

# Prognosis of the co-twin following spontaneous single intrauterine fetal death in twin pregnancies

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

3

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23

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25

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

27

## 28 **Abstract**

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

31 **Objectives:** Determine the prognosis of the surviving co-twin following spontaneous  
32 single intrauterine fetal death ~~UFDs~~ to aid counselling patients and highlight areas-of  
33 future research areas.

34 **Search strategy:** Medline, Embase, Web of Science, and Cochrane Library, from  
35 1980 and June 2017.

36 **Selection criteria:** Studies of  $\geq 5$  cases of spontaneous single intrauterine fetal  
37 death after 14 weeks gestation, in diamniotic twin pregnancies.

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

41 **Main results:** In monochorionic twins, when single intrauterine fetal death occurred  
42 at  $< 28$  weeks gestation, this significantly increased the rate of co-twin intrauterine  
43 fetal death (OR 2.31[95%CI 1.02, 5.25],  $I^2=0.0\%$ , 12 studies, 184 pregnancies) and  
44 neonatal death (OR 2.84[95%CI 1.18, 6.77],  $I^2=0.0\%$ , 10 studies, 117 pregnancies)  
45 compared to when the single intrauterine fetal death ~~UFDs~~ occurred  $> 28$  weeks.

46 Neonatal death in monochorionic twins was significantly higher if the pregnancy was

47 | complicated by fetalintrauterine growth restriction (OR  
48 | 4.83[95%CI1.14,20.47], $I^2=0.0\%$ ,6 studies,60 pregnancies) or preterm birth (OR  
49 | 4.95[95%CI 1.71,14.30], $I^2=0.0\%$ ,11 studies,124 pregnancies). Abnormal antenatal  
50 | brain imaging was reported in 20.0% ([95%CI12.8,31.1] $I^2=21.9\%$ ,6 studies,116  
51 | pregnancies) of surviving monochorionic co-twins. The studies included in this meta-  
52 | analysis demonstrated small study effects and possible selection bias.

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

59 |  
60 | **Funding:** FLM is funded by the Richard and Jack Wiseman Trust but they had no  
61 | involvement in study design; in the collection, analysis and interpretation of the data;  
62 | in the writing of the report; and in the decision to submit the article for publication.

63 |  
64 | **Keywords:** co-twin death, fetal brain imaging, fetalintrauterine growth restriction,  
65 | neonatal death, neurodevelopmental comorbidity, preterm birth, prognosis, single  
66 | intrauterine fetal death, twin pregnancy, twin-twin transfusion syndrome

67 |  
68 | **Tweetable abstract:** Preterm birth highest risk in single #twin death. Abnormal  
69 | antenatal brain imaging in 1/5 surviving MC twins.

## 70 Introduction

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

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

100

101 The objective of the study wais to determine the prognosis of the surviving co-twin  
102 following spontaneous sIUFD. The outcomes explored wwereill-be: co-twin IUFD,  
103 preterm-birthPTB, abnormal postnatal brain imaging and neurodevelopmental  
104 comorbidity as analysed in our previous systematic review and meta-analysis, and  
105 the additional outcomes of abnormal antenatal brain imaging and neonatal death  
106 wwereill also be-examined. This review haswill-allow allowed inclusion of the recent  
107 literature informing clinical practice to aid counselling patients and highlight areas of  
108 future research.

109

## 110 **Methods**

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

### 117 *Eligibility criteria*

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

### 137 *Outcomes*

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

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

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

156

### 157 *Information sources*

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

161 | and neonatal death, the ~~information~~ searches were run from 1980 due to the  
162 | introduction of ultrasound into clinical practice, to 9<sup>th</sup> June 2017.

163

#### 164 | *Search strategy*

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

168

#### 169 | *Study selection and data extraction*

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

175

#### 176 | *Quality assessment of included studies*

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

179

#### 180 | *Assessment of heterogeneity*

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

184

#### 185 *Assessment of reporting bias*

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

190

#### 191 *Data synthesis*

192 With the additional 20 studies, we have produced a summary event rate statistic  
193 which has allowed for the non-independence of different studies when the data is  
194 pooled, as is appropriate in a meta-analysis. ~~This was calculated using the *metan*~~  
195 ~~command (1)~~. Odds ratios (ORs) with random effects were calculated to compare the  
196 risk in MC twin pregnancies with DC twin pregnancies ~~using the *metan* command~~.  
197 0.5 was added to 0 cells in all analyses to allow inclusion of more studies ~~(20)~~. (17). If  
198 a study only included MC twin pregnancies, the study was used to calculate the  
199 summary event rate for MC twins only, and was not included in the DC summary  
200 event rate or OR calculation of MC vs. DC twins, and vice versa if a study only  
201 included DC twin pregnancies. Sub-group analysis, in analyses of  $\geq 3$  studies, was  
202 planned to evaluate the effect of factors identified as potential causes of  
203 heterogeneity prior to commencing analysis: gestational age of sIUFD <28 weeks,  
204 TTTS (managed conservatively meaning no intervention but continued surveillance),

