 167 pregnancies
Abnormal antenatal brain fMRI	20.0% [95%CI 12.8, 31.1] I^2=21.9%, 6 studies, 116 pregnancies	NP	NP
Abnormal postnatal brain imaging	43.0% [95%CI 32.8, 56.3] I^2=12.4%, 12 studies, 140 pregnancies	21.2% [95%CI 10.6, 42.4] I^2=0.7%, 7 studies, 75 pregnancies	**5.41 [95%CI 1.03, 28.58] p=0.047, I^2=45.8%, 7 studies, 142 pregnancies**
Neuro-developmental comorbidity	28.5% [95%CI 19.0, 42.7] I^2=0.0%, 13 studies, 103 pregnancies	10% [95%CI 3.9, 27.7] I^2=0.0%, 8 studies, 62 pregnancies	3.06 [95%CI 0.88, 10.61] p=0.08, I^2=0.0%, 8 studies, 129 pregnancies
Neonatal death	27.9% [95%CI 21.1, 36.9] I^2=0.0%, 18 studies, 206 pregnancies	21.2% [95%CI 14.5, 31.2] I^2=0.0%, 12 studies, 130 pregnancies	1.95 [95%CI 1.00, 3.79] p=0.051, I^2=0.0%, 11 studies, 232 pregnancies

fMRI: fetal magnetic resonance imaging, NP: not possible to calculate. p value in the OR column denotes the significance of OR=1.

Table 2 Significant results for sub-group analysis of adverse outcomes in surviving co-twin following single intrauterine fetal death in monochorionic twin pregnancies

Adverse outcome in co-twin	GA of sIUFD <28 weeks	TTTS	~~IUGR~~FGR	Preterm birth versus no preterm birth
Co-twin intra-uterine fetal death	60.6% ([95%CI 45.8, 80.2] I^2=30.4%, 14 studies, 114 pregnancies) 29.6% ([95%CI 19.2, 45.6] I^2=0.0%, 15 studies, 85 pregnancies) **OR 2.31 ([95%CI 1.02, 5.25] p=0.046, I^2=0.0%, 12 studies, 184 pregnancies)**	NS	NS	NA
Preterm birth	NS	74.9% ([95%CI 54.0, 103.8] I^2=0.0%, 6 studies, 36 pregnancies) 43.3% ([95%CI 32.5, 57.6] I^2=76.0%, 7 studies, 47 pregnancies) **OR 3.48 ([95%CI 1.17, 10.84] p=0.03, I^2=0.0%, 6 studies, 80 pregnancies)**	NS	NA
Neonatal death	55.0% ([95%CI 36.4, 83.1] I^2=0.0%, 10 studies, 47 pregnancies) 25.2% ([95%CI 15.9, 40.0] I^2=0.0%, 12 studies, 76 pregnancies) **OR 2.84 ([95%CI 1.18, 6.77] p=0.019, I^2=0.0%, 10 studies, 117 pregnancies)**	NS	34.5% ([95%CI 23.5, 50.6] I^2=68.5%, 7 studies, 26 pregnancies) 25.3% ([95%CI 19.2, 33.4] I^2=0.0%, 7 studies, 50 pregnancies) **OR 4.83 ([95%CI 1.14, 20.47] p=0.03, I^2=0.0%, 6 studies, 60 pregnancies)**	41.9% (95%CI 33.6, 52.3] I^2=19.4%, 12 studies, 79 pregnancies) 11.3% (95%CI 8.6, 15.0] I^2=24.1%, 11 studies, 49 pregnancies) **OR 4.95 ([95%CI 1.71, 14.30] p=0.003, I^2=0.0%, 11 studies, 124 pregnancies)**

Figure 1 Quality assessment of included studies according to ‘Strengthening The Reporting of Observational studies in Epidemiology’ (STROBE) checklist



Study	Year	MC co-twin IUFD	MC no co-twin IUFD	DC co-twin IUFD	DC no co-twin IUFD	OR	(95%CI)
Cherouny	1989	0	8	0	4	0.50	(0.01, 30.16)
Fusi	1990	0	7	1	7	0.50	(0.01, 17.45)
Gaucherand	1994	0	6	0	2	0.33	(0.00, 23.00)
Ishimatsu	1994	0	12	0	3	0.25	(0.00, 15.37)
Kilby	1994	0	2	0	13	6.50	(0.10, 430.48)
Santema	1995	2	11	0	16	5.82	(0.24, 141.69)
Tordjeman	1996	0	2	0	8	4.00	(0.06, 270.79)
Sebire	1997	12	3	4	8	8.00	(1.40, 45.76)
Krayenbuhl	1998	0	12	0	7	0.58	(0.01, 32.79)
Axt	1999	0	4	0	2	0.50	(0.01, 35.82)
Petersen	1999	0	4	0	6	1.50	(0.02, 92.25)
Bajoria	1999	13	37	1	41	14.41	(1.80, 115.53)
Malinowski	2000	0	1	0	5	5.00	(0.06, 436.52)
Malinowski	2003	0	3	0	9	3.00	(0.05, 186.90)
Baghdadi	2003	1	0	2	10	10.00	(0.24, 412.14)
Chelli	2009	0	9	1	18	1.00	(0.03, 32.71)
Mahony	2011	5	6	2	9	3.75	(0.54, 26.04)
McPherson	2012	11	17	19	30	1.02	(0.39, 2.65)
Deveer	2013	0	9	0	16	1.78	(0.03, 97.46)
Overall (I^2=0.0%)						**2.06**	**(1.14, 3.71)**

NOTE: Weights are from random effects analysis