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

216

## 217 | **Results**

### 218 | *Study selection and characteristics*

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

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

231

### 232 *Risk of bias of included studies*

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

241 ~~publication bias.~~

242

243 **\*\*Figure 1 about here please\*\***

244

### 245 *Synthesis of results*

### 246 *Summary event rates*

247

248 **\*\*Table 1 about here please\*\***

249

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

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

262 ~~[Additional forest plots and extracted 2x2 data are shown in Appendix S3.](#)~~

263

264 \*\*Figure 2 about here please\*\*

265

### 266 *Sub-group*

267 Sub-group analysis demonstrated that in MC twin pregnancies, those with [anthe](#)  
268 sIUFD <28 weeks were significantly more likely to have a co-twin IUFD than those  
269 with [anthe](#) sIUFD ≥28 weeks. The pathologies of TTTS and [IUGRFGR](#) were not  
270 associated with an increased risk of co-twin IUFD (Table 2). Pregnancies

271 complicated by TTTS were significantly more likely to have a PTB than twin  
272 pregnancies without TTTS. When preterm birth was divided according to whether it  
273 was iatrogenic or spontaneous, in MC twins the summary event rate of iatrogenic  
274 PTB was 60.4% ([95%CI 33.5, 109.1]  $I^2=0.00\%$ , 3 studies, 7 pregnancies) compared  
275 to a spontaneous PTB rate of 37.1% % ([95%CI 20.5, 66.9]  $I^2=24.1\%$ , 3 studies, 4  
276 pregnancies). There were no significant sub-group results for abnormal postnatal  
277 brain imaging, or neurodevelopmental comorbidity in MC twins, and it was not  
278 possible to perform sub-group analysis for the abnormal antenatal brain imaging, as  
279 often this information was not included in the primary full manuscripts. -In DC twins  
280 the summary event rate of iatrogenic PTB was 32.4% ([95%CI 14.6, 72.1]  $I^2=32.7\%$ ,  
281 3 studies, 6 pregnancies) compared to a spontaneous PTB rate of 70.7% ([95%CI  
282 31.8, 157.4]  $I^2=0.0\%$ , 3 studies, 6 pregnancies), although the wide 95% CIs should  
283 be noted, which may be due to small sample size. Other sub-group analysis in DC  
284 twins was limited due to small numbers, but the following analyses were possible,  
285 none of which found a significant difference: sIUFD <28 weeks did not affect co-twin  
286 IUFD, PTB, abnormal postnatal brain imaging, neurodevelopmental comorbidity or  
287 NND; IUGR/FGFR did not affect co-twin IUFD or PTB, neurodevelopmental  
288 comorbidity or NND; PTB did not affect abnormal postnatal brain imaging,  
289 neurodevelopmental comorbidity or NND.

290

291 \*\*Table 2 about here please\*\*

292

293 All six MC twin pregnancy studies which reported antenatal brain imaging compared  
294 fMRI with fetal ultrasound in the same pregnancy (18, 26, 29, 38, 46, 48). Ultrasound  
295 “missed” 6/19 (31.5%) lesions detected on fMRI in 3 studies (29, 38, 46) and the  
296 other 3 studies demonstrated concordance between the two imaging modalities (18,  
297 26, 48), although this difference was not statistically significant. In abnormal  
298 postnatal brain imaging, it was not possible to perform sub-group analysis based on  
299 the imaging modalities of MRI or CT scan as 2 studies used ultrasound and MRI (43,  
300 48), 1 study used ultrasound and CT (32), and 2 studies did not state the mode of  
301 imaging (31, 44). The rate of NND was higher in MC twin pregnancies where the  
302 initial sIUFD occurred <28 weeks gestation, in those with **IUGR/FGFR**, and those with  
303 a PTB. No factors affected the risk of adverse outcome in DC twin survivors. It was  
304 not possible to calculate ORs for the year of publication sub-group analysis.

305

### 306 *Publication bias*

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

311

## 312 **Discussion**

### 313 *Main findings*

314 Abnormal antenatal brain imaging following sIUFD has not previously been meta-  
315 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

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

351

### 352 *Interpretation*

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

364 also be a consequence of an improved ability to determine chorionicity, better  
365 knowledge, and changes in monitoring over time. The lack of difference in adverse  
366 outcome, including co-twin IUFD, in TTTS pregnancies may be because of excluding  
367 TTTS pregnancies undergoing FLA or BCO, thus there was a higher proportion of  
368 milder cases of TTTS. This was different to the previous review but as the treatment  
369 for TTTS has advanced dramatically, ~~and~~ its use is more widespread since 2011,  
370 and there are different confounding factors compared to in spontaneous sIUFD, it  
371 was important to include this restriction. TTTS was associated with an increased  
372 PTB rate, although it was not possible to determine if ~~they in these cases the PTBs~~  
373 were spontaneous or iatrogenic. No difference was found in PTB between MC and  
374 DC surviving co-twins, suggesting that the mechanism of PTB in these cases is not  
375 inherent to chorionicity or vascular anastomoses, but to factors common to all twin  
376 pregnancies. With regards to abnormal antenatal and postnatal brain imaging, these  
377 results are difficult to interpret for reasons previously outlined. The higher rate of  
378 abnormal postnatal brain imaging in MC twins compared to DC twins was expected  
379 as it is believed that when one MC twin dies, acute transfusional events through  
380 inter-twin placental anastomoses occur as reviewed by ~~(as reviewed by Mackie et al.~~  
381 ~~62)~~(59) resulting in cerebral injury detectable on postnatal brain imaging in the  
382 surviving co-twin. Whereas in DC twins the cause of the cerebral pathology is more  
383 likely a result of the pathological condition which killed the other twin, rather than a  
384 consequence of the sIUFD. The similarity between chorionicities and sub-group  
385 analysis in the neurodevelopmental comorbidity outcome may be due to small study  
386 size, or be a reflection of there being no difference in PTB between the  
387 chorionicities. The borderline-significantly higher rate of NND in MC twins compared  
388 to DC twins was to be expected, particularly ~~as~~ if the initial sIUFD was <28 weeks, or

389 | IUGRFGR or PTB was involved, the rate of NND was significantly higher in MC  
390 | twins. It would be interesting to explore the relationship between these factors  
391 | further, but it was not possible.

392 |

### 393 | **Conclusion**

394 | Our results will help clinicians counsel parents with a sIUFD and give information  
395 | based upon chorionicity. The high rate of adverse outcomes highlights the  
396 | importance of close antenatal surveillance, particularly in MC surviving co-twins, and  
397 | those in which the sIUFD has occurred at <28 weeks. PTB was the commonest  
398 | adverse outcome and clinicians and parents should be aware of the high risk of PTB  
399 | in these pregnancies, and the potential requirement of neonatal unit admission.

400 | Outcomes regarding brain imaging and neurodevelopmental comorbidity are an  
401 | important area for future research as this outcome is important to parents and will  
402 | affect the quality of life of not only the surviving twin, but also other family members.

403 | The high rate of 20% of co-twins with an abnormal antenatal fMRI highlights that  
404 | parents should always be offered antenatal brain imaging. In line with our findings,  
405 | and those of the MERIDIAN study, the imaging modality should be fMRI not  
406 | ultrasound(60). A study is needed examining antenatal and postnatal brain imaging  
407 | and neurodevelopmental comorbidity in the same surviving co-twins, in a  
408 | standardised manner, with adequate follow-up. The studies included in this meta-  
409 | analysis were small and small study effects were shown to exist, consequently the  
410 | authors have recognised the need to perform a large population-based study and are  
411 | in the process of conducting a study using data from the UK Obstetric Surveillance  
412 | Survey (UKOSS). This will be the largest study of complications in the surviving co-

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

415

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429 interpretation, and amended the article. RKM assisted extracting the data,  
430 contributed to the analysis and data interpretation, and amended the article. MDK  
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610

611 **Table/figure caption list**

612 Table 1 Summary event rates and odds ratio of adverse outcome in surviving co-twin  
613 following single intrauterine fetal death in monochorionic (MC) and dichorionic (DC)  
614 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

640 | ~~Appendix S4 MOOSE checklist~~

641 | ~~Appendix S5 PRISMA checklist~~

642

**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 <sup>2</sup> =44.2%, 32 studies, 379 pregnancies	22.4% [95%CI 16.2, 30.9] I <sup>2</sup> =21.7%, 20 studies, 255 pregnancies	<b>2.06 [95%CI 1.14, 3.71] p=0.016, I<sup>2</sup>=0.0%, 19 studies, 441 pregnancies</b>
Preterm birth	58.5% [95%CI 48.2, 70.9] I <sup>2</sup> =11.7%, 20 studies, 202 pregnancies	53.7% [95%CI 40.8, 70.6] I <sup>2</sup> =0.0%, 12 studies, 107 pregnancies	1.42 [95%CI 0.67, 2.99] p=0.356, I <sup>2</sup> =1.5%, 10 studies, 167 pregnancies
Abnormal antenatal brain fMRI	20.0% [95%CI 12.8, 31.1] I <sup>2</sup> =21.9%, 6 studies, 116 pregnancies	NP	NP
Abnormal postnatal brain imaging	43.0% [95%CI 32.8, 56.3] I <sup>2</sup> =12.4%, 12 studies, 140 pregnancies	21.2% [95%CI 10.6, 42.4] I <sup>2</sup> =0.7%, 7 studies, 75 pregnancies	<b>5.41 [95%CI 1.03, 28.58] p=0.047, I<sup>2</sup>=45.8%, 7 studies, 142 pregnancies</b>
Neuro-developmental comorbidity	28.5% [95%CI 19.0, 42.7] I <sup>2</sup> =0.0%, 13 studies, 103 pregnancies	10% [95%CI 3.9, 27.7] I <sup>2</sup> =0.0%, 8 studies, 62 pregnancies	3.06 [95%CI 0.88, 10.61] p=0.08, I <sup>2</sup> =0.0%, 8 studies, 129 pregnancies
Neonatal death	27.9% [95%CI 21.1, 36.9] I <sup>2</sup> =0.0%, 18 studies, 206 pregnancies	21.2% [95%CI 14.5, 31.2] I <sup>2</sup> =0.0%, 12 studies, 130 pregnancies	1.95 [95%CI 1.00, 3.79] p=0.051, I <sup>2</sup> =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	<del>IUGR</del> <u>FGR</u>	Preterm birth versus no preterm birth
Co-twin intra-uterine fetal death	60.6% ([95%CI 45.8, 80.2] I <sup>2</sup> =30.4%, 14 studies, 114 pregnancies) 29.6% ([95%CI 19.2, 45.6] I <sup>2</sup> =0.0%, 15 studies, 85 pregnancies) <b>OR 2.31 ([95%CI 1.02, 5.25]</b> <b>p=0.046, I<sup>2</sup>=0.0%, 12 studies, 184 pregnancies)</b>	NS	NS	NA
Preterm birth	NS	74.9% ([95%CI 54.0, 103.8] I <sup>2</sup> =0.0%, 6 studies, 36 pregnancies) 43.3% ([95%CI 32.5, 57.6] I <sup>2</sup> =76.0%, 7 studies, 47 pregnancies) <b>OR 3.48 ([95%CI 1.17, 10.84]</b> <b>p=0.03, I<sup>2</sup>=0.0%, 6 studies, 80 pregnancies)</b>	NS	NA
Neonatal death	55.0% ([95%CI 36.4, 83.1] I <sup>2</sup> =0.0%, 10 studies, 47 pregnancies) 25.2% ([95%CI 15.9, 40.0] I <sup>2</sup> =0.0%, 12 studies, 76 pregnancies) <b>OR 2.84 ([95%CI 1.18, 6.77]</b> <b>p=0.019, I<sup>2</sup>=0.0%, 10 studies, 117 pregnancies)</b>	NS	34.5% ([95%CI 23.5, 50.6] I <sup>2</sup> =68.5%, 7 studies, 26 pregnancies) 25.3% ([95%CI 19.2, 33.4] I <sup>2</sup> =0.0%, 7 studies, 50 pregnancies) <b>OR 4.83 ([95%CI 1.14, 20.47]</b> <b>p=0.03, I<sup>2</sup>=0.0%, 6 studies, 60 pregnancies)</b>	41.9% (95%CI 33.6, 52.3] I <sup>2</sup> =19.4%, 12 studies, 79 pregnancies) 11.3% (95%CI 8.6, 15.0] I <sup>2</sup> =24.1%, 11 studies, 49 pregnancies) <b>OR 4.95 ([95%CI 1.71, 14.30]</b> <b>p=0.003, I<sup>2</sup>=0.0%, 11 studies, 124 pregnancies)</b>

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



